

# WHO South-East Asia Region Epidemiological Bulletin

WHO Health Emergencies Programme

WHO Regional Office for South-East Asia

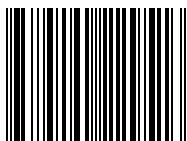
17<sup>th</sup> edition (2024), 21 August 2024. Reporting period: 5 to 18 August 2024



This epidemiological bulletin aims to provide the situation of key infectious diseases in the WHO South-East Asia Region to inform risk assessments and responses. The bulletin uses information from publicly available sources and will be published every two weeks. For feedback or suggestions, please write to [seoutbreak@who.int](mailto:seoutbreak@who.int).

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## Key events and updates

### Upsurge of mpox as a public health emergency of international concern

#### Key messages

- WHO Director-General has determined that the upsurge of mpox in the Democratic Republic of the Congo (DRC) and a growing number of countries in Africa constitutes a Public Health Emergency of International Concern (PHEIC), concurring with the advice offered by the International Health Regulations (IHR)(2005) Emergency Committee.
- The detection and rapid spread of a new strain of mpox (Clade 1b) in eastern DRC, its detection in neighboring countries that had not previously reported mpox, and the potential for further spread within Africa and beyond are the major concerns.

#### Situation overview (as of 17 August 2024)<sup>1 2 3 4</sup>

- Growing outbreaks in the DRC:** Since the beginning of this year, the **DRC has been experiencing a severe outbreak of mpox**, with more than 15 600 reported suspected (clinically compatible) cases and 537 related deaths.
  - This represents a 160% increase from the same period last year in DRC.
  - The increased case reporting is driven by two concomitant outbreaks, including (1) outbreaks in historically endemic parts of the DRC, affecting primarily children, and (2) a rapidly expanding outbreak of a new strain of MPXV clade I (clade Ib) which appears to be spreading predominantly through sexual networks, expanding geographically in DRC's eastern provinces, and affecting neighboring countries.
- New countries affected in Africa:** Four countries neighboring the DRC reported their first mpox cases in the past one month: Burundi, Kenya, Rwanda and Uganda. In total, 12 countries in Africa have reported mpox this year, with 9 countries with active outbreaks.
- New virus strain behind recent cases:** The current outbreak in the Eastern DRC is triggered by a new variant of the Clade I, called clade Ib.
  - Clade I (Clade Ia) has been historically circulated in DFC, while Clade II was responsible for the global outbreak that began in 2022.
  - Clade I is known to cause more severe disease than clade II. It is unknown if the two clade I variants, clade Ia and Ib, differ in disease severity.
  - Clade Ib is spreading among people, driven by sexual contact but also involving other type of contact.
  - Clade Ib has now been detected in countries in East and Central Africa (i.e. DRC, Burundi, Kenya, Rwanda and Uganda) and Sweden.
  - There are many scientific uncertainties and evidence gaps (e.g., modes of disease transmission, transmission dynamics, risk factors, and disease severity associated with the different mpox virus clades).
- Continued spread of mpox globally:** mpox remains a global public health concern, with cases and outbreaks still being reported worldwide. In June 2024, 26 countries reported over 930 cases and 4 deaths globally. Please see regular mpox section where mpox situation in WHO South-East Asia Region is summarized.
- The first case of the mpox Clade Ib outside Africa:** On August 15, the Public Health Agency of Sweden reported the first case of the mpox Clade Ib outside Africa.<sup>5 6</sup>
  - The infected individual has travel history to Central Africa, where a mpox outbreak is ongoing.

<sup>1</sup> [mpox HQ dashboard](#)

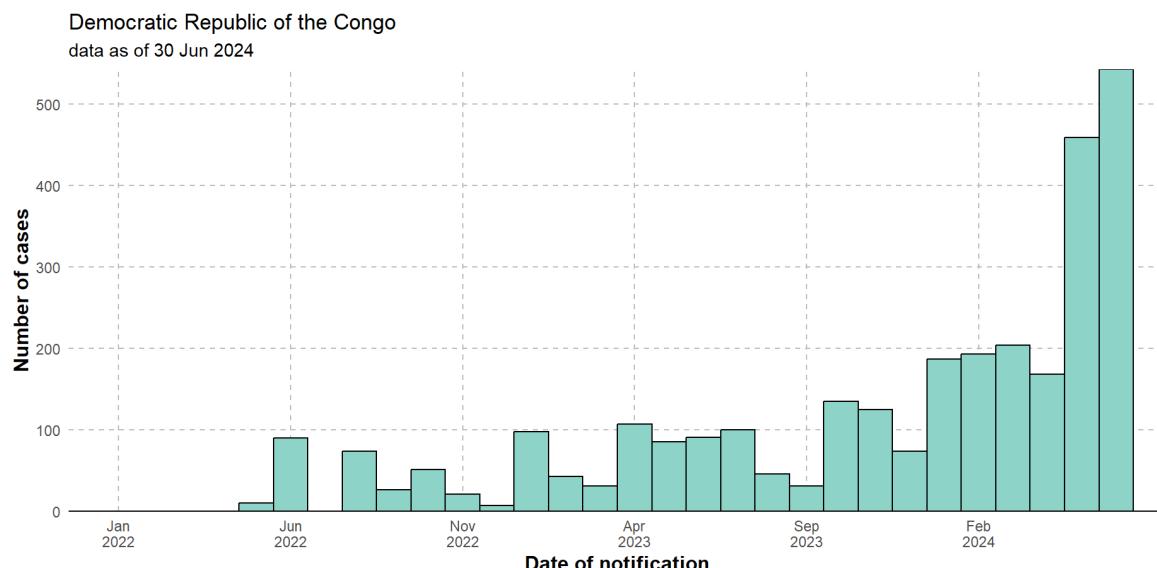
<sup>2</sup> [UN news](#)

<sup>3</sup> [WHO Director-General declares mpox outbreak a public health emergency of international concern](#)

<sup>4</sup> <https://www.who.int/publications/m/item/multi-country-outbreak-of-mpox--external-situation-report-35--12-august-2024>

<sup>5</sup> [One case of mpox clade I reported in Sweden - The Public Health Agency of Sweden \(folkhalsomyndigheten.se\)](#)

<sup>6</sup> [First case of more dangerous mpox found outside Africa \(bbc.com\)](#)

**Figure 1. Number of mpox cases reported in DRC.**

Source: WHO

**Table 1. Number of cumulative laboratory-confirmed mpox cases and deaths reported to WHO, by WHO Region, from 1 January 2022 through 30 June 2024.**

WHO Region	Total confirmed cases	Total deaths among confirmed cases	New cases reported in May	New cases reported in June	Monthly change in cases (%)
Region of the Americas	62 904	141	215	175	-19.0
European Region	27 529	10	141	100	-29.0
African Region	4 232	35	465	567	22.0
Western Pacific Region	3 491	10	120	81	-32.0
South-East Asia Region	925	11	22	11	-50.0
Eastern Mediterranean Region	95	1	0	0	-
<b>Total</b>	<b>99 176</b>	<b>208</b>	<b>963</b>	<b>934</b>	<b>-3.0</b>

NB: The number of reports for previous months include retroactively assigned case reports received since the report for May

### WHO response

- WHO Director General determined that the upsurge of mpox in the DRC and a growing number of countries constitutes a **public health emergency of international concern (PHEIC)** on 14 August, with the advice offered by the IHR Emergency Committee on the same day.
- In relation to PHEIC determination, [temporary recommendations](#) are issued to States Parties experiencing the upsurge of mpox, including, but not limited to, the DRC, Burundi, Kenya, Rwanda, and Uganda. They are intended to be implemented by those State Parties in addition to the standing recommendations for mpox (see below).
- The WHO Director-General's [standing recommendations](#) for mpox issued on 21 Aug 2023 are being extended for another year to cover more general guidance for all State Parties to address the chronic risk of mpox.
- WHO has regraded the global mpox multi-country event to an acute grade 3 emergency in accordance with the WHO Emergency Response Framework and issued an information posting to WHO Member States;
- The WHO Director-General has triggered the process towards Emergency Use Listing for mpox vaccines;
- Funds are being released from the WHO Contingency Fund for Emergencies (CFE) to scale up the response in the African Region;

## WHO resources on mpox

All current WHO interim technical guidance can be accessed on [this page](#) of the WHO website. WHO evidence-based guidance has been and will continue to be updated in line with the evolving situation and updated scientific evidence. The selected publications are listed below for easy reference, together with other relevant resources.

- **IHR Emergency Committee, Temporary Recommendations and Standing Recommendations**
  - [First meeting of the International Health Regulations \(2005\) Emergency Committee regarding the upsurge of mpox 2024](#)
- **Strategic framework**
  - [Strategic framework for enhancing prevention and control of mpox- 2024-2027](#) (24 May 2024)
- **General information on mpox**
  - [Monkeypox outbreak page \(2022\)](#)
  - [Mpox \(monkeypox\) health topic page](#)
  - [Mpox \(monkeypox\) Q&A](#)
- **Epidemiological situation**
  - Dashboard: [https://worldhealthorg.shinyapps.io/mpx\\_global/](https://worldhealthorg.shinyapps.io/mpx_global/)
  - [Multi-country outbreak of mpox, External situation report#35- 12 August 2024 \(who.int\)](#)
  - [Genomic epidemiology of monkeypox virus \(Nextstrain\)](#)
- **Technical documents**
  - [Diagnostic testing for the monkeypox virus \(MPXV\): interim guidance](#) (10 May 2024)
  - [Risk communication and community engagement readiness and response toolkit: mpox](#) (23 April 2024)
  - [Surveillance, case investigation and contact tracing for mpox \(monkeypox\): Interim guidance](#) (20 March 2024)
  - [Clinical characterization of mpox including monitoring the use of therapeutic interventions: statistical analysis plan](#) (13 October 2023)
  - [Monkeypox vaccines technical documents](#)
  - SAGE on mpox vaccines (page 16): <https://iris.who.int/bitstream/handle/10665/376936/WER9922-285-306.pdf?sequence=1>
  - [Responding to the global mpox outbreak: ethics issues and considerations: a policy brief](#) (19 July 2023)
- **Data collection tools**
  - Case report form: [Word](#)
  - Case investigation form: [PDF](#)
- **Mass gathering**
  - [Public health advice for gatherings during the current monkeypox outbreak](#)
  - [Interim advice for public health authorities on summer events during the monkeypox outbreak in Europe, 2022](#)
  - [Holding mass and large gathering events during the multi-country mpox outbreak in the WHO European Region: Lessons identified for future mass gathering preparedness](#) (22 February 2023)
  - [Catalogue of resources on mpox mass and large gathering event preparedness](#)

## Myanmar: Acute Watery Diarrhea

### Situation overview (as of 9 August 2024)

- [Myanmar Acute Watery Diarrhea/ Cholera Outbreak External Situation Report – the first edition](#) was published on 14 August 2024. The key points are summarized as follows.

#### Yangon

- According to the ministerial authorities for health, a total of 2 261 hospitalized cases of acute watery diarrhea (AWD) and 161 hospitalized cases of AWD with severe dehydration were reported from 44 townships of Yangon region as of 8 August 2024. Among them, 15 cases have died, however, the cause of death is unknown. Cholera infection is confirmed in some of those AWD cases.
- Most affected townships were Thaketa, Hlaingtharyar, Botahtaung, Dawbon, and Thingangyun.
- WHO is supporting the response to the outbreak in collaboration with partners.

#### Rakhine

- Starting from mid-June, AWD cases increased in Sittwe in Rakhine State, with a notable surge of the cases, including those with severe dehydration, in late July. Cholera infection is confirmed in some of those AWD cases.

## Nepal: Cholera

### Situation overview (as of 19 August 2024)<sup>7</sup>

- According to an official situation report from the Nepal Ministry of Health and Population, clusters of cholera cases have been reported in several districts across the country since 19 July 2024.
- *Vibrio cholerae O1 Ogawa* serotype has been confirmed in stool samples. All confirmed cholera cases have been confirmed by culture.
- As of 19 August 2024, there are **58 cases** in 4 districts: **Lalitpur (41), Kathmandu (7), Kailali (8), and Pyuthan (2)**. No epidemiological link has been established between the districts. No deaths have been reported.
- Individuals aged 15-24 years old represent the majority of cases (26%), followed by those aged 25-34 years old (21%).

#### Public health response

- EDCD is coordinating with all three provincial health directorates, PHEOCs, District Administrative offices, provincial public health labs, National reference laboratory and health facilities daily for enhanced responses.
- Weekly coordination meeting is held to discuss and strategize the cholera response.
- Initiation on discussion on use of reactive vaccination campaign.
- EDCD is coordinating with the Rapid Response focal person from districts and local municipalities for active case finding and testing for laboratory conformation. Alerts are investigated within 48 hours.
- All health facilities (n=144) have been alerted by the provincial and district offices to prepare for case management and referral services. Cases are managed at Sukraraj Tropical & Infectious Disease Hospital and Seti Hospital.
- Water, sanitation and hygiene (WASH) response: Decontamination of probable sources. Handwash activities being carried out. Chlorination of drinking water sources. Dissemination of WASH and cholera-related messages through social media platforms such as Facebook and Instagram.
- Risk communication and community engagement (RCCE): Cholera awareness brochures were distributed by local rapid response teams and district Offices. Public Service Announcement have been developed and disseminated. Health Directorate in the provinces rolling out RCCE activities by activating WASH cluster.

<sup>7</sup> [EDCD Nepal – Cholera and dengue situation update 19 August 2024](#)

## New Publication: Global guidance on monitoring public health and social measures policies during health emergencies

- This global guidance aims to facilitate systematic and harmonized data collection about, and monitoring of, public health and social measures (PHSM) policies implemented by governments during health emergencies.
- The guidance is intended for policy-makers, health authorities, responders and researchers in multiple sectors and at various levels responsible for responding to public health emergencies and developing PHSM policies, and provides key actions for PHSM policy monitoring in both preparedness and response.
- The guidance details standardized approaches and actionable steps for establishing and maintaining a robust PHSM monitoring system, a taxonomy of PHSM categories for coherent and comparable policy monitoring, and a process for consistent and transparent data collection.
- The guidance facilitates the availability of context-specific and real-time PHSM data alongside other key data sets drawn on during public health events for PHSM decision making. This guidance will be accompanied by flexible and customizable online tools.
- The guidance was published on 16 August 2024 and is available at the following link:  
<https://www.who.int/publications/i/item/9789240094444>



# COVID-19

## Situation overview as of 18 August 2024

- In the WHO South-East Asia Region, from 5 to 18 August 2024, 1 665 new COVID-19 cases, a decrease of 25.4% and 11 deaths, an increase of 175%, were reported, compared to the previous 14 days (Table 2).
  - From 5 to 18 August 2024, India (572 new cases, +2.9%) reported an increase in the number of new cases, while Thailand (954 new cases, -35.9%), Bangladesh (24 new cases, -63.6%) and Myanmar (39 new cases, -15.2%) and Indonesia (76 new cases, -11.6%) reported a decrease in the number of new cases, compared to the previous 14 days.
  - Data were not available from Bhutan, Maldives, Nepal, Sri Lanka and Timor-Leste for this period.
- The Region has recorded a cumulative total of 61 315 364 COVID-19 cases, including 808 814 deaths (Table 1).
- During week 30 in 2024, the proportion of respiratory samples collected at influenza sentinel surveillance sites in the selected countries that tested positive for COVID-19 ranged from 1.52% (Bangladesh) to 13.06% (Bhutan) (Figure 3).
- Please refer to the [WHO SEARO COVID-19 dashboard](#) for further information of COVID-19 in WHO South-East Asia Region.
- Globally, 775 867 547 COVID-19 cases, including 7 057 145 deaths have been cumulatively reported, as of 4 August<sup>8</sup>. Please visit the [WHO COVID-19 dashboard](#) for the global situation of COVID-19.

**Table 2. COVID-19 cases, deaths, and the weekly change in countries in the WHO South-East Asia Region in the week from 5 to 18 August 2024.**

Country	Cumulative cases	New cases (last 14 days)	% change in new cases	New cases per 1M pop	Cumulative deaths	New deaths (last 14 days)	% change in new deaths	New deaths per 1M pop
Thailand	4,800,134	954	-35.9	13.3	34,720	5	66.7	0.1
India	45,042,320	572	2.9	0.4	533,629	6	100.0	0.0
Bangladesh	2,051,372	24	-63.6	0.1	29,499	0	-100.0	0.0
Myanmar	642,924	39	-15.2	0.7	19,494	0	0.0	0.0
Indonesia	6,829,515	76	-11.6	0.3	162,059	0	0.0	0.0
Sri Lanka	672,798	NA	NA	NA	16,907	NA	NA	NA
Bhutan	62,697	NA	NA	NA	21	NA	NA	NA
Maldives	186,694	NA	NA	NA	316	NA	NA	NA
Nepal	1,003,450	NA	NA	NA	12,031	NA	NA	NA
Timor-Leste	23,460	NA	NA	NA	138	NA	NA	NA
SEAR Total	61,315,364	1,665	-25.4	NA	808,814	11	175.0	NA

### Notes:

Percent change in the number of newly confirmed cases/deaths in past 14 days, compared to the previous 14 days.

NA = data not available.

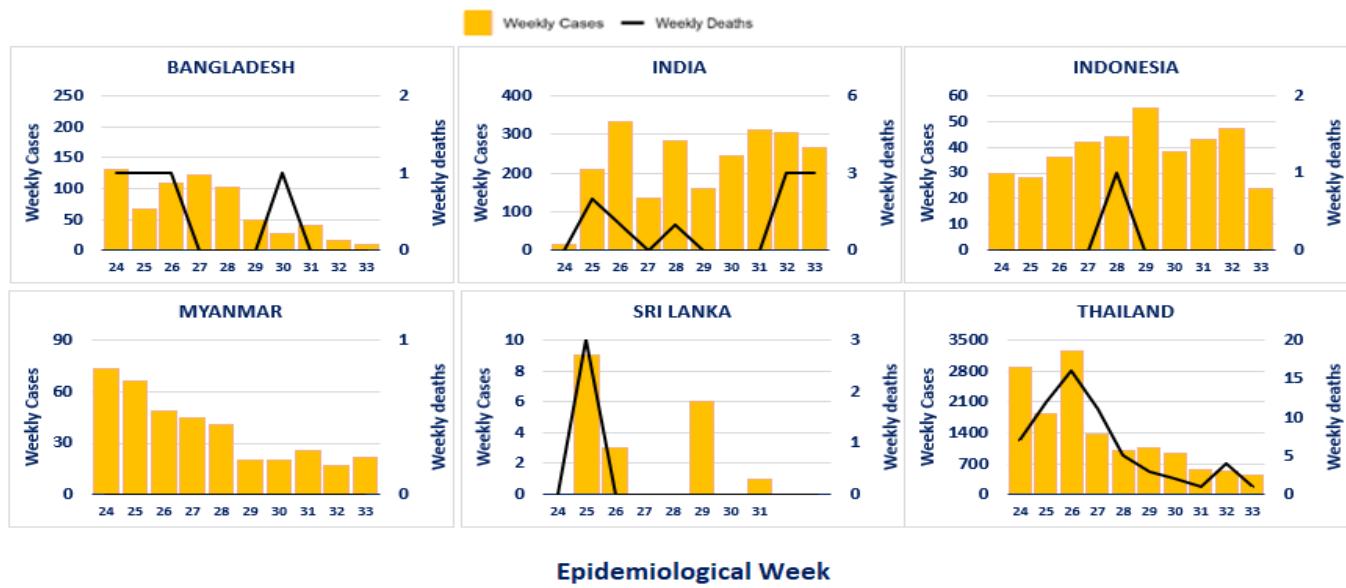
DPR Korea has not reported confirmed COVID-19 cases.

Indonesia and Thailand data were for the period from 4 to 17 August 2024 in comparison to the preceding 14 days.

As for cumulative numbers, Maldives data are as of 5 August 2023, Timor-Leste data as of 11 August 2023, Bhutan data as of 8 October 2023, Nepal data as of 20 October 2023 and Sri Lanka data as of 31 July 2024.

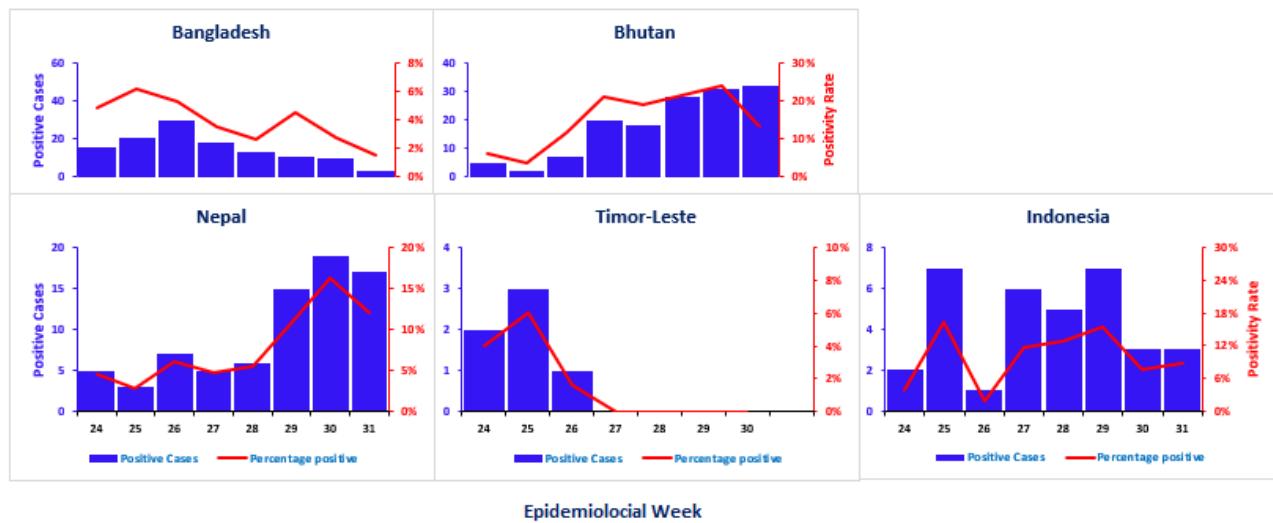
<sup>8</sup> [Global Dashboard](#) Data as 4 August 2024

**Figure 2. Weekly number of new COVID-19 cases reported during the previous ten weeks (as of 18 August 2024) in the WHO South-East Asia Region\*.**



\* Data for Maldives, Bhutan, Nepal, and Timor-Leste are not available. Sri Lanka data were as of 31 July.

**Figure 3. Weekly number of SARS-CoV-2 positive samples and test positivity from integrated influenza-SARS-CoV-2 sentinel surveillance systems in the previous eight weeks in selected countries\* (as of 18 August 2024).**



\* Countries routinely conducting SARS-CoV-2 testing of the samples collected through influenza sentinel surveillance sites (Bangladesh, Bhutan, Indonesia, Nepal, and Timor-Leste). Timor-Leste data is as of 28 July 2024.

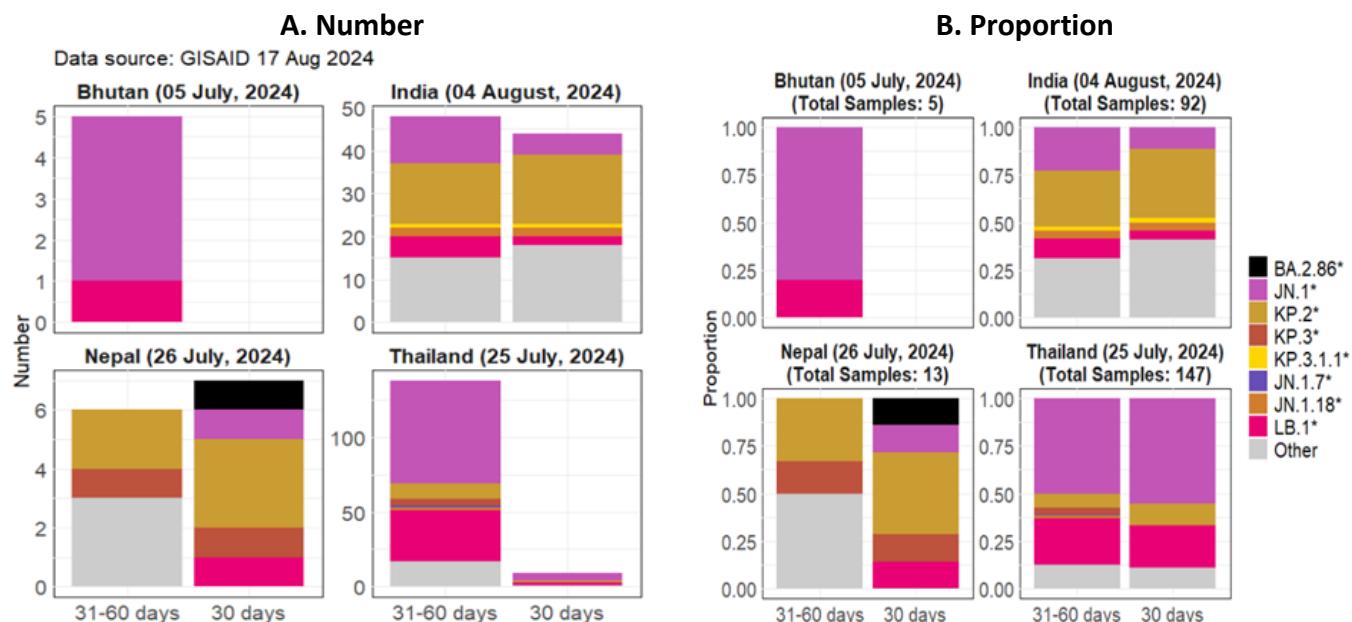
## Global circulation of SARS-CoV-2 variants

- WHO is currently tracking several SARS-CoV-2 variants and their sub-lineages including<sup>9</sup>:
  - Two variants of interest (VOIs): BA.2.86 and JN.1
  - Six variants under monitoring (VUMs): JN.1.7; KP.2; KP.3; KP.3.1.1; JN.1.18 and LB.1
- Information on the current status of the global SARS-CoV-2 variants can be found from [the WHO COVID-19 dashboard](#).

## SARS-CoV-2 variants in the South-East Asia Region

- The genomic sequence data submitted to GISAID<sup>10</sup> by countries in the South-East Asia region in the past 60 days by date of collection are shown in Figure 4 (as of 17 August 2024). Only a small number of genomic sequences have been submitted from countries and therefore the data should be interpreted with caution.
- In the last 60 days:
  - In **Bhutan**, 5 genomic sequences were submitted with JN.1\* accounting for 80% (n=4). One genomic sequence with LB.1\* were also submitted.
  - In **India**, 92 genomic sequences were submitted with KP.2\* accounting for 32.6% (n=30) followed by JN.1\* (17.4%, n=16), LB.1\* (7.6%, n=7), JN.1.18\* (4.3%, n=4) and KP.3.1.1.\* (2.2%, n=2).
  - In **Nepal**, 13 genomic sequences were submitted with KP.2\* accounting for 38.5% (n=5) followed by KP.3\* (15.4%, n=2). One genomic sequence each with BA.2.86\*, JN.1\* and LB.1\* were also submitted.
  - In **Thailand**, 147 genomic sequences were submitted with JN.1\* accounting for 50.3% (n=74) followed by LB.1\* (24.5%, n=36), KP.2\* (7.5%, n=11), KP.3\* (3.4%, n=5) and JN.1.18\* (1.4%, n=2). One genomic sequence with JN.1.7\* were also submitted.
  - Other countries have not submitted genomic sequences recently to GISAID.

**Figure 4. Number (A) and proportion (B) of SARS-CoV-2 VOI and VUM sequences submitted to GISAID within the past 30 days and 31-60 days as of 17 August by date of collection (countries in South-East Asia Region, with recent submissions)<sup>†</sup>:**



Other countries in the region have not submitted genomic sequences to GISAID in the past 60 days.

\* indicates the sub-lineage of each variant.

<sup>†</sup>The date next to the country name indicates the latest date of sample collection for sequence submission to GISAID.

XBB\* excludes XBB.1.16\*, XBB.1.5\*, XBB.1.9.1\*, and XBB.2.3\*.

Source: GISAID (<https://gisaid.org/>), as of 17 August 2024.

<sup>9</sup> <https://www.who.int/publications/m/item/covid-19-epidemiological-update-edition-170>

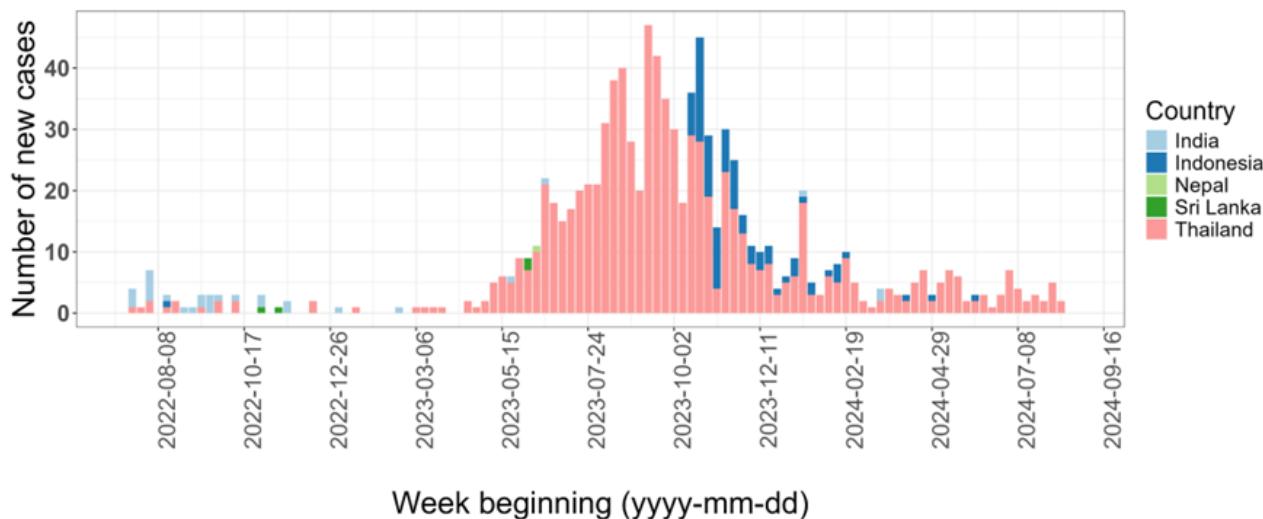
<sup>10</sup> <https://gisaid.org/>

## mmpox

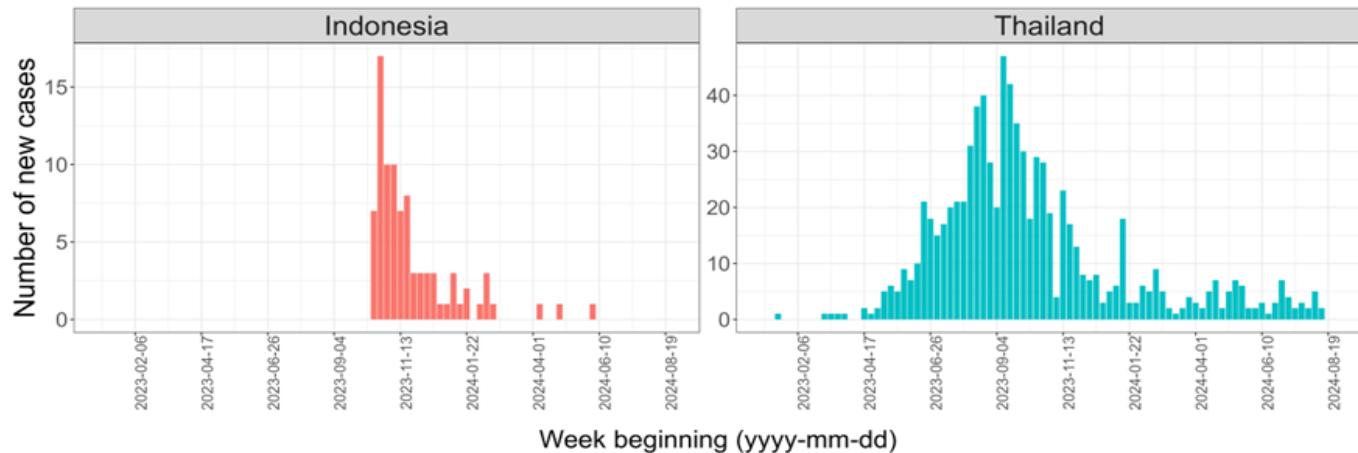
### Situation overview as of 18 August 2024

- In the WHO South-East Asia Region, a total of 952 laboratory-confirmed mpox cases, including 11 deaths, have been reported since 14 July 2022 (Figure 5).
- In epidemiological weeks 32 (05 to 11 August 2024) and 33 (12 to 18 August 2024), 7 new mpox cases were reported from Thailand<sup>11</sup> (Figure 6).
- In epidemiological weeks 32 and 33, no new mpox cases were reported from Indonesia<sup>12</sup> (Figure 6).
- For more information on the global situation of mpox outbreak, please visit the [global dashboard](#).

**Figure 5. Number of mpox cases reported in WHO South-East Asia Region by date of notification\* (14 July 2022 – 18 August 2024).**



**Figure 6. Weekly number of mpox cases reported in Indonesia (n=87) and Thailand (n=815) since 1 January 2023 by date of notification\* (as of 18 August 2024).**



\* Cases are plotted as per the week of notification (based on the date on which the case was notified to the public health authority). Where the date of notification is missing for cases in Indonesia, this was replaced with the date of diagnosis.

<sup>11</sup> [Thailand Mpx](#)

<sup>12</sup> [Indonesia Mpx](#)

**Table 3. Profile of the confirmed mpox cases reported in WHO South-East Asia Region in 2024 for which case-based information is available (as of 18 August 2024).**

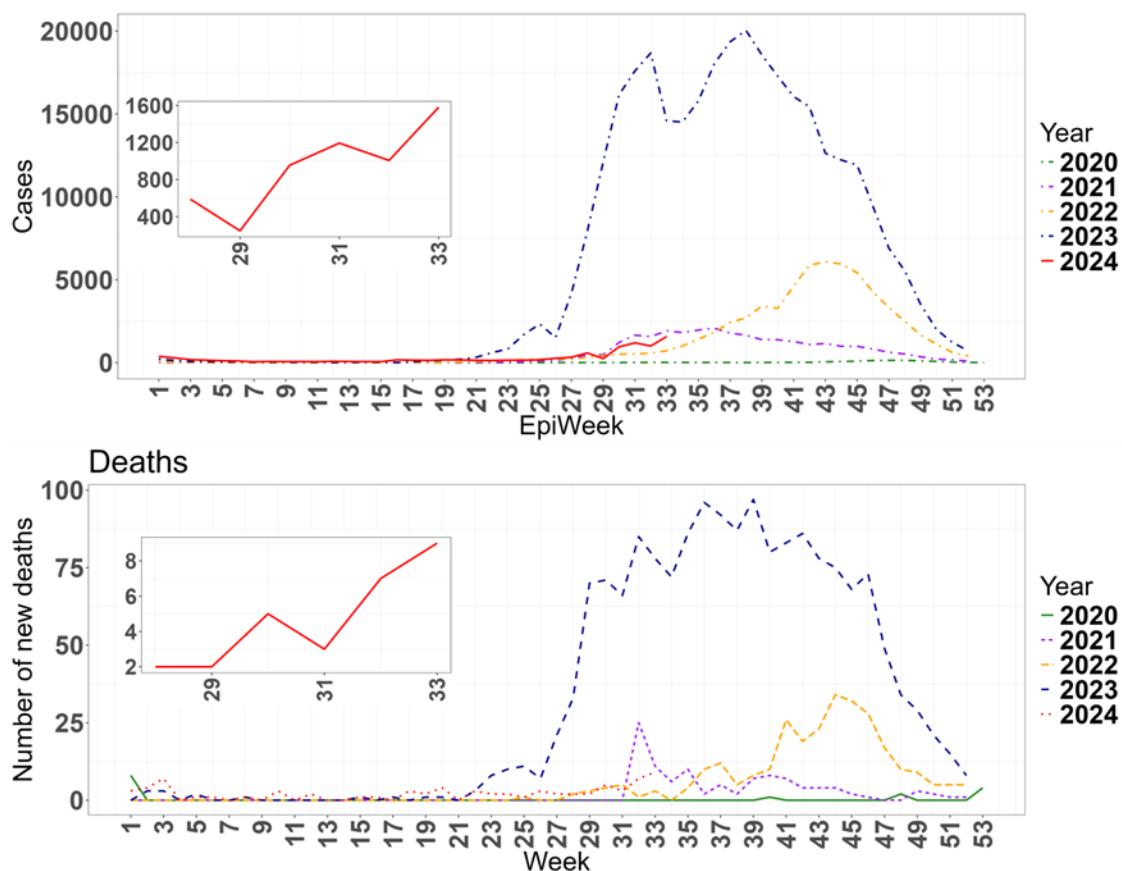
	Total (n = 923)	2024 (n=131)
<b>Country</b>		
India	27 (2.9%)	0 (0.0%)
Indonesia	88 (9.5%)	15 (11.5%)
Nepal	1 (0.1%)	0 (0.0%)
Sri Lanka	4 (0.4%)	0 (0.0%)
Thailand	803 (87.0%)	116 (88.5%)
<b>Gender</b>		
Female	36 (3.9%)	2 (1.5%)
Male	886 (96.0%)	129 (98.5%)
Transgender	1 (0.1%)	0 (0.0%)
<b>Age group (years)</b>		
Less than 18	4 (0.4%)	0 (0.0%)
18-29	315 (34.1%)	48 (36.6%)
30-39	389 (42.1%)	49 (37.4%)
40-49	179 (19.4%)	28 (21.4%)
50 and over	36 (3.9%)	6 (4.6%)
<b>Sexual orientation</b>		
Heterosexual	64 (6.9%)	7 (5.3%)
Men who have sex with men (MSM)	751 (81.4%)	110 (84.0%)
Bisexual	21 (2.3%)	8 (6.1%)
Other	26 (2.8%)	3 (2.3%)
Unknown	61 (6.6%)	3 (2.3%)
<b>Recent travel</b>		
Yes	45 (4.9%)	0 (0.0%)
No	870 (94.3%)	131 (100.0%)
Unknown	8 (0.9%)	0 (0.0%)

## Dengue

### Bangladesh<sup>1,2</sup>

- During week 33 2024 (12 to 18 August 2024), a total of 1 582 new dengue cases were reported in Bangladesh, a 57.1% increase compared to 1 007 cases reported during week 32 of 2024 (05 to 11 August 2024).
- During week 33, a total of 9 new dengue deaths were reported in Bangladesh, a 28.6% increase compared to 7 deaths reported during week 32.
- During 2024 (as of 18 August 2024), a total of 9 562 dengue cases and 74 dengue related deaths have been reported. This is 10% compared to the number of cases (n=99 953) and 16% compared to the number of deaths (n=476) reported during the same period in 2023.

**Figure 7. Number of new cases and deaths from dengue by week in Bangladesh from week 1 of 2020 to week 33 of 2024.**



Source: Health Emergency Operation Center and Control Room, DGHS Reported Monthly Dengue cases & Dengue Deaths in Bangladesh.  
Available at: <https://old.dghs.gov.bd/index.php/bd/home/5200-daily-dengue-status-report>

<sup>1</sup> [Bangladesh Dengue press releases](#)

<sup>2</sup> [Bangladesh daily Dengue press release 18 August 2024](#)

## India <sup>3</sup>

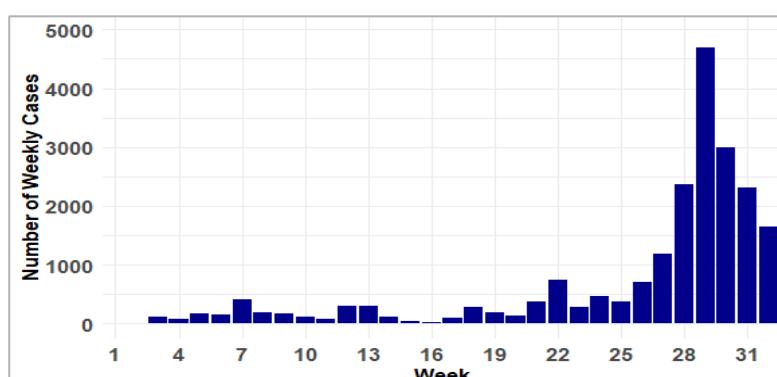
### Kerala <sup>4</sup>

- During week 32 of 2024 (05 August to 11 August 2024), a total of 812 new dengue cases were reported in Kerala, a 10.2% increase compared to 737 cases reported during week 31 (29 July to 4 August 2024).
- From the week one to week 32 in 2024, a total of 13 044 cases were reported.
- A total of 17 426 dengue cases were reported in the entirety of 2023.

### Karnataka <sup>5</sup>

- During week 32 of 2024 (05 August to 11 August 2024), a total of 1 643 new dengue cases were reported in Karnataka, a 29% decrease compared to 2 316 cases reported during week 31 (29 July to 4 August 2024).
- From the week one to week 32 in 2024, a total of 21 186 cases were reported.
- A total of 19 300 dengue cases were reported in the entirety of 2023.

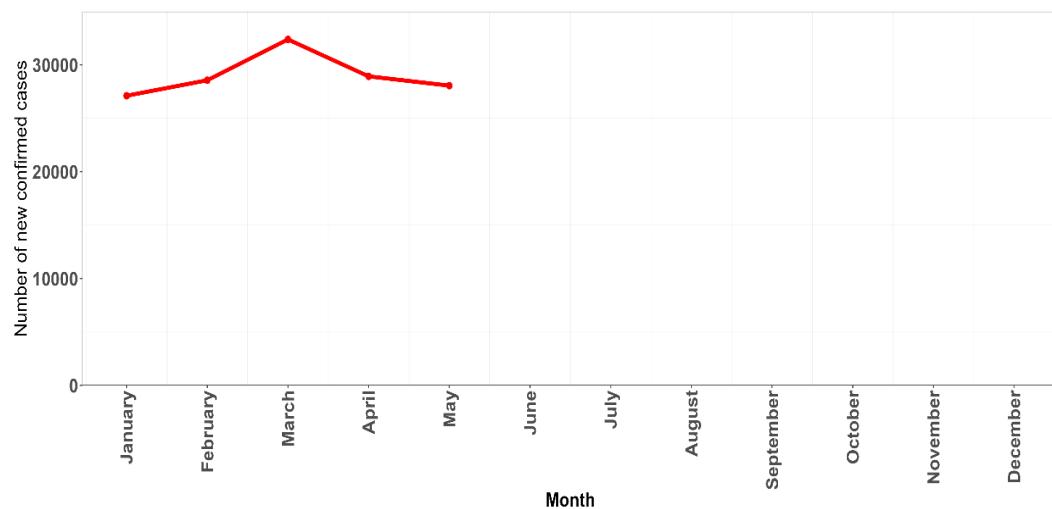
**Figure 9. Number of new dengue cases by week in Karnataka from week 1 to week 32 of 2024.**



## Indonesia <sup>6 7</sup>

- Between January and May 2024, total of 322 274 confirmed cases were reported in Indonesia.
- According to Ministry of Health, the total number of suspected dengue cases that were reported in the Early Warning, Alert, and Response System (EWARS) reached 373 528, as of week 22 in 2024.

**Figure 10. Number of new confirmed cases of dengue by month submitted to WHO Global Dengue Surveillance from January to May 2024.**



<sup>3</sup> NCVBDC

<sup>4</sup> Kerala

<sup>5</sup> Karnataka

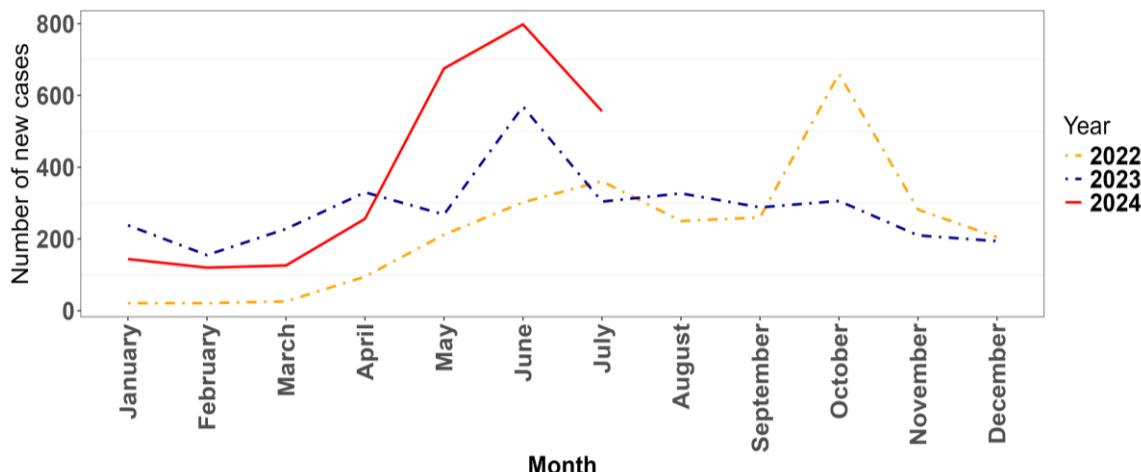
<sup>6</sup> WHO Global Dengue Surveillance

<sup>7</sup> 202405 - WHE Monthly Report - Eng.2 (who.int)

## Maldives<sup>8</sup>

- During July 2024, a total of 556 cases of dengue were reported in Maldives, a 30.3% decrease compared to June 2024 (n=798).
- During 2024, a total of 2 675 cases of dengue have been reported compared to 2 092 cases during the same period in 2023. A total of 3 417 cases were reported in the entirety of 2023.

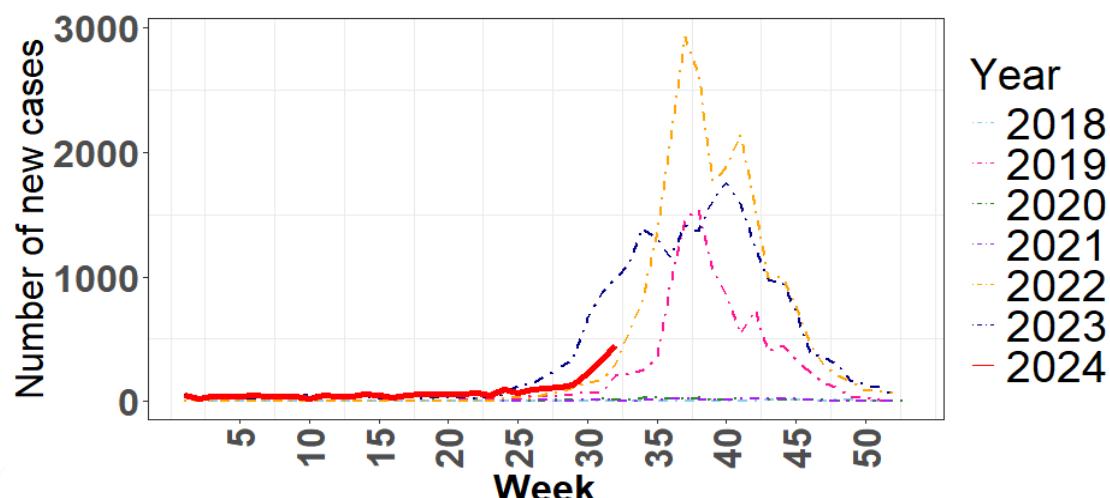
**Figure 11. Number of new cases of dengue by month in Maldives from January 2022 to July 2024.**



## Nepal<sup>9</sup>

- During week 32 (05 August to 11 August 2024), a total of 450 new dengue cases were reported via the Early Warning and Reporting System (EWARS) in Nepal, a 34.3% increase compared to 335 cases reported during week 31 (29 July to 04 August 2024).
- In 2024, a total of 2 645 dengue cases have been reported via EWARS compared to 4 420 and 982 during the same period in 2023 and 2022, respectively.

**Figure 12. Number of new cases of dengue by week reported by the Early Warning and Reporting System (EWARS) in Nepal from week 1 to week 32 of 2024.**



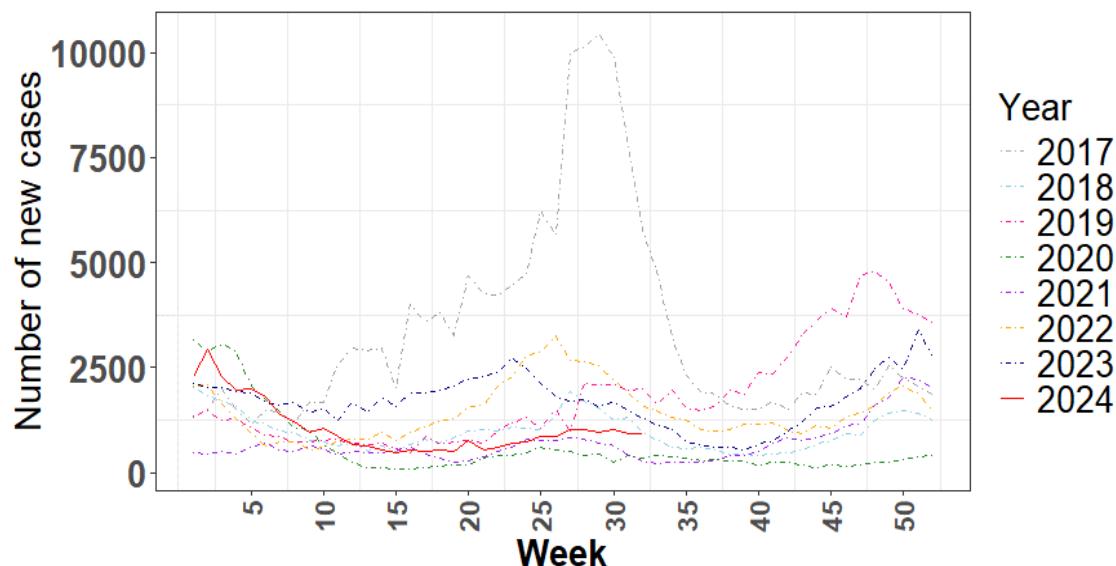
<sup>8</sup> [Maldives Monthly Communicable Diseases Report \(July 2024\)](#)

<sup>9</sup> [EWARS Weekly Bulletin](#)

## Sri Lanka <sup>10</sup>

- During week 32 (05 August to 11 August 2024), a total of 917 new dengue cases were reported in Sri Lanka, a 1.6% decrease compared to 932 cases reported during week 31 (29 July to 04 August 2024).
- From the week one to the week 32 in 2024, a total of 34 153 cases were reported compared to 59 048 and 49 941 during the same period in 2023 and 2022, respectively.

**Figure 13. Number of new dengue cases by week in Sri Lanka from week 1 of 2017 to week 32 of 2024.**



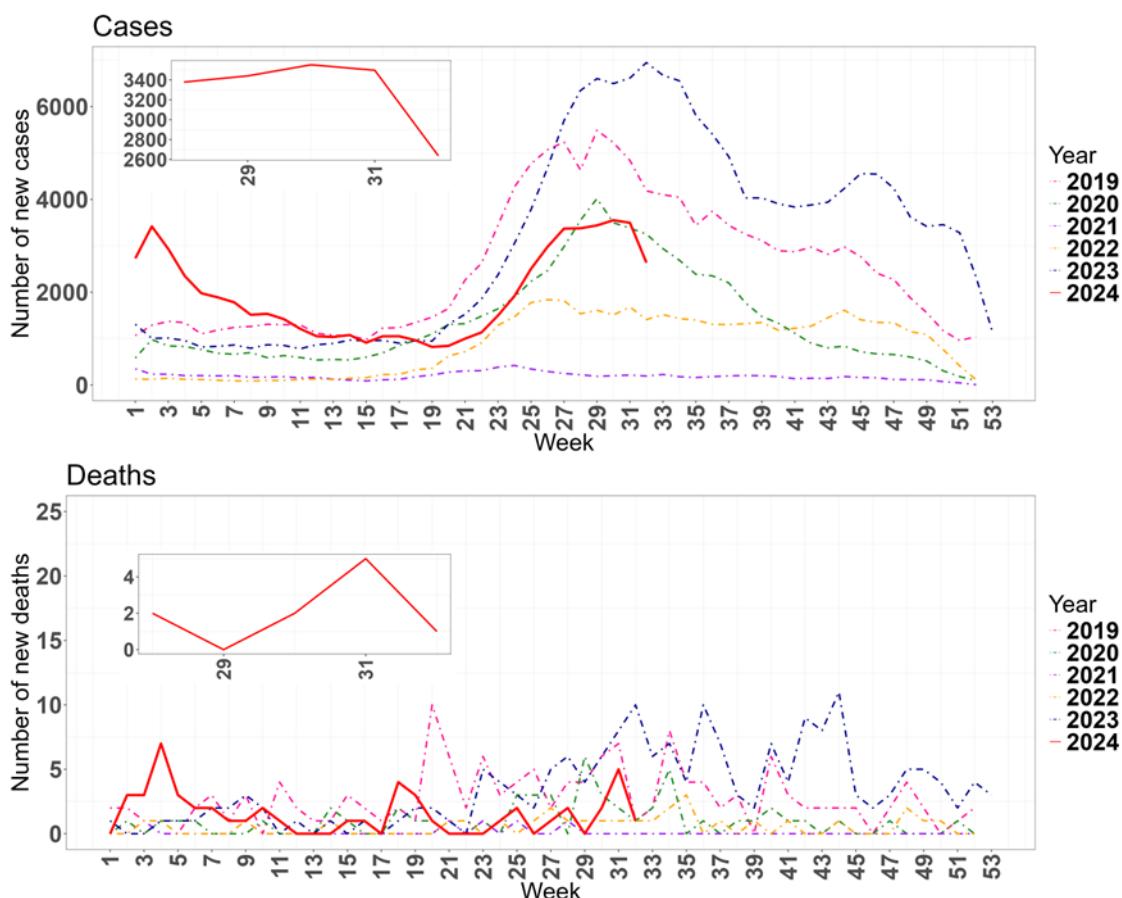
Sources: Epidemiology Unit and National Dengue Control Unit, Ministry of Health - [2017 to 2020](#); [2021 to 2024](#)

<sup>10</sup> Sri Lanka National Dengue Control Unit

## Thailand <sup>11 12 13</sup>

- During week 32 (05 August to 11 August 2024), a total of 2 637 new dengue cases were reported in Thailand, a 24.6% decrease compared to 3 497 cases reported during week 31 (29 July to 04 August 2024).
- During week 32, one new dengue death was reported in Thailand, a 80% decrease compared to 5 deaths reported during week 31 (29 July to 04 August 2024).
- In 2024, (as of week 32) a total of 62 487 cases including 49 deaths (CFR=0.08%) have been reported. This compares to 74 852 cases reported between week 1 and week 32 of 2023 including 75 deaths (CFR=0.10%).

**Figure 14. Number of new dengue cases and deaths by week in Thailand from 2019 to week 32 of 2024.**



Source: [Ministry of Public Health, Thailand](#)

<sup>11</sup> [Thailand Ministry of Public Health](#)

<sup>12</sup> [Thailand Ministry of Public Health](#)

<sup>13</sup> [Thailand Ministry of Public Health](#)

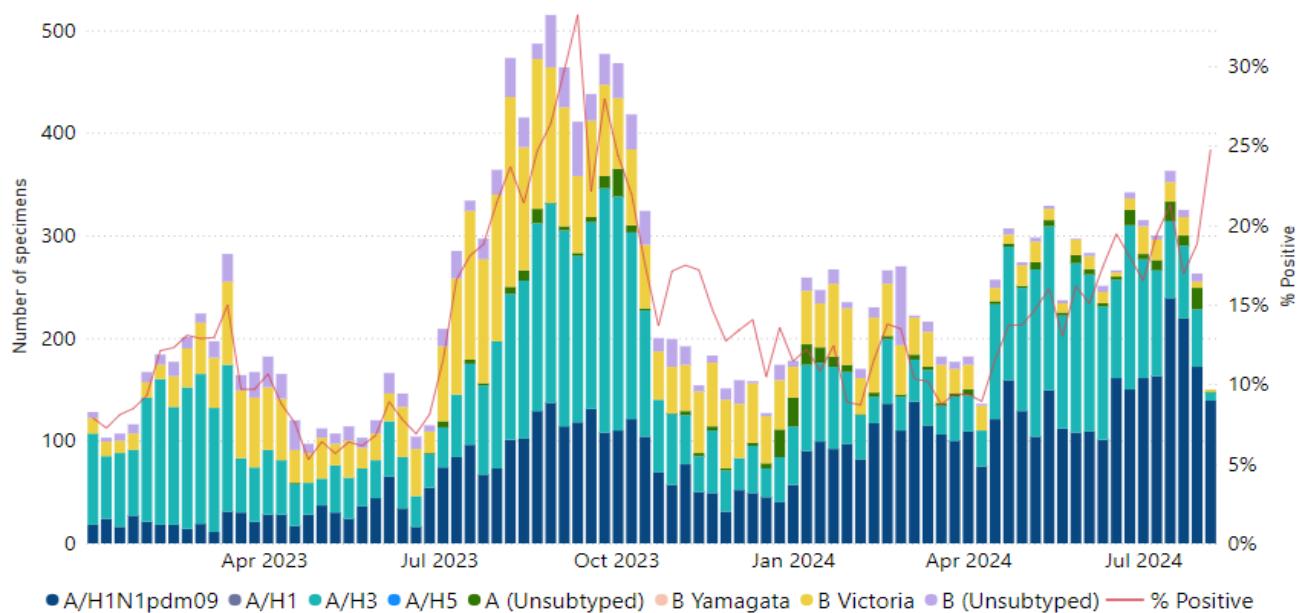
# Influenza

## WHO South-East Asia Region

### Situation as of 18 August 2024

- According to the data submitted to the FluMart of the Global Influenza Surveillance and Response system (GISRS), in the WHO South-East Asia Region, in epidemiological week 32 in 2024 (5 to 11 August), the weekly test positivity was at 24.8% and the most frequently reported strains were influenza A(H1N1)pdm09, influenza A(H3) and influenza B Victoria (Figure 15).
- Data sources and information on influenza, including updates of integrated surveillance of SARS-CoV-2 using influenza sentinel surveillance systems, are available at [WHO SEARO Influenza dashboard](#) and [WHO SEARO monthly updates](#).

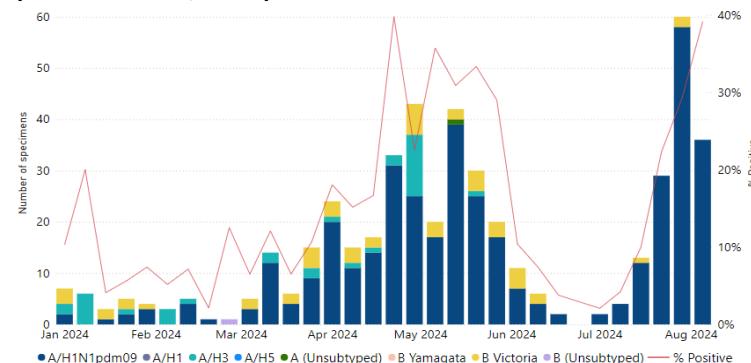
**Figure 15. Number of specimens positive for influenza by subtypes and the influenza test positivity in WHO South-East Asia Region during 2023 and 2024 (as of week 32 2024):**



## Bhutan

- As of 11 August 2024, 92 samples were tested on the integrated SARS-CoV-2 & influenza surveillance platform in week 32 (05 to 11 August 2024).
- 36 samples (39.1%) were tested positive for influenza.
- All the positive samples were of influenza A(H1N1)pdm09.

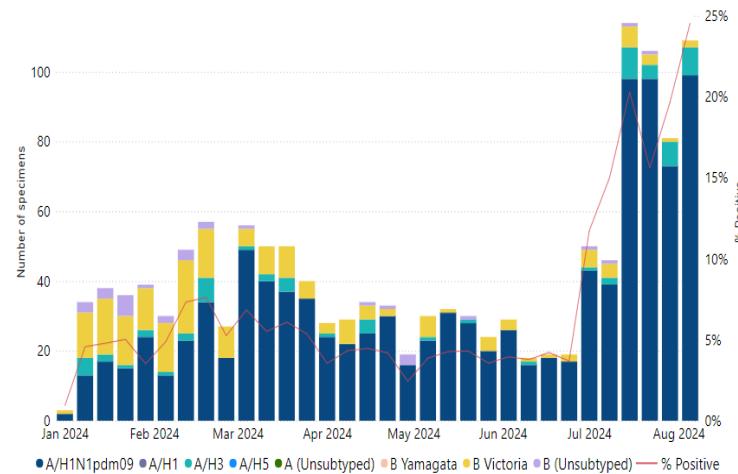
**Figure 16. Number of specimens positive for influenza by subtypes and the influenza test positivity in Bhutan in 2024 (as of week 32, 2024).**



## India

- As of 11 August 2024, 444 samples were tested on the integrated SARS-CoV-2 & influenza surveillance platform in week 32 (05 to 11 August 2024).
- 109 samples (24.6%) were tested positive for influenza.
- Of the samples tested positive for influenza (n=109), 90.8% (n=99) were positive for A(H1N1)pdm09 and 7.3% (n=8) for A(H3).
- Two samples were found to be influenza B Victoria and one samples was found to be Influenza B (unsubtyped).

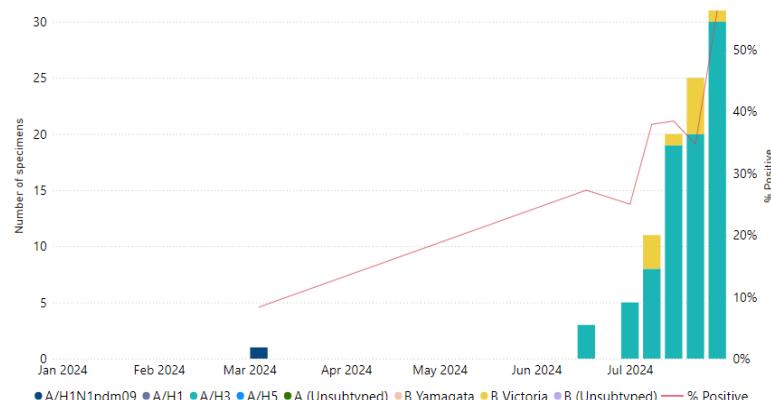
**Figure 17. Number of specimens positive for influenza by subtypes and the influenza test positivity in India in 2024 (as of week 32, 2024).**



## Myanmar

- As of 4 August 2024, 55 samples were tested on the integrated SARS-CoV-2 & influenza surveillance platform in week 31 (29 July to 4 August 2024).
- 31 samples (56.4%) were tested positive for influenza.
- Of the samples tested positive for influenza (n=31), 96.8% (n=30) were positive for influenza A(H3). One sample was tested positive for influenza B Victoria.

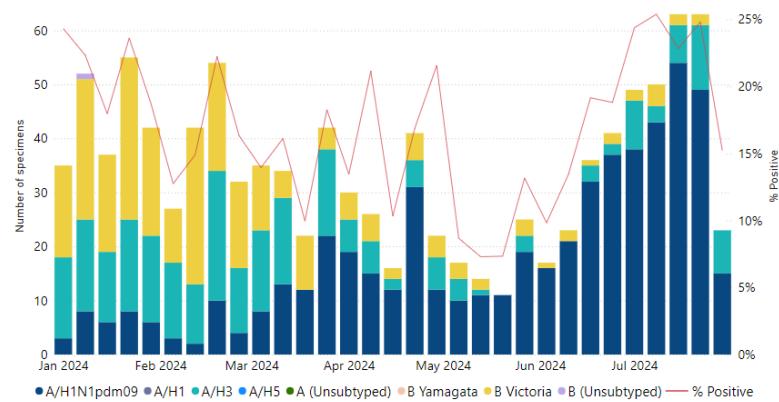
**Figure 18. Number of specimens positive for influenza by subtypes and the influenza test positivity in Myanmar in 2024 (as of week 31 of 2024).**



## Thailand

- As of 4 August 2024, 151 samples were tested on the integrated SARS-CoV-2 & influenza surveillance platform in week 31 (29 July to 4 August 2024).
- 23 samples (15.2%) were tested positive for influenza.
- Of the samples tested positive for influenza (n=23), 65.2% (n=15) were positive for A(H1N1)pdm09 and 34.8% (n=8) for A(H3).

**Figure 19. Number of specimens positive for influenza by subtypes and the influenza test positivity in Thailand in 2024 (as of week 31 of 2024).**



# WHO consolidated **guidelines** on tuberculosis

Module 3: Diagnosis



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Module 3: Diagnosis

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Web Annex B. Systematic reviews <a href="https://doi.org/10.2471/B09341">https://doi.org/10.2471/B09341</a>	

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# Abbreviations and acronyms

<b>AIDS</b>	acquired immunodeficiency syndrome
<b>AlereLAM</b>	Alere Determine TB LAM Ag
<b>aNAAT</b>	automated nucleic acid amplification test
<b>BAL</b>	bronchoalveolar lavage
<b>BCG</b>	bacille Calmette–Guérin
<b>BD</b>	Becton Dickinson
<b>cfu</b>	colony forming units
<b>CI</b>	confidence interval
<b>Crl</b>	credible interval
<b>CRS</b>	composite reference standard
<b>CSF</b>	cerebrospinal fluid
<b>DALY</b>	disability-adjusted life year
<b>DIAMA</b>	Diagnostics for Multidrug Resistant Tuberculosis in Africa
<b>DNA</b>	deoxyribonucleic acid
<b>DR-TB</b>	drug-resistant tuberculosis
<b>DST</b>	drug susceptibility testing
<b>ERG</b>	External external review group
<b>FIND</b>	Foundation for Innovative New Diagnostics
<b>FL-LPA</b>	first-line line probe assay
<b>GDG</b>	guideline development group
<b>Global Fund</b>	Global Fund to Fight AIDS, Tuberculosis and Malaria
<b>GRADE</b>	Grading of Recommendations Assessment, Development and EvaluationHIV human immunodeficiency virus
<b>ICER</b>	incremental cost–effectiveness ratio
<b>IGRA</b>	interferon-gamma release assay
<b>IVD</b>	in vitro diagnostic
<b>LAM</b>	lipoarabinomannan
<b>LAMP</b>	loop-mediated isothermal amplification
<b>LC-aNAAT</b>	low-complexity automated nucleic acid amplification test
<b>LC-mNAAT</b>	low-complexity manual nucleic acid amplification test
<b>LC-NAAT</b>	low-complexity nucleic acid amplification test
<b>LF-LAM</b>	lateral flow urine lipoarabinomannan assay
<b>LMIC</b>	low- and middle-income countries
<b>LPA</b>	line probe assay
<b>LSHTM</b>	London School of Hygiene & Tropical Medicine
<b>MC-aNAAT</b>	moderate-complexity automated nucleic acid amplification test
<b>MDR</b>	multidrug-resistant

<b>MDR/RR-TB</b>	multidrug-resistant tuberculosis or rifampicin-resistant tuberculosis
<b>MDR-TB</b>	multidrug-resistant tuberculosis
<b>MRS</b>	microbiological reference standard
<b><i>Mtb</i></b>	<i>Mycobacterium tuberculosis</i>
<b>MTBC</b>	<i>Mycobacterium tuberculosis</i> complex
<b>mWRD</b>	molecular WHO-recommended rapid diagnostic test
<b>NAAT</b>	nucleic acid amplification test
<b>NAT</b>	nucleic acid test
<b>NGS</b>	next-generation sequencing
<b>NTP</b>	national tuberculosis programme
<b>PCR</b>	polymerase chain reaction
<b>PI</b>	prediction interval
<b>PICO</b>	population, intervention, comparator and outcome
<b>PQ</b>	prequalification
<b>PZA</b>	pyrazinamide
<b>QES</b>	quality evidence synthesis
<b>QUADAS</b>	quality assessment of diagnostic accuracy studies
<b>RIF</b>	rifampicin
<b>RNA</b>	ribonucleic acid
<b>RRDR</b>	rifampicin-resistance determining region
<b>RR-TB</b>	rifampicin-resistant tuberculosis
<b>SL-LPA</b>	second-line line probe assay
<b>SRL</b>	supranational TB reference laboratory
<b>SSM</b>	sputum smear microscopy
<b>STARD</b>	Standards for Reporting Diagnostic Accuracy Studies
<b>TB</b>	tuberculosis
<b>TBST</b>	<i>Mtb</i> antigen-based skin test
<b>TPT</b>	tuberculosis preventive treatment
<b>TST</b>	tuberculin skin test
<b>UN</b>	United Nations
<b>United Kingdom</b>	United Kingdom of Great Britain and Northern Ireland
<b>UR</b>	uncertainty range
<b>USA</b>	United States of America
<b>USAID</b>	United States Agency for International Development
<b>UV</b>	ultraviolet
<b>WGS</b>	whole genome sequencing
<b>WHO</b>	World Health Organization
<b>WHO/GTB</b>	Global Programme on Tuberculosis & Lung Health of the World Health Organization
<b>WRD</b>	WHO-recommended rapid diagnostic test
<b>WTP</b>	willingness-to-pay
<b>XDR</b>	extensively drug-resistant
<b>XDR-TB</b>	extensively drug-resistant tuberculosis

# Definitions

**Advanced HIV disease:** for adults, adolescents, and children aged 5 years or more, “advanced HIV disease” is defined as a CD4 cell count of less than 200 cells/mm<sup>3</sup> or a WHO clinical stage 3 or 4 event at presentation for care. All children living with HIV aged under 5 years should be considered as having advanced disease at presentation.

**Age groups:** the following definitions for adults and children are used in these guidelines for the purpose of implementing recommendations (countries may have other definitions under their national regulations):

- an adult is a person aged 10 years and older;
- a child is a person aged under 10 years.

**Grading of Recommendations Assessment, Development and Evaluation (GRADE):** a system for rating quality of evidence and strength of recommendations; the GRADE approach is explicit, comprehensive, transparent and pragmatic, and is increasingly being adopted by organizations worldwide.

**HIV serious illness:** HIV serious illness is defined based on any of the following symptoms: respiratory rate of  $\geq 30/\text{minute}$ , temperature  $\geq 39\text{ }^{\circ}\text{C}$ , heart rate  $\geq 120/\text{minute}$ , or unable to walk unaided.

**Inpatient health care setting:** a health care facility where patients are admitted and assigned a bed while undergoing diagnosis and receiving treatment and care, for at least one overnight stay.

**Outpatient health care setting:** a health care facility where patients are undergoing diagnosis and receiving treatment and care but are not admitted for an overnight stay (e.g. an ambulatory clinic or a dispensary).

# Executive summary

It is estimated that about a quarter of the world's population is infected with *Mycobacterium tuberculosis* – the bacterium that causes tuberculosis (TB) disease. Testing for TB infection can identify individuals who would benefit the most from TB preventive treatment (TPT). However, despite the availability of preventive measures and disease treatment, TB remains a leading cause of death due to a single infectious agent. TB has probably replaced coronavirus disease (COVID-19) as the leading cause of death worldwide for the first time since the start of the global pandemic (1).

In recognition of the need to end TB globally, the United Nations (UN) held the world's first high-level meeting on TB in 2018. The political declaration from the meeting included commitments by Member States to achieving four new global targets (2), which were subsequently renewed at the second UN high-level meeting in 2023. The commitments included two that relied on diagnosis of TB infection and disease: providing TPT to at least 45 million people between 2024 and 2027, and reaching 90% of the estimated number of people who develop TB with quality-assured diagnosis and treatment from 2023 to 2027 (2). These commitments align with the World Health Organization's (WHO's) End TB Strategy, which calls for the detection of individuals living with TB infection who are at higher risk of progression to active TB so that they can receive TPT, as well as the early diagnosis of TB and drug-resistant TB (DR-TB) through universal drug susceptibility testing (DST). These global commitments and plans highlight the critical role of TB testing for the rapid and accurate detection of TB infection, disease and drug resistance (3).

To support countries in their efforts to strengthen detection of TB infection, disease and drug resistance, the WHO Global TB Programme issues evidence-based policy guidance on TB testing strategies and technologies; this guidance is routinely updated. Since the most recent consolidated guidelines on TB diagnosis were issued in 2024:

- new evidence has become available on the use of WHO-recommended rapid diagnostic tests (WRDs) for the initial detection of TB and resistance to rifampicin among populations that are at increased risk of TB-related morbidity and mortality (e.g. people living with HIV and children);
- a systematic assessment of evidence on molecular WRDs (mWRDs) previously recommended as individual products was completed to determine the placement of mWRDs within existing or new classes of TB diagnostic technologies; and
- a call from countries was received to combine the policy guidance on TB infection, disease and drug-resistance testing into these consolidated guidelines on TB diagnosis, to streamline implementation of national testing programmes.

In response, this document is being issued as the fourth edition of the consolidated guidelines on TB diagnosis. When compared with the third edition (issued in 2024), this guideline is the first to combine the WHO policy guidance on diagnosis of TB infection, disease and drug resistance into a single reference document; also, it establishes two new classes of TB diagnostic

technologies (for the initial detection of TB and resistance to rifampicin), and outlines new recommendations on concurrent testing of respiratory and non-respiratory samples among adults and adolescents with HIV, children with HIV, and children without HIV or with unknown HIV status. The main changes from the previous WHO guidelines are summarized in **Box A**.

The set of 21 new and existing recommendations for diagnosis of TB infection, disease and DR-TB are presented in **Table A**. These recommendations supersede those presented in previous editions of the guidelines and are supported by updated operational guidance that is published as the fourth edition of the *WHO operational handbook on tuberculosis. Module 3: diagnosis*. The operational handbook includes further details on the individual tests that are recommended for use; the selection, introduction and implementation of tests for TB infection, diagnosis and drug resistance; and updated diagnostic algorithms that reflect the updates contained within these guidelines.

#### Box A. Main changes to the guidance in this update

- ➔ Two new classes of TB diagnostic tests for the initial detection of TB and resistance to rifampicin were established; these classes differ in the level of procedure and test result automation, and include tests that were previously recommended as standalone products. The new low-complexity automated nucleic acid amplification test (LC-aNAAT) class includes the Xpert<sup>®</sup> MTB/RIF and Xpert MTB/RIF Ultra assays, and the Truenat<sup>®</sup> MTB Plus and MTB-RIF Dx assays. The low-complexity manual nucleic acid amplification test (LC-mNAAT) class includes the Loopamp<sup>™</sup> MTBC Detection Kit (TB LAMP) (Eiken Chemical). These new class-based recommendations supersede previous product-specific recommendations.
- ➔ Concurrent testing of respiratory and non-respiratory samples for the initial detection of TB and resistance to rifampicin is newly recommended for adults and adolescents living with HIV, children living with HIV, and children without HIV or with unknown HIV status.
- ➔ Existing guidelines on tests for TB infection were added, to consolidate policy guidance on testing for TB diagnosis, drug resistance and infection.
- ➔ A description of TB diagnostic test determination and the pathways for TB diagnostic product prequalification by WHO was added to the Background section.
- ➔ TB diagnostic test class description tables were revised to align with the class-determination criteria presented in the Background section.
- ➔ The four prior web annexes covering systematic review and guideline development group (GDG) evidence to inform policy updates were consolidated into two web annexes. Web Annex A includes the systematic reviews, Grading of Recommendations Assessment, Development and Evaluation (GRADE) tables and evidence to decision (EtD) tables, and Web Annex B includes the evidence synthesis and analysis findings. Both web annexes now present content by TB diagnostic class.

**Table A. Recommendations in the WHO consolidated guidelines on tuberculosis. Module 3: diagnosis, fourth edition**

- NEW
1. For adults and adolescents with signs or symptoms of TB or who screened positive<sup>1</sup> for pulmonary TB, low-complexity **automated** NAATs should be used on respiratory samples as initial diagnostic tests for TB, rather than smear microscopy or culture.  
*(Strong recommendation, high certainty of evidence)*

NEW

  2. For people with bacteriologically confirmed TB<sup>2</sup>, low-complexity **automated** NAATs should be used on respiratory samples as initial tests for detection of resistance to rifampicin, rather than culture-based DST.  
*(Strong recommendation, high certainty of evidence)*

NEW

  3. For people with signs and symptoms of TB meningitis, low-complexity **automated** NAATs on cerebral spinal fluid should be used for the initial diagnosis of TB meningitis, rather than smear microscopy or culture.  
*(Strong recommendation, moderate certainty of evidence)*

NEW

  4. For people with signs and symptoms of extrapulmonary TB, low-complexity **automated** NAATs on lymph node tissue aspirate, pleural tissue, pleural fluid, synovial fluid, peritoneal fluid or pericardial fluid should be used for the initial diagnosis of TB, rather than smear microscopy or culture.  
*(Strong recommendation, low certainty of evidence for synovial fluid and pericardial fluid; very low certainty of evidence for lymph node tissue aspirate, pleural tissue, pleural fluid and peritoneal fluid)*

NEW

  5. For people with signs and symptoms of pulmonary TB, moderate-complexity automated NAATs may be used on respiratory samples for the detection of pulmonary TB, and of rifampicin and isoniazid resistance, rather than culture and phenotypic DST.  
*(Conditional recommendation, moderate certainty of evidence)*

NEW

  6. For adults and adolescents with signs or symptoms or who screen positive for pulmonary TB, low-complexity **manual** NAATs should be used on respiratory samples as initial diagnostic tests for TB, rather than smear microscopy or culture.  
*(Strong recommendation, high certainty of evidence)*

<sup>1</sup> Having a positive result of a test, examination or other procedure used to distinguish people with a high likelihood of having TB disease from people who are highly unlikely to have TB. At present, the following tests are WHO-recommended as the screening tests: chest radiography (chest X-ray; CXR) with or without computer-aided detection (CAD), C-reactive protein (CRP) in people living with HIV, and molecular WHO-recommended rapid diagnostic test for TB (mWRD) (<https://www.who.int/publications/i/item/9789240022676>).

<sup>2</sup> A bacteriologically confirmed TB case is one from whom a biological specimen is positive by smear microscopy, culture or WRD (such as Xpert MTB/RIF). All such cases should be notified, regardless of whether TB treatment has started (<https://www.who.int/publications/i/item/9789241505345>).

**NEW**

7. For adults and adolescents with HIV who have signs or symptoms of TB, screen positive for TB, are seriously ill or have advanced HIV disease, **concurrent testing** using low-complexity automated NAATs on respiratory samples and LF-LAM on urine should be used as the initial diagnostic strategy for diagnosing TB, rather than low-complexity automated NAATs on respiratory samples alone.

*(Strong recommendation, low certainty of evidence)*

**NEW**

8. For children who are HIV-negative or have an unknown HIV status, who have signs or symptoms or screen positive for pulmonary TB, **concurrent testing** using low-complexity automated NAATs on respiratory and stool samples should be used as the initial diagnostic strategy for diagnosing TB, rather than low-complexity automated NAATs on respiratory or stool samples alone.

*(Strong recommendation, low certainty of evidence)*

**NEW**

9. For children with HIV who have signs or symptoms or screen positive for pulmonary TB, **concurrent testing** using low-complexity automated NAATs on respiratory and stool samples and LF-LAM on urine may be used as the initial diagnostic strategy for diagnosing TB, rather than low-complexity automated NAATs on respiratory or stool samples alone.

*(Conditional recommendation, low certainty of evidence)*

10. For people with bacteriologically confirmed pulmonary TB, low-complexity automated NAATs may be used on sputum for the initial detection of resistance to isoniazid and fluoroquinolones, rather than culture-based phenotypic DST.

*(Conditional recommendation, moderate certainty of evidence)*

11. For people with bacteriologically confirmed pulmonary TB and resistance to rifampicin, low-complexity automated NAATs may be used on sputum for the initial detection of resistance to ethionamide, rather than DNA sequencing of the *inhA* promoter.

*(Conditional recommendation, very low certainty of evidence)*

12. For people with bacteriologically confirmed pulmonary TB and resistance to rifampicin, low-complexity automated NAATs may be used on sputum for the initial detection of resistance to amikacin, rather than culture-based phenotypic DST.

*(Conditional recommendation, low certainty of evidence)*

13. For people with a sputum smear-positive specimen or a cultured isolate of MTBC, commercial molecular LPAs may be used as the initial test instead of phenotypic culture-based DST to detect resistance to rifampicin and isoniazid.

*(Conditional recommendation, moderate certainty of evidence)*

14. For people with confirmed MDR/RR-TB, SL-LPA may be used as the initial test, instead of phenotypic culture-based DST, to detect resistance to fluoroquinolones.

*(Conditional recommendation, moderate certainty of evidence for test accuracy)*

- 
15. For people with confirmed MDR/RR-TB, SL-LPA may be used as the initial test, instead of phenotypic culture-based DST, to detect resistance to the SLIDs.

(*Conditional recommendation, low certainty of evidence for test accuracy*)

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16. For people with bacteriologically confirmed TB, high-complexity reverse hybridization-based NAATs may be used on *Mtb* culture isolates for detection of pyrazinamide resistance rather than culture-based phenotypic DST.

(*Conditional recommendation, very low certainty of evidence*)

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17. For people with bacteriologically confirmed pulmonary TB disease, targeted next-generation sequencing technologies may be used on respiratory samples to diagnose resistance to rifampicin, isoniazid, fluoroquinolones, pyrazinamide and ethambutol, rather than culture-based phenotypic DST.

(*Conditional recommendation, certainty of evidence moderate [isoniazid and pyrazinamide] and low [rifampicin, fluoroquinolones and ethambutol]*)

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18. For people with bacteriologically confirmed rifampicin-resistant pulmonary TB disease, targeted next-generation sequencing technologies may be used on respiratory samples to diagnose resistance to isoniazid, fluoroquinolones, bedaquiline, linezolid, clofazimine, pyrazinamide, ethambutol, amikacin and streptomycin, rather than culture-based phenotypic DST.

(*Conditional recommendation, certainty of evidence high [isoniazid, fluoroquinolones and pyrazinamide], moderate [ethambutol], low [bedaquiline, linezolid, clofazimine and streptomycin] and very low [amikacin]*)

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19. *Mycobacterium tuberculosis* antigen-based skin tests may be used to test for TB infection.

(*Conditional recommendation, very low certainty of evidence for test accuracy*)

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20. Either a tuberculin skin test or an interferon-gamma release assay can be used to test for TB infection.

(*Strong recommendation, very low certainty of evidence for test accuracy*)

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21. Interferon-gamma release assays (IGRAs) and tuberculin skin tests (TSTs) should not be used in low- and middle-income countries for the diagnosis of pulmonary or extrapulmonary TB or for the diagnostic work-up of adults (including people living with HIV) with suspected active TB.

(*Strong recommendation*)

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DNA: deoxyribonucleic acid; DST: drug susceptibility testing; HIV: human immunodeficiency virus; LF-LAM: lateral flow urine lipoarabinomannan assay; LPA: line probe assay; MDR/RR-TB: multidrug-resistant or rifampicin-resistant TB; *Mtb*: *Mycobacterium tuberculosis*; MTBC: *Mycobacterium tuberculosis* complex; NAAT: nucleic acid amplification test; NGS: next-generation sequencing; SL-LPA: second-line line probe assay; SLID: second-line injectable drug; TB: tuberculosis; WHO: World Health Organization.

# 1. Introduction

## 1.1. Background

It is estimated that about a quarter of the world's population is infected with *Mycobacterium tuberculosis* (*Mtb*) – the bacterium that causes tuberculosis (TB) disease. Testing for TB infection can identify individuals who would benefit the most from TB preventive treatment (TPT). Without TPT, it is estimated that about 5–10% of people who are infected will develop TB disease over the course of their lives, usually within 5 years of the initial infection (1).

Despite the availability of preventive measures and disease treatment, TB remains a leading cause of death due to a single infectious agent, and has probably replaced coronavirus disease (COVID-19) as the leading cause of death worldwide for the first time since the start of the global pandemic (1). In 2023, it is estimated that 10.8 million people fell ill with TB, but only 8.2 million were diagnosed. In addition, resistance to the antibiotics that are used to treat TB remains a challenge, with an estimated 400 000 people (95% uncertainty interval [UI]: 370 000–450 000) having developed either rifampicin-resistant TB (RR-TB), or TB resistant to both rifampicin and isoniazid, defined as multidrug-resistant TB (MDR-TB).

In 2018, the United Nations (UN) held the world's first high-level meeting on TB. The political declaration from the meeting included commitments by Member States to achieve four new global targets (2). These commitments were subsequently renewed at the second UN high-level meeting in 2023; they included provision of TPT to at least 45 million people between 2024 and 2027, and reaching 90% of the estimated number of people who develop TB with quality-assured diagnosis and treatment from 2023 to 2027 (3). In addition, the World Health Organization's (WHO's) End TB Strategy calls for the detection of individuals living with TB infection who are at higher risk of progression to active TB so that they can receive TPT, as well as the early diagnosis of TB and universal drug susceptibility testing (DST). These global commitments and plans highlight the critical role of TB testing for the rapid and accurate detection of TB infection, disease and drug resistance (4).

Over recent years, the WHO Global TB Programme (WHO/GTB) has issued evidence-based policy guidance on diagnostic testing, to support countries in their efforts to detect TB infection, disease and drug resistance. When novel diagnostic tools are developed and evidence on their use and impact becomes available, WHO/GTB commissions systematic reviews and convenes guideline development groups (GDGs) to inform guideline updates. Since 2021, these updates have been issued in module-based consolidated guidelines. Until 2024, policy recommendations for testing for TB infection, TB disease and drug resistance were presented separately (in the consolidated guidelines on prevention and diagnosis, respectively).

This document is the fourth edition of WHO policy guidelines on TB diagnosis. Compared with the third edition, issued in 2024, this document:

- is the first to combine guidance on diagnosis of TB infection, disease and drug resistance into a single reference document;
- establishes two new classes of TB diagnostic technologies (for the initial detection of TB and resistance to rifampicin), which include tests previously recommended for use as individual products; and
- outlines new recommendations on concurrent testing of respiratory and non-respiratory samples among adults and adolescents with HIV, children with HIV, and children without HIV or with unknown HIV status.

## 1.2. WHO TB diagnostic class determination and product prequalification

Over the past 16 years, WHO has endorsed a range of diagnostic technologies (**Table 1.1.1**). The WHO assessment process for TB diagnostics has recently evolved to focus on evaluating classes of TB diagnostic technologies rather than specific products. Class determination is managed by WHO/GTB for new diagnostic testing technologies, and it includes an evaluation of the following characteristics:

- purpose of use (i.e. detection of TB or drug-specific resistance);
- principle of action;
- infrastructure and human resource requirements;
- complexity of the testing procedure and associated instrumentation;
- reporting method (automated versus manual); and
- intended setting of use (e.g. reference or peripheral low-complexity, near point-of-care).

These characteristics are compared between the new technology and each of the existing classes already recommended by WHO. When characteristics differ from existing classes, the new technology will undergo an evidence review as “first-in-class” via Pathway A (described below). When characteristics match those of an existing class, the new technology will undergo a “within-class” assessment (Pathway B below).

### 1.2.1 Pathway A

New technologies will require a Pathway A review if they differ from technologies in existing classes in terms of the characteristics listed above. Evidence synthesis and review and development of recommendations will be conducted through the established WHO/GTB guideline development process using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. If recommended by a GDG after evidence review, technologies will be referred for WHO prequalification assessment (as available). If a prequalification assessment procedure is not available, the WHO/GTB recommendation will stand until the prequalification procedure becomes available and is successfully completed.

## 1.2.2 Pathway B

Technologies will require a Pathway B review if they share characteristics with an existing class and are therefore not first-in-class. Review of these within-class technologies depends on availability of a prequalification assessment procedure for the class:

- If a prequalification assessment procedure is available, manufacturers may proceed directly with assessment.
- If a prequalification assessment procedure is not yet available, an evidence review will be conducted through a WHO/GTB evidence assessment process, facilitated by the Technical Advisory Group on TB Diagnostics and Laboratory Strengthening. If recommended by WHO/GTB, the technology will be added to the relevant class in the latest policy guidance. The recommendation will stand until the prequalification assessment procedure becomes available and is successfully completed.

## 1.3. Testing classes and products

As highlighted above, all technologies with a WHO/GTB recommendation are expected to undergo prequalification assessment, as available. Successful assessment will be required to maintain a WHO/GTB recommendation. The current set of TB diagnostic testing classes and included products are listed in **Table 1.1.1**, and the two new classes are discussed below.

**Table 1.1.1. Classes and products of TB tests for detection of TB, drug-resistant TB and TB infection included in the current guidelines**

Technology class	Included products
<b>Initial tests for TB diagnosis with drug-resistance detection</b>	
<b>NEW:</b> Low-complexity automated nucleic acid amplification tests (NAATs) for detection of TB and resistance to rifampicin	Xpert® MTB/RIF and Xpert MTB/RIF Ultra (Cepheid) Truenat® MTB Plus and Truenat MTB-RIF Dx (Molbio)
Moderate-complexity automated NAATs for detection of TB and resistance to rifampicin and isoniazid	Abbott RealTime® MTB and Abbott RealTime MTB RIF/INH (Abbott) BD MAX™ MDR-TB (Becton Dickinson) cobas® MTB and cobas MTB-RIF/INH (Roche) FluoroType® MTB and FluoroType MTBDR (Hain Lifescience/Bruker)
<b>Initial tests for TB diagnosis without drug-resistance detection</b>	
<b>NEW:</b> Low-complexity manual NAATs for detection of TB	Loopamp™ MTBC Detection Kit (TB LAMP) (Eiken Chemical)
Antigen detection in a lateral flow format (biomarker-based detection) (LF-LAM) for detection of TB	Determine™ TB LAM Ag (Alere/Abbott)

Technology class	Included products
<b>Follow-on tests for detection of TB drug resistance</b>	
Low-complexity automated NAATs for detection of resistance to isoniazid and second-line anti-TB agents	Xpert® MTB/XDR (Cepheid)
Line probe assays (LPAs) for detection of TB drug resistance	GenoType® MTBDRplus v1 and v2; and GenoType MTBDRsl (Hain Lifescience/Bruker) Genoscholar™ NTM+MDRTB II and Genoscholar PZA-TB II (Nipro)
Targeted next-generation sequencing (NGS) tests for detection of TB drug resistance	Deeplex® Myc-TB (GenoScreen/Illumina) AmPORE-TB® (Oxford Nanopore Technologies) TBseq® (Shengting Medical Technology Company)
<b>Tests for TB infection</b>	
<i>Mycobacterium tuberculosis</i> antigen-based skin tests (TBSTs)	Diaskintest® (Generium) Siiltibcy™ (Serum Institute of India) C-TST (Anhui Zhifei Longcom)
Interferon-gamma release assays (IGRAs)	T-SPOT.TB (T-Spot) (Revvity) TB-IGRA (Wantai BioPharm) QuantiFERON-TB Gold Plus (QFT-Plus) (QIAGEN) STANDARD E TB-Feron ELISA (SD BIOSENSOR) <sup>3</sup> LIAISON QFT-Plus CLIA (Diasorin) <sup>3</sup>
Tuberculin skin tests	Tuberculin purified protein derivative (PPD) products

NAAT: nucleic acid amplification test; TB: tuberculosis.

### 1.3.1 Initial tests for TB diagnosis with drug resistance detection

#### *Low-complexity automated nucleic acid amplification tests (NAATs) for detection of TB and resistance to rifampicin*

The low-complexity automated nucleic acid amplification tests (LC-aNAATs) include tools such as Xpert® MTB/RIF Ultra (Cepheid) and Truenat® MTB Plus with MTB-RIF Dx (Molbio). These tests provide largely automated solutions suitable for decentralized laboratories, and are currently the most widely used tests for the initial detection of TB and resistance to rifampicin. The testing instruments use software and hardware (computers) to report results, and they require well-established laboratory networks and trained personnel.

<sup>3</sup> For WHO statement and evidence assessment on new IGRAs see WHO operational handbook on tuberculosis. Module 3: diagnosis.

### ***Moderate-complexity automated NAATs for detection of TB and resistance to rifampicin and isoniazid***

The moderate-complexity automated NAATs (MC-aNAATs) are faster and less complex to perform than phenotypic culture-based DST and line probe assays (LPAs), and are largely automated after the sample preparation step. They may be used as an initial test for simultaneous detection of TB and resistance to rifampicin and isoniazid. This type of NAAT offers the potential for rapid provision of accurate results and for testing efficiency where high volumes of tests are required daily. Hence, they are suited to areas with a high population density and rapid sample referral systems.

### **1.3.2 Initial tests for TB diagnosis without drug resistance detection**

#### ***Low-complexity manual NAATs***

The low-complexity manual NAAT (LC-mNAAT), loop-mediated isothermal amplification (LAMP), is based on DNA amplification at a single temperature range; this contrasts with the polymerase chain reaction (PCR), which requires a thermocycler. Detection of amplified product is done visually, using an ultraviolet (UV) lamp, directly in the reaction tubes. The method requires only basic equipment and can be implemented at the lowest levels of the laboratory network. However, detection of mutations in resistance-associated genes is not available with the currently recommended technology.

#### ***Antigen detection in a lateral flow format (biomarker-based detection)***

The currently available lateral flow urine lipoarabinomannan assay (LF-LAM) has suboptimal sensitivity and specificity; thus, it is not suitable as a diagnostic test for TB in all populations. However, in contrast to traditional diagnostic methods, the urine LF-LAM assay demonstrates improved sensitivity for the diagnosis of TB among individuals coinfected with HIV.

### **1.3.3 Follow-on tests for detection of TB drug resistance**

#### ***Low-complexity automated NAATs for the detection of resistance to isoniazid and second-line anti-TB agents***

The LC-aNAATs are recommended for use as a reflex test in specimens determined to be positive for *Mtb* complex (MTBC); these tests offer rapid DST in intermediate and peripheral laboratories. The first product in this class simultaneously detects resistance to isoniazid, fluoroquinolones, ethionamide and amikacin. Results are available in under 90 minutes; this is faster than with the current standard of care, which includes LPAs and culture-based phenotypic DST.

#### ***Line probe assays***

LPAs are a family of DNA strip-based tests that can detect the MTBC DNA and determine its drug-resistance profile. The tests do this through the pattern of binding of amplicons (DNA amplification products) to probes that target specific parts of the MTBC genome; that is, common resistance-associated mutations to anti-TB drugs or the corresponding wild-type DNA sequence (5). LPAs are technically more complex to perform than the Xpert MTB/RIF assay; however, they can detect resistance to a broader range of first-line and second-line

agents, and they provide mutation-specific data for common variants. Testing platforms have been designed for a reference laboratory setting and are most applicable to high TB burden countries. Results can be obtained in 5 hours (5).

### **Targeted next-generation sequencing tests**

Tests based on targeted next-generation sequencing (NGS) are used for follow-on detection of resistance to a broad range of anti-TB drugs after the initial detection of TB or of rifampicin resistance. This class of tests is based on technology that combines amplification of selected genes with NGS to detect resistance to many drugs with a single test. Because targeted NGS can interrogate entire genes to identify specific mutations associated with resistance, the accuracy may be better than that of existing WHO-recommended rapid diagnostic tests (WRDs). In addition, new tests based on targeted NGS can detect resistance to new and repurposed drugs that are not currently included in any other molecular assays. Hence, this class of tests offers great potential to provide comprehensive resistance detection matched to modern treatment regimens.

## **1.3.4 Tests for TB infection**

### ***Mtb* antigen-based skin tests**

*Mtb* antigen-based skin tests (TBSTs) are used for the indirect detection of TB infection. TBSTs rely on intradermal injection of *Mtb*-specific antigens; the antigens elicit a localized skin reaction in infected individuals that is detected by measurement of a local induration 48–72 hours after administration. Although these tests continue to rely on patient injection and return visits for result interpretation, they are more specific than the WHO-recommended tuberculin skin tests (TSTs).

### **Interferon-gamma release assays**

Interferon-gamma release assays (IGRAs) are in vitro blood-based tests that are used to indirectly test for TB infection. They do this by measuring either the amount of interferon-gamma that is released by lymphocytes in whole blood after exposure to *Mtb*-specific antigens or the number of T-lymphocytes within the whole blood that produce interferon-gamma. IGRA testing requires days to perform owing to the blood incubation steps and it can be challenging to perform among patients for whom phlebotomy can be difficult (e.g. children); however, this is the only type of test for TB infection in which the results are not affected by prior bacille Calmette–Guérin (BCG) vaccination for TB. Hence, IGRAs are a promising alternative for detection of TB infection in settings with high rates of BCG vaccination.

### **Tuberculin skin tests**

TSTs were the first class of tests to be recommended for detection of TB infection; they rely on intradermal injection of a mix of antigens to *Mtb*, non-tuberculous mycobacteria and the BCG vaccine formulation, followed by detection of a localized skin induration-based response after 48–72 hours. As with the TBSTs, these tests can facilitate TB infection testing in children and other patients for whom phlebotomy is challenging, but they may also produce false positive results in people infected with mycobacteria other than TB and in those who are BCG vaccinated.

Regulatory approval from national regulatory authorities or other relevant bodies is required before implementation of new diagnostic tests.

## **1.4. Scope of the document**

This document provides background, justification and recommendations for novel diagnostic tools for detecting *MTBC*, the presence or absence of mutations in target genes proven to be associated with anti-TB drug resistance, and TB infection.

## **1.5. Target audience**

The target audience for these guidelines includes laboratory managers, clinicians and other health care staff, HIV and TB programme managers, policy-makers, technical agencies, donors and implementing partners supporting the use of TB diagnostic tests in resource-limited settings.

The document may also be of use to individuals responsible for programme planning, budgeting, mobilizing resources and implementing training activities for the programmatic management of drug-resistant TB (DR-TB).

## **1.6. Scope of the document**

This document provides background, justification and recommendations on novel diagnostic tools for detecting *MTBC*, the presence or absence of mutations in target genes proven to be associated with anti-TB drug resistance, and TB infection.

## **1.7. Target audience**

The target audience for these guidelines includes laboratory managers, clinicians and other health care staff, HIV and TB programme managers, policymakers, technical agencies, donors and implementing partners supporting the use of TB diagnostics in resource-limited settings.

Individuals responsible for programme planning, budgeting, mobilizing resources and implementing training activities for the programmatic management of DR-TB may also find this document useful.



# 2. Recommendations for diagnosis of TB disease

## 2.1. Initial diagnostic tests for diagnosis of TB with drug-resistance detection

### 2.1.1 LC-aNAATs for detection of TB and resistance to rifampicin

NEW

Rapid detection of TB and rifampicin resistance is a critical global priority. Over a decade ago, the first recommendation on molecular testing for the diagnosis of TB and detection of resistance significantly transformed the TB diagnostic landscape. These technologies have proven highly accurate compared with smear microscopy, and they can detect rifampicin resistance rapidly. They do not require highly skilled individuals or designated molecular laboratory infrastructure for testing. In addition, they are largely automated after sample loading, up to the final report generation. These features make this class of low-complexity automated tests appealing for use in low- and middle-income countries (LMIC).

Uptake of these technologies has been slowed by barriers related to costs, the supply chain, equipment maintenance and technical support. The lack of a healthy competitive environment has also been a contributory factor. The WHO Prequalification (PQ) programme for TB in vitro diagnostics (IVDs) has opened a pathway to allow more products to come to market and ensure quality. The current guidelines facilitated this process with the introduction of class-based recommendations for low-complexity NAATs. WHO PQ assessment progress for all low-complexity NAATs is reported on the WHO PQ website.<sup>4</sup>

<sup>4</sup> In Vitro Diagnostics Under Assessment | WHO – Prequalification of Medical Products (IVDs, Medicines, Vaccines and Immunization Devices, Vector Control).

## Diagnostic class description

The features shown in **Table 2.1.1.1** define the class of LC-aNAATs.:

**Table 2.1.1.1 Class criteria for LC-aNAATs**

Purpose	Detection of TB and rifampicin resistance
<b>Principle of action</b>	Nucleic acid amplification testing
<b>Complexity</b>	Reagents Most reagents are enclosed in a disposable sealed container to which a clinical specimen is added. The disposable sealed container does not have special storage requirements
Skills	Basic technical skills (e.g. basic pipetting, precision not critical)
Pipetting	Either no, or only one, pipetting step in the process
Testing procedure	<ul style="list-style-type: none"><li>• May require an initial manual specimen treatment step before transferring the specimen into the disposable sealed container for automated processing</li><li>• Automated DNA extraction</li><li>• Automated real-time PCR</li><li>• Results generation</li></ul>
<b>Type of test result reporting</b>	Automated
<b>Setting of use</b>	Basic laboratory (no special infrastructure needed)

DNA: deoxyribonucleic acid; LC-aNAAT: low-complexity automated nucleic acid amplification test; PCR: polymerase chain reaction; TB: tuberculosis.

The products for which eligible data met the class-based performance criteria for LC-aNAATs were:

- Xpert MTB/RIF Ultra (Cepheid, Sunnyvale, United States of America [USA]) – for pulmonary TB, extrapulmonary TB and resistance to rifampicin; and
- Truenat MTB Plus and Truenat MTB-RIF Dx (Molbio, Goa, India) – for pulmonary TB and resistance to rifampicin.

Data on Truenat MTB Plus and MTB-RIF Dx were more limited than those for Xpert Ultra.

Regulatory approval from national regulatory authorities or other relevant bodies is required before implementation of these diagnostic tests. Extrapolation to other brand-specific tests cannot be made, and any new in-class technologies, or new indications for technologies currently included in the class, will need to be evaluated by WHO PQ and WHO/GTB, respectively.

The publication *WHO operational handbook on tuberculosis. Module 3: Diagnosis* describes the tests included in this class.

## Recommendations

1. **For adults and adolescents with signs or symptoms of TB or who screened positive for pulmonary TB, low-complexity automated NAATs should be used on respiratory samples as initial diagnostic tests for TB rather than smear microscopy or culture.**

*(Strong recommendation, high certainty of evidence)*

### Remarks

- For adults, respiratory samples include sputum (expectorated or induced), tracheal aspirate or bronchoalveolar lavage (BAL).
- The term “person screened positive” refers to a person in whom a screening test has yielded a positive result.<sup>5</sup>
- Children and specifically children living with HIV are discussed in the section on the concurrent use of initial TB diagnostic tests in children.
- Adults and adolescents living with HIV are discussed in the section on the concurrent use of initial TB diagnostic tests in people living with HIV.
- The products for which eligible data met the class-based performance criteria for LC-aNAATs for this recommendation were Xpert MTB/RIF Ultra (Cepheid, Sunnyvale, United States of America [USA]) and Truenat MTB Plus (Molbio, Goa, India). Data on Truenat MTB Plus and MTB-RIF Dx were more limited than those for Xpert Ultra.

2. **For people with bacteriologically confirmed TB, low-complexity automated NAATs should be used on respiratory samples as initial tests for detection of resistance to rifampicin rather than culture-based DST.**

*(Strong recommendation, high certainty of evidence)*

### Remarks

- This recommendation applies to all people living with HIV.
- The recommendation was extrapolated to children based on the generalization of data from adults and limited data from children. For children, respiratory samples include sputum, BAL, induced sputum, nasopharyngeal aspirate and gastric aspirate.
- The recommendation was extrapolated to people with extrapulmonary TB based on the generalization of data from adults with pulmonary TB.
- The products for which eligible data met the class-based performance criteria for LC-aNAATs for this recommendation were Xpert MTB/RIF Ultra (Cepheid, Sunnyvale, United States of America [USA]) and Truenat MTB-RIF Dx (Molbio, Goa, India). Data on MTB-RIF Dx were more limited than those for Xpert Ultra.

<sup>5</sup> Having a positive result of a test, examination or other procedure used to distinguish people with a high likelihood of having TB disease from people who are highly unlikely to have TB. At present, the following tests are WHO-recommended as the screening tests: chest radiography (chest X-ray; CXR) with or without computer-aided detection (CAD), C-reactive protein (CRP) in people living with HIV, and molecular WHO-recommended rapid diagnostic test for TB (mWRD) (<https://www.who.int/publications/i/item/9789240022676>).

- 3. For people with signs and symptoms of TB meningitis, low-complexity automated NAATs on cerebral spinal fluid should be used for the initial diagnosis of TB meningitis rather than smear microscopy or culture.**

*(Strong recommendation, high certainty of evidence)*

## Remarks

- This recommendation applies to all people with signs and symptoms of TB meningitis, including people living with HIV and children.
- Where possible, culture may be performed in addition to automated NAAT testing, to maximize the opportunity for diagnosis and detection of DR-TB.
- The product for which eligible data met the class-based performance criteria for LC-aNAATs for this recommendation was Xpert MTB/RIF Ultra (Cepheid, Sunnyvale, United States of America [USA]). Data on Truenat MTB Plus and MTB-RIF Dx were limited and variable and thus were insufficient for evaluation.

- 4. For people with signs and symptoms of extrapulmonary TB, low-complexity automated NAATs on lymph node tissue aspirate, pleural tissue, pleural fluid, synovial fluid, peritoneal fluid or pericardial fluid should be used for the initial diagnosis of TB rather than smear microscopy or culture.**

*(Strong recommendation, high certainty of evidence)*

## Remarks

- This recommendation applies to all people with signs and symptoms of the respective form of extrapulmonary TB, including people living with HIV and children.
- Data on the performance of LC-aNAATs when used with urine and blood samples were limited or inconsistent.
- Where possible, culture may be performed in addition to automated NAAT testing, to maximize the opportunity for diagnosis and detection of DR-TB.
- The product for which eligible data met the class-based performance criteria for LC-aNAATs for this recommendation was Xpert MTB/RIF Ultra (Cepheid, Sunnyvale, United States of America [USA]). Data on Truenat MTB Plus and MTB-RIF Dx were limited and variable and thus were insufficient for evaluation.

## Justification and evidence

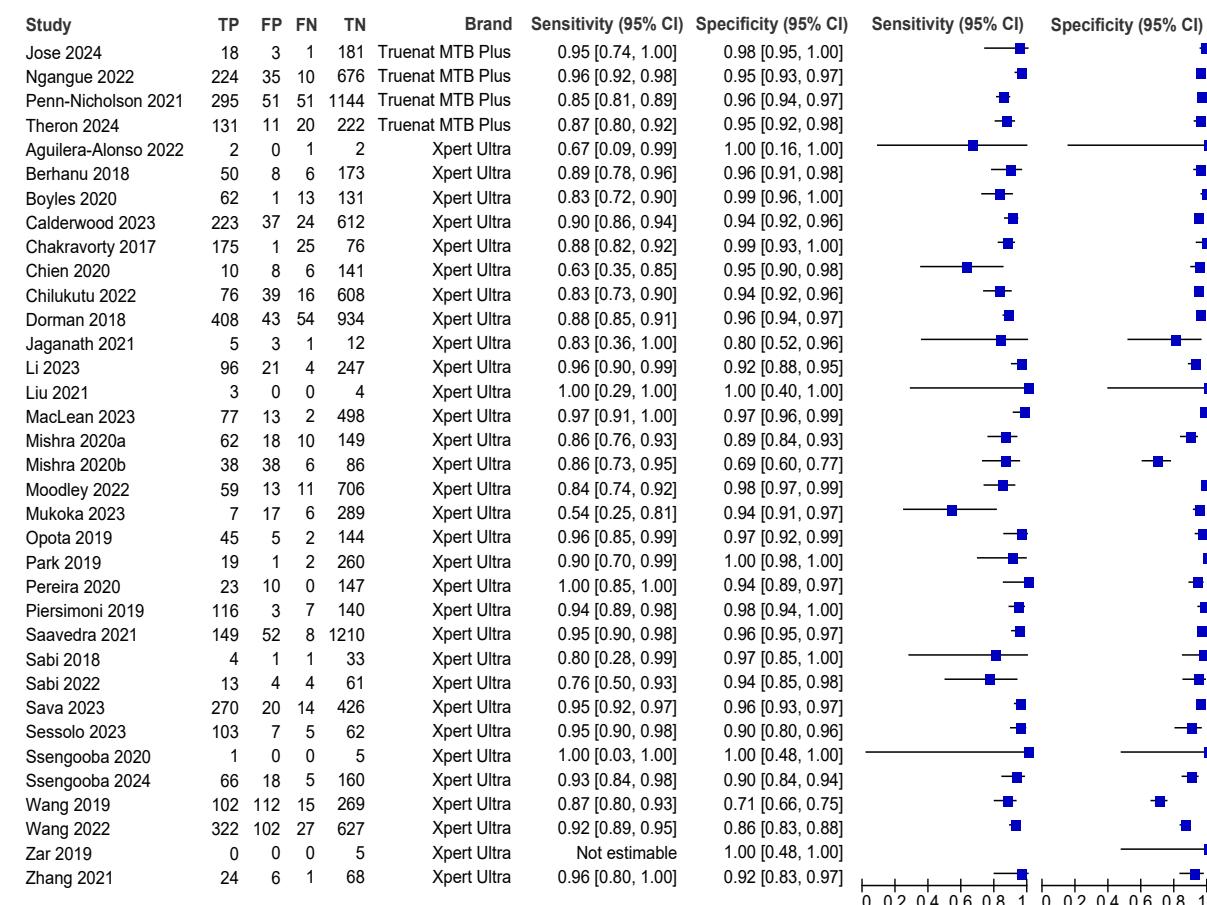
WHO/GTB initiated an update of the previous guidelines and commissioned a systematic review on the use of LC-aNAATs (Xpert Ultra, Truenat MTB Plus and Truenat MTB-RIF Dx assays) for the diagnosis of TB and resistance to rifampicin in people with signs and symptoms of TB, or who screened positive for TB. The data on the performance of LC-aNAATs alone in these populations, compared with smear microscopy and culture, are presented in Web Annexes B.1–B.4. Recommendations on concurrent testing for children and people living with HIV supersede the use of LC-aNAATs alone in these populations (see **Section 2.3** of this document).

## Detection of pulmonary TB

**Should LC-aNAATs on respiratory samples be used to diagnose pulmonary TB in adults and adolescents with signs and symptoms or who screened positive for pulmonary TB, against a microbiological reference standard?**

Thirty-five studies (14 845 participants) assessed diagnostic accuracy using sputum specimens and comparing with a microbiological reference standard (MRS); however, one of those studies had no people with TB (Zar 2019) and so sensitivity was not estimable. The sensitivities in the remaining 34 studies (14 840 participants) included in the meta-analysis were between 54% and 100%, and the specificities were between 71% and 100% (Fig. 2.1.1). The summary sensitivity was 90.4% (95% confidence interval [CI]: 88.0–92.4), and the summary specificity was 94.9% (95% CI: 93.0–96.3). The certainty of evidence for sensitivity and specificity was graded as “high”. For more details, see **Web Annex B.1**.

**Fig. 2.1.1. Forest plot of LC-aNAAT sensitivity and specificity for detection of pulmonary TB in sputum samples and MRS<sup>a</sup>**



CI: confidence interval; FN: false negative; FP: false positive; LC-aNAAT: low-complexity automated nucleic acid amplification test; MRS: microbiological reference standard; TB: tuberculosis; TN: true negative; TP: true positive.

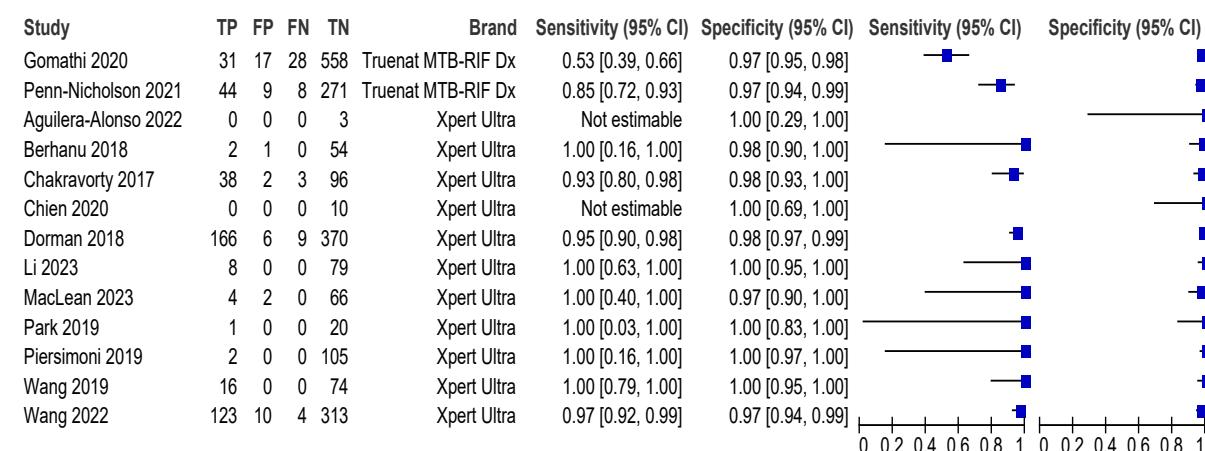
<sup>a</sup>Studies are sorted by assay and author.

## Detection of rifampicin resistance

**Should LC-aNAATs on respiratory samples be used to diagnose rifampicin resistance in adults and adolescents with signs and symptoms or who screened positive for pulmonary TB, against an MRS?**

Of the 13 studies (2553 participants) that evaluated sputum specimens, sensitivity for detecting rifampicin resistance was not estimable for two studies (**Fig. 2.1.2**). The sensitivities in the remaining 11 studies (2540 participants) included in the meta-analysis were between 53% and 100%, and the specificities were between 97% and 100%. The summary sensitivity was 95.1% (95% CI: 83.1–98.7), and the summary specificity was 98.1% (95% CI: 97.0–98.7). Only two of the 11 included studies assessed Truenat MTB-RIF Dx; one of them, a study from a single country, had a sensitivity outside of confidence interval limits (53%). Nevertheless, overall, the certainty of evidence for both sensitivity and specificity was considered high.

**Fig. 2.1.2. Forest plot of LC-aNAAT sensitivity and specificity for detection of rifampicin resistance in respiratory specimens and MRS<sup>a</sup>**



CI: confidence interval; FN: false negative; FP: false positive; LC-aNAAT: low-complexity automated nucleic acid amplification test; MRS: microbiological reference standard; TN: true negative; TP: true positive.

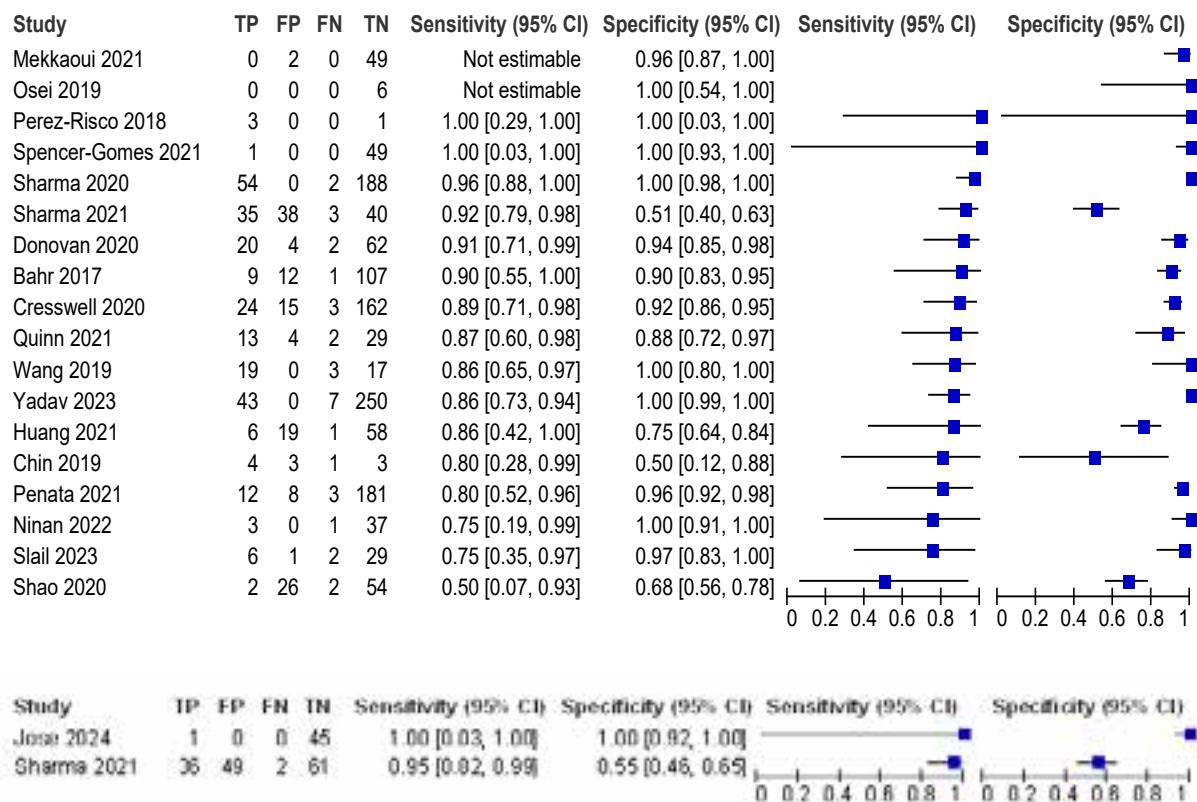
<sup>a</sup>Studies are sorted by assay and author.

## Detection of TB meningitis

**Should LC-aNAATs on cerebrospinal fluid (CSF) be used to diagnose TB meningitis in adults with signs and symptoms of TB meningitis, against an MRS?**

LC-aNAAT summary sensitivity and specificity were 88.2% (95% CI: 83.7–91.6) and 96.0% (95% CI: 86.8–98.9), respectively, based on 16 Xpert Ultra studies (1684 participants); the certainty of evidence was high for sensitivity and moderate for specificity (**Fig. 2.1.3**). Only data on Xpert Ultra were included in the evaluation to answer this population, intervention, comparator and outcome (PICO) question. Of note, trace results from Xpert Ultra were considered positive and formed a significant proportion of positive results (16–63%). Data on Truenat were limited and variable and thus were not included. For more details, see **Web Annex B.3**.

**Fig. 2.1.3. Forest plot of LC-aNAAT sensitivity and specificity for detection of TB meningitis in cerebrospinal fluid and MRS<sup>a</sup>**



CI: confidence interval; CSF: cerebrospinal fluid; FN: false negative; FP: false positive; LC-aNAAT: low-complexity automated nucleic acid amplification test; MRS: microbiological reference standard; TB: tuberculosis; TN: true negative; TP: true positive.

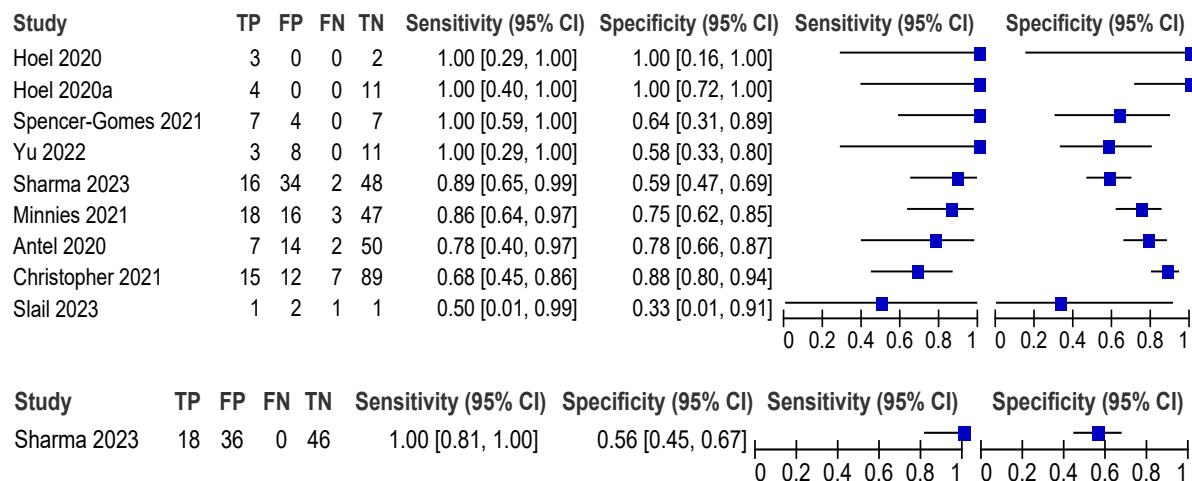
<sup>a</sup>Studies are sorted by decreasing sensitivity.

## Detection of extrapulmonary TB

**Should LC-aNAATs on lymph node fluid be used to diagnose lymph node TB in adults and adolescents with signs and symptoms of lymph node TB, against an MRS?**

LC-aNAAT summary sensitivity and specificity from nine Xpert Ultra studies (445 participants) to diagnose lymph node TB in lymph node fluid in adults and adolescents with signs and symptoms of lymph node TB (**Fig. 2.1.4**) were 85.3% (95% CI: 73.4–92.4) and 74.1% (95% CI: 63.5–82.5), respectively. The certainty of evidence was low for sensitivity and very low for specificity. Only data on Xpert Ultra were included in the evaluation to answer this PICO question. The diagnostic accuracy of LC-aNAATs against a composite reference standard (CRS) that comprised the MRS plus patients who received clinical diagnoses (but were bacteriologically unconfirmed) was also considered. The use of the CRS markedly increased specificity to 97.4% (95% CI: 82.2–99.7) but decreased sensitivity to 71.3% (95% CI: 64.3–77.4), highlighting the known challenges with culture-based confirmation of TB with this sample type (see **Web Annex B.3**). Data on Truenat were limited and thus were not included.

**Fig. 2.1.4. LC-aNAAT sensitivity and specificity for detection of lymph node TB in lymph node aspirate and MRS<sup>a</sup>**



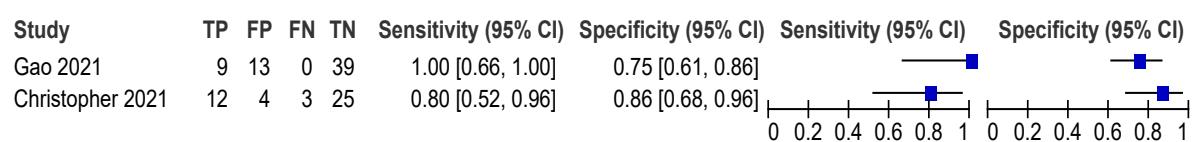
CI: confidence interval; FN: false negative; FP: false positive; LC-aNAAT: low-complexity automated nucleic acid amplification test; LN: lymph node; MRS: microbiological reference standard; TB: tuberculosis; TN: true negative; TP: true positive.

<sup>a</sup>Studies are sorted by decreasing sensitivity.

### **Should LC-aNAATs on pleural tissue be used to diagnose pleural TB in adults and adolescents with signs and symptoms of pleural TB, against an MRS?**

From two Xpert Ultra studies (105 participants), LC-aNAAT sensitivities were 80% and 100%, and specificities were 75% and 86% (**Fig. 2.1.5**); the certainty of evidence was low for sensitivity and very low for specificity. Only data on Xpert Ultra were included in the evaluation to answer this PICO question, as data on Truenat were not available. Given known challenges with culture-based confirmation of TB using this sample, the data using the CRS were also considered. The use of the CRS increased specificity of the LC-aNAAT on pleural tissue to 94–97%, but it decreased sensitivity to 54–81%<sup>6</sup> (see **Web Annex B.3**).

**Fig. 2.1.5. LC-aNAAT sensitivity and specificity for detection of pleural TB in pleural tissue and MRS<sup>a</sup>**



CI: confidence interval; FN: false negative; FP: false positive; LC-aNAAT: low-complexity automated nucleic acid amplification test; MRS: microbiological reference standard; TB: tuberculosis; TN: true negative; TP: true positive.

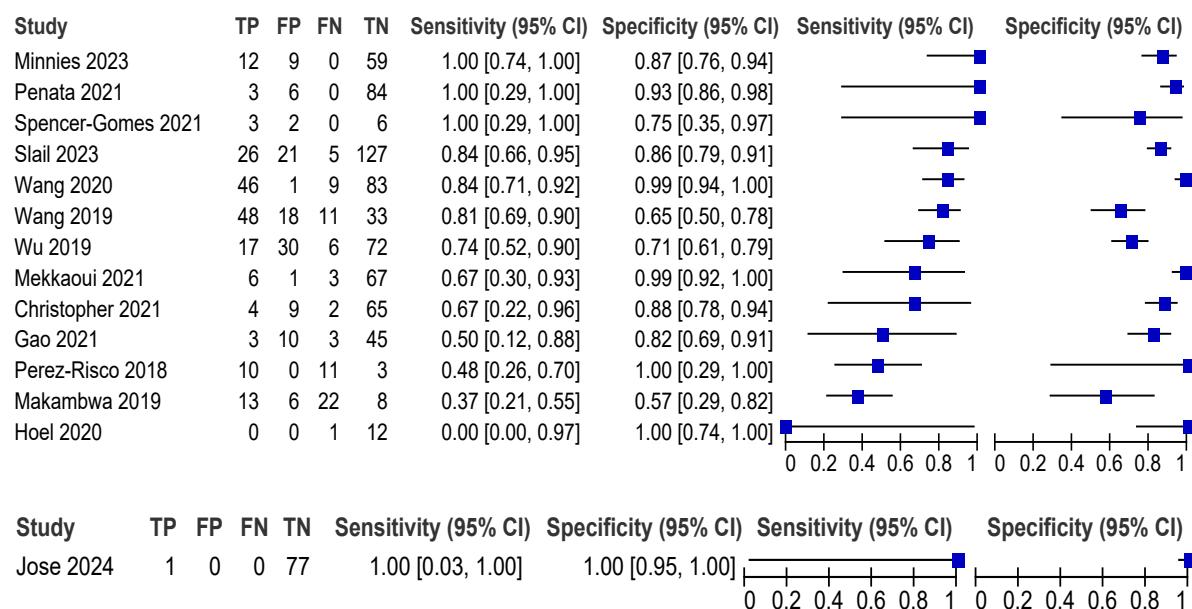
<sup>a</sup>Studies are sorted by decreasing sensitivity.

<sup>6</sup> Data were not pooled due to the limited number of studies.

## Should LC-aNAATs on pleural fluid be used to diagnose pleural TB in adults and adolescents with signs and symptoms of pleural TB, against an MRS?

LC-aNAAT summary sensitivity and specificity were 74.0% (95% CI: 60.8–83.9) and 88.1% (95% CI: 78.8–93.6), respectively, from 13 Xpert Ultra studies (1041 participants) (**Fig. 2.1.6**). The certainty of evidence was low for sensitivity and very low for specificity. Only one study (Jose 2024) provided accuracy estimates for pleural fluid for Truenat MTB Plus (88 participants), with sensitivity of 100% (95% CI: 0.03–100) and specificity of 100% (95% CI: 0.95–100). Similar to lymph node fluid and pleural tissue, the data using the CRS were also considered for this sample type. The use of the CRS increased specificity of LC-aNAATs on pleural fluid to 99.2% (95% CI: 95.2%–99.9%) but decreased sensitivity to 71.3% (95% CI: 64.3%–77.4%) (see **Web Annex B.3**). Only data on Xpert Ultra were included in the evaluation to answer this PICO question. Data on Truenat were limited.

**Fig. 2.1.6. LC-aNAAT sensitivity and specificity for detection of pleural TB in pleural fluid and MRS<sup>a</sup>**



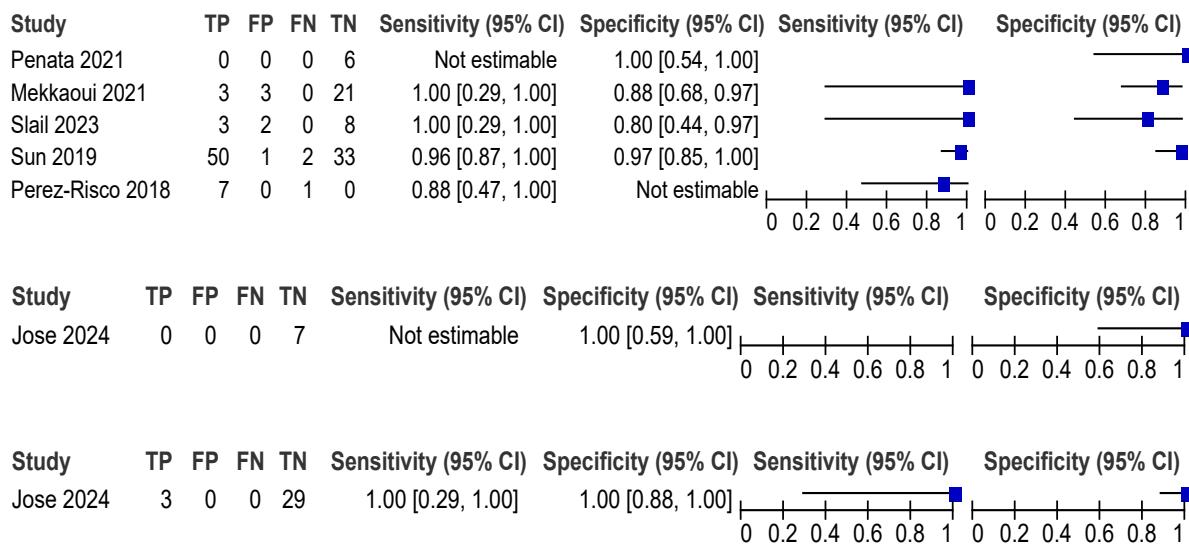
CI: confidence interval; FN: false negative; FP: false positive; LC-aNAAT: low-complexity automated nucleic acid amplification test; MRS: microbiological reference standard; TB: tuberculosis; TN: true negative; TP: true positive.

<sup>a</sup> Studies are sorted by decreasing sensitivity.

## Should LC-aNAATs on synovial fluid be used to diagnose bone or joint TB in adults and adolescents with signs and symptoms of bone or joint TB, against an MRS?

LC-aNAAT summary sensitivity and specificity were 96.6% (95% CI: 87.2–99.1) and 91.1% (95% CI: 80.8–96.2), respectively, from three Xpert Ultra studies (126 participants) (**Fig. 2.1.7**); the certainty of evidence was low. Similar to other extrapulmonary TB sample types, the data using the CRS were also considered. The use of the CRS increased specificity of the LC-aNAAT on synovial fluid to 97.0% (95% CI: 85.0–100.0), whereas the impact on sensitivity was minimal (96%) and largely involved tightening of the confidence interval (95% CI: 91–99%). Only data on Xpert Ultra were included in the evaluation to answer this PICO question. Data on Truenat were limited.

**Fig. 2.1.7. LC-aNAAT sensitivity and specificity for detection of bone or joint TB in synovial fluid or tissue and MRS<sup>a</sup>**



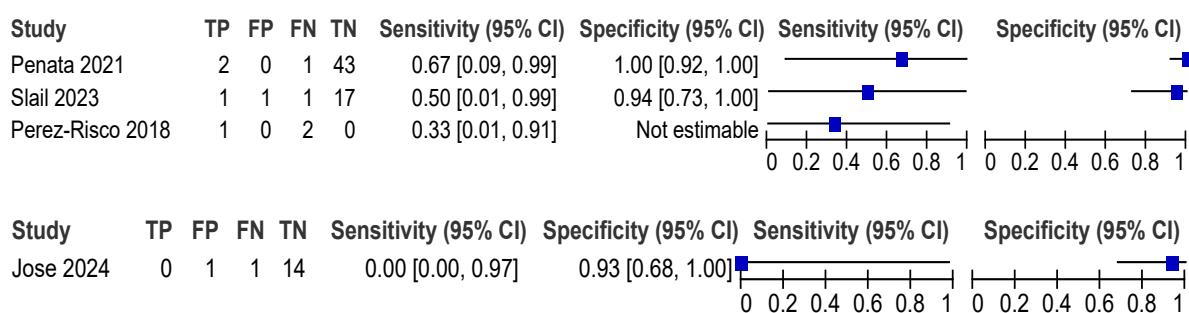
CI: confidence interval; FN: false negative; FP: false positive; LC-aNAAT: low-complexity automated nucleic acid amplification test; MRS: microbiological reference standard; TB: tuberculosis; TN: true negative; TP: true positive.

<sup>a</sup>Studies are sorted by decreasing sensitivity.

### Should LC-aNAATs on peritoneal fluid be used to diagnose peritoneal TB in adults and adolescents with signs and symptoms of peritoneal TB, against an MRS?

The sensitivities of the LC-aNAATs ranged from 33% to 67%, and the specificities from 94% to 100%, from three Xpert Ultra studies (69 participants); the certainty of evidence was very low for sensitivity and low for specificity (Fig. 2.1.8). Only data on Xpert Ultra were included in the evaluation to answer this PICO question. Data on Truenat were limited.

**Fig. 2.1.8. LC-aNAAT sensitivity and specificity for detection of peritoneal TB in peritoneal fluid and MRS<sup>a</sup>**



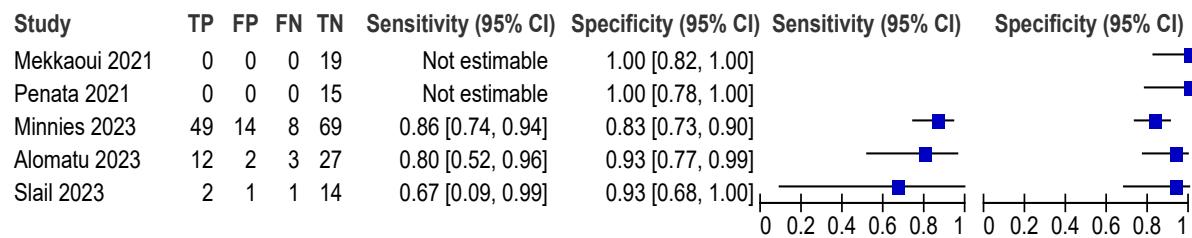
CI: confidence interval; FN: false negative; FP: false positive; LC-aNAAT: low-complexity automated nucleic acid amplification test; MRS: microbiological reference standard; TB: tuberculosis; TN: true negative; TP: true positive.

<sup>a</sup>Studies are sorted by decreasing sensitivity.

## Should LC-aNAATs on pericardial fluid be used to diagnose pericardial TB in adults and adolescents with signs and symptoms of pericardial TB, against an MRS?

LC-aNAAT summary sensitivity and specificity were 84.0% (95% CI: 73.9–90.7) and 86.6% (95% CI: 79.5–91.5), respectively, from three Xpert Ultra studies (202 participants); certainty of evidence was low for both sensitivity and specificity (**Fig. 2.1.9**).

**Fig. 2.1.9. LC-aNAAT sensitivity and specificity for detection of pericardial TB in pericardial fluid and MRS<sup>a</sup>**



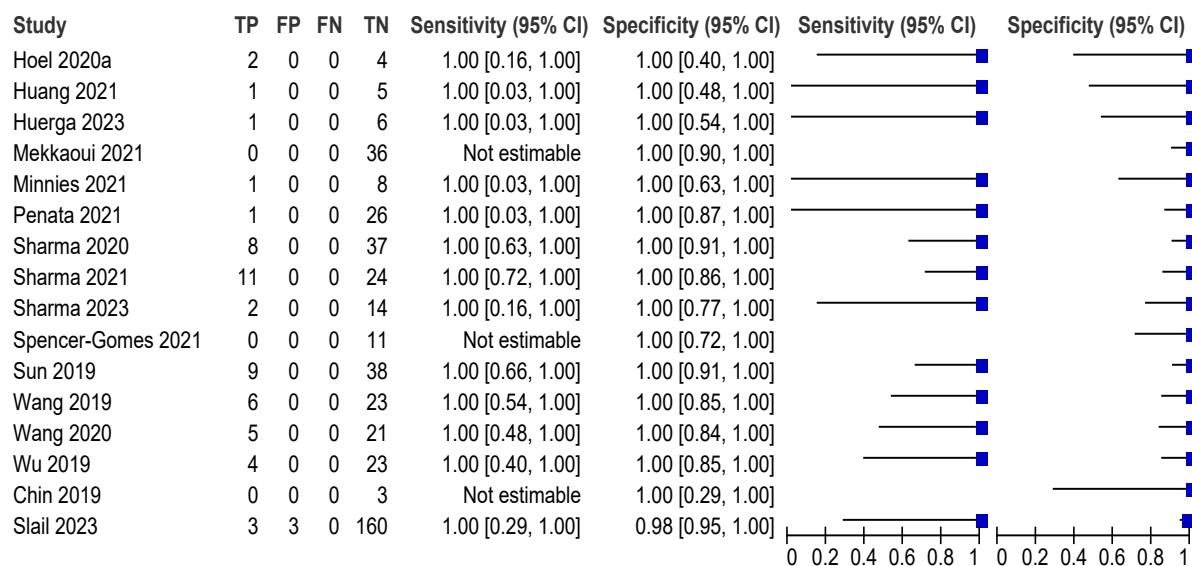
CI: confidence interval; FN: false negative; FP: false positive; LC-aNAAT: low-complexity automated nucleic acid amplification test; MRS: microbiological reference standard; TB: tuberculosis; TN: true negative; TP: true positive.

<sup>a</sup>Studies are sorted by decreasing sensitivity.

## Should LC-aNAAT on extrapulmonary specimens be used to diagnose rifampicin resistance in adults and adolescents with presumed extrapulmonary TB?

LC-aNAAT summary sensitivity and specificity were 100.0% (95% CI: 93.4–100.0) and 99.4% (95% CI: 92.1–100.0), respectively, from 13 Xpert Ultra studies (446 participants) (**Fig. 2.1.10**); certainty of evidence was high for both sensitivity and specificity.

**Fig. 2.1.10. LC-aNAAT sensitivity and specificity for detection of pericardial TB in pericardial fluid and MRS<sup>a</sup>**



CI: confidence interval; FN: false negative; FP: false positive; LC-aNAAT: low-complexity automated nucleic acid amplification test; MRS: microbiological reference standard; TB: tuberculosis; TN: true negative; TP: true positive.

<sup>a</sup>Studies are sorted by sensitivity.

## Cost-effectiveness analysis

This section deals with the following additional question:

### ***What are the comparative costs, affordability and cost-effectiveness of implementation of LC-aNAATs?***

WHO commissioned a systematic review to identify, evaluate and summarise the evidence on cost, affordability and cost-effectiveness of LC-aNAATs, among other technologies.

A total of 1534 studies were identified in the original search; after removing duplicates, 736 potentially relevant studies were screened. Of these, 107 were assigned for full-text review and were evaluated against the inclusion and exclusion criteria, and 29 studies were included in the final systematic review. Of the 29 included studies, 22 (76%) assessed Xpert MTB/RIF, six (21%) assessed Xpert Ultra, and one study (3%) evaluated Truenat tests (both Truenat MTB Plus and Truenat MTB-RIF Dx). Ten of the studies evaluating Xpert MTB/RIF were cost-effectiveness analyses, and 12 were cost analyses. All the included Xpert Ultra studies and the study evaluating Truenat were cost-effectiveness analyses.

The cost-effectiveness analysis on Xpert was considered because of similarity between two technologies and scarcity of the data on Ultra.

The studies included in the review were diverse, were conducted across various settings and covered all income levels. This broad spectrum of research provided a comprehensive view of the economic evidence on LC-aNAATs, with a focus on adults. Only three cost-effectiveness analyses included children. There were various comparator tests, including smear and culture. Most of the studies included sputum specimens. Six of the 10 cost-effectiveness analyses on Xpert MTB/RIF presented results in natural units (additional people with TB detected), and the other four presented utility outcomes (quality-adjusted life years and disability-adjusted life years [DALYs]).

The findings from the cost-effectiveness analyses showed that Xpert MTB/RIF was generally cost effective across the included studies when compared with smear or culture, except for one study from Thailand, where TB LAMP was the dominant strategy. In contrast, there was more heterogeneity in the methodology used in the cost-effectiveness studies for Xpert Ultra, and the findings showed that, for the Xpert Ultra versus sputum smear microscopy (SSM), an incremental cost-effectiveness ratio (ICER) ranged from US\$ 72.72 to US\$ 160.23 per DALY averted. In the only study on Truenat, it was found to be cost effective for children in India compared with Xpert MTB/RIF, with an ICER of US\$ 94.72 per DALY averted.

In general LC-aNAATs are likely to be cost effective across various settings when compared with SSM and culture.

More details on the economic evaluation of LC-aNAATs are available in **Web Annex B.9**.

## User perspective

This section deals with the following question:

***Are there implications for user preferences and values, patient equity, accessibility, feasibility and human rights from the implementation of Xpert MTB/RIF and Xpert Ultra?***

This review included 49 qualitative studies, of which 17 were identified in the updated search (since 2022). All studies about LC-aNAATs for detection of TB and DR-TB were conducted in high TB burden settings in Africa, Asia and Eastern Europe. Two studies provided user perspectives on Xpert Ultra and the rest on Xpert MTB/RIF or other rapid molecular tests. The studies about Xpert Ultra were conducted in Africa and Eastern Europe and focused on all people with presumptive TB, DR-TB and extrapulmonary TB.

Although standard Xpert MTB/RIF has been superseded by Xpert Ultra and other rapid NAATs, qualitative evidence for the latter NAATs is limited. Whereas LC-NAATs are generally valued for their accuracy, ease of use and potential to reduce time to diagnosis, the most recent generation of NAATs, such as Xpert Ultra, are valued for their greater accuracy in hard-to-diagnose patients, ease of implementation on existing GeneXpert platforms and ease of integration with rapid testing for other diseases. Challenges limiting the realization of these values for more recent NAATs are similar to those with Xpert MTB/RIF – that is, weak infrastructure, fragmented systems, heavy workloads, and limited availability of NAATs and their supplies. We recommend that qualitative studies be conducted to ascertain perspectives on concurrent use of NAATs.

There was high confidence in the evidence contributing to the findings of this review. More details on the qualitative evaluation of LC-aNAATs are available in **Web Annex B.10**.

## User preferences and values

Findings from Xpert MTB/RIF studies showed that providers valued its utility in making a diagnosis of drug resistance in people living with HIV, accuracy and resulting confidence in the test, rapid turnaround times, low costs of diagnostic testing for patients, and improved patient-provider relationships. Providers also valued the diversity of sample types that can be analysed by the test. Laboratory personnel valued its ease of use, and they reported increased staff satisfaction compared with sputum microscopy. People with TB valued receiving an accurate diagnosis, avoiding diagnostic delays and having low costs associated with diagnostic testing. Compared with Xpert MTB/RIF, providers valued Xpert Ultra's capacity for improving TB case detection among hard-to-diagnose patients (those with extrapulmonary TB, paediatric TB or coinfection with HIV) and detecting more people with TB.

Compared with Xpert MTB/RIF, providers valued Xpert Ultra for its ease of implementation and integration with testing for other diseases (made possible by its having been built on existing Xpert platforms). Acceptability of Xpert Ultra among providers seemed high, but there was uncertainty about its accuracy, potentially leading to reduced trust and litigation in the event of a false diagnosis.

## Patient equity

The limited availability of Xpert Ultra in health facilities and the high costs incurred by patients and health facilities for its use were reported as concerns in terms of equity.

## Acceptability

There were challenges to using Xpert MTB/RIF in the health care system. These challenges included underuse of the test and delays in the diagnostic pathway because of poor sample quality, insufficient resources and maintenance of the testing platforms, lack of functional data connectivity systems or record systems, inefficient patient flows, unavailability of updated clinical guidelines, and poor ownership of and accountability for the tests by health facilities. Overreliance on test results, rather than clinical judgement, and a lack of data-driven implementation processes were reported.

Access to the test may be limited owing to lack of sustainable funding, restrictions by donors, poor referral systems, dependence on outreach workers, unavailability of community TB diagnostic facilities and too many eligibility restrictions.

## Feasibility

As with Xpert MTB/RIF, implementation of Xpert Ultra could be hindered by infrastructural problems, such as power outages, staff shortages, limited availability of transportation for sputum samples and limited availability of Xpert testing platforms in health facilities.

## Implementation considerations

- Diagnostic products in the low-complexity classes of tests should be prequalified by WHO or approved by another regulator before clinical use.
- Diagnostic test manufacturers, laboratory and programme managers, and policy-makers should be educated on the WHO PQ process for TB IVDs (<https://extranet.who.int/prequal/>).
- Ensuring sufficient volume and specimen quality is important to obtain accurate results.
- Safe waste disposal of used test consumables needs to be planned in advance to minimize environmental risk.
- Trace positive results on respiratory samples may present false-positive results for TB disease (*M. tb*. non-viable but DNA detected) in those that are HIV negative or not at risk for HIV, and those with a prior history of TB and an end of treatment within the last 5 years.
- For tests that do not have integrated rifampicin-resistance detection as an all-in-one test, reflex testing for resistance should be performed at the same time for all TB-positive patients to support universal access to DST for rifampicin, at a minimum, and to reduce the risk of loss to follow-up.
- In settings with a very low prevalence of rifampicin resistance<sup>7</sup>, i.e. less than 2%, a positive test result for rifampicin resistance may represent a false positive result, and indicate a need for further testing with an alternative method or, at a minimum, repeat testing.

<sup>7</sup> The 2% prevalence was used as the lowest one in evidence synthesis and analysis to inform GDG meeting. At this prevalence level the number of false-positive results amounted to 19 out of 1000 eligible patients tested and equalized number of true-positive results.

- If rifampicin resistance is detected, further resistance testing for fluoroquinolones and bedaquiline is essential to guide selection of a shorter multidrug-resistant TB or rifampicin-resistant TB (MDR/RR-TB) treatment regimen.
- Use of a higher volume of CSF ( $\geq 6$  mL) with concentration, where possible, is encouraged to increase the sensitivity of LC-aNAATs.

## Monitoring and evaluation

- Track unsuccessful and indeterminate test result rates for currently recommended products and new products to be introduced in this class.
- Monitor the proportion of trace results from paucibacillary samples (e.g. CSF), including those that are culture-positive or culture-negative.
- Undertake surveillance to monitor the frequency of mutations (e.g. *I491F* mutation) outside of a *rpoB* rifampicin-resistance determining region (RRDR) over time.
- Monitor the proportion of people with bacteriologically confirmed TB without a rifampicin-resistance result or further recommended drug susceptibility reflex testing over time.

## Research priorities

- Review the field performance of the current technologies used in routine practice (programmatic settings).
- Conduct operational research to ensure that tests are used optimally in terms of both clinical efficiency and cost efficiency in intended settings.
- Evaluate the impact of LC-aNAAT testing on patient-important outcomes (cure, mortality, time to diagnosis and time to start of treatment).
- Evaluate the strengths, weaknesses and cost differences of different LC-aNAAT products to inform country selection.
- Evaluate the different classes of tests, including LC-aNAATs, to determine which classes or testing strategies yield superior diagnostic accuracy, cost-effectiveness and impact on equity and acceptability.
- Evaluate the impact on incremental accuracy and case detection and the cost-effectiveness of alternative sample types that are easier to collect.
- Evaluate the individual product performance with different paediatric and extrapulmonary TB sample types.
- Develop new tools that are rapid, affordable, feasible and acceptable to children and their parents.
- Optimize or develop tests or simple pre-step sample handling procedures for extrapulmonary TB.
- Identify an improved reference standard that accurately defines TB disease in children, paucibacillary specimens, and people who cannot produce sputum, because the sensitivity of all available diagnostics is suboptimal.
- Develop and apply standardized methods for cost-effectiveness and economic studies, to limit variability.

## 2.1.2 Moderate complexity automated NAATs for detection of TB and resistance to rifampicin and isoniazid

Rapid detection of TB and rifampicin resistance is increasingly available as new technologies are developed and adopted by countries. However, what has also emerged is the relatively high burden of isoniazid-resistant, rifampicin-susceptible TB that is often undiagnosed. Globally, isoniazid-resistant, rifampicin-susceptible TB is estimated to occur in 13.1% (95% CI: 9.9–16.9%) of new cases and 17.4% (95% CI: 0.5–54.0%) of previously treated cases (1).

A new class of technologies has come to market with the potential to address this gap. Several manufacturers have developed moderate complexity automated NAATs for detection of TB and resistance to rifampicin and isoniazid on high throughput platforms for use in laboratories. The tests belonging to this class are faster and less complex to perform than phenotypic culture-based drug susceptibility testing (DST) and line probe assays (LPA). They have the advantage of being largely automated following the sample preparation step. Moderate complexity automated NAATs may be used as an initial test for detection of TB and resistance to both first-line TB drugs simultaneously (rifampicin and isoniazid). They offer the potential for the rapid provision of accurate results (important to patients) and for testing efficiency where high volumes of tests are required daily (important to programmes). Hence, these technologies are suited to areas with a high population density and rapid sample referral systems.

**Table 2.1.2.1 Class criteria for MC-aNAATs**

Purpose	Detection of TB and resistance to rifampicin and isoniazid
<b>Principle of action</b>	Nucleic acid amplification testing
<b>Complexity</b>	Reagents Reagents are available within standardized kits and may have temperature requirements for storage. The sample is added automatically or manually to a disposable sealed container for testing.
Skills	Moderate technical skills (i.e., multiple sample or reagent handling steps, precision pipetting may be required, molecular workflows may be required)
Pipetting	One or more non-precision or precision pipetting steps required by the procedure.
Testing Procedure	May require multiple specimen treatment steps before transferring the specimen into a sealed test container for automated processing. Automated or manual DNA extraction Automated real-time PCR Results generation
<b>Type of test result reporting</b>	Automated
<b>Setting of use</b>	Laboratory (special infrastructure may be required)

## Recommendation

- 5. In people with signs and symptoms of pulmonary TB, moderate complexity automated NAATs may be used on respiratory samples for the detection of pulmonary TB, and of rifampicin and isoniazid resistance, rather than culture and phenotypic DST.**

*(Conditional recommendation, moderate certainty of evidence for diagnostic accuracy)*

There are several subgroups to be considered for this recommendation:

- The recommendation is based on evidence of diagnostic accuracy in respiratory samples of adults with signs and symptoms of pulmonary TB.
- The recommendation applies to people living with HIV (studies included a varying proportion of such individuals); performance on smear-negative samples was reviewed but was only available for TB detection, not for rifampicin and isoniazid resistance, and data stratified by HIV status were not available.
- The recommendation applies to adolescents and children based on the generalization of data from adults; an increased rate of indeterminate results may be found with paucibacillary TB disease in children.
- The review did not consider extrapolation of the finding for use in people with extrapulmonary TB and testing on non-sputum samples because data on diagnostic accuracy of technologies in the class for non-sputum samples were limited.

## Justification and evidence

The WHO Global TB Programme initiated an update of the current guidelines and commissioned a systematic review on the use of moderate complexity automated NAATs for detection of TB and resistance to rifampicin and isoniazid in people with signs and symptoms of TB.

Three PICO questions were designed to form the basis for the evidence search, retrieval and analysis:

1. Should moderate complexity automated NAATs be used on respiratory samples in people with signs and symptoms of pulmonary TB for detection of pulmonary TB, as compared with culture?
2. Should moderate complexity automated NAATs be used on respiratory samples in people with signs and symptoms of pulmonary TB for detection of resistance to rifampicin, as compared with culture-based phenotypic DST?
3. Should moderate complexity automated NAATs be used on respiratory samples in people with signs and symptoms of pulmonary TB for detection of resistance to isoniazid, as compared with culture-based phenotypic DST?

A comprehensive search of the following databases (PubMed, Embase, BIOSIS, Web of Science, LILACS and Cochrane) for relevant citations was performed. The search was restricted to the period January 2009 to July 2020. Reference lists from included studies were also searched. No language restriction was applied. Because there were few studies for the selected index tests,

the diagnostic companies were contacted for reports of their internal validation data. Studies were also included from the WHO public call for submission of data. Mycobacterial culture was used as the reference standard for evaluation of *Mtb* detection. Resistance detection was compared with a phenotypic DST reference standard and a composite reference standard (that combines phenotypic and genotypic DST results) in studies where both had been performed.

Bivariate random-effects meta-analyses were performed using Stata software, to obtain pooled sensitivity and specificity estimates with 95% CIs for rifampicin resistance, isoniazid resistance and *Mtb* detection. Where only a limited number of studies were available, descriptive analyses were conducted.

For meta-analysis, studies were first meta-analysed separately for each test. Studies from all the tests were then used to obtain a pooled estimate for all technologies.

To decide whether pooling of all the tests would give meaningful estimates, various criteria for pooling were developed and agreed upon by the GDG panel before they were applied. Data were also evaluated and visualized using head-to-head comparisons of the tests with Xpert® MTB/RIF or any other WHO-recommended test.

Data for all the index platforms were only pooled to answer PICO questions if they met the preconditions given in **Table 2.1.2.2** and fulfilled either Condition 1 or Condition 2.

**Table 2.1.2.2 Criteria for pooling studies on moderate complexity automated NAATs**

Parameters	Sensitivity	Specificity
Preconditions	$n \geq 50$ culture-positive TB	$n \geq 100$ culture-negative TB
Condition 1 (pool based on clinical grounds)	The pooled estimate of one test lies within $\pm 5\%$ of the overall pooled estimate	The pooled estimate of one test lies within $\pm 2\%$ of the overall pooled estimate
Condition 2 (pool based on statistical grounds)	The pooled estimate for one test lies within 95% CI of the overall pooled estimate AND The pooled estimate for one test lies within $\pm 10\%$ of the overall pooled estimate	The pooled estimate for one test lies within 95% CI of the overall pooled estimate AND The pooled estimate for one test lies within $\pm 5\%$ of the overall pooled estimate

CI: confidence interval; n: number; NAAT: nucleic acid amplification test; TB: tuberculosis.

Data synthesis was structured around the three preset PICO questions, as outlined below. Three web annexes<sup>8</sup> give additional information, as follows:

- details of studies included in the current analysis (**Web Annex 1.3: Moderate complexity automated NAATs**);
- a summary of the results and details of the evidence quality assessment (**Web Annex 2.3: Moderate complexity automated NAATs**); and

<sup>8</sup> A complete list of web annexes is provided at pp 172–173.

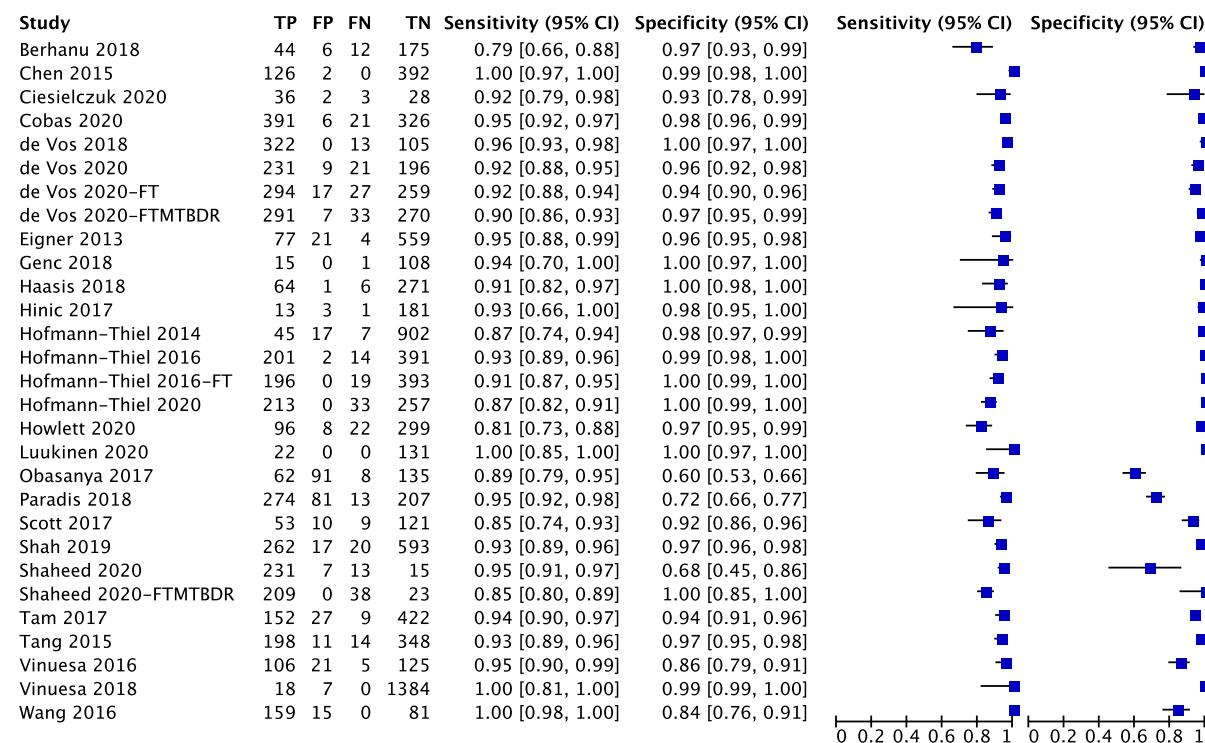
- a summary of the GDG panel judgements (**Web Annex 3.3: Moderate complexity automated NAATs**).

### **PICO 1: Should moderate complexity automated NAATs be used on respiratory samples in people with signs and symptoms of pulmonary TB for detection of pulmonary TB, as compared with culture?**

A total of 29 studies with 13 852 specimens provided data for evaluating TB detection from the five index tests (**Fig. 2.1.2.1**). Of these 29 studies, 12 were conducted on the Abbott RealTime MTB test, six on FluoroType MTB, four on FluoroType MTBDR, five on BD MAX and two on the cobas MTB test. The reference standard for each of these studies for TB detection was mycobacterial culture.

Of the 29 studies, 16 (55%) had high or unclear risk of bias because they tested specimens before inclusion in the study, used convenience sampling or did not report the method of participant selection. Thus, the evidence was downgraded one level for risk of bias. Overall, the certainty of the evidence was moderate for sensitivity and high for specificity.

**Fig. 2.1.2.1 Forest plot of included studies for TB detection with culture as the reference standard**



CI: confidence interval; FN: false negative; FP: false positive; TB: tuberculosis; TN: true negative; TP: true positive.

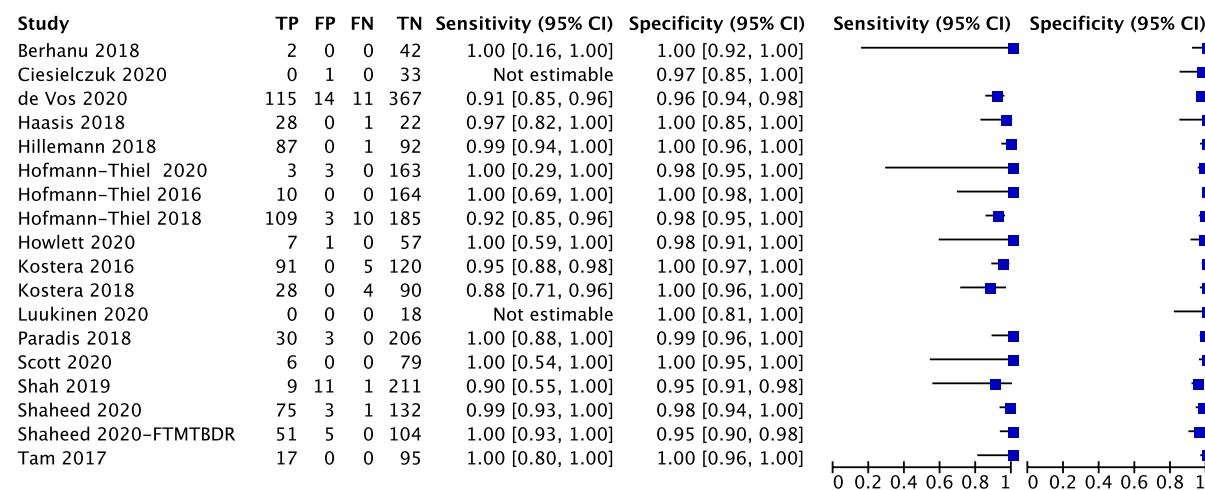
The overall sensitivity in these 29 studies ranged from 79% to 100%, and the specificity from 60% to 100%. **The pooled sensitivity was 93.0% (95% CI: 90.9–94.7%) and the pooled specificity was 97.7% (95% CI: 95.6–98.8%).**

**PICO 2: Should moderate complexity automated NAATs be used on respiratory samples in people with signs and symptoms of pulmonary TB for detection of resistance to rifampicin, as compared with culture-based phenotypic DST?**

A total of 18 studies with 2874 specimens provided data for resistance testing of rifampicin using moderate complexity automated NAATs (**Fig. 2.1.2.2**). Of these 18 studies, nine were conducted on the Abbott RealTime RIF/INH test, three on FluoroType MTBDR, four on BD MAX and two on the cobas RIF/INH test. The reference standard for each of these studies for resistance detection was phenotypic DST, using a composite reference standard with both phenotypic DST and sequencing results.

Eight (44%) of the 18 studies had high or unclear risk of bias because they did not report participant selection or tested specimens before inclusion in the study.

**Fig. 2.1.2.2 Forest plot of included studies for rifampicin resistance detection with phenotypic DST as the reference standard**



CI: confidence interval; DST: drug susceptibility testing; FN: false negative; FP: false positive; TB: tuberculosis; TN: true negative; TP: true positive.

The overall sensitivity for rifampicin resistance in these 18 studies ranged from 88% to 100% and the specificity from 98% to 100%. **The pooled sensitivity was 96.7% (95% CI: 93.1–98.4%) and the pooled specificity was 98.9% (95% CI: 97.5–99.5%).**

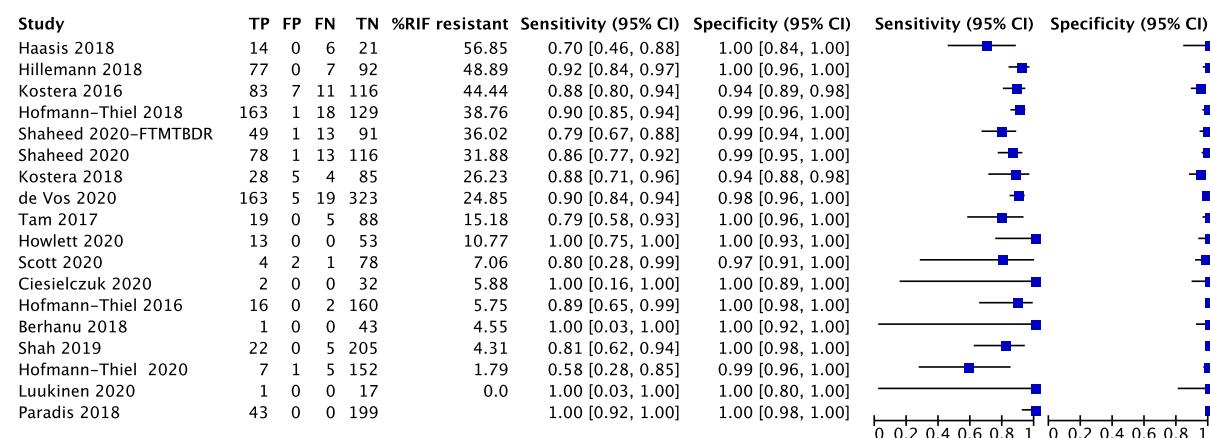
In determining rifampicin resistance, the results from genetic sequencing (genotypic DST) were obtained where possible, and a composite reference standard was developed that combined the results from phenotypic and genotypic DST. For rifampicin resistance detection, the diagnostic test accuracy of moderate complexity automated NAATs was similar for phenotypic DST and the composite reference standard.

### PICO 3: Should moderate complexity automated NAATs be used on respiratory samples in people with signs and symptoms of pulmonary TB for detection of resistance to isoniazid, as compared with culture-based phenotypic DST?

A total of 18 studies with 1758 specimens provided data for resistance testing of isoniazid using moderate complexity automated NAATs (**Fig. 2.1.2.3**). Of these 18 studies, nine were conducted on the Abbott RealTime RIF/INH test, three on FluoroType MTBDR, four on BD MAX and two on the cobas MTB-RIF/INH test. The reference standard for each of these studies for resistance detection was phenotypic DST, and a composite reference standard with both phenotypic DST and sequencing results.

Eight (44%) of the 18 studies had high or unclear risk of bias, because participant selection was not reported or prior testing was done on the included specimens.

**Fig. 2.1.2.3 Forest plot of included studies for isoniazid resistance detection with phenotypic DST as the reference standard**



CI: confidence interval; DST: drug susceptibility testing; FN: false negative; FP: false positive; RIF: rifampicin; TB: tuberculosis; TN: true negative; TP: true positive.

The overall sensitivity for isoniazid resistance in these 18 studies ranged from 58% to 100% and the specificity from 94% to 100%. **The pooled sensitivity was 86.4% (95% CI: 82.1–89.8%) and the pooled specificity was 99.8% (95% CI: 98.3–99.8%).**

In determining isoniazid resistance, the results from genetic sequencing (genotypic DST) were obtained where possible, and a composite reference standard was developed that combined the results from phenotypic and genotypic DST. For detecting isoniazid resistance, the diagnostic test accuracy of phenotypic DST was similar to that of the composite reference standard.

### Cost-effectiveness analysis

This section answers the following additional question:

**What is the comparative cost, affordability and cost-effectiveness of implementation of moderate complexity automated NAATs?**

A systematic review was conducted, focusing on economic evaluations of moderate complexity automated NAATs. Four online databases (Embase, Medline, Web of Science and Scopus) were searched for new studies published from 1 January 2010 through 17 September 2020. The citations of all eligible articles, guidelines and reviews were reviewed for additional studies. Experts and test manufacturers were also contacted to identify any additional unpublished studies.

The objective of the review was to summarize current economic evidence and further understand the costs, cost-effectiveness and affordability of moderate complexity automated NAATs.

Several commercially available tests were included as eligible tests in the moderate complexity automated NAATs category; however, no published studies were identified assessing the costs or cost-effectiveness of any of those tests. One unpublished study comparing available data on two technologies from moderate complexity automated NAATs class was identified, and the data from that study are described below.

Unpublished data from FIND was provided through direct communication. This costing-only study used time and motion studies combined with a bottom-up, ingredients-based approach to estimate the unit test cost for the two selected technologies.<sup>9</sup> Time and motion studies were conducted at a reference-level laboratory in South Africa. Several important simplifying assumptions were made that may limit the generalizability of the results; for example, 50% of laboratory operations dedicated to TB, a minimum daily throughput of 24 samples or the equivalent of one BD MAX run (24 tests/run), equipment costs fixed at US\$ 100 000 for both platforms, a 5% annual maintenance cost, and the standard 3% discount rate and 10 years expected useful life years.

Additional literature searches conducted to look for economic data using similar platforms from non-TB disease areas identified three additional studies from HIV and hepatitis C virus (HCV) with limited cost data: one (5) using Abbott RealTime HIV and two on HCV (6,7). Data were limited to cost per unit test kit and are not transferrable to test kit costs for the tests being considered in this review.

#### *How large are the resource requirements (costs)?*

Available unit test costs for two moderate complexity automated NAATs ranged from US\$ 18.52 (US\$ 13.79–40.70) and US\$ 15.37 (US\$ 9.61–37.40), with one study reporting cheaper per-test kit costs and higher operational costs associated with laboratory processing time. Equipment costs were strong drivers of cost variation and will vary across laboratory networks and operations. If equipment can be optimally placed or multiplexed to ensure high testing volume, the per-test cost can be minimized.

In one-way sensitivity analyses, annual testing volumes varied from fewer than 5000 tests/year to more than 25 000 tests/year. Per-test cost was highly sensitive to testing volume when fewer than 5000 tests were conducted per year; however, unit test costs begin to stabilize between 5000 and 10 000 tests/year, and above 10 000 tests/year, unit cost estimate was robust. When equipment can be multiplexed and used at capacity, per-test cost can be minimized.

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<sup>9</sup> Data courtesy of H Sohn and W Stevens at FIND (unpublished).

*What is the certainty of the evidence of resource requirements (costs)?*

Available per-test cost data were unpublished but did include overheads, equipment, building, staff and consumable costs; however, complete quality assessment of the study was not possible. Test cost will vary according to testing volume and laboratory operations. There is limited evidence to assess the important variability across sites, countries and implementation approaches.

*Does the cost-effectiveness of the intervention favour the intervention or the comparison?*

No studies were identified that assessed cost-effectiveness for any of the moderate complexity automated NAATs, and extrapolation was not appropriate given differences in standard of care, care cascades and associated costs, operational conditions, testing volume and diagnostic accuracy. Implementation considerations (e.g. test placement, laboratory network and ability of the programme to initiate treatment quickly) are all likely to affect unit test cost and cost-effectiveness. Economic modelling is needed across various settings to understand the range of cost-effectiveness profiles of moderate complexity automated NAATs, and how they are likely to vary under different operational criteria.

Additional details on economic evidence synthesis and analysis are provided in **Web Annex B.12: Systematic literature review of economic evidence for NAATs to detect TB and DR-TB in adults and children.**

## User perspective

This section answers the following questions about **key informants' views and perspectives on the use of moderate complexity automated NAATs:**

- Is there important uncertainty about or variability in how much end-users value the main outcomes?
- What would be the impact on health equity?
- Is the intervention acceptable to key stakeholders?
- Is the intervention feasible to implement?

User perspectives on the value, feasibility, usability and acceptability of diagnostic technologies are important in the implementation of such technologies. If the perspectives of laboratory personnel, clinicians, patients and TB programme personnel are not considered, the technologies risk being inaccessible to and underused by those for whom they are intended.

To address questions related to user perspective, two activities were undertaken:

- A systematic review of evidence on user perspectives and experiences with NAATs for detection of TB and TB drug resistance (moderate and low complexity automated assays, and high complexity hybridization-based assays) was undertaken from July to November 2020.
- A total of 14 semi-structured interviews with clinicians, programme officers, laboratory staff and patient advocates were conducted in India, Moldova and South Africa from October to November 2020.

The findings from these activities are discussed below.

## Systematic review

A total of 27 studies were identified that met inclusion criteria, of which 21 were sampled for inclusion in the analysis. All of the sampled studies were published between 2012 and 2020. Of the 21 included studies, 18 were located in high TB burden countries: six in India, four in South Africa, two each in Kenya and Uganda, and one each in Brazil, Cambodia, Myanmar and Viet Nam. One study covered projects in nine countries (Bangladesh, Cambodia, Democratic Republic of the Congo, Kenya, Malawi, Moldova, Mozambique, Nepal and Pakistan). In addition, there was one study located in Eswatini, one in Mongolia and one in Nepal. All studies focused on Xpert MTB/RIF, except for one that focused on Xpert MTB/RIF Ultra (Xpert Ultra).

A summary of the core characteristics of studies included in this review is presented in a study characteristics table in **Web Annex B.13: User perspectives on NAATs to detect TB and DR-TB: results from qualitative evidence synthesis: systematic review**.

## Interviews

The aim of the interviews was to understand participants' experiences of using the various technologies (i.e. NAATs for detection of TB and TB drug resistance) and their general TB diagnostic experiences. The three countries – India, Moldova and South Africa – were selected based on them being on WHO's list of 30 high MDR-TB burden countries (1) and that index tests have been used to some extent in research contexts within these countries. Due to the short time frame, participants were purposively sampled and approached based on convenience through personal contacts and colleagues.

An overview of the participants is given in **Table 2.1.2.3** To mask the identity of study participants they were coded by their country (Moldova [M], India [I] or South Africa [S]), their profession (clinician or medical doctor [M], patient advocate/representative [R], laboratory personnel [L] or programme officers [P]) and a number.

**Table 2.1.2.3 Overview of participants for the end-users' interviews**

	Moldova	India	South Africa
<b>Clinician or medical doctor</b>	1	1	1
<b>Patient advocate/representative</b>	1	1	1
<b>Laboratory personnel</b>	2 <sup>a</sup>	5 <sup>a</sup>	2
<b>Programme officers</b>	2 <sup>a</sup>	2	1

<sup>a</sup> Participants were interviewed as a group.

Interviews were conducted using Zoom, Skype or phone. Topics discussed included:

- current approach to diagnosing TB, MDR-TB and extensively drug-resistant TB (XDR-TB), including specific challenges;
- experiences with using molecular TB diagnostics and the index tests specifically, including details on steps taken in the diagnostic process;
- experiences with determining eligibility and treatment initiation, and challenges and benefits of using the index tests;

- overall usefulness of the index tests;
- the feasibility of implementing the index tests;
- the potential impact of the index tests on health equity; and
- how the potential impact of the index tests relates to current policy context.

Several important limitations of this approach were noted. Only a few participants were interviewed per country. Owing to the use of Zoom, Skype or phone for interviews, it was not possible to triangulate interview data with other evidence commonly collected through ethnographic approaches (e.g. multiple interviews and informal conversations at the same facility, observations or site visits). In addition, only some of the participants had personal experience with one or all of the index tests, and those participants who did have experience with the tests had used them in research settings rather than for routine practice.

More details on these interviews are given in **Web Annex B.14: User perspectives on nucleic acid amplification tests for tuberculosis and tuberculosis drug resistance: Interviews study.**

## **Findings of the review and interviews**

The main findings of the systematic review and interviews are given below. Where information is from the review, a level of confidence in the quality evidence synthesis (QES) is given; where it is from interviews, this is indicated with 'Interviews'.

### **Is there important uncertainty about or variability in how much end-users value the main outcomes?**

- Patients in high burden TB settings value:
  - getting an accurate diagnosis and reaching diagnostic closure (finally knowing "what is wrong with me");
  - avoiding diagnostic delays because they exacerbate existing financial hardships and emotional and physical suffering, and make patients feel guilty for infecting others (especially children);
  - having accessible facilities; and
  - reducing diagnosis-associated costs (e.g. travel, missing work) as important outcomes of the diagnostic.

*QES: moderate confidence*

- Moderate complexity automated NAATs meet several preferences and values of clinicians and laboratory staff, in that they:
  - are faster than culture-based phenotypic DST (similar to LPA or cartridge-based tests);
  - have the advantage of being automated (unlike LPA);
  - provide additional clinically relevant drug-resistance information such as high versus low resistance (unlike the current Xpert MTB/RIF cartridge).

*Interviews*

### **What would be the impact on health equity?**

- Various factors – for example, lengthy diagnostic delays, underuse of diagnostics, lack of TB diagnostic facilities at lower levels and too many eligibility restrictions – hamper access to prompt and accurate testing and treatment, particularly for vulnerable groups.

*QES: high confidence*

- Staff and managers voiced concerns about:
  - sustainability of funding and maintenance;
  - complex conflicts of interest between donors and implementers; and
  - the strategic and equitable use of resources, which negatively affects creating equitable access to cartridge-based diagnostics.

*QES: high confidence*

- Access to clear and comprehensible information for TB patients on what TB diagnostics are available to them and how to interpret results is a vital component of equity, and lack of such access represents an important barrier for patients.

*Interviews*

- New treatment options need to be matched with new diagnostics. It is important to improve access to treatment based on new diagnostics and to improve access to diagnostics for new treatment options.

*Interviews*

- The speed at which WHO guidelines are changing does not match the speed at which many country programmes are able to implement the guidelines. This translates into differential access to new TB diagnostics and treatment:

- between countries (i.e. between those that can and cannot quickly keep up with the rapidly changing TB diagnostic environment); and
- within countries (i.e. between patients who can and cannot afford the private health system that is better equipped to quickly adopt new diagnostics and policies).

*Interviews*

- The identified challenges with the use of NAATs for detection of TB and DR-TB, and accumulated delays, risk compromising the added value as identified by the users, ultimately leading to underuse. The challenges also hamper access to prompt and accurate testing and treatment, particularly for vulnerable groups.

*QES: high confidence*

### **Is the intervention acceptable to key stakeholders?**

- Patients can be reluctant to test for TB or MDR-TB because of:
  - stigma related to MDR-TB or having interrupted treatment in the past;
  - fears of side-effects;
  - failure to recognize symptoms;
  - inability to produce sputum; and
  - cost, distance and travel concerns related to (repeat) clinic visits.

*QES: high confidence*

- Health workers can be reluctant to test for TB or MDR-TB because of:
  - TB-associated stigma and consequences for their patients;
  - fear of acquiring TB;
  - fear from supervisors when reclassifying patients already on TB treatment who turn out to be misclassified;
  - fear of side-effects of drugs in children; and
  - community awareness of disease manifestations in children.

*QES: high confidence*

- In relation to the acceptability of moderate complexity automated NAATs:
  - the automation of this class of technologies, which recognizes the high workload of laboratory staff, improves their acceptability;
  - in terms of the physical size of the platform and how it fits into the laboratory space and workflow, a smaller footprint may be more acceptable; and
  - the number of samples run on the system is acceptable provided that the platform is placed within a laboratory that receives a sufficient sample load to run the system.

*Interviews*

### **Is the intervention feasible to implement?**

- The feasibility of all diagnostic technologies is challenged if there is an accumulation of diagnostic delays or underuse (or both) at every step in the process, mainly because of health system factors such as:
  - non-adherence to testing algorithms, testing for TB or MDR-TB late in the process, empirical treatment, false negatives due to technology failure, large sample volumes and staff shortages, poor or delayed sample transport and sample quality, poor or delayed communication of results, delays in scheduling follow-up visits and recalling patients, and inconsistent recording of results;
  - lack of sufficient resources and maintenance (i.e. stock-outs; unreliable logistics; lack of funding, electricity, space, air conditioners and sputum containers; dusty environment; and delayed or absent local repair option);
  - inefficient or unclear workflows and patient flows (e.g. inefficient organizational processes, poor links between providers, and unclear follow-up mechanisms or information on where patients need to go); and
  - lack of data-driven and inclusive national implementation processes.

*QES: high confidence*

- The feasibility of moderate complexity automated NAATs is also challenged by:
  - how or whether the platform fits into the physical space of the laboratory (considering bench size and weight of the platform) and sample workflow;
  - a poorly functioning sample transport system that affects the quality of samples; and
  - the need to ensure that clinicians and laboratory staff have time to communicate effectively regarding diagnostic results if the platform is centralized, while also ensuring that the laboratory location is central enough to receive adequate numbers of samples to make the machine worth running.

*Interviews*

- Implementation of new diagnostics must be accompanied by training for clinicians to help them interpret results from new molecular tests and understand how this information is translated into prompt and proper patient management. In the past, with the introduction of Xpert MTB/RIF, this has been a challenge.

*QES: high confidence and interviews*

- Introduction of new diagnostics must be accompanied by guidelines and algorithms that support clinicians and laboratories in communicating with each other, such that they can discuss discordant results and interpret laboratory results in the context of drug availability, patient history and patient progress on a current drug regimen.

*Interviews*

## Implementation considerations

Factors to consider when implementing moderate complexity automated NAATs for detection of TB and resistance to rifampicin and isoniazid are as follows:

- local epidemiological data on resistance prevalence should guide local testing algorithms, whereas pretest probability is important for the clinical interpretation of test results;
- the cost of a test varies depending on parameters such as the number of samples in a batch and the staff time required; therefore, a local costing exercise should be performed;
- low, moderate and high complexity tests have successive increase in technical competency needs (qualifications and skills) and staff time, which affects planning and budgeting;
- availability and timeliness of local support services and maintenance should be considered when selecting a provider;
- laboratory accreditation and compliance with a robust quality management system (including appropriate quality control) are essential for sustained service excellence and trust;
- training of both laboratory and clinical staff is needed to ensure effective delivery of services and clinical impact;
- use of connectivity solutions for communication of results is encouraged, to improve efficiency of service delivery and reduce time to treatment initiation;
- moderate complexity automated NAATs may already be used programmatically for other diseases – for example, severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), HIV and antimicrobial resistance (AMR) – which could potentially facilitate implementation of TB testing on shared platforms;
- implementation of moderate complexity automated NAATs requires laboratories with the required infrastructure, space and efficient sample referral systems;
- although these are automated tests, well-trained skilled staff are needed to set up assays and complete maintenance requirements; and
- implementation of these tests should be context specific; thus, it should take into account access issues, especially in remote areas, where less centralized WHO-recommended technologies may be more appropriate.

## Research priorities

Research priorities for moderate complexity automated NAATs for detection of TB and resistance to rifampicin and isoniazid are as follows:

- diagnostic accuracy in specific patient populations (e.g. children, people living with HIV, and patients with signs and symptoms of extrapulmonary TB) and in non-sputum samples;
- impact of diagnostic technologies on clinical decision-making and outcomes that are important to patients (e.g. cure, mortality, time to diagnosis and time to start treatment) in all patient populations;
- impact of specific mutations on treatment outcomes among people with DR-TB;
- use, integration and optimization of diagnostic technologies in the overall landscape of testing and care, as well as diagnostic pathways and algorithms;
- economic studies evaluating the costs, cost–effectiveness and cost–benefit of different diagnostic technologies;
- qualitative studies evaluating equity, acceptability, feasibility and end-user values of different diagnostic technologies;

- effect of non-actionable results (indeterminate, non-determinate or invalid) on diagnostic accuracy and outcomes that are important to patients;
- operational research on the advantages and disadvantages of individual technologies within the class of moderate complexity automated NAATs;
- effect of moderate complexity automated NAATs in fostering collaboration and integration between disease programmes; and
- the potential utility of detecting *katG* resistance to identify MDR-TB clones that may be missed because they do not have an RRDR mutation (e.g. the Eswatini MDR-TB clone, which has both the *katG S315T* and the non-RRDR *rpoB I491F* mutation).

## 2.2. Initial diagnostic tests for diagnosis of TB without drug-resistance detection

A new class of low-complexity manual NAATs (LC-mNAATs) has now emerged for alternative molecular solutions that have improved accuracy when compared with smear microscopy and very basic infrastructure, power and equipment requirements (e.g. heat block). LC-mNAATs can be performed at the microscopy level and are currently cheaper than other molecular tests. Collectively, these characteristics are useful for testing in constrained settings. However, like smear microscopy, this class of tests does not incorporate rifampicin-resistance detection and therefore requires reflex testing with a complementary solution for drug-resistance determination.

### 2.2.1 Low-Complexity manual NAATs for detection of TB

NEW

#### Diagnostic class description

The features shown in **Table 2.2.1.1** define the class of LC-mNAATs.

**Table 2.2.1.1 Class criteria for LC-mNAATs**

Purpose	Detection of TB
<b>Principle of action</b>	Nucleic acid amplification testing
<b>Complexity</b>	Reagents
	Reagents are enclosed in multiple disposable sealed containers not requiring special storage requirements
Skills	Basic technical skills (e.g. basic pipetting, precision not critical)
Pipetting	Multiple pipetting steps (maximum of 10) from processed sample to result generation
Testing procedure	At least three distinct steps: <ul style="list-style-type: none"> <li>• Specimen treatment step before transferring the specimen into the disposable sealed container</li> <li>• DNA extraction</li> <li>• PCR amplification</li> <li>• Results visualization</li> </ul>
<b>Type of test result reporting</b>	Automated or manual
<b>Setting of use</b>	Basic laboratory (no special infrastructure needed)

DNA: deoxyribonucleic acid; LC-mNAAT: low-complexity manual nucleic acid amplification test; PCR: polymerase chain reaction; TB: tuberculosis.

The only product for which eligible data met the class-based performance criteria for LC-mNAATs is Loopamp MTBC Detection Kit (TB LAMP) (Eiken Chemical, Tokyo, Japan) for pulmonary TB.

Regulatory approval from national regulatory authorities or other relevant bodies is required before implementation of this diagnostic test. Extrapolation to other brand-specific tests cannot be made, and any new in-class technologies or new indications for the technology currently included in the class will need to be evaluated by WHO PQ and WHO/GTB, respectively.

The publication *WHO operational handbook on tuberculosis. Module 3: Diagnosis* describes the tests included in this class.

## Recommendations

- 6. For adults and adolescents with signs or symptoms or who screen positive for pulmonary TB, low-complexity manual NAATs should be used on respiratory samples as initial diagnostic tests for TB rather than smear microscopy or culture.**

(Strong recommendation, high certainty of evidence)

## Remarks

- This recommendation applies to all people living with HIV, with the caveat of low to moderate certainty of evidence. However, wherever available, concurrent testing with an LC-aNAAT and LF-LAM is recommended for people living with HIV. For more details, see Section 2.3.1.
- This recommendation was extrapolated to children for use with respiratory samples (including induced sputum and gastric aspirate) based on the generalization of data from adults and very limited data for children, acknowledging the difficulties of collecting sputum specimens from this population. However, wherever available, concurrent testing with an LC-aNAAT on a respiratory and stool samples is recommended for children. For more details, see Section 2.3.2.
- Data on the use of the test with paediatric stool samples were very limited, and there were no data on the use of nasopharyngeal aspirates. The recommendation was, therefore, not extrapolated to these sample types.
- No recommendation was made on test use for extrapulmonary TB due to insufficient data.
- As LC-mNAATs do not provide rifampicin-resistance results, all positive diagnostic tests for TB require follow-up and referral for DST for, at a minimum, rifampicin.

## Justification and evidence

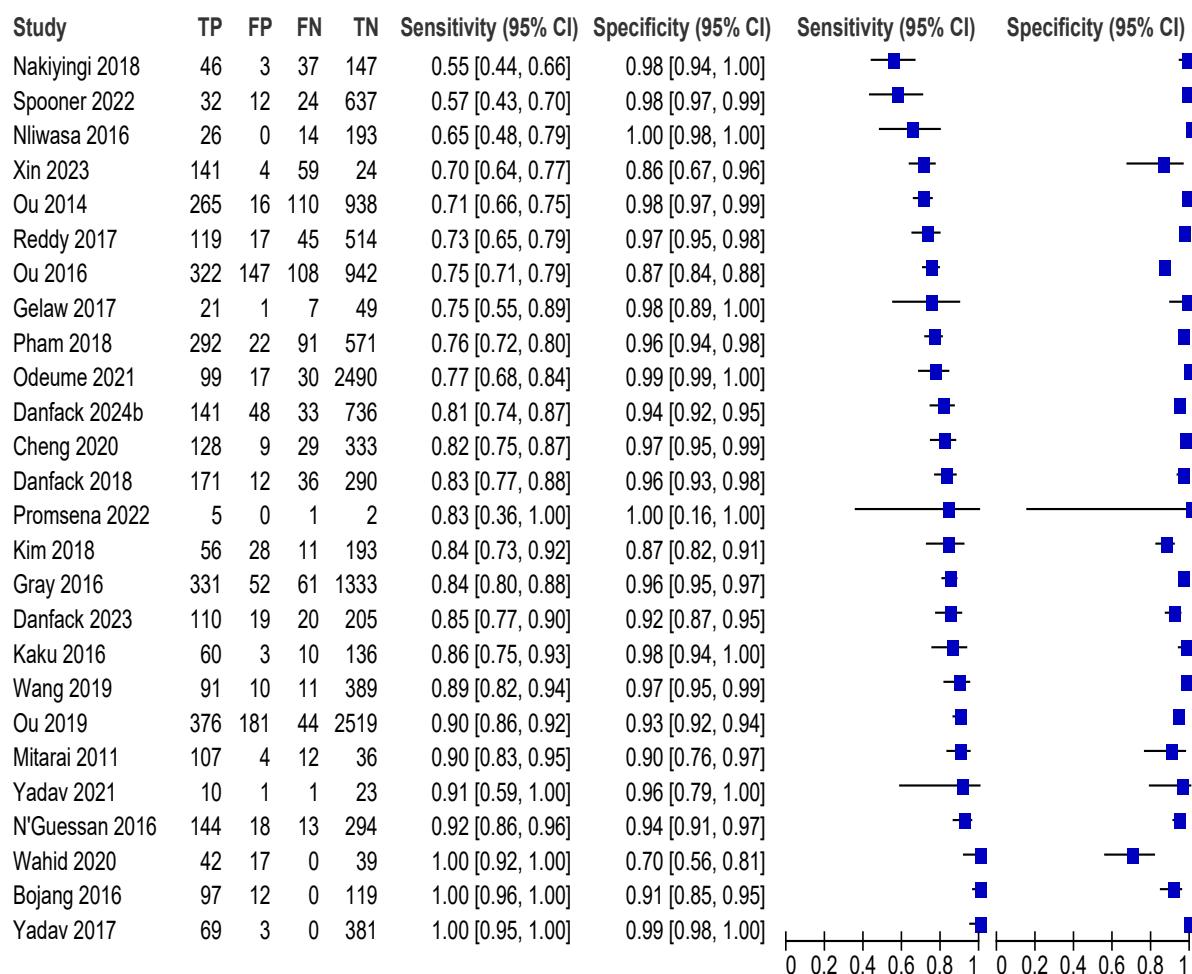
WHO/GTB initiated an update of the previous guidelines and commissioned a systematic review on the use of LC-mNAATs (TB LAMP) for the diagnosis of TB in people with signs and symptoms of TB, or who screened positive for TB.

## Detection of pulmonary TB

**Should LC-mNAATs on respiratory samples be used to diagnose pulmonary TB in adults and adolescents with signs and symptoms or who screened positive for pulmonary TB, against an MRS?**

Twenty-six studies (18 297 participants) assessed diagnostic accuracy using sputum specimens and comparing with an MRS. The sensitivities were between 55% and 100%, and the specificities were between 70% and 100% (Fig. 2.2.1.1). The summary sensitivity was 84.1% (95% CI: 78.3–88.6), and the summary specificity was 96.1% (95% CI: 94.2–97.4). The certainty of evidence for sensitivity and specificity was high.

**Fig. 2.2.1.1 Forest plot of LC-mNAAT sensitivity and specificity for detection of pulmonary TB in respiratory samples and MRS<sup>a</sup>**



CI: confidence interval; FN: false negative; FP: false positive; LC-mNAAT: low-complexity manual nucleic acid amplification test; MRS: microbiological reference standard; TB: tuberculosis; TN: true negative; TP: true positive.

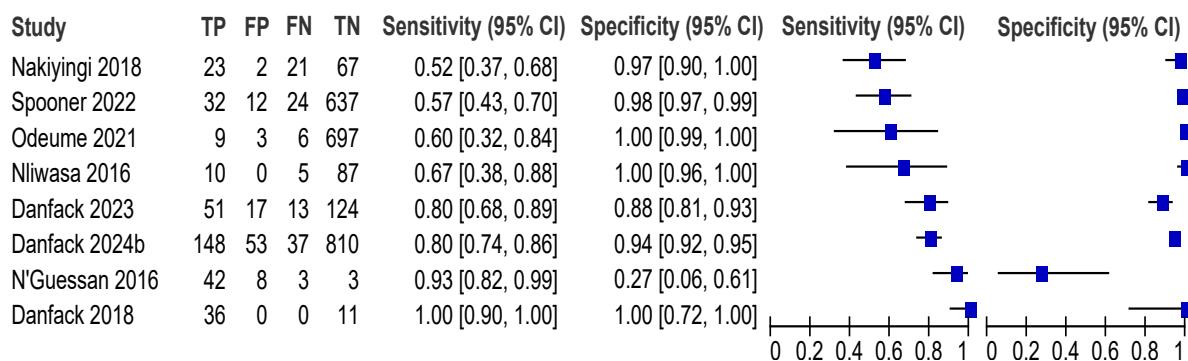
<sup>a</sup>Studies are sorted by increasing sensitivity.

## Detection of TB in people living with HIV

**Should LC-mNAATs on respiratory samples be used to diagnose pulmonary TB in adult and adolescent living with HIV with signs and symptoms of pulmonary TB, against an MRS?**

In the eight studies (2991 participants) included in this meta-analysis, the sensitivities ranged between 52% and 100%, and the specificities between 27% and 100% (**Fig. 2.2.1.2**). The summary sensitivity was 77.1% (95% CI: 60.8–87.9), and the summary specificity was 95.9% (95% CI: 84.9–99.0). The certainty of evidence was low for sensitivity and moderate for specificity.

**Fig. 2.2.1.2 Forest plot of LC-mNAAT sensitivity and specificity for detection of pulmonary TB in respiratory samples from people living with HIV and MRS<sup>a</sup>**



CI: confidence interval; FN: false negative; FP: false positive; HIV: human immunodeficiency virus; LC-mNAAT: low-complexity manual nucleic acid amplification test; MRS: microbiological reference standard; TB: tuberculosis; TN: true negative; TP: true positive.

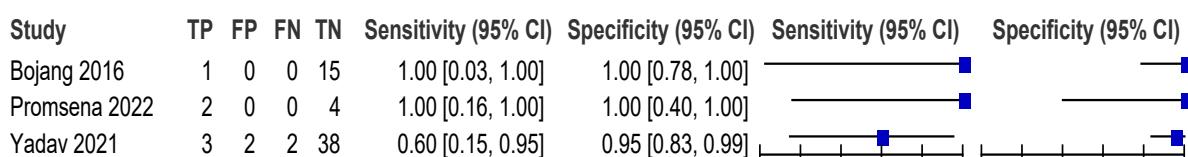
<sup>a</sup>Studies are sorted by increasing sensitivity.

## Detection of TB in children

**Should LC-mNAATs on respiratory samples be used to diagnose pulmonary TB in children with signs and symptoms of pulmonary TB, against an MRS?**

Three studies (62 participants, including eight with pulmonary TB) assessed the accuracy of LC-mNAATs for detecting pulmonary TB using respiratory samples (sputum, BAL and tracheal aspirate) and an MRS (**Fig. 2.2.1.3**). The sensitivities were between 60% and 100%, and the specificities were between 95% and 100%. The certainty of evidence was very low for sensitivity and low for specificity.

**Fig. 2.2.1.3 Forest plot of LC-mNAAT sensitivity and specificity for detection of pulmonary TB in respiratory samples and MRS<sup>a</sup>**



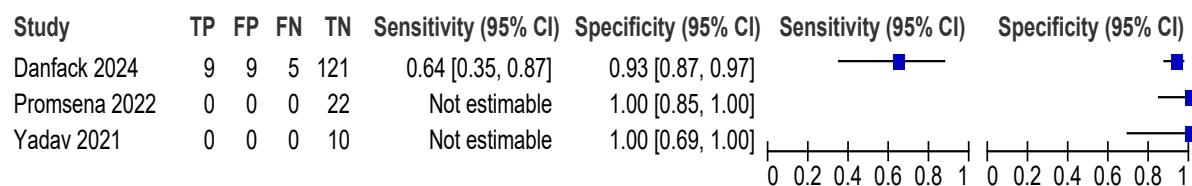
CI: confidence interval; FN: false negative; FP: false positive; LC-mNAAT: low-complexity manual nucleic acid amplification test; MRS: microbiological reference standard; TB: tuberculosis; TN: true negative; TP: true positive.

<sup>a</sup>Studies are sorted by increasing sensitivity.

### **Should LC-mNAATs on gastric aspirate be used to diagnose pulmonary TB in children with signs and symptoms of pulmonary TB, against an MRS?**

Three studies (176 participants, including 14 with pulmonary TB) assessed the accuracy of LC-mNAATs for detecting pulmonary TB using gastric aspirate against a MRS (**Fig. 2.2.1.4**). Sensitivity was not estimable for two studies and was 64% in the third study. The specificities were between 93% and 100%.

**Fig. 2.2.1.4 Forest plot of LC-mNAAT sensitivity and specificity for detection of pulmonary TB in gastric aspirate and MRS<sup>a</sup>**



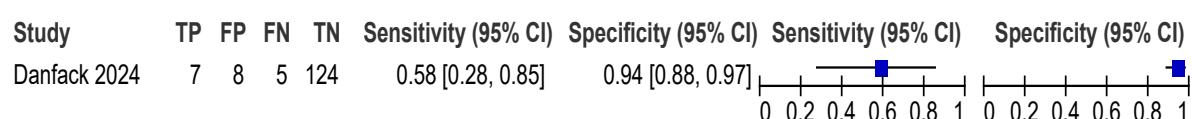
CI: confidence interval; FN: false negative; FP: false positive; LC-mNAAT: low-complexity manual nucleic acid amplification test; MRS: microbiological reference standard; TB: tuberculosis; TN: true negative; TP: true positive.

<sup>a</sup>Studies are sorted by increasing sensitivity.

### **Should LC-mNAATs on nasopharyngeal aspirate be used to diagnose pulmonary TB in children with signs and symptoms of pulmonary TB, against an MRS?**

One study (144 participants including 12 with pulmonary TB) assessed the accuracy of LC-mNAATs for detecting pulmonary TB using nasopharyngeal aspirate against an MRS (**Fig. 2.2.1.5**). The sensitivity was 58% and specificity was 94%. Due to limited data, a recommendation on using LC-mNAATs with nasopharyngeal aspirate for detection of pulmonary TB was not made.

**Fig. 2.2.1.5 Forest plot of LC-mNAAT sensitivity and specificity for detection of pulmonary TB in nasopharyngeal aspirate and MRS<sup>a</sup>**



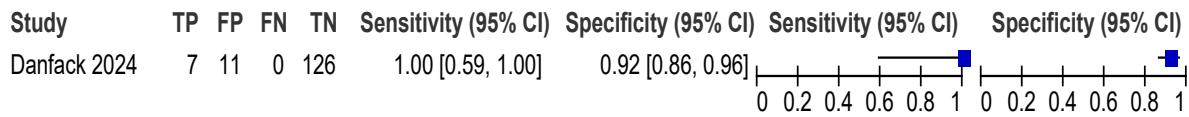
CI: confidence interval; FN: false negative; FP: false positive; LC-mNAAT: low-complexity manual nucleic acid amplification test; MRS: microbiological reference standard; TB: tuberculosis; TN: true negative; TP: true positive.

<sup>a</sup>Studies are sorted by increasing sensitivity.

### **Should LC-mNAATs on stool be used to diagnose pulmonary TB in children with signs and symptoms of pulmonary TB, against an MRS?**

One study (144 participants, including seven with pulmonary TB) assessed the accuracy of LC-mNAATs for detecting pulmonary TB using stool against a MRS (**Fig. 2.2.1.6**). The sensitivity was 100% and specificity was 92%. The certainty of evidence was very low for sensitivity and moderate for specificity. Due to limited data, a recommendation on using LC-mNAATs with stool for detection of pulmonary TB was not made.

**Fig. 2.2.1.6 Forest plot of LC-mNAAT sensitivity and specificity for detection of pulmonary TB in stool and MRS**



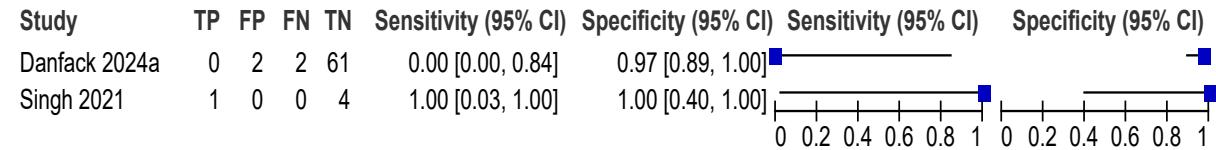
CI: confidence interval; FN: false negative; FP: false positive; LC-mNAAT: low-complexity manual nucleic acid amplification test; MRS: microbiological reference standard; TB: tuberculosis; TN: true negative; TP: true positive.

## Detection of TB meningitis

### *Should LC-mNAATs on CSF be used to diagnose TB meningitis in adults and adolescents with signs and symptoms of TB meningitis, against an MRS?*

Two studies (70 participants, including three with TB meningitis) assessed the accuracy of LC-mNAATs for detecting TB meningitis using CSF and an MRS (Fig. 2.2.1.7). Estimated sensitivity and specificity were both 100% in one study, and 0% and 97%, respectively, in the other. The certainty of evidence was very low for sensitivity and low for specificity. Due to limited data, a recommendation on using LC-mNAATs with CSF for detection of TB meningitis was not made.

**Fig. 2.2.1.7 Forest plot of LC-mNAAT sensitivity and specificity for detection of TB meningitis in CSF and MRS**



CI: confidence interval; CSF: cerebrospinal fluid; FN: false negative; FP: false positive; LC-mNAAT: low-complexity manual nucleic acid amplification test; MRS: microbiological reference standard; TB: tuberculosis; TN: true negative; TP: true positive.

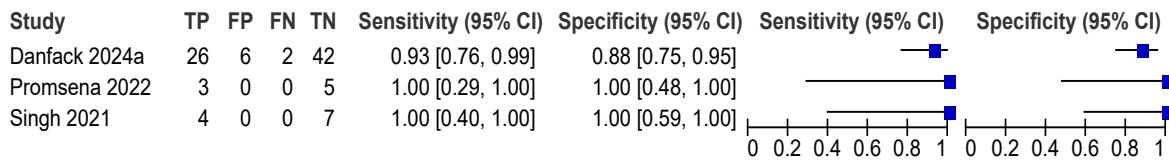
## Detection of extrapulmonary TB

### *Should LC-mNAATs on lymph node tissue be used to diagnose lymph node TB in adults and adolescents with signs and symptoms of lymph node TB, against an MRS?*

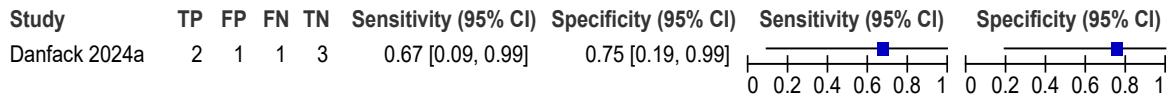
Three studies (95 participants, including 35 people with TB) assessed the accuracy of LC-mNAATs for detecting lymph node TB using lymph node tissue from biopsy and an MRS (Fig. 2.2.1.8). The estimated sensitivities were between 93% and 100%, and specificities were between 88% and 100%. The summary sensitivity was 94.3% (95% CI: 79.8–98.6), and the summary specificity was 90.0% (95% CI: 79.5–95.4). The certainty of evidence was low for both sensitivity and specificity. Due to limited data, a recommendation on using LC-mNAATs with lymph node tissue for the detection of lymph node TB was not made.

**Fig. 2.2.1.8 Forest plot of LC-mNAAT sensitivity and specificity for detection of lymph node TB in lymph node tissue and MRS**

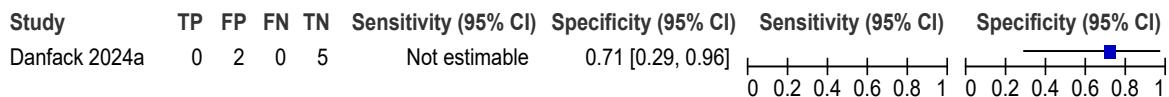
TB-LAMP for lymph node TB in lymph node biopsy



TB-LAMP for lymph node in lymph node aspirate



TB-LAMP for lymph node TB in lymph node pus



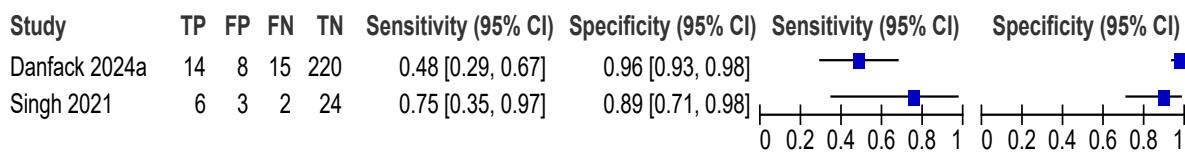
CI: confidence interval; FN: false negative; FP: false positive; LC-mNAAT: low-complexity manual nucleic acid amplification test; LN: lymph node; MRS: microbiological reference standard; TB: tuberculosis; TN: true negative; TP: true positive.

**Should LC-mNAATs on pleural fluid be used to diagnose pleural TB in adults and adolescents with signs and symptoms of pleural TB, against an MRS?**

Two studies (292 participants, including 37 people with TB) assessed the accuracy of LC-mNAATs for detecting pleural TB using pleural fluid and an MRS (**Fig. 2.2.1.9**). Estimated sensitivities were 48% and 75%, and estimated specificities were 89% and 96%. Due to limited data, a recommendation on using LC-mNAATs with pleural fluid for detection of pleural TB was not made.

**Fig. 2.2.1.9 Forest plot of LC-mNAAT sensitivity and specificity for detection of pleural TB in pleural fluid and MRS**

TB-LAMP for pleural TB in pleural fluid

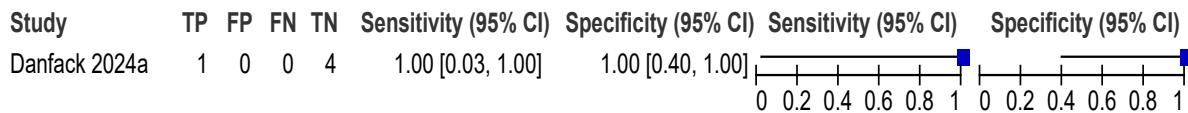


CI: confidence interval; FN: false negative; FP: false positive; LC-mNAAT: low-complexity manual nucleic acid amplification test; MRS: microbiological reference standard; TB: tuberculosis; TN: true negative; TP: true positive.

**Should LC-mNAATs on synovial fluid be used to diagnose bone or joint TB in adults and adolescents with signs and symptoms of bone or joint TB, against an MRS?**

One study (five participants, including one case) assessed the accuracy of LC-mNAATs for detecting bone or joint TB using synovial fluid and an MRS (**Fig. 2.2.1.10**). Estimated sensitivity and specificity were both 100%. Due to limited data, a recommendation on using LC-mNAATs with synovial fluid for detection of bone or joint TB was not made.

**Fig. 2.2.1.10 Forest plot of LC-mNAAT sensitivity and specificity for detection of bone or joint TB in synovial fluid and MRS**

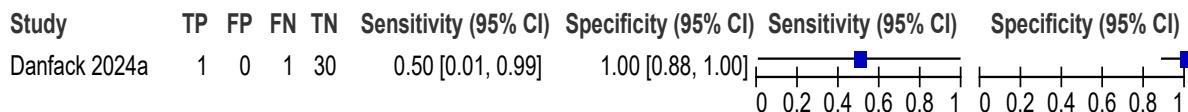


CI: confidence interval; FN: false negative; FP: false positive; LC-mNAAT: low-complexity manual nucleic acid amplification test; MRS: microbiological reference standard; TB: tuberculosis; TN: true negative; TP: true positive.

### **Should LC-mNAATs on urine be used to diagnose genitourinary TB in adults and adolescents with signs and symptoms of genitourinary TB, against an MRS?**

One study (32 participants, including two people with TB) assessed the accuracy of LC-mNAATs for detecting genitourinary TB using urine and an MRS (**Fig. 2.2.1.11**). Estimated sensitivity and specificity were 50% and 100%, respectively. Due to limited data, a recommendation on using LC-mNAATs with urine for detection of genitourinary TB was not made.

**Fig. 2.2.1.11 Forest plot of LC-mNAAT sensitivity and specificity for detection of genitourinary TB in urine and MRS**



CI: confidence interval; FN: false negative; FP: false positive; LC-mNAAT: low-complexity manual nucleic acid amplification test; MRS: microbiological reference standard; TB: tuberculosis; TN: true negative; TP: true positive.

### **Cost-effectiveness analysis**

This section deals with the following additional question:

#### **What are the comparative costs, affordability and cost-effectiveness of implementation of LC-mNAATs?**

A systematic review commissioned by WHO aimed to identify, evaluate and summarize the findings of available economic evidence on LC-mNAATs, among other technologies. The systematic review provided an in-depth analysis of the financial implications and cost-effectiveness of implementing TB LAMP in diverse settings. Through a range of economic analyses, including cost-utility, cost-benefit and cost-affordability assessments, this study contributes valuable insights into the potential role of TB LAMP in TB diagnostics.

After removing 638 duplicate studies from those identified in the original search, 1990 unique studies remained. Of these, six studies were included in the final systematic review. Studies that did not involve people with TB, used TB LAMP as a diagnostic intervention or did not contain cost data were excluded. Of the six included studies, one performed a cost-utility analysis, and two performed a cost-affordability analysis. The three other studies estimated the cost of TB LAMP.

All included studies were conducted in LMIC. Specifically, two studies were conducted in Thailand, one in Malawi, one in both Malawi and Viet Nam, and one each in India and Cameroon. The studies were conducted between 2014 and 2021 across various settings, such as outpatient departments at health centres, peripheral laboratories, a laboratory for the development of modified TB LAMP, and prisons and villages involving inmates and refugees. One study used sputum samples from people known to have TB, and another used fine needle aspiration of lymph node samples from HIV-positive patients with TB lymphadenitis. The other four studies used sputum samples from people with presumptive TB.

According to the three costing studies, the cost per test ranged from US\$ 1 to US\$ 19 (all values in 2024 US dollars). All these studies used in-house techniques and were not using the commercially available TB LAMP test. The reviewed studies found that factors such as batching scenarios and larger test capacity influence the per-test cost, with the cost per test decreasing in specific scenarios. Testing volumes, location and operational parameters can also affect the cost. Notably, the cost–utility analysis positioned TB LAMP favourably in terms of cost–effectiveness compared with other diagnostic algorithms.

The findings of the cost–utility analysis suggested that TB LAMP, followed by DST, is not only effective but also cost-saving when compared with the standard diagnostic approach (i.e. smear, culture and DST). These results provide valuable insights for health care practitioners and policy-makers in terms of optimizing TB diagnostic strategies while considering cost–effectiveness.

One cost–affordability analysis, conducted in peripheral laboratories in Malawi and Viet Nam, highlighted the economic considerations of implementing TB LAMP and Xpert MTB/RIF. The study showed that per-test costs for TB LAMP were lower than those for Xpert MTB/RIF. However, the potential financial burden of widespread implementation underscored the importance of cost–effectiveness assessments in shaping diagnostic strategies. For more details see **Web Annex B.9**.

The reviewed studies had some limitations, such as variations in settings, sample sources and comparators, which may influence the generalizability of findings. Additionally, the cost–affordability analysis underscores the financial implications of nationwide implementation, suggesting the need for careful budgetary planning and allocation. Furthermore, the Global Drug Facility’s recent decrease in the price of TB LAMP (new price, US\$ 6) may have an impact on the results of economic evaluations, potentially enhancing the cost–effectiveness and affordability of implementing TB LAMP in diverse settings.

These collective findings suggest that TB LAMP holds promise as a cost-effective and efficient diagnostic tool for TB when integrated into broader diagnostic algorithms, particularly in resource-constrained settings.

More details on the economic evaluation of LC-mNAATs are available in **Web Annex B.9**.

## User perspective

*This section deals with the following question:*

## ***Are there implications for user preferences and values, acceptability, feasibility, patient equity and human rights from the implementation of LC-mNAATs?***

The findings from the studies that focused on LC-aNAATs are largely applicable to LC-mNAATs, with the caveat of slightly lower sensitivity and the lack of ability to detect resistance to rifampicin.

A systematic review of the qualitative evidence of LC-NAATs (Web Annex B.10) did not identify any studies focused on LC-mNAATs (acknowledging that a few studies did not specify the type of NAAT they were focusing on).

However, selected findings from the interview study, did focus specifically on TB-LAMP:

- In 2018, Nigeria adopted the use of TB LAMP (along with GeneXpert and Truenat). At the time of the interview, there were 199 TB LAMP machines in Nigeria. These are placed both in sites where GeneXpert is available, to decrease workload, and in peripheral laboratories where the infrastructure is insufficient to accommodate GeneXpert. Positive results from TB LAMP are sent to the nearest site with a GeneXpert or Truenat machine for DST.
- The Philippines National TB Programme (NTP) guidelines advise the use of TB LAMP as an alternative primary diagnostic test in settings where access to GeneXpert is limited and that currently rely on sputum transport riders (STRiders). TB LAMP was piloted in 2019 (April to September) and 2020 (October to February 2021) in a rural health unit, polyclinic and private hospital, and for TB mass screening in a rural health unit. The pilot implementation only tested sputum with TB LAMP and did not test for TB in MDR risk groups, children or people living with HIV. According to a laboratory manager, there are about six or seven TB LAMP machines in the Philippines. These are not currently in use but could be if there was support for buying reagents.

According to Nigeria's TB LAMP guidelines, the following criteria should be used to prioritize sites for TB LAMP testing:

- facilities with high workload;
- facilities with or without an existing molecular platform;
- laboratories with adequate space and infrastructure;
- availability of qualified medical laboratory personnel;
- an adequate number of medical laboratory personnel; and
- a storage facility (e.g. refrigerator) for laboratory and administrative supply.

## ***User preferences and values***

An interview study on TB LAMP involving sites in Nigeria and the Philippines found the following views of laboratory personnel and programme officers:

- TB LAMP is making laboratory work easier over time through familiarity and because it clears the workbench;
- compared to SSM, TB LAMP is easier to use; and
- in direct comparison with Xpert Ultra, TB LAMP is more hands-on and requires more user steps and time for preparing and processing specimens.

## **Acceptability**

Acceptability of the test seems to be slightly reduced because TB LAMP cannot test for rifampicin resistance and has no multiplexing opportunities.

## **Feasibility**

Summarized findings from the interview study on TB LAMP are as follows. TB LAMP improves access to TB diagnosis for people who would otherwise have been missed, because it can run in laboratories with limited infrastructure, has high throughput, is more accurate than SSM and reduces workload at GeneXpert sites. It allows decentralization of testing and therefore has the potential to reduce catastrophic cost to patients. However, TB LAMP adoption decisions are also driven by donors and investment considerations.

Overall, TB LAMP allows staff to carry out more tests, and faster. Its high throughput contributes to acceptability and utilization. Laboratory staff in Nigeria are given incentives for the number of tests they carry out, making use of TB LAMP even more attractive. These incentives also support swift action when maintenance or repair of the devices is needed.

Programmatic feasibility seems to be less of a concern than with GeneXpert. Compared with implementing GeneXpert, programme officers find TB LAMP more feasible to implement due to its lower requirements for infrastructure, skills level and maintenance. As with all LC-mNAATs, staffing and reagent supply issues challenge its use. TB LAMP's impact on the overall turnaround time for DR-TB diagnosis, MDR-TB treatment initiation and loss to follow-up at sites without Xpert Ultra testing depends on the efficiency and robustness of the sample transport or referral system.

More details on the qualitative evaluation of LC-mNAATs are available in **Web Annex B.10**.

## **Implementation considerations**

- Diagnostic products in the low-complexity classes of tests should be prequalified by WHO or approved by another regulator before clinical use.
- Diagnostic test manufacturers, laboratory and programme managers, and policy-makers should be educated on the WHO PQ process for TB IVDs.
- Ensuring sufficient volume and specimen quality is important to obtain accurate results.
- Safe waste disposal of used test consumables needs to be planned in advance to minimize environmental risk.

## **Monitoring and evaluation**

- Track errors and invalid test result rates for currently recommended products and new products to be introduced in this class.
- Monitor the proportion of people with bacteriologically confirmed TB without rifampicin-resistance reflex testing or access to further DST over time.

## **Research priorities**

- Evaluate the performance of this class using alternative sample types for paediatric TB (e.g. gastric and nasopharyngeal aspirates, stool, induced sputum, BAL) and extrapulmonary TB.
- Evaluate the impact of LC-mNAAT testing on patient-important outcomes (cure, mortality, time to diagnosis and time to start of treatment).
- Evaluate the effect of sample concentration approaches (e.g. centrifugation) and volume on the performance of LC-mNAAT technologies, including in extrapulmonary TB sample types.
- Evaluate the impact on incremental accuracy and case detection of alternative sample types that are easier to collect.
- Develop a test in this class that can detect TB drug resistance.
- Review the field performance of the current technologies used in programmatic settings.
- Conduct operational research to ensure that tests are used optimally in intended settings.
- Evaluate the different classes of tests, including LC-mNAATs, to determine which classes or testing strategies yield superior diagnostic accuracy, cost-effectiveness and impact on equity and acceptability.
- Identify an improved reference standard that accurately defines TB disease in children, paucibacillary specimens and people who cannot produce sputum, because the sensitivity of all available diagnostics is suboptimal.
- Assess the budget impact and cost-effectiveness of LC-mNAATs compared with other classes of tests.
- Develop and apply standardized methods for assessment of costs and cost-effectiveness, to improve comparability and scope of economic evidence.

## **2.3. Concurrent use of initial diagnostic tests for diagnosis of TB in People living with HIV and children**

There are significant burdens of tuberculosis in people living with HIV and children, particularly in low- and middle-income countries (LMICs). Persons living with HIV are at substantially higher risk of developing TB disease due to immunosuppression, with TB being a leading cause of death among this population. Children, especially those under five, are at high risk of progression from TB infection to TB disease and rapid disease progression and often present with broad respiratory symptoms, which complicate diagnosis and increase morbidity and mortality if not promptly treated. Addressing TB in these at-risk populations requires concerted efforts that account for their unique clinical presentations and diagnostic needs.

Diagnosing TB in persons living with HIV and children is challenging, particularly because of unspecific clinical presentations and often low and varying numbers of mycobacteria in their samples that lower the sensitivity of existing diagnostic tests. Furthermore, children and people living with HIV with advanced immunosuppression may be unable to provide sputum samples and can have disseminated TB, which is challenging to confirm with laboratory methods. To, in part address this challenge, WHO recommends the use of stool to aid in laboratory confirmation of TB in children, and the use of urine to aid in the confirmation of TB in persons living with HIV. However, even highly sensitive tests for TB diagnosis, such as LC-aNAATs, can miss TB in these

groups. There is therefore a need for improved diagnostic approaches to accurately confirm TB in these higher-risk populations to ensure early and effective treatment.

Tests based on the detection of the lipoarabinomannan (LAM) antigen are biomarker-based tests that may be used on urine at the point of care for TB detection. The currently available urinary LAM assay is rapid (<1 hour to result) but has suboptimal sensitivity and is therefore not suitable as general diagnostic tests for TB. However, unlike traditional diagnostic methods, it demonstrates improved sensitivity for the diagnosis of TB among individuals coinfected with HIV. The estimated sensitivity is even greater in patients with low CD4 cell counts. The lateral flow urine LAM assay (LF-LAM) strip-test – the Abbott/Alere Determine TB LAM Ag (USA), hereafter referred to as LF-LAM – is currently the only commercially available urinary LAM test.

Using concurrent<sup>10</sup> testing of different sample types offers a promising approach that considers the diagnostic testing barriers for HIV-positive adults and adolescents, HIV-positive children, and children without HIV or for whom HIV status is unknown. For instance, testing of sputum and stool during the same visit, when feasible, using LC-aNAATs increases the likelihood of detecting TB in children who may have scant bacilli in respiratory samples alone. Similarly, for persons living with HIV, testing of sputum and urine during the same visit, when sputum can be produced, using LC-aNAATs and LF-LAM increases the likelihood of detecting TB with a rapid point-of-care result while also ensuring detection of rifampicin resistance. This concurrent testing approach builds on the prior recommendation for LF-LAM test use among eligible persons living with HIV, which underscored the need for mWRD testing of available respiratory samples to support universal patient access to resistance testing services.

Implementing a diagnostic approach that includes concurrent sample testing could simplify diagnostic processes, shorten the patient journey, and improve TB detection rates and health outcomes for these at-risk populations. At the same time, the inability to collect one or more specimens at the same initial visit, or lack of one of the two test types should not delay testing of available specimens and tests, but instead trigger specimen collection and testing as soon as possible.

The following three scenarios of recommendations:

- LC-aNAAT on respiratory samples and urine LF-LAM among adults and adolescents living with HIV
- LC-aNAAT on respiratory samples and stool in children
- LC-aNAAT on respiratory samples and stool, as well as urinary LF-LAM among children with HIV

These recommendations should be implemented within recommendations for the comprehensive diagnosis and management of persons living with HIV and children.

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<sup>10</sup> Concurrent use of tests: samples are taken simultaneously (when possible), and testing is conducted for both tests. A positive result on either test is a positive result for the combination.

## 2.3.1 Concurrent use of tests in people living with HIV

NEW

### Recommendations

7. For adults and adolescents with HIV who have signs or symptoms of TB, screen positive for TB, are seriously ill or have advanced HIV disease, concurrent testing using low-complexity automated NAATs on respiratory samples and LF-LAM on urine should be used as the initial diagnostic strategy for diagnosing TB rather than low-complexity automated NAATs on respiratory samples alone.

(Strong recommendation, low certainty of evidence)

### Remarks

- Serious illness in people living with HIV is defined based on any of the following symptoms: respiratory rate  $\geq 30$  breaths per minute, temperature  $\geq 39$  °C, heart rate  $\geq 120$  beats per minute or unable to walk unaided.
- Advanced HIV disease is defined in people living with HIV who have a CD4 cell count of  $<200$  cells/mm<sup>3</sup> or presenting with a WHO Stage 3/4 AIDS-defining illness.
- This concurrent testing recommendation supersedes prior guidance on using LF-LAM for people living with HIV and the use of a single molecular test for diagnosis of TB in this group.
- This recommendation is strong despite the low certainty of evidence because the findings indicate large desirable effects (i.e. rapid and accurate diagnosis of TB in a highly vulnerable population – people living with HIV – in whom diagnosing TB is often challenging) over small undesirable effects (i.e. negative consequences of this testing strategy).
- The LC-aNAAT products for which eligible data met the class-based performance criteria for this recommendation were Xpert MTB/RIF Ultra and Truenat MTB Plus. Data for performance of Truenat MTB Plus and MTB-RIF Dx were only available for testing among persons living with HIV without concurrent LF-LAM testing.

### Justification and evidence

In a 2016 Cochrane systematic review of the diagnostic accuracy of LF-LAM, sensitivity increased by 13% when combining LF-LAM and sputum Xpert MTB/RIF, compared with sputum Xpert alone, while the specificity decreased by 4%. However, results were based on only a few studies, and analyses were restricted to participants able to produce sputum.

### Incremental diagnostic accuracy

In 2023, WHO commissioned a series of systematic reviews to evaluate the incremental diagnostic accuracy<sup>11</sup> of concurrent use of either two different tests – LC-aNAAT on respiratory samples and LF-LAM on urine among people living with HIV – or the same test on two samples (LC-aNAAT on respiratory and stool samples) in children, or alternatively LC-aNAAT on respiratory and stool samples along with LF-LAM on urine among children with HIV.

<sup>11</sup> Incremental change in diagnostic accuracy with concurrent testing compared with individual sample testing.

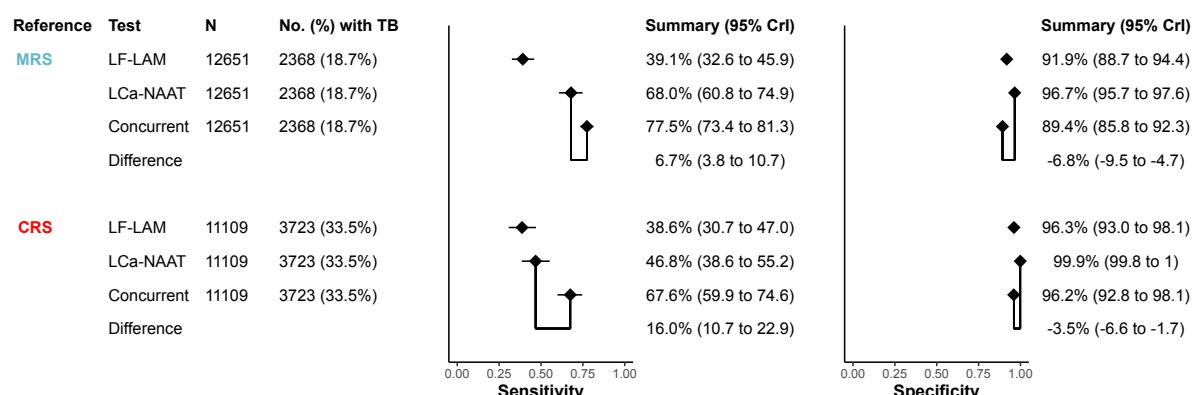
**What is the incremental diagnostic accuracy of concurrent use of respiratory LC-aNAATs and LF-LAM on urine for diagnosis of TB disease in adults and adolescents with HIV who present with presumptive TB, compared with any of the tests alone?**

Of 31 studies, 27 evaluated diagnostic accuracy against an MRS, and 23 against a CRS, with 20 studies evaluating accuracy against both reference standards.

A total of 27 studies (12 651 participants, including 2368 [18.7%] with TB) compared the accuracy of the concurrent use of LC-aNAAT on a respiratory sample and LF-LAM versus each of the tests alone, using an MRS. The pooled differences in sensitivity and specificity between concurrent testing versus LC-aNAAT alone were 6.7% (95% credible interval [Crl]: 3.8 to 10.7; 95% prediction interval [PI]: 0.6 to 45.9) and -6.8% (95% Crl: -9.5 to -4.7; 95% PI: -32.8 to -6.8), respectively (**Fig. 2.3.1.1**). Certainty of evidence was low for both sensitivity and specificity.

A total of 23 studies (11 109 participants, including 3723 [33.5%] with TB) compared the accuracy of the concurrent use of LC-aNAAT and LF-LAM versus LC-aNAAT alone, using a CRS. The pooled differences in sensitivity and specificity between concurrent testing versus LC-aNAAT alone were 16.0% (95% Crl: 10.7 to 22.9; 95% PI: 2.3 to 60.3) and -3.5% (95% Crl: -6.6 to -1.7; 95% PI: -47.2 to -0.1), respectively (**Fig. 2.3.1.1**). Certainty of evidence was low for sensitivity and very low for specificity.

**Fig. 2.3.1.1. Forest plot of pooled differences in sensitivity and specificity (all studies combined) by index test: LF-LAM, LC-aNAAT and their concurrent use<sup>a</sup>**



Crl: credible interval; CRS: composite reference standard; LC-aNAAT: low-complexity automated nucleic acid amplification test; LF-LAM: lateral flow urine lipoarabinomannan assay; MRS: microbiological reference standard; TB: tuberculosis.

<sup>a</sup> The diamonds represent the pooled sensitivity and specificity, and the black horizontal line its 95% Crl. The pooled difference in sensitivity and specificity between concurrent testing and LC-aNAAT alone is indicated by a line connecting two diamonds. This pooled difference may not correspond to the difference between the pooled single test accuracy estimates (see **Web Annex B.8**).

In addition to diagnostic accuracy, clinical outcome data on mortality, time to diagnosis and time to treatment were assessed. Data on cure and loss to follow-up were not assessed due to a lack of data. The data from three studies indicated that an intervention including LC-aNAAT on respiratory samples and LF-LAM on urine in adult inpatients with HIV was associated with slightly reduced 8-week mortality (risk ratio: 0.93; 95% CI: 0.74–1.17). The adjusted hazard ratio of time to diagnosis in adult inpatients with HIV was 1.55 (95% CI: 1.29–1.87). This means

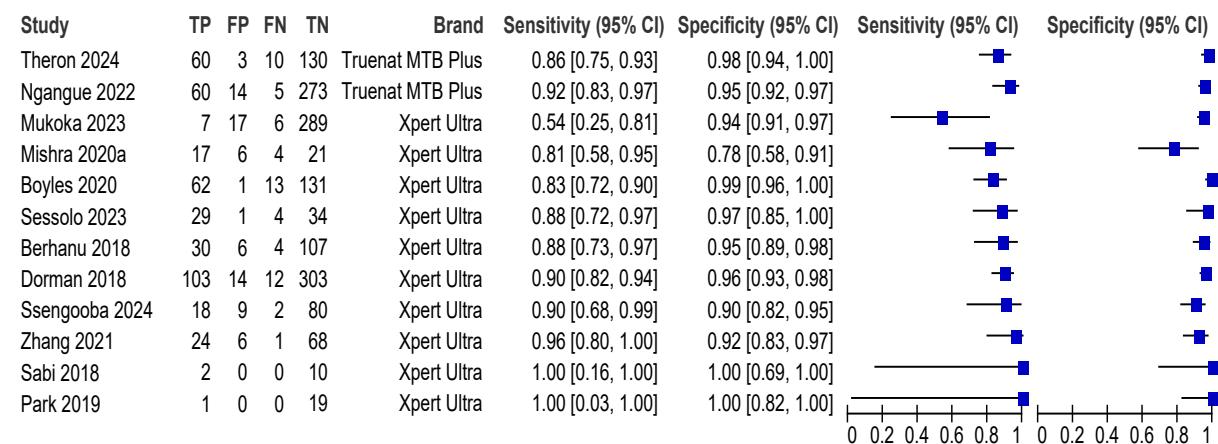
that participants in the intervention groups (i.e. those undergoing concurrent LC-aNAAT on respiratory samples and LF-LAM on urine) were 1.55 times more likely to be diagnosed with TB within fewer days (relative reduction of 2 days and 1 day to same-day) than those in the control group. The pooled risk ratio of adult inpatients with HIV diagnosed with TB was 1.56 (95% CI: 1.29–1.88), indicating that the intervention group had 1.56 times the risk of being diagnosed with TB (either microbiologically confirmed or clinically diagnosed) compared with the standard of care, which included LC-aNAAT on sputum alone. The pooled risk ratio of adult inpatients with HIV with a bacteriologically confirmed TB diagnosis was 3.06 (95% CI: 1.82–5.16), indicating that the intervention group had three times the risk of being microbiologically confirmed with TB compared with the standard of care. Finally, the pooled risk ratio of adult inpatients with HIV treated for TB was 1.47 (95% CI: 1.25–1.73), indicating that the intervention group had 1.47 times the likelihood of being treated for TB, compared with the standard of care.

### ***Single sample testing in people living with HIV compared with the MRS***

#### ***Should LC-aNAATs on respiratory samples be used to diagnose pulmonary TB in PLHIV (adults and adolescents) with signs and symptoms or screened positive for pulmonary TB, against a microbiological reference standard?***

Twelve studies (2016 participants) evaluated sputum specimens from people living with HIV (**Fig. 2.3.1.2**). The sensitivities ranged between 54% and 100% and the specificities between 78% and 100%. The summary sensitivity (95% CI) was 87.4% (83.8 to 90.3) and the summary specificity was 95.2% (92.7 to 96.9). The certainty of evidence for both sensitivity and specificity were graded as "High".

**Fig. 2.3.1.2 Forest plot of LC-aNAAT sensitivity and specificity for detection of pulmonary TB in PLHIV using a microbiological reference standard**



Studies are sorted on the plot by assay and sensitivity (low to high). FN: false negative; FP: false positive; TN: true negative; TP: true positive.

### ***Cost-effectiveness analysis***

To date, evidence of cost-effectiveness for concurrent testing is limited. Several studies have assessed Xpert MTB/RIF with LF-LAM for diagnosing TB among people living with HIV. These studies have shown that concurrent testing is likely to increase the life expectancy of people living with HIV and be cost effective compared with using Xpert MTB/RIF in sputum samples

alone. Fekuda et al. evaluated the cost-effectiveness of concurrently using Xpert Ultra and LF-LAM among people living with HIV and concluded that concurrent testing is the preferred cost-effective strategy. Previous cost-effectiveness analyses primarily focused on Xpert MTB/RIF or Xpert Ultra, leaving a gap in evidence regarding the other technologies that may meet the LC-aNAAT class criteria. For details of particular studies see **Web Annex B.9**.

In preparation for the GDG meeting in May 2024, WHO commissioned a study to assess the cost-effectiveness of using LC-aNAATs (including Xpert Ultra, Truenat and other novel LC-aNAATs in the development pipeline) for the detection of TB when used concurrently among people living with HIV and children, including children with HIV, across two different country settings (Malawi and the Philippines). An objective of the study was to assess the cost-effectiveness of concurrent use of LC-aNAAT on respiratory samples and LF-LAM on urine for TB diagnosis and rifampicin-resistance detection among adult people living with HIV with presumptive TB, compared with a single LC-aNAAT on respiratory samples alone.

In the hypothetical model, a cohort of people living with HIV with signs and symptoms of TB progressed through a decision analytical framework. In the intervention arm, TB diagnosis involved the concurrent use of LC-aNAAT on respiratory samples and LF-LAM on urine, whereas the comparator arm exclusively used LC-aNAAT on respiratory specimens. The probability of being able to provide a respiratory sample was considered, and testing was carried out, either on both respiratory and urine samples concurrently or solely on urine. In both intervention and comparator arms, participants not diagnosed through the diagnostic strategy had the opportunity for clinical diagnosis. People with bacteriologically confirmed TB underwent DST for rifampicin and began either drug-susceptible TB or DR-TB treatment, depending on the DST result. All individuals were followed over time, including those with false negative or false positive diagnostic results, to account for unnecessary treatment or additional mortality due to missed diagnoses.

The cost-effectiveness results of concurrent use of LC-aNAAT with LF-LAM among people living with HIV, when used in the emblematic settings of Malawi and the Philippines, are shown in Table 2.3.1.1 In Malawi, the average cost of implementing an LC-aNAAT on a respiratory sample was US\$ 276, with a corresponding average DALY of 2.44. When used concurrently with LF-LAM, the average cost rose to US\$ 298, while the average DALY decreased to 1.93. The resulting incremental cost per DALY averted was US\$ 42, with a 95% uncertainty range (UR) of US\$ 18 to US\$ 345. Similarly, in the Philippines, LC-aNAAT on a respiratory sample had an average cost of US\$ 220, with an average DALY of 2.78, whereas concurrent use with LF-LAM incurred an average cost of US\$ 238 and an average DALY of 2.13. The incremental cost per DALY averted was US\$ 28 (95% UR: 12–249).

**Table 2.3.1.1 Cost-effectiveness analysis of concurrent use of LC-aNAAT and LF-LAM among people living with HIV in Malawi and the Philippines**

Country	Diagnostic strategy	Cost, US\$	Effectiveness, DALYs	ICER (95% UR), US\$
Malawi	LC-aNAAT on respiratory sample	276	2.44	Ref
	LC-aNAAT on respiratory sample and LF-LAM	298	1.93	42 (18–345)
Philippines	LC-aNAAT on respiratory sample	220	2.78	Ref
	LC-aNAAT on respiratory sample and LF-LAM	238	2.13	28 (12–249)

DALY: disability-adjusted life year; HIV: human immunodeficiency virus; ICER: incremental cost-effectiveness ratio; LC-aNAAT: low-complexity automated nucleic acid amplification test; LF-LAM: lateral flow urine lipoarabinomannan assay; UR: uncertainty range.

More information on the cost-effectiveness analysis of concurrent use of tests in people living with HIV is available in **Web Annex B.9**.

## User perspective

*This section deals with the following question:*

***Are there implications for user preferences and values, equity, acceptability, feasibility and human rights from the implementation of a concurrent testing approach (LC-aNAATs + LF-LAM)?***

The GDG assessed whether concurrent testing of multiple samples would increase the diagnostic accuracy (i.e. the benefit to patients or the programme in terms of finding more people with TB). Three PICO questions concerned the different concurrent sample combinations for specific groups facing challenges from reliance on respiratory samples alone (children and people living with HIV). One question focused on the concurrent use of LC-aNAAT on a respiratory sample and LF-LAM on urine for the diagnosis of TB in people living with HIV.

### ***User preferences and values***

As important outcomes of the diagnostic test, people in high TB burden settings value:

- getting an accurate diagnosis and reaching diagnostic closure (finally knowing “what is wrong with me”);
- avoiding diagnostic delays, as they exacerbate existing financial hardships and emotional and physical suffering and make people feel guilty for infecting others (especially children);
- having accessible facilities; and
- reducing diagnosis-associated costs (e.g. travel, missing work).

More details on patient-important outcomes are available in **Web Annex B.10**.

## **Equity**

Concurrent specimen testing was not practiced in the interview study countries. However, it was believed to improve access to care by minimizing repeat visits and loss to follow-up. According to the interview study respondents, using non-sputum specimens has the potential to improve access to care, especially with a test that can be performed at all levels of the health care system. Challenges with producing a sufficient quality and quantity of sputum are well documented and can lead to repeat testing or false results.

## **Acceptability**

Based on the results of the interview study, LF-LAM is being used inconsistently for people living with HIV and only for very ill patients who cannot produce sputum. Our results are in accordance with published literature on LF-LAM.

Prior research on user perspectives on LF-LAM showed that it is generally described as acceptable by key stakeholders, due to its fast turnaround time, ease of use (lack of technical expertise required), low or no maintenance and equipment required, and urine being more accessible and less stigmatized than sputum. LF-LAM is deemed particularly acceptable when used in combination with other tests and clinical considerations. As the sensitivity of LF-LAM is especially low where the pretest probability is low, participants commented that it should not be used as a standalone test but should instead be used in combination with other tests, and that the results should be interpreted by a doctor considering the full clinical context, rather than being considered in isolation.

## **Feasibility**

Interview study findings highlighted that the benefits of LF-LAM are crucially dependent on how several feasibility challenges are addressed.

- Hygienic, safe and private sanitary facilities with running water are necessary for LF-LAM implementation at a testing site, but they are not always available, particularly in rural areas. Investments in staffing and sanitary facilities are required.
- Not everybody can spontaneously produce or collect urine samples. This can be the case, for example, when the patient is too ill or septic or has to be catheterized because collecting urine samples from diapers is impossible, or if the hospital has no clean, private space to produce urine.
- Visibility of faint results and result interpretation can be problematic. Comprehensive health care worker training in test interpretation (including mandatory use of the reference reading card, where appropriate) is crucial to ensure accurate result interpretation for clinical action.
- The need for CD4 cell count results to select people for the test is problematic because these are not always immediately available. To facilitate implementation and benefit a wider range of individuals, eliminating the CD4 cell count as an eligibility criterion for people living with HIV should be considered.
- In a hospital setting, bedside testing may violate patient confidentiality.
- Results must be captured in a standardized way that feeds into facility and NTP reporting systems.
- Quality assurance schemes need to be rolled out, and external quality controls need to be made available, to ensure tests and testing processes are quality controlled.

Concurrent testing needs to be framed as a more efficient way of working (i.e. testing two samples concurrently during the same visit, instead of testing one sample during each of two separate visits) that also allows increasing access and reducing costs for patients. According to a laboratory manager, this framing of the benefits outweighing the additional workload, and potentially resulting in reduced work in the long run, will be critical to avoid concurrent testing being perceived as additional work for already overburdened health care workers (see **Web Annex B.10**).

Prior investments made in frontrunner technologies, donor preferences, limited health systems thinking and unnecessary competition between manufacturers all pose challenges to policy adoption and implementation of novel molecular diagnostics. In addition, national in-country health technology and cost-efficacy assessments can delay decisions to implement newer technologies and diagnostic strategies using different samples (see **Web Annex B.10**).

## Implementation considerations

- Global and national HIV and TB programmes need to communicate regularly and clearly, indicating responsibilities for concurrent testing for people living with HIV.
- Concurrent testing maximizes diagnostic opportunity and accuracy of case detection, is a more efficient way to address the needs of this population and is preferred even if the testing workload may increase.
- A positive result on either test is sufficient to confirm TB diagnosis.
- Patient loss to follow-up for the second test result should be monitored and prevented. Patients should be provided with information to understand the concurrent testing approach and the need for follow-up.
- The LF-LAM performed in point-of-care settings may be the first positive result and is sufficient to make the initial diagnosis. A respiratory sample is still required for rifampicin-resistance detection, and is also required when the LF-LAM result is negative.
- Where LF-LAM is not available for testing of people living with HIV, efforts should be made to ensure access to testing.
- LF-LAM does not differentiate *Mtb* from other mycobacterial species. However, the LAM antigen detected in a clinical sample in TB endemic areas is most likely attributable to *Mtb*.
- When LF-LAM results are consistently positive, without positive LC-aNAAT results, investigation of the quality of testing and local epidemiology of non-tuberculosis mycobacteria and extrapulmonary TB in the tested population is warranted to understand the difference.
- Interpreting bands on the LF-LAM test strip should be performed using the manufacturer's reading card to minimize incorrect results.
- LF-LAM test strips must be stored according to the manufacturer's instructions (e.g. between 2 and 30 °C) in sealed bags and not used after expiration.
- Infrastructure to collect a urine sample privately should be available. Patients should be instructed how to properly and sanitarily collect a urine sample to minimize contamination and prevent false positive results.
- Trained staff will be required to perform the LF-LAM test at the point of care.
- As with all WHO-recommended TB diagnostics, quality assurance programmes and quality controls for both tests are required.

- LF-LAM is designed to detect mycobacterial LAM antigen in human urine. Other samples (e.g. sputum, serum, plasma, CSF and other body fluids) or pooled urine specimens should not be used.

### ***Monitoring and evaluation***

- Monitor simultaneous specimen collection and turnaround time for the test results in a concurrent testing approach.
- Monitor patient access to, and loss to follow-up from, a second test in a concurrent testing approach.
- Monitor patient access to, and loss to follow-up from, follow-on DST among those with a positive LF-LAM result but a negative LC-aNAAT result.
- Monitor trends in the discordance rate between the LF-LAM and LC-aNAAT results. If these differences vary from other local or regional patterns, or if the trends change, further investigation is required and outcomes should be tracked for recurrence over time.

### **Research priorities**

- Conduct more rigorous studies with higher quality reference standards, including multiple specimen types and extrapulmonary samples, to improve confidence in specificity estimates.
- Gather evidence on the impact of concurrent testing on TB treatment initiation and mortality.
- Determine training, competency and quality assessment needs by setting and by cadre of staff (i.e. health care worker, laboratory technician or clinical staff).
- Perform country-specific cost–effectiveness and cost–benefit analyses of the concurrent testing approaches or sequential testing approaches in different programmatic settings.
- Develop and apply standardized methods for assessment of costs and cost–effectiveness, to improve comparability and scope of economic evidence.
- Perform operational research on availability, requirements and best practices for the point-of-care set-up: private specimen collection facility, tabletop space for testing samples, and reporting system (preferably digital) for entry of results, with linkages to existing information management systems (i.e. health and laboratory information management systems).

## **2.3.2 Concurrent use of tests in children without HIV or with unknown HIV status**

**NEW**

### **Recommendations**

- 8. For children who are HIV-negative or have an unknown HIV status, who have signs or symptoms or screen positive for pulmonary TB, concurrent testing using low-complexity automated NAATs on respiratory and stool samples should be used as the initial diagnostic strategy for diagnosing TB rather than low-complexity automated NAATs on respiratory or stool samples alone.**

*(Strong recommendation, low certainty of evidence for test accuracy)*

## Remarks

- This recommendation prioritizes concurrent testing of two different sample types over the use of a single molecular test for diagnosis of TB in children.
- Use of LC-aNAATs on isolated specimens was also evaluated. The findings supported the use of LC-aNAATs for initial diagnostic testing for TB in children with signs or symptoms or who screen positive for pulmonary TB, using respiratory sample, gastric aspirate, stool or nasopharyngeal aspirate, rather than smear or culture.
- This recommendation is strong despite the low certainty of evidence because the findings indicate large desirable effects (i.e. rapid and accurate diagnosis of TB in a highly vulnerable population – children – in whom diagnosing TB is often challenging) over trivial undesirable effects (i.e. negative consequences of this testing strategy) (for more details, see GRADE evidence to decision [EtD] table, **Web Annex A.4**).
- The product for which eligible data met the LC-aNAAT class-based performance criteria for this recommendation was Xpert MTB/RIF Ultra. The performance of Truenat MTB Plus and MTB-RIF Dx for this recommendation could not be assessed, as data were unavailable.

## Justification and evidence

LC-aNAATs on respiratory and stool samples are recommended as the first test for symptomatic children presenting with presumptive TB disease, and are widely used to diagnose TB.

Previous systematic reviews have traditionally assessed diagnostic accuracy of LC-aNAATs on two samples in isolation for the detection of TB in children, but in clinical practice the tests may be used concurrently (i.e. LC-aNAAT on a respiratory sample and a stool sample) and together they increase sensitivity.

### *Incremental diagnostic accuracy of concurrent testing compared with single sample testing*

***What is the incremental diagnostic accuracy of concurrent use of LC-aNAATs on respiratory and stool samples for diagnosis of pulmonary TB disease in children who are HIV-negative or have an unknown HIV status, with signs and symptoms or who screened positive for pulmonary TB, compared with use of an LC-aNAAT on one sample type (either respiratory or stool)?***

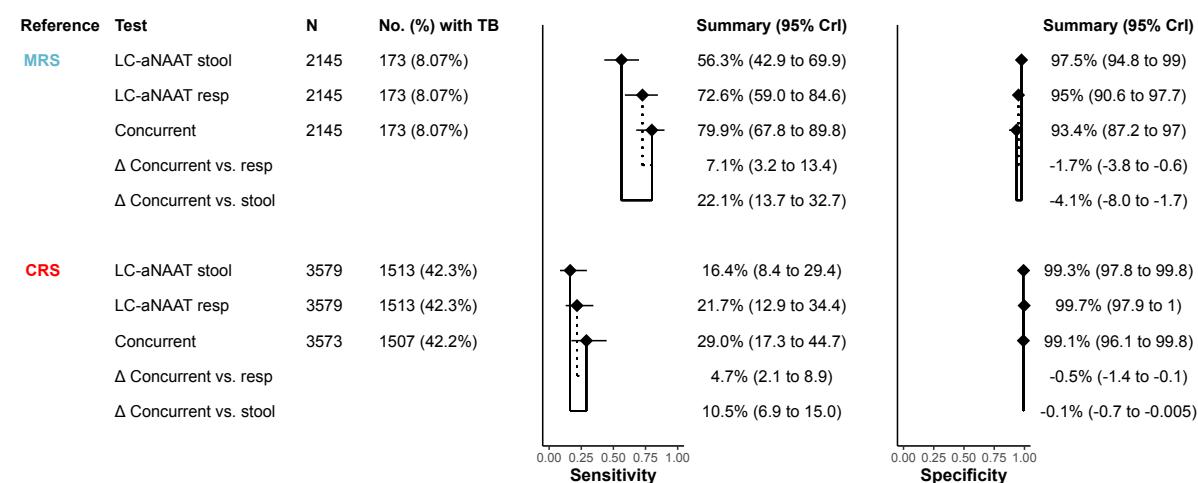
Eight studies (2145 participants, 173 [8.1%] of whom had TB disease) compared the accuracy of concurrent use of LC-aNAATs with respiratory and stool samples (LC-aNAATs combined) versus LC-aNAAT on one sample type (either respiratory or stool) against an MRS.

Compared with LC-aNAAT on respiratory samples alone, concurrent testing had 7.1 percentage points (95% CrI: 3.2 to 13.4) higher sensitivity and -1.7 percentage points (95% CrI: -3.8 to -0.6) lower specificity. Certainty of evidence for both sensitivity and specificity was low for comparison with LC-aNAAT on respiratory samples alone. Compared with LC-aNAAT on stool alone, concurrent testing had 22.1 percentage points (95% CrI: 13.7 to 32.7) higher sensitivity and -4.1 percentage points (95% CrI: -8.0 to -1.7) lower specificity. Certainty of evidence was moderate for sensitivity and low for specificity for comparison with LC-aNAAT on stool alone.

Twelve studies (3579 participants, 1464 [40.9%] of whom had TB disease) compared the accuracy of LC-aNAATs combined versus each LC-aNAAT alone against a CRS.

Compared with LC-aNAAT on respiratory samples alone, concurrent testing had 4.7 percentage points (95% CrI: 2.1 to 8.9) higher sensitivity and -0.5 percentage points (95% CrI: -1.4 to 0) lower specificity. Compared with LC-aNAAT on stool alone, concurrent testing had 10.5 percentage points (95% CrI: 6.9 to 15.0) higher sensitivity and -0.1 percentage points (95% CrI: -0.7 to -0.005) lower specificity. Certainty of evidence was very low for both sensitivity and specificity for both comparisons (concurrent testing versus respiratory sample alone and stool alone) under a CRS (**Fig. 2.3.2.1**). The data on Truenat MTB Plus and MTB-RIF Dx were unavailable.

**Fig. 2.3.2.1 Forest plot of pooled sensitivity and specificity for all studies, by each index test**



CrI: credible interval; CRS: composite reference standard; LC-aNAAT: low-complexity automated nucleic acid amplification test; MRS: microbiological reference standard; TB: tuberculosis.

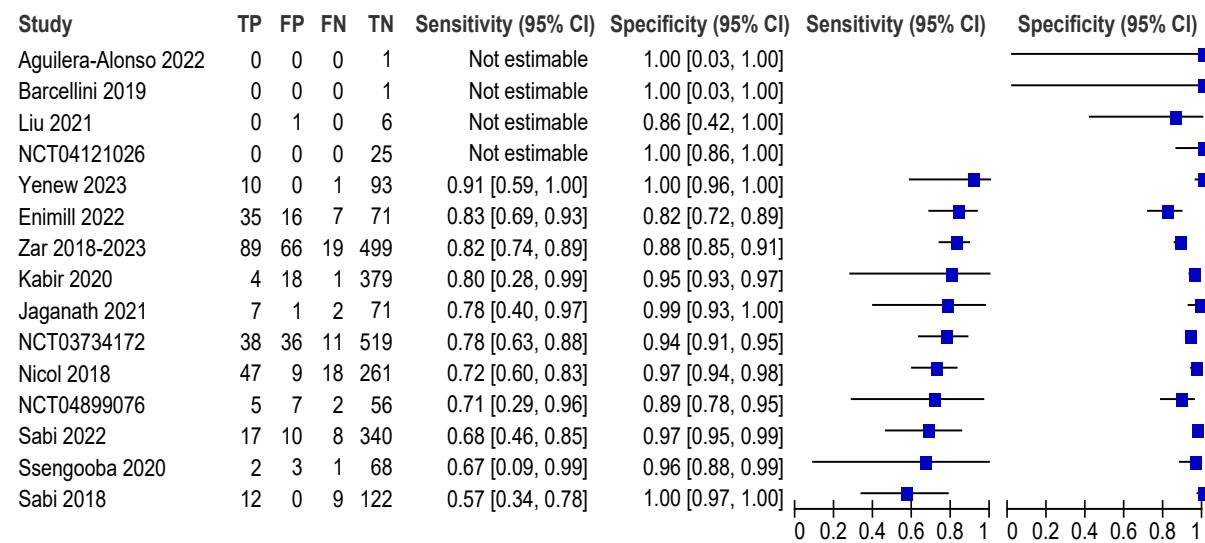
The diamonds represent pooled sensitivity and specificity, and the black horizontal line its 95% CrI. The difference in accuracy between index tests is indicated by solid lines (concurrent versus stool) or dotted lines (concurrent versus respiratory) connecting the diamonds.

### **Single sample testing in children compared with the MRS**

#### **Should LC-aNAATs on respiratory samples be used to diagnose pulmonary TB in children with signs and symptoms or who screened positive for pulmonary TB, against an MRS?**

Fifteen studies (3024 participants) evaluating sputum were identified, with sensitivities ranging between 57% and 91% and specificities between 82% and 100% (**Fig. 2.3.2.2**). Eleven studies (2990 participants) were included in the meta-analysis. The summary sensitivity was 75.3% (95% CI: 68.9–80.8) and summary specificity was 95.9% (95% CI: 92.3–97.9). Certainty of evidence was high for both sensitivity and specificity. The data on Truenat MTB Plus and MTB-RIF Dx were unavailable.

**Fig. 2.3.2.2 Forest plot of LC-aNAAT sensitivity and specificity for detection of pulmonary TB in sputum samples and MRS**

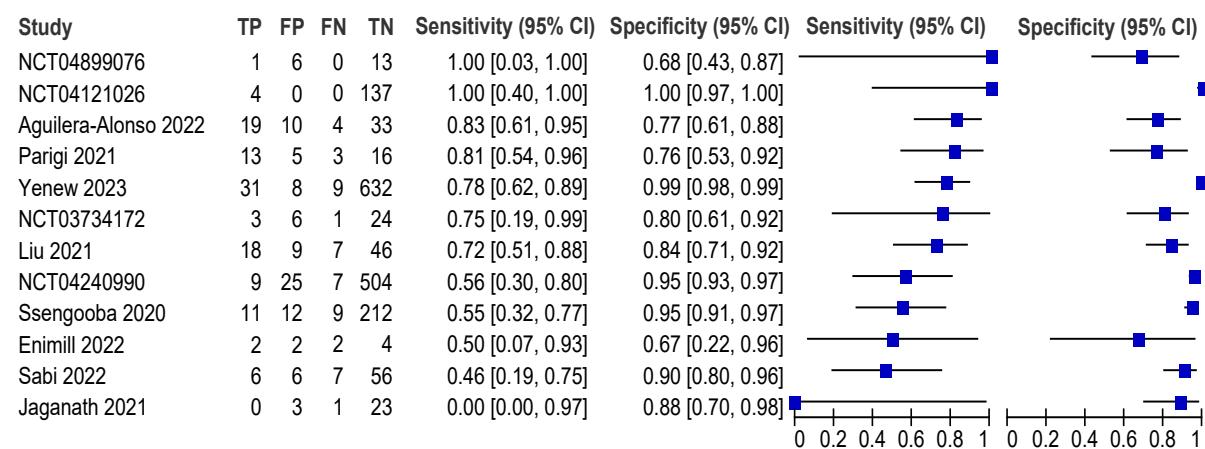


CI: confidence interval; FN: false negative; FP: false positive; LC-aNAAT: low-complexity automated nucleic acid amplification test; MRS: microbiological reference standard; TB: tuberculosis; TN: true negative; TP: true positive.

**Should LC-aNAATs on gastric aspirate specimens be used to diagnose pulmonary TB in children with signs and symptoms or who screened positive for pulmonary TB, against an MRS?**

Twelve studies (1959 participants) were identified, with sensitivities between 0% and 100% and specificities between 67% and 100% (**Fig. 2.3.2.3**). All 12 studies were included in the meta-analysis. The summary sensitivity was 69.6% (95% CI: 60.3–77.6) and summary specificity was 91.0% (95% CI: 82.5–95.6). Certainty of evidence was moderate for both sensitivity and specificity. The data on Truenat MTB Plus and MTB-RIF Dx were unavailable.

**Fig. 2.3.2.3 Forest plot of LC-aNAAT sensitivity and specificity for detection of pulmonary TB in gastric aspirate and MRS<sup>a</sup>**



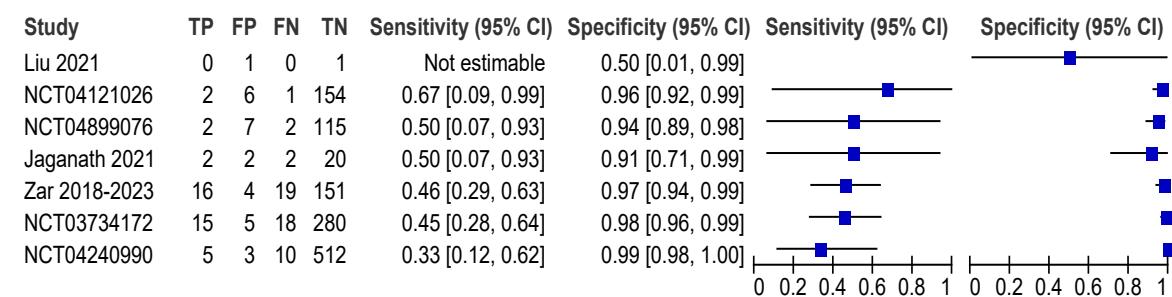
CI: confidence interval; FN: false negative; FP: false positive; LC-aNAAT: low-complexity automated nucleic acid amplification test; MRS: microbiological reference standard; TB: tuberculosis; TN: true negative; TP: true positive.

<sup>a</sup> Studies are sorted on the plot by decreasing sensitivity and specificity.

**Should LC-aNAATs on nasopharyngeal aspirate specimens be used to diagnose pulmonary TB in children with signs and symptoms or who screened positive for pulmonary TB, against an MRS?**

Seven studies (1355 participants) were identified, with sensitivities between 33% and 67% and specificities between 50% and 99% (**Fig. 2.3.2.4**). Six studies (1353) were included in the meta-analysis. The summary sensitivity was 46.2% (95% CI: 34.9–57.9) and summary specificity was 97.5% (95% CI: 95.1–98.7). Certainty of evidence was moderate for sensitivity and high for specificity. The data on Truenat MTB Plus and MTB-RIF Dx were unavailable.

**Fig. 2.3.2.4 Forest plot of LC-aNAAT sensitivity and specificity for detection of pulmonary TB in nasopharyngeal aspirate samples and MRS**

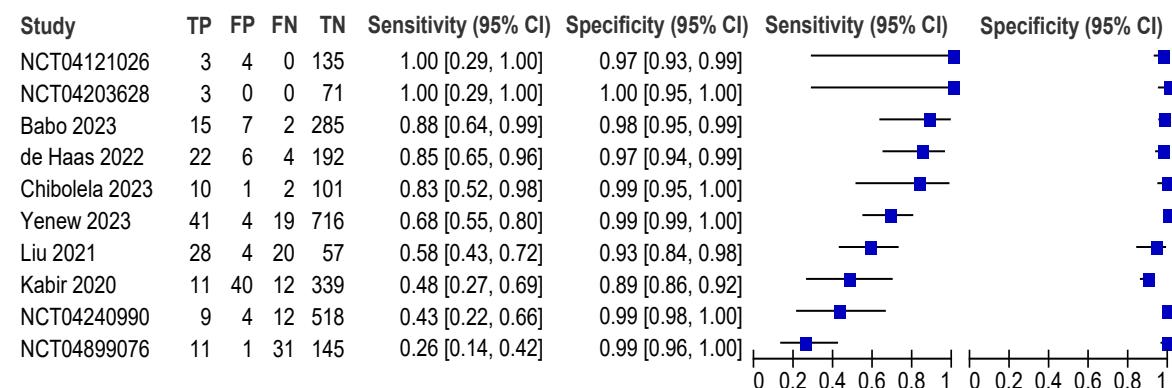


CI: confidence interval; FN: false negative; FP: false positive; LC-aNAAT: low-complexity automated nucleic acid amplification test; MRS: microbiological reference standard; TB: tuberculosis; TN: true negative; TP: true positive.

**Should LC-aNAATs on stool be used to diagnose pulmonary TB in children with signs and symptoms or who screened positive for pulmonary TB, against an MRS?**

Ten studies (2855 participants) were identified, with sensitivities between 26% and 100% and specificities between 89% and 100% (**Fig. 2.3.2.5**). All 10 studies were included in the meta-analysis. The summary sensitivity was 68.0% (95% CI: 50.3–81.7) and summary specificity was 98.2% (95% CI: 96.3 to 99.1). Certainty of evidence was moderate for sensitivity and high for specificity. The data on Truenat MTB Plus and MTB-RIF Dx were unavailable.

**Fig. 2.3.2.5 Forest plot of LC-aNAAT sensitivity and specificity for detection of pulmonary TB in stool and MRS<sup>a</sup>**



CI: confidence interval; FN: false negative; FP: false positive; LC-aNAAT: low-complexity automated nucleic acid amplification test; MRS: microbiological reference standard; TB: tuberculosis; TN: true negative; TP: true positive.

<sup>a</sup>Studies are sorted on the plot by decreasing sensitivity.

## Cost-effectiveness analysis

As part of the preparatory process for the GDG meeting in May 2024, WHO commissioned a modelled study to assess the cost-effectiveness of using LC-aNAATs (including Xpert Ultra, Truenat and other novel LC-aNAATs in the development pipeline) for the detection of TB when used concurrently among people living with HIV and children, including children with HIV, across two different country settings (Malawi and the Philippines).

A study objective was to assess the cost-effectiveness of concurrent use of LC-aNAATs on respiratory and stool samples for TB diagnosis and rifampicin-resistance detection among children (aged <10 years) with presumptive TB and without HIV infection, compared with a single LC-aNAAT on a respiratory sample alone.

In this hypothetical model, a cohort of children with presumptive TB progressed through a decision analytical framework. In the intervention arm, TB diagnosis involved the concurrent use of LC-aNAATs on both respiratory and stool samples, whereas the comparator arm solely used LC-aNAATs on respiratory specimens. The probability of being able to provide a respiratory sample was considered, and testing was conducted, either for both respiratory and stool samples concurrently or solely for stool. In both the intervention and comparator arms, participants not diagnosed through the diagnostic strategy had the opportunity for clinical diagnosis. Children with bacteriologically confirmed TB underwent DST for rifampicin and began either drug-susceptible TB or DR-TB treatment, depending on the DST result. All individuals were followed over time, including those with false negative or false positive diagnostic results, to account for unnecessary treatment or additional mortality due to missed diagnoses.

When using the high TB burden setting of Malawi to parametrize the model, cost-effectiveness modelling found that the use of an LC-aNAAT on a respiratory sample resulted in an average cost of US\$ 144, with a corresponding average DALY of 0.93. In contrast, the concurrent use of LC-aNAATs on respiratory and stool samples yielded an average cost of US\$ 204, and a DALY of 0.57, resulting in an incremental cost per DALY averted of US\$ 253 (95% UR: 123–2317) (**Table 2.3.2.1**).

Similarly, in the Philippines, the cost of an LC-aNAAT on a respiratory sample was US\$ 84, associated with a DALY of 1.04. Concurrent testing in the Philippines resulted in an average cost of US\$ 149 and a DALY of 0.66, with an ICER of US\$ 156 per DALY averted (95% UR: 79–888) (**Table 2.3.2.1**).

**Table 2.3.2.1 Cost–effectiveness analysis of concurrent use of LC-aNAATs among children in Malawi and the Philippines**

Country	Diagnostic strategy	Cost, US\$	Effectiveness, DALYs	ICER (95% UR), US\$
<b>Malawi</b>	LC-aNAAT on respiratory sample	114	0.93	Reference
	LC-aNAATs on respiratory and stool samples	204	0.57	253 (123–2317)
<b>Philippines</b>	LC-aNAAT on respiratory sample	84	1.04	Reference
	LC-aNAATs on respiratory and stool samples	149	0.62	156 (79–888)

DALY: disability-adjusted life year; ICER: incremental cost–effectiveness ratio; LC-aNAAT: low-complexity automated nucleic acid amplification test; UR: uncertainty range.

More information on the cost–effectiveness analysis of concurrent use of tests in children is available in **Web Annex B.9**.

## User perspective

The GDG assessed whether concurrent testing of multiple samples would increase the diagnostic yield (i.e. the benefit to patients or the programme in terms of finding more people with TB). One of the PICO questions focused on the concurrent use of LC-aNAATs on respiratory and stool samples for the diagnosis of TB in children.

## User preferences and values

As important outcomes of the diagnostic test, people in high TB burden settings value:

- getting an accurate diagnosis and reaching diagnostic closure (finally knowing “what is wrong with me”);
- avoiding diagnostic delays, as they exacerbate existing financial hardships and emotional and physical suffering and make people feel guilty for infecting others (especially children);
- having accessible facilities; and
- reducing diagnosis-associated costs (e.g. travel, missing work).

Participants appreciate that stool collection is far less invasive than gastric lavage and can thereby reduce physical and emotional suffering of children and their parents (see **Web Annex B.10**).

## Equity

Concurrent specimen testing was not practiced in the interview study countries. However, it was believed to improve access to care by minimizing repeat visits and loss to follow-up.

According to the interview study respondents, using non-sputum specimens has the potential to improve access to care, especially with a test that can be performed at all levels of the health

care system. Challenges with producing a sufficient quality and quantity of sputum are well documented and can lead to repeat testing or false results.

## Acceptability

Most participants, including health workers and caregivers, did not immediately understand why multiple samples would be tested concurrently at the same visit, if a respiratory sample is available. They highlighted that a sputum sample is the preferred choice, and they would only collect the second-best sample if that were not available. However, participants also thought that concurrent sample testing could be possible if there was a WHO recommendation, altered diagnostic algorithms and specific training and capacity strengthening to facilitate it (see **Web Annex B.10**).

For young children, stool seems to be an acceptable specimen, especially after adequate training in how to process it. Stool from adults is considered more difficult in terms of both acceptance and processing time. In general, participants had confidence in the results from stool tested by GeneXpert (see **Web Annex B.10**).

## Feasibility

Important feasibility challenges are related to the deteriorating quality of stool, caused by delays between time of collection and time of processing in the laboratory (see **Web Annex B.10**).

Concurrent testing needs to be framed as a more efficient way of working (i.e. testing two samples concurrently during the same visit, instead of testing one sample during each of two separate visits) that also allows increasing access and reducing costs for patients. The practice of concurrent testing needs to be framed as generating sufficient benefit to justify the additional short-term workload and having the potential to reduce the workload in the longer term. Without such framing, there is a risk that already overburdened health care workers will avoid concurrent testing (see **Web Annex B.10**).

Prior investments made in frontrunner technologies, donor preferences, limited health systems thinking and unnecessary competition between manufacturers all pose challenges to policy adoption and implementation of novel molecular diagnostics. In addition, national in-country health technology and cost-efficacy assessments can delay decisions to implement newer technologies and diagnostic strategies using different samples (see **Web Annex B.10**).

More information on the qualitative evidence analysis and synthesis for concurrent use of tests in children is available from **Web Annex B.10**.

## Implementation considerations

- Concurrent testing maximizes diagnostic opportunity and accuracy of case detection, is a more efficient way to address the needs of this population and is preferred even if the testing workload may increase.
- A positive result on either test is sufficient to confirm TB diagnosis.
- Patient loss to follow-up for the second test result should be monitored and prevented. Patients should be provided with information to understand the concurrent testing approach and the need for follow-up.

- Testing capacity should be secured for the second test, as volumes will increase.
- Adequate staffing capacity and training are needed to improve the collection of different sample types and laboratory processing of collected samples.
- Performing the same test on a new sample may need additional regulatory approval on a national and international level.
- Infrastructure and training on how to collect a stool sample privately should be available.
- As with all WHO-recommended TB diagnostics, quality assurance programmes for both sample types are required.
- At a primary health care level, in a situation of sputum paucity or absence, stool and nasopharyngeal aspirate may be feasible, whereas collection of more invasive specimen types (i.e. induced sputum, BAL and gastric aspirate) would require upward referral, depending local capacity and expertise. In these circumstances, performing stool testing at primary health care level and waiting for a test result before upward referral of the child may be appropriate.

## Monitoring and evaluation

- Monitor simultaneous specimen collection and turnaround time for the test results in a concurrent testing approach.
- Monitor patient loss to follow-up from a second test in a concurrent testing approach.
- Monitor trends in the rate of indeterminate test results for both sample types with LC-aNAATs.
- Monitor trends in the discordance rate between the respiratory and stool LC-aNAAT results. If these differences vary from other local or regional patterns, or if the trends change, further investigation is required.

## Research priorities

- Evaluate the impact of concurrent specimen testing on patient-important outcomes for children (cure, mortality, time to diagnosis and time to start of treatment).
- Evaluate the impact of concurrent specimen testing on affordability and cost-effectiveness in the intended settings of use.
- Evaluate the performance of other LC-aNAATs in concurrent testing approaches.
- Identify an improved reference standard that accurately defines TB disease in children and paucibacillary specimens because the sensitivity of all available diagnostics is suboptimal.
- Develop new tools that correctly diagnose a higher proportion of TB in children. Ideally, the new tools will be rapid, affordable, feasible and acceptable to children and their parents.
- Develop rapid point-of-care diagnostic tests and simpler alternative sample types for paucibacillary and extrapulmonary TB in children.
- Perform operational research to ensure that tests are used optimally in intended settings.
- Develop and apply standardized methods for assessment of costs and cost-effectiveness, to improve comparability and scope of economic evidence.

## 2.3.3 Concurrent use of tests in children with HIV

NEW

### Recommendations

9. For children with HIV who have signs or symptoms or screen positive for pulmonary TB, concurrent testing using low-complexity automated NAATs on respiratory and stool samples and LF-LAM on urine may be used as the initial diagnostic strategy for diagnosing TB rather than low-complexity automated NAATs on respiratory or stool samples alone.

*(Conditional recommendation, low certainty of evidence for test accuracy)*

### Remarks

- This recommendation prioritizes concurrent testing over the use of molecular testing and LF-LAM in isolation for diagnosis of TB in children with HIV.
- Use of LC-aNAATs on isolated specimens was also evaluated. The findings supported the use of LC-aNAATs for initial diagnostic testing for TB in HIV-positive children with signs or symptoms or who screen positive for pulmonary TB, using sputum, gastric aspirate, stool or nasopharyngeal aspirate, rather than smear or culture.
- This recommendation is conditional because the findings indicate moderate undesirable effects (i.e. decreased specificity, resulting in more false positive test results) when compared with a single test strategy.
- The product for which eligible data met the LC-aNAAT class-based performance criteria for this recommendation was Xpert MTB/RIF Ultra. The performance of Truenat MTB Plus and MTB-RIF Dx for this recommendation could not be assessed, as data were unavailable.

### Justification and evidence

LC-aNAATs on respiratory and stool sample and LF-LAM on urine are recommended as the first test for symptomatic children with HIV presenting with presumptive TB disease, and should be used to diagnose TB.

Previous systematic reviews have traditionally assessed diagnostic accuracy of LC-aNAATs on two samples and LF-LAM on urine in isolation for the detection of TB in children, but in clinical practice the tests may be used concurrently (i.e. LC-aNAAT on a respiratory and stool sample and LF-LAM on urine) and together they increase sensitivity.

### Incremental diagnostic accuracy

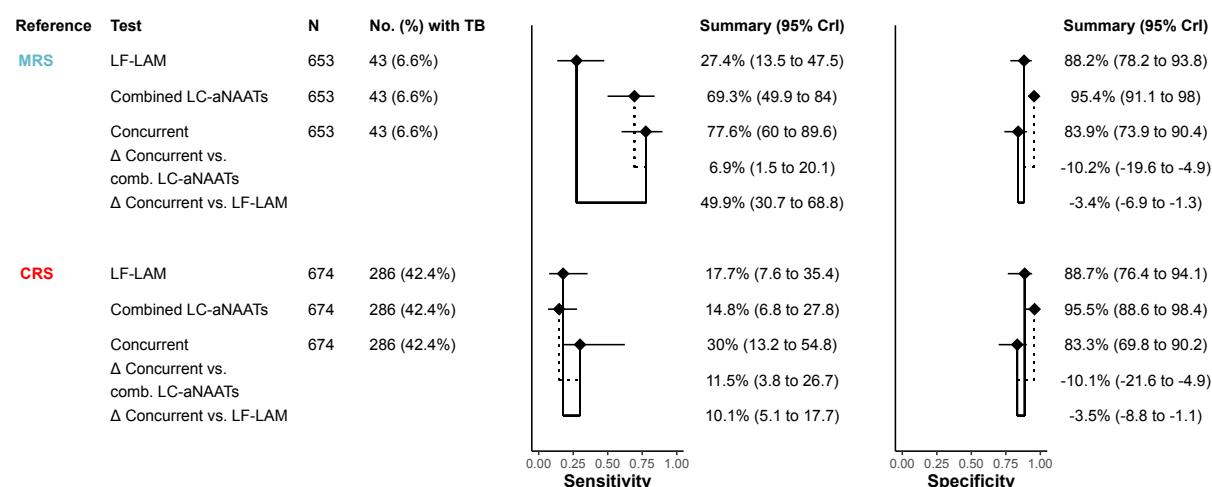
***What is the incremental diagnostic accuracy of concurrent use of LC-aNAATs on respiratory and stool samples and LF-LAM on urine versus each sample type alone for diagnosis of pulmonary TB disease in children with HIV, with signs and symptoms or who screened positive for pulmonary TB, compared with any of the tests (either LC-aNAATs combined or LF-LAM) alone?***

Based on six studies (653 participants, including 43 [6.6%] with TB) included in the meta-analysis for an MRS, the estimated diagnostic accuracy of the concurrent use of LC-aNAAT on respiratory

samples plus LC-aNAAT on stool and LF-LAM on urine had a pooled sensitivity of 77.8% (95% CrI: 59.9 to 89.8) and a pooled specificity of 83.9% (95% CrI: 73.9 to 90.4) (**Fig. 2.3.7**). Compared with LC-aNAAT on respiratory samples alone, concurrent testing had 6.9 percentage points (95% CrI: 1.5 to 20.1) higher sensitivity and -10.1 percentage points (95% CrI: -21.6 to -4.9) lower specificity. Certainty of evidence was low for specificity and moderate for sensitivity.

Based on six studies (674 participants, including 286 [42.4%] with TB) included in the meta-analysis for a CRS, the estimated diagnostic accuracy of the concurrent use of LC-aNAAT on respiratory samples plus LC-aNAAT on stool and LF-LAM on urine had a pooled sensitivity of 30.1% (95% CrI: 13.2 to 54.9) and a pooled specificity of 83.3% (95% CrI: 69.6 to 90.2) (**Fig. 2.3.3.1**). Compared with LC-aNAAT on respiratory samples alone, concurrent testing had 14.9 percentage points (95% CrI: 0 to 41.1) higher sensitivity and -12.0 percentage points (95% CrI: -27.0 to -2.6) lower specificity. Certainty of evidence was very low for sensitivity and low for specificity.

**Fig. 2.3.3.1 Forest plot of pooled sensitivity and specificity for all studies, by each index test**



CrI: credible interval; CRS: composite reference standard; LC-aNAAT: low-complexity automated nucleic acid amplification test; LF-LAM: lateral flow urine lipoarabinomannan assay; MRS: microbiological reference standard; TB: tuberculosis.

<sup>a</sup>The diamonds represent pooled sensitivity and specificity, and the black horizontal line its 95% CrI. The difference in accuracy between index tests is indicated by solid lines (concurrent versus stool) or dotted lines (concurrent versus respiratory) connecting the diamonds.

## Cost-effectiveness analysis

In addition to the economic evidence regarding concurrent use of tests in people living with HIV and children (see Sections 2.3.1 and 2.3.2), WHO commissioned a third study that aimed to assess the cost-effectiveness of using LC-aNAATs (including Xpert Ultra, Truenat and other novel LC-aNAATs in the development pipeline) for the detection of TB when used concurrently among children with HIV, across two different country settings (Malawi and the Philippines).

An objective of this study was to assess the cost-effectiveness of concurrent use of LC-aNAATs on respiratory and stool samples and LF-LAM on urine for TB diagnosis and rifampicin-resistance

detection among children (aged <10 years) living with HIV and with presumptive TB, compared with a single LC-aNAAT on a respiratory sample alone.

In the hypothetical model that informed this study, a cohort of children with HIV and with signs and symptoms of TB progressed through a decision analytical framework. In the intervention arm, TB diagnosis involved the concurrent use of LC-aNAATs on both respiratory and stool samples, alongside LF-LAM on urine. The comparator arm used LC-aNAAT on respiratory samples alone. The probability of providing a respiratory sample was considered, and testing was conducted, either concurrently on respiratory and stool samples alongside LF-LAM, or on stool alone alongside LF-LAM. In both the intervention and comparator arm, participants not diagnosed through the diagnostic strategy had the opportunity for clinical diagnosis. Children with bacteriologically confirmed TB underwent DST for rifampicin and began either drug-susceptible TB or DR-TB treatment, depending on the DST result. All individuals were followed over time, including those with false negative or false positive diagnostic results, to account for unnecessary treatment or additional mortality due to missed diagnoses.

The study findings shown in **Table 2.3.3.1** show the cost-effectiveness of the concurrent use of LC-aNAATs on respiratory and stool samples and LF-LAM on urine among children with HIV in Malawi and the Philippines. In Malawi, the average cost of implementing an LC-aNAAT on a respiratory sample was US\$ 319, with a corresponding average DALY of 5.08. When used concurrently, the average cost increased to US\$ 460, while the average DALY decreased to 1.8. The resulting ICER per DALY averted was US\$ 43 (95% UR: 28–89). Similarly, in the Philippines, implementation of an LC-aNAAT on a respiratory sample alone cost US\$ 249, with an average DALY of 5.13, whereas concurrent use incurred an average cost of US\$ 345 and an average DALY of 1.77. The ICER per DALY averted was US\$ 29 (95% UR: 18–63).

**Table 2.3.3.1 Cost-effectiveness analysis of concurrent use of LC-aNAATs among children living with HIV in Malawi and the Philippines**

Country	Diagnostic strategy	Cost, US\$	Effectiveness, DALYs	ICER (95% UR), US\$
Malawi	LC-aNAAT on respiratory sample	320	5.08	Reference
	LC-aNAAT on respiratory and stool samples and LF-LAM	460	1.8	43 (28–89)
Philippines	LC-aNAAT on respiratory sample	249	5.13	Reference
	LC-aNAAT on respiratory and stool samples and LF-LAM	345	1.77	29 (18–63)

DALY: disability-adjusted life year; HIV: human immunodeficiency virus; ICER: incremental cost-effectiveness ratio; LC-aNAAT: low-complexity automated nucleic acid amplification test; LF-LAM: lateral flow urine lipoarabinomannan assay; UR: uncertainty range.

More information on the cost-effectiveness analysis of concurrent use of tests in children with HIV is available in **Web Annex B.9**.

## User perspective

The GDG assessed whether concurrent testing of multiple samples would increase the diagnostic yield (i.e. the benefit to patients or the programme in terms of finding more people with TB). One of the PICO questions focused on concurrent use of LC-aNAATs on respiratory and stool samples and LF-LAM on urine for the diagnosis of TB in children living with HIV.

## User preferences and values

The interview study and quality evidence synthesis produced no data on the use of LF-LAM in children living with HIV. However, in general, as important outcomes of the diagnostic test, patients in high TB burden settings value:

- getting an accurate diagnosis and reaching diagnostic closure (finally knowing “what is wrong with me”);
- avoiding diagnostic delays, as they exacerbate existing financial hardships and emotional and physical suffering and make people feel guilty for infecting others (especially children);
- having accessible facilities; and
- reducing diagnosis-associated costs (e.g. travel, missing work).

Participants appreciate that stool sample collection is far less invasive than gastric aspirate (see **Web Annex B.10**).

## Equity

Concurrent sample testing was not practiced in the study countries. However, concurrent sample testing could improve access to care by minimizing repeat visits and loss to follow-up (see **Web Annex B.10**).

Using non-sputum samples can improve access to care, especially with a test that can be performed at all levels of the health care system. Challenges with producing sputum of sufficient quality and quantity are well documented and can lead to repeat testing or false results. Participants highlighted the impact that using stool has on increasing case-finding and access to care, particularly among destitute families (see **Web Annex B.10**).

## Acceptability

The interview study produced no data on the use of LF-LAM in children living with HIV.

Most participants (including parents and legal representatives of children) did not immediately understand why multiple samples would be tested concurrently at the same visit, if a respiratory sample is available. They highlighted that a sputum sample is the preferred choice, and they would only collect the second-best sample if that were not available. However, participants also thought that concurrent sample testing could be possible if there was a WHO recommendation, altered diagnostic algorithms and specific training and capacity strengthening to facilitate it (see **Web Annex B.10**).

For young children, stool seems to be an acceptable specimen, especially after adequate training in how to process it. Stool from adults is considered more difficult in terms of both acceptance and processing time. There was general confidence among participants regarding results from stool tested by GeneXpert (see **Web Annex B.10**).

## Feasibility

The interview study produced no data on the use of LF-LAM in children living with HIV. In younger and sicker children, urine sample collection is more cumbersome, as it requires both the child's and the caregiver's cooperation, and it may be affected by medical issues, such as dehydration (see **Web Annex B.10**).

Important feasibility challenges are related to the deteriorating quality of the stool sample caused by delays between time of collection and time of processing in the laboratory (see **Web Annex B.10**).

Concurrent testing needs to be framed as a more efficient way of working (i.e. testing two samples concurrently during the same visit, instead of testing one sample during each of two separate visits) that also allows increasing access and reducing costs for patients. According to a laboratory manager, this framing of the benefits outweighing the additional workload, and potentially resulting in reduced work in the long run, will be critical to avoid concurrent testing being perceived as additional work for already overburdened health care workers (see **Web Annex B.10**).

Prior investments made in frontrunner technologies, donor preferences, limited health systems thinking and unnecessary competition between manufacturers all pose challenges to policy adoption and implementation of novel molecular diagnostics. In addition, national in-country health technology and cost-efficacy assessments can delay decisions to implement newer technologies and diagnostic strategies using different samples (see **Web Annex B.10**).

## Implementation considerations

- The implementation considerations are the same as those in Sections 2.3.1 and 2.3.2.

## Monitoring and evaluation

- The monitoring and evaluation considerations are the same as those in Sections 2.3.1 and 2.3.2.

## Research priorities

- The research priorities are the same as those in Sections 2.3.1 and 2.3.2.

## 2.4. Follow-on diagnostic tests for detection of additional drug-resistance after TB confirmation

### 2.4.1 Low complexity automated NAATs for detection of resistance to isoniazid and second-line anti-TB agents

Among 105 countries possessing representative data on resistance to fluoroquinolones from the past 15 years, the proportion of MDR/RR-TB cases with resistance to any fluoroquinolone for which testing was done was 20.1% (95% CI: 15.5–25.0%) (1). Thus, rapid and early testing for the detection of fluoroquinolone resistance is essential for determining eligibility for treatment with the all-oral 9–12 month standardized shorter regimen for MDR/RR-TB. However, the current limitation with testing for fluoroquinolone resistance is the limited accessibility of current technologies (which are often only available at higher tiers of the health system) and poor yield in paucibacillary specimens.

Low complexity automated NAATs are a new class of diagnostics intended for use as a reflex test in specimens determined to be *Mtb* complex (MTBC)-positive; they offer rapid DST in intermediate and peripheral laboratories. The first product in this class simultaneously detects resistance to isoniazid, fluoroquinolones, ethionamide and amikacin. Results are available in under 90 minutes, leading to faster time to results than the current standard of care, which includes LPAs and culture-based phenotypic DST.

An additional value of the tests is the accurate and rapid detection of isoniazid resistance, which is relevant for both RR-TB and rifampicin-susceptible TB; the latter is often undiagnosed and contributes to a large burden of disease. Globally, rifampicin-susceptible TB is estimated to occur in 13.1% (95% CI: 9.9–16.9%) of new cases and 17.4% (95% CI: 0.5–54.0%) of previously treated cases (1). Thus, this test could also be used as a reflex test to complement existing technologies that only test for rifampicin, allowing the rapid and accurate detection of isoniazid-resistant, rifampicin-susceptible TB.

Although these new technologies are excellent at detecting resistance to selected drugs, conventional culture-based phenotypic DST remains important to determine resistance to other anti-TB agents, particularly the new and repurposed medicines such as bedaquiline and linezolid.

### Recommendations

- 10. In people with bacteriologically confirmed pulmonary TB, low complexity automated NAATs may be used on sputum for the initial detection of resistance to isoniazid and fluoroquinolones, rather than culture-based phenotypic DST.**

*(Conditional recommendation, moderate certainty of evidence for diagnostic accuracy)*

**11. In people with bacteriologically confirmed pulmonary TB and resistance to rifampicin, low complexity automated NAATs may be used on sputum for the initial detection of resistance to ethionamide, rather than DNA sequencing of the *inhA* promoter.**

*(Conditional recommendation, very low certainty of evidence for diagnostic accuracy)*

**12. In people with bacteriologically confirmed pulmonary TB and resistance to rifampicin, low complexity automated NAATs may be used on sputum for the initial detection of resistance to amikacin, rather than culture-based phenotypic DST.**

*(Conditional recommendation, low certainty of evidence for diagnostic accuracy)*

There are several subgroups to be considered for these recommendations:

- The recommendations are based on the evidence of diagnostic accuracy in sputum of adults with bacteriologically confirmed pulmonary TB, with or without rifampicin resistance.
- The recommendations are extrapolated to adolescents and children, based on the generalization of data from adults.
- The recommendations apply to people living with HIV (studies included a varying proportion of such individuals); data stratified by HIV status were not available.
- The recommendations are extrapolated to people with extrapulmonary TB, and testing of non-sputum samples was considered appropriate, which affects the certainty. The panel did not evaluate test accuracy in non-sputum samples directly, including in children; however, extrapolation was considered appropriate given that WHO has recommendations for similar technologies for use on non-sputum samples (e.g. Xpert MTB/RIF and Xpert Ultra).
- Recommendations for detection of resistance to amikacin and ethionamide are only relevant for people who have bacteriologically confirmed pulmonary TB and resistance to rifampicin.

## Justification and evidence

The WHO Global TB Programme initiated an update of the current guidelines and commissioned a systematic review on the use of low complexity automated NAATs for the detection of resistance to isoniazid and second-line TB drugs in people with signs and symptoms of TB.

The PICO questions were designed to form the basis for the evidence search, retrieval and analysis:

1. Should low complexity automated NAATs be used on sputum in people with signs and symptoms of pulmonary TB, irrespective of resistance to rifampicin, for detection of resistance to isoniazid, as compared with culture-based phenotypic DST?
2. Should low complexity automated NAATs be used on sputum in people with signs and symptoms of pulmonary TB, irrespective of resistance to rifampicin, for detection of resistance to fluoroquinolones, as compared with culture-based phenotypic DST?

3. Should low complexity automated NAATs be used on culture isolates in people with signs and symptoms of pulmonary TB, and detected resistance to rifampicin, for detection of resistance to ethionamide, as compared with genotypic sequencing of the *inhA* promoter?
4. Should low complexity automated NAATs be used on sputum in people with signs and symptoms of pulmonary TB, and detected resistance to rifampicin, for detection of resistance to amikacin, as compared with culture-based phenotypic DST?

The databases Ovid Medline (Ovid, 1946 to present) and Embase (Ovid, 1947 to present) were searched for studies evaluating cartridge-based tests using the following search terms: tuberculosis, pulmonary AND Xpert, GeneXpert, Truenat, cartridge, point-of-care systems, drug susceptibility test, isoniazid resistance, fluoroquinolone resistance and second-line injectable drug resistance. Clinicaltrials.gov and the WHO International Clinical Trials Registry Platform were also searched for trials in progress. Searches were run up to 6 September 2020 without language restriction. On 4 November 2020, an additional search was run using the search terms Zeesan and MeltPro.

Researchers at FIND, the WHO Global TB Programme, the manufacturer and other experts in the field of TB diagnostics were contacted for information about ongoing and unpublished studies. Data submitted in response to the WHO public call were reviewed.

Drug resistance was compared against a phenotypic reference standard (or a genotypic reference standard for ethionamide resistance), as well as a composite reference standard that was constructed by combining the results of phenotypic and genotypic DST results in studies where both had been performed.

Data synthesis was structured around the four preset PICO questions, as outlined below. Three web annexes give additional information, as follows:

- details of studies included in the current analysis (**Web Annex A.6: Low complexity automated NAATs**);
- a summary of the results and details of the evidence quality assessment (**Web Annex A.6: Low complexity automated NAATs**); and
- a summary of the GDG panel judgements (**Web Annex A.6: Low complexity automated NAATs**).

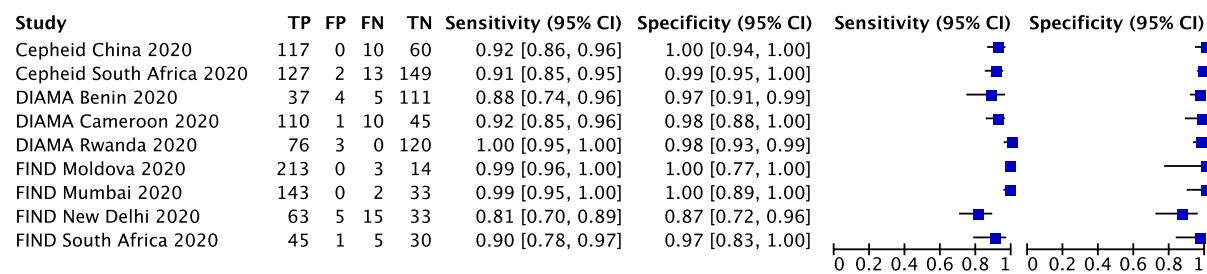
**PICO 1: Should low complexity automated NAATs be used on sputum in people with signs and symptoms of pulmonary TB, irrespective of resistance to rifampicin, for detection of resistance to isoniazid, as compared with culture-based phenotypic DST?**

Three multinational studies with 1605 participants provided data for evaluating isoniazid resistance detection. The reference standard for each of these studies was culture-based phenotypic DST. Each study centre in the multinational studies was analysed as a separate study (**Fig. 2.4.1.1**).

Several concerns were expressed about indirectness in the study populations. First, the median prevalence of isoniazid resistance in the included studies was 67.2% (range, 26.8% [Diagnostics for Multidrug Resistant Tuberculosis in Africa – DIAMA, Benin] to 93.9% [FIND, Moldova]), which is higher than the global estimates for isoniazid resistance. Hence, applicability to settings

with a lower prevalence of isoniazid resistance comes with some uncertainty. Second, there are potential differences in the mutations present in isoniazid monoresistant strains and MDR strains; that is, some studies suggest that the mutations found in monoresistant strains are more diverse than the mutations found in MDR strains. Third, although the population for this PICO question is “irrespective of rifampicin resistance”, enrolment criteria in the studies meant that most participants within the included studies had RR-TB. As a result of these concerns, certainty of evidence was downgraded one level for indirectness both for sensitivity and specificity, and the quality (certainty) of evidence was rated moderate both for sensitivity and specificity.

**Fig. 2.4.1.1 Forest plot of included studies for isoniazid resistance detection, irrespective of rifampicin resistance with culture-based phenotypic DST as the reference standard**



CI: confidence interval; DIAMA: Diagnostics for Multidrug Resistant Tuberculosis in Africa; DST: drug susceptibility testing; FIND: Foundation for Innovative New Diagnostics; FN: false negative; FP: false positive; TB: tuberculosis; TN: true negative; TP: true positive.

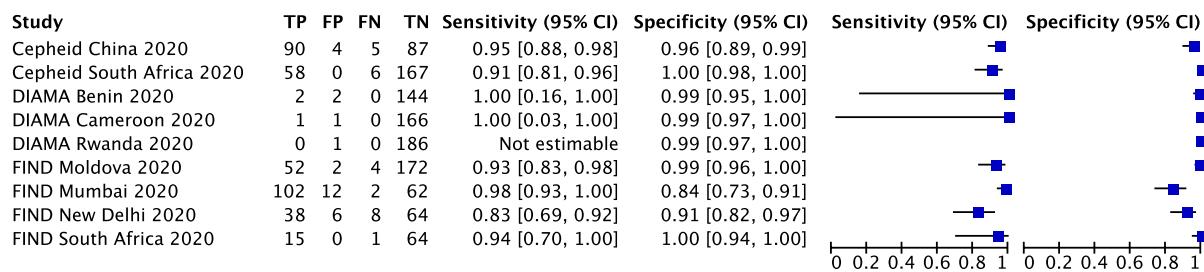
The sensitivity in these three studies ranged from 81% to 100% and the specificity from 87% to 100%. **The pooled sensitivity was 94.2% (95% CI: 89.3–97.0%) and the pooled specificity was 98.0% (95% CI: 95.2–99.2%).**

**PICO 2: Should low complexity automated NAATs be used on sputum in people with signs and symptoms of pulmonary TB, irrespective of resistance to rifampicin, for detection of resistance to fluoroquinolones, as compared with culture-based phenotypic DST?**

Three multinational studies with 1337 participants provided data for evaluation of detection of fluoroquinolone resistance. The reference standard for each of these studies was culture-based phenotypic DST. Each study centre in the multinational studies was analysed as a separate study (**Fig. 2.4.1.2**).

Specificity estimates were inconsistent, at 84% (FIND, Mumbai), 91% (FIND, New Delhi) and more than 96% for other studies. The heterogeneity in specificity estimates could not be explained. Consequently, the certainty of the evidence was downgraded one level for inconsistency; the quality (certainty) of the evidence was rated high for sensitivity and moderate for specificity.

**Fig. 2.4.1.2 Forest plot of included studies for fluoroquinolone resistance detection, irrespective of rifampicin resistance with culture-based phenotypic DST as the reference standard**



CI: confidence interval; DIAMA: Diagnostics for Multidrug Resistant Tuberculosis in Africa; DST: drug susceptibility testing; FIND: Foundation for Innovative New Diagnostics; FN: false negative; FP: false positive; TB: tuberculosis; TN: true negative; TP: true positive.

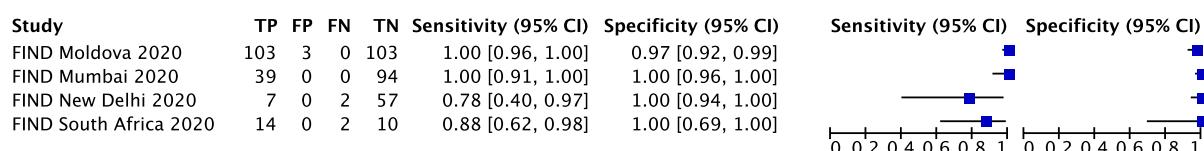
The sensitivity for fluoroquinolone resistance in these three studies ranged from 83% to 100% and the specificity from 84% to 100%. **The pooled sensitivity was 93.1% (95% CI: 88.0–96.1%) and the pooled specificity was 98.3% (95% CI: 94.5–99.5%).**

**PICO 3: Should low complexity automated NAATs be used on culture isolates in people with signs and symptoms of pulmonary TB, and detected resistance to rifampicin, for detection of resistance to ethionamide, as compared with genotypic sequencing of the *inhA* promoter?**

One multinational study with 434 participants provided data for evaluating resistance to ethionamide. The reference standard for this study was DNA sequencing of the *inhA* promoter. Each study centre in the multinational study was analysed as a separate study (**Fig. 2.4.1.3**).

The study was judged to be at very serious risk of bias in the reference standard domain because it did not include all loci (i.e. *ethA*, *ethR* and *inhA* promoter) required for the reference standard to classify the target condition correctly. Against a reference standard of phenotypic DST, the pooled sensitivity was considerably lower, at 51.7% (95% CI: 33.1–69.8%). Consequently, certainty of evidence was downgraded two levels for risk of bias for both sensitivity and specificity. In addition, the 95% CIs were wide for both sensitivity and specificity, which could lead to different decisions, depending on which confidence limits are assumed. Consequently, the certainty of the evidence was downgraded one level for imprecision for both sensitivity and specificity; the quality (certainty) of evidence was rated very low for both sensitivity and specificity.

**Fig. 2.4.1.3 Forest plot of included studies for ethionamide resistance detection with genotypic DST as the reference standard**



CI: confidence interval; DST: drug susceptibility testing; FIND: Foundation for Innovative New Diagnostics; FN: false negative; FP: false positive; TB: tuberculosis; TN: true negative; TP: true positive.

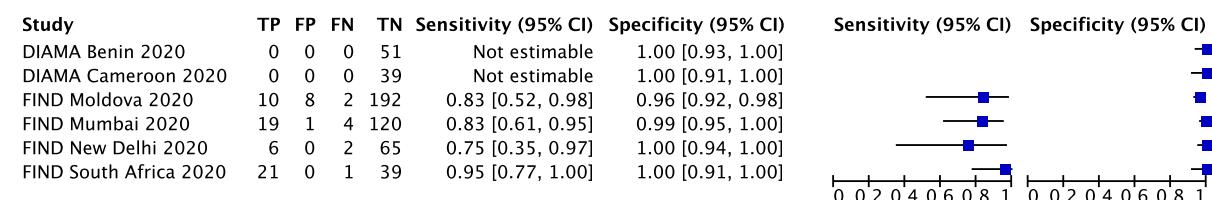
The sensitivity for ethionamide resistance in this study ranged from 78% to 100% and the specificity from 97% to 100%. **The pooled sensitivity was 98.0% (95% CI: 74.2–99.9%) and the pooled specificity was 99.7% (95% CI: 83.5–100.0%).**

**PICO 4: Should low complexity automated NAATs be used on sputum in people with signs and symptoms of pulmonary TB, and detected resistance to rifampicin, for detection of resistance to amikacin, as compared with culture-based phenotypic DST?**

One multinational study with 490 participants provided data for evaluating resistance to amikacin. The reference standard for this study was culture-based phenotypic DST. Each study centre in this multinational study was analysed as a separate study (**Fig. 2.4.1.4**).

The 95% CI for sensitivity was wide, which could lead to different decisions around true positives and false negatives, depending on which confidence limits are assumed. Also, there were few participants with amikacin resistance contributing to this analysis for the observed sensitivity. Consequently, the certainty of the evidence was downgraded two levels for imprecision. Also, there were few participants with amikacin resistance contributing to this analysis for the observed sensitivity. Consequently, the certainty of the evidence was downgraded two levels for imprecision; the quality (certainty) of evidence was rated low for sensitivity and high for specificity.

**Fig. 2.4.1.4 Forest plot of included studies for amikacin resistance detection with culture-based phenotypic DST as the reference standard**



CI: confidence interval; DIAMA: Diagnostics for Multidrug Resistant Tuberculosis in Africa; DST: drug susceptibility testing; FIND: Foundation for Innovative New Diagnostics; FN: false negative; FP: false positive; TB: tuberculosis; TN: true negative; TP: true positive.

The sensitivity for amikacin resistance in this study ranged from 75% to 95% and the specificity from 96% to 100%. **The pooled sensitivity was 86.1% (95% CI: 75.0–92.7%) and the pooled specificity was 98.9% (95% CI: 93.0–99.8%).**

## Cost-effectiveness analysis

This section answers the following additional question:

**What is the comparative cost, affordability and cost-effectiveness of implementation of low complexity automated NAATs?**

A systematic review was conducted, focusing on economic evaluations of low complexity automated NAATs. Four online databases (Embase, Medline, Web of Science and Scopus) were searched for new studies published from 1 January 2010 through 17 September 2020. The citations of all eligible articles, guidelines and reviews were reviewed for additional studies. Experts and test manufacturers were also contacted to identify any additional unpublished studies.

The objective of the review was to summarize current economic evidence and further understand the costs, cost-effectiveness and affordability of low complexity automated NAATs.

Two low complexity automated NAATs were identified: the MeltPro MTB/RIF (Xiamen Zeesan Biotech Co Ltd, China) and the Xpert MTB/XDR assay (Cepheid, Sunnyvale, USA). Only data concerning Xpert MTB/XDR are included in this review. As is the case with Xpert MTB/RIF, the novel XDR assay can be used to test either unprocessed or concentrated sputum. No published studies providing direct evidence on the cost or cost-effectiveness of low complexity automated NAATs were identified.

Through direct communication from the Xpert MTB/XDR manufacturer, Cepheid, the low- and middle-income country (LMIC) cost for the XDR cartridge is expected to be US\$ 19.80 ex-works. Shipping and customs costs will be additional and will be borne by the ordering nations or organizations, as is currently the case for Xpert MTB/RIF and Ultra cartridges.

As with the Xpert MTB/RIF and Ultra assays, the test cartridge costs represent just one component of the total unit test costs that must be considered, with equipment being another important consideration. The Xpert MTB/XDR test will not work on existing six-colour modules and will require laboratories to upgrade to 10-colour GeneXpert modules. There will be different upgrade options for the 10-colour system, with different price points depending on the needs and resources available. Upgrade options include:

- a new 10-colour system – this is the most costly option, at US\$ 9420 for one module to US\$ 72 350 for 16 modules, including the GeneXpert platform, computer and scanner;
- a new 10-colour satellite instrument with the GeneXpert connected to an existing system – this costs from US\$ 6495 for one module to US\$ 69 525 for 16 modules; and
- converting an existing GeneXpert system from a six-colour to a 10-colour system by replacing modules – a 10-colour module kit costs US\$ 3860.

Additional cost considerations for Xpert MTB/XDR include additional testing or repeated testing in the case of indeterminate or non-actionable results (indeterminate, non-determinate or invalid). The potential cost burden of this is likely to vary, depending on the proportion of indeterminate test results across settings and the associated re-testing protocols.

No studies that have directly assessed the cost-effectiveness of the Xpert MTB/XDR cartridge were identified. Although extrapolation from other platforms and testing approaches for costing may be appropriate, extrapolation of cost-effectiveness data from Xpert MTB/RIF (Ultra) or other NAATs is not advised because of differences in diagnostic accuracy, costs associated with XDR treatment, and the different testing and treatment cascade of care.

Several factors are likely to influence the cost-effectiveness of Xpert MTB/XDR; they include diagnostic accuracy, which may lead to more or fewer individuals being diagnosed compared with the standard of care (which in turn will vary, depending on the local standard of care). In addition to diagnostic accuracy associated with the test itself, the diagnostic algorithm and placement of the Xpert MTB/XDR test within the algorithm has important implications.

The novel Xpert MTB/XDR provides results in less than 90 minutes. Thus, introduction of this test is likely to result in faster time to a result for genotypic DST and could affect cost-effectiveness by improving the numbers of patients initiating treatment, reducing loss to follow-up and improving survival rates. Costs associated with XDR treatment are likely to be an important driver of cost

and cost-effectiveness because previous work has shown that these costs are high compared to diagnostic and other treatment costs. As larger numbers of XDR-positive individuals requiring treatment are identified, total resources required to treat these individuals will increase.

In the absence of transmission modelling studies, there is no information on the long-term population level impact of introducing Xpert MTB/XDR. Nevertheless, the benefits of identifying more cases earlier could lead to a reduction in ongoing transmission and potential cost-savings over the long term. This requires thorough investigations through transmission modelling.

*How large are the resource requirements (costs)?*

No published studies provided direct evidence about the total resources required. Resource requirements will include the purchase of cartridges (US\$ 19.80/cartridge), upgrading of existing platforms to 10-colour modules (an upgrade that will eventually be required for all Xpert platforms: US\$ 3860 to >US\$ 72 350) and operational and programmatic costs associated with implementing the novel diagnostic. Resource requirements for XDR treatment (e.g. drugs, hospital capacity and staff) are also likely to increase as the number of people diagnosed increases. Total costs will vary, depending on testing volume and prevalence of XDR in the population; also, the impact on the budget will depend on the current standard of care and associated resource use.

*What is the certainty of the evidence of resource requirements (costs)?*

Direct costs related to the purchase of cartridges and machinery are provided from the manufacturer; however, several important items related to resource use for implementing Xpert MTB/XDR have not been investigated (e.g. staff time, overhead and operational costs). Differences in resource use between Xpert MTB/XDR and existing approaches will vary across settings using different phenotypic and genotypic DST. There is important variability in costs of staff time and operational costs (e.g. testing volume) across settings.

*Does the cost-effectiveness of the intervention favour the intervention or the comparison?*

No cost-effectiveness studies using Xpert MTB/XDR were identified. Extrapolation of cost-effectiveness data from Xpert MTB/RIF or other NAATs is not advised because of differences in diagnostic accuracy, and costs associated with XDR treatment and the testing and treatment cascade of care.

More details on economic evidence synthesis and analysis are provided in **Web Annex B.20: Systematic literature review of economic evidence for NAATs to detect TB and DR-TB in adults and children**.

## User perspective

This section answers the following question about **key informants' views and perspectives on the use of low complexity automated NAATs**:

- Is there important uncertainty about or variability in how much end-users value the main outcomes?
- What would be the impact on health equity?
- Is the intervention acceptable to key stakeholders?
- Is the intervention feasible to implement?

The synthesis and analysis of qualitative evidence on end-users' perspectives are discussed above in the section "User perspective" for moderate complexity automated NAATs: chapter 2.1.2 of the current guidelines.

## Findings of the review and interviews

The main findings of the systematic review and interviews are given below. Where information is from the review, a level of confidence in the QES is given; where it is from interviews, this is indicated with 'Interviews'.

### Is there important uncertainty about or variability in how much end-users value the main outcomes?

- **Patients** in high burden TB settings value:
  - getting an accurate diagnosis and reaching diagnostic closure (finally knowing "what is wrong with me");
  - avoiding diagnostic delays because they exacerbate existing financial hardships and emotional and physical suffering, and make patients feel guilty for infecting others (especially children);
  - having accessible facilities; and
  - reducing diagnosis-associated costs (e.g. travel, missing work) as important outcomes of the diagnostic.

*QES: moderate confidence*

- Low complexity automated NAATs, when compared with existing tests or sputum microscopy, are appreciated by **health care professionals** because of:
  - the rapidity and accuracy of the results;
  - the confidence that a result generates to start treatment and motivate patients;
  - the diversity of sample types;
  - the ability to detect drug resistance earlier or at all, for as many drugs as possible (altering a clinician's risk perception of drug resistance in children), and the consequence of avoiding costlier investigations or hospital stays.

*QES: high confidence*

- Compared with other available diagnostic methods, the cartridge has a quicker turnaround time for first- and second-line DST. Health care professionals value the faster turnaround time, the potential ability to reflex samples from the Xpert MTB/RIF to the Xpert MTB/XDR cartridge, and receiving information on multiple drugs and high-level or low-level resistance simultaneously, because it could enable quicker diagnosis and optimized treatment for patients.

*Interviews*

- **Laboratory technicians** appreciate low complexity automated NAATs for the following reasons:
  - Overall, the tests improve laboratory work compared with sputum microscopy in terms of ease of use, ergonomics and biosafety.

*QES: high confidence*

- These tests require minimal user steps, and the GeneXpert platform is a familiar system that people feel comfortable running and interpreting.

*Interviews*

- **Laboratory managers** appreciate that monitoring of laboratory work and training is easier than with sputum microscopy, and that use of low complexity automated NAATs eases staff retention because it increases staff satisfaction and is symbolic of progress within the TB world.  
*QES: low confidence*

### **What would be the impact on health equity?**

The impact on health equity would be similar to that of moderate complexity automated NAATs: Chapter 2.1.2 of the current guidelines.

### **Is the intervention acceptable to key stakeholders?**

The acceptability to key stakeholders is similar to that of moderate complexity automated NAATs: Chapter 2.1.2 of the current guidelines.

The identified challenges in implementing the use of low complexity automated NAATs and accumulated delays at every step may compromise the added value and benefits identified by the users (e.g. avoiding delays, keeping costs low, accurate results, information on drug resistance and easing laboratory work), ultimately leading to use. *QES: high confidence* If these values are not met, it can be assumed that users are less likely to find low complexity automated NAATs acceptable.

### **Is the intervention feasible to implement?**

- Low complexity automated NAATs may decrease the workload in the laboratory in terms of freeing up time for laboratory staff. However, based on experience with Xpert MTB/RIF (Ultra), the introduction of a new class of technologies may increase the workload of laboratory staff if added onto existing work without adjusting staffing arrangements or if the new technology does not replace existing diagnostic tests.  
*QES: moderate confidence*
- Low complexity automated NAATs require less user training than other DST methods (e.g. LPA and culture), making these tests more feasible to implement than methods with more user steps and those that require significant additional training.

#### *Interview study*

Implementation of new diagnostics must be accompanied by training for clinicians, to help them interpret results from new molecular tests and understand how this relates to the treatment of a patient. In the past, with the introduction of Xpert MTB/RIF (Ultra), this has been a challenge and has led to underuse.

#### *QES: high confidence and interview study*

Introduction of Xpert MTB/RIF (Ultra) has also led to overreliance on results of cartridge-based NAATs at the expense of clinical acumen.

#### *QES: moderate confidence*

- Introduction of new diagnostics must also be accompanied by guidelines and algorithms that support clinicians and laboratories in communicating with each other; for example, these resources allow clinicians and laboratories to discuss discordant results, and interpret laboratory results in the context of drug availability, patient history and patient progress on a current drug regimen.

#### *Interviews*

- An efficient sample transportation system, with sustainable funding mechanisms, is crucial for feasibility, especially if an algorithm requires multiple samples at different times from different collection points, as is the case when dealing with DR-TB. If mishandled during preparation, there is a risk that the sample may become contaminated and yield inconclusive results on molecular diagnostics. Participants cited good personnel skills, standardized operating procedures and significant laboratory infrastructure as essential in reducing sample contamination in their laboratory.

*Interviews*

- The feasibility of low complexity automated NAATs is challenged if there is an accumulation of diagnostic delays or underuse (or both) at every step in the process, mainly because of health system factors:
  - non-adherence to testing algorithms, testing for TB or MDR-TB late in the process, empirical treatment, false negatives due to technology failure, large sample volumes and staff shortages, poor or delayed sample transport and sample quality, poor or delayed communication of results, delays in scheduling follow-up visits and recalling patients, and inconsistent recording of results;
  - lack of sufficient resources and maintenance (e.g. stock-outs; unreliable logistics; lack of funding, electricity, space, air conditioners and sputum containers; dusty environment; and delayed or absent local repair option);
  - inefficient or unclear workflows and patient flows (e.g. inefficient organizational processes, poor links between providers, and unclear follow-up mechanisms or information on where patients need to go); and
  - lack of data-driven and inclusive national implementation processes.

*QES: high confidence*

- The feasibility of using low complexity automated NAATs is also challenged by the value of diagnosing MTB over DR-TB at primary care. This situation makes the NAAT less feasible as a baseline test, although it would fit at a district or intermediate level laboratory.

## Implementation considerations

Factors to consider when implementing low complexity automated NAATs for detection of resistance to isoniazid and second-line anti-TB agents are as follows:

- local epidemiological data on resistance prevalence should guide local testing algorithms, whereas pretest probability is important for the clinical interpretation of test results;
- the cost of a test varies depending on parameters such as the number of samples in a batch and the staff time required; therefore, a local costing exercise should be performed;
- low, moderate and high complexity tests have successive increase in technical competency needs (qualifications and skills) and staff time, which affects planning and budgeting;
- availability and timeliness of local support services and maintenance should be considered when selecting a provider;
- laboratory accreditation and compliance with a robust quality management system (including appropriate quality control) are essential for sustained service excellence and trust;
- training of both laboratory and clinical staff will ensure effective delivery of services and clinical impact;
- use of connectivity solutions for communication of results is encouraged, to improve efficiency of service delivery and time to treatment initiation;

- rapid and early testing for the detection of fluoroquinolone resistance is essential before starting treatment with the all-oral MDR/RR-TB shorter regimen (i.e. 6–9 months); this may also become relevant (depending on the epidemiological context) if new shorter drug-susceptible TB regimens that include fluoroquinolones are introduced;
- these tests can be used to rule in ethionamide resistance, but not to rule out resistance, because mutations conferring resistance to ethionamide are not limited to the *inhA* promoter region – they also include *ethA*, *ethR* and other genes;
- culture-based phenotypic DST may still be required, particularly among those with a high pretest probability of resistance when the low complexity automated NAATs does not detect drug resistance; in addition, culture-based phenotypic DST:
  - remains important to determine resistance to other anti-TB agents, particularly the new and repurposed medicines, and to monitor the emergence of additional drug resistance;
  - does not apply to ethionamide because it is unreliable and poorly reproducible;
- for second-line injectable drugs, the panel evaluated the performance in detecting resistance to amikacin only because both kanamycin and capreomycin are no longer recommended for the treatment of DR-TB; and
- culture-based phenotypic DST may be important to confirm amikacin susceptibility in situations where it is appropriate to use this medicine, to balance risk and benefit.

## Research priorities

Research priorities for low complexity automated NAATs for detection of resistance to isoniazid and second-line anti-TB agents are as follows:

- diagnostic accuracy, in specific patient populations (e.g. children, people living with HIV, and patients with signs and symptoms of extrapulmonary TB) and in non-sputum samples;
- impact of diagnostic technologies on clinical decision-making and outcomes that are important to patients (e.g. cure, mortality, time to diagnosis and time to start treatment) in all patient populations;
- impact of specific mutations on treatment outcomes among people with DR-TB;
- use, integration and optimization of diagnostic technologies in the overall landscape of testing and care, as well as diagnostic pathways and algorithms;
- economic studies evaluating the costs, cost-effectiveness and cost-benefit of different diagnostic technologies;
- qualitative studies evaluating equity, acceptability, feasibility and end-user values of different diagnostic technologies;
- effect of non-actionable results (indeterminate, non-determinate or invalid) on diagnostic accuracy and outcomes that are important to patients;
- evaluation of low complexity automated NAATs for initial TB detection, in addition to its use as a follow-on test, in all people with signs and symptoms of TB, in children and in people living with HIV; and
- the potential utility of *katG* resistance detection to identify MDR-TB clones that may be missed because they do not have an RRDR mutation (e.g. the Eswatini MDR-TB clone, which has both the *katG S315T* and the non-RRDR *rpoB I491F* mutation).

## 2.4.2 First-line LPAs

In 2008, WHO approved the use of commercial LPAs for detecting MTBC in combination with resistance to rifampicin and isoniazid in sputum smear-positive specimens (direct testing) and in cultured isolates of MTBC (indirect testing). A systematic review at that time evaluated the diagnostic accuracy of two commercially available LPAs – the INNO-LiPA Rif.TB assay (Innogenetics, Ghent, Belgium), and the GenoType® MTBDRplus (version 1), hereafter referred to as Hain version 1 – and provided evidence for WHO's endorsement (37, 38). Excellent accuracy was reported for both tests in detecting rifampicin resistance, but their diagnostic accuracy for isoniazid resistance had lower sensitivity, despite the high specificity. Because there were inadequate data to allow stratification by smear status, WHO's recommendation for using LPAs was limited to culture isolates or smear-positive sputum specimens. Further data have since been published on the use of LPAs; newer versions of LPA technology have now been developed, such as the Hain GenoType MTBDRplus version 2, hereafter referred to as Hain version 2; and other manufacturers have entered the market, including Nipro (Tokyo, Japan), which developed the Genoscholar™ NTM+MDRTB II, hereafter referred to as Nipro.

In 2015, FIND evaluated the Nipro and the Hain version 2 LPAs, and compared them with Hain version 1. The study demonstrated equivalence among the three commercially available LPAs for detecting TB and resistance to rifampicin and isoniazid (5).

**Table 2.4.2.1 Class criteria for LPAs**

Purpose	Detection of resistance to first- and/ or second-line TB drugs
<b>Principle of action</b>	DNA-based reverse hybridization, or line probe, assays
<b>Complexity</b>	<b>Reagents</b> Reagents are available within standardized kits and may have temperature requirements for storage.  <b>Skills</b> Advanced technical skills (i.e., multiple sample or reagent handling steps, precision pipetting, molecular workflows may be required)  <b>Pipetting</b> Multiple precision pipetting steps required by the procedure.
<b>Testing Procedure</b>	May require multiple specimen treatment steps before transferring the specimen into a sealed container for multi-step testing.  Manual or automated DNA extraction Manual or automated real-time PCR Instrument-based reverse hybridization
<b>Type of test result reporting</b>	Manual
<b>Setting of use</b>	Molecular laboratory (special infrastructure and separate of spaces for different parts of the testing procedure are required)

## Recommendation

**13. For persons with a sputum smear-positive specimen or a cultured isolate of MTBC, commercial molecular LPAs may be used as the initial test instead of phenotypic culture-based DST to detect resistance to rifampicin and isoniazid.**

*(Conditional recommendation, moderate certainty in the evidence for the test's accuracy)*

## Remarks

1. These recommendations apply to the use of LPAs for testing sputum smear-positive specimens (direct testing) and cultured isolates of MTBC (indirect testing) from both pulmonary and extrapulmonary sites.
2. LPAs are not recommended for the direct testing of sputum smear-negative specimens.
3. These recommendations apply to the detection of MTBC and the diagnosis of MDR-TB, but acknowledge that the accuracy of detecting resistance to rifampicin and isoniazid differs and, hence, that the accuracy of a diagnosis of MDR-TB is reduced overall.
4. These recommendations do not eliminate the need for conventional culture-based DST, which will be necessary to determine resistance to other anti-TB agents and to monitor the emergence of additional drug resistance.
5. Conventional culture-based DST for isoniazid may still be used to evaluate patients when the LPA result does not detect isoniazid resistance. This is particularly important for populations with a high pretest probability of resistance to isoniazid.
6. These recommendations apply to the use of LPA in children based on the generalization of data from adults.

## Test description

LPAs are a family of DNA strip-based tests that can detect the MTBC strain and determine its drug resistance profile through the pattern of binding of amplicons (DNA amplification products) to probes targeting the following: specific parts of the MTBC genome (for MTBC detection), the most common resistance-associated mutations to first-line and second-line agents, or the corresponding wild-type DNA sequence (for detection of resistance to anti-TB drugs) (38).

LPAs are based on reverse hybridization DNA strip technology and involve three steps: DNA extraction from *M. tuberculosis* culture isolates or directly from patient specimens, followed by multiplex PCR amplification and then reverse hybridization with visualization of amplicon binding (or lack thereof) to wild-type and mutation probes (8).

Although LPAs are more technically complex to perform than the Xpert MTB/RIF assay, they can detect isoniazid resistance. Testing platforms have been designed for a reference laboratory setting and are thus most applicable to high TB burden countries. Results can be obtained in 5 hours.

Some of these steps can be automated, making the method quicker and more robust, and reducing the risk of contamination.

The Hain version 1 and version 2 assays include *rpoB* probes to detect rifampicin resistance, *katG* probes to detect mutations associated with high-level isoniazid resistance, and *inhA* promoter probes to detect mutations usually associated with low-level isoniazid resistance. The probes used to detect wild-type and specific mutations are the same for both versions of the Hain LPA.

Similarly, the Nipro assay allows for the identification of MTBC, and resistance to rifampicin and isoniazid. The Nipro assay also differentiates *M. avium*, *M. intracellulare* and *M. kansasii* from other non-tuberculous mycobacteria.

The *rpoB*, *katG* and *inhA* promoter mutation probes are the same for the three assays, with the exception of the *katG* S315N mutation, which is included in the Nipro assay but not in Hain version 1 or version 2. There are some minor variations in the codon regions covered for the wild type among Hain version 1 and version 2, and the Nipro.

## Justification and evidence

In 2015, WHO commissioned an updated systematic review of the accuracy of commercial LPAs for detecting MTBC, and resistance to rifampicin and isoniazid. A total of 74 studies were identified, comprising 94 unique datasets (see **Web Annex A.7: "FL-LPA"**). Of these 94 datasets, 83 evaluated Hain version 1, five evaluated Hain version 2, and six evaluated the Nipro assay. Only one of the studies performed head-to-head testing of all three target LPAs on directly tested clinical specimens and indirectly tested isolates, and these data were included as six separate datasets (9). No studies performed LPA testing on specimens and culture isolates from the same patients, precluding direct within-study comparisons.

Following the 2015 systematic review, the WHO Global TB Programme convened a GDG in March 2016 to assess the data and update the 2008 policy recommendations on using commercial LPAs to detect MTBC, and resistance to isoniazid and rifampicin. The PICO questions are given in **Box 2.4.2.1**.

LPAs were compared with a phenotypic culture-based DST reference standard, and a composite reference standard that combined the results from genetic sequencing with results from phenotypic culture-based DST. Phenotypic DST was the primary reference standard applied to all participants for all analyses. These analyses were stratified – first, by susceptibility or resistance to rifampicin or isoniazid (or both) and second, by type of LPA testing (indirect testing or direct testing).

### Box 2.4.2.1 PICO questions

1. Should LPAs be used to guide clinical decisions to use rifampicin in the direct testing of specimens and the indirect testing of culture isolates from patients with signs and symptoms consistent with TB?
2. Should LPAs be used to guide clinical decisions to use isoniazid in the direct testing of specimens and the indirect testing of culture isolates from patients with signs and symptoms consistent with TB?
3. Should LPAs be used to diagnose MDR-TB in patients with signs and symptoms consistent with TB?
4. Should LPAs be used to diagnose TB in patients with signs and symptoms consistent with TB but for whom sputum-smear results are negative?

Several studies contributed to either sensitivity (no true positives and no false negatives) or specificity (no true negatives and no false positives) but not to both. For these studies, a univariate, random-effects meta-analysis of the estimates of sensitivity or specificity was performed separately, to make optimal use of the data. The results from the univariate analysis (using all studies) were compared with the results from the bivariate analysis of the subset of studies that contributed to estimates of both sensitivity and specificity.

If there were at least four studies for index tests with data that contributed only to sensitivity or specificity, a univariate, random-effects meta-analysis was performed to assess one summary estimate, assuming no correlation between sensitivity and specificity. In cases in which there were fewer than four studies, or where substantial heterogeneity was evident on forest plots that precluded a meta-analysis, a descriptive analysis was performed for these index tests. Forest plots were visually assessed for heterogeneity among the studies within each index test and in the summary plots, for variability in estimates and the width of the prediction region (a wider prediction region suggests more heterogeneity).

### Implementation considerations

Adopting LPAs to detect rifampicin and isoniazid resistance does not eliminate the need for conventional culture and DST capacity. Culture and phenotypic culture-based DST have critical roles in monitoring patients' responses to treatment and detecting additional resistance to second-line agents.

- The adoption of LPA should be phased in, starting at national or central reference laboratories, or those with proven capability to conduct molecular testing. Expansion could be considered, within the context of a country's plans for laboratory strengthening, the availability of suitable personnel in peripheral centres and the quality of specimen transport systems.
- Adequate and appropriate laboratory infrastructure and equipment should be provided, to ensure that the required precautions for biosafety and the prevention of contamination are met – specimen processing for culture and procedures for manipulating cultures must be performed in biological safety cabinets in TB-containment laboratories.

- Laboratory facilities for LPAs require at least three separate rooms, one each for DNA extraction, pre-amplification procedures, and amplification and post-amplification procedures. To avoid contamination, access to molecular facilities must be restricted, a unidirectional workflow must be implemented and stringent cleaning protocols must be established.
- Appropriate laboratory staff should be trained to conduct LPA procedures. Staff should be supervised by a senior staff member with adequate training and experience in molecular assays. A programme for the external quality assessment of laboratories using LPAs should be developed as a priority.
- Mechanisms for rapidly reporting LPA results to clinicians must be established, to provide patients with the benefit of early diagnosis. The same infrastructure used for performing LPAs can be used also to perform second-line LPAs.
- LPAs are designed to detect TB and resistance to rifampicin and isoniazid in the direct testing of processed sputum samples, and in the indirect testing of culture isolates of MTBC. The use of LPAs with other respiratory samples (e.g. from BAL or gastric aspiration) or extrapulmonary samples (e.g. tissue samples, CSF or other body fluids) have not been adequately evaluated.
- The availability of second-line agents is critical in the event that resistance to rifampicin or isoniazid, or both, is detected.
- For patients with confirmed MDR/RR-TB, second-line LPAs are recommended to detect additional resistance to second-line anti-TB agents.

## Research priorities

- Development of improved understanding of the correlation between the detection of resistance-conferring mutations using culture-based DST and patient outcomes.
- Review of evidence to confirm or revise different critical concentrations used in culture-based DST methods.
- Determination of the limit of detection for LPA in detecting heteroresistance.
- Determination of needs for training, assessing competency and ensuring quality assurance.
- Gathering of more evidence on the impact on mortality of initiating appropriate treatment for MDR-TB.
- Meeting the STARD for future diagnostic studies.
- Performance of country-specific cost–effectiveness and cost–benefit analyses of LPA use in different programmatic settings.

### 2.4.3 Second-line LPAs

Genotypic (molecular) methods have considerable advantages for scaling up programmatic management and surveillance of DR-TB, offering rapid diagnosis, standardized testing, potential for high throughput and fewer requirements for laboratory biosafety. Molecular tests for detecting drug resistance – for example, the GenoType MTBDRs/ assay (Hain Lifescience, Nehren, Germany), hereafter referred to as MTBDRs/ (10) – have shown promise for the diagnosis of DR-TB. These tests are rapid (can be performed in a single working day) and detect the presence of mutations associated with drug resistance. MTBDRs/ belongs to a category of molecular genetic tests called second-line LPAs (SL-LPAs).

MTBDRs/ (version 1.0) was the first commercial SL-LPA for detection of resistance to second-line TB drugs. In 2015, the manufacturer developed and made commercially available version 2.0 of the MTBDRs/ assay. Version 2.0 detects the mutations associated with fluoroquinolones and second-line injectable drug (SLID) resistance detected by version 1.0, and additional mutations. Once a diagnosis of MDR/RR-TB has been established, an SL-LPA can be used to detect additional resistance to second-line drugs.

The MTBDRs/ assay incorporates probes to detect mutations within genes that are associated with resistance to either fluoroquinolones or SLIDs (*gyrA* and *rrs* for version 1.0 and those genes plus *gyrB* and the *eis* promoter for version 2.0). The presence of mutations in these regions does not necessarily imply resistance to all the drugs within a particular class. Although specific mutations within these regions may be associated with different levels of resistance (i.e. different minimum inhibitory concentrations) to each drug within these classes, the extent of cross-resistance is not completely understood.

## Recommendations

**14. For patients with confirmed MDR/RR-TB, SL-LPA may be used as the initial test, instead of phenotypic culture-based DST, to detect resistance to fluoroquinolones.**

(conditional recommendation, moderate certainty in the evidence for test accuracy)

**15. For patients with confirmed MDR/RR-TB, SL-LPA may be used as the initial test, instead of phenotypic culture-based DST, to detect resistance to the SLIDs.**

(conditional recommendation, low certainty in the evidence for test accuracy)

## Remarks

- These recommendations apply to the use of SL-LPA for testing sputum specimens (direct testing) and cultured isolates of *M. tuberculosis* (indirect testing) from both pulmonary and extrapulmonary sites. Direct testing on sputum specimens allows for the earlier initiation of appropriate treatment.
- These recommendations apply to the direct testing of sputum specimens from MDR/RR-TB, irrespective of the smear status, while acknowledging that the indeterminate rate is higher when testing smear-negative sputum specimens than with smear-positive sputum specimens.
- These recommendations do not eliminate the need for conventional phenotypic DST capacity, which will be necessary to confirm resistance to other drugs and to monitor the emergence of additional drug resistance.
- Conventional phenotypic DST can still be used in the evaluation of patients with negative SL-LPA results, particularly in populations with a high pretest probability for resistance to fluoroquinolones or SLID (or both).
- These recommendations apply to the use of SL-LPA in children with confirmed MDR/RR-TB, based on the generalization of data from adults.
- Resistance-conferring mutations detected by SL-LPA are highly correlated with phenotypic resistance to ofloxacin and levofloxacin.

- Resistance-conferring mutations detected by SL-LPA are highly correlated with phenotypic resistance to SLID.
- Given the high specificity for detecting resistance to fluoroquinolones and SLID, the positive results of SL-LPA could be used to guide the implementation of appropriate infection control precautions.

## Test description

The SL-LPA is based on the same principle as the first-line LPA. The assay procedure can be performed **directly** using a processed sputum sample or **indirectly** using DNA isolated and amplified from a culture of *M. tuberculosis*. Direct testing involves the following steps:

1. Decontamination (e.g. with sodium hydroxide) and concentration of a sputum specimen by centrifugation.
2. Isolation and amplification of DNA.
3. Detection of the amplification products by reverse hybridization.
4. Visualization using a streptavidin-conjugated alkaline phosphatase colour reaction.

Indirect testing includes only Steps 2–4. The observed bands, each corresponding to a wild-type or resistance-genotype probe, can be used to determine the drug susceptibility profile of the analysed specimen. The assay can be performed and completed within a single working day. Further details on the test process and practical support for implementation can be found in the WHO operational handbook. Module 3: diagnosis.

The index test used was MTBDRs/ versions 1.0 and 2.0. These SL-LPAs detect specific mutations associated with resistance to the class of fluoroquinolones (including ofloxacin, levofloxacin, moxifloxacin and gatifloxacin) and SLIDs (including kanamycin, amikacin and capreomycin) in the MTBC. The MTBDRs/ LPA detects mutations in the *gyrA* quinolone resistance-determining region (codons 85–97) and *rrs* (codons 1401, 1402 and 1484), and version 2.0 of the test added detection of mutations in the *gyrB* quinolone resistance-determining region (codons 536–541) and the *eis* promoter region (codons –10 to –14) (40). Version 2.0 is therefore expected to have improved sensitivity for resistance detection to these classes of drugs. Lastly, while version 1.0 included detection of mutations in *embB* that may encode for resistance to ethambutol, it was omitted from version 2.0 due to its status as a first line anti-TB drug. Therefore, this review did not determine the accuracy for ethambutol resistance.

More data are needed to better understand the correlation of the presence of certain fluoroquinolone resistance-conferring mutations with phenotypic DST resistance and with patient outcomes.

## Justification and evidence

In March 2016, the WHO Global TB Programme convened a GDG to assess available data on the use of the MTBDRs/ assay. WHO commissioned a systematic review on the accuracy and clinical use of assays for the detection of mutations associated with resistance to fluoroquinolones and SLID in people with MDR/RR-TB.

The PICO questions in **Box 2.4.3.1** were designed to form the basis for the evidence search, retrieval and analysis.

#### Box 2.4.3.1 PICO questions

1. **Should the MTBDR<sub>SI</sub> test be used to guide clinical decisions to use fluoroquinolones in patients with confirmed MDR/RR-TB?**
  - ➔ Direct testing (stratified by smear grade: smear negative; scanty; 1+; ≥2+).
  - ➔ Indirect testing.
2. **Should the MTBDR<sub>SI</sub> test be used to guide clinical decisions to use SLIDs in patients diagnosed with MDR/RR-TB?**
  - ➔ Direct testing (stratified by smear grade: smear negative; scanty; 1+; ≥2+).
  - ➔ Indirect testing.

Twenty-nine unique studies were identified; of these, 26 evaluated the MTBDRs/ version 1.0 assay (including 21 studies from the original Cochrane review). Three studies (one published and two unpublished) evaluated version 2.0. Data for version 1.0 and version 2.0 of the MTBDRs/ assay were analysed separately. A phenotypic culture-based DST reference standard was used for the primary analyses. These analyses were stratified first by susceptibility or resistance to a particular drug, and second by type of SL-LPA testing (indirect testing or direct testing).

### Performance of SL-LPA on sputum specimens and culture isolates

In patients with MDR/RR-TB, a positive SL-LPA result for fluoroquinolone resistance (as a class) or SLID resistance (as a group) can be treated with confidence. The diagnostic accuracy of SL-LPA is similar when performed directly on sputum specimens or indirectly on cultured isolates of *M. tuberculosis*.

Given the confidence in a positive result and the ability of the test to provide rapid results, the GDG felt that SL-LPA may be considered for use as an initial test for resistance to the fluoroquinolones and when relevant SLIDs. However, when the test shows a negative result, phenotypic culture-based DST may be necessary, especially in settings with a high pretest probability for resistance to either fluoroquinolones or SLIDs (or both). The use of SL-LPA in routine care should improve the time to the diagnosis of fluoroquinolone and where relevant SLIDs, especially when used for the direct testing of sputum specimens of patients with confirmed MDR/RR-TB. Early detection of drug resistance should allow for the earlier initiation of appropriate patient therapy and improved patient health outcomes. Overall, the test performs well in the direct testing of sputum specimens from patients with confirmed MDR/RR-TB, although the indeterminate rate is higher when testing smear-negative sputum specimens compared with smear-positive sputum specimens.

When the MTBDRs/ assay is used in the direct testing of smear-negative sputum specimens from a population of patients with confirmed DR-TB, up to 44% of the results may be indeterminate

(less with version 2.0, although very limited data) and hence require repeat or additional testing. However, if the same test were to be applied to the testing of smear-negative sputum specimens from patients without confirmed TB or DR-TB (i.e. patients suspected of having DR-TB), the indeterminate rate for the test would be significantly higher. Given the test's sensitivity and specificity when an SL-LPA is done directly on sputum, the GDG felt that SL-LPAs can be used for the testing of all sputum specimens from patients with confirmed MDR/RR-TB, irrespective of whether the microscopy result is positive or negative.

For the reasons mentioned above (inadequate data owing to too few studies on version 2.0), results are not presented here for version 2.0. For MTBDRs/ version 2.0, the data were either too sparse or too heterogeneous to combine in a meta-analysis or to compare indirect and direct testing.

Three studies evaluated the MTBDRs/ version 2.0 in 562 individuals, including 111 confirmed cases of TB with fluoroquinolone resistance by indirect testing on a culture of *M. tuberculosis* compared with a phenotypic culture-based DST reference standard. Estimates of sensitivity ranged from 84% to 100% and specificity from 99% to 100%.

See **Web Annex B.15: Drug concentrations used in culture-based DST SL-LPA** for details of the drug concentrations used in culture-based DST to evaluate the performance of SL-LPAs in each included study.

## Implementation considerations

The SL-LPA should only be used to test specimens from patients with confirmed MDR/RR-TB. Adoption of SL-LPAs does not eliminate the need for conventional culture and DST capability. Despite good specificity of SL-LPAs for the detection of resistance to fluoroquinolones and the SLIDs, culture and phenotypic DST is required to completely exclude resistance to these drug classes as well as to other second-line drugs. The following implementation considerations apply:

- SL-LPAs cannot determine resistance to individual drugs in the class of fluoroquinolones. Resistance-conferring mutations detected by SL-LPAs are highly correlated with phenotypic resistance to ofloxacin and levofloxacin.
- Mutations in some regions (e.g. the *eis* promoter region) may be responsible for causing resistance to one drug in a class more than other drugs within that class. For example, the *eis* C14T mutation is associated with kanamycin resistance in strains from Eastern Europe.
- SL-LPAs should be used in the direct testing of sputum specimens, irrespective of whether samples are smear negative or smear positive.
- SL-LPAs are designed to detect TB and resistance to fluoroquinolones and SLIDs from sputum samples. Other respiratory samples (e.g. BAL and gastric aspirates) or extrapulmonary samples (tissue samples, CSF or other body fluids) have not been adequately evaluated.
- Culture and phenotypic DST plays a critical role in the monitoring of a patient's response to treatment, and in detecting additional resistance to second-line drugs during treatment.
- SL-LPAs are suitable for use at the central or national reference laboratory level; they can also be used at the regional level if the appropriate infrastructure can be ensured (three separate rooms are required).
- All patients identified by SL-LPAs should have access to appropriate treatment and ancillary medications.

## Research priorities

- Development of improved understanding of the correlation between the detection of resistance-conferring mutations with phenotypic DST results and with patient outcomes.
- Development of improved knowledge of the presence of specific mutations detected with SL-LPA correlated with minimum inhibitory concentrations for individual drugs within the classes of fluoroquinolones and SLIDs.
- Determination of the limit of detection of SL-LPA for the detection of heteroresistance.
- Gathering of more evidence on the impact of MTBDRs/ on appropriate MDR-TB treatment initiation and mortality.
- Strongly encourage that future studies follow the recommendations in the STARD (11) statement to improve the quality of reporting.
- Performance of country-specific cost–effectiveness and cost–benefit analyses of the use of SL-LPA in different programmatic settings.

### 2.4.4 High complexity reverse hybridization-based NAATs for detection of pyrazinamide resistance

Pyrazinamide is an important antibiotic for the treatment of both drug-susceptible TB and DR-TB because of its unique ability to eradicate persisting bacilli and its synergistic properties with other antibiotics. Mono-resistance to pyrazinamide is rare; however, pyrazinamide resistance is strongly associated with MDR/RR-TB, with an estimated 30–60% of MDR/RR-TB also resistant to pyrazinamide. Thus, for people diagnosed with RR-TB, it is important to detect the presence of pyrazinamide resistance so that clinicians can make an informed decision on whether to include or exclude pyrazinamide in the treatment regimen. The high complexity hybridization-based NAAT may be used for diagnosis of pyrazinamide resistance on patient isolates; however, performance of this test requires appropriate infrastructure and skilled staff.

#### Recommendation

- 16. In people with bacteriologically confirmed TB, high complexity reverse hybridization-based NAATs may be used on *Mtb* culture isolates for detection of pyrazinamide resistance rather than culture-based phenotypic DST.**

*(Conditional recommendation, very low certainty of evidence for diagnostic accuracy)*

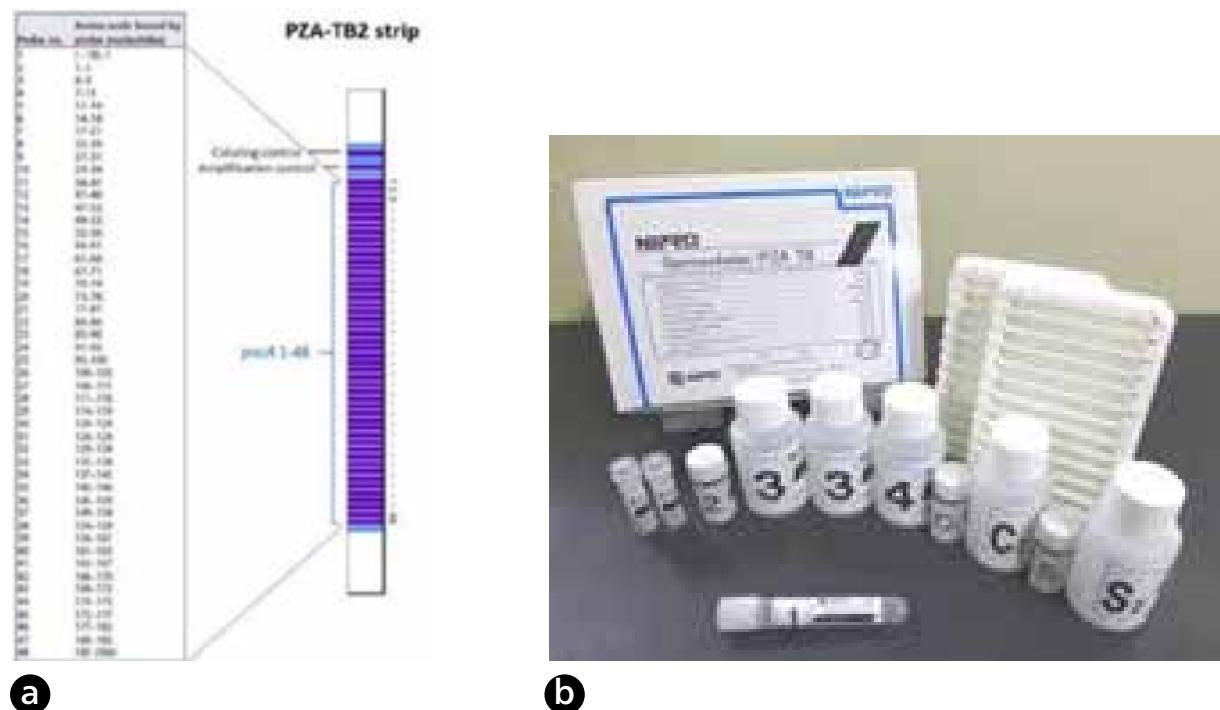
In terms of subgroups to be considered for this recommendation, no special considerations are required (e.g. for children, people living with HIV and those with extrapulmonary TB), given that the test is recommended for use on culture isolates.

#### Test description

Nipro (Osaka, Japan) developed Genoscholar™ PZA-TB, an LPA with reverse hybridization-based technology for detection of pyrazinamide resistance (12). This assay is a commercially available rapid molecular test for detection of pyrazinamide resistance. Compared with MTBDRplus and MTBDRs/ LPA, the Genoscholar PZA-TB LPA does not include specific mutant

probes because resistance mutations are widespread across the entire *pncA* gene with no predominant mutations. Instead, the Genoscholar PZA-TB assay targets a 700 base pair (bp) fragment covering the entire *pncA* gene and promoter region up to nucleotide –18 of the wild-type H37Rv reference strain.

**Fig. 2.4.4.1 Nipro GenoScholar PZA-TB II strip (a) and Nipro GenoScholar PZA-TB II kit contents (b)**



DNA extracted from cultures is amplified with primers by PCR. Amplified DNA is then hybridized to complementary oligonucleotide probes that are bound on a membrane strip. Streptavidin labelled with alkaline phosphatase is then added, to bind to any hybrids formed in the previous step. Next, a substrate is added, and an enzymatic reaction results in purple bands, which are visually interpreted. The absence of wild-type probe binding indicates the presence of a mutation. The first version of the assay contained 47 probes, which covered the *pncA* promoter and open reading frame. The second version contained 48 probes, three of which (*pncA* 16, 17 and 35) represent silent mutations known to be genetic markers not associated with pyrazinamide resistance: Gly60Gly (probe 16), Ser65Ser (probe 17) and Thr142Thr (probe 35).

### Justification and evidence

The Genoscholar PZA-TB LPA assay, which is already commercially available, could potentially be implemented for diagnosis of pyrazinamide resistance in routine care. However, limited data have been published on the diagnostic accuracy of the assay. This systematic review with meta-analysis aimed to assist in collating all the available data to understand the diagnostic accuracy of the pyrazinamide LPA assay for detection of pyrazinamide resistance in TB patients, to guide policy-makers and clinicians.

The WHO Global TB Programme initiated an update of the current guidelines and commissioned a systematic review on the use of high complexity reverse hybridization-based NAATs for detection of pyrazinamide resistance in people with signs and symptoms of TB.

Two PICO questions were designed to form the basis for the evidence search, retrieval and analysis:

1. Should high complexity reverse hybridization-based NAATs on sputum be used to diagnose pyrazinamide resistance in patients with microbiologically confirmed pulmonary TB, irrespective of resistance to rifampicin, as compared with culture-based phenotypic DST or composite reference standard?
2. Should high complexity reverse hybridization-based NAATs on isolates be used to diagnose pyrazinamide resistance in patients with microbiologically confirmed pulmonary TB, irrespective of resistance to rifampicin, as compared with culture-based phenotypic DST?

The databases searched were PubMed, Web of Science and Embase, and they were searched without language or date restrictions. The search query was (PZA OR pyrazinamide OR pncA) AND (tuberculosis) AND (“line-probe assay” OR LPA OR “hybridization-based technology”). In addition, we approached Nipro (Osaka, Japan) to identify non-published data.

The microbiological reference standard was defined either as phenotypic culture-based DST performed using BD MGIT 960 PZA liquid assay or another acceptable phenotypic assay, or as genotypic DST performed using either targeted sequencing of the *pncA* gene or whole genome sequencing. In the case of genotypic DST, all samples with a *pncA* wild type were defined as being susceptible, while any variant in *pncA* was considered resistant, which implicitly would categorize “silent” mutations as resistant. In contrast, the composite reference standard was defined by classifying all samples with *pncA* wild type, *pncA* silent mutations and neutral mutations as being susceptible, while any other variant in *pncA* was considered resistant (13).

Data synthesis was structured around the two preset PICO questions, as outlined below. Three web annexes give additional information, as follows:

- details of studies included in the current analysis (**Web Annex A.9: High complexity reverse hybridization-based NAATs**);
- a summary of the results and details of the evidence quality assessment (**Web Annex A.9: High complexity reverse hybridization-based NAATs**); and
- a summary of the GDG panel judgements (**Web Annex A.9: High complexity reverse hybridization-based NAATs**).

**PICO 1: Should high complexity reverse hybridization-based NAATs on sputum be used to diagnose pyrazinamide resistance in patients with microbiologically confirmed pulmonary TB, irrespective of resistance to rifampicin, as compared with culture-based phenotypic DST or composite reference standard?**

Three studies with a total of 122 participants provided data for evaluation of these NAATs for detection of pyrazinamide resistance, including two studies (101 participants) with phenotypic culture-based reference standard and one study (21 participants) with genotypic reference

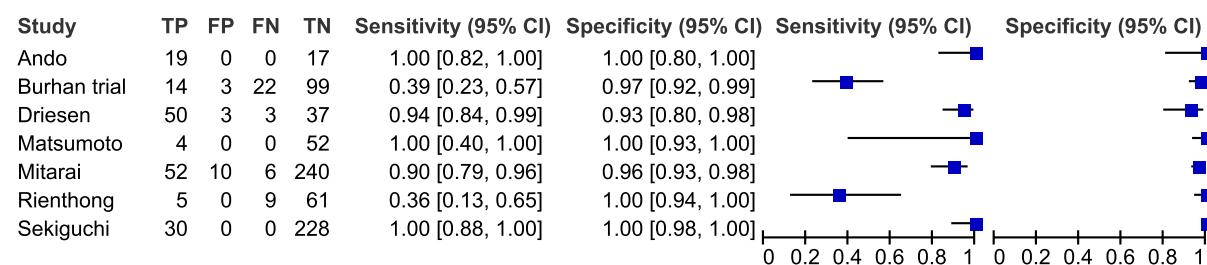
standard. **The number of studies and participants were considered insufficient to make a conclusion on a diagnostic accuracy of high complexity reverse hybridization-based NAATs on sputum.**

**PICO 2: Should high complexity reverse hybridization-based NAATs on isolates be used to diagnose pyrazinamide resistance in patients with microbiologically confirmed pulmonary TB, irrespective of resistance to rifampicin, as compared with culture-based phenotypic DST?**

Seven studies with a total of 964 participants provided data for evaluation of these NAATs for detection of pyrazinamide resistance compared with a phenotypic culture-based reference standard (**Fig. 2.4.4.2**).

The studies suffered from selection bias because they selected isolates with a wide range of different *pncA* mutations rather than a representative sample from a population. Thus, the evidence was downgraded by one level for risk of bias. The included studies did not directly address the review question; hence, the evidence was downgraded one level for indirectness. The Burhan trial and the Rienthong study are outliers for their sensitivities compared with the other studies; hence, the evidence was downgraded one level for inconsistency. Taking these judgements together, the quality (certainty) of evidence was rated very low for sensitivity and low for specificity.

**Fig. 2.4.4.2 Forest plot of included studies for pyrazinamide resistance detection, irrespective of rifampicin resistance with culture-based phenotypic DST as the reference standard**



CI: confidence interval; DST: drug susceptibility testing; FN: false negative; FP: false positive; TB: tuberculosis; TN: true negative; TP: true positive.

The overall sensitivity for pyrazinamide resistance in these seven studies ranged from 36% to 100% and the specificity from 96% to 100%. **The pooled sensitivity was 81.2% (95% CI: 75.4–85.8%) and specificity was 97.8% (95% CI: 96.5–98.6%).**

More details on diagnostic accuracy of the high complexity reverse hybridization-based NAATs, including comparison with genotypic and composite reference standards are available in **Web Annex 4.17: High complexity reverse hybridization-based NAATs: diagnostic accuracy for detection of resistance to pyrazinamide. A systematic review.**

## Cost-effectiveness analysis

This section answers the following additional question:

### **What is the comparative cost, affordability and cost-effectiveness of implementation of high complexity reverse hybridization-based NAATs?**

A systematic review was carried out, focusing on economic evaluations of high complexity reverse hybridization-based NAATs. Four online databases (Embase, Medline, Web of Science and Scopus) were searched for new studies published from 1 January 2010 through 17 September 2020. The citations of all eligible articles, guidelines and reviews were reviewed for additional studies. The experts and test manufacturers were also contacted to identify any additional unpublished studies.

The objective of the review was to summarize current economic evidence and further understand the costs, cost-effectiveness and affordability of high complexity reverse hybridization-based NAATs.

No published studies were identified assessing costs or cost-effectiveness using the commercially available high complexity hybridization-based NAAT (Genoscholar PZA-TB II, Nipro Japan). Indirect evidence was available from several sources. Four studies examining other commercially available LPAs (Genotype MTBDRs/ and MTBDRplus, Hain Lifescience) were identified.

The Genoscholar PZA LPA was developed for use with the Nipro automated MultiBlot; however, a recent unpublished trial<sup>12</sup> demonstrated that the Twincubator by Hain Lifescience could be used successfully with this LPA. This finding could make it easier to implement the Genoscholar PZA LPA in selected settings where Hain Lifescience equipment is already in use.

#### *How large are the resource requirements (costs)?*

No direct evidence from published studies was found regarding the total resources required. Resource requirements will include the purchase of test kits (Genoscholar PZA LPA: US\$ 16/test kit consumables only), and the equipment, which is available for US\$ 14 000. Operational costs are frequently several times greater than test kit costs (and will vary across settings), but are not accounted for usually. Nipro hopes that further reductions in test costs can be achieved when the Genoscholar PZA-TB II product is distributed globally.

Unit test costs for the Genotype MTBDRs/ and MTBDRplus ranged from US\$ 23.46 to US\$ 108.70 (14–15), with higher unit test costs in countries such as China and South Africa, largely driven by higher staff wages and operational costs. Extrapolations from unit test costs using different LPAs should be done with caution, and they are not intended to be directly transferrable estimates. Nevertheless, these indirect data do suggest that the total unit test cost of the Genoscholar PZA-TB II is likely several-fold higher than the unit test kit consumable cost of US\$ 16.

Total costs will vary, depending on testing volume, numbers eligible for testing and prevalence of pyrazinamide resistance in the population. The impact on the budget will depend on the current standard of care, diagnostic and care pathways, and associated resource use.

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<sup>12</sup> Leen Rigouts: Validation study of Genoscholar PZA LPA in three Supranational TB Reference Laboratories.

*What is the certainty of the evidence of resource requirements (costs)?*

Direct costs related to test kits and machinery are available, whereas several important items related to resource use (e.g. staff time, and overhead and operational costs associated with implementing Genoscholar PZA-TB II) have not been investigated. Differences in resource use between Genoscholar PZA-TB II and existing approaches will vary across settings that are using different phenotypic and genotypic DST. Also, there is important variability in costs of staff time and operation (e.g. testing volume) across settings.

*Does the cost-effectiveness of the intervention favour the intervention or the comparison?*

No cost-effectiveness studies were identified using the Genoscholar PZA-TB II. Extrapolation of cost-effectiveness data from other LPAs is not advised owing to differences in diagnostic accuracy, resistance prevalence, and the testing and treatment cascade of care.

More details on economic evidence synthesis and analysis are given in **Web Annex 4.9: Systematic literature review of economic evidence for NAATs to detect TB and DR-TB in adults and children**.

## User perspective

This section answers the following questions about **key informants' views and perspectives on the use of high complexity reverse hybridization-based NAATs**:

- Is there important uncertainty about or variability in how much end-users value the main outcomes?
- What would be the impact on health equity?
- Is the intervention acceptable to key stakeholders?
- Is the intervention feasible to implement?

## Findings of the review and interviews

The main findings of the systematic review and interviews are given below. Where information is from the review, a level of confidence in the QES is given; where it is from interviews, this is indicated with 'Interviews'.

### **Is there important uncertainty about or variability in how much end-users value the main outcomes?**

- **Patients** in high burden TB settings value:
  - getting an accurate diagnosis and reaching diagnostic closure (finally knowing "what is wrong with me");
  - avoiding diagnostic delays because they exacerbate existing financial hardships and emotional and physical suffering, and make patients feel guilty for infecting others (especially children);
  - having accessible facilities; and
  - reducing diagnosis-associated costs (e.g. travel, missing work) as important outcomes of the diagnostic.

*QES: moderate confidence*

- The high complexity reverse hybridization-based NAATs meet some preferences and values of **laboratory staff** and **clinicians**, in that the current test:
  - provides quicker results about pyrazinamide resistance than other available methods (e.g. culture DST);
  - can provide information on different concentration levels; and
  - targets a drug that is widely used in first-line TB treatment.

*Interviews*

### **What would be the impact on health equity?**

The impact on health equity would be similar to that of moderate complexity automated NAATs (Section 2.1.2), plus the following:

- Lengthy diagnostic delays, underuse of diagnostics, lack of TB diagnostic facilities at lower levels and too many eligibility restrictions hamper access to prompt and accurate testing and treatment, particularly for vulnerable groups.

*QES: high confidence*

*Applicability to three index tests also confirmed in interviews*

- Staff and managers voiced concerns about the sustainability of funding and maintenance, complex conflicts of interest between donors and implementers, and the strategic and equitable use of resources, which makes it difficult to ensure equitable access to cartridge-based diagnostics.

*QES: high confidence*

- For patients, access to clear, comprehensible and dependable information on what TB diagnostics are available to them and how to interpret results is a vital component of equity; lack of such access represents an important barrier for patients.

*Interviews*

- New treatment options need to be matched with new diagnostics: it is important to improve access to treatment based on new diagnostics, and to improve access to diagnostics for new treatment options.

*Interviews*

- The speed at which WHO guidelines are changing does not match the speed at which many country programmes are able to implement the guidelines. This translates into differential access to new TB diagnostics and treatment:
  - between countries (i.e. between those that can and cannot quickly keep up with the rapidly changing TB diagnostic environment); and
  - within countries (i.e. between patients who can and cannot afford the private health system that is better equipped to quickly adopt new diagnostics and policies).

*Interviews*

### **Is the intervention acceptable to key stakeholders?**

- Acceptability of a high complexity reverse hybridization-based NAAT depends on how well the test performs on different samples, because laboratory staff question how well LPA methods work on smear-negative samples. If samples need to be cultured before the pyrazinamide LPA is run, this may undermine the benefits of this method's quicker turnaround time compared with phenotypic DST for pyrazinamide. Acceptability also depends on how well the test actually detects mutations specific to pyrazinamide resistance; clinicians and

laboratory staff may require further clarification and justification in some settings as to why this specific drug test is being prioritized, given that it is not currently part of routine DST.

- Specific feasibility challenges (training and infrastructure requirements, sample quality result interpretation system), general feasibility challenges (as identified in the interview study and QES, respectively) and accumulated delays risk undoing the added value and benefits identified by the users (e.g. avoiding delays and drug-resistance information). *QES high confidence and interviews*

### **Is the intervention feasible to implement?**

- The feasibility of implementing the pyrazinamide LPA is challenged by the significant training and laboratory infrastructure required to implement this method. Feasibility also hinges on the availability of an automated interpretation system, because the result is difficult to interpret. *Interviews*

## **Implementation considerations**

Factors to consider when implementing a high complexity hybridization-based NAAT for detection of pyrazinamide resistance are as follows:

- There are specific concerns about the complexity and difficulty of interpretation. The large number of bands makes it difficult to read the result of the high complexity reverse hybridization-based NAAT.
- Local epidemiological data on resistance prevalence should guide local testing algorithms, whereas pretest probability is important for the clinical interpretation of test results.
- The cost of a test varies, depending on the number of samples in a batch, staff time and other parameters requiring a local costing exercise to be performed.
- Low, moderate, and high complexity tests have a successive increase in technical competency needs (qualifications and skills) and staff time, impacting planning and budgeting.
- Availability and timeliness of local support service and maintenance should be considered when selecting a provider.
- Laboratory accreditation and compliance with a robust quality management system (including appropriate quality control) is essential for sustained service excellence and trust.
- Training of both laboratory and clinical staff will ensure effective delivery of services and clinical impact.
- Use of connectivity solutions for communication of results is encouraged, to improve efficiency of service delivery and time to treatment initiation.
- Based on a multinational, population-based study, levels of pyrazinamide resistance varied widely in the surveyed settings (3.0–42.1%). In all settings, pyrazinamide resistance was significantly associated with rifampicin resistance (49).
- Implementation of a high complexity hybridization-based NAAT requires laboratories with the required infrastructure, space and functional sample referral systems.
- Because there are several manual steps involved, well-trained staff are needed to set up assays and maintain instruments. Special training and experience are required for reading of banding patterns on the strip.

## Research priorities

Research priorities for a high complexity hybridization-based NAAT for detection of pyrazinamide resistance are as follows:

- diagnostic accuracy of high complexity hybridization-based NAATs indirect testing on sputum and non-sputum samples in people with signs and symptoms of TB, with or without resistance to rifampicin;
- impact of diagnostic technologies on clinical decision-making and outcomes important to patients (e.g. cure, mortality, time to diagnosis and time to start treatment) in all patient populations;
- impact of specific mutations on treatment outcomes among people with DR-TB;
- use, integration and optimization of diagnostic technologies in the overall landscape of testing and care, as well as diagnostic pathways and algorithms;
- economic studies evaluating the costs, cost-effectiveness and cost-benefit of diagnostic technologies;
- qualitative studies evaluating equity, acceptability, feasibility and end-user values of diagnostic technologies; and
- interpretation of the results from a high complexity hybridization-based NAAT compared with sequencing and newer evidence on genotypic and phenotypic associations.

### 2.4.5 Targeted next-generation sequencing

Targeted NGS technology couples amplification of selected genes with NGS technology to detect resistance to many drugs with a single test. Also, since targeted NGS can interrogate entire genes to identify specific mutations associated with resistance, tests based on this technology may be more accurate than existing WRDs. In addition, new tests based on NGS can detect resistance to new and repurposed drugs that are not currently included in any other molecular assays. Hence, tests based on targeted NGS offer great potential to provide comprehensive resistance detection matched to modern treatment regimens.

## Recommendations

**17. In people with bacteriologically confirmed pulmonary TB disease, targeted next-generation sequencing technologies may be used on respiratory samples to diagnose resistance to rifampicin, isoniazid, fluoroquinolones, pyrazinamide and ethambutol rather than culture-based phenotypic drug susceptibility testing.**

*(Conditional recommendation, certainty of evidence moderate [isoniazid and pyrazinamide], low [rifampicin, fluoroquinolones and ethambutol])*

## Remarks

- Priority should be assigned to those at higher risk of resistance to first-line treatment medications, including individuals who:
  - continue to be smear or culture positive after 2 or more months of treatment, or experience treatment failure;
  - have previously had TB treatment,

- are in contact with a person known to have resistance to TB drugs; or
- reside in settings or belong to subgroups where there is a high probability of resistance to either rifampicin, isoniazid or fluoroquinolone (used in new shorter regimens), or where there is a high prevalence of *M. tuberculosis* strains harbouring mutations not detected by other rapid molecular tests.
- This recommendation is conditional because of the lack of data on health benefits, the variable certainty of evidence on diagnostic accuracy, and the fact that accuracy is suboptimal for certain drugs. In addition, because this is a new technology that has not yet been widely implemented, there is still limited and variable evidence on costs, cost-effectiveness and feasibility of implementation.

**18. In people with bacteriologically confirmed rifampicin-resistant pulmonary TB disease, targeted NGS technologies may be used on respiratory samples to diagnose resistance to isoniazid, fluoroquinolones, bedaquiline, linezolid, clofazimine, pyrazinamide, ethambutol, amikacin and streptomycin rather than culture-based phenotypic drug susceptibility testing.**

*(Conditional recommendation, certainty of evidence high [isoniazid, fluoroquinolones and pyrazinamide], moderate [ethambutol], low [bedaquiline, linezolid, clofazimine and streptomycin], very low [amikacin])*

### Remarks

- Priority should be given to those at a higher risk of resistance to medications used for the treatment of RR-TB, including individuals who:
  - continue to be smear or culture positive after 2 months or more of treatment or have experienced treatment failure;
  - have previously had TB treatment, including with the new and repurposed drugs;
  - are in contact with a person known to have resistance to TB drugs, including the new and repurposed drugs; or
  - have pre-XDR-TB with resistance to fluoroquinolones.
- As above, this recommendation is conditional because of the lack of data on health benefits, the variable certainty of evidence on diagnostic accuracy, the fact that accuracy is suboptimal for certain drugs, and limited and variable evidence on costs, cost-effectiveness and feasibility of implementation.

### Box 2.4.5.1

The products and drugs for which eligible data met the class-based performance criteria are listed below:

**Deeplex® Myc-TB** (Genoscreen, France): rifampicin, isoniazid, pyrazinamide, ethambutol, fluoroquinolones, bedaquiline, linezolid, clofazimine, amikacin and streptomycin

**AmPORE-TB®** (Oxford Nanopore Diagnostics, United Kingdom): rifampicin, isoniazid, fluoroquinolones, linezolid, amikacin and streptomycin

**TBseq®** (Hangzhou ShengTing Medical Technology Co., China): ethambutol

Where a product has not yet met the requirements for a specific drug (i.e., the drug is not listed), further improvements to the product are needed, and a review of the evidence is necessary before clinical use.

## Test description

Three products met the inclusion criteria for detection of drug resistance to at least one of the anti-TB drugs under evaluation.

- The **Deeplex® Myc-TB test** (Genoscreen, France) is a targeted NGS-based kit for the simultaneous identification of mycobacterial species, genotyping and prediction of drug resistance of MTBC strains, directly applicable on sputum samples (50). The assay relies on deep sequencing of a 24-plex amplicon mix, and it targets 18 MTBC gene regions associated with resistance to anti-TB drugs (rifampicin, isoniazid, pyrazinamide, ethambutol, fluoroquinolones, amikacin, kanamycin, capreomycin, streptomycin, ethionamide, bedaquiline, clofazimine and linezolid). Mycobacterial species identification is performed by targeting the *hsp65* gene; the spoligotyping target (CRISPR/Direct Repeat locus) and phylogenetic single nucleotide polymorphisms (SNPs) in targets associated with drug resistance are used for MTBC strain genotyping. The assay is performed using the Nextera XT and DNA Flex library preparation kits on the iSeq 100, MiniSeq, MiSeq and NextSeq sequencing platforms (Illumina). The solution includes an automated analysis pipeline of the sequencing data in a secure online application with integrated databases for results interpretation.
- The **AmPORE-TB® test** (Oxford Nanopore Diagnostics, United Kingdom) – previously referred to as Nano-TB – is a targeted NGS-based kit for the simultaneous identification of mycobacterial species and the detection of MTBC genetic variants associated with antimicrobial resistance in DNA extracted from sputum samples.<sup>13</sup> The assay relies on sequencing of a 27-plex amplicon mix: 24 drug-resistance targets, a genotyping target, a non-tuberculous mycobacteria (NTM) identification target (*hsp65*) and an internal control. The 24 drug-resistance targets are MTBC gene regions that are associated with resistance to various TB drugs (rifampicin, isoniazid, pyrazinamide, ethambutol, fluoroquinolones,

<sup>13</sup> Oxford Nanopore Diagnostics provided a draft protocol for the test.

amikacin, kanamycin, capreomycin, streptomycin, ethionamide, bedaquiline, clofazimine, linezolid and delamanid). Mycobacterial species identification is performed by targeting the *hsp65* gene; the spoligotyping target (CRISPR/Direct Repeat locus) is used for MTBC strain genotyping. The assay is performed using the OND AmPORE-TB kit (OND-TBDR001-XX) and Flow Cells (OND-FLO-MIN001-XX) on the GridION Diagnostic Sequencing System (OND). The sequencing control software on the device can automatically start and report the results for the analysis workflows installed. The AmPORE-TB includes analysis software pre-installed on a device that processes readouts produced by the sequencing control software and creates an easy-to-interpret report, all performed locally on the device.

- The **TBseq® test** (Hangzhou ShengTing Medical Technology Co., China) is a kit based on targeted NGS that is used for the simultaneous identification of mycobacterial species and the prediction of drug resistance of MTBC strains; it is directly applicable to clinical specimens such as sputum and BAL fluid (51). The assay relies on deep sequencing of a multiplex amplification mix and it targets 21 MTBC genes associated with resistance to TB drugs (rifampicin, isoniazid, pyrazinamide, ethambutol, fluoroquinolones, amikacin, kanamycin, capreomycin, streptomycin, para-aminosalicylic acid, cycloserine, ethionamide or prothionamide, bedaquiline, clofazimine and linezolid). Mycobacterial species identification is performed by targeting the 16S and *hsp65* gene regions. The assay is performed using the Universal Gene Sequencing Kit (ShengTing) to generate libraries that are sequenced on either a MinION or a GridION platform (Oxford Nanopore Technologies). The solution includes automated analysis software (Nano TNGS V1.0) for sequencing data processing and a secure online application (TBseq® Web App) with integrated databases for interpretation of results.

## Justification and evidence

### Diagnostic accuracy and health benefits

Two health questions were designed using the PICO approach, to form the basis for the evidence search, retrieval and analysis.

1. Should targeted NGS as the initial test be used to diagnose drug resistance in individuals with bacteriologically confirmed pulmonary TB disease?

This question applies to:

- rifampicin, using a composite reference standard of phenotypic DST and whole genome sequencing (WGS), and Xpert MTB/RIF® or Xpert Ultra®;
- isoniazid, using phenotypic DST as the reference standard;
- levofloxacin, using phenotypic DST as the reference standard;
- moxifloxacin, using phenotypic DST as the reference standard;
- pyrazinamide, using a composite reference standard of phenotypic DST and WGS; and
- ethambutol, using a composite reference standard of phenotypic DST and WGS.

2. Should targeted NGS be used to diagnose drug resistance in individuals with bacteriologically confirmed rifampicin-resistant pulmonary TB disease?

This question applies to:

- isoniazid, using phenotypic DST as the reference standard;
- levofloxacin, using phenotypic DST as the reference standard;

- moxifloxacin, using phenotypic DST as the reference standard;
- pyrazinamide, using a composite reference standard of phenotypic DST and WGS;
- bedaquiline, using phenotypic DST as the reference standard;
- linezolid, using phenotypic DST as the reference standard;
- clofazimine, using phenotypic DST as the reference standard;
- amikacin, using phenotypic DST as the reference standard;
- ethambutol, using a composite reference standard of phenotypic DST and WGS; and
- streptomycin, using phenotypic DST as the reference standard.

A broad search was conducted to find, appraise and synthesize evidence about health benefits and the diagnostic test accuracy of targeted NGS compared with phenotypic drug sensitivity testing for patients with bacteriologically confirmed TB or with bacteriologically confirmed rifampicin-resistant pulmonary TB disease. A comprehensive search of three databases (Medline, Ovid Embase and Scopus) for relevant citations was performed. No date restriction was applied and the search was initially performed on 7 September 2022 and repeated on 17 January 2023. In addition, WHO made a public call for data and contacted well-known experts in the field to ask whether they had, or knew of, unpublished data that could contribute.

No data were found for the impact of targeted NGS on patient-level health effects. For the analysis of diagnostic accuracy, because few data were available in the literature, all data identified from the literature were included after correspondence with the authors. Hence, no manual data extraction from publications was required. A post-hoc decision was made to perform only an individual patient data (IPD) meta-analysis; thus, any study that could not provide IPD was excluded. Two report authors made independent assessments of methodological quality using QUADAS-2. Disagreements were resolved by discussion and uncertainties or disagreements were reviewed by an independent third party.

Subanalyses were performed to assess the diagnostic test accuracy in PLHIV and for semiquantitative results (derived from cycle thresholds) from Xpert MTB/RIF<sup>®</sup> or Xpert Ultra<sup>®</sup>, where “very low” or “low” concentrations of *M. tuberculosis* were compared with “medium” or “high” concentrations. The very low or low semiquantitative categories represent paucibacillary disease states, such as those frequently observed in paediatric TB.

Data were included from both published and unpublished prospective, observational clinical studies of targeted NGS platform diagnostic accuracy. All studies where targeted NGS had been performed directly from processed clinical samples were included, whereas those performed exclusively on cultured isolates were excluded. All studies were required to have comparator phenotypic DST data as a reference; in the cases of rifampicin, ethambutol and pyrazinamide, studies were required to also have WGS, to allow a composite reference to be generated. Rifampicin resistance results and semiquantitative results from Xpert MTB/RIF<sup>®</sup> or Xpert Ultra<sup>®</sup> were requested from all studies.

Given that this was a review of the diagnostic accuracy of a class of diagnostic platforms, all the data from each platform alone were analysed to assess which to include in an analysis to inform a class recommendation. Where the performance of any one platform appeared to be an outlier for sensitivity or specificity, that platform was excluded from subsequent meta-analyses. A platform was considered to be an outlier for a particular drug if the point estimate

for sensitivity was more than 10 percentage points worse than the best performing platform, or where the point estimate for specificity was more than 5 percentage points worse.

An IPD meta-analysis was performed instead of a classical meta-analysis, because the studies identified in the literature were generally too small to contribute to a classical meta-analysis, particularly for the new and repurposed drugs. In addition, this type of approach allowed for relevant co-variables to be included in the model; it could also control for repeated testing on the same samples using different platforms, which was the case for much of the available data.

For each dependent variable, a multivariable model included a number of co-variables as fixed effects. These included rifampicin resistance as determined by Xpert MTB/RIF® or Xpert Ultra® for all drugs other than rifampicin; semiquantitative cycle threshold (CT) value from Xpert MTB/RIF® or Xpert Ultra®; and a co-variable to indicate which samples featured in duplicate, meaning that some samples were sequenced on two different platforms and thus were represented twice in the analysis. For models looking specifically at diagnostic test accuracy in PLHIV, the HIV test result was included as a co-variable. Finally, the study site was included as a random effect. The models were run in Stata (version 17) using the melogit command, and the outputs were transformed using the margins command. Models were run for all PICO questions for sensitivity and specificity.

The certainty of the evidence of the pooled studies was assessed systematically for each of the PICO questions using the GRADE approach, which produces an overall quality assessment (or certainty) of evidence and has a framework for translating evidence into recommendations.

The GRADEpro Guideline Development Tool software (16) was used to generate summary of findings tables for the sensitivity and specificity of each drug. The numbers of samples classified as true, false positive or negative were then calculated across a range of three prevalences of drug resistance, chosen to be representative of different global settings. The quality of evidence was rated as high (not downgraded), moderate (downgraded one level), low (downgraded two levels) or very low (downgraded more than two levels), based on five factors: risk of bias, indirectness, inconsistency, imprecision and other considerations. The quality (certainty) of evidence was downgraded by one level when a serious issue was identified and by two levels when a very serious issue was identified in any of the factors used to judge the quality of evidence.

The data sources for the IPD data analysis are shown in **Fig. 2.4.5.1**. The analysis included data from published studies, a large multicountry trial conducted by FIND, and several other studies across multiple countries. Most of the studies only evaluated the Deeplex assay, while the FIND trial evaluated both the Deeplex and the AmPORE-TB. Only one study evaluated TBseq. For each drug, one or two platforms were dropped from the analysis based on the overall number of resistant or susceptible samples available for that platform and drug, or because the accuracy of the platform did not meet the diagnostic test accuracy criteria for inclusion when compared with the best performing platform.

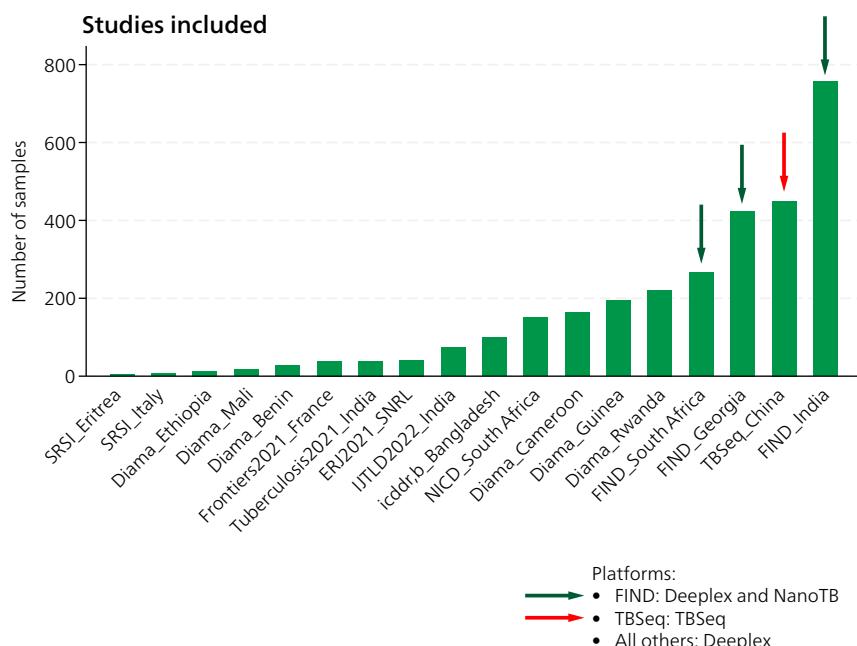
**Fig. 2.4.5.1 Studies included in the IPD meta-analysis for targeted NGS**

**From the literature:**

- ERJ 2021 (SNRL Germany)
- Frontiers 2021 (France)
- Tuberculosis 2021 (India)
- IJLD 2022 (India)

**Unpublished:**

- FIND
  - Georgia
  - India
  - South Africa
- Diamu
  - Benin
  - Guinea
  - Cameroon
  - Rwanda
  - Mali
  - Ethiopia
- NICD, South Africa
- icddr,b (Bangladesh)
- San Raffaele Scientific Institute, Italy
  - Italy
  - Eritrea
- TBSeq, China



ERJ: European Respiratory Journal; FIND: Foundation for Innovative New Diagnostics; IPD: individual patient data; NGS: next-generation sequencing; NICD: National Institute for Communicable Diseases; UTLD: International Union Against Tuberculosis and Lung Diseases.

Data synthesis was structured around the two preset PICO questions, as outlined below.

**PICO 1: Should targeted NGS as the initial test be used to diagnose drug resistance in patients with bacteriologically confirmed pulmonary TB disease?**

The available evidence included in the final pooled analysis varied by drug, from 12 studies with 1440 participants for the sensitivity of isoniazid to three studies with 269 participants for the specificity of pyrazinamide (**Table 2.4.5.1**). The pooled estimates were determined using a multivariable, mixed-effects model. All drugs were downgraded by one level for indirectness for sensitivity and specificity, because all studies were enriched for rifampicin resistance, leading to applicability concerns. In addition, for rifampicin, levofloxacin and pyrazinamide, specificity was downgraded a further level for imprecision; however, for ethambutol, it was downgraded for risk of bias because different samples were used for the index and reference tests. The overall certainty of the evidence for test accuracy ranged from moderate to very low.

The test performance was determined to be accurate for all drugs included in the assessment, with a **pooled sensitivity of at least 95% for isoniazid, moxifloxacin and ethambutol, more than 93% for rifampicin and levofloxacin, and 88% for pyrazinamide. The pooled specificity was at least 96% for all drugs.**

The reference standard was culture-based phenotypic DST for isoniazid, levofloxacin and moxifloxacin, and a combination of phenotypic DST and WGS for rifampicin, pyrazinamide and ethambutol. The percentage of tests with indeterminate results ranged from 9% (levofloxacin and moxifloxacin) to 18% (pyrazinamide), with higher indeterminate rates in samples with lower bacterial load (semiquantitative category low or very low).

**Table 2.4.5.1 The accuracy and certainty of evidence of targeted NGS for the detection of resistance to anti-TB drugs among bacteriologically confirmed pulmonary TB**

Drug	Reference standard	Accuracy % (95% CI)	Studies (persons)	Certainty in evidence
<b>Rifampicin</b>	Phenotypic DST+WGS	Se: 93.1 (87.0–99.2)	9 (1436)	Moderate
	Phenotypic DST+WGS	Sp: 96.2 (88.6–100)	7 (271)	Low
<b>Isoniazid</b>	Phenotypic DST	Se: 95.8 (92.8–98.7)	12 (1440)	Moderate
	Phenotypic DST	Sp: 97.0 (95.1–98.9)	12 (517)	Moderate
<b>Levofloxacin</b>	Phenotypic DST	Se: 94.2 (88.4–99.9)	6 (654)	Low
	Phenotypic DST	Sp: 96.2 (93.4–98.9)	7 (913)	Moderate
<b>Moxifloxacin</b>	Phenotypic DST	Se: 95.6 (92.4–98.7)	6 (652)	Moderate
	Phenotypic DST	Sp: 96.3 (93.2–99.5)	8 (921)	Moderate
<b>Pyrazinamide</b>	Phenotypic DST+WGS	Se: 88.4 (85.2–91.7)	3 (346)	Moderate
	Phenotypic DST+WGS	Sp: 98.5 (97.1–100)	3 (269)	Moderate
<b>Ethambutol</b>	Phenotypic DST+WGS	Se: 95.8 (94.0–97.6)	4 (432)	Low
	Phenotypic DST+WGS	Sp: 99.3 (98.2–100)	4 (268)	Low

CI: confidence interval; DST: drug susceptibility testing; NGS: next-generation sequencing; Se: sensitivity; Sp: specificity; TB: tuberculosis; WGS: whole genome sequencing.

There were no data on the impact of targeted NGS on patient outcomes such as time to treatment or treatment outcome.

**PICO 2: Should targeted NGS be used to diagnose drug resistance in patients with bacteriologically confirmed rifampicin-resistant pulmonary TB disease?**

The available evidence varied by drug, from 12 studies with 1440 participants for sensitivity of isoniazid to three studies with 31 participants for sensitivity of bedaquiline (**Table 2.4.5.2**). The pooled estimates were determined using a multivariable, mixed-effects model.

The overall certainty was high for some of the drugs. Levofloxacin was downgraded one level for inconsistency. Bedaquiline and linezolid were downgraded by two levels for imprecision in sensitivity because the number of resistant samples was below the threshold set and the confidence intervals were wide. Clofazimine was also downgraded by two levels, one for inconsistency (because two studies were outliers) and another level for imprecision (because the confidence intervals were wide). Amikacin was downgraded by one level for sensitivity and specificity because critical concentrations outside those recommended by WHO were used for a large proportion of samples. Amikacin sensitivity was further downgraded by two more levels, one for inconsistency and the other for imprecision. Ethambutol was downgraded by one level for risk of bias because different samples were used for the index and reference tests. Streptomycin specificity was downgraded by two levels, one for inconsistency and the other for imprecision. The overall certainty of the evidence for test accuracy ranged from high to very low.

The test performance among people with RR-TB was determined to be **accurate for isoniazid, levofloxacin, moxifloxacin, ethambutol and streptomycin (pooled sensitivity  $\geq 95\%$ )** and **acceptable for pyrazinamide (90%), bedaquiline (68%), linezolid (69%), clofazimine (70%) and amikacin (87%)**. The pooled specificity was 95% or greater for all drugs except **streptomycin (75%)**. The reference standard was culture-based phenotypic DST for all drugs except for ethambutol and pyrazinamide, where a combination of phenotypic DST and WGS was used. The percentage of tests with indeterminate results ranged from 9% (levofloxacin and moxifloxacin) to 21% (ethambutol); indeterminate rates were higher in samples with a lower bacterial load (semiquantitative category low or very low).

**Table 2.4.5.2 The accuracy and certainty of evidence of targeted NGS for the detection of resistance to anti-TB drugs among bacteriologically confirmed rifampicin-resistant pulmonary TB**

Drug	Reference standard	Accuracy % (95% CI)	Studies (persons)	Certainty in evidence
<b>Isoniazid</b>	Phenotypic DST	Se: 96.5 (93.8–99.2)	12 (1440)	High
	Phenotypic DST	Sp: 95.8 (91.8–99.8)	12 (517)	High
<b>Levofloxacin</b>	Phenotypic DST	Se: 95.8 (90.4–100)	6 (654)	Moderate
	Phenotypic DST	Sp: 96.0 (93.1–98.9)	7 (913)	High
<b>Moxifloxacin</b>	Phenotypic DST	Se: 96.5 (93.6–99.5)	6 (652)	High
	Phenotypic DST	Sp: 95.2 (91.0–99.4)	8 (921)	High
<b>Pyrazinamide</b>	Phenotypic DST+WGS	Se: 90.0 (86.8–93.2)	3 (346)	High
	Phenotypic DST+WGS	Sp: 98.6 (96.8–100)	3 (269)	High
<b>Bedaquiline</b>	Phenotypic DST	Se: 67.9 (42.6–93.2)	3 (31)	Low
	Phenotypic DST	Sp: 97.0 (94.3–99.7)	4 (519)	High
<b>Linezolid</b>	Phenotypic DST	Se: 68.9 (38.7–99.1)	4 (31)	Low
	Phenotypic DST	Sp: 99.8 (99.6–100)	6 (1093)	High
<b>Clofazimine</b>	Phenotypic DST	Se: 70.4 (34.6–100)	4 (36)	Low
	Phenotypic DST	Sp: 96.3 (93.2–99.3)	6 (789)	High
<b>Amikacin</b>	Phenotypic DST	Se: 87.4 (74.5–100)	5 (115)	Very low
	Phenotypic DST	Sp: 99.0 (98.4–99.6)	8 (1003)	Moderate
<b>Ethambutol</b>	Phenotypic DST+WGS	Se: 96.7 (95.0–98.4)	4 (431)	Moderate
	Phenotypic DST+WGS	Sp: 98.4 (96.1–100)	4 (123)	Moderate
<b>Streptomycin</b>	Phenotypic DST	Se: 98.1 (96.1–100)	5 (493)	High
	Phenotypic DST	Sp: 75.0 (59.5–90.5)	5 (250)	Low

CI: confidence interval; DST: drug susceptibility testing; NGS: next-generation sequencing; Se: sensitivity; Sp: specificity; TB: tuberculosis; WGS: whole genome sequencing.

There were no data on the impact of targeted NGS on patient outcomes such as time to treatment or treatment outcome.

Three web annexes give additional information, as follows:

- details of studies included in the current analysis (**Web Annex A.10: Review of the diagnostic accuracy of targeted NGS technologies for detection of drug resistance among people diagnosed with TB**);
- a summary of the results and details of the evidence quality assessment (**Web Annex A.10: GRADE profiles of targeted next-generation sequencing for detection of TB drug resistance**); and
- a summary of the GDG panel judgements (**Web Annex A.10: Evidence to decision tables: targeted next-generation sequencing for detection of TB drug resistance**).

## Cost-effectiveness analysis

The cost and cost-effectiveness data for targeted NGS were assessed through a systematic review of the published literature and a generalized model-based cost-effectiveness analysis commissioned by WHO.

The systematic review on the cost and cost-effectiveness of using either targeted NGS or WGS to diagnose DR-TB searched three databases: PubMed, Embase and Scopus. The search was run on 30 October 2022 and had no time restriction. All costing data were inflated to 2021 US dollars. Findings were synthesized descriptively, given the considerable degree of heterogeneity in study methodology and outcomes. Among the studies included in the systematic review, three were on targeted NGS only, three were on targeted NGS and WGS, and four were on WGS only. For targeted NGS based on a single study (n=1), the cost per sample was between US\$ 69.64 for Illumina MiSeq on 24 samples, and US\$ 73.47 for Nanopore MinION on 12 samples; however, this costing was limited to only some components and did not include human resource costs or overhead costs. For WGS (n=5), cost per sample ranged from US\$ 63.00 on Nanopore MinION to US\$ 277.00 on Illumina MiSeq; given that studies used an inconsistent number of component costs, comparisons were challenging. Based on the review, the most significant cost component was the sequencing step, and the largest component costs were reagents and consumables, including those necessary for sequencing, sample processing and targeted NGS steps library preparation. Study authors identified four major cost drivers: use of different sequencers, depth and breadth of coverage, inefficiencies in initial sample runs, and economies of scale via batching or cross-batching.

The cost data from the systematic review were limited; therefore, an empirical unit costing was performed, in consultation with manufacturers and FIND. At the time of this work, only pricing for Deeplex Myc-TB was available and it was used for estimation of cost for the class. Unit costs included consumables, equipment, staffing and overheads (where available); also, costs assumed targeted NGS testing for all drugs. Based on the empirical analysis, the cost of targeted NGS was estimated to be:

- US\$ 134 to US\$ 257 in South Africa;
- US\$ 120 to US\$ 198 in Georgia; and
- US\$ 121 to US\$ 175 in India.

These costs are dependent on patient volume, batching and negotiated cost per targeted NGS kit.

Recognizing the lack of economic evidence on this topic, a hypothetical cost–effectiveness modelling study was undertaken to assess the cost–effectiveness (Objective 1) and affordability (Objective 2) of these tests for the diagnosis of DR-TB in various high TB burden settings.

**Objective 1: To assess the potential cost–effectiveness of introducing the targeted NGS technology for the diagnosis of DR-TB in Georgia, India and South Africa.**

This assessment included modelling the cost–effectiveness of targeted NGS in three separate scenarios with distinct comparison options:

- a) Cost–effectiveness of targeted NGS for DST among individuals with RR-TB after a rapid molecular test for rifampicin resistance as a replacement for phenotypic DST (PICO 2).
- b) Cost–effectiveness of targeted NGS for DST among individuals with RR-TB after a rapid molecular test for rifampicin resistance as a replacement for current in-country DST practice (PICO 2).
- c) Cost–effectiveness of targeted NGS as the initial test for TB drug resistance in patients with bacteriologically confirmed TB compared with rapid molecular testing for drug resistance and phenotypic DST in a high DR-TB burden setting (PICO 1).

In the first scenario, targeted NGS was compared with universal phenotypic DST; in the second scenario, targeted NGS was compared with current in-country phenotypic DST practice among individuals with detected rifampicin resistance (PICO 2). This was done across three countries: Georgia, India and South Africa. Current DST practice in Georgia and South Africa includes Xpert XDR® followed by phenotypic DST; in India it includes LPAs and phenotypic DST done in parallel. A final scenario included targeted NGS compared to rapid molecular testing for drug resistance and phenotypic DST as initial tests for TB drug resistance among all TB patients (PICO 1) but was modelled for only one setting, Georgia – a high DR-TB burden setting. Epidemiological data were sourced from published literature; targeted NGS diagnostic accuracy data were sourced from the systematic review and IDP analysis conducted for this guideline. Economic data were sourced from published literature and a systematic and scoping review done in parallel by our team and supplemented with empirical data collection.

A decision analysis modelling approach was used to estimate the incremental cost–effectiveness of using targeted NGS for the diagnosis of DR-TB compared with various existing DST scenarios. This was done from the perspective of the health care system and accounts only for the health care system costs required to diagnose and treat TB. The estimation did not account for societal costs, or any direct or indirect costs incurred by patients. In addition, costs for sample transportation were not included in this analysis. The primary outcome was the incremental cost–effectiveness ratio (ICER), which was calculated as the incremental cost in US dollars per disability-adjusted life year (DALY) averted.

***Main findings for PICO 1: Using targeted NGS as an initial test***

Using targeted NGS as an initial test for DST in the high DR-TB burden setting of Georgia led to more health gains (DALYs=0.49) compared with Xpert MTB/RIF or Xpert Ultra, followed by

phenotypic DST (DALY=0.51). The ICER per DALY averted was US\$ 9261 (95% uncertainty range [UR]: US\$ 5258–32 040/DALY averted), which was considered cost effective at a willingness-to-pay (WTP) threshold of three times the country GDP per capita (US\$ 15 609), with 80% of simulated iterations falling below the WTP threshold.

### **Main findings for PICO 2: Using targeted NGS among those with RR-TB**

Using targeted NGS as a *replacement for universal phenotypic DST* among RR-TB patients, targeted NGS was dominated by phenotypic DST, with targeted NGS having higher costs and leading to fewer health gains. This finding was driven by the high diagnostic accuracy of phenotypic DST (which was assumed to be universal in this scenario), and an assumption of no difference in loss to follow-up between targeted NGS and phenotypic DST. When in-country DST practice was used as the comparator (instead of universal phenotypic DST), targeted NGS led to more health gains than in-country DST across all three countries. Targeted NGS was cost effective in South Africa (ICER: US\$ 15 619/DALY averted, 95% UR: cost saving –US\$ 114 782, at a WTP threshold of US\$ 21 165), but was not cost effective in Georgia (ICER: US\$ 18,375/DALY averted, UR: cost saving –US\$ 158 972/DALY averted, at a WTP threshold of US\$ 15 065). In India, where LPA, liquid culture and DST are being used as part of in-country DST, targeted NGS dominated the country's current DST practice, with lower costs and more health gains (95% UR: cost saving –US\$ 60 083).

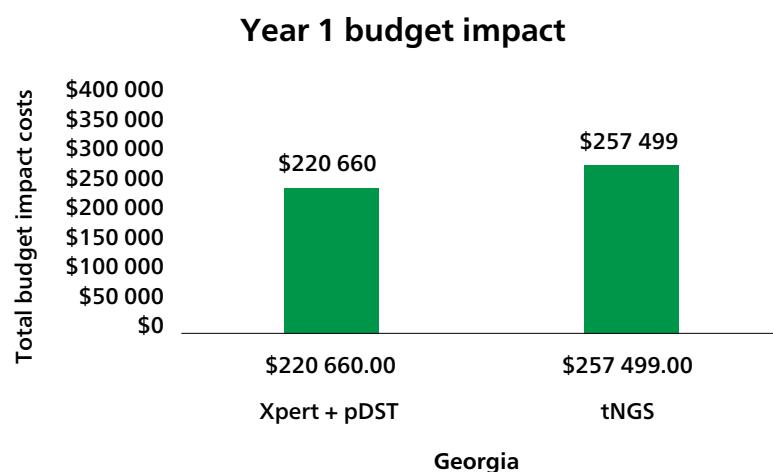
### **Main findings: scenario analyses**

Several key scenario analyses were investigated. In the base case approach, loss to follow-up was assumed to be equivalent between phenotypic DST and targeted NGS; in a scenario where there was no loss to follow-up in targeted NGS compared with 10% in phenotypic DST, targeted NGS was cost effective in South Africa (ICER: US\$ 13 004/DALY averted, WTP: US\$ 21 165) and Georgia (ICER: US\$ 13 640/DALY averted, WTP: US\$ 15 069) and targeted NGS still dominated in-country DST practice in India. In scenarios where sequencing platforms are used for multiple different diseases to reduce the unit test cost of targeted NGS, the cost-effectiveness of targeted NGS improves in all three countries. A batching scenario was investigated, with an assumed 20% fewer samples per targeted NGS run, and led to an increased unit test cost for targeted NGS; in this scenario, the targeted NGS approach retained cost-effectiveness only in South Africa. When a 50% price reduction in targeted NGS test kit cost was assumed, targeted NGS cost-effectiveness further improved in all countries.

### **Objective 2: To assess the financial impact of introducing targeted NGS as a replacement for existing DST for diagnosis of DR-TB among TB patients across three countries: Georgia, India and South Africa.**

A budget impact assessment was undertaken to estimate the financial consequences of adopting targeted NGS for DST for all patients diagnosed with TB, and replacing in-country DST practice in Georgia (PICO 1). The analysis suggested that implementing targeted NGS for all patients diagnosed with TB would be more expensive than testing all patients with Xpert MTB/RIF or Xpert Ultra, followed by phenotypic DST (see **Fig. 2.4.5.2**).

**Fig. 2.4.5.2 Budget impact assessment results comparing current standard practice for DST with implementation of targeted NGS for all patients diagnosed with TB in Georgia**

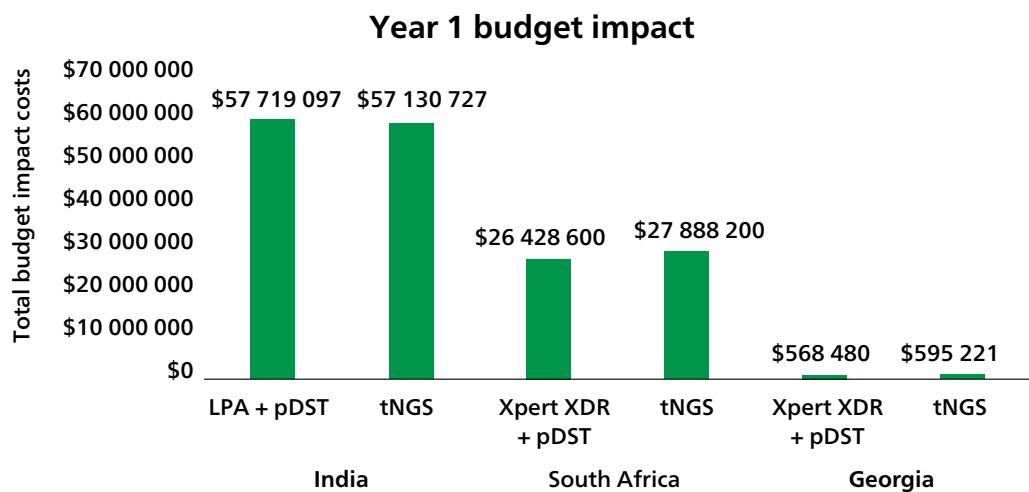


DST: drug susceptibility testing; NGS: next-generation sequencing; pDST: phenotypic DST; TB: tuberculosis; tNGS: targeted NGS.

A budget impact assessment was undertaken to estimate the financial consequences of adopting targeted NGS for DST after a rapid molecular test for rifampicin resistance, and replacing in-country DST practice in Georgia, India and South Africa (PICO 2). In-country DST practice included Xpert XDR combined with phenotypic DST in Georgia and South Africa, and Xpert XDR combined with LPA in Georgia over a 1-year and 5-year period. It was assumed that the eligible RR-TB patient populations requiring DST were 58 837, 8200 and 187 in South Africa, India and Georgia, respectively, and that the TB reduction rate over the 5 years was stable (2). To estimate the impact on the country-specific budget, the economic costs generated by the model were multiplied by the number of patients.

Results from a 1-year budget impact assessment for PICO 2 are presented in **Fig. 2.4.5.3** In India, it was estimated that implementing targeted NGS would cost about US\$ 57 130 727 – slightly lower than the current practice of LPA combined with phenotypic DST, which has a cost of US\$ 57 719 097. In South Africa, it was estimated that implementing targeted NGS would result in a rise in budget to about US\$ 27 888 200, slightly more than LPA combined with phenotypic DST, which has a cost of US\$ 26 428 600. Finally in Georgia, where there are fewer bacteriologically confirmed patients, it was estimated that implementing targeted NGS would cost about US\$ 592 221, slightly more than LPA combined with phenotypic DST, which has a cost of US\$ 568 480.

**Fig. 2.4.5.3 Budget impact assessment results comparing current standard practice for DST to implementing targeted NGS for patients with RR-TB in India, South Africa and Georgia**



DST: drug susceptibility testing; LPA: line probe assay; NGS: next-generation sequencing; pDST: phenotypic DST; RR-TB: rifampicin-resistant TB; TB: tuberculosis; tNGS: targeted NGS.

## User perspective

A rapid review was commissioned to identify and synthesize qualitative evidence on the use of targeted NGS for the detection of TB drug resistance; in particular, the aim was to examine the implementation considerations related to acceptability, feasibility, and values, preferences and equity. The review searched Medline with no year or language limits. The search was run on 19 August 2022, and then rerun on 10 October 2022 to include WGS-related studies for the detection of TB drug resistance. The review did not identify any eligible studies for analysis and synthesis. Based on the systematic search, three records were identified; in addition, based on the open, hand and expert searches, 27 records were found. On full-text review of the 30 records, none were found to be eligible for inclusion. Given that no direct evidence was found, note was made of a Cochrane qualitative evidence synthesis published in 2022 that examined recipient and provider perspectives on rapid molecular tests for TB and drug resistance (52); that study provides relevant (though indirect) evidence on the subject. The authors noted that people with TB valued reaching diagnostic closure with an accurate diagnosis, avoiding diagnostic delays and keeping diagnostic associated costs low, whereas health care providers valued aspects of accuracy and the resulting confidence in low complexity NAAT results, rapid turnaround times and low costs to people seeking a diagnosis.

To address the direct evidence gap, WHO commissioned an additional qualitative cross-sectional study comprising semi-structured interviews, primarily with laboratory staff and management personnel directly involved with implementing targeted NGS in the three FIND trial sites, as well as with three global experts involved in TB care and diagnostics. In total, there were 17 respondents, and the work was conducted during September to October 2022. The objective was to explore the perceptions and experiences of those implementing targeted NGS technology, with respect to acceptability, feasibility, and values, preferences and equity. The main findings are summarized below.

## **Acceptability**

A consistently positive sentiment was expressed for the acceptability and potential utility of targeted NGS technology. Targeted NGS was seen as a “major advancement” in molecular MDR-TB diagnostics.

1. The main reasons for the **high level of acceptability were the comprehensiveness** (resistance diagnosis for more drugs and for the newest and repurposed drugs), **the convenience of using a sputum sample** (as compared with culture samples), **and the rapidity** (quick results compared with phenotypic testing times; 3–5 days as compared with 4–6 weeks).
2. There was also the sense that there is **a good window of opportunity to benefit from the utility of targeted NGS technology**; that is, the technology is arriving at the right time, given that resistance to newer TB drugs is likely to increase as the use of these drugs becomes routine.

## **Feasibility**

Although there was high praise for the capability and potential utility of targeted NGS technology, **several challenges were identified when testing samples using the targeted NGS platforms**, which may limit the feasibility of targeted NGS for routine uptake at the present time. The overall sentiment was that the targeted NGS technology needs to be further developed before it can be considered fully ready for operational use.

The following feasibility challenges were identified:

- **Start-up and setting-up challenges:** Multiple problems were identified with starting and setting up the technology. These problems related to the newness of the technology and the trial setting, importing technology and specialist supplies, lack of in-country technical assistance for problem-solving and need for more hands-on training practice.
- **High technical complexity of the test:** Targeted NGS technology was seen as a high complexity molecular test that was technically challenging. For example, preparing the sample for sequencing involves multiple steps that require attention to detail and precision, leaving little room for error. Preparation of the library is particularly complex for the Deeplex platform, although both the Deeplex and the Nanopore platforms are quite complex. In both platforms, it was thought that there were too few opportunities for early recognition and correction of errors, increasing the risk of failed runs.
- **Specialized laboratory infrastructure and human resource requirements:** Because targeted NGS is a molecular-based testing platform, it requires highly specialized laboratory infrastructure (e.g. multiple rooms to prevent amplicon contamination and specialized cold storage facilities). Also, highly specialized molecular and medical scientists are needed to perform the tests. In LMIC settings, such specialized laboratory infrastructure and staff may only be available at centralized laboratories (i.e. not at regional laboratories).
- **Special requirements for operating the test:** In addition to highly specialized laboratory infrastructure and staff, the testing technology also requires an uninterrupted supply of electricity, high internet connectivity, high computer capacity, clean water and temperature controls – requirements that may pose challenges in some LMIC settings.

- **Supply chain challenges:** Major challenges were reported relating to the required supply chain for implementing targeted NGS. Procurement bottlenecks and delays coupled with shelf-life limitations of reagents jeopardize continuous access to specialist supplies.
- **Data management and storage requirements:** There were concerns that data analysis and data storage requirements were not fully developed, including systems for backing up data, ownership of data and security of data. Another issue that needs to be considered is how targeted NGS and routine laboratory information systems can be interlinked.
- **Continuous updating of the WHO catalogue of mutations is required:** There was agreement that the usefulness of the targeted NGS technology depends on the informational support provided by the WHO catalogue of mutations (53), which allows for meaningful interpretation of resistance data; thus, there is a need for the WHO catalogue to be continuously updated.
- **Feasibility concerns differed for the different targeted NGS platforms:** The overall sentiment was that all targeted NGS platforms needed to be further developed before they are fully ready for operational use, some more than others. The high level of technical complexity of the sample preparation stages (mainly the library preparation stage) was considered a key challenge for the Deeplex platform, and the need for improved computer analysis and storage capacity was a challenge for the Oxford Nanopore platform, although both required a high level of precision and attention to detail. There is also a need to incorporate steps for early error recognition.

## Values, preferences and equity

The overall sentiment is that **MDR-TB diagnostic technology needs to balance accuracy, speed, affordability, equity and cost-effectiveness**, and that targeted NGS technology would need to address these considerations before it can be implemented in LMIC settings. These considerations were consistent across the different stakeholder groups who participated in the study.

- 1. Centralized versus decentralized placement may have equity implications for access:** Given the high-level specialized laboratory infrastructure, specialized human resources and technical complexity needed for targeted NGS, the technology may be suitable for placement only at centralized, reference laboratories. This may have equity access considerations if it means less access for some regions of a country that lack reference laboratories. This may also have implications for costs (e.g. costs for transport of sputum), probability of sample loss and time to results.
- 2. Affordability and cost-effectiveness are major concerns:** There was a major concern about the financial costs of the targeted NGS technology and the affordability for LMIC. Participants were worried about the cost of the equipment and the costs of ongoing specialist supplies (especially reagents), as well as the cost of maintaining equipment. They noted that costing calculations should be comprehensive and should include the cost of special consumables, extra general laboratory consumables and additional infrastructure needs (e.g. extra space, temperature control and internet connectivity). There were concerns that cost-effectiveness calculations should be comprehensive and should include assessment of the impact of the use of targeted NGS testing on improving TB outcomes.

### **3. The MDR/RR-TB case burden of a country could influence equitable access at centralized levels.**

In some settings with high caseloads, the targeted NGS technology capacity in central laboratories may not be sufficient for processing large caseloads in good time; also, in settings with low caseloads, waiting for sufficient samples to batch-test will cause delays.

## **Implementation considerations**

Although the evidence that is available supports the use of targeted NGS to detect drug resistance after TB diagnosis, to guide clinical decision-making for DR-TB treatment, the following factors need to be considered when implementing these tests:

- Regulatory approval from national regulatory authorities or other relevant bodies is required before implementation of these diagnostic tests.
- In its current format, targeted NGS is a high complexity test that is most suitable for centralized laboratories equipped with specialized skills and infrastructure.
- Targeted NGS tests do not replace existing rapid tests that are more accessible and easier to perform for detecting resistance to rifampicin, isoniazid and fluoroquinolones. However, if targeted NGS can be performed rapidly, it can be considered as an alternative initial option for prioritized populations. Those who will benefit most from these tests are individuals who require rapid and comprehensive DST but have limited access to phenotypic DST.
- Priority should be given to samples with a high bacillary load as determined by initial bacteriological tests (e.g. semiquantitative high/medium or smear-positive grading). In situations where the bacillary load is low (e.g. semiquantitative low/very low/trace or smear-negative grading), the recommendations still hold, although rates of indeterminate results are likely to be higher; therefore, phenotypic DST is likely still required for samples with a low bacillary load.
- Similarly, the recommendations apply to children, adolescents and PLHIV populations because these populations have a higher frequency of samples with low bacterial load.
- The recommendation is based on data obtained from sputum and BAL specimens, and can be extrapolated to other lower respiratory tract samples (e.g. endotracheal aspirates). However, further research is needed to evaluate the use of these tests on alternative sample types for diagnosing pulmonary TB in children (e.g. nasopharyngeal and stool samples) and diagnosing extrapulmonary TB.
- Since sensitivity for bedaquiline, linezolid and clofazimine resistance is suboptimal, consideration of the pretest probability is important in interpreting the targeted NGS results for these drugs. Further testing of samples with a susceptible result (using culture-based phenotypic DST) would be warranted, particularly when the risk of resistance is high. Since specificity is high, a result that indicates resistance may be used to guide the therapy, particularly among those at risk for resistance. In the case of pretomanid, the basis for resistance has not been fully elucidated; hence, culture-based DST is also required for this drug.

## **Research priorities**

Several key research priorities emerged from the reviews of the available evidence on targeted NGS for detecting TB drug resistance. They fall into three main categories: clinical research, implementation research, and monitoring and evaluation.

### ***Clinical research:***

- Conduct clinical trials to assess the impact of targeted NGS on patient-important outcomes<sup>14</sup>.
- Evaluate the accuracy and impact on patient-important outcomes of targeted NGS among populations of individuals diagnosed with TB, across a range of prevalences of rifampicin or other drug resistance).
- Assess the accuracy and impact on patient-important outcomes of targeted NGS for detecting resistance to new and repurposed drugs, including pretomanid, across varied geographical and epidemiological settings.
- Assess the accuracy and impact on patient-important outcomes of targeted NGS for analysing extrapulmonary samples, including CSF for meningitis, non-sputum samples (e.g. nasopharyngeal aspirate, gastric aspirate or stool) for children, and alternative sample types (e.g. tongue swabs) in both adults and children.
- Undertake additional qualitative and quantitative research to further understand the perspectives of end-users and clinicians regarding the acceptability and feasibility of using targeted NGS.

### ***Implementation research:***

- Develop and evaluate effective and efficient implementation models by integrating targeted NGS into laboratory networks and optimizing algorithms, with the aim of enhancing timely access to testing and treatment initiation, and improving patient outcomes.
- Develop strategies to enhance the efficiency of targeted NGS testing, including sample processing and concentration techniques, determining optimal thresholds of bacterial load from initial tests before performing targeted NGS, and employing molecular transport medium for the ambient storage and transfer of samples to testing sites.
- Regularly update the WHO catalogue of mutations (53), incorporating additional genetic targets and including new drugs (e.g. pretomanid) to enhance the sensitivity and specificity of targeted NGS.
- Explore technological advancements to simplify the testing process, automate steps (especially library preparation), develop decentralized targeted NGS solutions and investigate potential synergies with existing initial tests (e.g. using leftover DNA or smear-positive slides).
- Conduct comprehensive mapping of sequencing capacity within countries and perform diagnostic network optimization exercises. Placement of the technology should consider the demand for sequencing across multiple diseases, facilitating cross-disciplinary use of the machines and shared costs.
- Compile and use lessons learned from applying targeted NGS technology in other diseases (e.g. COVID-19) to develop effective implementation strategies for TB.

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<sup>14</sup> Mortality, Cure, Lost to follow up; Time to diagnosis; Time to treatment.

### ***Monitoring and evaluation:***

- Standardize the nomenclature for reporting of results across different targeted NGS technologies, for integration into health information data systems.
- Ensure separate recording of true failures and unclassified mutations, and monitor trends over time as an essential component of result reporting.
- Regularly monitor performance data, including overall resistance rates, resistance rates by specific drugs or targets and turnaround times (both total and in-laboratory).
- Incorporate quality monitoring measures, such as tracking indeterminate rates, sequencing coverage and depth, and participating in external quality assurance programmes.
- Establish an external quality assurance programme for sequencing that covers all relevant targets of interest.
- Integrate the sequencing data generated into existing surveillance systems to monitor the prevalence and trends in drug resistance effectively. Share the data to update the WHO mutation catalogue.
- Collect cost data to address important questions, such as the costs associated with introducing and scaling up targeted NGS in different settings, the trade-offs between turnaround time and batching, and the optimal balance in various settings.
- Assess the impact of multidisease testing on programme operations and costs, including disease-specific testing volumes, turnaround times, costing, resource sharing and resource requirements.
- Evaluate the impact of time to treatment initiation or modification, treatment outcomes and overall cost-effectiveness of targeted NGS implementation.

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# 3. Recommendations for diagnosis of TB infection

## 3.1. *Mycobacterium tuberculosis* antigen-based skin tests for the diagnosis of TB infection

Since 2011, the World Health Organization (WHO) has issued recommendations on the use of IGRAs for the diagnosis of TB infection. In 2018, WHO updated the recommendations to stipulate that the TST or IGRAs (or both) can be used to test for TB infection in LMIC. The TST is a widely used point-of-care test that involves intradermal injection of purified protein derivative (PPD), a crude mixture of different mycobacterial antigens, which stimulates a delayed-type hypersensitivity response and causes induration at the injection site within 48–72 hours. This test has relatively low specificity in those with recent bacille Calmette-Guérin (BCG) vaccination and low sensitivity in immunosuppressed individuals (e.g. people living with HIV [PLHIV]); hence, interpretive cut-offs must be adapted for these populations. A follow-up clinic visit is required after the placement of the TST, and results must be read within the suggested time frame to be valid. In contrast, IGRAs are in vitro tests that measure release of interferon- gamma (IFN- $\gamma$ ) by T-cells following stimulation by the early secretory antigenic target 6 kDa protein (ESAT-6) and culture filtrate protein 10 (CFP-10) antigens that are specific to Mtb. Unlike the TST, IGRAs are not affected by prior BCG vaccination, or by infection with nontuberculous mycobacteria (NTM), with few exceptions. However, IGRA platforms are more expensive to run and require specialized facilities and trained personnel; consequently, the TST is the most commonly used test for TB infection globally. Recent global shortages of PPD have underscored the need for alternatives.

In addition to the TB skin tests and interferon gamma release assays previously recommended by WHO, Mtb antigen-based skin tests (TBSTs) based on specific antigens have recently been developed, using the same ESAT-6 and CFP-10 antigens; these tests combine the simpler skin-test platform with the specificity of IGRAs. TBSTs include the Cy-Tb (Serum Institute of India, India), Diaskintest® (Generium, Russian Federation) and C-TST (formerly known as ESAT6-CFP10 test, Anhui Zhifei Longcom, China). All tests use intradermal injection of antigen and, like the TST, are read after 48–72 hours as induration in millimetres, using the method suggested by Mantoux. Emerging evidence suggests that, compared with IGRAs, the tests may have similar specificity and provide more reliable results in children and adolescents as well as in PLHIV than the TST. However, the evidence had not been systematically reviewed.

In 2021, WHO commissioned a systematic review of published and unpublished data on this new class of tests for TB infection not previously reviewed by WHO. The systematic review included

data on diagnostic accuracy, safety, economic aspects and qualitative evidence on feasibility, acceptability, equity, end-user values and preferences. A Guideline Development Group (GDG) was convened by WHO from 31 January to 3 February 2022, to discuss the findings of the systematic reviews and to make recommendations on this class of diagnostic technologies for TB infection.

The following technologies were included in the evaluation:

- Cy-Tb (Serum Institute of India, India);
- Diaskintest (Generium, Russian Federation); and
- C-TST (formerly known as ESAT6-CFP10 test, Anhui Zhifei Longcom, China)

**Table 3.1.1 PICO questions for assessment of TBSTs**

Population	Intervention	Comparator	Outcome
<ul style="list-style-type: none"> <li>• PLHIV</li> <li>• Children aged &lt;5 years</li> <li>• Household and other close contacts</li> <li>• Other at-risk groups:           <ul style="list-style-type: none"> <li>• Immune compromised (e.g. individuals receiving anti-TNF-<math>\alpha</math> treatment               <ul style="list-style-type: none"> <li>– or dialysis; individuals undergoing preparation for an organ or haematological transplant; patients with silicosis; pregnant women; or individuals who are malnourished, have diabetes mellitus, use steroids or smoke tobacco)</li> <li>– High risk of prior TB exposure (e.g. prisoners, health workers, immigrants from high TB burden countries, individuals with CXR abnormalities, homeless people and people who use drugs, and inhabitants of high TB burden settings)<sup>a</sup></li> </ul> </li> </ul> </li> <li>• BCG-vaccinated versus non-vaccinated (in identified groups at risk of TB infection – stratified or in combination, as appropriate)</li> </ul>	<ul style="list-style-type: none"> <li>• TBSTs:           <ul style="list-style-type: none"> <li>• TST</li> <li>• Diaskintest</li> <li>• Cy-Tb</li> <li>• C-TST</li> <li>• Others</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Efficacy of TPT based on diagnostic test results</li> <li>• Predictive value for progression to TB disease</li> <li>• Correlation with exposure gradient</li> <li>• Sensitivity and specificity<sup>b</sup> for TB infection<sup>c</sup></li> <li>• Concordance with the TST</li> <li>• Concordance with IGRAs</li> <li>• Proportion started on TPT</li> </ul>	

The current recommendations are based on the evaluation of data for the tests that were included in the present evaluation. The findings cannot be extrapolated to other brand-specific tests; also, any new in-class technologies will need to be specifically evaluated by WHO.

Guidelines are disseminated through the WHO Global TB Programme (WHO/GTB) listservs to WHO regional offices, Member States, the Stop TB Partnership and other stakeholders (e.g. the Global Laboratory Initiative and the TB Supranational Reference Laboratory Network); they are also published on the websites of the WHO/GTB and Global Laboratory Initiative. The updated policy is incorporated into the WHO TB Knowledge Sharing Platform – an online reference resource for global TB policies and derivative products.

## Recommendation

**18. *Mycobacterium tuberculosis* antigen-based skin tests (TBSTs) may be used to test for TB infection.**

*(Conditional recommendation for the intervention, very low certainty of the evidence)*

### Evidence base

In 2021, WHO commissioned a systematic review of published and unpublished data on the new class of tests for TB infection not previously reviewed by WHO. The overarching policy question was: Should Mtb antigen-based skin tests (TBSTs) for TB infection be used as an alternative to the tuberculin skin test (TST) or WHO-endorsed interferon- $\gamma$  release assays (IGRAs) to identify individuals most at risk of progression from TB infection to TB disease? Based on the overarching policy question, four domains for evidence search and generation were included: diagnostic accuracy, safety, economic aspects and qualitative aspects. For each domain, specific population, intervention, comparator and outcome (PICO) or research questions were defined.

**Domain 1 – Diagnostic accuracy (PICO question): Do TBSTs have similar or better diagnostic performance than the TST or IGRAs to detect TB infection?**

**Domain 2 – Safety: Do TBSTs for TB infection cause more adverse reactions than the TST or IGRAs?**

- What is the risk of adverse events of TBSTs compared with the current TST or IGRAs?
- Consider data on both local and systemic reactions graded by type, severity and seriousness, and stratified by subgroup.
- Compute relative risks where possible; however, if there is no control group receiving a comparator test, report frequency (%) of adverse events.

**Domain 3 – Cost-effectiveness analysis: What are economic considerations of TBSTs compared with the TST or IGRAs?**

- How large are the resource requirements (costs)?
- What is the certainty of the evidence on resource requirements (costs)?
- Does the cost-effectiveness of the intervention favour the intervention or the comparison?

## **Domain 4 – User perspective: What are end-user<sup>4</sup> views and perspectives on use of novel skin-based *in vivo* tests for TB infection use?**

- Is there important uncertainty about, or variability in, how much end-users value the main outcomes?
- What would be the impact on health equity?
- Is the intervention acceptable to key stakeholders?
- Is it feasible to implement the intervention?

The certainty of the evidence of the pooled studies was assessed systematically through PICO questions, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (2, 3). The GRADE approach produces an overall quality assessment (or certainty) of evidence, and has a framework for translating evidence into recommendations; also, under this approach, even if diagnostic accuracy studies are of observational design, they start as high-quality evidence.

GRADEpro Guideline Development Tool software (4) was used to generate summary of findings tables. The quality of evidence was rated as high (not downgraded), moderate (downgraded one level), low (downgraded two levels) or very low (downgraded more than two levels), based on five factors: risk of bias, indirectness, inconsistency, imprecision and other considerations. The quality (certainty) of evidence was downgraded by one level when a serious issue was identified and by two levels when a very serious issue was identified in any of the factors used to judge the quality of evidence. For data from the systematic reviews that were of a qualitative nature, the GRADE-CERQual tool was used. The tool examines the methodological limitations of the included studies, the coherence of each review finding, the adequacy of the data in support of a review finding and the relevance of the included studies to the review research questions; it is used to assess data quality from qualitative research studies.

Data synthesis was structured around the preset PICO question, as outlined above. The following web annexes provide additional information to evidence synthesis and analysis:

- **Web Annex A.** Accuracy of *Mycobacterium tuberculosis* antigen-based skin tests: a systematic review and meta-analysis
- **Web Annex B.** Safety of *Mycobacterium tuberculosis* antigen-based skin tests: a systematic review and meta-analysis
- **Web Annex C.** GRADE profiles of *Mycobacterium tuberculosis* antigen-based skin tests
- **Web Annex D.** Cost-effectiveness of *Mycobacterium tuberculosis* antigen-based skin tests: a systematic review
- **Web Annex E.** Modelling for economic evidence for the use of *Mycobacterium tuberculosis* antigen-based skin tests
- **Web Annex F.** Qualitative evidence for the use of *Mycobacterium tuberculosis* antigen-based skin tests
- **Web Annex G.** *Mycobacterium tuberculosis* antigen-based skin tests: evidence-to-decision table

## Diagnostic accuracy

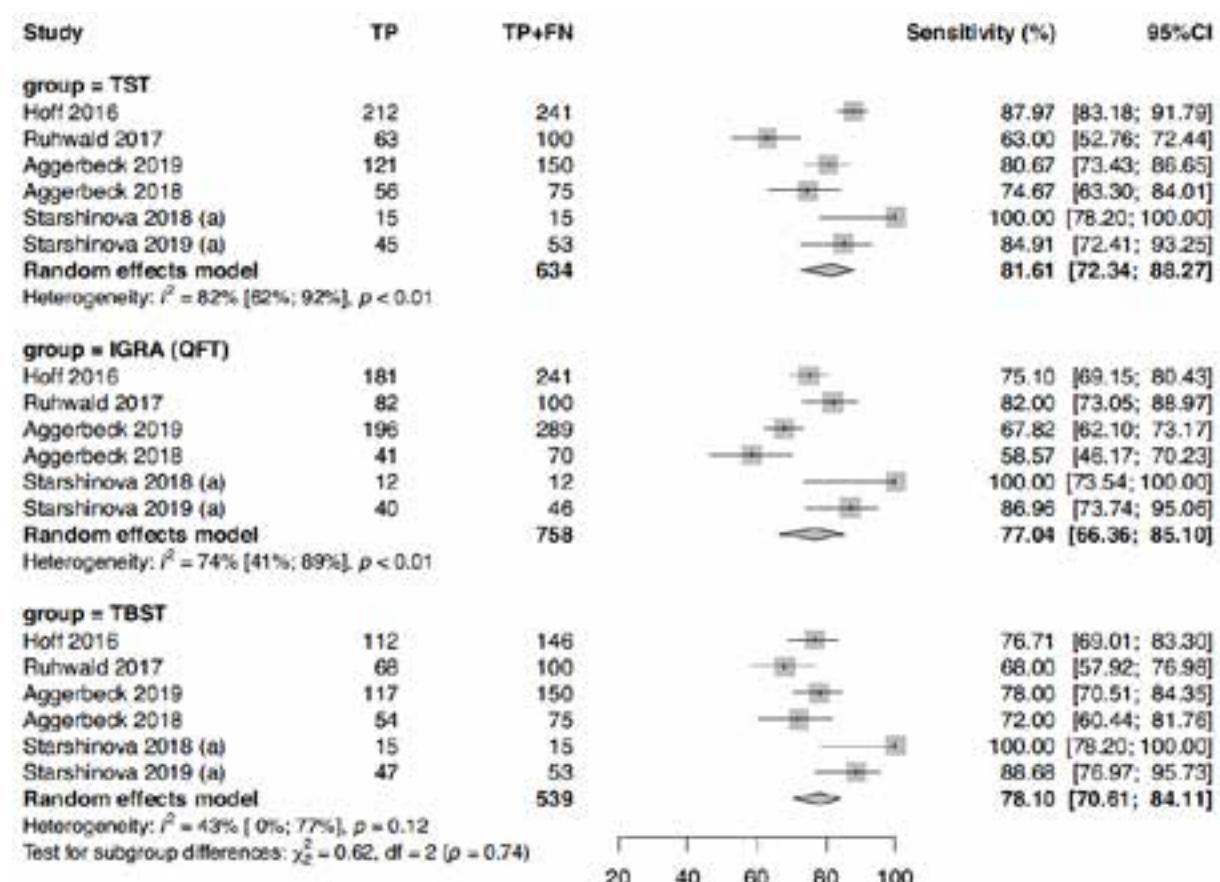
Diagnostic accuracy studies evaluating sensitivity, specificity and concordance (agreement) of TBSTs were identified. There were no identified studies on the efficacy of TPT based on diagnostic test results, on the predictive value for progression to TB disease or on the proportion started on TPT.

The assessed evidence for Cy-Tb and C-TST has included a manufacturer-recommended induration of at least 5 mm as the cut-off. According to the Diaskintest instructions for use, the presence of induration of any size is considered a positive response. However, the assessed evidence also included some studies for Diaskintest that used an induration of at least 5 mm as a cut-off, specified where applicable.

### Sensitivity

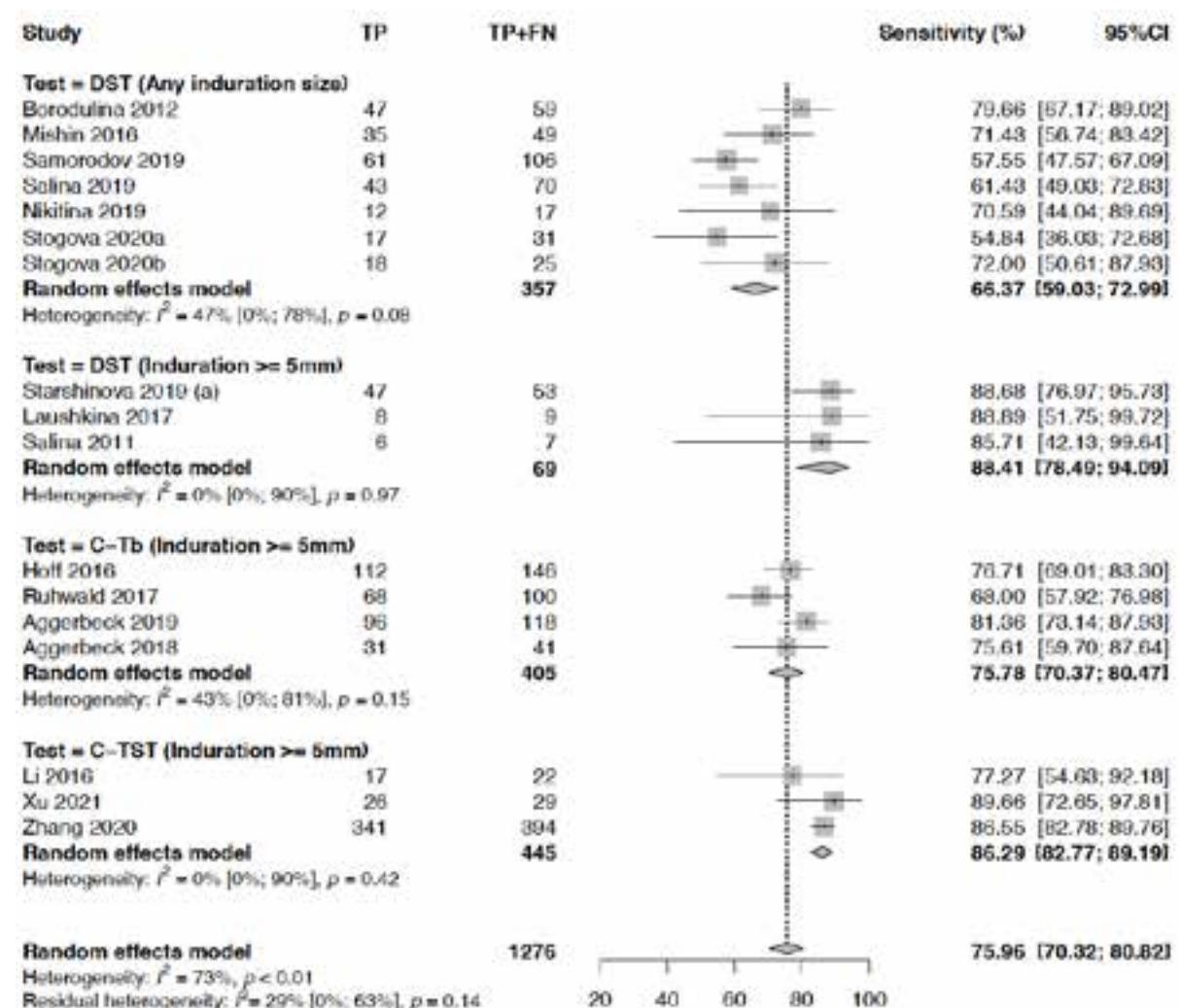
A total of 20 studies involving 1627 participants provided data for evaluating the sensitivity of TBSTs in people with microbiologically confirmed TB, which was used as a proxy for sensitivity to diagnose TB infection. Of these, six studies with 539 participants were head-to-head comparisons with the TST or IGAs (or both); 17 studies included 1276 participants who were HIV-negative or whose HIV status was unknown; five studies included 317 PLHIV; and four studies included 34 participants aged under 18 years. Of the included studies, 14 evaluated Diaskintest, four Cy-Tb and three C-TST, as shown in **Figs. 3.1.1.1–3.1.1.2**.

**Fig. 3.1.1.1 Sensitivity of TBSTs in head-to-head studies**



The pooled sensitivity against the microbiological reference standard for TB disease in six head-to-head studies (**Fig. 3.1.1.1**) was 78.1% (95% confidence interval [CI]: 70.6–84.1%). The evidence was considered to be of high certainty and was not downgraded. Starshinova 2018 (5) and Starshinova 2019 (6) evaluated Diaskintest results with a cut-off of induration of at least 5 mm; the rest of the studies were head-to-head studies evaluating Cy-Tb. The assessed evidence for Cy-Tb included a cut-off of at least 5 mm in all studies. The TST cut-off was 5 mm for PLHIV and 15 mm for people who were HIV-negative in four studies (7–10). Only studies on Diaskintest and Cy-Tb were included in this analysis.

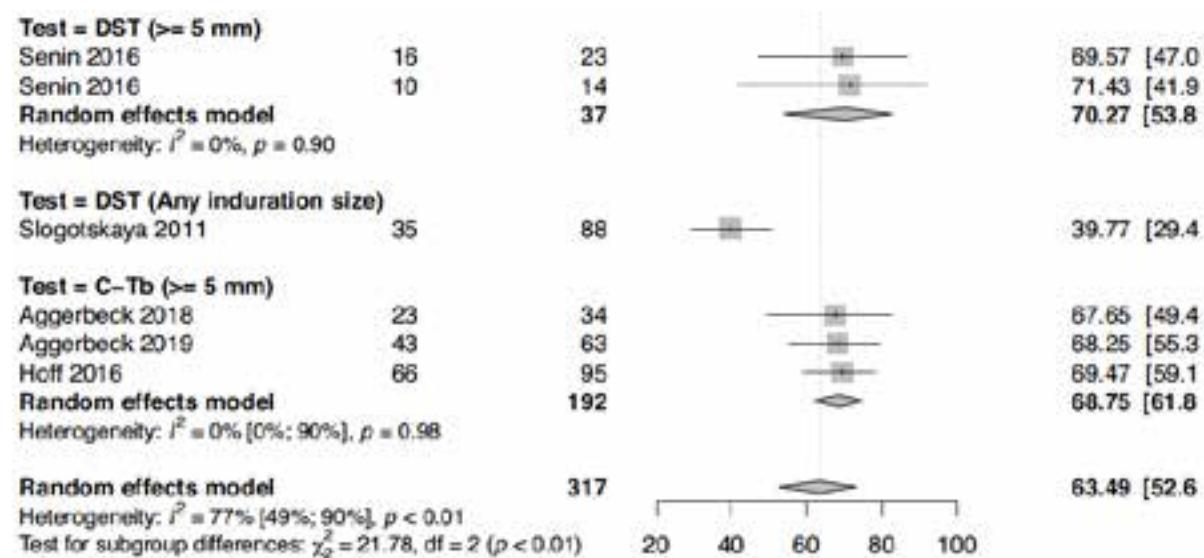
**Fig. 3.1.1.2 Sensitivity of TBSTs in all studies in individuals with HIV-negative or unknown status**



The pooled sensitivity in 17 studies presented in **Fig. 3.1.1.2** among participants who were HIV-negative or HIV status unknown was 76.0% (95% CI: 70.3–80.8%). The sensitivity estimates were lower in the studies using Diaskintest (any induration size). The reason for this is unclear; it may reflect different study populations or study quality. As a result, the evidence certainty was downgraded one level for inconsistency and another level for imprecision. Consequently, the certainty of the evidence was considered very low. Despite the manufacturer's recommendation to use induration of any size as a positive result, the sensitivity in studies using a Diaskintest result of at least 5 mm as the cut-off was more closely aligned with the other tests in the class, which all use a cut-off of at least 5 mm.

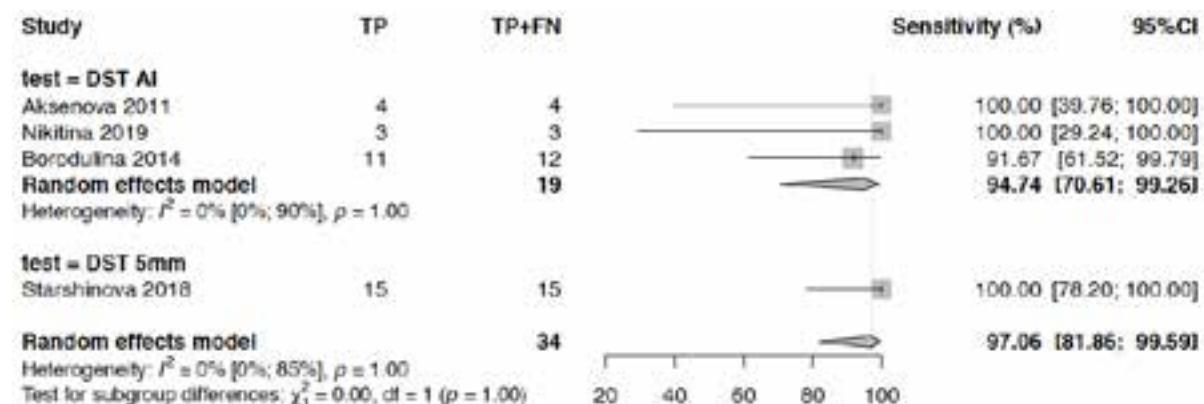
Risk of bias was considered serious due to the person having knowledge of the reference standards when interpreting the results of index tests. In most Diaskintest studies, the selection of participants and of the reference standard were unclear; hence, the certainty of the evidence was downgraded one level for risk of bias. The sensitivity ranged from 55% to 100% (the reasons for this heterogeneity are unknown); consequently, the certainty of the evidence was downgraded one level for inconsistency. Thus, the overall certainty of the evidence was considered low.

**Fig. 3.1.1.3 Sensitivity of TBSTs in PLHIV**



Only studies on Diaskintest and Cy-Tb were included in the analysis presented in **Fig. 3.1.1.3**. The pooled sensitivity among PLHIV in five studies was 63.5% (95% CI: 52.6–73.2%). Risk of bias was considered serious for Diaskintest studies because of the person having knowledge of the reference standards when interpreting the results of index tests; hence, the evidence certainty was downgraded one level for risk of bias. The sensitivity estimates were lowest (39.8%) in the one study that used Diaskintest (any induration size). The reason for low sensitivity for Diaskintest (any induration size) is unclear, and the evidence certainty was downgraded one level for inconsistency. Certainty was also downgraded one level for imprecision. Consequently, the certainty of the evidence was considered to be very low.

**Fig. 3.1.1.4 Sensitivity of TBSTs in children and adolescents**

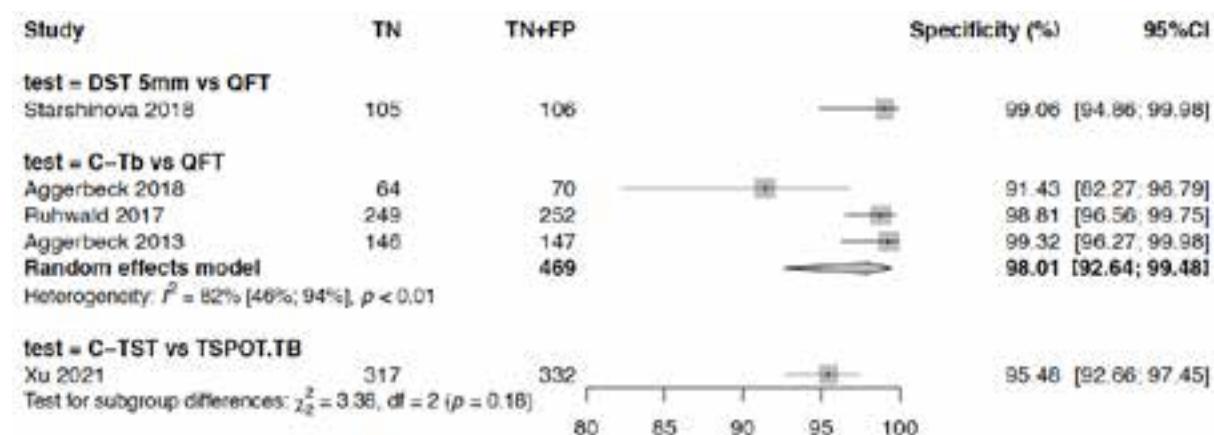


Sensitivity of TBSTs among children and adolescents is shown in **Fig. 3.1.1.4**. The pooled sensitivity in four studies for this class of tests was 97.1% (95% CI: 81.9–99.6%). The number of participants included in this analysis was small – only 34 participants in four studies; hence the studies were downgraded two levels for imprecision. Therefore, the evidence certainty was considered low. Only studies on Diaskintest were available for this analysis. Aggerbeck (7) estimated the sensitivity of Cy-Tb in 12 children and adolescents with TB, of whom only two were bacteriologically confirmed and were not included in the figure.

## Specificity

A total of 14 studies involving 3792 participants provided data for evaluating specificity of TBSTs (including difference in specificity compared with the reference test); three of the studies included 1104 children and adolescents and three included 587 BCG-vaccinated individuals. Specificity was measured in healthy individuals with negative IGRA results. Difference in specificity was used as an alternative specificity measure, and was calculated as the difference in the proportion of negative results between TBSTs and the TST or IGRAs in healthy populations.

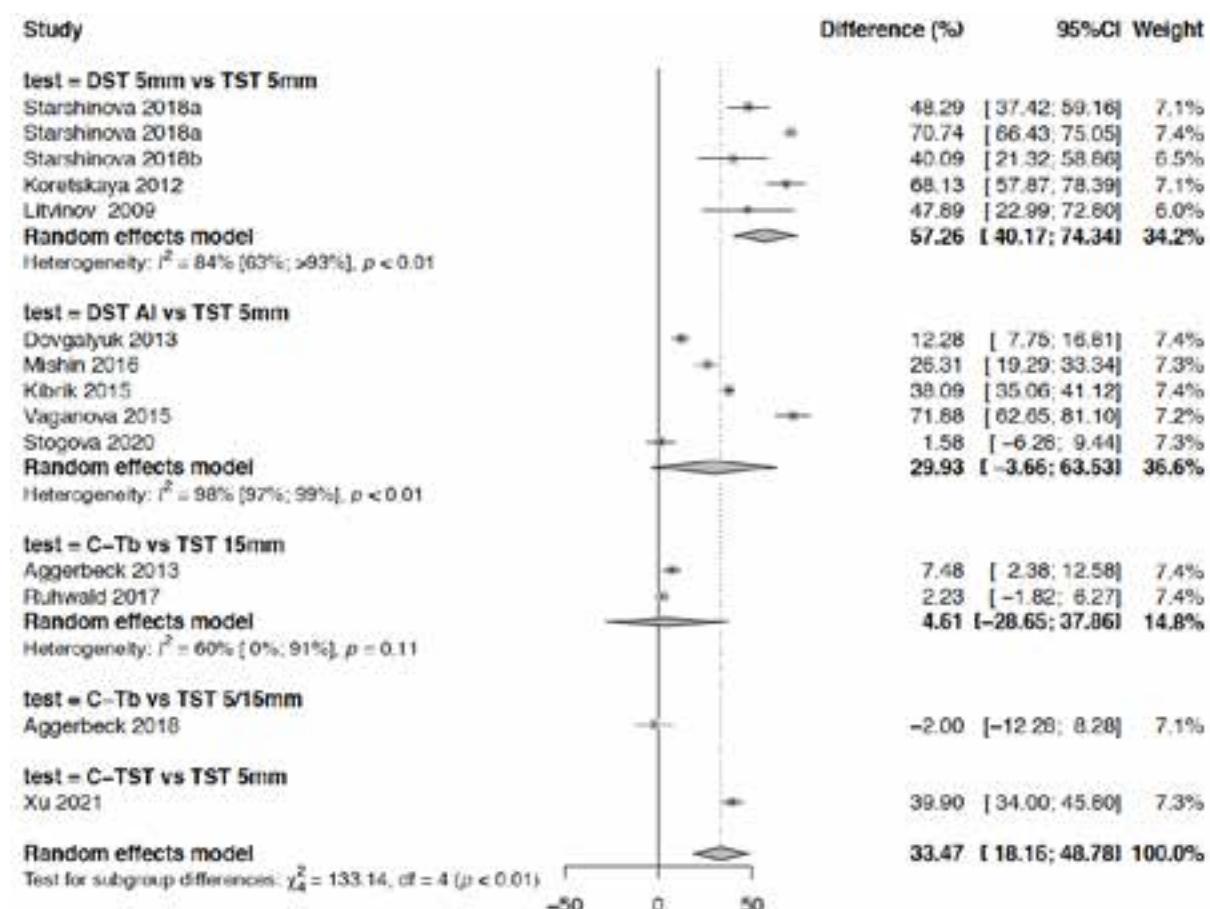
**Fig. 3.1.1.5 Specificity in healthy individuals with negative IGRA results**



The specificity assessed in the five studies presented in **Fig. 3.1.1.5** was high for all three tests in the TBST class. For Diaskintest it was 99.1% (95% CI: 93.6–99.9%), as compared with QFT; for Cy-Tb it was 98.0% (95% CI: 92.6–99.5%), as compared with QFT; and for C-TST it was 95.5% (95% CI: 92.6–97.3%), as compared with T-Spot. During the GDG meeting, participants noted that – considering the totality of evidence (which included studies of very low quality) – the overall certainty of the evidence on tests' effects for specificity was very low.

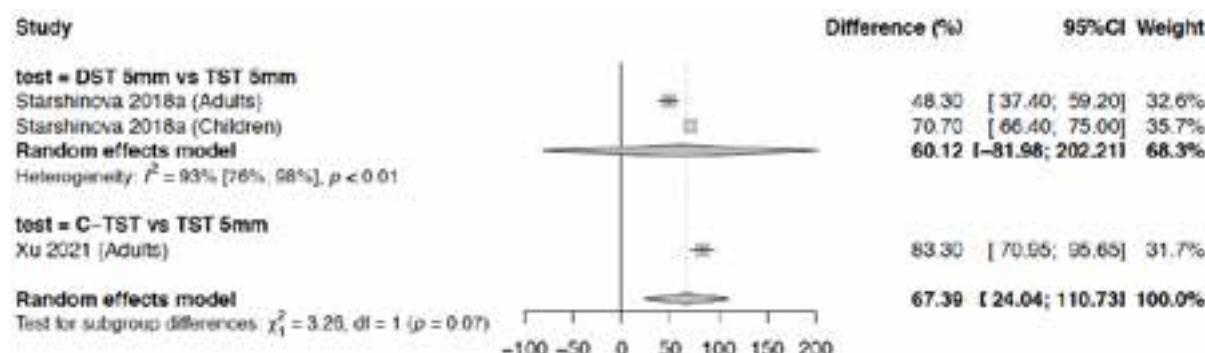
Specificity in children and adolescents (2 studies, 176 patients), as determined in individuals with negative IGRA results, was high. For Diaskintest with a cut-off of at least 5 mm it was 99.1% (95% CI: 94.9–99.9%), as compared with QFT, and for Cy-Tb it was 91.4% (95% CI: 82.2–96.1%), as compared with QFT. Specificity in BCG-vaccinated individuals (3 studies, 292 patients), as determined in healthy individuals with negative IGRA results, was also high, being 97–99% (depending on the test), with a pooled value of 99.0% (95% CI: 96.9–99.7%). More details can be found in **Web Annex A**.

**Fig. 3.1.1.6 Difference in specificity – TBSTs versus the TST**



The overall pooled difference in specificity in 14 studies (Fig. 3.1.1.6) comparing TBSTs and the TST was 33.5% (95% CI: 18.2–48.8%) higher for TBSTs. In studies of Diaskintest and C-TST done in high TB incidence settings, the differences in specificity were higher for Diaskintest versus the TST (with both tests having a cut-off of at least 5 mm) (57.3%, 95% CI: 40.2–74.3%), than with Diaskintest (any induration size) versus the TST with a cut-off of at least 5 mm (29.9%, 95% CI: -3.66–63.5%). For C-TST versus the TST with a cut-off of at least 5 mm, the difference in specificity was 39.9% (95% CI: 34.0–45.8%). In contrast, in studies of Cy-Tb undertaken in low TB incidence settings, the difference in specificity between Cy-Tb and the TST was less prominent, but was greater with the TST with a cut-off of at least 15 mm (4.61%, 95% CI: -28.6–37.9%) than with the TST with a cut-off of 5 or 15 mm (-2.0%, 95% CI: -12.3–8.3%). The difference may be explained by the background level of BCG in the study populations or by the cut-offs that were used. Fig. 3.1.1.7 has more details on the specificity of TBSTs versus the TST in BCG-vaccinated people. Overall risk of bias was considered serious because test allocation by arm was not blinded in any of the studies except those for Cy-Tb. In most Diaskintest studies, the selection of participants and the diagnosis of the reference standard were unclear. The certainty of the evidence was therefore downgraded one level for risk of bias. The difference in specificity ranged from -2% to 72%; hence, the certainty of the evidence was downgraded one more level for inconsistency. Consequently, the certainty of the evidence for difference in specificity between TBSTs and the TST was low.

**Fig. 3.1.1.7 Difference in specificity – TBSTs versus the TST in BCG-vaccinated population**



Two studies (three analyses) provided data on difference in specificity in BCG-vaccinated populations, which was even higher for this population than in populations where only some people had received BCG vaccination; the pooled difference in specificity was 67.4% (95% CI: 24.0–110.7%). Overall risk of bias was considered serious because test allocation by arm was not blinded; hence, the certainty of the evidence was downgraded one level for risk of bias. The CI was broad, ranging from 24.0% to 110.7%, so the certainty of the evidence was downgraded one more level for imprecision. Consequently, certainty of the evidence for difference in specificity between TBSTs and the TST in BCG-vaccinated populations was low.

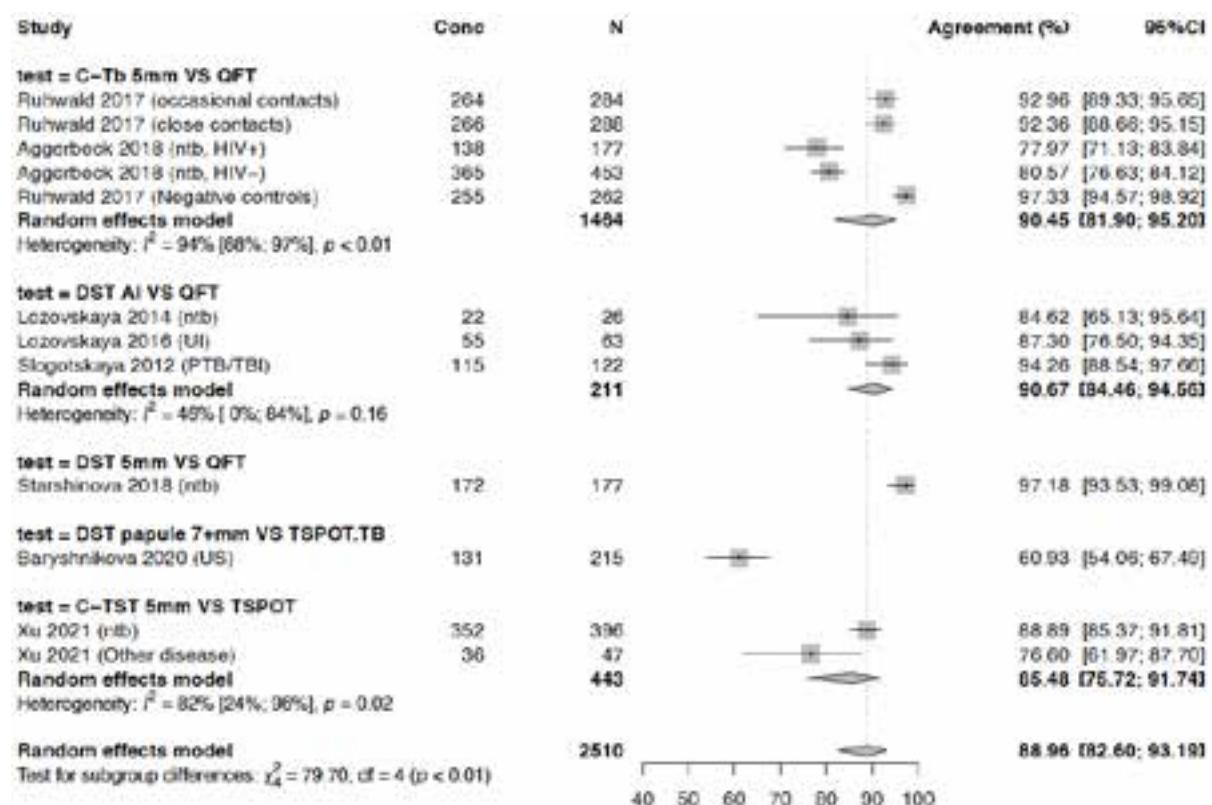
The pooled difference in specificity in six studies comparing TBSTs and IGRAs was low, at 2.3% (95% CI: −1.6–6.2%), meaning that TBSTs were similar to IGRAs in terms of specificity.

## Agreement

Overall, 16 studies involving 3198 participants (among which four studies with 1307 participants recruited people aged under 18 years) were included to assess agreement of the index tests with comparator tests (the TST or IGRAs, or both).

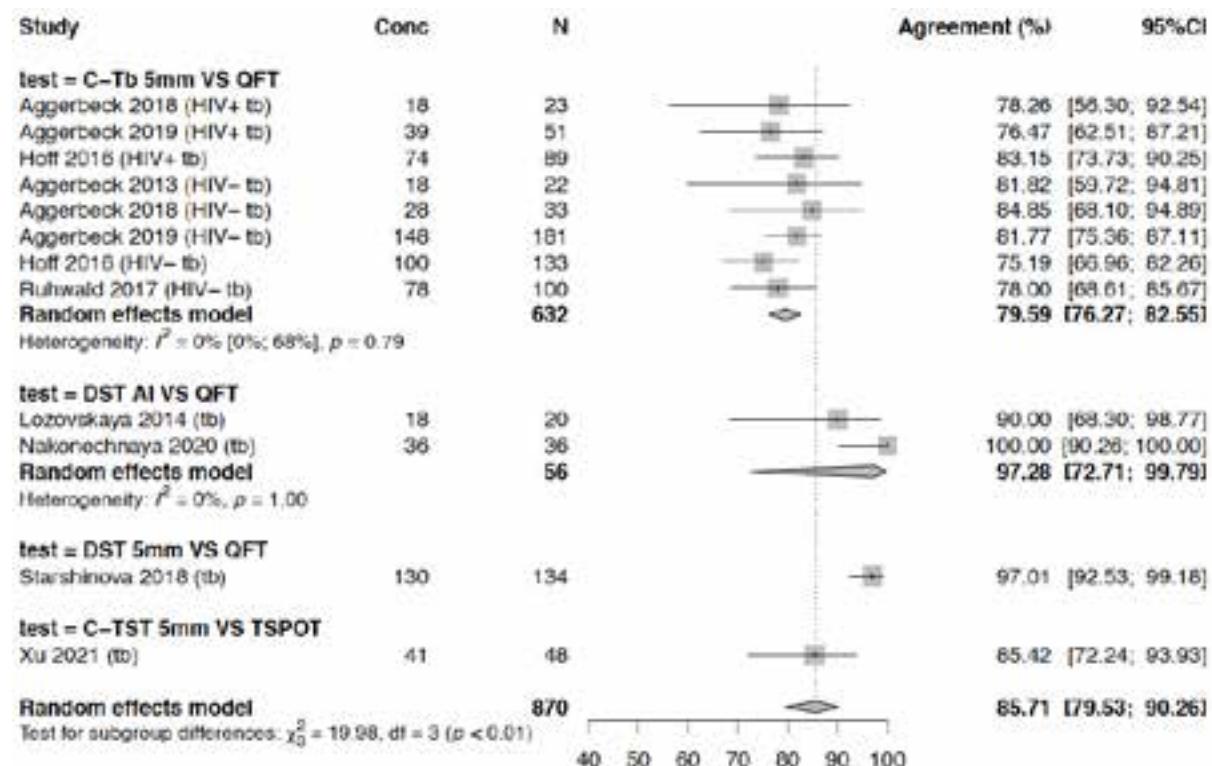
In participants without TB disease, agreement was high ( $\geq 90\%$ ) for Cy-Tb and Diaskintest – (any induration size) and Diaskintest 5 mm induration – compared with QFT (Fig. 3.1.1.8). Agreement was slightly lower at 85.5% (95% CI: 75.7–91.7%) for C-TST compared with T-Spot. In one study, which evaluated Diaskintest with induration of at least 7 mm compared with T-Spot, the agreement was considerably lower, at 60.9% (95% CI: 54.3–67.2%). Risk of bias was considered serious because the allocation of tests was not blinded in five studies; hence, certainty of the evidence was downgraded one level for risk of bias. Agreement ranged widely (from 61% to 97%) for various tests and studies, so the certainty of the evidence was downgraded one level for inconsistency. Consequently, certainty of the evidence for agreement between TBSTs and IGRAs was low.

**Fig. 3.1.1.8 Agreement of TBSTs versus IGRAs in all studies including participants without active TB**



In participants with TB disease, high agreement between TBSTs and IGRAs as the comparator (85.7%) was observed (Fig. 3.1.1.9). Some variability in agreement was seen between the different tests: 79.6% (95% CI: 76.3–82.6%) for Cy-Tb 5 mm compared with QFT; 97.3% (95% CI: 72.7–99.8%) for Diaskintest (any induration size) compared with QFT; and 97.0% (95% CI: 92.3–98.9%) for DST 5 mm induration compared with QFT. Agreement was slightly lower at 85.4% (95% CI: 72.4–92.9%) for C-TST compared with T-Spot. Risk of bias was considered serious because, in four studies, the allocation of tests by arm was not blinded; hence, the certainty of the evidence was downgraded one level for risk of bias. The agreement ranged from 75% to 100% for various tests and studies, so certainty of the evidence was downgraded one level for inconsistency. The overall certainty of the evidence for agreement between TBSTs and IGRAs in people with TB disease was considered low.

**Fig. 3.1.1.9 Agreement of TBSTs versus IGRAs in all studies including people with active TB**



## Safety

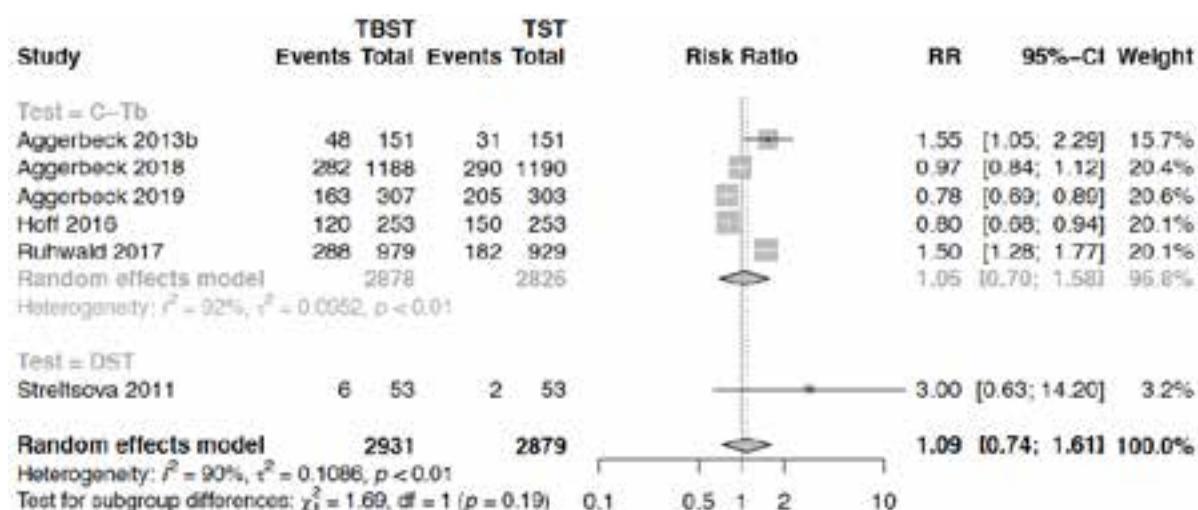
A systematic review of studies reporting the outcomes of interest, including local reactions – that is, injection site reactions (ISR) and systemic adverse events from TBSTs – was undertaken. The following databases were searched for studies from inception until 30 July 2021: Medline, Embase, e-library, the Chinese Biomedical Literature Database and the China National Knowledge Infrastructure Database. The test manufacturers were contacted for individual studies, and studies were identified through a public call for data by WHO. Longitudinal and case–control studies reporting adverse events of the index tests alone or compared with recognized comparator tests (e.g. QFT, T-Spot and the TST) in humans were included with no language restrictions. Screening of titles and abstracts as well as full-text articles and the assessment of quality were performed by two investigators in duplicate. A meta-analysis was conducted using a random-effects model, and studies that were considered to be clinically homogenous were pooled.

Overall, seven studies for Cy-Tb, five for C-TST and 11 for Diaskintest were identified. Characteristics of studies were as follows:

- Cy-Tb: clinical trials – three studies in South Africa and four in Europe. Most participants were adults; in studies in South Africa, 20–40% of participants were PLHIV. Five of seven studies included random allocation of Cy-Tb versus the TST into two arms and thus allowed comparison of ISR. All five studies were included in the pooled evidence assessment on any ISR. Only one study provided comparable data on systemic reactions. This study was also included in the pooled evidence assessment on systemic reactions.

- C-TST: all five studies were conducted in China and included only HIV-negative adults. All of them included non-random allocation of C-TST versus the TST into two arms; thus, no study evaluating C-TST was included in the pooled evidence assessment on any ISR. Also, no studies including any comparable data on systemic reactions were available.
- Diaskintest: cross-sectional studies using routinely collected data mostly in the Russian Federation, and one in Ukraine, including various populations (adults, children and adolescents – healthy, contacts of TB patients and with TB). Two studies on Diaskintest provided comparable data on ISR; however, one of them provided no information about the number of participants who experienced any ISR; thus, only one study on Diaskintest was included in the meta-analysis.

**Fig. 3.1.1.10 Any injection site reactions**



Proportion of PLHIV: Aggerbeck 2018 (7) (25%), Aggerbeck 2019 (8) (20%); Hoff 2016 (10) (39.5%). Other studies included HIV-negative individuals. Aggerbeck 2018 (7) included children aged under 5 years (20%) and aged 5–17 years (31%); Ruhwald 2017 (9) included children aged under 5 years (3.5%) and aged 5–17 years (8.8%). Other studies included adults. Hoff 2016 (10), Aggerbeck 2019 (8) and Streltsova 2011 (11) included people with TB only.

The pooled risk of any ISR due to Cy-Tb (n=2878, 5 studies) and Diaskintest (n=53, 1 study) presented in **Fig. 3.1.1.10** was not significantly different from the TST (risk ratio [RR] 1.09; 95% CI: 0.74–1.61). The risk of any systemic reaction was only analysable in one study (Cy-Tb) that allowed such comparison, and was not significantly different from the TST (RR 0.84; 95% CI: 0.60–1.10). The Diaskintest study was considered to have high risk of bias, while the overall certainty of evidence from the randomized controlled trials for any ISR was judged as high. For any systemic reactions, overall certainty of evidence was judged to be moderate because of the small sample size and wide CI.

Following the request from GDG members for the post-marketing surveillance data for Diaskintest, the following data were reported by the manufacturer: in 2019–2021, over a 55.7 mln Diaskintest tests were done, with 27 serious adverse effects and 30 non-serious adverse effects. Based on the totality of data, the GDG rated the certainty of evidence as high.

Based on the data presented at the GDG meeting, it was concluded that the safety profile of novel TBSTs is similar to that of the TST, and is associated with mostly mild ISR such as itching and pain. From the reviewed studies, there appears to be no safety signal that might affect the choice between specific TBSTs and the TST. However, the group also noted that this was not a full safety review covering product safety, animal or preclinical studies. Regulatory assessment for safety is needed before any of the TBST products are implemented.

## Cost and cost-effectiveness analysis

Two reviews following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were carried out to look at costs and cost-effectiveness of:

- novel TBST, such as Diaskintest, C-TST and Cy-Tb (primary review); and
- TST and IGRA tests (secondary review).

The articles searched were those presenting economic evaluations of the diagnostic tests (costs and cost-effectiveness) using a health provider perspective and related to TB infection in humans. The articles reviewed were those written in English, Chinese or Russian languages, and published in Medline, OVID, Chinese Biomedical Literature, China National Knowledge Infrastructure and Russian e-library databases. Quality of studies was assessed using Drummond's checklist.

In addition, a Markov-chain model was developed for the purposes of the GDG meeting, to study the cost-effectiveness of TBSTs versus the currently available tests, the TST and IGAs. When simulating a cohort of individuals transitioning among different states and steps along the TB cascade of care, the model took into consideration the following parameters:

- prevalence of TB infection in TB-negative individuals, percentage;
- people completing treatment after initiation following a positive TB infection result, percentage;
- people not initiating treatment after testing positive for TB infection, percentage;
- people interrupting treatment after initiation following a positive TB infection test result, percentage;
- progression from TB infection to active TB, probability;
- efficacy of TB infection treatment;
- active TB treatment coverage;
- recovery from active TB (treated + untreated);
- death from active TB (treated + untreated);
- probability of a true positive test result if the patient has TB infection (sensitivity); and
- probability of a true negative test result if the patient does not have TB infection (specificity).

Model parameters, unit costs and estimates of diagnostic test accuracy were sourced from the literature, including from the systematic reviews mentioned above. The manufacturers of novel TBSTs were also contacted to source costs of the new tests. However, only Generium, the manufacturer of Diaskintest, provided estimated test costs, including delivery costs, for different delivery volumes. Consequently, the modelling study focused on Diaskintest as the representative of the TBST class of tests.

The model was parameterized to three countries: Brazil, South Africa and the United Kingdom. Three testing strategies were considered in this analysis: Diaskintest (index); the TST; and

QuantiFERON-TB IGRAs, either Gold In-Tube or Gold Plus (comparator tests). Outcomes reported included unit cost (in US dollars)<sup>5</sup> per patient, incremental cost-effectiveness ratio (ICER) and incremental net benefit per quality-adjusted life year (QALY) gained. Unit costs considered in each country included test kit, staff time, laboratory and disposable costs. Costs were considered from a health system perspective and did not reflect patient or societal costs.

Given that only information on Diaskintest was available, a univariate sensitivity analysis on TBST unit costs and a comparison of the results of the three strategies was performed to identify possible maximum unit costs of new TBSTs, for the strategy to remain cost saving or cost-effective, but without specifying a particular type of TBST.

The conclusions were based on the predefined research questions outlined below.

### **How large are the resource requirements (costs)?**

In the eight studies that assessed Diaskintest, most estimated a cost of \$1.60 per test. One study evaluated the unit costs considering staff time, consumables and laboratory costs, resulting in a cost of \$5.07. This study, using the same costing factors, also estimated the unit cost of C-TST as \$9.96. The 29 studies on IGRAs or the TST (or both) estimated an average cost of \$37.84 for the TST and \$89.33 for IGRAs (accounting for different ingredients). The cost-effectiveness of the tests varied among and within risk groups, with no clear economic consensus around the cost-effectiveness of comparison tests.

### **What is the certainty of the evidence of resource requirements (costs)?**

Based on Drummond's scores, the quality of studies that have assessed cost-effectiveness of C-TST and Diaskintest in this review was concerning; only one out of eight studies was of high quality. However, the quality of the studies that assessed cost-effectiveness of the TST and IGRAs was generally high.

### **Does the cost-effectiveness of the intervention favour the intervention or the comparison?**

Based on the systematic review results, there was insufficient evidence regarding both the cost and cost-effectiveness of novel TBSTs. The quality of the studies was concerning according to the Drummond's checklist for economic evaluations. More high-quality studies are needed that consider different health settings and risk populations to estimate the cost-effectiveness and the likely economic impact of these tests.

Results of the Markov-chain model conducted for the purposes of the GDG meeting concluded that, in Brazil, Diaskintest is cost saving compared with the TST and IGRAs. Compared with the TST, Diaskintest is cost saving at \$5.60, with an incremental gain of 0.02 QALYs per patient. Compared with IGRAs, Diaskintest is cost saving at \$8.40, with an incremental gain of 0.01 QALYs. In South Africa, Diaskintest is more cost saving than the TST or IGRAs. Compared with the TST, Diaskintest is cost saving at \$4.39, with an incremental gain of 0.02 QALYs, and compared with IGRAs, it is cost saving at \$64.41, with an incremental gain of 0.01 QALYs. In the United Kingdom, Diaskintest is cost saving compared with the TST but not with IGRAs. Compared with the TST, Diaskintest is cost saving at \$73.33, with an incremental gain of 0.04 QALYs; however, compared with IGRAs, Diaskintest showed an increase in cost of \$15.80 but still an incremental gain of 0.03 QALYs.

In summary, the modelling and univariate sensitivity analysis results show that, in Brazil and South Africa, use of Diaskintest would potentially save costs per patient and result in greater health gains (QALYs per patient) compared with the TST and IGRAs. In the United Kingdom, Diaskintest results in health gains but is more expensive in terms of expected cost per patient than IGRAs. Our results also show that, in Brazil and South Africa, IGRAs are more costly to implement than the TST but would result in health gains. However, in the United Kingdom, IGRAs are cheaper to implement and are more cost-effective than the TST.

## User perspective

User perspectives on the value, feasibility, usability and acceptability of diagnostic technologies are important in the implementation of such technologies. If the perspectives of laboratory personnel, clinicians, patients and TB programme personnel are not considered, the technologies risk being inaccessible to and underused by those for whom they are intended.

To address questions related to user perspective, the following activities were undertaken:

- Two systematic reviews, which synthesized the qualitative research evidence on end-user values and preferences for the use of specific TBSTs for TB infection, compared with existing tests (IGRAs and the TST). Study quality and confidence in the evidence were evaluated in accordance with the GRADE-CERQual.
- Twenty semi-structured interviews with a diverse range of clinicians, laboratory staff, programme officers and individuals living with TB infection (referred to as "consumers" throughout this report).
- A discrete choice experiment (DCE) survey, drawing from themes derived in systematic reviews and semi-structured interviews. DCE methodology was used to elicit stated values and preferences from participants (end-users) without directly asking them to state their preferred options.

Four studies were identified that met the inclusion criteria for both systematic reviews. From the review on specific TBST, only one data source was identified (from the Russian Federation), and that came from a WHO public call for data relating to the feasibility and acceptability of TBSTs. Participants were parents of children and adolescents with TB infection. From the review on current IGRAs and the TST, three peer-reviewed articles were found to meet the inclusion criteria; these three papers were from the Netherlands, South Africa and the United States of America (USA). Participants included a range of health professionals involved in TB care (Netherlands, South Africa and USA) and PLHIV (South Africa). The overall confidence in the quality of the evidence from the studies was low to moderate based on the GRADE-CERQual assessments, because the data lacked richness, with most studies reporting only summaries of participant quotes or limited direct quotes. All studies were conducted on specific subgroups (e.g. PLHIV, or parents of children and adolescents with TB infection).

For user interviews, 20 participants were recruited – 13 were TB health care providers (8 from low- and middle-income countries [LMIC]) and seven were people affected by TB (3 from LMIC). Health care providers included programme executives and decision-makers, public health practitioners and advocates, physicians, researchers and laboratory technicians, and a nurse.

For DCE, a total of 234 participants completed this activity (186 providers and 48 consumers). Overall, 59% of respondents were female and 56% were aged 36–55 years; the main countries in which respondents were based were India (26%), the USA (16%), South Africa (9%), Pakistan (8%) and Zimbabwe (7%).

The conclusions were based on the predefined research questions outlined below.

### **Is there important uncertainty about or variability in how much end-users value the main outcomes?**

Qualitative data from the systematic reviews and end-user interviews, and quantitative data from the DCE indicated that health care consumers and providers had similar values and preferences in terms of TB infection tests. Key end-user values included test accuracy, convenience, positive patient experience, cost and resource requirements. In particular, end-users valued tests with high accuracy such as TBST and IGRAs (i.e. low false positive and false negative rates), because they reduce the risk of downstream consequences associated with false positive and false negative results (e.g. anxiety, and the need for additional testing or unnecessary treatment). End-users also preferred having a test that was convenient to administer and access. This included valuing tests that can be accessed in a community or primary care setting, that do not require follow-up visits to read test results, and that can be administered without the need for additional systems or infrastructure to be developed. These findings were initially identified from themes emerging from the systematic reviews and end-user interviews, and were confirmed by the DCE findings.

From the qualitative data from the reviews and interviews, all TB infection test options were found to have strengths and limitations in terms of convenience. End-users valued a positive consumer experience. This meant that tests with fewer psychological effects (e.g. anxiety, stigma and stress) and physical consequences (e.g. discomfort) were preferred. Tests that were more accurate tended to be associated with better consumer experience, although some aspects of consumer experience were worse in skin tests (e.g. stigma from the welt and discomfort) compared with non-skin-based tests. Low-cost tests were generally preferred due to greater accessibility in resource-limited contexts (e.g. TBST and the TST). Tests with lower resource requirements were preferred in resource-limited settings (e.g. TBST and the TST); however, this appeared to be less of a consideration in high-income countries. End-users showed a preference towards TB infection tests that used existing infrastructure in their health care setting. Data from the DCE confirmed that not requiring an in-person follow-up appointment and not requiring specialist staff or equipment to interpret or administer the test were important end-user preferences for TB testing.

### **What would be the impact on health equity?**

Qualitative evidence from reviews and end-user interviews indicates that specific TBSTs are unlikely to create any new equity issues. Rather, TBSTs are likely to improve health equity through the provision of a more accurate, low-cost test for resource-limited settings where the TST is already in use. Moreover, their portability and low cost make them suited to use in large-scale screening programmes in vulnerable, hard-to-reach communities. However, it is possible that TBSTs may not affect health equity in low-resource settings that do not already use the TST, because there are barriers to accessing skin and other health care tests in these

settings, which would need to be addressed first, regardless of the type of TB test available. In terms of test accessibility, the data from the DCE found that consumers had a strong preference for testing in the community and primary care settings, compared with hospital locations; this finding could have health equity implications.

### **Is the intervention acceptable to key stakeholders?**

Qualitative data from systematic reviews and end-user interviews suggest that TBSTs were perceived to have greater specificity and sensitivity than the TST. Having greater test accuracy was deemed desirable to avoid the negative consequences of false positives or negatives. However, TBSTs were expected to have many of the same limitations as skin tests in terms of patient experience (e.g. the need for a return visit, discomfort, a welt on the arm and stigma) compared with IGRAs. IGRAs were deemed the preferred test option in countries that already have IGRAs in use, because the required supporting infrastructure is already in place, and because TBSTs would have comparable accuracy and performance, thus would not add value. There were also broader concerns about skin tests because these tests were viewed as a dated, basic technology that is subject to human error and interpretation. Suggestions for improving the acceptability of TBSTs included careful communication during the implementation of this test, with endorsement by health care providers and organizations (e.g. WHO). Data from the DCE found strong and consistent preferences among both health care providers and consumers for tests that minimize false positive and false negative results. The DCE also found that consumers had a strong preference for testing in the community and primary care settings compared with hospital locations.

### **Is the intervention feasible to implement?**

Findings from the qualitative evidence synthesis (reviews and end-user interviews) support the feasibility of use of TBSTs, but only in settings where the TST is already in use, and the required resourcing and training is already in place. TBST are likely to be low-cost, portable tests that can be well-suited for low-resource health care settings, which may not be able to support IGRAs owing to the greater cost and resources required to implement IGRAs. However, if health care settings already have the necessary infrastructure in place to implement IGRAs, then that is a more feasible test option than any skin tests because IGRAs do not require a return visit to read the result (a step where patients may be lost to follow-up). Results from the DCE found that not requiring an in-person follow-up appointment, or specialist staff or equipment to interpret or administer the test, were important preferences for TB testing that would influence feasibility. There was some suggestion that providers preferred more expensive tests (when offered a choice based on a hypothetical cost of \$50 compared with \$25), although test cost was the least important determinant of test choice.

## **Implementation considerations**

Considerations for implementation were as follows:

- regulatory approval from national regulatory authorities or other relevant bodies is required before implementation of in vivo diagnostic tests;
- appropriate communication on the new class of tests is necessary, highlighting the difference between the TST and TBSTs;
- implementation of TBSTs requires a cold chain;

- well-trained skilled staff are needed to administer and interpret this class of tests;
- multiuse vials will require effective operational planning and batching; hence, single-use vials or vials with fewer doses to match daily needs are preferred;
- procurement and stock management aspects will have to be considered, as with implementing any new class of tests;
- because the reading of the TBST results requires a second patient visit, linkage to care requires reinforcement, to decrease loss to follow-up;
- global market availability and necessary volumes of the new class of tests must be considered; and
- measurement of the TBST reaction size and interpretation must be standardized.

## **Monitoring and evaluation**

Factors that will require monitoring and evaluation are as follows:

- adverse event monitoring is a gap with the current TST use; thus, recording and reporting systems for results and adverse events need to be introduced when implementing the new tests; and
- there is a need to monitor the linkage between results of the new class of the tests and number of people placed on TPT.

## **Research priorities**

Research priorities are as follows:

- specificity of Diaskintest and C-TST in populations with a low prevalence of TB infection, and direct head-to-head comparisons of all three TBST;
- assessing the barriers for implementation and patient access;
- additional accuracy studies on high-risk groups: children aged under 5 years, children (aged 5–10 years) and adolescents (aged 10–18 years), PLHIV, prisoners and migrants;
- studies evaluating the epidemiologic and economic impact of TBST use in the TB infection diagnosis and TPT cascade;
- longitudinal studies to assess the predictive value for active TB compared with current tests;
- economic studies (e.g. cost and cost-effectiveness of TBSTs under different scenarios); and
- studies evaluating the use of digital tools for reading of results, to avoid return patient visits.

## **3.2. TB skin tests and interferon gamma release assays for the diagnosis of TB infection**

Testing for TB infection increases the certainty that individuals targeted for treatment will benefit from it. However, there is no gold-standard test to diagnose TB infection. Both currently available tests – the TST and IGRAs – are indirect and require a competent immune response to identify people infected with TB. A positive test result by either method is not by itself a reliable indicator of the risk of progression to active disease. This section discusses the evidence and the recommendations for TB infection testing.

## Recommendation

- 19. Either a tuberculin skin test (TST) or interferon-gamma release assays (IGRAs) can be used to test for TB infection.**

*(Strong recommendation, very low certainty of the evidence)*

### Justification

A systematic review has informed the comparison of the predictive performance of IGRAs and the TST for identifying incident active TB in countries with a TB incidence of more than 100 per 100 000 population (12). Only studies in which the TST was compared with IGRAs in the same population (i.e. “head-to-head” studies) were included. Relative risk ratios for TB for people who tested positive and those who tested negative with the TST and IGRAs were estimated.

Five prospective cohort studies were identified, with a total of 7769 participants. The pooled risk ratio estimate for the TST was 1.49 (95% CI: 0.79–2.80), and for IGRAs was 2.03 (95% CI: 1.18–3.50). Although the estimate for IGRAs was slightly higher than that for the TST, the 95% CIs for the estimates for the TST and IGRAs overlapped and were imprecise.

The GDG concluded that the comparison of the TST and IGRAs in the same population does not provide strong evidence that one test should be preferred over the other for predicting progression to active TB disease. The TST may require significantly fewer resources than IGRAs and may be more familiar to practitioners in resource-limited settings; however, recurrent global shortages and stock-outs of the TST reduce prospects for the scale-up of this test and for the programmatic management of TPT. The GDG also noted that equity and access could affect the choice and type of test used. The preferences of people to be tested and programmes depend on several factors, such as the requirement for an adequately equipped laboratory (e.g. for IGRAs) and possible additional costs for people being tested (e.g. for travel) and programmes (e.g. for infrastructure and testing). The GDG strongly recommended the two tests as equivalent options, with relatively similar advantages and disadvantages. The GDG stressed that the global shortage of the TST should be addressed urgently, and called for more investment into research on novel tests for TB infection with better predictive value. The GDG cautioned that imperfect performance of these tests can lead to false negative results, particularly in young children and immunocompromised individuals such as PLHIV with low CD4 counts. The GDG noted the importance of the tests to identify recent conversion from negative to positive, particularly among contacts of people with pulmonary TB, which is good practice when initiating TPT. Nevertheless, recent studies among health care workers in the USA tested serially for TB infection showed that conversions from negative to positive and reversions from positive to negative are more commonly identified with IGRAs than with the TST (13). Thus, clinical judgement must still be used to interpret the results of serial TB infection tests.

The evidence reviewed and the recommendations given apply only to the use of the two commercially available IGRAs (QuantiFERON-TB Gold In-Tube and T-Spot).

## Evidence base

### PICO question

Could IGRA be used as an alternative to the TST, to identify individuals most at risk of progression from TB infection to active TB in high TB incidence settings?

### Evidence on intervention effect

Five prospective cohort studies were identified, with a total of 7769 participants; four of the studies were newly identified. Three of the studies were conducted in South Africa and two in India (14–18). The studies included PLHIV, pregnant women, adolescents, health care workers and household contacts. The pooled risk ratio estimate for the TST was 1.49 (95% CI: 0.79–2.80), and for IGRAs was 2.03 (95% CI: 1.18–3.50). Although the estimate for IGRAs was slightly higher than that for the TST, the 95% CIs for the estimates for the TST and IGRAs overlapped and were imprecise. Furthermore, there was limited evidence for the predictive utility of the tests in specific at-risk populations.

### Cost-effectiveness

IGRA testing is more costly than the TST and requires appropriate laboratory services. TST testing is less costly and can be performed in the field, but it requires a cold chain, two health care visits and training in intradermal injection, reading and interpretation. The incremental cost-effectiveness of IGRAs and the TST appears to be influenced mainly by their accuracy.

### User perspective

The preferences of people to be tested and programmes depend on several factors, such as the requirement for an adequately equipped laboratory (e.g. for IGRAs) and possible additional costs for people being tested (e.g. for travel) and programmes (e.g. for infrastructure and testing).

### Implementation considerations

Where it is feasible, TB infection testing is desirable to identify individuals at highest risk for developing active TB. However, it is not required in PLHIV or in household contacts aged under 5 years. In HIV-negative household contacts aged 5 years and older, and in other risk groups, TB infection tests are recommended, but their unavailability should not be a barrier to treating people who are judged to be at higher risk. The GDG noted that the availability and affordability of the tests could determine which TB infection test is used. Other considerations include the structure of the health system, feasibility of implementation and infrastructure requirements.

Operational difficulties should be considered in deciding which test to use. For example, IGRAs require phlebotomy, which can be difficult, particularly in young children; they also require laboratory infrastructure, technical expertise and expensive equipment, and their sensitivity is reduced in children aged under 2 years and PLHIV. However, only a single visit is required to do an IGRA test (although patients may have to make a second visit to receive the result). The TST requires a cold chain, two health care visits and training in intradermal injection, reading and interpretation. One other practical advantage of IGRAs over the TST is that IGRAs are not susceptible to a “booster response”, which makes a two-step approach necessary for the TST in situations where reactivity to the TST has waned since infection.

BCG vaccination plays a decisive role in reducing the specificity of the TST, although the GDG noted that the impact of BCG vaccination on the specificity of the TST depends on the strain of vaccine used, the age at which the vaccine is given and the number of doses administered. When BCG is given at birth, as is the case in most parts of the world, it has a variable, limited impact on TST specificity (19).

The GDG agreed that a history of BCG vaccination has a limited effect on interpretation of TST results later in life; hence, BCG vaccination should not be a determining factor in selecting a test. Neither the TST nor IGRAs are to be used to diagnose active TB disease; also, they are not to be used for diagnostic work-up of adults suspected of having active TB.

## Research priorities

There is a critical need for diagnostic tests with improved performance and predictive value for progression to active TB. In addition, the performance of TB infection tests should be evaluated in various risk groups, to assess reinfection and to understand how best to use available tools in each population (e.g. in combination, or sequential use of the TST and IGRAs).

Data synthesis was structured around the preset PICO question, as outlined above. See Web Annex H for additional information on evidence synthesis and analysis.

## 3.3. TB skin tests and interferon gamma release assays for the diagnosis of TB disease

### Recommendation

**20. Interferon-gamma release assays (IGRAs) (and the tuberculin skin test [TST]) should not be used in low- and middle-income countries for the diagnosis of pulmonary or extrapulmonary TB, or for the diagnostic work-up of adults (including people living with HIV) suspected of active TB in these settings**  
*(strong recommendation)*

The Guideline Development Group concluded that both the sensitivity and specificity of IGRAs in detecting active TB among individuals presumed of having TB were suboptimal and the quality of evidence was low. They also recommended that these tests not be used as a replacement for conventional microbiological diagnosis of pulmonary and extrapulmonary TB.

The Guideline Development Group noted that current evidence did not support the use of IGRAs or the TST as part of the diagnostic work-up of adults presumed of active TB, irrespective of HIV status. This recommendation placed a high value on avoiding the consequences of unnecessary treatment (owing to a high number of false positive results), given the low specificity of IGRAs and the TST in these settings.

## Evidence base

A systematic, structured, evidence-based process for TB diagnostic policy generation was followed. The first step constituted systematic reviews and meta-analysis of available data (published and unpublished), using standard methods appropriate for diagnostic accuracy studies. The second step involved the convening of a GDG to evaluate the strength of the evidence base, evaluate the risks and benefits of using IGRAs in LMIC and identify gaps to be addressed in future research. Based on the Expert Group findings, the third and final step involved development of a WHO policy guidance, with eventual dissemination to WHO Member States for implementation.

The GRADE system, adopted by WHO for all policy and guideline development, was used by the GDG. Given the absence of studies evaluating patient-important outcomes among TB suspects randomized to treatment based on IGRA results, reviews were focused on the diagnostic accuracy of IGRAs versus the TST in detecting TB infection or TB disease. Recognizing that test results may be surrogates for patient-important outcomes, the GDG evaluated the accuracy of IGRAs while also drawing inferences on the likely impact of these tests on patient outcomes, as reflected by false negatives (i.e. cases of TB infection missed) or false positives.

Systematic reviews were undertaken following detailed protocols with predefined questions relevant to the individual topics. Summaries of methodologies followed for each topic are given in the relevant sections below.

### PICO questions

What is the diagnostic accuracy of commercial IGRAs for pulmonary TB in adult pulmonary TB suspects and confirmed TB cases in LMIC as compared with microbiological (culture or smear-microscopy) or clinical diagnosis of pulmonary TB?

### Hierarchy of reference standards

Studies evaluating the performance of IGRAs are hampered by the lack of a gold standard to distinguish the presence or absence of TB infection. Since diagnostic accuracy for TB infection could not be directly assessed, a hierarchy of reference standards was developed and agreed beforehand with the systematic reviewers, to evaluate the role of IGRAs, depending on the individual topic (i.e. not all systematic reviews necessarily used the hierarchy). Primary outcomes were predefined for each systematic review as relevant; for example, the predictive value of IGRAs for development of active TB, the sensitivity of IGRAs in individuals with culture- confirmed active TB (as a surrogate reference standard for TB infection), and the correlation between IGRA and TST results. In addition to primary outcomes, specific characteristics of IGRAs that could influence their overall utility were evaluated where relevant; for example, the proportion of indeterminate IGRA results (i.e. not able to be interpreted, either due to a high IFN- $\gamma$  response in the negative control or a low IFN- $\gamma$  response in the positive control), the impact of HIV-related immunosuppression (i.e. CD4+ cell count) on test performance where available and correlation of IGRA results with an exposure gradient (typically used in contact and outbreak investigations).

## **Studies search, selection and quality assessment**

All studies evaluating IGRAs published up to the end of May 2010 were reviewed using predefined data search strings. In addition to database searches, bibliographies of reviews and guidelines were reviewed, citations of all included studies were screened, and experts in the field as well as IGRA manufacturers were contacted to identify additional studies (published, unpublished and ongoing). Pertinent information not reported in the original publications was requested from the primary authors of all studies included by the systematic reviewers.

Studies that evaluated the performance of currently available commercial IGRAs, published in all languages and in all LMIC, were reviewed by individual topic. Only studies evaluating IGRA performance in LMIC were included in this analysis. Excluded were studies that evaluated non-commercial (i.e. in-house) IGRAs, older generation IGRAs (i.e. PPD-based IGRAs) and IGRAs performed in specimens other than blood; studies that were focused on the effect of anti-TB treatment on the IGRA response; studies including fewer than 10 individuals; studies reporting insufficient data to determine diagnostic accuracy measures; and conference abstracts and letters without original data, and reviews.

Study quality was assessed by relevant standardized methods, depending on the topic. For primary outcomes focused on test accuracy, quality was appraised using a subset of relevant criteria from QUADAS, a validated tool for diagnostic accuracy studies. For studies of the predictive value of IGRAs, quality was appraised with a modified version of the Newcastle-Ottawa Scale (NOS) for longitudinal or cohort studies. Conflicts of interest are a known concern in TB diagnostic studies; therefore, the systematic reviews added a quality item about involvement of commercial test manufacturers in published studies; they also reported whether IGRA manufacturers had any involvement with the design or conduct of each study, including donation of test materials, provision of monetary support, work or financial relationships with study authors, and participation in data analysis.

## **Data synthesis and meta-analysis**

A standardized overall approach was specified a priori for each systematic review, to account for significant heterogeneity in results expected between studies. First, data were synthesized separately for each commercial IGRA and by the World Bank country income classification (LMIC versus high-income countries) as a surrogate for TB incidence. Second, heterogeneity was visually assessed using forest plots, and the variation in study results attributable to heterogeneity was characterized (I-squared statistic) and statistically tested (chi-squared test). Third, pooled estimates were calculated using random-effects modelling, which provides more conservative estimates than fixed-effects modelling when heterogeneity is present. For each individual study, all outcomes for which data were available were assessed. First, forest plots were generated to display the individual study estimates and their 95% CIs. Pooled estimates were calculated when at least three studies were available in any subgroup, and individual study results were summarized when fewer than four studies were available. Standard statistical packages were used for analyses.

## Use of IGRAs in the diagnosis of active TB

Studies included were those that evaluated the performance of the technologies of interest for the diagnosis of TB disease among adult (>15 years) with presumed TB or people with TB in LMIC.

The initial search yielded 789 citations. After full-text review of 185 papers evaluating IGRAs for the diagnosis of active TB, 22 were determined to meet eligibility criteria, covering 33 unique evaluations of one or more IGRAs (hereafter referred to as studies) in 19 published and three unpublished reports. Of the 33 studies, 10 (30%) were from low-income countries and 23 (70%) were from middle-income countries. Seventeen studies (52%) included PLHIV ( $n=1057$ ), and 27 studies (82%) involved ambulatory subjects (outpatients as well as hospitalized patients). IGRAs were performed in people suspected of having active TB in 19 studies (58%) and in people with known active TB in 14 studies (42%). Because of the focus on diagnostic accuracy for active TB and the high prevalence of TB infection in high TB burden settings, IGRA specificity was estimated exclusively among studies enrolling TB suspects where the diagnostic work-up ultimately showed no evidence of active disease.

The results demonstrated the following in LMIC:

- The sensitivity of IGRAs in detecting active TB among people suspected of having TB ranged from 73% to 83% and specificity from 49% to 58%. Therefore, one in four patients, on average, with culture-confirmed active TB could be expected to be IGRA-negative in LMIC, with serious consequences for patients in terms of morbidity and mortality.
- There was no evidence that IGRAs have added value beyond conventional microbiological tests for the diagnosis of active TB. Among studies that enrolled TB suspects (i.e. patients with diagnostic uncertainty), both IGRAs demonstrated suboptimal “rule-out” values for TB disease.
- Even though data were limited, the sensitivity of both IGRAs was lower among PLHIV (about 60–70%), suggesting that nearly one in three PLHIV with active TB would be IGRA-negative.
- There was no consistent evidence that either of the two IGRAs was more sensitive than the TST for active TB diagnosis, although comparisons with pooled estimates of TST sensitivity were difficult to interpret owing to substantial heterogeneity.
- The few available head-to-head comparisons between QFT-GIT and T-Spot demonstrated higher sensitivity for the T-Spot platform, although this difference did not reach statistical significance.
- The specificity of both IGRAs for active TB was low, regardless of HIV status, and results suggested that one in two patients without active TB would be IGRA-positive, with adverse consequences for patients because of unnecessary therapy for TB and a missed differential diagnosis.
- Two unpublished reports reported no incremental or added value of IGRA test results combined with important baseline patient characteristics (e.g. demographics, symptoms or chest radiograph findings). Thus, these reports did not support a meaningful contribution of IGRAs for the diagnosis of active TB beyond readily available patient data and conventional tests.

- The systematic review focused on the use of IGAs to diagnose active pulmonary TB, given that data for extrapulmonary TB were lacking; nevertheless, the GDG consensus was that recommendations for pulmonary TB could reasonably be extrapolated to extrapulmonary TB.
- Industry involvement was unknown in 18% of studies and acknowledged in 27% of studies, including donation of IGRA kits as well as work or financial relationships between authors and IGRA manufacturers.

## Strengths and limitations of the evidence base

Strengths and limitations were as follows:

- Heterogeneity was substantial for the primary outcomes of sensitivity and specificity. Activities performed to minimize heterogeneity were empirical random-effects weighting, excluding studies contributing fewer than 10 eligible individuals, and separately synthesizing data for currently manufactured IGAs.
- No standard criteria exist for defining high TB incidence countries, and the World Bank income classification is an imperfect surrogate for national TB incidence; nevertheless, results were fundamentally unchanged when restricted to countries with an arbitrarily chosen annual TB incidence of at least 50 per 100 000 population.
- It is possible that ongoing studies were missed, despite systematic searching. It is also possible that studies that found poor IGRA performance were less likely to be published. Given the lack of statistical methods to account for publication bias in diagnostic meta-analyses, it would be prudent to assume some degree of overestimation of estimates due to publication bias.
- The systematic review focused on test accuracy (i.e. sensitivity and specificity) and indirect assessment of patient impact (false positive and false negative results). None of the studies reviewed provided information on patient-important outcomes (i.e. showing that IGAs used in a given situation resulted in a clinically relevant improvement in patient care or outcomes). In addition, no information was available on the values and preferences of patients.

Data synthesis was structured around the preset PICO question, as outlined above. Web Annex I provides additional information on evidence synthesis and analysis.

## Operational aspects of the use of IGAs

Operational aspects of the use of IGAs were as follows:

- Cost of IGAs was mentioned by four studies, which all stated that the assays are too expensive and that this is a limitation to their use.
- Only one study addressed reproducibility of T-Spot by assessing inter-observer agreement; it showed excellent correlation. No other study mentioned the issue of test reproducibility.
- Twelve studies reported on accepted transport times of samples to the laboratory, which were mainly less than 6 hours (i.e. within the limit accepted by the test manufacturers). One study accepted a transport time of 16 hours and another 24 hours. None reported on the impact of the transport times (i.e. delay between drawing the blood and initiating the IGRA test) and IGRA test results or performance.
- No study reported on time-to-result for IGAs.

- Four studies reported on the impact of IGAs on TB therapy. In two studies, IGRA results were reported to clinicians; one study did not discuss the consequences, and in the other study QFT-positive children and adolescents received preventive chemotherapy. The other two studies commented on the reduced number of patients that would require preventive therapy if IGAs were part of the diagnostic algorithm.
- The following aspects related to the feasibility of IGAs were highlighted:
  - blood amounts required may be an issue; however, tests were performed with less than 2 mL of blood (T-Spot) in some studies;
  - a strong interferon response in negative control tubes (high background results) in QFT may reflect the influence of other coincident diseases;
  - standardization and generation of automated, quantitative results should render IGAs more objective than the TST; and
  - a well-equipped laboratory, expensive equipment and training are required for IGRA test performance, which may cause logistical problems.

## Research priorities

Targeted further research to identify IGAs with improved accuracy is strongly encouraged. Such research should be based on adequate study design, including quality principles such as representative suspect populations, prospective follow-up, and adequate and explicit blinding. It is also strongly recommended that proof-of-principle studies be followed by evidence produced from prospectively implemented and well-designed evaluation and demonstration studies, including assessment of patient impact.

## 3.4. References

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# Annex 1. Guideline development methods

## Methods used to develop World Health Organization guidelines

To develop new or update existing guidelines for methods and tools to diagnose tuberculosis (TB), the World Health Organization (WHO) Global TB Programme commissions systematic reviews on the performance or use of the tool or method in question. A systematic review provides a summary of the current literature on diagnostic accuracy or user aspects, for the diagnosis of TB or the detection of anti-TB drug resistance in adults or children (or both) with signs and symptoms of TB.

The certainty of the evidence is assessed consistently for documented evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. GRADE produces an overall quality assessment (or certainty) of evidence and a framework for translating evidence into recommendations. The certainty of the evidence is rated as high, moderate, low or very low. These four categories imply a gradient of confidence in the estimates. Even if a diagnostic accuracy study is of observational design, it would initially be considered high-quality evidence in the GRADE approach (1).

In addition, the WHO Global TB Programme commissions systematic reviews to collect evidence in the field of resource use (i.e. cost and cost-effectiveness), as well as end-user perspectives on particular diagnostic tests or interventions. This evidence-to-recommendation process will inform domains such as feasibility, accessibility, equity and end-user values.

If systematic review evidence is unavailable or is scarce, the potential subsequent effects can be modelled for both diagnostic accuracy as well as cost and cost-effectiveness. For instance, the prevalence of the disease in question, combined with the sensitivity and specificity of a certain test, can be used to estimate the number of false positives and false negatives in a population. Similarly, data on expenditures and cost-effectiveness ratios can be estimated and modelled, based on economical and epidemiological data. Finally, qualitative evidence on the end-user perspective of using a particular test may be generated through end-user interviews if data are scarce in the public domain.

Following a systematic review, the WHO Global TB Programme convenes a Guideline Development Group (GDG) meeting to review the collected evidence. The GDG is made up of external experts whose central task is to develop evidence-based recommendations. The GDG also performs the important task of finalizing the scope and key questions of the guideline in PICO (i.e. population, intervention, comparator and outcomes) format.

This group should be established early in the guideline development process, once the Steering Group has defined the guideline's general scope and target audience, and has begun drafting the key questions. The GDG should be composed of relevant technical experts; end-users, such as programme managers and health professionals, who will adopt, adapt and implement the guideline; representatives of groups most affected by the guideline's recommendations, such as service users and representatives of disadvantaged groups; experts in assessing evidence and developing guidelines informed by evidence; and other technical experts as required (e.g. a health economist or an expert on equity, human rights and gender).

Recommendations are developed based on consensus among GDG members, where possible. When it is not possible to reach consensus, a vote is taken. When a draft guideline is developed by a WHO steering committee, it is reviewed initially by GDG members and subsequently by an External Review Group (ERG). The ERG is made up of individuals interested in the subject, and may include the same categories of specialists as the GDG. When the ERG reviews the final guideline, its role is to identify any errors or missing data, and to comment on clarity, setting, specific issues and implications for implementation – not to change the recommendations formulated by the GDG (2).

## Formulation of the recommendations

Evidence is synthesized and presented in GRADE evidence tables. The evidence to decision (EtD) framework is used subsequently to facilitate consideration of the evidence and development of recommendations in a structured and transparent manner. Finally, recommendations are developed based on consensus among GDG members where possible. If it is not possible to reach consensus, then voting takes place. Decisions on the direction and strength of the recommendations are also made using the EtD framework.

Factors that influenced the direction and strength of a recommendation in this guideline were:

- priority of a problem;
- test accuracy;
- balance between desirable and undesirable effects;
- certainty of:
  - evidence of test accuracy;
  - evidence on direct benefits and harms from the test;
  - management guided by the test results;
  - link between test results and management;
- confidence in values and preferences and their variability;
- resource requirements;
- cost-effectiveness;
- equity;
- acceptability; and
- feasibility.

These factors are discussed below.

## **Priority of a problem**

The GDG considers whether the overall consequences of a problem (e.g. increased morbidity, mortality and economic effects) are serious and urgent. The global situation is considered and available data reviewed. In most cases, the problem must be serious and urgent to be considered by a GDG.

## **Test accuracy**

The pooled sensitivity and specificity presented in the GRADE evidence profile is assessed. Preferably and if available the review includes studies with both microbiological reference standards (culture) as well as composite reference standards (e.g. in children and in patients with extrapulmonary TB).

## **Balance between desirable and undesirable effects**

Under this component, GDG members are asked to judge the anticipated benefits and harms from the test in question, including direct effects of the test (e.g. benefits such as faster diagnosis, and harms such as adverse effects from administration of the test). In addition, the possible subsequent effects of the test must be included; for instance, effects of treatment after a positive diagnosis (cure or decrease in mortality), and the effect of no treatment or further testing after a negative test result. Evidence, ideally retrieved from systematic reviews of randomized controlled trials (RCTs) of the test, should inform the GDG of these downstream effects. If evidence from RCTs is not available, diagnostic accuracy studies can be used. In the latter, true positive and true negative diagnosed cases are taken as benefits, whereas false positive and false negative cases are taken as harms.

## **Certainty of the evidence**

Certainty of the evidence of test accuracy is judged scored on a scale from very low, via low and moderate, to high. Certainty of the evidence on direct benefits and harms from the test are assessed and scored in a similar way.

## **Certainty of management**

For certainty of patient management being guided by the test results, the GDG focuses on whether the management would be any different, should it be guided by the test results.

For certainty of the link between test results and management, the panel assesses how quickly and effectively test results can transfer to management decisions.

## **Confidence in values and preferences and their variability**

The value of the test to improve diagnosis and its impact on patient care is evaluated and scored with the help of evidence from qualitative research. The impact on notification and, moreover, the ability of the test to increase case notification is also evaluated and scored, taking into account the entire diagnostic cascade, including, for example, issues related to feasibility of implementation, rate of use, staff's confidence in test results and turnaround time of results.

## Resource requirements

In relation to resource requirements, the following questions are answered:

- How large are the resource requirements for test implementation?
- What is the certainty of the evidence about resource requirements?
- Does the cost-effectiveness of the intervention favour the intervention or the comparison?

## Cost-effectiveness

Available evidence on cost-effectiveness is evaluated and scored.

## Equity

GDG members consider whether implementing the tool or method will positively or negatively affect access to health care (e.g. will it be possible to implement the test in distinct levels of health care or through self-administration, or are there other ways to make the tools or method available to all levels of the health care system).

## Acceptability

In terms of acceptability, the panel considers whether the tool or method will be acceptable by all relevant stakeholders, such as health workers, health managers and patients.

## Feasibility

The GDG considers how feasible it is to implement a tool or method in various settings. Aspects such as training and refresher training needs, hands-on time, biosafety requirements, time to results, service and maintenance, calibration, and effect on diagnostic algorithms are all taken into account in the final score.

For more details on the transition from evidence to recommendations, see **Web Annex 3: Evidence to decision tables**.

## Reference for Annex 1

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# Annex 2. Conflict of interest assessment for Guideline Development Group and External Review Group members

Before being considered for group membership, each Guideline Development Group (GDG) and External Review Group candidate was required to submit a completed declaration of interest (DOI) form. In addition, a preliminary internet search was performed to identify any obvious public controversies or interests that may lead to compromising situations for the World Health Organization (WHO) and the expert concerned.

The candidate's curriculum vitae (CV) and DOI, and information retrieved from the internet, were examined by steering committee members to assess whether there were, or may be, actual or perceived conflicts of interest and, if so, whether a management plan was required. This evaluation process, and resultant management plans, were based on the *Guidelines for declaration of interests (WHO experts)* (1) and the *WHO handbook for guideline development (2nd edition)* (2).

Both financial and non-financial interests were considered. A "significant" conflict of interest would include:

- "intellectual bias", where an individual may have repeatedly and publicly taken a position on an issue under review, which may affect the individual's objectivity and independence in the global policy development process;
- involvement in research or publication of materials related to issues under review; and
- a financial interest above US\$ 5000.

Developers of any assay are never involved in the process of policy development; this is automatically considered a conflict of interest.

Once a determination was made that either no conflict of interest existed, or any conflict of interest could be appropriately managed, and a decision had been made to appoint the candidate, the name and a brief biography of each candidate were published on the WHO website for at least 14 days before the meeting, for public notice and comment.

DOI statements are summarized by the WHO steering committee at the start of the meeting. Selected individuals with intellectual or research involvement were invited as technical resource persons to provide technical input and answer technical questions. These individuals did not participate in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) evaluation process and were excluded from the group discussions when recommendations were developed.

**Table A.2.1. Summary of the declarations of interest statements for the GDG members: “Molecular assays intended as initial tests”, 7–18 December 2020**

GDG member	Interests declared	Conclusion
Holger Schünemann	None declared	No conflict of interest
Jeremiah Chakaya Muhwa	None declared	No conflict of interest
Denise Arakaki-Sanchez	None declared	No conflict of interest
David Branigan	None declared	No conflict of interest
Daniela Cirillo	Evaluation of an XDR test prototype. Project funded by Cepheid and FIND. Budget (Research Unit): US\$ 14 296; 2018. Member of the Scientific Advisory Board (BIOMERIEUX). Budget (self): US\$ 1000; 2020–2021. Evaluation of the blood stability for VIDAS (BIOMERIEUX). Budget (Research Unit): US\$ 11 200; 2019.	Significant conflict of interest – excluded from the deliberations on low complexity automated NAATs
Celina Anna Maria Garfin	None declared	No conflict of interest
Petra de Haas	None declared	No conflict of interest
Patricia Hall	Receives funding from PEPFAR; uses PEPFAR funding to procure TB diagnostics tests and supplies for TB, HIV infant diagnostic and HIV viral load testing across multiple countries. Provides technical input into the PEPFAR Country Operational Guidance, including inputs on the appropriate procurement and use of TB and HIV instrumentation and test types. Oversees a global Cepheid GeneXpert-based proficiency testing program and provides technical assistance to PEPFAR-supported CDC country offices and partner ministries of health on the selection and implementation of TB and HIV diagnostic tests and testing resources.	Non-significant conflict of interest
Rumina Hasan	None declared	No conflict of interest

GDG member	Interests declared	Conclusion
Xia Hui	None declared	No conflict of interest
Farzana Ismail	Evaluation of an XDR test prototype (Cepheid). Budget (Research Unit): US\$ 140 000; 2020. Bedaquiline post-marketing surveillance and emerging resistance (Janssen). Budget (Research Unit): US\$ 300 000; ongoing. Latent TB infection in health care workers (Qiagen). Budget (Research Unit): consumables and personnel; ongoing. Sponsorship to the IUATLD conference participation, Den Haag (self); 2018.	Significant conflict of interest – excluded from the deliberations on low complexity automated NAATs
Katharina Kranzer	EDCTP: total budget about €3.2 million across 6 institutions; FIND: non-TB-related study (study on antimicrobial resistance), US\$ 21 000; Cepheid: non-TB-related study (study on STIs), in-kind contributions of 3000 cartridges and the loan of an Xpert machine; Cepheid: TB-related study about 3 gene signature, in-kind contribution of 3500 cartridges and a loan of an Xpert machine; Roche: consumables for validations study in 2015–2016.	Significant conflict of interest – excluded from the deliberations on moderate complexity automated NAATs
Blessina Kumar	None declared	No conflict of interest
Nagalineswaran Kumarasamy	None declared	No conflict of interest
Lindiwe Mvusi	None declared	No conflict of interest
Viet Nhung Nguyen	None declared	No conflict of interest
Mark Nicol	Research grant funding received by the institution for studies of a broad range of novel diagnostics for TB, including NAATs (among others, BD MAX™, one of the tests of interest for the actual GDG). Gates Foundation; NIH; Wellcome Trust; FIND. Employer (University) received funding. Significant (several million US dollars). Ongoing funding from FIND, NIH; co-shares a pending patent for a novel method to extract and purify DNA from sputum samples (not related to or used by any commercial test for TB). Patent belongs to incumbent. No commercial value at present.	Significant conflict of interest – excluded from the deliberations on moderate complexity automated NAATs

GDG member	Interests declared	Conclusion
Leen Rigouts	<p>Research support: the research unit received financial support through FIND for the coordination of and participation in a multicentre evaluation of the Genoscholar PZA-LPA. Part of that funding came from Nipro. Non-monetary renumeration: the research unit received the Genoscholar PZA-LPA kits to conduct evaluations of the test (multicentre study via FIND plus additional ongoing evaluation in the unit).</p>	<p>Significant conflict of interest – excluded from the deliberations on high complexity hybridization-based NAATs</p>
Thomas Shinnick	<p>As an independent consultant, received contracts and travel support from WHO, FIND and USAID for work related to laboratory strengthening and developing global guidance documents; ongoing.</p>	<p>Non-significant conflict of interest</p>
Hojoon Sohn	None declared	No conflict of interest
Sabira Tahseen	None declared	No conflict of interest
Ezio Tavora dos Santos Filho	<p>Has coordinated community advisory boards to the PROVE-IT study (TREAT-TB grant, Union/USAID) in Brazil (REDE-TB) from 2010 to 2015. Currently following up, as an interested party (not as a member of the study team, but as a community advisory board coordinator of other studies), the implementation of the Truenat validation study in Brazil, among other BRICS cooperation studies. Intends to follow up the study, settling establishing system of community advisory boards oversight and protocol analysis in Brazil and other partner countries.</p>	<p>Significant conflict of interest perceived for Molbio Truenat evaluation – excluded from a discussion on Molbio Truenat</p>
Carrie Tudor	<p>Employment (starting January 2015) in the International Council of Nurses, whose TB project received funding from the Eli Lilly Foundation – Lilly MDR-TB Partnership. Funding received was approx US\$ 1 million from 2013 to 2019. Current funding period for 2019 is approx. US\$ 100 000.</p>	<p>Non-significant conflict of interest</p>
Diana Vakhrusheva	None declared	No conflict of interest

GDG member	Interests declared	Conclusion
Elisabetta Walters	Recipient of grants and a scholarship for doctoral research which included work on GeneXpert MTB/RIF for the diagnosis of intrathoracic TB in children. South African Medical Research Council grant (2012–2015) and scholarship (2015–2018). South African National Research Foundation. FIND. TBTC (CDC); (Research Unit): ZAR 4.2 million; US\$ 90 000; 2012–2018.	Non-significant conflict of interest

AIDS: acquired immunodeficiency syndrome; BRICS: Brazil, Russia, India, China and South Africa; CDC: Centers for Disease Control and Prevention; DNA: deoxyribonucleic acid; EDCTP: European and Developing Countries Clinical Trials Partnership; FIND: Foundation for Innovative New Diagnostics; GDG: Guideline Development Group; HIV: human immunodeficiency virus; IUATLD: International Union Against Tuberculosis and Lung Disease; MDR-TB: multidrug-resistant TB; NAAT: nucleic acid amplification test; NIH: National Institutes of Health; PEPFAR: United States President's Emergency Plan for AIDS Relief; STI: sexually transmitted infection; TB: tuberculosis; TBTC: Tuberculosis Trials Consortium; USAID: United States Agency for International Development; WHO: World Health Organization; XDR: extensively drug-resistant.

**Table A.2.2. Summary of the declarations of interest statements for the ERG members: “Molecular assays intended as initial tests”, 7–18 December 2020**

ERG member	Interests declared	Conclusion
Lucilaine Ferrazoli	None declared	No conflict of interest
Alaine Umubyeyi Nyaruahirira	None declared	No conflict of interest
Elisa Tagliani	Involved in the WHO Expert Review Panel for Diagnostics Round 15; specifically, in the evaluation of the BD MAX platform; €5940. A unit at San Raffaele has received funding from an EDCTP grant (TB-CAPT) to FIND. Incumbent has collaborated with FIND in a multicentre clinical study to assess the performance of the Xpert MTB/XDR assay.	Non-significant conflict of interest for External reviewer. Management of potential conflict of interest by interpretation of the comments in the context of conflict of interest
Francis Varaine	None declared	No conflict of interest
Danila Zimenkov	None declared	No conflict of interest

EDCTP: European and Developing Countries Clinical Trials Partnership; ERG: External Review Group; FIND: Foundation for Innovative New Diagnostics; WHO: World Health Organization.

**Table A.2.3. Summary of the declarations of interest statements for the GDG: “Targeted next-generation sequencing” 2–5 May 2023**

GDG member	Interests declared	Conclusion
Nimalan Arinaminpathy	Employment: Imperial College London. Consulting: Global Fund, WHO, WHO Regional Office for South-East Asia, Clinton Health Access Initiative, Copenhagen Consensus, Stop TB Partnership, USAID. Research support: Gates Foundation, US CDC, USAID, United Kingdom Medical Research Council. Member of various expert advisory bodies, the most relevant to this work being the regional Green Light Committee for the WHO South-East Asia Region, and the TB Strategic and Technical Advisory Group (STAG-TB) for WHO.	Not significant conflict of interest
David Branigan	None declared	No conflict of interest
Daniela Cirillo	Research support including the following: IMI Unite4TB, including coordinating microbiology workplan for clinical trials, monitoring of trials sites and retesting (ongoing); EUCAST, coordinating work for standard protocol for different TB drugs involving reference laboratories (ongoing); TB Alliance, unrestricted grant multipartner to test mic for pretomanid (ended 2020). No studies evaluating targeted NGS, no contracts paid by companies related to targeted NGS.	Not significant conflict of interest
Petra de Haas	Research support including the following: funding for the evaluation of MinION (Oxford Nanopore Technologies), a 5-year KNCV project funded by a national postcode lottery, evaluating implementation and use of targeted NGS for diagnosis of multiple infectious diseases across three countries.	Not significant conflict of interest
Patricia Hall-Eidson	Employed by the US CDC, as a funding organization to support TB research and oversee implementation of WHO TB policies and recommendations globally, including use of NGS for surveillance purposes.	Not significant conflict of interest
Rumina Hasan	None declared	No conflict of interest
Sirinapha Jittimanee	None declared	No conflict of interest
Kobto Koura	None declared	No conflict of interest
Blessina Kumar	None declared	No conflict of interest

GDG member	Interests declared	Conclusion
Nicole Menezes de Souza	None declared	No conflict of interest
Jeremiah Chakaya Muhwa	None declared	No conflict of interest
Norbert Ndjeka	None declared	No conflict of interest
Mark Nicol	Research support: Employer (University of Cape Town, South Africa) has received grant funding to conduct studies of a range of novel diagnostics for TB in children (including Xpert, LAM, RNAseq, and others). No funding for or studies of targeted NGS technologies.	Not significant conflict of interest
Thomas Shinnick	Work as a consultant, through which contracts and travel support have been received from WHO, FIND and USAID for work related to laboratory strengthening and developing global guidance documents.	Not significant conflict of interest
Hojoon Sohn	None declared	No conflict of interest
Sabira Tahseen	None declared	No conflict of interest
Ezio Tavora dos Santos	As an advocate and researcher working in community engagement in research and improvement of policies, the results of this work can potentially benefit the community with which he works.	Not significant conflict of interest
Nguyen Viet Nhung	None declared	No conflict of interest
Elisabetta Walters	Employment: Stellenbosch University, South Africa, no studies assessing or using targeted NGS technologies.	Not significant conflict of interest
Yanlin Zhao	None declared	No conflict of interest

EUCAST: European Committee on Antimicrobial Susceptibility Testing; FIND: Foundation for Innovative New Diagnostics; GDG: Guideline Development Group; Global Fund: Global Fund to Fight AIDS, Tuberculosis and Malaria; IMI: Innovative Medicines Initiative; LAM: lipoarabinomannan antigen test; NGS: next-generation sequencing; TB: tuberculosis; United Kingdom: United Kingdom of Great Britain and Northern Ireland; USAID: United States Agency for International Development; US CDC: United States Centers for Disease Control and Prevention; WHO: World Health Organization.

**Table A.2.4. Summary of the declarations of interest statements for the ERG: “Targeted Next-Generation Sequencing” 2–5 May 2023**

ERG member	Interests declared	Conclusion
Nagalineswaran Kumarasamy	None	No conflict of interest
Katharina Kranzer	Employment at LSHTM; research support from EDCTP.	Not significant conflict of interest
Farzana Ismail	Research support: Research Unit was included as one of the sites for the FIND Multi-centre Clinical Trial to Assess the Performance of Culture-free, End-to-end Targeted NGS Solutions for Diagnosis of Drug Resistant TB.	Not significant conflict of interest
Mitarai Satoshi	None	No conflict of interest
John Metcalfe	Research support from NIH; patent application entitled “Methods for Producing Circular Deoxyribonucleic Acids”.	Not significant conflict of interest

EDCTP: European and Developing Countries Clinical Trials Partnership; ERG: External Review Group; FIND: Foundation for Innovative New Diagnostics; LSHTM: London School of Hygiene & Tropical Medicine; NGS: next-generation sequencing; NIH: United States National Institutes of Health; TB: tuberculosis.

**Table A.2.4. Summary of the declarations of interest statements for the GDG: “Low complexity nucleic acid amplification testing for detection of TB and resistance to rifampicin” 6–10 May 2024**

NEW

GDG member(s)	Interests declared	Conclusion
David Branigan	None declared	No conflict of interest
Jeremaya Chakaya Muhva	None declared	No conflict of interest
Chamreun Sok Choub	None declared	No conflict of interest
Katherine Fielding	None declared	No conflict of interest
Rumina Hasan	None declared	No conflict of interest
Kobto Gislain Koura	None declared	No conflict of interest
Andrei Maryandyshev	None declared	No conflict of interest
Norbert Ndjeka	None declared	No conflict of interest
Thomas Shinnick	None declared	No conflict of interest
Hojoon Sohn	None declared	No conflict of interest
Sabira Tahseen	None declared	No conflict of interest

GDG member(s)	Interests declared	Conclusion
Timothy Walker	None declared	No conflict of interest
Ou Xichao	None declared	No conflict of interest
Daniela Cirillo	Validation of the standard method for determination of MIC (BD/Janssen), for research unit, ceased in 2023	Not significant conflict of interest
Keertan Dheda	Research grant to evaluate transcriptomic signature for BioMerieux (Awarded to UCT Lung Institute); Honoraria for being on speakers bureau or providing training Otsuka TB Drug; Honoraria for speakers on bureau (African Society of Laboratory Medicine) Cepheid – US\$ 1200.	Not significant conflict of interest
Patricia Hall-Eidson	All travel costs associated with meeting attendance were supported by the US CDC. Employed and salaried by the US President's Emergency Plan for AIDS Relief, a global health program that recommends, procures, and provides virtual and in-country technical assistance on TB low complexity automated nucleic acid amplification tests (and other TB assays) in low, moderate, and high burden countries to aid in TB case finding efforts among pediatric, adolescent, and adult persons living with HIV.	Not significant conflict of interest
Sirinapha Jittimanie	Consultancy for GFATM country coordination mechanism in Thailand	Not significant conflict of interest
Katharina Kranzer	Employment at LSHTM; Pretomanid consultancy for WHO; Research grant from EDCTP: ERASE-TB. In-kind contribution from Cepheid, SD-Biosensor for ERASE-TB.	Not significant conflict of interest
Shaheed Vally Omar	Clinical Evaluation of the Xpert MTB/RIF assay using the GeneXpert OMNI; Clinical Evaluation of the Xpert® MTB/XDR Assay; Head-to-Head Evaluation of the CAT-A Enzyme Xpert MTB/RIF Ultra test vs. the Current on Market Xpert MTB/RIF Ultra V2 test, Cepheid, USD 66,390, for research unit, ceased in 2023.	Not significant conflict of interest

## References for Annex 2

1. Declaration of interests [website]. Geneva: World Health Organization; 2023 (<https://www.who.int/about/ethics/declarations-of-interest>).
2. Handbook for guideline development 2nd ed. Geneva: World Health Organization; 2014 (<https://apps.who.int/iris/handle/10665/145714>).

# Annex 3. GDG members expertise, region, gender

**Table A.3.1. Guideline development group members: “Targeted next-generation sequencing” 2–5 May 2023**

GDG member	Expertise	WHO region	Gender
Nimalan Arinaminpathy	TB epidemiological modeling	European Region	M
David Branigan	Patient rights; Community care; TB detection and diagnosis	Region of the Americas	M
Daniela Cirillo	TB laboratory diagnosis	European Region	F
Petra de Haas	TB laboratory diagnosis	European Region	F
Patricia Hall-Eidson	TB laboratory diagnosis	Region of the Americas	F
Rumina Hasan	TB laboratory diagnosis	Eastern Mediterranean Region	F
Sirinapha Jittimanee	TB nursing care	Western Pacific Region	F
Kobto Koura	TB treatment	European Region	M
Blessina Kumar	Patient rights; Community care	South-East Asia Region	F
Nicole Menezes de Souza	TB laboratory diagnosis	Region of the Americas	F
Jeremiah Chakaya Muhwa	TB detection and diagnosis/ TB treatment	African Region	M
Norbert Ndjeka	TB treatment	African Region	M
Mark Nicol	TB diagnostics research	Western Pacific Region	M
Thomas Shinnick	TB laboratory diagnosis	Region of the Americas	M
Hojoon Sohn	Health Economics	Western Pacific Region	M

GDG member	Expertise	WHO region	Gender
Sabira Tahseen	TB laboratory diagnosis	Eastern Mediterranean Region	M
Ezio Tavora dos Santos	Patient rights; Community care; TB detection and diagnosis	Region of the Americas	M
Nguyen Viet Nhung	TB program management	Western Pacific Region	M
Elisabetta Walters	Pediatric TB diagnosis and treatment	African Region	F
Yanlin Zhao	TB program management	Western Pacific Region	M

GDG: Guideline Development Group; WHO: World Health Organization.

**Table A.3.2. Summary of the declarations of interest statements for the GDG: “Low complexity nucleic acid amplification testing for detection of TB and resistance to rifampicin” 6–10 May 2024**

NEW

GDG member	Expertise	WHO Region	Gender
David Branigan	Patient advocacy and rights; Community care; TB detection and diagnosis	Region of the Americas	M
Jeremaya Chakaya Muhva	TB detection and diagnosis/ TB treatment	African Region	M
Chamreun Sok Choub	Patient advocacy and rights	Western Pacific Region	M
Katherine Fielding	TB epidemiology and data science	European Region	F
Rumina Hasan	TB laboratory diagnosis	Eastern Mediterranean Region	F
Kobto Gislain Koura	TB treatment	European Region	M
Andrei Maryandyshev	TB clinical management and treatment	European Region	M
Norbert Ndjeka	TB program management	African Region	M
Thomas Shinnick	TB laboratory diagnosis	Region of the Americas	M
Hojoon Sohn	Health Economics	Western Pacific Region	M

GDG member	Expertise	WHO Region	Gender
Sabira Tahseen	TB laboratory diagnosis	Eastern Mediterranean Region	M
Timothy Walker	TB laboratory diagnosis and treatment	European Region	M
Ou Xichao	TB laboratory diagnosis	Western Pacific Region	M
Daniela Cirillo	TB laboratory diagnosis	European Region	F
Keertan Dheda	TB treatment	African Region	M
Patricia Hall-Eidson	TB laboratory diagnosis	Region of the Americas	F
Sirinapha Jittimanie	Patient advocacy and rights; Community care; Health program management (Nursing)	Southeast Asia Region	F
Katharina Kranzer	TB epidemiology and treatment	European Region	F
Shaheed Vally Omar	TB laboratory diagnosis	African Region	M







For further information, please contact:

**Global Programme on Tuberculosis & Lung Health**  
**World Health Organization**  
20, Avenue Appia CH-1211 Geneva 27 Switzerland  
Web site: [www.who.int/tb](http://www.who.int/tb)

# The selection and use of essential medicines, 2025

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Report of the 25th WHO Expert Committee  
on Selection and Use of Essential Medicines,  
executive summary





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## Related publications

WHO Model List of Essential Medicines, 24<sup>th</sup> List (2025)

<https://iris.who.int/handle/10665/382243>

WHO Model List of Essential Medicines for Children, 10th List (2025)

<https://iris.who.int/handle/10665/382242>

WHO AWaRe (access, watch, reserve) classification of antibiotics for evaluation and monitoring of use, 2025.

<https://iris.who.int/handle/10665/382244>

## Acknowledgements

WHO gratefully acknowledges the significant contributions of the Expert Committee members and temporary advisers who participated in the meeting of the 25th WHO Expert Committee on Selection and Use of Essential Medicines, Geneva, Switzerland, from 5 to 9 May 2025.

## List of participants

### *Expert Committee members*

**Loice Achieng Ombajo**, Infectious disease specialist and senior lecturer, Department of Medicine and Co-director of the Center for Epidemiological Modelling and Analysis, University of Nairobi, Nairobi, Kenya.

**Elie Akl**, Professor of Medicine and Vice Provost for Research, American University of Beirut, Beirut, Lebanon.

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**Andrew Roberts**, Clinical Haematologist, Royal Melbourne Hospital and Peter MacCallum Cancer Centre; Professor and deputy director, the Walter & Eliza Hall Institute; Metcalf Chair of Leukaemia Research, University of Melbourne, Melbourne, Australia.

**Zoubida Tazi Mezalek**, Professor of Internal Medicine and Head of the Clinical Hematology Department, Faculty of Medicine and Pharmacy, Mohammed V University of Rabat, Rabat, Morocco.

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**Jessica Bartoszko**, Consultant, EML Secretariat, Department of Health Product Policy and Standards, Access to Medicines and Health Products.

**Rehab Rayan**, Consultant, EML Secretariat, Department of Health Product Policy and Standards, Access to Medicines and Health Products.

**Nathália Alvarez**, Intern, EML Secretariat, Department of Health Product Policy and Standards, Access to Medicines and Health Products.

### ***External invited presenters during the Open Session***

**Michael Muenzberg**, Chief Executive Officer, Targeted Solutions AG, Zug, Switzerland.

## Declaration of interests

To be effective, the work of WHO and the contributions of its experts must be, and must be perceived to be, objective and independent. In this regard, to ensure the highest integrity and public confidence in its activities, WHO requires that experts serving in an advisory role disclose any circumstances that could give rise to a potential or reasonably perceived conflict of interest related to the subject of the activity in which they will be involved. Declarations of interest and management of any disclosures is an important process governed by the WHO Guidelines for Declaration of Interests (WHO Experts). More information on WHO's policy on declarations of interest is available on the WHO website (1).

Before being invited to participate in the 25th meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines, all experts submitted written declarations of interest. In reviewing and assessing these declarations, the Secretariat of the WHO Essential Medicines List sought the advice of the Office of Compliance, Risk Management and Ethics.

The declaration of interest process resulted in the participation of the Expert Committee Members, Temporary Advisers and invited external speakers during the Open Session, as reported in the list of participants.

Experts who declared having no conflicts of interest were Elie Akl, Rita Banzi, Francesco Ceppi, Patrick Okwen and Gabriela Prutsky-Lopez.

The following experts disclosed interests, which were assessed by the Secretariat for actual or potential conflicts and management strategies (if required).

### **Committee members**

Loice Achieng Ombajo disclosed receiving honoraria from GSK to serve on a scientific advisory board for the Africa Open Lab research programme, supporting the selection of high-quality infectious diseases research proposals that have the potential to deliver significant health impact in Africa (interest ceased in 2024). She disclosed having received honoraria from Merck Sharp and Dohme for speaker engagements and conference travel on topics not related to medicines under evaluation at this meeting (interest ceased in 2024). The latter payment was below the threshold of significant financial interest. She disclosed funding to her institution (University of Nairobi) from ViiV Healthcare and Gilead Sciences for investigator-initiated clinical trials on medicines for HIV, for which she is the principal investigator. The three trials investigated switching between antiretroviral treatments (i.e. bictegravir, emtricitabine and tenofovir alafenamide to dolutegravir/lamivudine; ritonavir-boosted protease inhibitor regimen to dolutegravir; antiretroviral regimen to bictegravir, emtricitabine and tenofovir alafenamide). These trials do not include antiretroviral treatments under evaluation at this meeting. Dr Achieng Ombajo is the principal investigator of a country grant programme to improve surveillance of *Candida auris* in Kenya (funded by the US Centers for Disease Control and Prevention). She also disclosed funding to the university from the Gates Foundation for studying optimal management of dolutegravir failure, for which she is the principal investigator and for the Center for Epidemiological Modelling and Analysis. These disclosures were considered minor and did not require further management. Dr Achieng Ombajo currently serves as the Chair of the WHO Technical Advisory Group on AWaRe (TAG-AWaRe) and was involved in the TAG-AWaRe's evaluation of antibiotic applications under consideration at the Expert Committee meeting. This position is unpaid. This disclosure was considered not to represent a conflict.

Elisabeth de Vries disclosed that she served as an expert in data safety monitoring committees for an ongoing trial investigating atezolizumab in adjuvant breast cancer sponsored by a non-profit research programme (National Surgical Adjuvant Breast and Colon Project) and for a completed trial investigating trastuzumab deruxtecan in advanced breast cancer sponsored by a for-profit company (Daiichi Sankyo). She also disclosed that she provided advice to Crescendo Biologics on improving the quality of the design and conduct of preclinical and phase I clinical studies exploring biological activity of bispecific molecules for the treatment of cancers. Sponsors provide funding to

Dr de Vries' institution (University Medical Center Groningen) to cover her time commitment. She also disclosed that her institution is involved in early-phase clinical trials to explore the therapeutic and diagnostic/prognostic roles of cancer medicines and biomarkers. Her institution receives institutional funding from Amgen, Crescendo Biologics, Genentech, G1 Therapeutics, Regeneron, Roche and Servier. In two cases, the studies involved using medicines under evaluation at this meeting (atezolizumab and cemiplimab). However, these studies as well as the others, assessed radioactive tracers used in imaging tests to monitor disease progression in patients with solid tumours and did not involve assessment of medicines. Payment was made to the institution and no personal salary support was received. These disclosures were considered to be unrelated, or not directly related, to the subject matter of the Expert Committee meeting and did not require further management. Regarding public statements and positions, Professor de Vries disclosed that she is a member of the European Society of Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) working party and of the ESMO Cancer Medicines Working Group and was a member of the Response Evaluation Criteria in Solid Tumours (RECIST) Committee. These disclosures were considered not to represent a conflict.

Claudia Garcia Serpa Osorio de Castro disclosed that she has received grant funding for consultancy work from Oswaldo Cruz Foundation Funding Agency to support a project on litigation for access to high-cost medicines sponsored by the Brazilian Ministry of Health and research grant funding from the Brazilian National Council for Scientific and Technological Development. She also disclosed being a member of the Medicines Registration Technical Committee at the Brazilian Health Regulatory Agency, Anvisa, an unpaid position. These disclosures were considered not to represent a conflict and did not require further management.

Bishal Gyawali disclosed receiving consult fees from Vivio Health, a public benefit company, to provide patient-specific advice on treatment strategies. He declared having held stock options of OneCell Diagnostics (a liquid biopsy technology company, now divested). These disclosures were considered minor, unrelated to the subject matter of the Expert Committee meeting and did not require further management.

Zoubida Tazi Mezalek disclosed receiving honoraria below the threshold for significant financial interest from pharmaceutical companies for participating in advisory boards on herpes zoster vaccine (GSK) and asciminib for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukemia (Novartis). These disclosures were considered minor, unrelated to the subject matter of the Expert Committee meeting and did not require further management.

Andrew Roberts disclosed collaboration with BeiGene and research support to his institution from BeiGene for studies evaluating zanubrutinib, a medicine under evaluation at this meeting. These collaborations date back more than 4 years (i.e. 2014), the current limit to which the WHO's conflict of interest assessment extends. Nevertheless, this disclosure was assessed in detail. The first study (NCT02343120) is a phase I study in patients with relapsed/refractory B-cell malignancies, receiving dose-escalating zanubrutinib (2). The study primarily assessed safety, tolerability and pharmacokinetics/pharmacodynamics. A second study (NCT02343120) evaluated zanubrutinib in a phase I/II study in patients with Waldenström macroglobulinemia (3). Subsequently, data from this trial were included in a safety analysis of zanubrutinib based on data from six pooled studies (4). The long-term monitoring phase of the study, to follow up surviving enrolled participants on the trial, will cease in 2025, as per standard practice in this type of study. Given the distant timing and the fact that the studies were phase I/II or focused on the safety and toxicity of zanubrutinib, and that none of the identified studies was used to support the request of the application received, this disclosure, made verbally at the start of the meeting, was considered minor and did not require further management.

Professor Roberts disclosed that he receives financial benefit from his employer, the Walter and Eliza Hall Institute (WEHI), in the form of a share of the income the Institute has received related to the drug venetoclax. Venetoclax was created during a partnership between WEHI and the pharmaceutical companies AbbVie and Genentech. AbbVie and Genentech are responsible for the commercial development of venetoclax. WEHI has no role in its clinical trial development, commercialization or marketing. WEHI has a commercialization policy that allows distribution of a small

share of any royalties and commercial income to staff who have invented or made a major contribution to the product. The amounts received by individual staff are based on specific criteria related to their contributions and are not related to the outcome of clinical trials, nor to future drug sales. In 2017, WEHI entered a commercial agreement with CPPIB Credit Europe S.à r.l., a wholly owned subsidiary of the Canada Pension Plan Investment Board, trading future venetoclax royalties for a lump-sum payment. Professor Roberts disclosed that he was a major contributor to research that led to venetoclax, but is not a patent holder, and to early clinical trial discovery research. His contributions pre-date the 2017 commercial agreement with the Canadian pension fund. For his contribution, he has been awarded a small fraction of past commercial income to WEHI, which is diversified, independently managed and paid by his employer. Venetoclax was not under evaluation by the Expert Committee at this meeting, but it can be used as an alternative to or as a partner in combination with inhibitors of Bruton's tyrosine kinase (e.g. ibrutinib, already included in the EML, and zanubrutinib, under evaluation during the meeting). Any interest or interests that could directly influence, or could appear to influence, his professional judgement in relation to the subject matter of the Expert Committee meeting were not identified.

Professor Roberts disclosed he is the chair of the Life Saving Drugs Program Expert Panel which advises the Australian Government on the appropriateness of public subsidy for medicines to treat patients with ultra-rare conditions that are not considered cost-effective at the time of the evaluation. He also disclosed that in 2023 and 2024 he served on the Health Technology Assessment Review Reference Committee appointed by the Australian Government to provide recommendations about the conduct of Health Technology Assessment in Australia. Both positions are remunerated. These disclosures were considered not to represent a conflict and did not require further management.

Indah Widyahening disclosed that her institution received a research sponsorship from PT Sarihusada Generasi Mahardhika, a nutritional products company, for a study of growth tracker using artificial intelligence. This disclosure was considered minor and did not require further management.

Mei Zeng disclosed receiving research support for her research unit from Shanghai Roche Pharmaceuticals Ltd for a clinical trial of baloxavir marboxil in paediatric and adolescent patients with influenza. Her role in the study is lead principal investigator. This trial did not include medicines under evaluation at this meeting. This disclosure was considered minor and did not require further management.

#### ***Temporary advisers***

Alfonso Iorio disclosed receiving research support for his institution, McMaster University, from F. Hoffmann-La Roche Ltd for an observational study on the long-term effectiveness and safety of emicizumab in people with haemophilia A based on the Canadian Hemophilia Bleeding Disorders Registry. Emicizumab is a medicine under evaluation at this meeting. This disclosure was considered minor. As a temporary adviser to WHO during the Expert Committee meeting, Professor Iorio participated in the discussion about medicines and blood products used in bleeding disorders but did not participate in the decision-making nor in formulating the recommendations on emicizumab.

Melissa Barber reported employment as a consultant for Médecins Sans Frontières. This disclosure was considered not to represent a conflict. As a temporary adviser to WHO during the Expert Committee meeting, Dr Barber participated in discussions about market analyses of medicines under evaluation but did not participate in the decision-making or in formulating the recommendations.

#### ***Invited external speakers during the Open session***

Michael Muenzberg declared having provided consultancies to advance affordable medicines, collaborating with regulators and suppliers from low- and middle-income countries. All consultancies were unpaid. He declared that in 2024, he funded a Switzerland-based platform to support global access efforts to medicines, with a primary interest in biosimilars.

## Executive summary

The meeting of the 25th WHO Expert Committee on the Selection and Use of Essential Medicines took place at WHO headquarters in Geneva, Switzerland, from 5 to 9 May 2025. The aim of the meeting was to review and evaluate applications for the 24th WHO Model List of Essential Medicines (EML) and the 10th WHO Model List of Essential Medicines for Children (EMLc) (the “Model Lists”).

Essential medicines are those that satisfy the priority health care needs of a population. They are selected with due regard to disease prevalence and public health relevance, evidence of efficacy and safety, and comparative cost-effectiveness. They are intended to always be available in functioning health systems, in appropriate dosage forms, of assured quality and at prices individuals and health systems can afford.

The WHO Model Lists are updated every two years, intended as a guide for countries or regional authorities to adopt or adapt in accordance with local priorities and treatment guidelines for the development and updating of national essential medicines lists. Selection of a limited number of medicines as essential, taking into consideration national disease burden and clinical need can lead to improved access through streamlined procurement and distribution of quality-assured medicines, support more rational or appropriate prescribing and use, and lower costs for both health care systems and for patients.

The Expert Committee considered a total of 59 applications, including 31 proposals for the addition of new medicines or medicine classes, 10 proposals for new indications for currently listed medicines, three proposals for the addition of new formulations of currently listed medicines, one proposal for the removal of a currently listed medicine, and 14 other applications relevant to the Model Lists and the WHO AWaRe classification of antibiotics. In accordance with procedures endorsed by the 109th Executive Board in the Report by the Secretariat EB109/8 in 2001, the Expert Committee reviewed and evaluated the scientific evidence for the effectiveness, safety, and comparative cost and cost-effectiveness of the medicines in question.

In summary, the Expert Committee:

- recommended the addition of 20 new medicines to the EML (16 to the core list and 4 to the complementary list);
- recommended the addition of 15 new medicines to the EMLc (12 to the core list and 3 to the complementary list);
- recommended adding additional indications for 7 currently listed medicines;
- recommended the addition of new formulations of 19 medicines on the EML and of 49 medicines on the EMLc;
- recommended the deletion of 3 medicines from the EML and 4 medicines from the EMLc and of specific formulations of a further 20 medicines from the EML and 29 medicines from the EMLc; and
- did not recommend proposals for addition of new medicines, or new indications for 24 medicines, or medicine classes.

The recommended changes bring the total number of medicines (including fixed-dose combinations) on the EML to 523 (from 502 in 2023), including 374 on the EMLc (from 361 in 2023). These totals do not include medicines recommended on the Model Lists as therapeutic alternatives.

Changes to the Model Lists are shown in Tables 1 – 3. Applications for proposed changes to the Model Lists that were not recommended are shown in Table 4. Changes to the AWaRe classification of antibiotics are shown in Table 5.

The Expert Committee’s recommendations are briefly described in this document.

All applications and documents reviewed by the Expert Committee are available on the WHO website (5).

## ***Section 1: Anaesthetics, preoperative medicines, and medical gases***

### **Section 1.1.1 Inhalational medicines**

The Expert Committee recommended:

- the removal of halothane from the EML and EMLc to reinforce the importance of prioritizing alternative inhalational anaesthetic agents (e.g. sevoflurane);
- the inclusion of a note with the listing of nitrous oxide on the EML and EMLc regarding preferential supply via point-of-care cylinders instead of centrally supplied (piped) delivery systems.

The Expert Committee recognized that halothane and nitrous oxide are potent greenhouse gases and ozone depleting substances with significant environmental consequences. These recommendations support efforts to reduce the impact of essential anaesthetic gases on climate change. The Expert Committee considered that substitution of halothane with alternatives that have a lower propensity for environmental impact (e.g. sevoflurane) while delivering high-quality care is an important action for health care systems. Equally, minimizing system waste and adopting a nitrous oxide waste reduction strategy and transitioning to point-of-care cylinders from centrally piped infrastructure should be encouraged in national health care systems.

## ***Section 5: Medicines for neurological disorders***

The Expert Committee endorsed changes to the structure of Section 5 of the Model Lists, incorporating the suggestions made by Médecins Sans Frontières in the contribution received during the public consultation period. Additional changes to this section following other recommendations made during the meeting are also endorsed. The changes are summarized in Table 3.

### **Section 5.1 Medicines for central nervous system disorders**

The Expert Committee did not recommend inclusion of risdiplam on the EML and EMLc for use in the treatment of spinal muscular atrophy at this time. As was the case when an application for risdiplam was considered by the 2023 Expert Committee, the Committee noted that greater benefits of treatment in terms of motor function were observed in younger children. In particular, the Committee noted the preliminary reporting of positive and relevant outcomes from the RAINBOWFISH trial in pre-symptomatic infants, but that the trial results have to date only been reported in a conference presentation and have not yet been evaluated by the clinical and scientific community and published in a peer-reviewed journal. As such, the internal and external validity of the results could not be fully assessed by the Expert Committee due to limited available information. The Committee requested that a further update be sought in a resubmission to the 2027 Expert Committee meeting, with the latest published RAINBOWFISH trial results. The Committee also considered that if the preliminary results of the 24-month follow-up of the RAINBOWFISH trial are confirmed for patient-important outcomes (e.g. ability to sit without support, need for respiratory support), if the risk of bias associated with the trial is low, if eligible pre-symptomatic patients can be identified, and if no evidence emerges against use of risdiplam in this population (e.g. serious safety concerns), then a positive recommendation to include risdiplam on the EMLc could be possible in the future.

#### **Section 5.1.1 Antiseizure medicines**

The Expert Committee recommended extending the listing for prednisolone on the EMLc to include the new indication of infantile epileptic spasms syndrome, based on clinical need, evidence of favourable effectiveness and safety, lower costs and better cost-effectiveness than alternative first-line treatment options.

#### **Section 5.1.4 Medicines for cerebral palsy**

The Expert Committee recommended the addition of intrathecal baclofen to the EML and EMLc in the treatment of spasticity associated with cerebral palsy based on evidence of a favourable balance of efficacy and harms. Oral baclofen was also recommended for addition in recognition of its use to assess responsiveness to intrathecal therapy

prior to surgery to install the administration pump, as a complementary therapy during the intrathecal dose titration when the pump is installed, as supportive therapy when intrathecal baclofen therapy is discontinued, and to prevent and treat baclofen withdrawal, which can be severe and life-threatening.

### Section 5.1.5 Medicines for headache disorders

The Expert Committee did not recommend inclusion of carbamazepine for the new indication of trigeminal neuralgia because the available clinical evidence was of insufficient quality and therefore confidence in the reported benefits and harms was limited.

#### Section 5.1.5.1 Medicines for acute migraine attacks

The Expert Committee recommended the addition of eletriptan, ibuprofen and naproxen to the EML for acute treatment of migraine based on evidence of favourable benefit to harm profiles, and the possibility of increasing the choice of medicines for acute migraine for patients, while maintaining a parsimonious number of options at the pharmacological class level. Naproxen is listed as a therapeutic alternative to ibuprofen and eletriptan is listed as a therapeutic alternative to sumatriptan under square box listings.

#### Section 5.1.5.2 Medicines for migraine prophylaxis

The Expert Committee did not recommend inclusion of amitriptyline or bisoprolol for migraine prophylaxis due to inadequate evidence for relative benefit compared to currently listed propranolol. The Committee did not recommend inclusion of fremanezumab for prophylaxis of high-frequency or chronic migraine. The Committee considered that fremanezumab demonstrated favourable outcomes compared to placebo. However, the absence of direct comparative evidence for fremanezumab versus currently listed propranolol and resultant uncertainty regarding the relative benefit made it impossible to adequately justify the substantial cost difference between the two medicines.

#### Section 5.1.5.3 Medicines for cluster headache

The Expert Committee recommended inclusion of sumatriptan, prednisolone and verapamil in the EML for the acute treatment and prophylaxis of cluster headache based on a favourable balance of benefits to harms, while also noting the key role of rapid-flow oxygen for this indication.

### ***Section 6: Anti-infective medicines***

#### Section 6.1.2 Antifilarials

The Expert Committee recommended inclusion of moxidectin on the EML and EMLc as a therapeutic alternative to ivermectin for treatment of onchocerciasis and lymphatic filariasis based on evidence of a favourable balance of benefits to harms.

#### Section 6.1.3 Antischistosomals and other antitrematode medicines

The Expert Committee recommended inclusion of arpraziquantel, a dispersible or orodispersible tablet, on the EMLc for the treatment of schistosomiasis in preschool-aged children based on evidence of similar efficacy and safety when compared with praziquantel. The Committee recognized the medical need for a more palatable, easy-to-administer paediatric formulation of praziquantel and efforts to develop innovative orodispersible tablet formulations for praziquantel for paediatric use. The Committee noted that arpraziquantel is the active enantiomer of praziquantel. The Committee considered that the proposed formulation was age-appropriate for the target population, allowing precise dosing of children and infants of different body weights and with better palatability and acceptability than praziquantel for this age group. Listing is recommended for arpraziquantel as a therapeutic alternative to praziquantel (which remains the class representative) under a square box listing.

### Section 6.2.3 Reserve group antibiotics

The Expert Committee did not recommended the inclusion of imipenem + cilastatin + relebactam for the treatment of infections caused by multidrug-resistant organisms for the same reasons as given by the previous Expert Committee: imipenem + cilastatin + relebactam lacks in vitro activity against the carbapenemase genotypes most commonly associated with carbapenem resistance in Enterobacteriales globally, and other reserve antibiotics with a similar spectrum of activity are already included on the Model Lists. However, the Committee advised that future evaluation of an application for inclusion of imipenem + cilastatin + relebactam on the Model List could be considered following any changes to the definition of the AWaRe Reserve category arising from the planned revision (see Other matters considered by the Expert Committee).

### Section 6.2.5 Antituberculosis medicines

The Expert Committee recommended inclusion of a dispersible tablet formulation of rifapentine 150 mg on the EMLc for use in tuberculosis preventive treatment regimens in children in accordance with recommendations in WHO guidelines.

The Committee recommended removal of the footnote regarding the limitation for use of rifabutin only to patients with HIV receiving protease inhibitors, and to transfer the listings of medicines used in multidrug-resistant tuberculosis from the complementary (e.g. secondary care level) to the core list (e.g. primary care level).

### Section 6.4.2 Antiretrovirals

The Expert Committee recommended inclusion of a fixed-dose combination dispersible tablet formulation of abacavir + dolutegravir + lamivudine on the EMLc for the treatment of children with HIV in accordance with recommendations in WHO guidelines.

### Section 6.4.3 Other antivirals

The Expert Committee recommended the removal of ribavirin from the EML and EMLc as a treatment for viral haemorrhagic fevers. The Committee noted how the interpretation of evidence supporting ribavirin for viral haemorrhagic fevers (VHFs) has shifted significantly since the 1980s. Ribavirin was recommended as a routine treatment based largely on a quasi-experimental study conducted during that time, which suggested potential benefits, particularly in Lassa fever. However, that early evidence was methodologically limited, with substantial risks of bias, including lack of randomization, small sample sizes and inadequate control groups. Over time, as standards for evaluating clinical interventions have become more rigorous, the limitations of the original evidence have become more apparent. Recent reviews have highlighted the lack of high-quality randomized controlled trials and have raised concerns about the potential for harm, such as haemolytic anaemia and other adverse effects. The Committee noted that WHO guidance for the clinical management of VHFs is currently under development in which it is expected that ribavirin treatment will be recommended only within the context of clinical trials to evaluate safety and efficacy.

### Section 6.5.5 Antitrypanosomal medicines

The Expert Committee recommended extending the listing for fexinidazole on the EML and EMLc to include the new indication of treatment for first- and second-stage human African trypanosomiasis due to *Trypanosoma brucei rhodesiense* in adults and children aged 6 years and older based on evidence of effectiveness and safety compared to alternative treatments. Compared to suramin (for first stage) or melarsoprol (for second stage), fexinidazole is the preferred treatment for both stages of the disease, is administered orally and it is not associated with fatal reactive encephalopathy, a rare but severe and often deadly complication of melarsoprol.

## Section 7: Medicines for cystic fibrosis

The Expert Committee recommended the inclusion of elexacaftor + tezacaftor + ivacaftor fixed-dose combination and single-agent ivacaftor on the core list of the EML and EMLc for the treatment of cystic fibrosis in people aged 2 years

and older with at least one F508del mutation or another responsive cystic fibrosis transmembrane conductance regulator (CFTR) mutation based on evidence of a favourable balance of benefits to harms. The Committee acknowledged the relevant benefits across multiple outcomes, including improvement in lung function, reduction in pulmonary exacerbations due to infections or inflammation, improvements in quality of life and potential to prevent or at least delay long-term complications, including premature death. The Committee recognized that the evidence base supporting use of elexacaftor + tezacaftor + ivacaftor is solid, originating in multiple high-quality randomized controlled trials and with post-approval observational studies confirming effectiveness and safety in more populations than those enrolled in trials. The Committee noted that elexacaftor + tezacaftor + ivacaftor therapy is effective for most patients with cystic fibrosis, significantly expanding the cohort of patients that can benefit from this therapy compared to earlier CFTR modulators, which only benefited smaller subgroups. The Committee acknowledged the high cost and limited availability of the medicines but considered that inclusion could support efforts to expand regulatory approval across countries, stimulate generic development and promote equitable access and affordability. Listing is recommended in a new section of the Model Lists for medicines for cystic fibrosis.

## ***Section 8: Immunomodulators and antineoplastics***

### **Section 8.2.1 Cytotoxic medicines**

The Expert Committee did not recommend the inclusion of temozolomide on the EML and EMLc for the treatment of high-grade glioma (as monotherapy), relapsed or refractory high-risk neuroblastoma (in combination with irinotecan or topotecan), relapsed Ewing sarcoma (in combination with irinotecan), or as monotherapy for treatment of other relapsed or refractory paediatric solid tumours as palliative treatment. The Committee noted that temozolomide has not been demonstrated to improve survival in patients with neuroblastoma or Ewing sarcoma, and while the medicine has shown a small survival benefit in some patients with high-grade glioma, the evidence is limited. Temozolomide is also associated with an increased risk of severe haematological toxicity. Thus, the Committee considered that the balance of benefit to harm was not favourable.

### **Section 8.2.2 Targeted therapies**

The Expert Committee did not recommend the inclusion of panitumumab, a monoclonal antibody targeting the epidermal growth factor receptor (EGFR), on the EML for the treatment of KRAS wild-type metastatic colorectal cancer based on evidence of limited survival benefit and risk of harms. The Committee noted that the overall survival benefit in the second- and third-line settings was below the established threshold for EML eligibility (i.e. a minimum overall survival benefit of 4–6 months). In the first-line setting the overall survival benefit was modest and not consistent across all patients and may be influenced by factors like tumour location and additional RAS/BRAF mutations. The Committee noted the need to exclude patients with RAS mutations, given that the addition of panitumumab to chemotherapy in this population has been shown to decrease overall survival. The Committee also noted substantial toxicities.

The Expert Committee recommended the inclusion of zanubrutinib, a Bruton's tyrosine kinase inhibitor, on the EML for the treatment of relapsed or refractory chronic lymphocytic leukaemia/small lymphocytic leukaemia (CLL/SLL) based on evidence of a survival advantage compared to chemo-immunotherapy, and similar survival benefit to that previously observed for ibrutinib, with fewer side effects (e.g., less atrial fibrillation and bleeding in some trials). Evidence in the first-line setting is promising but is not yet as well established as in the relapsed or refractory setting. An application presenting the evidence for this class of medicines in the first-line treatment of CLL/SLL is encouraged for 2027. Listing is recommended for zanubrutinib as a therapeutic alternative to ibrutinib (which remains the class representative) under a square box listing. The Committee acknowledged that ibrutinib remains highly priced in most countries. Ibrutinib may face competition from newer-generation BTK inhibitors like zanubrutinib, which is more accessible in some countries, with a better domestic cost-effectiveness profile and potentially could better align with local medicine policy priorities.

### Section 8.2.3 Immunomodulators

The Expert Committee recognized that cancer is a growing societal, public health and economic problem globally, and is responsible for nearly one in three premature deaths from noncommunicable disease. The proportion of patients with advanced stage at first presentation remains substantial. Solid tumors that are amenable to effective therapy using PD-1/PD-L1 immune checkpoint inhibitors represent major causes of rising burdens with respect to lives lost and costs of management. The Committee noted the rapid pace of innovation in immuno-oncology and emphasized the importance of reducing inequities in cancer care by increasing access to immune checkpoint inhibitors, among other strategies.

In consideration of the application proposing inclusion on the EML of multiple PD-1 / PD-L1 immune checkpoint inhibitors for multiple cancer indications, the Expert Committee:

- appreciated the approach taken by the WHO Collaborating Centre on Evidence Synthesis and Evaluation of Novel Cancer Therapies at the University of Cologne, Germany, to identify the PD-1 / PD-L1 immune checkpoint inhibitor-indication pairings proposed for EML listing from among the many approved and available. The Committee considered that the approach taken was up-to-date, comprehensive, systematic, transparent and evidence based and provided a solid basis for its decision-making;
- noted that all proposed pairings are approved by the European Medicines Agency for the first-line treatment of adults for the therapeutic indications for which they are proposed, have evidence from randomized trials, and received a score of four or higher on the European Society of Medical Oncology's Magnitude of Clinical Benefit Scale in the non-curative setting;
- applied the EML principle for cancer medicines to demonstrate at least 4-6 months overall survival gain in randomized controlled trials;
- appreciated and took into consideration the review of the application undertaken by the EML Cancer Experts group and the evidence to decision frameworks following the GRADE approach prepared by the Secretariat.

The Committee favoured pairings where the evidence strongly supported a large benefit-to-risk ratio. The Committee considered monotherapy more positively than combination therapy for indications where both are approved and a trade-off between additional efficacy, toxicity and cost would typically occur.

The Expert Committee **recommended** the inclusion of the following:

- pembrolizumab, atezolizumab and cemiplimab as first-line monotherapy of metastatic non-small cell lung cancer with ≥50% PD-L1 expression. EML listing is for pembrolizumab with a square box as class representative and atezolizumab and cemiplimab as specified therapeutic alternatives;
- pembrolizumab as first-line monotherapy for deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) metastatic colorectal cancer;
- pembrolizumab, in combination with platinum-based chemotherapy, as first-line treatment of metastatic cervical cancer with ≥1% PD-L1 expression.

The Committee considered that these recommendations for inclusion provide the best chance at minimizing financial toxicity and concentrating expenditure into the areas with the most favorable incremental gain in benefit to risk ratio. The Committee noted that use of immune checkpoint inhibitors in adults with solid tumours that have predictive biomarkers (e.g., high PD-L1 expression for non-small cell lung cancer) rather than all patients is the highest priority, to enable greater access in settings where budgetary constraints may require prioritization of scenarios that offer the greatest clinical value.

With the recommendation to list pembrolizumab for the above-mentioned indications, the Committee recommended changing the current square box listing of nivolumab as the class representative and pembrolizumab as a specified therapeutic alternative for metastatic melanoma, to make pembrolizumab the class representative with nivolumab as

specified therapeutic alternative. This is intended to signal to countries the possibility of aggregating procurement of a single molecule, pembrolizumab, across multiple cancer indications, influencing price negotiations with manufacturers. Limiting procurement fragmentation by focusing on a select few immune checkpoint inhibitors is likely to facilitate central purchasing through competitive tendering and better competition from pembrolizumab biosimilars, thereby increasing access.

In addition to its recommendations on which immune checkpoint inhibitors to prioritize for inclusion on the EML, the Committee also recognized the value and recommended the use of strategies to improve access, particularly in resource-constrained settings, as presented in the report from the EML cancer experts consultation meeting. The Committee noted that these strategies were based on evaluation of available evidence and pragmatic considerations. The Committee considered the strategies to improve access to care in two components: clinical strategies and health system strategies. The Committee acknowledged that while clinical strategies (over which doctors and patients have greater control) and health system strategies (requiring government-led policy legislations and reforms) should complement each other, clinical strategies can be implemented immediately, delivering rapid benefits for access.

#### *Clinical strategies – doctors and patients*

The Committee acknowledged the importance of patients being empowered to make an informed and consensual decision about their treatment, including information on benefits, harms, accessibility, and feasibility of care. This might require comparing alternatives that may differ from each other in one or more of the aforementioned dimensions. Strategies that can be considered to improve access include: dose optimization according to patient weight (weight-based dosing); rounding down doses to the closest vial size and strength (dose banding); or hybrid dosing regimens that combine the two; and if relevant, vial sharing. Additionally, longer intervals between treatment administration or shorter durations of treatment can be also considered. The Committee also noted that ongoing studies are investigating outcomes with “ultra-low dose” immunotherapy. If the results are favourable, ultra-low dose immunotherapy could be a viable strategy to further improve access.

#### *Health system strategies – policy makers*

To enable better value procurement through tendering and competition leading to increased access for individuals and health systems, the Committee recommended that national policies should take advantage of similar clinical performance among different immune checkpoint inhibitors, regardless of their biological target (i.e. PD-1 or PD-L1). The Committee opted to recommend four immune checkpoint inhibitors for non-small cell lung cancer using the square box concept, indicating interchangeability at the health system level for this indication. The recommended medicines have different pharmacological properties but are considered therapeutic alternatives. Where there is no relevant difference in terms of efficacy and safety data, the preferred medicine at country level should be the one that is generally available at the lowest price. At the country level, the interpretation of the square box should be extensive (i.e. a class effect), potentially covering other equally effective and safe immune checkpoint inhibitors of assured quality where these are offered at an advantageous price.

The Committee also recommended that quality assured biosimilars of the listed immune checkpoint inhibitors be considered therapeutic alternatives to the corresponding reference medicine (even if not yet available), to signal to countries the importance of strategies to encourage rapid entry of biosimilars into markets.

The Committee recognized the need for companion in-vitro diagnostic tests to identify patients eligible for treatment with the recommended immune checkpoint inhibitors. The Committee noted that access to diagnostic capacity is limited in less-resourced settings and may be a barrier to appropriate and optimal use of these medicines. However, the Committee highlighted that this scenario is more variable in middle-income countries, where testing for molecular alterations is more readily available and the price associated with tests is a small fraction of the price associated with treatment. The Committee recognized that the requirement for companion diagnostics adds additional cost but offers

a pathway to limit inappropriate use of immune checkpoint inhibitors (i.e., outside of recommended indications) and serves to prevent the waste of resources with non-essential or lower-value use.

The Committee considered that countries can apply their own affordability criteria in determining which (if any) of the recommended immune checkpoint inhibitors can be reasonably incorporated into national EMLs and reimbursement schemes. In addition, the Committee considered that countries can apply their own feasibility criteria in assessing health system readiness for immune checkpoint inhibitor implementation, in terms of diagnostic infrastructure, healthcare worker training in immuno-oncology, resources for the management of immune-mediated side-effects and monitoring capabilities, to ensure their safe and effective use.

The Expert Committee **did not recommend** listing for the following:

- cemiplimab, durvalumab plus tremelimumab, nivolumab plus ipilimumab, or pembrolizumab – each in combination with chemotherapy – for the treatment of oncogenic-driver wild-type metastatic non-small cell lung cancer regardless of PD-L1 expression;
- tislelizumab in combination with chemotherapy for oncogenic-driver wild-type metastatic non-small cell lung cancer with ≥50% PD-L1 expression;
- nivolumab plus ipilimumab for the treatment of dMMR/MSI-H phenotype metastatic colorectal cancer or metastatic melanoma;
- dostarlimab in combination with chemotherapy for dMMR/MSI-H phenotype metastatic endometrial cancer;
- pembrolizumab or nivolumab, in combination with chemotherapy, for first-line treatment of metastatic ERBB2-negative gastric or gastro-esophageal junction adenocarcinoma with ≥1% or ≥5% PD-L1 expression, respectively;
- durvalumab in combination with chemotherapy for first-line treatment of biliary tract cancer regardless of PD-L1 expression;
- durvalumab monotherapy, durvalumab plus tremelimumab, or atezolizumab plus bevacizumab for first-line treatment for metastatic hepatocellular carcinoma regardless of PD-L1 expression;
- pembrolizumab in combination with chemotherapy for first-line treatment of metastatic head and neck squamous cell carcinoma;
- pembrolizumab, nivolumab, or nivolumab + ipilimumab, each in combination with chemotherapy, for first-line treatment of metastatic esophageal squamous cell cancer
- nivolumab + ipilimumab, pembrolizumab + axitinib, or pembrolizumab + lenvatinib for the first-line treatment of metastatic renal cell carcinoma regardless of PD-L1 expression;
- pembrolizumab in combination with chemotherapy for first-line treatment of triple-negative breast cancer CPS≥10 given.

Reasons not to recommend inclusion of these pairings variably included prioritization of monotherapy over combination therapy, magnitude of overall survival gains of less than 4-6 months, limited or absence of mature overall survival data, unfavourable benefit to risk profiles, uncertainty around optimal immune checkpoint inhibitor and tyrosine kinase inhibitor positioning (i.e. in sequence or in combination), and uncertainty around optimal use across different patient cohorts which may vary with the immunogenicity of tumour types.

The Expert Committee did not recommend the inclusion of tislelizumab or toripalimab on the EML for the treatment of oesophageal squamous cell carcinoma at this time. In the first-line setting, the Committee considered that the reported overall survival gains offered by these medicines were relatively consistent (suggesting that these medicines could be considered therapeutic alternatives). However, the Committee judged the overall survival gains to be moderate in size and that the benefit of these gains was offset by the unclear role of PD-L1 expression as a predictive biomarker. The Committee also noted the potential for increased harm in patients with poorer prognosis at baseline.

In the second-line setting, the Committee noted that the magnitude of benefit was smaller compared with the first-line setting and did not meet the established 4–6 months threshold.

The Expert Committee did not recommend the inclusion of toripalimab on the EML for the treatment of nasopharyngeal carcinoma. The Committee considered that toripalimab in combination with chemotherapy showed promising overall survival gains compared to chemotherapy alone in the first line setting, but noted that benefit in the second-line setting was more limited. The Committee also noted that trials of other immune checkpoint inhibitors are ongoing in nasopharyngeal carcinoma. The Committee underscored that the maturation of additional data, in the context of all immune checkpoint inhibitors approved for nasopharyngeal carcinoma, especially concerning overall survival and quality of life, will be pivotal to inform judgements on whether to include toripalimab on the EML in the future.

The Expert Committee recommended the inclusion of blinatumomab on the EML and EMLc for the treatment of CD-19-positive B-lineage acute lymphoblastic leukaemia (B-ALL) based on compelling evidence from randomized clinical trials showing superiority of blinatumomab over chemotherapy in meaningfully improving survival in: (i) children, adolescents and adults with relapsed B-ALL; (ii) survival in adults with B-ALL in the front-line setting; and (iii) disease-free survival in children with B-ALL in the front-line setting. Blinatumomab is associated with fewer grade ≥3 adverse events compared to chemotherapy but has specific adverse events that would require specialist management and may represent a barrier to implementation in most low-resource settings. Blinatumomab is available as IV formulation. It requires continuous infusion over 28 days per cycle to maintain stable plasma levels due to its very short half-life (~2 hours). This continuous exposure is crucial to maintain therapeutic efficacy and minimize cytokine release syndrome. The limited feasibility of blinatumomab should be contrasted against the limited feasibility of the comparator – standard chemotherapy – which involves highly toxic, multi-agent regimens over an extended period of time. In both paediatric and adult patients, standard chemotherapy requires frequent hospitalizations and supportive care, including long-term sequelae of prolonged myelosuppression.

Overall, the Committee considered that the balance of benefit to harm of blinatumomab was strongly favourable in a disease where clinical cure is a realistic goal. The Committee noted the current high cost of blinatumomab treatment, and that while it has been determined to be cost-effective in some high-income settings, cost-effectiveness studies in other settings have been variable, depending on patient population and line of therapy. In considering the feasibility of implementing blinatumomab, the Committee recognized that countries in resource-limited settings considering including blinatumomab on their national EMLs must consider their capacity to accommodate requirements for safe administration, management of adverse events and local prioritization of implementation with respect to age and line of treatment.

#### Section 8.2.5 Supportive medicines

The Expert Committee did not recommend the expansion of the indications for erythropoiesis stimulating agents (e.g. epoetin alfa) on the EML and EMLc to include supportive management of chemotherapy-induced anaemia, based on evidence of a potentially unfavourable long-term benefit to harm profile. The Committee noted that judicious use of erythropoiesis-stimulating agents in patients receiving chemotherapy improves haemoglobin levels, may reduce transfusion requirements, and may be associated with improvements in quality of life. However, they have not been shown to improve overall survival, with some clinical studies reporting inferior survival and worse cancer outcomes as these medicines might stimulate tumour growth directly or affect the tumour microenvironment. The Committee also noted that guidelines from professional societies (e.g., the American Society of Clinical Oncology and the European Society of Medical Oncology) recommend careful patient selection, informed consent about risks and conservative dosing – factors which represent important limitations in terms of feasibility in the use of this class of medicines in this context.

## ***Section 10: Medicines affecting the blood***

### **Section 10.2 Medicines affecting coagulation**

The Expert Committee recommended the inclusion of emicizumab on the EML and EMLc for prophylactic treatment of haemophilia A with and without factor VIII inhibitors based on a favourable balance of benefits to harms. The Committee also made some important remarks regarding the implementation of the recommendation depending on the level of available resources. In recognition of the current high price of emicizumab, the Committee highlighted that the value of emicizumab prophylaxis is greatest in people with haemophilia A with FVIII inhibitors, in whom factor replacement is ineffective. In people with severe haemophilia A without FVIII inhibitors, prophylaxis with plasma-derived or recombinant FVIII may represent a better value, more affordable, treatment option. In considering inclusion of emicizumab on national essential medicine lists in resource-limited settings, and in line with national needs, decision-makers may wish to prioritize/limit selection and use of emicizumab in the first instance to the population of people with haemophilia A with FVIII inhibitors, extending selection and use to people with severe haemophilia A without inhibitors when the price of emicizumab is lower and/or if resources allow.

The Expert Committee recommended the inclusion of phytomenadione mixed micelle solution formulation on the EML and EMLc for the management of haemorrhage due to severe hypoprothrombinaemia, and on the EMLc for the prophylaxis and treatment of haemorrhagic disease of the newborn. The Committee considered that the proposed formulation represents an additional effective treatment option that offers flexibility for administration, with evidence of comparable efficacy and safety to currently listed formulations.

### **Section 10.3 Medicines for haemoglobinopathies**

The Expert Committee endorsed the proposed changes to Section 10.3 of the Model Lists made by the Secretariat, incorporating the suggestions made by the WHO Department of Maternal, Newborn, Child and Adolescent Health, and Ageing to title the section “Medicines for haemoglobinopathies” and to transfer the listing of hydroxyurea (hydroxycarbamide) from the complementary to the core list.

## ***Section 11: Blood products, coagulation factors, and plasma substitutes***

### **Section 11.1 Blood and blood components**

The Expert Committee recommended that non-pathogen-reduced (i.e. native) cryoprecipitate and pathogen-reduced cryoprecipitate be removed from the Model Lists for use in prophylactic treatment of haemophilia A and von Willebrand disease. The Committee recognized the increased risks of transfusion-transmitted infections associated with repeated transfusions in patients with these conditions.

The Expert Committee recommended that non-pathogen-reduced (i.e., native) cryoprecipitate be retained on the EML and EMLc as a therapeutic alternative to pathogen-reduced cryoprecipitate for use in cases of life-threatening major haemorrhage and rapid loss of blood volume (e.g. severe trauma, major surgery, obstetric haemorrhage). The Committee considered that at this time and under the aforementioned clinical circumstances, native cryoprecipitate still represents a therapeutic alternative to coagulation factors or pathogen-reduced cryoprecipitate when these are not available. In such situations, the iatrogenic risks are clearly outweighed by the potential life-saving benefits of native cryoprecipitate. The Committee recognized the importance of preferential use of pathogen-reduced cryoprecipitate over native cryoprecipitate due to the reduced risk of transfusion-transmitted infections. However, the Committee noted that widespread global access to pathogen-reduced cryoprecipitate is currently limited. In settings where pathogen-reduced cryoprecipitate is not available, native cryoprecipitate represents a last resort alternative.

The Expert Committee recommended that the current listings for plasma-derived coagulation factors VIII and IX be transferred from the complementary to the core list of the EML and EMLc. For consistency across listings for other

medicines used in the treatment of haemophilia and von Willebrand disease, the Committee recommended that the listing for desmopressin also be transferred from the complementary to the core list.

The Expert Committee recommended the removal of coagulation factor IX complex as a therapeutic alternative under the square box listing of plasma-derived coagulation factor IX on the EML and EMLc given the increased risk of thrombosis associated with this product.

### **Section 11.3 Coagulation factors**

The Expert Committee recommended the inclusion of recombinant coagulation factor VIII for prophylactic treatment and on-demand treatment of acute bleeds in people with haemophilia A, and of recombinant coagulation factor IX for prophylactic treatment and on-demand treatment of acute bleeds in people with haemophilia B to the core list of the EML and EMLc. The recommendation is made based on evidence of equal effectiveness to plasma-derived coagulation factors for outcomes including reduced bleeding rates, the percentage of patients without bleeding events, improving joint health scores and improving health-related quality of life measurement scores. Compared with plasma-derived coagulation factors, recombinant coagulation factors are not associated with an increased risk of bloodborne virus transmission. Nevertheless, the Committee recognized that plasma-derived coagulation factors continue to represent an important treatment option, may offer advantages over recombinant products in the context of inhibitor development and may be more affordable in some settings.

## ***Section 12: Cardiovascular medicines***

### **Section 12.3 Antihypertensive medicines**

The Expert Committee recommended the inclusion of triple fixed-dose combination (FDC) antihypertensive formulations containing an angiotensin converting enzyme inhibitor or angiotensin II receptor blocker, a long-acting dihydropyridine calcium channel blocker and a thiazide or thiazide-like diuretic on the EML based on a favourable balance of benefits to harms in patients with uncontrolled blood pressure on dual therapy or in high-risk patients (e.g. with diabetes, kidney disease, cardiovascular disease). The Committee considered the benefits of triple combination therapy in terms of reductions in systolic and diastolic blood pressure and some evidence of improved adherence and persistence compared to free equivalent combination therapy. The Committee considered that the addition of the triple FDC is part of an overall strategy aimed at meeting the different needs that both patients and health systems may have in addressing hypertension, ensuring patients can choose based on preference, and standardizing supply, procurement and training. Adverse effects are generally mild and manageable, and consistent with the known adverse event profiles of the components. Cost comparisons of FDCs with the sum of the component monotherapies are variable across settings and should be considered in national selection decisions. The Committee reiterated the importance of continued availability of single-agent antihypertensives.

## ***Section 13: Dermatological medicines***

### **Section 13.1 Antifungal medicines**

The Expert Committee did not recommend the inclusion of ciclopirox hydroxypropyl chitosan nail hydrolacquer on the EML for the treatment of onychomycosis in adults because of concerns including the lack of compelling evidence of comparative benefits and safety versus oral or combined oral and topical antifungal treatments, and unknown cost-effectiveness.

### **Section 13.4 Medicines affecting skin differentiation and proliferation**

The Expert Committee considered that the inclusion of effective and safe biologics for psoriasis on the EML would address an important public health need and support global advocacy efforts to reduce the global burden of psoriasis, especially in low and middle-income countries. The Committee acknowledged that a large number of biologic disease-

modifying medicines for psoriasis are available and the need to prioritize the most effective, tolerable and affordable options.

The Expert Committee recommended the inclusion of adalimumab and ustekinumab on the complementary list of the EML and EMLc for the treatment of adults and children with moderate-to-severe psoriasis, based on evidence of favourable efficacy and safety, as second line treatment alternatives. Listing complements the non-biologic therapies used in first line for psoriasis currently listed on the Model Lists (e.g. topical corticosteroids, systemic methotrexate).

The Committee considered that adalimumab and other tumour necrosis factor alpha inhibitors could be considered therapeutic alternatives to each other in most clinical scenarios and that including multiple within-class alternatives on the Model Lists could support greater competition to lower prices. The Committee therefore recommended adalimumab be listed with a square box as the class representative with certolizumab pegol, etanercept and infliximab as specified therapeutic alternatives.

The Committee recommended inclusion of ustekinumab in addition to adalimumab because of some advantages ustekinumab has over adalimumab and other tumour necrosis factor alpha inhibitors. When considering the administration schedule, adalimumab is administered every two weeks while ustekinumab is administered every 12 weeks. Less frequent injections are more convenient, with reduced disruption to daily life for patients and reduced burden and costs for health systems. Ustekinumab is preferred to adalimumab in patients with heart disease and in settings where tuberculosis is endemic as it is associated with a lower risk of tuberculosis reactivation. While ustekinumab is currently more highly priced than adalimumab, biosimilars are becoming increasingly available. For ustekinumab, the Committee did not recommend listing with a square box. The Committee acknowledged the data supporting similar or better effectiveness of other monoclonal antibodies targeting IL-12 and IL-23 (e.g. guselkumab, risankizumab and tildrakizumab) but considered the alternatives to have less supportive evidence, biosimilars are not yet available, and there is no information regarding their costs in most jurisdictions which were assumed to be higher than ustekinumab.

Quality-assured biosimilars are recommended as therapeutic alternatives of both adalimumab (and therapeutic alternatives) and ustekinumab.

### Section 13.6 Moisturizers

The Expert Committee recommended inclusion of urea- and glycerol-based moisturizing creams on the EML and EMLc for the treatment of atopic dermatitis based on evidence of benefit, acceptable safety and public health need. Recommended formulations are creams containing 5% urea and creams containing 15% to 20% glycerol with regulatory approval as emollients.

### Section 13.7 Sunscreens, broad spectrum

The Expert Committee recommended the inclusion of therapeutic broad-spectrum topical sunscreen on the EML and EMLc for the prevention of skin cancer in people with albinism. The Committee recognized the higher susceptibility to the harmful effects of UV radiation, including (but not limited to) non-melanoma skin cancer among people with albinism and the therapeutic need for effective and safe sun protection products in this population. Therapeutic broad-spectrum sunscreens should contain proven active ingredients in appropriate amounts to absorb or filter UVA and UVB radiation and have a high sun protection factor (SPF). The Committee was not able to recommend specific formulations for listing at this time. The Committee considered that listing sunscreens, even without a preferred formulation, was important to stimulate greater investment in research to compare and identify among the various formulations available those associated with a better profile. The Committee invited the submission of proposals outlining optimal formulation specifications for future consideration by the Expert Committee.

## **Section 15: Antiseptics and disinfectants**

The Expert Committee recommended that an explicit listing for hypochlorous acid solution as an environmental disinfectant, separate from its general inclusion as a chlorine-based compound, be included on the EML and EMLc to aid differentiation between hypochlorite and hypochlorous acid products.

The Expert Committee did not recommend inclusion of hypochlorous acid solution for topical use in antisepsis and wound care, because the application did not provide an updated comprehensive review of clinical studies to inform the decision-making, as was the request of the Expert Committee in 2021. As was the case in 2021, the evidence base in the application supporting topical use of hypochlorous acid solution in antisepsis and wound care was inconclusive.

## **Section 18: Medicines for endocrine disorders**

### **Section 18.1 Adrenal hormones and synthetic substitutes**

The Expert Committee recommended the inclusion of prednisolone 1 mg tablets on the core list of the EML and EMLc for treatment of adults and children with adrenal insufficiency based on evidence of an acceptable balance of benefits and harms and potential better affordability in some settings than currently listed hydrocortisone. Listing is recommended for prednisolone with a square box, specifying prednisone as a therapeutic alternative.

#### **Section 18.5.1 Insulins**

The Expert Committee recommended the inclusion of rapid-acting insulin analogues (insulin lispro, insulin aspart and insulin glulisine, and their quality-assured biosimilars as therapeutic alternatives) on the core list of the EML and EMLc for the treatment of people with type 1 and type 2 diabetes mellitus, and people with gestational diabetes. The Committee considered that the available evidence indicates generally comparable efficacy and safety between rapid-acting insulin analogues and regular human insulin. The Committee noted that some studies provide evidence of higher patient satisfaction scores with rapid-acting insulin analogues, and others suggest that rapid-acting insulin analogues may be associated with lower rates of complications, with medicine costs offset by reduced demand for high-cost treatments and health services for complications, particularly in type 1 diabetes. However, the Committee considered these arguments for including rapid-acting insulin analogues in the Model Lists to be somewhat tenuous. The Committee recognized that rapid-acting insulin analogues may be more expensive than regular human insulin and may be less affordable in some resource-limited settings. However, in other settings the prices of rapid-acting insulin analogues do not exceed the price of regular human insulin. The Committee's reason for recommending listing of rapid-acting insulin analogues is to support access, recognizing the progressive withdrawal of regular human insulin from markets, and to signal to countries the need for multi-pronged policy, pricing and procurement strategies to strengthen affordable access. The inclusion of rapid-acting insulin analogues also serves to enlarge the number of insulin products on the Model Lists and complements the listing of long-acting insulin analogues for use in basal-bolus regimens. This is also consistent with the listings for short- and intermediate-acting human insulins. Larger insulin markets could help in stabilizing prices, securing supply chains of quality-assured products, and mitigating the risks of shortages. Countries in which insulin prices are excessive should consider strengthening the regulatory framework, implementing or maintaining price control, or reference pricing mechanisms. The outcomes of price controls and reference pricing for essential medicines should be closely monitored as these policies can have several potential unintended consequences. The Committee emphasized the importance of commitment and action from WHO, Member States, insulin producers, procurement agencies and other stakeholders to address the problem of equitable and affordable access to insulin products globally.

The Expert Committee also recommended the inclusion of 10 mL vial formulations of long-acting insulin analogues, in addition to the currently listed 3 mL pre-filled pen and cartridge formulations.

## Section 18.5.2 Hypoglycaemic agents

The Expert Committee recommended the inclusion of glucagon-like peptide-1 (GLP-1) receptor agonists (semaglutide, dulaglutide and liraglutide) and GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) dual receptor agonists (tirzepatide) on the core list of the EML as add-on glucose lowering therapy for adults with type 2 diabetes mellitus and (i) with established cardiovascular disease (CVD) or chronic kidney disease (CKD); and (ii) with obesity (body mass index (BMI)  $\geq 30\text{kg/m}^2$ ) having a significant impact on their physical health and/or quality of life. This recommendation is made based on evidence of a meaningful and favourable balance of benefits to harms in this patient population. Listing is recommended for semaglutide with a square box, with dulaglutide, liraglutide and tirzepatide as specified therapeutic alternatives.

The Expert Committee did not recommend inclusion of GLP-1 and GLP-1/GIP dual agonists on the EML for the treatment of people with obesity without the abovementioned comorbidities (type 2 diabetes mellitus and established cardiovascular disease or chronic kidney disease) because of limited and less mature evidence for benefit for cardiovascular outcomes and mortality in this population and lack of data regarding long-term safety.

The Expert Committee considered two separate applications: one for the treatment of adults with type 2 diabetes mellitus and established or at high-risk of cardiovascular disease and one for the treatment of adults with obesity.

While keeping the recommendations for the diabetes and obesity applications separate, the Expert Committee evaluated the applications together to better contrast possible differences between benefits and harms across the two conditions and appreciate implications of coverage for the two cohorts of patients at global, regional and national level. The Committee also recalled that previous applications (in 2017, 2021 and 2023) for inclusion of GLP-1 receptor agonists for use in the treatment of diabetes had been evaluated and not recommended.

The Committee recognized that diabetes and obesity currently represent two major global health challenges, with both conditions reaching epidemic proportions across diverse populations and regions. In 2022, there were over 800 million people worldwide living with diabetes, a number projected to exceed 1.3 billion by 2050, reflecting dramatic increases across all age groups, sexes and countries regardless of income level. Simultaneously, the prevalence of obesity has increased globally – more than doubling in adults since 1990 – and now affecting more than 1 billion people. Growth in the prevalence of obesity is most rapid in low- and middle-income countries. Both diabetes and obesity are major contributors to mortality and morbidity, responsible for substantial disability-adjusted life years and straining health systems worldwide. Notably, the relationship between obesity and diabetes is both causal and cyclical; excess adiposity significantly increases the risk of type 2 diabetes through mechanisms involving insulin resistance and chronic inflammation. Furthermore, diabetes and obesity together exacerbate the risk of cardiovascular diseases, forming a triad of interlinked conditions that influence each other and jointly account for a substantial proportion of preventable deaths. The Committee noted that 30% to 50% of people with type 2 diabetes have established cardiovascular disease and obesity, representing a large global cohort with this triad of comorbidities. The Committee also noted that for people with all three of these conditions, the risk of death is much higher than in people with either diabetes or obesity alone.

The Committee noted the evidence from multiple large-scale randomized controlled trials and systematic reviews demonstrating the efficacy of GLP-1 receptor agonists and GLP-1/GIP dual agonists compared to placebo in people with diabetes in improving glycemic control, reducing the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke), reducing the risk of end stage kidney disease, reducing all-cause mortality, improving health-related quality of life and promoting weight loss. The Committee noted the consistency of benefits across studies. The Committee also acknowledged that, while some degree of benefit is possible across all patients irrespective of risk of cardiovascular diseases, the cohort of patients with type 2 diabetes with known cardiovascular or chronic kidney disease represents a high-risk subgroup that is likely to experience the most relevant benefit, with a ten-fold decreased risk of premature death compared to the cohort of patients at low

risk. The large difference in benefit between those at low risk and those at high risk for premature mortality is an important factor that could be used to identify those patients to be prioritized in the introduction of these medicines at country level.

The Committee noted the evidence from the large systematic review demonstrating the efficacy GLP-1 receptor agonists and GLP-1/GIP dual agonists (particularly subcutaneous semaglutide and tirzepatide) compared to lifestyle modification alone in people with obesity for achieving clinically meaningful weight loss and improving quality of life. However, the Committee agreed that evidence for benefits in cardiovascular outcomes and mortality in people with obesity without diabetes is currently limited to a single, large, randomized controlled trial of semaglutide versus placebo. While the outcomes of this trial for cardiovascular outcomes were positive, there were more discontinuations due to adverse events among people receiving semaglutide. The Committee noted that the trial reported outcomes after almost 40 months of follow-up and considered that the available evidence with respect to mortality outcomes was still at an early stage, and limited.

Overall, the Committee considered that the magnitude of benefits and certainty of evidence were greater for people with diabetes than for people with obesity, particularly for important outcomes of cardiovascular events and mortality, upon which the Committee placed greater value compared to outcomes of glycaemic control and weight loss.

Considering the population of people with type 2 diabetes, the Committee identified those with comorbid established cardiovascular or chronic kidney disease as being the cohort for whom the net benefit of treatment was the greatest. The Committee then decided to include comorbid obesity ( $BMI \geq 30 \text{ kg/m}^2$ ) as an additional eligibility criterion, thereby establishing a defined high-risk cohort of people for whom these medicines are listed as essential. The Committee considered the following reasons a support of a triple target population: (i) obesity is a condition that can negatively affect both the mental and physical health of people with diabetes, stalling or worsening the health status; (ii) certain molecules within the pharmacological classes of GLP-1 receptor agonists and GLP-1/GIP dual agonists have an important effect on body weight, being associated with major weight reductions, far exceeding the weight reductions associated with other hypoglycaemic agents on the EML (e.g. sodium-glucose cotransporter 2 inhibitors); and (iii) to highlight the importance of obesity as a public health priority – one that requires effective treatment and commitment at both scientific and policy levels.

The Committee noted that all proposed GLP-1 (semaglutide, liraglutide and dulaglutide) and GLP-1/GIP dual agonists (tirzepatide) were associated with important cardiovascular benefits in patients with type 2 diabetes. However, the Committee noted that there are important differences between these medicines with respect to weight loss, with semaglutide and tirzepatide being associated with more relevant body weight reductions compared to the other molecules. The Committee noted that availability and use of semaglutide and tirzepatide are constrained by a price that currently limits their use to only well-resourced health care systems.

The Committee acknowledged the current high price of these medicines and noted the reported cost-effectiveness ratios that exceed willingness-to-pay thresholds in many settings, particularly when used in low-risk patients. The Committee also noted the recent or upcoming patent expiry for liraglutide and semaglutide, which will introduce the possibility for biosimilar entry, increased competition and lower prices. The Expert Committee believed that significant price reductions could be achieved with biosimilar entry and competition, given the size and ubiquity of the market for these medicines. The Committee noted that when a large eligible patient population exists, robust biosimilar competition has consistently proven to be more reliable at sustainably reducing prices than other price-reduction mechanisms. The Committee's decision to recommend a square box listing for semaglutide, with dulaglutide, liraglutide and tirzepatide (and quality-assured biosimilars) as therapeutic alternatives aims to foster competition among available alternatives. The Committee hoped that having multiple EML-listed options would serve to facilitate the rapid introduction of prequalified biosimilar formulations and would support countries in negotiating lower medicine prices, selecting the product that represent the best value option.

The Expert Committee recommended listing of GLP-1 and GLP-1/GIP agonists in the core list to underscore the importance of these medicines being available in the primary care setting. Type 2 diabetes and its complications, including obesity, are managed primarily in primary care. Delaying access by requiring hospital referral can reduce benefits associated with early intervention, adding costs and limiting availability in rural areas or underserved communities.

In recognition of the financial implications of including GLP-1 receptor agonists and GLP-1/GIP dual agonists in national health systems at their current prices, particularly in resource-limited settings, the Committee emphasized the importance of targeting use in the first instance to those patients in whom the greatest value health benefit can be realized. The Committee also recommended that WHO continue to monitor the evolving landscape of this class of medicines, including benefits associated with use in people with obesity, potential long-term toxicities and approval of oral formulations. The Committee also recommended that WHO work on existing approaches for managing prices and evaluate alternative strategies to improve affordability and access to reduce the global burden of diabetes.

## ***Section 19: Immunologicals***

### **Section 19.3 Vaccines**

The Expert Committee endorsed the inclusion of vaccines for Ebola and mpox on the core list of the EML and EMLc, vaccines for hepatitis E and respiratory syncytial virus on the core list of the EML, and vaccines for malaria on the core list of the EMLc, in line with recommendations of the WHO Strategic Advisory Group of Experts (SAGE) on Immunization and corresponding WHO vaccine position papers.

## ***Section 22: Medicines for reproductive health and perinatal care***

### **Section 22.3 Uterotonics**

The Expert Committee accepted the rationale presented in the application and endorsed the proposed changes to Section 22.3 of the Model Lists, as summarized in Table 3.

The Expert Committee also noted the advice of the decision by WHO to remove the boxed text associated with the listing for mifepristone and misoprostol.

## ***Section 24: Medicines for mental and behavioural disorders***

The Expert Committee did not recommend inclusion of methylphenidate on the EML and EMLc for the treatment of children and adolescents with attention-deficit hyperactivity disorder (ADHD) because of limitations in the available evidence for benefits and safety of long-term use, which reduced confidence in the estimates of prolonged beneficial effect.

The Committee acknowledged that methylphenidate is widely recommended and used in many countries as the standard of care for children and adolescents with ADHD and has wide regulatory approval and market availability. Furthermore, it is already included in the national essential medicines lists of some countries. The Committee noted there are currently no medicines for ADHD on the Model Lists.

The Committee recalled the recommendation of the 2021 Expert Committee to not include methylphenidate on the Model Lists because of enduring uncertainty regarding the benefit-to-harm ratio for the long-term use of the medicine. The 2021 Committee also recommended that any future consideration of methylphenidate should address evidence for the effectiveness and safety of methylphenidate in the treatment of ADHD of at least 52 weeks duration; outcomes of the revision of the WHO mhGAP guidelines; and evaluation of health system capacity to provide appropriate diagnostic, non-pharmacological and pharmacological treatment and monitoring in low-resource settings.

The 2025 Expert Committee appreciated the efforts of the applicants of the current application in presenting evidence and information addressing the 2021 Committee's concerns and gaps in the evidence base previously proposed for evaluation.

In consideration of the evidence presented in the current application for longer-term efficacy and safety of methylphenidate, the Committee noted that randomized controlled trials evaluating long-term treatment (>6 months) were few and all had some methodological limitations. Selected pharmacoepidemiologic studies presented some real-world evidence for benefit in functional outcomes, reductions in all-cause mortality and unintentional injuries associated with long-term use of methylphenidate, however these studies also had intrinsic methodological limitations. In particular, the Committee noted the findings of the 1999 Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder (MTA study), in which ADHD treatment with stimulant medication (not limited only to methylphenidate) was associated with greater improvements in ADHD symptoms when compared to behavioural management over a period of 14 months, as rated by parents, teachers or independent investigators. Stimulant treatment was not associated with an increase in serious adverse events. The Committee noted evidence identified during the review process from follow-up analyses of the MTA study which showed that the magnitude of benefit of stimulant treatment compared to behavioural management seen at 14 months attenuated over time (after 2 years, 3 years, and into adulthood). The Committee noted that at longer follow up the advantage associated with methylphenidate in symptom control was not retained when compared to other strategies, including behavioral therapy alone or community care. The Committee was unable to discern if the loss in sustained benefits was due to tolerance, less adherence, crossover between different strategies, and if change in effectiveness was associated with characteristics of the children and adolescents or of the syndrome, such as baseline severity. Regarding long-term safety, the Committee noted mixed evidence of a potential association between methylphenidate use and effects on growth (height and weight) and potential for cardiovascular adverse effects.

The Committee considered the conditional recommendation in the 2023 WHO mhGAP guidelines, based on low certainty of evidence, that methylphenidate may be considered for use in children (from 6 years) and adolescents with ADHD under clearly specified circumstances. The Committee considered that the mhGAP guidelines provide an important framework for supporting and increasing health system capacity to ensure the appropriate use of methylphenidate in children and adolescents. The Committee noted that the guidelines highlight, amongst other things, the limited evidence on efficacy and tolerability of methylphenidate beyond 12 weeks of treatment, that specialist reassessment of the patient's ADHD management plan should occur at least once per year, and the need for methylphenidate treatment to be offered only in the context of a comprehensive management plan. The Committee expressed concern regarding the current capacity of some health systems to ensure appropriate diagnosis, treatment (both pharmacological and non-pharmacological) and management of ADHD, particularly in low- and middle-income settings, where reported rates of mental health workers for children and adolescents are low and among whom specialist psychiatrists are a small minority.

## Section 24.1 Medicines used in psychotic disorders

The Expert Committee recommended the inclusion of aripiprazole once-monthly long-acting injection on the core list of the EML for the treatment of adults with schizophrenia based on acceptable evidence for similar efficacy and a potentially lower risk of metabolic adverse effects compared with other long-acting injectable antipsychotics currently included on the EML (i.e. paliperidone, risperidone). Listing is recommended for aripiprazole as a therapeutic alternative under the square box listing for paliperidone once-monthly long-acting injection.

## Section 24.2 Medicines used in mood disorders

The Expert Committee did not recommend the inclusion of brexpiprazole on the EML for adjunctive treatment of major depressive disorder in adults based on evidence from short-term studies showing only modest incremental benefits compared to placebo, and noting other atypical antipsychotics and lithium had similar or superior gains. The Committee noted that the EML does not currently include any medicines for adjunctive treatment of major depressive disorder and advised that any future application should present a comprehensive evaluation of the evidence for all relevant treatment options for this indication, in preference to an application that focuses on a single medicine.

### Section 24.5.2 Medicines for nicotine use disorders

The Expert Committee recommended the inclusion of cytisine (INN cytisinicline) on the core list of the EML for use as an aid to stopping smoking and tobacco use, based on a favourable balance of benefits and harms, in an area of major public health need. The Committee considered that the availability of different smoking cessation treatments serves to provide valuable options and choice for patients and clinicians, could facilitate market competition, reduce costs and improve access to effective smoking and tobacco cessation treatments for national health systems.

### ***Section 27: Vitamins and minerals***

The Expert Committee recommended deletion of iodine capsules from the EML and EMLc for prevention and treatment of iodine deficiency, noting that the formulation is no longer marketed or used in iodine supplementation programmes in countries.

## ***Other matters considered by the Expert Committee***

### **Age-appropriateness of formulations of essential medicines for children**

In consideration of the review of the age-appropriateness of formulations of medicines on the EMLc, the Expert Committee recommended changes to the EMLc for addition of new, age-appropriate formulations and strengths of existing essential medicines, deletion of unavailable or age-inappropriate formulations and strengths and other listing modifications as proposed in the review. Corresponding changes to the EML were made for consistency, as appropriate. All changes are reported in Tables 1, 2 and 3. The Committee also noted the proposals made in the review for consideration by the Global Accelerator for Paediatric Formulations (GAP-f) network, where gaps in the availability of age-appropriate formulations of essential medicines for children exist.

### **Revision of AWaRe (Access, Watch, Reserve) definitions, classification and reclassification of antibiotics**

The Expert Committee considered the applications proposing:

- a revision of the current AWaRe definitions for AWaRe classification and criteria for inclusion of AWaRe antibiotics on the Model Lists;
- classification of antibiotics not currently included in the WHO AWaRe classification database; and
- reclassification of cefoperazone + sulbactam from ‘not recommended’ to the AWaRe Watch group.

The Committee acknowledged the growing importance and adoption of AWaRe as a global tool for antibiotic selection, stewardship, surveillance and policy development, and its strong relationship with the WHO Model Lists of Essential Medicines.

The Committee noted that the definitions of AWaRe groups were developed between 2017 and 2019, reflecting the evaluation of antibiotics that were recommended for inclusion in the Model Lists. The Committee accepted that the current definition of Reserve antibiotics – intended for use as “last resort” options in life-threatening infections due to multidrug-resistant bacteria – should adapt to the needs of changing public health policies and priorities. The Committee considered that there are several aspects of the current definition that could evolve, expand, or be modified. These include expanding guidance on the level of evidence required to demonstrate “proven activity” against WHO priority pathogens, clarifying whether the relationship between the Reserve definition and the WHO Bacterial Priority Pathogens List is binding, and developing standardized definitions for multidrug resistance. The Committee also recognized the limited clinical evidence available to guide empiric use of Reserve antibiotics, particularly in low-resource settings. The Committee determined that there was also a need to consider additional dimensions in the selection of Reserve antibiotics for the Model Lists, including innovation criteria, access challenges and strategies to increase access and the role of real-world evidence.

The Committee noted a growing debate about how the definition of Reserve antibiotics should evolve. The Committee also noted the comments from the WHO Technical Advisory Group on AWaRe (TAG-AWaRe), calling for a comprehensive reassessment of all AWaRe categories, with the establishment of clear criteria for AWaRe classification groups. This reassessment should consider dimensions including efficacy, safety, impact on the emergence and spread of resistance, impact on the microbiome, and should link to other WHO products, including (but not limited to) the Bacterial Priority Pathogens Lists, the Medically Important Antimicrobial List and the report of antibacterial agents in clinical and preclinical development.

Considering the complexity of the challenges posed in refining definitions for all AWaRe categories, the Expert Committee requested the WHO Secretariat to coordinate a structured, inclusive review process, involving broad stakeholder consultation and a review of available evidence, with the aim of strengthening the AWaRe framework as a cornerstone of global antimicrobial stewardship and access policy. The recommendations of this review should be

submitted for consideration by the 2027 Expert Committee. Therefore, the Committee did not recommend any changes to the current AWaRe definitions.

Consequently, until such time as the definitions of AWaRe categories are revised, the Committee did not recommend any change to the current classification of cefoperazone + sulbactam. The Committee also noted that numerous other beta-lactam + beta-lactamase inhibitor combinations are also currently classified as ‘not recommended’ and considered that reclassifying only one such combination at this time would introduce inconsistency.

In consideration of the request to classify antibiotics not currently included in the AWaRe classification, the Expert Committee accepted the rationale presented in the application and recommended the antibiotics identified in the application be classified as Access, Watch, Reserve, not recommended, or remain unclassified, as proposed (Table 5).

### Commemoration of the 50th anniversary of the WHO Model List of Essential Medicines in 2027

The Expert Committee noted the report of the meeting on revising the procedures for updating the Model Lists of Essential Medicines, convened by WHO at its headquarters in Geneva in November 2023 (6). The Committee welcomed and endorsed all key messages that emerged during the meeting, namely:

- The importance of strengthening alignment and integration of the EML with related WHO guidelines and products to reduce redundant efforts, mitigate contradicting messages and facilitate coordinated evidence-based policymaking. This involves harmonizing procedures, identifying and then addressing situations of potential discordance.
- The importance of improving dissemination strategies related to the selection of medicines, bringing out not only information about medicines that are listed but also those that have not been recommended for listing. Rejections can be informative, as medicines rejected for addition to the EML might have drawbacks in terms of efficacy and safety, equity, feasibility, cost effectiveness, or access, with implications for national EMLs.
- The value of developing a structured process for prioritizing disease areas and medicines for EML applications to ensure an orderly, proactive approach, particularly in overlooked disease areas. Coordinated applications could be developed by leveraging partnerships with professional societies.
- The need to improve the extent and quality of information on price, cost and cost-effectiveness considered in EML selection by, among other strategies, incorporating data on pricing of medicines (including generics and biosimilars and their availability) and financial impact on patients (in terms of out-of-pocket expenditure).
- Modernizing and investigating resources that can aid the selection process. Electronic support systems such as digital submission form, artificial intelligence to increase efficiency and precision in administrative processes and increased human resources to enable the Secretariat to improve quality of the selection process were proposed.
- The need to ensure sustained progress on improving access requires addressing systemic barriers beyond medicine selection. It is crucial to study the accessibility of certain medicines once they have been listed to see if their essential medicine status can contribute to improved access, understanding the role of pricing opacity, production barriers limiting generic availability, inconsistent supply and delivery and inappropriate marketing influences.

The Committee considered that many of these recommendations relate directly to activities that address WHO’s mandate to assist Member States in advising on the selection and procurement of essential medicines that offer the best value health outcomes.

The Committee highlighted that the 50th anniversary of the Essential Medicines List (EML) presents a valuable opportunity for Member States to actively participate in commemorating the WHO EML and recognizing its impact on national policies and essential medicines lists. The Committee considered that updates of national lists in 2027 should be a central activity of the commemorations. These updates should not be aimed solely at adding new medicines to national lists but should also aim to achieve greater alignment between national EMLs and national reimbursement

lists, with transparent reporting of what is made available as part of universal health coverage policies. Consideration should be given to strengthening national EMLs by developing lists that specify the indications for which medicines are considered essential.

Other important elements of the commemoration updates include:

- transparent inclusion of medicines and age-appropriate formulations for children. Disappointingly, less than 15% of countries prioritize medicines and formulations for children in their national lists (7);
- clear reporting of priority formulations to guide supply and procurement, to limit fragmentation;
- optimizing interpretation and implementation of therapeutic alternative guidance (square box listings) in the WHO EML.

The 50th anniversary of the WHO Model List of Essential Medicines is a key opportunity for Member States to reaffirm the fundamental right to access essential medicines. By participating in the celebration, updating national tools, promoting public engagement and strengthening policies, countries can help ensure that essential medicines remain a living, evolving and effective instrument for health equity.

### Improving the quality of EML applications

The Expert Committee noted a general improvement in the quality of applications under evaluation at the current meeting, although considerable variability remained between applications.

The Committee expressed appreciation for the open and participatory nature of the application process, where applications may be submitted by individuals, institutions, public and private sector organizations and other stakeholders. However, in many cases, applications are developed on an ad hoc and voluntary basis and sometimes lack sufficient scientific rigour (e.g. management of inherent biases), fail to present benefits across different patient subgroups and often lack comprehensive analyses of feasibility, cost-effectiveness and budget impact in different settings. The Committee considered that applications for the EML would benefit from following a process similar to that of WHO's guideline development processes, which should also facilitate alignment of the recommendations in these two WHO tools, and orient selection and appropriate use of medicines recommended by WHO.

The Committee commended two applications for exemplifying a high standard of scrutiny and comprehensive evaluation of multiple therapeutic options within specific disease areas: the 2023 application proposing essential medicines for the treatment of multiple sclerosis (8) and the 2025 application proposing PD-1/PD-L1 immune checkpoint inhibitors for various cancers (9). These applications were the result of a coordinated effort by multiple entities including academic groups, scientific societies, methodological supporting teams and close connection with the EML Secretariat. Notable strengths were the use of a comprehensive, disease-focused strategy with clear prioritization criteria, rather than a narrower focus on individual medicines, and the systematic use of GRADE Evidence to Decision (EtD) tables to summarize the findings.

The Committee highlighted that the adoption of guiding decision-making frameworks to suit EML requirements, particularly their capacity to clarify how the magnitude of benefits varied across different therapeutic options and patient subgroups, was highly valuable in facilitating the Committee's decision-making. The Committee appreciated the efforts of the WHO Secretariat to better align the EML selection process with established guideline development tools, such as the GRADE EtD framework, to enhance transparency and evidence quality assessment.

The Committee advised that the incorporation of EtD tables in EML applications going forward was highly desirable. However, the Committee recognized that it would take time for a methodological and reporting approach to become an integral part of the application process, and that it may preclude or discourage applicants without the necessary expertise or capacity to develop EtD tables from participating in the EML process, an outcome that should be avoided. The Committee considered that a possible way to mitigate this risk would be to develop a structured process for setting priorities for EML applications where broad applicant participation can be assured.

Finally, the Committee observed that the number of applications for newer, patented, highly-priced medicines has grown considerably over time. The Committee considered that the voluntary nature of the current application process has the potential to give rise to gaps in selection and coverage for other older (but no less important) medicines for which there may be less commercial interest. The Committee recommended WHO develop a strategy guided by priority needs to complement the existing application process, to ensure applications for essential medicine candidates are submitted, regardless of their stage in the medicine life cycle.

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<sup>1</sup> All references in the document were last accessed on 25 June 2025.

**Table 1: Recommended changes on the 2025 EML**

EML – New medicines added	
Medicine	Indication
Baclofen	Spasticity in cerebral palsy
Blinatumomab	CD-19 positive, B-lineage acute lymphoblastic leukaemia
Coagulation factor VIII (recombinant)	Haemophilia A
Coagulation factor IX (recombinant)	Haemophilia B
Cytisine	Smoking and tobacco cessation
Ebola vaccine	Ebola virus disease
Elexacaftor + tezacaftor + ivacaftor	Cystic fibrosis
Emicizumab	Haemophilia A
Glycerol (cream, 15%-20%)	Atopic dermatitis
Hepatitis E vaccine	Hepatitis E
Insulin, analogue rapid-acting	Type 1 and type 2 diabetes
Ivacaftor	Cystic fibrosis
Mpox vaccine	Mpox
Pembrolizumab (with atezolizumab and cemiplimab as therapeutic alternatives)	Metastatic cervical cancer, metastatic colorectal cancer, metastatic non-small cell lung cancer
Perindopril + amlodipine + indapamide (with within-class medicines as therapeutic alternatives)	Hypertension
Respiratory syncytial virus vaccine	Maternal RSV vaccination
Semaglutide (with dulaglutide, liraglutide and tirzepatide as therapeutic alternatives)	Type 2 diabetes in people with established cardiovascular or chronic kidney disease, and with obesity
Sunscreen, broad-spectrum	Prevention of skin cancer in persons with albinism
Ustekinumab	Moderate to severe psoriasis
Valsartan + amlodipine + hydrochlorothiazide (with within-class medicines as therapeutic alternatives)	Hypertension
EML - New indications	
Medicine	Indication
Adalimumab (with certolizumab pegol, etanercept and infliximab as therapeutic alternatives)	Moderate to severe psoriasis
Fexinidazole	Human African trypanosomiasis due to <i>Trypanosoma brucei rhodesiense</i> infection
Ibuprofen	Acute migraine
Prednisolone	Adrenal insufficiency, cluster headache
Sumatriptan (sub-cutaneous formulation)	Cluster headache
Urea (cream 5%)	Atopic dermatitis
Verapamil	Cluster headache

<b>EML - New formulation/strength</b>	
<b>Medicine</b>	<b>Formulation/strength</b>
Acetylsalicylic acid	Suppository: 300 mg Tablet (dispersible): 75 mg, 300 mg, 500 mg.
Aciclovir	Solution for infusion: 25 mg/mL (as sodium) in vial
Aripiprazole	Injection (prolonged-release): 300 mg; 400 mg as powder and solvent for suspension (as therapeutic alternative to paliperidone prolonged-release injection)
Artemether	Oily injection: 20 mg/mL, 40 mg/mL in 1 mL ampoule
Artesunate	Powder for injection: 30 mg; 60 mg, 120 mg in vial
Artesunate – sulfadoxine + pyrimethamine	Co-packaged scored tablets: artesunate 50 mg [3] and sulfadoxine + pyrimethamine 500 mg + 25 mg [1] (Section 6.5.3.1)
Budesonide	Powder for inhalation: 100 micrograms per actuation, 200 micrograms per actuation in dry powder inhaler  Suspension for inhalation: 100 micrograms per actuation, 200 micrograms per actuation in pressurized metered-dose inhaler.
Charcoal, activated	Granules for oral suspension: 50 g
Dihydroartemisinin + piperaquine	Tablet: 60 mg + 480 mg (phosphate), 80 mg + 640 mg (phosphate)
Dimercaprol	Injection in oil: 100 mg/mL in 3 mL ampoule
Insulin, analogue long-acting	Injection solution: 100 IU/mL in 10 mL vial
Mesna	Injection: 100 mg/mL in 2 mL ampoule
Midazolam	Solution for oromucosal administration: 5 mg/mL in 0.5 mL, 1 mL, 1.5 mL 3 mL pre-filled syringe; 10 mg/mL in 0.25 mL, 0.5 mL, 0.75 mL, 1 mL pre-filled syringe (Section 2.3)
Omeprazole	Powder for oral liquid: 1 mg/mL, 4 mg/mL
Phytomenadione	Injection: 2 mg/0.2 mL; 10 mg/mL in ampoule (mixed micelle solution).  Tablet: 5 mg
Pyridostigmine	Injection: 5 mg/mL (bromide) in ampoule or vial
Retinol	Injection (water-miscible): 50 000 IU/mL (as palmitate) in 2 mL ampoule or vial
Salbutamol	Injection 500 micrograms/mL in 1 mL, 5 mL ampoule  Solution for inhalation: 100 micrograms (as sulfate) per actuation in pressurized metered dose inhaler; 2.5 mg/2.5 mL, 5 mg/2.5 mL (as sulfate) in 2.5 mL single-dose ampoules for use in nebulizers; 5 mg/mL (as sulfate) in multi-dose bottle for use in nebulizers
Warfarin	Tablet (scored): 3 mg (sodium)
<b>EML – Medicines/formulations deleted</b>	
<b>Medicine</b>	<b>Formulation/strength</b>
Acetylcysteine	Oral liquid: 10%, 20%
Acetylsalicylic acid	Suppository: 50 mg
Amodiaquine	Tablet: 153 mg or 200 mg (as hydrochloride)
Artemether	Oily injection: 80 mg/mL

Artesunate	Injection: ampoules containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution  Rectal dosage form: 50 mg, 200 mg capsules  Tablet: 50 mg
Budesonide	Inhalation (aerosol): 100 micrograms per dose, 200 micrograms per dose
Charcoal, activated	Powder
Chloroquine	Tablet: 100 mg (as phosphate or sulfate)
Coagulation factor IX complex (plasma-derived)	Removed as a therapeutic alternative to Coagulation factor IX (plasma-derived)
Cryoprecipitate (pathogen-reduced, non-pathogen reduced)	Removed for indications of haemophilia A, von Willebrand disease
Halothane	Inhalational anaesthetic
Iodine	Capsule 190 mg  Iodized oil: 0.5 mL (240 mg iodine) in ampoule (oral or injectable), 0.57 mL (308 mg iodine) in dispenser bottle.
Mefloquine	Tablet: 250 mg (as hydrochloride) (Section 6.5.3.1)
Methimazole	Tablet: 20 mg
Omeprazole	Powder for oral liquid: 20 mg, 40 mg sachets
Phytomenadione	Tablet: 10 mg
Proguanil	Tablet: 100 mg (as hydrochloride)
Propranolol	Tablet: 20 mg (hydrochloride)
Pyridostigmine	Injection: 1 mg in 1 mL ampoule
Quinine	Tablet: 300 mg (sulfate) or 300 mg (bisulfate)
Retinol	Tablet (sugar-coated): 100 000 IU (as palmitate)  Water-miscible injection: 100 000 IU (as palmitate) in 2 mL ampoule
Ribavirin	All listed formulations and strengths for viral haemorrhagic fevers
Salbutamol	Injection: 50 micrograms/mL (as sulfate) in 5 mL ampoule  Metered dose inhaler (aerosol): 100 micrograms (as sulfate) per dose
Sulfadoxine + pyrimethamine	Tablet: 500 mg + 25 mg (Section 6.5.3.1)  Tablet: 250 mg + 12.5 mg (Section 6.5.3.2)
Suxamethonium	Powder for injection: (chloride) in vial

## Table 2: Recommended changes on the 2025 EMLc

EMLc – New medicines added	
Medicine	Indication
Abacavir + dolutegravir + lamivudine	HIV
Baclofen	Spasticity in cerebral palsy
Blinatumomab	CD-19 positive, B-lineage acute lymphoblastic leukaemia
Coagulation factor VIII (recombinant)	Haemophilia A
Coagulation factor IX (recombinant)	Haemophilia B
Ebola vaccine	Ebola virus disease
Elexacaftor + tezacaftor + ivacaftor	Cystic fibrosis
Emicizumab	Haemophilia A
Glycerol (cream, 15%-20%)	Atopic dermatitis
Insulin, analogue rapid-acting	Type 1 and type 2 diabetes
Ivacaftor	Cystic fibrosis
Malaria vaccine	Malaria
Mpox vaccine	Mpox
Sunscreen, broad-spectrum	Prevention of skin cancer in persons with albinism
Ustekinumab	Moderate to severe psoriasis
EMLc - New indications	
Medicine	Indication
Adalimumab (with certolizumab pegol, etanercept and infliximab as therapeutic alternatives)	Moderate to severe psoriasis
Fexinidazole	Human African trypanosomiasis due to Trypanosoma brucei rhodesiense infection
Prednisolone	Adrenal insufficiency, infantile spasm
Urea (cream 5%)	Atopic dermatitis
EMLc - New formulation/strength	
Medicine	Formulation/strength
Acetylsalicylic acid	Suppository: 300 mg Tablet (dispersible): 75 mg, 300 mg, 500 mg.
Aciclovir	Solution for infusion: 25 mg/mL (as sodium) in vial
Allopurinol	Powder for injection: 500 mg (as sodium)
Amitriptyline	Oral liquid: 25 mg/5 mL (Section 2.3)
Amodiaquine – sulfadoxine + pyrimethamine	Co-packaged dispersible tablets: amodiaquine 75 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 250 mg + 12.5 mg [1]; amodiaquine 150 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 500 mg + 25 mg [1]
Amoxicillin + clavulanic acid	Tablet (dispersible): 250 mg (as trihydrate) + 62.5 mg (as potassium salt) (Section 6.2.5)
Artemether	Oily injection: 20 mg/mL, 40 mg/mL in 1 mL ampoule

Artesunate	Powder for injection: 30 mg; 60 mg, 120 mg in vial
Artesunate – sulfadoxine + pyrimethamine	Co-packaged scored tablets: artesunate 50 mg [3] and sulfadoxine + pyrimethamine 500 mg + 25 mg [1]
Atropine	Injection: 400 micrograms/mL (sulfate) in 1 mL ampoule or vial
Budesonide	Nasal spray: 30 micrograms per actuation, 64 micrograms per actuation Powder for inhalation: 100 micrograms per actuation, 200 micrograms per actuation in dry powder inhaler Suspension for inhalation: 100 micrograms per actuation, 200 micrograms per actuation in pressurized metered-dose inhaler.
Charcoal, activated	Granules for oral suspension: 50 g
Desmopressin	Nasal spray: 150 micrograms (acetate) per actuation
Dexamethasone	Oral liquid: 0.5 mg/5 mL (as sodium phosphate) Tablet: 0.5 mg; 0.75 mg; 1.5 mg; 5 mg (as dexamethasone base) (Sections 2.3, 3, 8.2.4 and 17.2)
Diazepam	Tablet (scored): 2 mg (Section 2.3)
Dihydroartemisinin + piperaquine	Tablet: 60 mg + 480 mg (phosphate), 80 mg + 640 mg (phosphate) Tablet (dispersible): 20 mg + 160 mg (phosphate), 40 mg + 320 mg (phosphate)
Dimercaprol	Injection in oil: 100 mg/mL in 3 mL ampoule
Docusate sodium	Oral liquid: 12.5 mg/5 mL
Ferrous salts	Oral liquid: equivalent to 9 mg/mL elemental iron
Fludrocortisone	Oral liquid: 100 micrograms/mL (acetate)
Folic acid	Oral liquid: 1 mg/mL
Hydrochlorothiazide	Solid oral dosage form: 12.5 mg
Hydrocortisone	Granules: 0.5 mg, 1 mg, 2 mg, 5 mg in capsule
Insulin, analogue long-acting	Injection solution: 100 IU/mL in 10 mL vial
Ketamine	Injection: 10 mg/mL (as hydrochloride) in vial
Lidocaine	Injection: 0.5% (hydrochloride)
Loratadine	Tablet (chewable): 5 mg, 10 mg
Mesna	Injection: 100 mg/mL in 2 mL ampoule
Methylprednisolone	Powder for injection: 125 mg (as sodium succinate) in vial
Midazolam	Solution for oromucosal administration: 5 mg/mL in 0.5 mL, 1 mL, 1.5 mL 3 mL pre-filled syringe; 10 mg/mL in 0.25 mL, 0.5 mL, 0.75 mL, 1 mL pre-filled syringe (Section 2.3)
Morphine	Injection: 1 mg/mL; 2 mg/mL (morphine hydrochloride or morphine sulfate) in 1 mL vial (Section 1.3, Section 2.2) Oral liquid: 5 mg/5 mL (morphine hydrochloride or morphine sulfate) (Section 2.2) Solid oral dosage form (slow-release): 5 mg (Section 2.2)
Omeprazole	Powder for oral liquid: 1 mg/mL, 4 mg/mL
Ondansetron	Injection: 2 mg/mL in 4 mL ampoule (as hydrochloride dihydrate) (Section 2.3, Section 17.2)
Oseltamivir	Powder for oral liquid: 6 mg/mL (as phosphate)

Phytomenadione	Injection, mixed micelle solution: 2 mg/0.2 mL; 10 mg/mL in ampoule Injection: 1 mg/0.5 mL Tablet: 5 mg
Propranolol	Tablet: 10 mg (hydrochloride)
Pyridostigmine	Injection: 5 mg/mL (bromide) in ampoule or vial
Pyridoxine	Tablet: 10 mg
Quinine	Solution for infusion: 60 mg/mL (hydrochloride) in 2 mL ampoule
Retinol	Injection (water-miscible): 50 000 IU/mL (as palmitate) in 2 mL ampoule or vial
Rifapentine	Tablet (dispersible, scored): 150 mg
Salbutamol	Injection 500 micrograms/mL in 1 mL, 5 mL ampoule  Solution for inhalation: 100 micrograms (as sulfate) per actuation in pressurized metered dose inhaler; 2.5 mg/2.5 mL, 5 mg/2.5 mL (as sulfate) in 2.5 mL single-dose ampoules for use in nebulizers; 5 mg/mL (as sulfate) in multi-dose bottle for use in nebulizers
Sofosbuvir	Granules: 200 mg in sachet
Sofosbuvir + velpatasvir	Granules: 150 mg + 37.5 mg; 200 mg + 50 mg in sachet
Spironolactone	Tablet 12.5 mg
Sulfadoxine + pyrimethamine	Tablet (dispersible): 250 mg + 12.5 mg
Thiamine	Injection: 50 mg/mL (hydrochloride) in ampoule or vial
Warfarin	Tablet (scored): 3 mg (sodium)
Xylometazoline	Nasal drops: 0.05%

**EMLc – Medicines/formulations deleted**

Medicine	Formulation/strength
Acetylcysteine	Oral liquid: 10%, 20%
Acetylsalicylic acid	Suppository: 50 mg
Amodiaquine	Tablet: 153 mg or 200 mg (as hydrochloride)
Aprepitant	Capsule: 80 mg, 125 mg, 165 mg
Artemether	Oily injection: 80 mg/mL
Artesunate	Injection: ampoules containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution  Rectal dosage form: 50 mg, 200 mg capsules  Tablet: 50 mg
Budesonide	Inhalation (aerosol): 100 micrograms per dose, 200 micrograms per dose  Nasal spray: 100 micrograms per dose
Charcoal, activated	Powder
Chloroquine	Tablet: 100 mg (as phosphate or sulfate)
Coagulation factor IX complex (plasma-derived)	Removed as a therapeutic alternative to Coagulation factor IX (plasma-derived)
Cryoprecipitate (pathogen-reduced, non-pathogen reduced)	Removed for indications of haemophilia A, von Willebrand disease
Desmopressin	Nasal spray: 10 micrograms (as acetate) per dose

Diazepam (Section 2.3)	Injection: 5 mg/mL
Docusate sodium	Capsule: 100 mg
Halothane	Inhalation
Iodine	Capsule 190 mg  Iodized oil: 0.5 mL (240 mg iodine) in ampoule (oral or injectable), 0.57 mL (308 mg iodine) in dispenser bottle.
Mefloquine	Tablet: 250 mg (as hydrochloride)
Methadone	Tablet: 10 mg (hydrochloride)  Oral liquid: 10 mg/5 mL (hydrochloride)  Concentrate for oral liquid: 10 mg/mL (hydrochloride)
Methimazole	Tablet: 20 mg
Methylprednisolone	Injection: 80 mg/mL (Section 8.2.4)
Midazolam	Tablet: 7.5 mg; 15 mg
Morphine	Granules (slow release; to mix with water): 200 mg (morphine sulfate)  Tablet (slow release): 200 mg (morphine hydrochloride or morphine sulfate)
Neostigmine	Tablet: 15 mg (bromide)
Omeprazole	Powder for oral liquid: 20 mg, 40 mg sachets
Phytomenadione	Tablet: 10 mg
Proguanil	Tablet: 100 mg (as hydrochloride)
Propranolol	Tablet: 20 mg (hydrochloride)
Pyridostigmine	Injection: 1 mg in 1 mL ampoule
Quinine	Tablet: 300 mg (sulfate) or 300 mg (bisulfate)
Retinol	Tablet (sugar-coated): 100 000 IU (as palmitate)  Water-miscible injection: 100 000 IU (as palmitate) in 2 mL ampoule
Ribavirin	All listed formulations and strengths for viral haemorrhagic fevers
Salbutamol	Injection: 50 micrograms/mL (as sulfate) in 5 mL ampoule  Metered dose inhaler (aerosol): 100 micrograms (as sulfate) per dose
Spironolactone	Oral liquid: 5 mg/5 mL, 10 mg/5 mL
Sulfadoxine + pyrimethamine	Tablet: 500 mg + 25 mg (Section 6.5.3.1)  Tablet: 250 mg + 12.5 mg (Section 6.5.3.2)
Suxamethonium	Powder for injection: (chloride) in vial

**Table 3: Other changes on the 2025 EML and EMLc**

Other changes to listings – EML and/or EMLc		
Acetic acid	Modify formulation description to better describe available dosage forms.	EMLc
Acetylsalicylic acid	Modify formulation description to include a strength range for tablets from 75 mg to 500 mg.	EMLc
Aciclovir	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Arpraziquantel	Addition of arpraziquantel 150 mg dispersible tablets to the EMLc as a therapeutic alternative to praziquantel for treatment of schistosomiasis.	EMLc
Artemether + lumefantrine	Remove note.	EML & EMLc
Artesunate	Amend note.	EML & EMLc
Artesunate + amodiaquine	Remove note.	EML & EMLc
Artesunate + mefloquine	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Artesunate + pyronaridine	Modify formulation descriptions to better describe available dosage forms. Remove note.	EML & EMLc
Atropine	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Budesonide	Remove flunisolide as a therapeutic alternative.	EML & EMLc
Bupivacaine	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Calcium gluconate	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Charcoal, activated	Add note stating “alternative formulations of activated charcoal may be used in granules are not available”	EML & EMLc
Chloroquine	Modify formulation descriptions to better describe available dosage forms. Listing of chloroquine in malaria chemoprevention section transferred to new sub-section for malaria chemoprophylaxis in travellers.	EML & EMLc
Cyclizine	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Daclatasvir	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Daclatasvir + sofosbuvir	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Dexamethasone	Modify formulation description to reflect amount of dexamethasone in terms of salt or base.	EML & EMLc
Dihydroartemisinin + piperaquine phosphate	Modify formulation descriptions to better describe available dosage forms. Remove note.	EML & EMLc
Diloxanide	Proposed for deletion in 2027.	EML & EMLc
Doxycycline	Listings of doxycycline in malaria treatment and chemoprevention sections transferred to new sub-section for malaria chemoprophylaxis in travellers.	EML & EMLc
Eletriptan	Addition of eletriptan to the EML as a therapeutic alternative to sumatriptan for acute migraine.	EML
Ferrous salts	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Fomepizole	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Glucagon	Modify formulation description to better describe available dosage forms.	EML & EMLc
Heparin sodium	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Hydroxocobalamin	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Hypochlorous acid	Separate listing for hypochlorous acid solution as an environmental disinfectant	EML & EMLc

Insulin injection (soluble)	Modify formulation descriptions to better describe available dosage forms. Update medicine description to better differentiate between human and analogue insulins.	EML & EMLc
Intermediate-acting insulin	Modify formulation descriptions to better describe available dosage forms. Update medicine description to better differentiate between human and analogue insulins.	EML & EMLc
Intraperitoneal dialysis solution	Modify formulation description to better describe available dosage forms.	EML & EMLc
Iodine	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Isoniazid	Modify formulation descriptions to better describe available dosage forms.	EMLc
Ketamine	Remove specification of vial size.	EML & EMLc
Lactulose	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Levetiracetam	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Lidocaine	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Lidocaine + epinephrine (adrenaline)	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Linezolid	Modify formulation descriptions to better describe available dosage forms.	EMLc
Long-acting insulin analogues	Modify formulation descriptions to better describe available dosage forms. Update medicine description to better differentiate between human and analogue insulins.	EML & EMLc
Lugol's solution	Modify formulation descriptions to better describe available dosage forms. Update medicine description to reflect active ingredients.	EML & EMLc
Mannitol	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Medicines for multidrug-resistant tuberculosis	Transferred from complementary to core list	EML & EMLc
Mefloquine	Listings of mefloquine in malaria chemoprevention section transferred to new sub-section for malaria chemoprophylaxis in travellers.	EML & EMLc
Mesna	Add note to indicate injection solution may also be used for oral administration.	EML & EMLc
Methadone	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Metoclopramide	Modify formulation description to better describe available dosage forms. Remove note.	EML & EMLc
Midazolam	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Mifepristone - misoprostol	Transfer listing to the new sub-section for medicines for medical abortion.	EML
Misoprostol	Transfer listing for the indication of management of incomplete abortion to the new sub-section for medicines for medical abortion.	EML
Morphine	Modify formulation descriptions to better describe available dosage forms. Replace strength ranges for slow-release granules and solid oral dosage forms with specific strengths.	EML & EMLc
Moxidectin	Addition of moxidectin to the EML and EMLc as a therapeutic alternative to ivermectin for treatment of onchocerciasis and lymphatic filariasis	EML & EMLc
Naproxen	Addition of naproxen to the EML as a therapeutic alternative to ibuprofen for acute migraine.	EML
Nivolumab / pembrolizumab	Reverse the current listing for malignant melanoma to make pembrolizumab the representative medicine and nivolumab a therapeutic alternative.	EML
Ondansetron	Modify formulation description to better describe available dosage forms.	EML & EMLc
Oral rehydration salts	Modify formulation description to better describe available dosage forms.	EML & EMLc

Oral rehydration salts – zinc sulfate	Modify formulation description to better describe available dosage forms.	EML & EMLc
Pancreatic enzymes	Modify formulation description to better describe available dosage forms.	EML & EMLc
Phenobarbital	Replace strength range for tablet formulation with specific strengths (15 mg, 30 mg, 60 mg, 100 mg)	EML & EMLc
Potassium iodide	Modify formulation description to better describe available dosage forms.	EML & EMLc
Primaquine	Amend note.	EML & EMLc
Prostaglandin E1/ E2	Update medicine descriptions to reflect active ingredients by international non-proprietary names (alprostadil / dinoprostone).	EML & EMLc
Protamine sulfate	Modify formulation description to better describe available dosage forms.	EML & EMLc
Pyridostigmine	Modify formulation description to better describe available dosage forms.	EML & EMLc
Quinine	Modify formulation descriptions to better describe available dosage forms. Amend note.	EML & EMLc
Rasburicase	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Retinol	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Surfactant	Update medicine and formulation description to reflect active ingredients by international non-proprietary names (beractant, poractant alfa) and corresponding dosage forms.	EMLc
Valganciclovir	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Warfarin	Modify formulation descriptions to better describe available dosage forms. Specify acenocoumarol as a therapeutic alternative.	EML & EMLc
Xylometazoline	Remove note.	EMLc
Zanubrutinib	Addition of zanubrutinib to the EML as a therapeutic alternative to ibrutinib for treatment of relapsed/refractory chronic lymphocytic leukaemia/small lymphocytic lymphoma.	EML
Zinc sulfate	Modify formulation description to better describe available dosage forms.	EML & EMLc

**Changes to sections and sub-sections**

	2023	2025
Section 5	Medicines for diseases of the nervous system	Medicines for neurological disorders
Section 5.1	Antiseizure medicines	<p>Medicines for central nervous system disorders</p> <p>5.1.1 Antiseizure medicines</p> <p>5.1.2 Medicines for multiple sclerosis</p> <p>5.1.3 Medicines for parkinsonism</p> <p>5.1.4 Medicines for cerebral palsy</p> <p>5.1.5 Medicines for headache disorders</p> <ul style="list-style-type: none"> <li>– 5.1.5.1 Medicines for acute migraine attacks</li> <li>– 5.1.5.2 Medicines for migraine prophylaxis</li> <li>– 5.1.5.3 Medicines for cluster headache</li> </ul> <p>5.1.6 Medicines for central nervous system infections</p> <ul style="list-style-type: none"> <li>– 5.1.6.1 Medicines for bacterial central nervous system infections</li> <li>– 5.1.6.2 Medicines for viral central nervous system infections</li> </ul>

Section 5.2	Medicines for multiple sclerosis	Medicines for peripheral nervous system disorders 5.2.1 Medicines for Guillain-Barre syndrome 5.2.2 Medicines for myasthenia gravis
Section 5.3	Medicines for parkinsonism	N/A
Section 6.5.3.3	N/A	Medicines for chemoprophylaxis in travellers
Section 7	Antimigraine medicines	Medicines for cystic fibrosis
Section 10.3	Other medicines for haemoglobinopathies	Medicines for haemoglobinopathies
Section 11	Blood products of human origin and plasma substitutes	Blood products, coagulation factors and plasma substitutes
Section 11.2	Plasma-derived medicines	Human immunoglobulins
Section 11.3	Plasma substitutes	Coagulation factors
Section 11.4	N/A	Plasma substitutes
Section 13.6	N/A	Moisturizers
Section 13.7	N/A	Sunscreens, broad-spectrum
Section 18.5.2	Oral hypoglycaemic agents	Hypoglycaemic agents
Section 22.4	Antioxytocics (tocolytics)	Medicines for medical abortion
Section 22.5	Other medicines administered to the mother	Antioxytocics (tocolytics)
Section 22.6	Medicines administered to the neonate	Other medicines administered to the mother
Section 22.7	N/A	Medicines administered to the neonate

**Table 4: Applications not recommended**

New medicines / indications	
Addition of brexpiprazole for adjunctive treatment of major depressive disorder	EML
Addition of temozolomide for high grade glioma, Ewing sarcoma, neuroblastoma	EMLc
Addition of erythropoiesis-stimulating agents for the new indication of chemotherapy-induced anaemia	EML & EMLc
Addition of methylphenidate for treatment of attention deficit hyperactivity disorder	EML & EMLc
Addition of pembrolizumab for treatment of metastatic: endometrial cancer, gastric or gastro-oesophageal junction adenocarcinoma, head and neck squamous cell carcinoma, oesophageal squamous cell carcinoma, renal cell carcinoma, triple-negative breast cancer.	EML
Addition of nivolumab and ipilimumab (as combination treatment) for treatment of metastatic: colorectal cancer, malignant melanoma, non-small cell lung cancer, oesophageal squamous cell carcinoma, renal cell carcinoma.	EML
Addition of nivolumab for treatment of metastatic: gastric or gastro-oesophageal junction adenocarcinoma, oesophageal squamous cell carcinoma.	EML
Addition of durvalumab for treatment of metastatic: biliary tract cancer, endometrial cancer, hepatocellular carcinoma.	EML
Addition of atezolizumab for treatment of metastatic hepatocellular carcinoma.	EML
Addition of durvalumab and tremelimumab (as combination treatment) for treatment of metastatic: hepatocellular carcinoma, non-small cell lung cancer.	EML
Addition of dostarlimab for treatment of metastatic endometrial cancer.	EML
Addition of tislelizumab for treatment of metastatic: non-small cell lung cancer, oesophageal squamous cell carcinoma.	EML
Addition of sugemalimab for treatment of metastatic non-small cell lung cancer.	EML
Addition of toripalimab for treatment of nasopharyngeal carcinoma, oesophageal squamous cell carcinoma.	EML
Addition of glucagon-like peptide 1 (GLP-1) receptor agonists for the treatment of obesity.	EML
Addition of amitriptyline for the new indication of migraine prophylaxis.	EML
Addition of bisoprolol for the new indication of migraine prophylaxis as a therapeutic alternative to propranolol	EML
Addition of fremanezumab for prophylaxis in high-frequency and chronic migraine.	EML
Addition of risdiplam for treatment of spinal muscular atrophy.	EML & EMLc
Addition of carbamazepine for the new indication of treatment of trigeminal neuralgia.	EML
Addition of imipenem + cilastatin + relebactam for treatment of multidrug-resistant infections.	EML
Addition of ciclopirox hydroxypropyl chitosan for treatment of onychomycosis.	EML
Addition of hypochlorous acid for the new indications of antisepsis and wound management.	EML & EMLc
Addition of panitumumab for the treatment of KRAS wild type metastatic colorectal cancer.	EML

**Table 5: Changes to the AWaRe classification of antibiotics**

Antibiotic	AWaRe classification
Azanidazole	Access
Amoxicillin + sulbactam	Access
Aztreonam + avibactam	Reserve
Benzathine phenoxymethylpenicillin	Access
Benzylpenicillin + procaine benzylpenicillin + benzathine-benzylpenicillin	Not recommended
Cefuroxime + metronidazole	Not recommended
Gepotidacin	Watch
Metronidazole + diloxanide	Not recommended
Metronidazole + furazolidone	Not recommended
Nalidixic acid (oral)	Watch
Nimorazole	Access
Norfloxacin + tinidazole	Not recommended
Ofloxacin + nitazoxanide	Not recommended
Ofloxacin + tinidazole	Not recommended
Paromomycin (oral)	Watch
Penicillins in combinations with other antibacterials	Not recommended
Pivampicillin + pivmecillinam	Not recommended
Propenidazole	Access
Satranidazole	Access
Sulfacarbamide + sulfadiazine + sulfadimidine	Not recommended
Sulfonamides in combinations with other antibacterials (excluding trimethoprim)	Not recommended
Tetracycline + chlortetracycline + demeclocycline	Not recommended
Tetracycline + nystatin	Not recommended
Ticarcillin + clavulanic acid	Watch
Tinidazole + diloxanide	Not recommended



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# World Health Organization Model List of Essential Medicines

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22nd List  
(2021)



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# WHO Model List of Essential Medicines – 22nd List (2021)

## Explanatory notes

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The **core list** presents a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

Where the [c] symbol is placed next to an individual medicine or strength of medicine on the core list it signifies that there is a specific indication for restricting its use to children.

The **complementary list** presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings.

Where the [c] symbol is placed next to an individual medicine or strength of medicine on the complementary list it signifies that the medicine(s) require(s) specialist diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training for their use in children.

The **square box symbol (□)** is intended to indicate therapeutic alternatives to the listed medicine that may be considered for selection in national essential medicines lists. Alternatives may be individual medicines, or multiple medicines within a pharmacological class or chemical subgroup, defined at the 4th level of the [Anatomical Therapeutic Chemical \(ATC\) classification](#), which have similar clinical effectiveness and safety. The listed medicine should be the example of the class or subgroup for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. Not all square box listings are applicable to medicine selection for children. A square box is not used to indicate alternative generic brands of the same small molecule medicines, nor alternative biosimilars of biological medicines. However, the selection and use of quality-assured generics and biosimilars of essential medicines at country level is recommended.

National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price.

The [a] symbol indicates that there is an age or weight restriction on use of the medicine; details for each medicine can be found in Table 1.1.

The presence of an entry on the Essential Medicines List carries no assurance as to pharmaceutical quality. It is the responsibility of the relevant national or regional drug regulatory authority to ensure that each product is of appropriate pharmaceutical quality (including stability) and that, when relevant, different products are interchangeable.

For recommendations and advice concerning all aspects of the quality assurance of medicines see the WHO website <https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/guidelines/quality-assurance>

Medicines and dosage forms are listed in alphabetical order within each section and the order of listing does not imply preference for one form over another. Standard treatment guidelines should be consulted for information on appropriate dosage forms.

The main terms used for dosage forms in the Essential Medicines List can be found in Table 1.2.

Definitions of many of these terms and pharmaceutical quality requirements applicable to the different categories are published in the current edition of *The International Pharmacopoeia*.  
<https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/pharmacopoeia>.

# WHO Model List of Essential Medicines – 22nd List (2021)

1. ANAESTHETICS, PREOPERATIVE MEDICINES AND MEDICAL GASES	
1.1 General anaesthetics and oxygen	
1.1.1 Inhalational medicines	
halothane	Inhalation.
isoflurane	Inhalation.
nitrous oxide	Inhalation.
oxygen	Inhalation (medical gas).
1.1.2 Injectable medicines	
ketamine	<b>Injection:</b> 50 mg/mL (as hydrochloride) in 10 mL vial.
<input type="checkbox"/> propofol Therapeutic alternatives: - thiopental	<b>Injection:</b> 10 mg/mL; 20 mg/mL.
1.2 Local anaesthetics	
<input type="checkbox"/> bupivacaine Therapeutic alternatives to be reviewed (2023)	<b>Injection:</b> 0.25%; 0.5% (hydrochloride) in vial. <b>Injection for spinal anaesthesia:</b> 0.5% (hydrochloride) in 4 mL ampoule to be mixed with 7.5% glucose solution.
<input type="checkbox"/> lidocaine Therapeutic alternatives to be reviewed (2023)	<b>Injection:</b> 1%; 2% (hydrochloride) in vial. <b>Injection for spinal anaesthesia:</b> 5% (hydrochloride) in 2 mL ampoule to be mixed with 7.5% glucose solution. <b>Topical forms:</b> 2% to 4% (hydrochloride).
lidocaine + epinephrine (adrenaline)	<b>Dental cartridge:</b> 2% (hydrochloride) + epinephrine 1:80 000. <b>Injection:</b> 1%; 2% (hydrochloride or sulfate) + epinephrine 1:200 000 in vial.
<i>Complementary List</i>	
ephedrine	<b>Injection:</b> 30 mg/mL (hydrochloride) in 1 mL ampoule. (For use in spinal anaesthesia during delivery, to prevent hypotension).
1.3 Preoperative medication and sedation for short-term procedures	
atropine	<b>Injection:</b> 1 mg (sulfate) in 1 mL ampoule.
<input type="checkbox"/> midazolam Therapeutic alternatives to be reviewed (2023)	<b>Injection:</b> 1 mg/mL. <b>Oral liquid:</b> 2 mg/mL [c]. <b>Tablet:</b> 7.5 mg; 15 mg.
morphine	<b>Injection:</b> 10 mg (sulfate or hydrochloride) in 1 mL ampoule.

# WHO Model List of Essential Medicines – 22nd List (2021)

## 1.4 Medical gases

oxygen*	<b>Inhalation</b> For use in the management of hypoxaemia. *No more than 30% oxygen should be used to initiate resuscitation of neonates less than or equal to 32 weeks of gestation.
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## 2. MEDICINES FOR PAIN AND PALLIATIVE CARE

### 2.1 Non-opioids and non-steroidal anti-inflammatory medicines (NSAIDs)

acetylsalicylic acid	<b>Suppository:</b> 50 mg to 150 mg. <b>Tablet:</b> 100 mg to 500 mg.
ibuprofen <small>a</small>	<b>Oral liquid:</b> 200 mg/5 mL. <b>Tablet:</b> 200 mg; 400 mg; 600 mg. <small>a</small> Not in children less than 3 months.
paracetamol*	<b>Oral liquid:</b> 120 mg/5 mL; 125 mg/5 mL. <b>Suppository:</b> 100 mg. <b>Tablet:</b> 100 mg to 500 mg. *Not recommended for anti-inflammatory use due to lack of proven benefit to that effect.

### 2.2 Opioid analgesics

codeine	<b>Tablet:</b> 30 mg (phosphate).
fentanyl*	<b>Transdermal patch:</b> 12 micrograms/hr; 25 micrograms/hr; 50 micrograms/hr; 75 micrograms/hr; 100 micrograms/hr *For the management of cancer pain
<input type="checkbox"/> morphine Therapeutic alternatives: - hydromorphone - oxycodone	<b>Granules (slow release; to mix with water):</b> 20 mg to 200 mg (morphine sulfate). <b>Injection:</b> 10 mg (morphine hydrochloride or morphine sulfate) in 1 mL ampoule. <b>Oral liquid:</b> <b>Tablet (slow release):</b> 10 mg to 200mg (morphine hydrochloride or morphine sulfate). <b>Tablet (immediate release):</b> 10 mg (morphine sulfate).

### Complementary list

methadone*	<b>Tablet:</b> 5 mg; 10 mg (hydrochloride) <b>Oral liquid:</b> 5 mg/5 mL; 10 mg/5 mL (hydrochloride) <b>Concentrate for oral liquid:</b> 5 mg/mL; 10 mg/mL (hydrochloride) *For the management of cancer pain.
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## WHO Model List of Essential Medicines – 22nd List (2021)

2.3 Medicines for other common symptoms in palliative care	
amitriptyline	Tablet: 10 mg; 25 mg; 75 mg.
cyclizine [c]	Injection: 50 mg/mL. Tablet: 50 mg.
dexamethasone	Injection: 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule. Oral liquid: 2 mg/5 mL. Tablet: 2 mg [c]; 4 mg.
diazepam	Injection: 5 mg/mL. Oral liquid: 2 mg/5 mL. Rectal solution: 2.5 mg; 5 mg; 10 mg. Tablet: 5 mg; 10 mg.
docusate sodium	Capsule: 100 mg. Oral liquid: 50 mg/5 mL.
fluoxetine [a]	Solid oral dosage form: 20 mg (as hydrochloride). [a] > 8 years.
haloperidol	Injection: 5 mg in 1 mL ampoule. Oral liquid: 2 mg/mL. Solid oral dosage form: 0.5 mg; 2mg; 5 mg.
hyoscine butylbromide	Injection: 20 mg/mL.
hyoscine hydrobromide [c]	Injection: 400 micrograms/mL; 600 micrograms/mL. Transdermal patches: 1 mg/72 hours.
lactulose [c]	Oral liquid: 3.1 to 3.7 g/5 mL.
loperamide	Solid oral dosage form: 2 mg.
metoclopramide	Injection: 5 mg/mL (hydrochloride) in 2 mL ampoule. Oral liquid: 5 mg/5 mL. Solid oral form: 10 mg (hydrochloride).
midazolam	Injection: 1 mg/mL; 5 mg/mL. Oral liquid: 2mg/mL [c]. Solid oral dosage form: 7.5 mg; 15 mg.
□ ondansetron [a] Therapeutic alternatives: - dolasetron - granisetron - palonosetron - tropisetron	Injection: 2 mg base/mL in 2 mL ampoule (as hydrochloride). Oral liquid: 4 mg base/5 mL. Solid oral dosage form: Eq 4 mg base; Eq 8 mg base. [a] > 1 month.
senna	Oral liquid: 7.5 mg/5 mL.

# WHO Model List of Essential Medicines – 22nd List (2021)

3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS	
dexamethasone	<b>Injection:</b> 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule.
epinephrine (adrenaline)	<b>Injection:</b> 1 mg/mL (as hydrochloride or hydrogen tartrate) in 1 mL ampoule.
hydrocortisone	<b>Powder for injection:</b> 100 mg (as sodium succinate) in vial.
<input type="checkbox"/> loratadine*	<b>Oral liquid:</b> 1 mg/mL. <b>Tablet:</b> 10 mg.  *There may be a role for sedating antihistamines for limited indications (EMLc).
<input type="checkbox"/> prednisolone	<b>Oral liquid:</b> 5 mg/mL [c]. <b>Tablet:</b> 5 mg; 25 mg.
4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS	
4.1 Non-specific	
charcoal, activated	<b>Powder.</b>
4.2 Specific	
acetylcysteine	<b>Injection:</b> 200 mg/mL in 10 mL ampoule. <b>Oral liquid:</b> 10% [c]; 20% [c].
atropine	<b>Injection:</b> 1 mg (sulfate) in 1 mL ampoule.
calcium gluconate	<b>Injection:</b> 100 mg/mL in 10 mL ampoule.
methylthioninium chloride (methylene blue)	<b>Injection:</b> 10 mg/mL in 10 mL ampoule.
naloxone	<b>Injection:</b> 400 micrograms (hydrochloride) in 1 mL ampoule.
penicillamine	<b>Solid oral dosage form:</b> 250 mg.
potassium ferric hexacyano-ferrate(II) -2H <sub>2</sub> O (Prussian blue)	<b>Powder for oral administration.</b>
sodium nitrite	<b>Injection:</b> 30 mg/mL in 10 mL ampoule.
sodium thiosulfate	<b>Injection:</b> 250 mg/mL in 50 mL ampoule.
<i>Complementary List</i>	
deferoxamine	<b>Powder for injection:</b> 500 mg (mesilate) in vial.
dimercaprol	<b>Injection in oil:</b> 50 mg/mL in 2 mL ampoule.
fomepizole	<b>Injection:</b> 5 mg/mL (sulfate) in 20 mL ampoule or 1 g/mL (base) in 1.5 mL ampoule.
sodium calcium edetate	<b>Injection:</b> 200 mg/mL in 5 mL ampoule.
succimer	<b>Solid oral dosage form:</b> 100 mg.

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## 5. ANTICONVULSANTS/ANTIEPILEPTICS

carbamazepine	<p><b>Oral liquid:</b> 100 mg/5 mL.</p> <p><b>Tablet (chewable):</b> 100 mg; 200 mg.</p> <p><b>Tablet (scored):</b> 100 mg; 200 mg.</p>
diazepam	<p><b>Gel or rectal solution:</b> 5 mg/mL in 0.5 mL; 2 mL; 4 mL tubes.</p>
lamotrigine*	<p><b>Tablet:</b> 25 mg; 50 mg; 100 mg; 200 mg.</p> <p><b>Tablet (chewable, dispersible):</b> 2 mg; 5 mg; 25 mg; 50 mg; 100 mg; 200 mg.</p> <p>*For use as adjunctive therapy for treatment-resistant partial or generalized seizures.</p>
□ lorazepam  Therapeutic alternatives: - diazepam (injection) - midazolam (injection)	<p><b>Injection:</b> 2 mg/mL in 1 mL ampoule; 4 mg/mL in 1 mL ampoule.</p>
magnesium sulfate*	<p><b>Injection:</b> 0.5 g/mL in 2 mL ampoule (equivalent to 1 g in 2 mL; 50% weight/volume); 0.5 g/mL in 10 mL ampoule (equivalent to 5 g in 10 mL; 50% weight/volume).</p> <p>*For use in eclampsia and severe pre-eclampsia and not for other convulsant disorders.</p>
midazolam	<p><b>Solution for oromucosal administration:</b> 5 mg/mL; 10 mg/mL.</p> <p><b>Ampoule*:</b> 1 mg/mL; 10 mg/mL.</p> <p>*For buccal administration when solution for oromucosal administration is not available.</p>
phenobarbital	<p><b>Injection:</b> 200 mg/mL (sodium).</p> <p><b>Oral liquid:</b> 15 mg/5 mL.</p> <p><b>Tablet:</b> 15 mg to 100 mg.</p>
phenytoin	<p><b>Injection:</b> 50 mg/mL (sodium) in 5 mL vial.</p> <p><b>Oral liquid:</b> 25 mg to 30 mg/5 mL.*</p> <p><b>Solid oral dosage form:</b> 25 mg; 50 mg; 100 mg (sodium).</p> <p><b>Tablet (chewable):</b> 50 mg.</p> <p>*The presence of both 25 mg/5 mL and 30 mg/5 mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided.</p>
valproic acid (sodium valproate)*  <i>*Avoid use in pregnancy and in women and girls of child-bearing potential, unless alternative treatments are ineffective or not tolerated because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb.</i>	<p><b>Oral liquid:</b> 200 mg/5 mL.</p> <p><b>Tablet (crushable):</b> 100 mg.</p> <p><b>Tablet (enteric-coated):</b> 200 mg; 500 mg.</p>

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<i>Complementary List</i>	
ethosuximide	<b>Capsule:</b> 250 mg. <b>Oral liquid:</b> 250 mg/5 mL.
valproic acid (sodium valproate)*  *Avoid use in pregnancy and in women and girls of child-bearing potential, unless alternative treatments are ineffective or not tolerated because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb.	<b>Injection:</b> 100 mg/mL in 4 mL ampoule; 100 mg/mL in 10 mL ampoule.
6. ANTI-INFECTIVE MEDICINES	
6.1 Anthelmintics	
6.1.1 <i>Intestinal anthelmintics</i>	
albendazole	<b>Tablet (chewable):</b> 400 mg.
ivermectin	<b>Tablet (scored):</b> 3 mg.
levamisole	<b>Tablet:</b> 50 mg; 150 mg (as hydrochloride).
mebendazole	<b>Tablet (chewable):</b> 100 mg; 500 mg.
niclosamide	<b>Tablet (chewable):</b> 500 mg.
praziquantel	<b>Tablet:</b> 150 mg; 600 mg.
pyrantel	<b>Oral liquid:</b> 50 mg/mL (as embonate or pamoate). <b>Tablet (chewable):</b> 250 mg (as embonate or pamoate).
6.1.2 <i>Antifilarials</i>	
albendazole	<b>Tablet (chewable):</b> 400 mg.
diethylcarbamazine	<b>Tablet:</b> 50 mg; 100 mg (dihydrogen citrate).
ivermectin	<b>Tablet (scored):</b> 3 mg.
6.1.3 <i>Antischistosomal and other antitrematode medicines</i>	
praziquantel	<b>Tablet:</b> 600 mg.
triclabendazole	<b>Tablet:</b> 250 mg.
<i>Complementary List</i>	
oxamniquine*	<b>Capsule:</b> 250 mg. <b>Oral liquid:</b> 250 mg/5 mL.  *For use when praziquantel treatment fails.
6.1.4 <i>Cysticidal medicines</i>	
<i>Complementary List</i>	
albendazole	<b>Tablet (chewable):</b> 400 mg.
mebendazole	<b>Tablet (chewable):</b> 500 mg.
praziquantel	<b>Tablet:</b> 500 mg; 600 mg.

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## 6.2 Antibacterials

To assist in the development of tools for antibiotic stewardship at local, national and global levels and to reduce antimicrobial resistance, the Access, Watch, Reserve (AWaRe) classification of antibiotics was developed – where antibiotics are classified into different groups to emphasize the importance of their appropriate use.

### ACCESS GROUP ANTIBIOTICS

This group includes antibiotics that have activity against a wide range of commonly encountered susceptible pathogens while also showing lower resistance potential than antibiotics in the other groups. Selected Access group antibiotics are recommended as essential first or second choice empiric treatment options for infectious syndromes reviewed by the EML Expert Committee and are listed as individual medicines on the Model Lists to improve access and promote appropriate use. They are essential antibiotics that should be widely available, affordable and quality assured.

### WATCH GROUP ANTIBIOTICS

This group includes antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the [Critically Important Antimicrobials for Human Medicine](#) and/or antibiotics that are at relatively high risk of selection of bacterial resistance. These medicines should be prioritized as key targets of stewardship programs and monitoring.

Selected Watch group antibiotics are recommended as essential first or second choice empiric treatment options for a limited number of specific infectious syndromes and are listed as individual medicines on the Model Lists.

### RESERVE GROUP ANTIBIOTICS

This group includes antibiotics and antibiotic classes that should be reserved for treatment of confirmed or suspected infections due to multi-drug-resistant organisms. Reserve group antibiotics should be treated as “last resort” options. Selected Reserve group antibiotics are listed as individual medicines on the Model Lists when they have a favourable risk-benefit profile and proven activity against “Critical Priority” or “High Priority” pathogens identified by the [WHO Priority Pathogens List](#), notably carbapenem resistant *Enterobacteriaceae*. These antibiotics should be accessible, but their use should be tailored to highly specific patients and settings, when all alternatives have failed or are not suitable. These medicines could be protected and prioritized as key targets of national and international stewardship programs involving monitoring and utilization reporting, to preserve their effectiveness.

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## 6.2.1 Access group antibiotics

	<b>Injection:</b> 250 mg/mL (as sulfate) in 2 mL vial.	
amikacin	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>High-risk febrile neutropenia</i></li> <li>– <i>Pyelonephritis or prostatitis (severe)</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Sepsis in neonates and children [c]</i></li> </ul>
	<b>Powder for injection:</b> 250 mg; 500 mg; 1 g (as sodium) in vial. <b>Powder for oral liquid:</b> 125 mg/5 mL; 250 mg/5 mL (as trihydrate) [c]. <b>Solid oral dosage form:</b> 250 mg; 500 mg; 1g (as trihydrate).	
amoxicillin	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Community acquired pneumonia (mild to moderate)</i></li> <li>– <i>Community acquired pneumonia (severe) [c]</i></li> <li>– <i>Complicated severe acute malnutrition [c]</i></li> <li>– <i>Exacerbations of COPD</i></li> <li>– <i>Otitis media</i></li> <li>– <i>Pharyngitis</i></li> <li>– <i>Progressive apical dental abscess</i></li> <li>– <i>Sepsis in neonates and children [c]</i></li> <li>– <i>Sinusitis</i></li> <li>– <i>Uncomplicated severe acute malnutrition [c]</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Acute bacterial meningitis</i></li> </ul>
amoxicillin + clavulanic acid	<b>Powder for injection:</b> 500 mg (as sodium) + 100 mg (as potassium salt); 1000 mg (as sodium) + 200 mg (as potassium salt) in vial. <b>Powder for oral liquid:</b> 125 mg (as trihydrate)+ 31.25 mg (as potassium salt)/5 mL; 250 mg (as trihydrate) + 62.5 mg (as potassium salt)/5mL [c]. <b>Tablet:</b> 500 mg (as trihydrate) + 125 mg (as potassium salt); 875 mg (as trihydrate) + 125 mg (as potassium salt).	
amoxicillin + clavulanic acid	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Community acquired pneumonia (severe) [c]</i></li> <li>– <i>Complicated intraabdominal infections (mild to moderate)</i></li> <li>– <i>Exacerbations of COPD</i></li> <li>– <i>Hospital acquired pneumonia</i></li> <li>– <i>Low-risk febrile neutropenia</i></li> <li>– <i>Lower urinary tract infections</i></li> <li>– <i>Sinusitis</i></li> <li>– <i>Skin and soft tissue infections</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Bone and joint infections</i></li> <li>– <i>Community-acquired pneumonia (mild to moderate)</i></li> <li>– <i>Community acquired pneumonia (severe)</i></li> <li>– <i>Otitis media</i></li> <li>– <i>Surgical prophylaxis</i></li> </ul>

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	Powder for injection: 500 mg; 1 g (as sodium) in vial.	
ampicillin	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Community acquired pneumonia (severe) [c]</i></li> <li>– <i>Complicated intraabdominal infections [c]</i></li> <li>– <i>Complicated severe acute malnutrition [c]</i></li> <li>– <i>Sepsis in neonates and children [c]</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Acute bacterial meningitis</i></li> </ul>
benzathine benzylpenicillin	Powder for injection: 1.2 million IU ( $\approx$ 900 mg) in vial [c]; 2.4 million IU ( $\approx$ 1.8 g) in vial.	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Syphilis</i></li> </ul>	<b>SECOND CHOICE</b>
benzylpenicillin	<b>Powder for injection:</b> 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial.	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Community acquired pneumonia (severe) [c]</i></li> <li>– <i>Complicated severe acute malnutrition [c]</i></li> <li>– <i>Sepsis in neonates and children [c]</i></li> <li>– <i>Syphilis</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Acute bacterial meningitis [c]</i></li> </ul>
cefalexin	<b>Powder for oral liquid:</b> 125 mg/5 mL; 250 mg/5 mL (anhydrous). <b>Solid oral dosage form:</b> 250 mg; 500 mg (as monohydrate).	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Skin and soft tissue infections</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Exacerbations of COPD</i></li> <li>– <i>Pharyngitis</i></li> </ul>
cefazolin <sup>a</sup>	<b>Powder for injection:</b> 1 g (as sodium salt) in vial. <small>[a] &gt; 1 month.</small>	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Surgical prophylaxis</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Bone and joint infections</i></li> </ul>
chloramphenicol	<b>Capsule:</b> 250 mg. <b>Oily suspension for injection*</b> : 0.5 g/mL (as sodium succinate) in 2 mL ampoule. <small>*Only for the presumptive treatment of epidemic meningitis in children older than 2 years and in adults.</small>	
	<b>Oral liquid:</b> 150 mg/5 mL (as palmitate). <b>Powder for injection:</b> 1 g (sodium succinate) in vial.	
	<b>FIRST CHOICE</b>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Acute bacterial meningitis</i></li> </ul>

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clindamycin	<p><b>Capsule:</b> 150 mg (as hydrochloride).</p> <p><b>Injection:</b> 150 mg/mL (as phosphate); 600 mg/4 mL (as phosphate); 900 mg/6 mL (as phosphate).</p> <p><b>Oral liquid:</b> 75 mg/5 mL (as palmitate) [c].</p>	
	<b>FIRST CHOICE</b> – <i>Necrotizing fasciitis</i>	<b>SECOND CHOICE</b> – <i>Bone and joint infections</i>
<input checked="" type="checkbox"/> cloxacillin*  Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (J01CF Beta-lactamase resistant penicillins)	<p><b>Capsule:</b> 500 mg; 1 g (as sodium).</p> <p><b>Powder for injection:</b> 500 mg (as sodium) in vial.</p> <p><b>Powder for oral liquid:</b> 125 mg/5 mL (as sodium).</p> <p>*cloxacillin, dicloxacillin and flucloxacillin are preferred for oral administration due to better bioavailability.</p>	
	<b>FIRST CHOICE</b> – <i>Bone and joint infections</i> – <i>Skin and soft tissue infections</i>	<b>SECOND CHOICE</b> – <i>Sepsis in neonates and children</i> [c]
doxycycline <input checked="" type="checkbox"/>	<p><b>Oral liquid:</b> 25 mg/5 mL [c]; 50 mg/5 mL (anhydrous) [c].</p> <p><b>Powder for injection:</b> 100 mg in vial.</p> <p><b>Solid oral dosage form:</b> 50 mg [c]; 100 mg (as hyclate).</p> <p><input checked="" type="checkbox"/> Use in children &lt;8 years only for life-threatening infections when no alternative exists.</p>	
	<b>FIRST CHOICE</b> – <i>Cholera</i> – <i>Sexually transmitted infection due to Chlamydia trachomatis</i>	<b>SECOND CHOICE</b> – <i>Cholera</i> [c] – <i>Community acquired pneumonia (mild to moderate)</i> – <i>Exacerbations of COPD</i>
gentamicin	<p><b>Injection:</b> 10 mg/mL (as sulfate); 40 mg/mL (as sulfate) in 2 mL vial.</p>	
	<b>FIRST CHOICE</b> – <i>Acute bacterial meningitis in neonates</i> [c] – <i>Community acquired pneumonia (severe)</i> [c] – <i>Complicated intraabdominal infections</i> [c] – <i>Complicated severe acute malnutrition</i> [c] – <i>Sepsis in neonates and children</i> [c]	<b>SECOND CHOICE</b> – <i>Gonorrhoea</i> – <i>Surgical prophylaxis</i>

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	<p><b>Injection:</b> 500 mg in 100 mL vial.</p> <p><b>Oral liquid:</b> 200 mg/5 mL (as benzoate).</p> <p><b>Suppository:</b> 500 mg; 1 g.</p> <p><b>Tablet:</b> 200 mg to 500 mg.</p>	
metronidazole	<p><b>FIRST CHOICE</b></p> <ul style="list-style-type: none"> <li>– <i>C. difficile infection</i></li> <li>– <i>Complicated intraabdominal infections (mild to moderate)</i></li> <li>– <i>Complicated intrabdominal infections (severe)</i></li> <li>– <i>Necrotizing fasciitis</i></li> <li>– <i>Surgical prophylaxis</i></li> <li>– <i>Trichomoniasis</i></li> </ul>	<p><b>SECOND CHOICE</b></p> <ul style="list-style-type: none"> <li>– <i>Complicated intraabdominal infections (mild to moderate)</i></li> </ul>
nitrofurantoin	<p><b>Oral liquid:</b> 25 mg/5 mL [c].</p> <p><b>Tablet:</b> 100 mg.</p>	
	<p><b>FIRST CHOICE</b></p> <ul style="list-style-type: none"> <li>– <i>Lower urinary tract infections</i></li> </ul>	<p><b>SECOND CHOICE</b></p>
phenoxyethylpenicillin	<p><b>Powder for oral liquid:</b> 250 mg/5 mL (as potassium).</p> <p><b>Tablet:</b> 250 mg; 500 mg (as potassium).</p>	
	<p><b>FIRST CHOICE</b></p> <ul style="list-style-type: none"> <li>– <i>Community acquired pneumonia (mild to moderate)</i></li> <li>– <i>Pharyngitis</i></li> <li>– <i>Progressive apical dental abscess</i></li> </ul>	<p><b>SECOND CHOICE</b></p>
procaine benzylpenicillin*	<p><b>Powder for injection:</b> 1 g (=1 million IU); 3 g (=3 million IU) in vial.</p> <p>*Procaine benzylpenicillin is not recommended as first-line treatment for neonatal sepsis except in settings with high neonatal mortality, when given by trained health workers in cases where hospital care is not achievable.</p>	
	<p><b>FIRST CHOICE</b></p> <ul style="list-style-type: none"> <li>– <i>Syphilis (congenital)</i> [c]</li> </ul>	<p><b>SECOND CHOICE</b></p> <ul style="list-style-type: none"> <li>– <i>Syphilis</i></li> </ul>
spectinomycin	<p><b>Powder for injection:</b> 2 g (as hydrochloride) in vial.</p>	
	<p><b>FIRST CHOICE</b></p>	<p><b>SECOND CHOICE</b></p> <ul style="list-style-type: none"> <li>– <i>Gonorrhoea</i></li> </ul>
sulfamethoxazole + trimethoprim	<p><b>Injection:</b> 80 mg + 16 mg/mL in 5 mL ampoule; 80 mg + 16 mg/mL in 10 mL ampoule.</p> <p><b>Oral liquid:</b> 200 mg + 40 mg/5 mL.</p> <p><b>Tablet:</b> 100 mg + 20 mg; 400 mg + 80 mg; 800 mg + 160 mg.</p>	
	<p><b>FIRST CHOICE</b></p> <ul style="list-style-type: none"> <li>– <i>Lower urinary tract infections</i></li> </ul>	<p><b>SECOND CHOICE</b></p> <ul style="list-style-type: none"> <li>– <i>Acute invasive diarrhoea / bacterial dysentery</i></li> </ul>

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trimethoprim	<b>Tablet:</b> 100 mg; 200 mg. <b>Oral liquid:</b> 50 mg/5 mL [c].	
	<b>FIRST CHOICE</b> – <i>Lower urinary tract infections</i>	<b>SECOND CHOICE</b>
<b>6.2.2 Watch group antibiotics</b>		
azithromycin	<b>Capsule:</b> 250 mg; 500 mg (anhydrous). <b>Oral liquid:</b> 200 mg/5 mL.	
	<b>FIRST CHOICE</b> – <i>Cholera [c]</i> – <i>Enteric fever</i> – <i>Gonorrhoea</i> – <i>Sexually transmitted infection due to Chlamydia trachomatis</i> – <i>Trachoma</i> – <i>Yaws</i>	<b>SECOND CHOICE</b> – <i>Acute invasive bacterial diarrhoea / dysentery</i> – <i>Gonorrhoea</i>
cefixime	<b>Powder for oral liquid:</b> 100 mg/5 mL [c]. <b>Solid oral dosage form:</b> 200 mg; 400 mg (as trihydrate).	
	<b>FIRST CHOICE</b>	<b>SECOND CHOICE</b> – <i>Acute invasive bacterial diarrhoea / dysentery</i> – <i>Gonorrhoea</i>
cefotaxime*	<b>Powder for injection:</b> 250 mg (as sodium) in vial. *3rd generation cephalosporin of choice for use in hospitalized neonates.	
	<b>FIRST CHOICE</b> – <i>Acute bacterial meningitis</i> – <i>Community acquired pneumonia (severe)</i> – <i>Complicated intraabdominal infections (mild to moderate)</i> – <i>Complicated intraabdominal infections (severe)</i> – <i>Hospital acquired pneumonia</i> – <i>Pyelonephritis or prostatitis (severe)</i>	<b>SECOND CHOICE</b> – <i>Bone and joint infections</i> – <i>Pyelonephritis or prostatitis (mild to moderate)</i> – <i>Sepsis in neonates and children [c]</i>

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ceftriaxone* <span style="border: 1px solid black; padding: 2px;">a</span>	<p><b>Powder for injection:</b> 250 mg; 1 g; 2 g (as sodium) in vial.</p> <p>*Do not administer with calcium and avoid in infants with hyperbilirubinaemia.</p> <p><span style="border: 1px solid black; padding: 2px;">a</span> &gt; 41 weeks corrected gestational age.</p>	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– Acute bacterial meningitis</li> <li>– Community acquired pneumonia (severe)</li> <li>– Complicated intraabdominal infections (mild to moderate)</li> <li>– Complicated intrabdominal infections (severe)</li> <li>– Endophthalmitis</li> <li>– Enteric fever</li> <li>– Gonorrhoea</li> <li>– Hospital acquired pneumonia</li> <li>– Necrotizing fasciitis</li> <li>– Pyelonephritis or prostatitis (severe)</li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– Acute invasive bacterial diarrhoea / dysentery</li> <li>– Bone and joint infections</li> <li>– Pyelonephritis or prostatitis (mild to moderate)</li> <li>– Sepsis in neonates and children [c]</li> </ul>
cefuroxime	<p><b>Powder for injection:</b> 250 mg; 750 mg; 1.5 g (as sodium) in vial.</p>	
	<b>FIRST CHOICE</b>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– Surgical prophylaxis</li> </ul>
ciprofloxacin	<p><b>Oral liquid:</b> 250 mg/5 mL (anhydrous) [c].</p> <p><b>Solution for IV infusion:</b> 2 mg/mL (as hydrate) [c].</p> <p><b>Solid oral dosage form:</b> 250 mg; 500 mg (as hydrochloride).</p>	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– Acute invasive bacterial diarrhoea / dysentery</li> <li>– Enteric fever</li> <li>– Low-risk febrile neutropenia</li> <li>– Pyelonephritis or prostatitis (mild to moderate)</li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– Cholera</li> <li>– Complicated intraabdominal infections (mild to moderate)</li> </ul>
□ clarithromycin† Therapeutic alternatives: - erythromycin*	<p><b>Powder for oral liquid:</b> 125 mg/5 mL; 250 mg/5 mL.</p> <p><b>Powder for injection:</b> 500 mg in vial.</p> <p><b>Solid oral dosage form:</b> 500 mg.</p> <p>†clarithromycin is also listed for use in combination regimens for eradication of <i>H. pylori</i> in adults.</p>	
*as second choice treatment for pharyngitis in children (EMLc only)	<b>FIRST CHOICE</b> <p>Community acquired pneumonia (severe)</p>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– Pharyngitis</li> </ul>

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piperacillin + tazobactam	<b>Powder for injection:</b> 2 g (as sodium) + 250 mg (as sodium); 4 g (as sodium) + 500 mg (as sodium) in vial.	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Complicated intraabdominal infections (severe)</i></li> <li>– <i>High-risk febrile neutropenia</i></li> <li>– <i>Hospital acquired pneumonia</i></li> <li>– <i>Necrotizing fasciitis</i></li> </ul>	<b>SECOND CHOICE</b>
vancomycin	<b>Capsule:</b> 125 mg; 250 mg (as hydrochloride).	
	<b>FIRST CHOICE</b>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>C. difficile infection</i></li> </ul>
<b>Complementary List</b>		
ceftazidime	<b>Powder for injection:</b> 250 mg; 1 g (as pentahydrate) in vial.	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Endophthalmitis</i></li> </ul>	<b>SECOND CHOICE</b>
<input type="checkbox"/> meropenem* <small>[a]</small>  Therapeutic alternatives*: - imipenem + cilastatin  *complicated intraabdominal infections and high-risk febrile neutropenia only. Meropenem is the preferred choice for acute bacterial meningitis in neonates.	<b>Powder for injection:</b> 500 mg (as trihydrate); 1 g (as trihydrate) in vial.  [a] > 3 months.	
	<b>FIRST CHOICE</b>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Acute bacterial meningitis in neonates [c]</i></li> <li>– <i>Complicated intraabdominal infections (severe)</i></li> <li>– <i>High-risk febrile neutropenia</i></li> </ul>
vancomycin	<b>Powder for injection:</b> 250 mg; 500 mg; 1 g (as hydrochloride) in vial.	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Endophthalmitis</i></li> <li>– <i>Necrotizing fasciitis</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>High-risk febrile neutropenia</i></li> </ul>
<b>6.2.3 Reserve group antibiotics</b>		
<b>Complementary List</b>		
cefiderocol	<b>Powder for injection:</b> 1 g (as sulfate toxylate) in vial.	
ceftazidime + avibactam	<b>Powder for injection:</b> 2 g + 0.5 g in vial.	
colistin	<b>Powder for injection:</b> 1 million IU (as colistemethate sodium) in vial.	
fosfomycin	<b>Powder for injection:</b> 2 g; 4 g (as sodium) in vial.	
linezolid	<b>Injection for intravenous administration:</b> 2 mg/mL in 300 mL bag.	
	<b>Powder for oral liquid:</b> 100 mg/5 mL.	
	<b>Tablet:</b> 400 mg; 600 mg.	
meropenem + vaborbactam	<b>Powder for injection:</b> 1 g (as trihydrate) + 1 g in vial.	
plazomicin	<b>Injection:</b> 500 mg/10 mL.	
polymyxin B	<b>Powder for injection:</b> 500,000 IU in vial.	

# WHO Model List of Essential Medicines – 22nd List (2021)

## 6.2.4 Antileprosy medicines

Medicines used in the treatment of leprosy should never be used except in combination. Combination therapy is essential to prevent the emergence of drug resistance. Colour-coded blister packs (MDT blister packs) containing standard two-medicine (paucibacillary leprosy) or three-medicine (multibacillary leprosy) combinations for adult and childhood leprosy should be used. MDT blister packs can be supplied free of charge through WHO.

clofazimine	<b>Capsule:</b> 50 mg; 100 mg.
dapsone	<b>Tablet:</b> 25 mg; 50 mg; 100 mg.
rifampicin	<b>Solid oral dosage form:</b> 150 mg; 300 mg.

## 6.2.5 Antituberculosis medicines

WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

ethambutol	<b>Oral liquid:</b> 25 mg/mL [c]. <b>Tablet:</b> 100 mg; 400 mg (hydrochloride). <b>Tablet (dispersible):</b> 100 mg [c]
ethambutol + isoniazid + pyrazinamide + rifampicin	<b>Tablet:</b> 275 mg + 75 mg + 400 mg + 150 mg.
ethambutol + isoniazid + rifampicin	<b>Tablet:</b> 275 mg + 75 mg + 150 mg.
isoniazid	<b>Oral liquid:</b> 50 mg/5 mL [c]. <b>Tablet:</b> 100 mg; 300 mg. <b>Tablet (dispersible):</b> 100 mg [c].
isoniazid + pyrazinamide + rifampicin	<b>Tablet (dispersible):</b> 50 mg + 150 mg + 75 mg [c].
isoniazid + rifampicin	<b>Tablet:</b> 75 mg + 150 mg; 150 mg + 300 mg. <b>Tablet (dispersible):</b> 50 mg + 75 mg [c].
isoniazid + rifapentine	<b>Tablet (scored):</b> 300 mg + 300 mg.
moxifloxacin	<b>Tablet:</b> 400 mg.
pyrazinamide	<b>Oral liquid:</b> 30 mg/mL [c]. <b>Tablet:</b> 400 mg; 500 mg <b>Tablet (dispersible):</b> 150 mg.
rifabutin	<b>Solid oral dosage form:</b> 150 mg.* *For use only in patients with HIV receiving protease inhibitors.
rifampicin	<b>Oral liquid:</b> 20 mg/mL [c]. <b>Solid oral dosage form:</b> 150 mg; 300 mg.
rifapentine	<b>Tablet:</b> 150 mg; 300 mg.

# WHO Model List of Essential Medicines – 22nd List (2021)

## Complementary List

Medicines for the treatment of multidrug-resistant tuberculosis (MDR-TB) should be used in specialized centres adhering to WHO standards for TB control.

<i>amikacin</i>	<b>Injection:</b> 100 mg/2 mL (as sulfate) in 2 mL vial; 250 mg/mL (as sulfate) in 2 mL vial.
<i>amoxicillin + clavulanic acid*</i>	<b>Powder for oral liquid:</b> 250 mg (as trihydrate) + 62.5 mg (as potassium salt)/5mL [c]. <b>Tablet:</b> 500 mg (as trihydrate) + 125 mg (as potassium salt). *For use only in combination with meropenem or imipenem+cilastatin.
<i>bedaquiline</i> <b>a</b>	<b>Tablet:</b> 20 mg [c]; 100 mg. <b>a</b> ≥ 5 years
<i>clofazimine</i>	<b>Solid oral dosage form:</b> 50 mg; 100 mg.
<input type="checkbox"/> <i>cycloserine</i> Therapeutic alternatives: - <i>terizidone</i>	<b>Solid oral dosage form:</b> 125 mg [c]; 250 mg.
<i>delamanid</i> <b>a</b>	<b>Tablet (dispersible):</b> 25 mg [c]. <b>a</b> ≥ 3 years <b>Tablet:</b> 50 mg. <b>a</b> ≥ 6 years
<input type="checkbox"/> <i>ethionamide</i> Therapeutic alternatives: - <i>prontosilamide</i>	<b>Tablet:</b> 125 mg; 250 mg. <b>Tablet (dispersible):</b> 125 mg [c].
<i>levofloxacin</i>	<b>Tablet:</b> 250mg; 500 mg; 750 mg. <b>Tablet (dispersible):</b> 100 mg [c].
<i>linezolid</i>	<b>Powder for oral liquid:</b> 100 mg/5 mL. <b>Tablet:</b> 600 mg. <b>Tablet (dispersible):</b> 150 mg [c].
<input type="checkbox"/> <i>meropenem</i> Therapeutic alternatives: - <i>imipenem + cilastatin</i>	<b>Powder for injection:</b> 500 mg (as trihydrate); 1 g (as trihydrate) in vial.
<i>moxifloxacin</i>	<b>Tablet:</b> 400 mg. <b>Tablet (dispersible):</b> 100 mg [c].
<i>p-aminosalicylic acid</i>	<b>Granules:</b> 4 g in sachet.
<i>streptomycin</i> [c]	<b>Powder for injection:</b> 1 g (as sulfate) in vial.

# WHO Model List of Essential Medicines – 22nd List (2021)

6.3 Antifungal medicines	
amphotericin B	<b>Powder for injection:</b> 50 mg (as sodium deoxycholate or liposomal complex) in vial.
clotrimazole	<b>Vaginal cream:</b> 1%; 10%. <b>Vaginal tablet:</b> 100 mg; 500 mg.
fluconazole	<b>Capsule:</b> 50 mg. <b>Injection:</b> 2 mg/mL in vial. <b>Oral liquid:</b> 50 mg/5 mL.
flucytosine	<b>Capsule:</b> 250 mg. <b>Infusion:</b> 2.5 g in 250 mL.
griseofulvin	<b>Oral liquid:</b> 125 mg/5 mL [c]. <b>Solid oral dosage form:</b> 125 mg; 250 mg.
itraconazole*	<b>Capsule:</b> 100 mg. <b>Oral liquid:</b> 10 mg/mL. *For treatment of chronic pulmonary aspergillosis, histoplasmosis, sporotrichosis, paracoccidioidomycosis, mycoses caused by <i>T. marneffei</i> and chromoblastomycosis; and prophylaxis of histoplasmosis and infections caused by <i>T. marneffei</i> in AIDS patients.
nystatin	<b>Lozenge:</b> 100 000 IU. <b>Oral liquid:</b> 50 mg/5 mL [c]; 100 000 IU/mL [c]. <b>Pessary:</b> 100 000 IU. <b>Tablet:</b> 100 000 IU; 500 000 IU.
voriconazole*	<b>Tablet:</b> 50 mg; 200 mg <b>Powder for injection:</b> 200 mg in vial <b>Powder for oral liquid:</b> 40 mg/mL *For treatment of chronic pulmonary aspergillosis and acute invasive aspergillosis.
<i>Complementary List</i>	
<input type="checkbox"/> <i>micafungin</i> <i>Therapeutic alternatives:</i> - <i>anidulafungin</i> - <i>caspofungin</i>	<b>Powder for injection:</b> 50 mg (as sodium); 100 mg (as sodium) in vial.
<i>potassium iodide</i>	<b>Saturated solution.</b>

# WHO Model List of Essential Medicines – 22nd List (2021)

## 6.4 Antiviral medicines

### 6.4.1 Antitherpes medicines

<input type="checkbox"/> aciclovir Therapeutic alternatives: - valaciclovir (oral)	Oral liquid: 200 mg/5 mL [c]. Powder for injection: 250 mg (as sodium salt) in vial. Tablet: 200 mg.
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### 6.4.2 Antiretrovirals

Based on current evidence and experience of use, medicines in the following classes of antiretrovirals are included as essential medicines for treatment and prevention of HIV (prevention of mother-to-child transmission, pre-exposure prophylaxis (where indicated) and post-exposure prophylaxis). WHO emphasizes the importance of using these products in accordance with global and national guidelines. WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

Scored tablets can be used in children and therefore can be considered for inclusion in the listing of tablets, provided that adequate quality products are available.

#### 6.4.2.1 Nucleoside/Nucleotide reverse transcriptase inhibitors

abacavir	Tablet: 300 mg (as sulfate).
lamivudine	Oral liquid: 50 mg/5 mL [c]. Tablet: 150 mg.
tenofovir disoproxil fumarate†	Tablet: 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil). †also indicated for pre-exposure prophylaxis.
zidovudine	Capsule: 250 mg. Oral liquid: 50 mg/5 mL. Solution for IV infusion: 10 mg/mL in 20 mL vial. Tablet: 300 mg.

#### 6.4.2.2 Non-nucleoside reverse transcriptase inhibitors

efavirenz	Tablet: 600 mg.
nevirapine [a]	Oral liquid: 50 mg/5 mL. Tablet: 50 mg (dispersible); 200 mg. [a] > 6 weeks

#### 6.4.2.3 Protease inhibitors

Selection of protease inhibitor(s) from the Model List will need to be determined by each country after consideration of international and national treatment guidelines and experience. Ritonavir is recommended for use in combination as a pharmacological booster, and not as an antiretroviral in its own right. All other protease inhibitors should be used in boosted forms (e.g. with ritonavir).

atazanavir + ritonavir	Tablet (heat stable): 300 mg (as sulfate) + 100 mg.
darunavir [a]	Tablet: 75 mg; 400 mg; 600 mg; 800 mg [a] > 3 years
lopinavir + ritonavir	Solid oral dosage form: 40 mg + 10 mg [c]. Tablet (heat stable): 100 mg + 25 mg; 200 mg + 50 mg.
ritonavir	Tablet (heat stable): 25 mg; 100 mg.

# WHO Model List of Essential Medicines – 22nd List (2021)

## 6.4.2.4 Integrase inhibitors

dolutegravir <small>a</small>	<p><b>Tablet (dispersible, scored):</b> 10 mg [c].</p> <p><b>[a]</b> ≥ 4 weeks and ≥ 3 kg</p> <p><b>Tablet:</b> 50 mg</p> <p><b>[a]</b> ≥ 25 kg</p>
raltegravir*	<p><b>Granules for oral suspension:</b> 100 mg in sachet.</p> <p><b>Tablet (chewable):</b> 25 mg.</p> <p><b>Tablet:</b> 400 mg.</p> <p>*For use in pregnant women and in second-line regimens in accordance with WHO treatment guidelines.</p>

## 6.4.2.5 Fixed-dose combinations of antiretroviral medicines

abacavir + lamivudine	<b>Tablet (dispersible, scored):</b> 120 mg (as sulfate) + 60 mg.
dolutegravir + lamivudine + tenofovir	<b>Tablet:</b> 50 mg + 300 mg + 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil)
efavirenz + <input type="checkbox"/> emtricitabine + tenofovir Therapeutic alternatives: - lamivudine (for emtricitabine)	<b>Tablet:</b> 600 mg + 200 mg + 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil).
efavirenz + lamivudine + tenofovir	<b>Tablet:</b> 400 mg + 300 mg + 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil)
<input type="checkbox"/> emtricitabine + tenofovir† Therapeutic alternatives: - lamivudine (for emtricitabine)	<b>Tablet:</b> 200 mg + 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil). † combination also indicated for pre-exposure prophylaxis
lamivudine + zidovudine	<b>Tablet:</b> 30 mg + 60 mg [c]; 150 mg + 300 mg.

## 6.4.2.6 Medicines for prevention of HIV-related opportunistic infections

isoniazid + pyridoxine + sulfamethoxazole + trimethoprim	<b>Tablet (scored):</b> 300 mg + 25 mg + 800 mg + 160 mg
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## 6.4.3 Other antivirals

ribavirin*	<p><b>Injection for intravenous administration:</b> 800 mg and 1 g in 10 mL phosphate buffer solution.</p> <p><b>Solid oral dosage form:</b> 200 mg; 400 mg; 600 mg.</p> <p>*For the treatment of viral haemorrhagic fevers</p>
valganciclovir*	<p><b>Tablet:</b> 450 mg.</p> <p>*For the treatment of cytomegalovirus retinitis (CMVr).</p>

# WHO Model List of Essential Medicines – 22nd List (2021)

<i>Complementary list</i>	
oseltamivir*	<p><b>Capsule:</b> 30 mg; 45 mg; 75 mg (as phosphate).</p> <p>*Severe illness due to confirmed or suspected influenza virus infection in critically ill hospitalized patients</p>
valganciclovir*[c]	<p><b>Powder for oral solution:</b> 50 mg/mL</p> <p><b>Tablet:</b> 450 mg.</p> <p>*For the treatment of cytomegalovirus retinitis (CMVr).</p>
<b>6.4.4 Antihepatitis medicines</b>	
<b>6.4.4.1 Medicines for hepatitis B</b>	
<b>6.4.4.1.1 Nucleoside/Nucleotide reverse transcriptase inhibitors</b>	
entecavir	<p><b>Oral liquid:</b> 0.05 mg/mL</p> <p><b>Tablet:</b> 0.5 mg; 1 mg</p>
tenofovir disoproxil fumarate	<b>Tablet:</b> 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil).
<b>6.4.4.2 Medicines for hepatitis C</b>	
Pangenotypic direct-acting antivirals should be considered as therapeutic alternatives for the purposes of selection and procurement at national level.	
<b>6.4.4.2.1 □ Pangenotypic direct-acting antiviral combinations</b>	
daclatasvir*	<p><b>Tablet:</b> 30 mg; 60 mg (as hydrochloride).</p> <p>*Pangenotypic when used in combination with sofosbuvir</p>
daclatasvir + sofosbuvir	<b>Tablet:</b> 60 mg + 400 mg.
glecaprevir + pibrentasvir	<p><b>Tablet:</b> 100 mg + 40 mg.</p> <p><b>Granules:</b> 50 mg + 20 mg in sachet [c].</p>
sofosbuvir*	<p><b>Tablet:</b> 200 mg; 400 mg.</p> <p>*Pangenotypic when used in combination with daclatasvir</p>
sofosbuvir + velpatasvir	<b>Tablet:</b> 200 mg + 50 mg [c]; 400 mg + 100 mg.
<b>6.4.4.2.2 Non-pangenotypic direct-acting antiviral combinations</b>	
dasabuvir	<b>Tablet:</b> 250 mg.
ledipasvir + sofosbuvir	<b>Tablet:</b> 90 mg + 400 mg.
ombitasvir + paritaprevir + ritonavir	<b>Tablet:</b> 12.5 mg + 75 mg + 50 mg.

# WHO Model List of Essential Medicines – 22nd List (2021)

## 6.4.4.2.3 Other antivirals for hepatitis C

ribavirin*	<p><b>Injection for intravenous administration:</b> 800 mg and 1 g in 10 mL phosphate buffer solution.</p> <p><b>Solid oral dosage form:</b> 200 mg; 400 mg; 600 mg.</p> <p>*For the treatment of hepatitis C, in combination with direct acting anti-viral medicines</p>
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### Complementary list

pegylated interferon alfa (2a or 2b) *	<p><b>Vial or pre-filled syringe:</b></p> <p>180 micrograms (peginterferon alfa-2a).</p> <p>80 micrograms, 100 micrograms (peginterferon alfa-2b).</p> <p>*To be used in combination with ribavirin.</p>
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## 6.5 Antiprotozoal medicines

### 6.5.1 Antiamoebic and antiangiardiasis medicines

diloxanide <b>a</b>	<p><b>Tablet:</b> 500 mg (furoate).</p> <p><b>[a]</b> &gt; 25 kg.</p>
<input type="checkbox"/> metronidazole Therapeutic alternatives: - tinidazole	<p><b>Injection:</b> 500 mg in 100 mL vial.</p> <p><b>Oral liquid:</b> 200 mg/5 mL (as benzoate).</p> <p><b>Tablet:</b> 200 mg to 500 mg.</p>

### 6.5.2 Antileishmaniasis medicines

amphotericin B	<b>Powder for injection:</b> 50 mg in vial (as sodium deoxycholate or liposomal complex).
miltefosine	<b>Solid oral dosage form:</b> 10 mg; 50 mg.
paromomycin	<b>Solution for intramuscular injection:</b> 750 mg of paromomycin base (as sulfate).
sodium stibogluconate <b>or</b> meglumine antimoniate	<b>Injection:</b> 100 mg/mL, 1 vial = 30 mL <b>or</b> 30%, equivalent to approximately 8.1% antimony (pentavalent) in 5 mL ampoule.

### 6.5.3 Antimalarial medicines

#### 6.5.3.1 For curative treatment

Medicines for the treatment of *P. falciparum* malaria cases should be used in combination. The list currently recommends combinations according to treatment guidelines. WHO recognizes that not all of the fixed dose combinations (FDCs) in the WHO treatment guidelines exist, and encourages their development and rigorous testing. WHO also encourages development and testing of rectal dosage formulations.

amodiaquine*	<p><b>Tablet:</b> 153 mg or 200 mg (as hydrochloride).</p> <p>*To be used in combination with artesunate 50 mg.</p>
artemether*	<p><b>Oily injection:</b> 80 mg/mL in 1 mL ampoule.</p> <p>*For use in the management of severe malaria.</p>
artemether + lumefantrine*	<p><b>Tablet:</b> 20 mg + 120 mg.</p> <p><b>Tablet (dispersible):</b> 20 mg + 120 mg [c].</p> <p>*Not recommended in the first trimester of pregnancy or in children below 5 kg.</p>

## WHO Model List of Essential Medicines – 22nd List (2021)

artesunate*	<p><b>Injection:</b> ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution. For use in the management of severe malaria.</p> <p><b>Rectal dosage form:</b> 50 mg [c]; 100 mg [c]; 200 mg capsules (for pre-referral treatment of severe malaria only; patients should be taken to an appropriate health facility for follow-up care) [c].</p> <p><b>Tablet:</b> 50 mg.</p> <p>*To be used in combination with either amodiaquine, mefloquine or sulfadoxine + pyrimethamine.</p>
artesunate + amodiaquine*	<p><b>Tablet:</b> 25 mg + 67.5 mg; 50 mg + 135 mg; 100 mg + 270 mg.</p> <p>*Other combinations that deliver the target doses required such as 153 mg or 200 mg (as hydrochloride) with 50 mg artesunate can be alternatives.</p>
artesunate + mefloquine	<p><b>Tablet:</b> 25 mg + 55 mg; 100 mg + 220 mg.</p>
artesunate + pyronaridine tetraphosphate [a]	<p><b>Granules:</b> 20 mg + 60 mg [c].</p> <p><b>Tablet:</b> 60 mg + 180 mg.</p> <p>[a] &gt; 5 kg</p>
chloroquine*	<p><b>Oral liquid:</b> 50 mg/5 mL (as phosphate or sulfate).</p> <p><b>Tablet:</b> 100 mg; 150 mg (as phosphate or sulfate).</p> <p>*For use only for the treatment of <i>Plasmodium vivax</i> infection.</p>
dihydroartemisinin + piperaquine phosphate [a]	<p><b>Tablet:</b> 20 mg + 160 mg; 40 mg + 320 mg.</p> <p>[a] &gt; 5 kg</p>
doxycycline*	<p><b>Capsule:</b> 100 mg (as hydrochloride or hyclate).</p> <p><b>Tablet (dispersible):</b> 100 mg (as monohydrate).</p> <p>*For use only in combination with quinine.</p>
mefloquine*	<p><b>Tablet:</b> 250 mg (as hydrochloride).</p> <p>*To be used in combination with artesunate 50 mg.</p>
primaquine*	<p><b>Tablet:</b> 7.5 mg; 15 mg (as diphosphate).</p> <p>*Only for use to achieve radical cure of <i>Plasmodium vivax</i> and <i>Plasmodium ovale</i> infections, given for 14 days.</p>
quinine*	<p><b>Injection:</b> 300 mg/mL (hydrochloride) in 2 mL ampoule.</p> <p><b>Tablet:</b> 300 mg (sulfate) or 300 mg (bisulfate).</p> <p>*For use only in the management of severe malaria and should be used in combination with doxycycline.</p>
sulfadoxine + pyrimethamine*	<p><b>Tablet:</b> 500 mg + 25 mg.</p> <p>*Only in combination with artesunate 50 mg.</p>

# WHO Model List of Essential Medicines – 22nd List (2021)

## 6.5.3.2 For chemoprevention

amodiaquine – sulfadoxine + pyrimethamine [c]	<b>Co-packaged dispersible tablets:</b> amodiaquine 76.5 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 250 mg + 12.5 mg [1]; amodiaquine 153 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 500 mg + 25 mg [1].
chloroquine*	<b>Oral liquid:</b> 50 mg/5 mL (as phosphate or sulfate). <b>Tablet:</b> 150 mg (as phosphate or sulfate). *For use only in central American regions, for <i>Plasmodium vivax</i> infections.
doxycycline <b>[a]</b>	<b>Solid oral dosage form:</b> 100 mg (as hydrochloride or hydiate). <b>[a]</b> > 8 years.
mefloquine <b>[a]</b>	<b>Tablet:</b> 250 mg (as hydrochloride). <b>[a]</b> > 5 kg or > 3 months.
proguanil*	<b>Tablet:</b> 100 mg (as hydrochloride). *For use only in combination with chloroquine.
sulfadoxine + pyrimethamine	<b>Tablet:</b> 250 mg + 12.5 mg [c]; 500 mg + 25 mg.

## 6.5.4 Antipneumocystosis and antitoxoplasmosis medicines

pyrimethamine	<b>Tablet:</b> 25 mg.
sulfadiazine	<b>Tablet:</b> 500 mg.
sulfamethoxazole + trimethoprim	<b>Injection:</b> 80 mg + 16 mg/mL in 5 mL ampoule; 80 mg + 16 mg/mL in 10 mL ampoule. <b>Oral liquid:</b> 200 mg + 40 mg/5 mL [c]. <b>Tablet:</b> 100 mg + 20 mg; 400 mg + 80 mg [c]; 800 mg + 160 mg

## Complementary List

pentamidine	<b>Tablet:</b> 200 mg; 300 mg (as isethionate).
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## 6.5.5 Antitrypanosomal medicines

### 6.5.5.1 African trypanosomiasis

fexinidazole*	<b>Tablet:</b> 600 mg *For the treatment of 1 <sup>st</sup> and 2 <sup>nd</sup> stage of human African trypanosomiasis due to <i>Trypanosoma brucei gambiense</i> infection.
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### Medicines for the treatment of 1<sup>st</sup> stage African trypanosomiasis

pentamidine*	<b>Powder for injection:</b> 200 mg (as isetionate) in vial. *To be used for the treatment of <i>Trypanosoma brucei gambiense</i> infection.
suramin sodium*	<b>Powder for injection:</b> 1 g in vial. *To be used for the treatment of the initial phase of <i>Trypanosoma brucei rhodesiense</i> infection.

# WHO Model List of Essential Medicines – 22nd List (2021)

## Medicines for the treatment of 2<sup>nd</sup> stage African trypanosomiasis

eflornithine*	<b>Injection:</b> 200 mg/mL (hydrochloride) in 100 mL bottle. *To be used for the treatment of <i>Trypanosoma brucei gambiense</i> infection.
melarsoprol	<b>Injection:</b> 180 mg/5 mL in 5 mL ampoule (3.6% solution).
nifurtimox *	<b>Tablet:</b> 120 mg. *Only to be used in combination with eflornithine, for the treatment of <i>Trypanosoma brucei gambiense</i> infection.

### Complementary List

melarsoprol [c]	<b>Injection:</b> 180 mg/5 mL in 5 mL ampoule (3.6% solution).
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## 6.5.5.2 American trypanosomiasis

benznidazole	<b>Tablet:</b> 12.5 mg [c];100 mg. <b>Tablet (scored):</b> 50 mg.
nifurtimox	<b>Tablet:</b> 30 mg; 120 mg; 250 mg.

## 6.6 Medicines for ectoparasitic infections

ivermectin	<b>Tablet (scored):</b> 3 mg
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## 7. ANTIMIGRAINE MEDICINES

### 7.1 For treatment of acute attack

acetylsalicylic acid	<b>Tablet:</b> 300 mg to 500 mg.
ibuprofen [c]	<b>Tablet:</b> 200 mg; 400 mg.
paracetamol	<b>Oral liquid:</b> 120 mg/5 mL [c]; 125 mg/5 mL [c]. <b>Tablet:</b> 300 mg to 500 mg.
sumatriptan	<b>Tablet:</b> 50 mg

### 7.2 For prophylaxis

<input type="checkbox"/> propranolol Therapeutic alternatives to be reviewed (2023)	<b>Tablet:</b> 20 mg; 40 mg (hydrochloride).
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# WHO Model List of Essential Medicines – 22nd List (2021)

## 8. IMMUNOMODULATORS AND ANTINEOPLASTICS

### 8.1 Immunomodulators for non-malignant disease

#### *Complementary List*

*adalimumab\**

*Therapeutic alternatives\*:*

- *certolizumab pegol*
- *etanercept*
- *golimumab*
- *infliximab*

\*including quality-assured biosimilars

*Injection:* 40 mg/0.8 mL; 40 mg/0.4 mL.

*azathioprine*

*Powder for injection:* 100 mg (as sodium salt) in vial.

*Tablet (scored):* 50 mg.

*ciclosporin*

*Capsule:* 25 mg.

*Concentrate for injection:* 50 mg/mL in 1 mL ampoule.

*tacrolimus*

*Capsule (immediate-release):* 0.5 mg; 0.75 mg; 1 mg; 2 mg; 5 mg.

*Granules for oral suspension:* 0.2 mg; 1 mg.

*Injection:* 5 mg/mL in 1 mL vial.

### 8.2 Antineoplastics and supportive medicines

Medicines listed below should be used according to protocols for treatment of the diseases.

#### *8.2.1 Cytotoxic medicines*

#### *Complementary List*

*arsenic trioxide*

*Concentrate for solution for infusion:* 1 mg/mL

- Acute promyelocytic leukaemia

*asparaginase\**

\*including quality-assured biosimilars

*Powder for injection:* 10 000 IU in vial.

- Acute lymphoblastic leukaemia.

*bendamustine*

*Injection:* 45 mg/0.5 mL; 180 mg/2 mL.

- Chronic lymphocytic leukaemia
- Follicular lymphoma

*bleomycin*

*Powder for injection:* 15 mg (as sulfate) in vial.

- Hodgkin lymphoma
- Kaposi sarcoma
- Ovarian germ cell tumour
- Testicular germ cell tumour

*calcium folinate*

*Injection:* 3 mg/mL in 10 mL ampoule.

*Tablet:* 5 mg; 15 mg; 25 mg.

- Burkitt lymphoma
- Early stage colon cancer
- Early stage rectal cancer
- Gestational trophoblastic neoplasia
- Metastatic colorectal cancer
- Osteosarcoma

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<i>capecitabine</i>	<p><b>Tablet:</b> 150 mg; 500 mg.</p> <ul style="list-style-type: none"> <li>– Early stage colon cancer</li> <li>– Early stage rectal cancer</li> <li>– Metastatic breast cancer</li> <li>– Metastatic colorectal cancer</li> </ul>
<i>carboplatin</i>	<p><b>Injection:</b> 50 mg/5 mL; 150 mg/15 mL; 450 mg/45 mL; 600 mg/60 mL.</p> <ul style="list-style-type: none"> <li>– Cervical cancer</li> <li>– Early stage breast cancer</li> <li>– Epithelial ovarian cancer</li> <li>– Head and neck cancer (as a radio-sensitizer)</li> <li>– Low-grade glioma</li> <li>– Nasopharyngeal cancer</li> <li>– Nephroblastoma (<i>Wilms tumour</i>)</li> <li>– Non-small cell lung cancer</li> <li>– Osteosarcoma</li> <li>– Ovarian germ cell tumour</li> <li>– Retinoblastoma</li> <li>– Testicular germ cell tumour</li> </ul>
<i>chlorambucil</i>	<p><b>Tablet:</b> 2 mg.</p> <ul style="list-style-type: none"> <li>– Chronic lymphocytic leukaemia</li> </ul>
<i>cisplatin</i>	<p><b>Injection:</b> 10 mg/10 mL; 20 mg/20 mL; 50 mg/50 mL; 100 mg/100 mL.</p> <ul style="list-style-type: none"> <li>– Cervical cancer</li> <li>– Head and neck cancer (as a radio-sensitizer)</li> <li>– Low-grade glioma</li> <li>– Nasopharyngeal cancer (as a radio-sensitizer)</li> <li>– Non-small cell lung cancer</li> <li>– Osteosarcoma</li> <li>– Ovarian germ cell tumour</li> <li>– Testicular germ cell tumour</li> </ul>
<i>cyclophosphamide</i>	<p><b>Powder for injection:</b> 500 mg; 1 g; 2 g in vial.</p> <p><b>Tablet:</b> 25 mg, 50 mg.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Burkitt lymphoma</li> <li>– Chronic lymphocytic leukaemia</li> <li>– Diffuse large B-cell lymphoma</li> <li>– Early stage breast cancer</li> <li>– Ewing sarcoma</li> <li>– Follicular lymphoma</li> <li>– Gestational trophoblastic neoplasia</li> <li>– Hodgkin lymphoma</li> <li>– Low-grade glioma</li> <li>– Metastatic breast cancer</li> <li>– Multiple myeloma</li> <li>– Nephroblastoma (<i>Wilms tumour</i>)</li> <li>– Rhabdomyosarcoma</li> </ul>
<i>cytarabine</i>	<p><b>Powder for injection:</b> 100 mg in vial.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Acute myeloid leukaemia</li> <li>– Acute promyelocytic leukaemia</li> <li>– Burkitt lymphoma.</li> </ul>

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<i>dacarbazine</i>	<b>Powder for injection:</b> 100 mg in vial. – Hodgkin lymphoma
<i>dactinomycin</i>	<b>Powder for injection:</b> 500 micrograms in vial. – Ewing sarcoma – Gestational trophoblastic neoplasia – Nephroblastoma (Wilms tumour) – Rhabdomyosarcoma
<i>daunorubicin</i>	<b>Powder for injection:</b> 50 mg (hydrochloride) in vial. – Acute lymphoblastic leukaemia – Acute myeloid leukaemia – Acute promyelocytic leukaemia
<i>docetaxel</i>	<b>Injection:</b> 20 mg/mL; 40 mg/mL. – Early stage breast cancer – Metastatic breast cancer – Metastatic prostate cancer
<i>doxorubicin</i>	<b>Powder for injection:</b> 10 mg; 50 mg (hydrochloride) in vial. – Acute lymphoblastic leukaemia – Burkitt lymphoma – Diffuse large B-cell lymphoma – Early stage breast cancer – Ewing sarcoma – Follicular lymphoma – Hodgkin lymphoma – Kaposi sarcoma – Metastatic breast cancer – Multiple myeloma – Nephroblastoma (Wilms tumour) – Osteosarcoma
<i>etoposide</i>	<b>Capsule:</b> 50 mg, 100 mg. <b>Injection:</b> 20 mg/mL in 5 mL ampoule. – Acute lymphoblastic leukaemia – Acute myeloid leukaemia – Burkitt lymphoma – Ewing sarcoma – Gestational trophoblastic neoplasia – Hodgkin lymphoma – Nephroblastoma (Wilms tumour) – Non-small cell lung cancer – Osteosarcoma – Ovarian germ cell tumour – Retinoblastoma – Testicular germ cell tumour
<i>fludarabine</i>	<b>Powder for injection:</b> 50 mg (phosphate) in vial. <b>Tablet:</b> 10 mg – Chronic lymphocytic leukaemia.

## WHO Model List of Essential Medicines – 22nd List (2021)

<i>fluorouracil</i>	<p><b>Injection:</b> 50 mg/mL in 5 mL ampoule.</p> <ul style="list-style-type: none"> <li>– Early stage breast cancer</li> <li>– Early stage colon cancer</li> <li>– Early stage rectal cancer</li> <li>– Metastatic colorectal cancer</li> <li>– Nasopharyngeal cancer</li> </ul>
<i>gemcitabine</i>	<p><b>Powder for injection:</b> 200 mg; 1 g in vial.</p> <ul style="list-style-type: none"> <li>– Epithelial ovarian cancer</li> <li>– Non-small cell lung cancer</li> </ul>
<i>hydroxycarbamide</i>	<p><b>Solid oral dosage form:</b> 200 mg; 250 mg; 300 mg; 400 mg; 500 mg; 1 g.</p> <ul style="list-style-type: none"> <li>– Chronic myeloid leukaemia</li> </ul>
<i>ifosfamide</i>	<p><b>Powder for injection:</b> 500 mg; 1 g; 2 g in vial.</p> <ul style="list-style-type: none"> <li>– Burkitt lymphoma</li> <li>– Ewing sarcoma</li> <li>– Nephroblastoma (Wilms tumour)</li> <li>– Ovarian germ cell tumour</li> <li>– Osteosarcoma</li> <li>– Rhabdomyosarcoma</li> <li>– Testicular germ cell tumour</li> </ul>
<i>irinotecan</i>	<p><b>Injection:</b> 40 mg/2 mL in 2 mL vial; 100 mg/5 mL in 5 mL vial; 500 mg/25 mL in 25 mL vial.</p> <ul style="list-style-type: none"> <li>– Metastatic colorectal cancer</li> <li>– Nephroblastoma (Wilms tumour)</li> <li>– Rhabdomyosarcoma</li> </ul>
<i>melphalan</i>	<p><b>Tablet:</b> 2 mg</p> <p><b>Powder for injection:</b> 50 mg in vial</p> <ul style="list-style-type: none"> <li>– Multiple myeloma.</li> </ul>
<i>mercaptopurine</i>	<p><b>Tablet:</b> 50 mg.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Acute promyelocytic leukaemia.</li> </ul>
<i>methotrexate</i>	<p><b>Powder for injection:</b> 50 mg (as sodium salt) in vial.</p> <p><b>Tablet:</b> 2.5 mg (as sodium salt).</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Acute promyelocytic leukaemia</li> <li>– Burkitt lymphoma</li> <li>– Early stage breast cancer</li> <li>– Gestational trophoblastic neoplasia</li> <li>– Osteosarcoma</li> </ul>
<i>oxaliplatin</i>	<p><b>Injection:</b> 50 mg/10 mL in 10 mL vial; 100 mg/20 mL in 20 mL vial; 200 mg/40 mL in 40 mL vial.</p> <p><b>Powder for injection:</b> 50 mg; 100 mg in vial.</p> <ul style="list-style-type: none"> <li>– Early stage colon cancer</li> <li>– Metastatic colorectal cancer</li> </ul>

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<i>paclitaxel</i>	<p><b>Injection:</b> 6 mg/mL in vial.</p> <ul style="list-style-type: none"> <li>– Cervical cancer</li> <li>– Epithelial ovarian cancer</li> <li>– Early stage breast cancer</li> <li>– Metastatic breast cancer</li> <li>– Kaposi sarcoma</li> <li>– Nasopharyngeal cancer</li> <li>– Non-small cell lung cancer</li> <li>– Ovarian germ cell tumour</li> </ul>
<i>pegaspargase*</i> <small>*including quality-assured biosimilars</small>	<p><b>Injection:</b> 3,750 units/5 mL in vial.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> </ul>
<i>procarbazine [c]</i>	<p><b>Capsule:</b> 50 mg (as hydrochloride).</p> <ul style="list-style-type: none"> <li>– Hodgkin lymphoma</li> </ul>
<i>realgar-Indigo naturalis formulation</i>	<p><b>Tablet:</b> 270 mg (containing tetra-arsenic tetra-sulfide 30 mg).</p> <ul style="list-style-type: none"> <li>– Acute promyelocytic leukaemia</li> </ul>
<i>tioguanine [c]</i>	<p><b>Solid oral dosage form:</b> 40 mg.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> </ul>
<i>vinblastine</i>	<p><b>Injection:</b> 10 mg/10 mL (sulfate) in vial.  <b>Powder for injection:</b> 10 mg (sulfate) in vial.</p> <ul style="list-style-type: none"> <li>– Hodgkin lymphoma</li> <li>– Kaposi sarcoma</li> <li>– Low-grade glioma</li> <li>– Ovarian germ cell tumour</li> <li>– Testicular germ cell tumour</li> </ul>
<i>vincristine</i>	<p><b>Injection:</b> 1 mg/mL (sulfate); 2 mg/2 mL (sulfate) in vial.  <b>Powder for injection:</b> 1 mg; 5 mg (sulfate) in vial.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Burkitt lymphoma</li> <li>– Diffuse large B-cell lymphoma</li> <li>– Ewing sarcoma</li> <li>– Follicular lymphoma</li> <li>– Gestational trophoblastic neoplasia</li> <li>– Hodgkin lymphoma</li> <li>– Kaposi sarcoma</li> <li>– Low-grade glioma</li> <li>– Nephroblastoma (Wilms tumour)</li> <li>– Retinoblastoma</li> <li>– Rhabdomyosarcoma</li> </ul>
<i>vinorelbine</i>	<p><b>Capsule:</b> 20 mg; 30 mg; 80 mg.  <b>Injection:</b> 10 mg/mL in 1 mL vial; 50 mg/5 mL in 5 mL vial.</p> <ul style="list-style-type: none"> <li>– Non-small cell lung cancer</li> <li>– Metastatic breast cancer</li> <li>– Rhabdomyosarcoma</li> </ul>

# WHO Model List of Essential Medicines – 22nd List (2021)

## 8.2.2 Targeted therapies

### Complementary List

<i>all-trans retinoid acid (ATRA)</i>	<b>Capsule:</b> 10 mg. – Acute promyelocytic leukaemia.
<i>bortezomib</i>	<b>Powder for injection:</b> 3.5 mg in vial. – Multiple myeloma
<i>dasatinib</i>	<b>Tablet:</b> 20 mg; 50 mg; 70 mg; 80 mg; 100 mg; 140 mg. – Imatinib-resistant chronic myeloid leukaemia
<input checked="" type="checkbox"/> <i>erlotinib</i>  Therapeutic alternatives: - afatinib - gefitinib	<b>Tablet:</b> 100 mg, 150 mg. – EGFR mutation-positive advanced non-small cell lung cancer
<i>everolimus</i>	<b>Tablet:</b> 2.5 mg; 5 mg; 7.5 mg; 10 mg. <b>Tablet (dispersible):</b> 2 mg; 3 mg; 5 mg. – Subependymal giant cell astrocytoma
<i>ibrutinib</i>	<b>Capsule:</b> 140 mg. – Relapsed/refractory chronic lymphocytic leukaemia
<i>imatinib</i>	<b>Solid oral dosage form:</b> 100 mg; 400 mg. – Chronic myeloid leukaemia – Gastrointestinal stromal tumour – Philadelphia chromosome positive acute lymphoblastic leukaemia
<i>nilotinib</i>	<b>Capsule:</b> 150 mg; 200 mg. – Imatinib-resistant chronic myeloid leukaemia
<i>rituximab*</i>  *including quality-assured biosimilars	<b>Injection (intravenous):</b> 100 mg/10 mL in 10 mL vial; 500 mg/50 mL in 50 mL vial. – Diffuse large B-cell lymphoma – Chronic lymphocytic leukaemia – Follicular lymphoma
<i>trastuzumab*</i>  *including quality-assured biosimilars	<b>Powder for injection:</b> 60 mg; 150 mg; 440 mg in vial. – Early stage HER2 positive breast cancer – Metastatic HER2 positive breast cancer

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## 8.2.3 Immunomodulators

### Complementary List

<p><i>filgrastim*</i></p> <p>*including quality-assured biosimilars</p>	<p><b>Injection:</b> 120 micrograms/0.2 mL; 300 micrograms/0.5 mL; 480 micrograms/0.8 mL in pre-filled syringe.</p> <p><b>Injection:</b> 300 micrograms/mL in 1 mL vial; 480 micrograms/1.6 mL in 1.6 mL vial.</p> <ul style="list-style-type: none"> <li>– Primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy.</li> <li>– Secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy</li> <li>– To facilitate administration of dose dense chemotherapy regimens</li> </ul>
<p><i>lenalidomide</i></p>	<p><b>Capsule:</b> 25 mg.</p> <ul style="list-style-type: none"> <li>– Multiple myeloma</li> </ul>
<p><input type="checkbox"/> <i>nivolumab*</i></p> <p>Therapeutic alternatives*:</p> <ul style="list-style-type: none"> <li>- pembrolizumab</li> </ul> <p>*including quality-assured biosimilars</p>	<p><b>Concentrate solution for infusion:</b> 10 mg/mL.</p> <ul style="list-style-type: none"> <li>– Metastatic melanoma</li> </ul>
<p><i>thalidomide</i></p>	<p><b>Capsule:</b> 50 mg.</p> <ul style="list-style-type: none"> <li>– Multiple myeloma</li> </ul>

## 8.2.4 Hormones and antihormones

### Complementary List

<p><input type="checkbox"/> <i>abiraterone</i></p> <p>Therapeutic alternatives:</p> <ul style="list-style-type: none"> <li>- enzalutamide</li> </ul>	<p><b>Tablet:</b> 250 mg; 500 mg.</p> <ul style="list-style-type: none"> <li>– Metastatic castration-resistant prostate cancer</li> </ul>
<p><input type="checkbox"/> <i>anastrozole</i></p> <p>Therapeutic alternatives:</p> <ul style="list-style-type: none"> <li>- 4<sup>th</sup> level ATC chemical subgroup (L02BG Aromatase inhibitors)</li> </ul>	<p><b>Tablet:</b> 1 mg.</p> <ul style="list-style-type: none"> <li>– Early stage breast cancer</li> <li>– Metastatic breast cancer</li> </ul>
<p><input type="checkbox"/> <i>bicalutamide</i></p> <p>Therapeutic alternatives:</p> <ul style="list-style-type: none"> <li>- flutamide</li> <li>- nilutamide</li> </ul>	<p><b>Tablet:</b> 50 mg.</p> <ul style="list-style-type: none"> <li>– Metastatic prostate cancer</li> </ul>
<p><i>dexamethasone</i></p>	<p><b>Injection:</b> 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule.</p> <p><b>Oral liquid:</b> 2 mg/5 mL [c].</p> <p><b>Tablet:</b> 2 mg [c]; 4 mg.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Burkitt lymphoma</li> <li>– Multiple myeloma</li> </ul>
<p><i>hydrocortisone</i></p>	<p><b>Powder for injection:</b> 100 mg (as sodium succinate) in vial.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Burkitt lymphoma</li> </ul>

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<p><input type="checkbox"/> leuprorelin Therapeutic alternatives: - goserelin - triptorelin</p>	<p><b>Injection:</b> 7.5 mg; 22.5 mg in pre-filled syringe.</p> <ul style="list-style-type: none"> <li>– Early stage breast cancer</li> <li>– Metastatic prostate cancer.</li> </ul>
<p>methylprednisolone [c]</p>	<p><b>Injection:</b> 40 mg/mL (as sodium succinate) in 1 mL single-dose vial and 5 mL multi-dose vials; 80 mg/mL (as sodium succinate) in 1 mL single-dose vial.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukemia</li> <li>– Burkitt lymphoma</li> </ul>
<p><input type="checkbox"/> prednisolone Therapeutic alternatives: - prednisone</p>	<p><b>Oral liquid:</b> 5 mg/mL [c].</p> <p><b>Tablet:</b> 5 mg; 25 mg.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Burkitt lymphoma</li> <li>– Chronic lymphocytic leukaemia</li> <li>– Diffuse large B-cell lymphoma</li> <li>– Follicular lymphoma</li> <li>– Hodgkin lymphoma</li> <li>– Metastatic castration-resistant prostate cancer</li> <li>– Multiple myeloma</li> </ul>
<p>tamoxifen</p>	<p><b>Tablet:</b> 10 mg; 20 mg (as citrate).</p> <ul style="list-style-type: none"> <li>– Early stage breast cancer</li> <li>– Metastatic breast cancer.</li> </ul>

### 8.2.5 Supportive medicines

#### Complementary List

<p>allopurinol [c]</p>	<p><b>Tablet:</b> 100 mg; 300 mg.</p> <ul style="list-style-type: none"> <li>– Tumour lysis syndrome</li> </ul>
<p>mesna</p>	<p><b>Injection:</b> 100 mg/mL in 4 mL and 10 mL ampoules.</p> <p><b>Tablet:</b> 400 mg; 600 mg.</p> <ul style="list-style-type: none"> <li>– Burkitt lymphoma</li> <li>– Ewing sarcoma</li> <li>– Nephroblastoma (Wilms tumour)</li> <li>– Ovarian germ cell tumour</li> <li>– Osteosarcoma</li> <li>– Rhabdomyosarcoma</li> <li>– Testicular germ cell tumour</li> </ul>
<p>rasburicase</p>	<p><b>Powder and solvent for solution for infusion:</b> 1.5 mg; 7.5 mg in vial</p> <ul style="list-style-type: none"> <li>– Tumour lysis syndrome</li> </ul>
<p>zoledronic acid</p>	<p><b>Concentrate solution for infusion:</b> 4 mg/5 mL in 5 mL vial.</p> <p><b>Solution for infusion:</b> 4 mg/100 mL in 100 mL bottle.</p> <ul style="list-style-type: none"> <li>– Malignancy-related bone disease</li> </ul>

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9. ANTIPARKINSONISM MEDICINES	
□ biperiden Therapeutic alternatives: – trihexyphenidyl	<b>Injection:</b> 5 mg (lactate) in 1 mL ampoule. <b>Tablet:</b> 2 mg (hydrochloride).
levodopa + □ carbidopa Therapeutic alternatives: – benserazide (for carbidopa)	<b>Tablet:</b> 100 mg + 10 mg; 100 mg + 25 mg; 250 mg + 25 mg.
10. MEDICINES AFFECTING THE BLOOD	
10.1 Antianaemia medicines	
ferrous salt	<b>Oral liquid:</b> equivalent to 25 mg iron (as sulfate)/mL. <b>Tablet:</b> equivalent to 60 mg iron.
ferrous salt + folic acid	<b>Tablet:</b> equivalent to 60 mg iron + 400 micrograms folic acid. *nutritional supplement for use during pregnancy
folic acid	<b>Tablet:</b> 400 micrograms*; 1 mg; 5 mg. *periconceptual use for prevention of first occurrence of neural tube defects
hydroxocobalamin	<b>Injection:</b> 1 mg/mL (as acetate, as hydrochloride or as sulfate) in 1 mL ampoule.
<i>Complementary List</i>	
□ erythropoiesis-stimulating agents* Therapeutic alternatives: - epoetin alfa, beta and theta - darbepoetin alfa - methoxy polyethylene glycol-epoetin beta  *including quality-assured biosimilars	<b>Injection: pre-filled syringe</b> 1000 IU/0.5 mL; 2000 IU/0.5 mL; 3000 IU/0.3 mL; 4000 IU/0.4 mL; 5000 IU/0.5 mL; 6000 IU/0.6 mL; 8000 IU/0.8mL; 10 000 IU/1 mL; 20 000 IU/0.5 mL; 40 000 IU/1 mL.
10.2 Medicines affecting coagulation	
□ dabigatran Therapeutic alternatives: - apixaban - edoxaban - rivaroxaban	<b>Capsule:</b> 110 mg; 150 mg.
□ enoxaparin* Therapeutic alternatives*: - dalteparin - nadroparin  *including quality-assured biosimilars	<b>Injection: ampoule or pre-filled syringe</b> 20 mg/0.2 mL; 40 mg/0.4 mL; 60 mg/0.6 mL; 80 mg/0.8 mL; 100 mg/1 mL; 120 mg/0.8 mL; 150 mg/1 mL.
heparin sodium	<b>Injection:</b> 1000 IU/mL; 5000 IU/mL; 20 000 IU/mL in 1 mL ampoule.
phytomenadione	<b>Injection:</b> 1 mg/mL [c]; 10 mg/mL in ampoule. <b>Tablet:</b> 10 mg.
protamine sulfate	<b>Injection:</b> 10 mg/mL in 5 mL ampoule.

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tranexamic acid	<b>Injection:</b> 100 mg/mL in 10 mL ampoule.
<input type="checkbox"/> warfarin Therapeutic alternatives to be reviewed (2023)	<b>Tablet:</b> 1 mg; 2 mg; 5 mg (sodium).
<b>Complementary List</b>	
desmopressin [c]	<b>Injection:</b> 4 micrograms/mL (as acetate) in 1 mL ampoule. <b>Nasal spray:</b> 10 micrograms (as acetate) per dose.
heparin sodium [c]	<b>Injection:</b> 1000 IU/mL; 5000 IU/mL in 1 mL ampoule.
protamine sulfate [c]	<b>Injection:</b> 10 mg/mL in 5 mL ampoule.
<input type="checkbox"/> warfarin [c] Therapeutic alternatives to be reviewed (2023)	<b>Tablet:</b> 0.5 mg; 1 mg; 2 mg; 5 mg (sodium).
10.3 Other medicines for haemoglobinopathies	
<b>Complementary List</b>	
<input type="checkbox"/> deferoxamine Therapeutic alternatives: - deferasirox (oral)	<b>Powder for injection:</b> 500 mg (mesilate) in vial.
hydroxycarbamide	<b>Solid oral dosage form:</b> 200 mg; 500 mg; 1 g.
<b>11. BLOOD PRODUCTS OF HUMAN ORIGIN AND PLASMA SUBSTITUTES</b>	
<b>11.1 Blood and blood components</b>	
In accordance with the World Health Assembly resolution WHA63.12, WHO recognizes that achieving self-sufficiency, unless special circumstances preclude it, in the supply of safe blood components based on voluntary, non-remunerated blood donation, and the security of that supply are important national goals to prevent blood shortages and meet the transfusion requirements of the patient population. All preparations should comply with the WHO requirements.	
fresh-frozen plasma	
platelets	
red blood cells	
whole blood	
<b>11.2 Plasma-derived medicines</b>	
All human plasma-derived medicines should comply with the WHO requirements.	
<b>11.2.1 Human immunoglobulins</b>	
anti-D immunoglobulin	<b>Injection:</b> 250 micrograms in single-dose vial.
anti-rabies immunoglobulin	<b>Injection:</b> 150 IU/mL in vial.
anti-tetanus immunoglobulin	<b>Injection:</b> 500 IU in vial.

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Complementary List	
<i>normal immunoglobulin</i>	<p><i>Intramuscular administration:</i> 16% protein solution.*</p> <p><i>Intravenous administration:</i> 5%; 10% protein solution.**</p> <p><i>Subcutaneous administration:</i> 15%; 16% protein solution.*</p> <p>*Indicated for primary immune deficiency.</p> <p>**Indicated for primary immune deficiency and Kawasaki disease.</p>
11.2.2 Blood coagulation factors	
Complementary List	
<input type="checkbox"/> coagulation factor VIII Therapeutic alternatives to be reviewed (2023)	<b>Powder for injection:</b> 500 IU/vial.
<input type="checkbox"/> coagulation factor IX Therapeutic alternatives to be reviewed (2023)	<b>Powder for injection:</b> 500 IU/vial, 1000 IU/vial.
11.3 Plasma substitutes	
<input type="checkbox"/> dextran 70 Therapeutic alternatives: - Polygeline injectable solution 3.5%	<b>Injectable solution:</b> 6%.
12. CARDIOVASCULAR MEDICINES	
12.1 Antianginal medicines	
<input type="checkbox"/> bisoprolol Therapeutic alternatives: - carvedilol - metoprolol	<b>Tablet:</b> 1.25 mg; 5 mg.
glyceryl trinitrate	<b>Tablet (sublingual):</b> 500 micrograms.
isosorbide dinitrate	<b>Tablet (sublingual):</b> 5 mg.
verapamil	<b>Tablet:</b> 40 mg; 80 mg (hydrochloride).
12.2 Antiarrhythmic medicines	
<input type="checkbox"/> bisoprolol Therapeutic alternatives: - carvedilol - metoprolol	<b>Tablet:</b> 1.25 mg; 5 mg.
digoxin	<b>Injection:</b> 250 micrograms/mL in 2 mL ampoule. <b>Oral liquid:</b> 50 micrograms/mL. <b>Tablet:</b> 62.5 micrograms; 250 micrograms.
epinephrine (adrenaline)	<b>Injection:</b> 100 micrograms/mL (as acid tartrate or hydrochloride) in 10 mL ampoule.
lidocaine	<b>Injection:</b> 20 mg/mL (hydrochloride) in 5 mL ampoule.
verapamil	<b>Injection:</b> 2.5 mg/mL (hydrochloride) in 2 mL ampoule. <b>Tablet:</b> 40 mg; 80 mg (hydrochloride).

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<i>Complementary List</i>	
<i>amiodarone</i>	<p><b>Injection:</b> 50 mg/mL (hydrochloride) in 3 mL ampoule.</p> <p><b>Tablet:</b> 100 mg; 200 mg; 400 mg (hydrochloride).</p>
12.3 Antihypertensive medicines	
<input type="checkbox"/> amlodipine  Therapeutic alternatives:  - 4 <sup>th</sup> level ATC chemical subgroup (C08CA Dihydropyridine derivatives)	  <b>Tablet:</b> 5 mg (as maleate, mesylate or besylate).
<input type="checkbox"/> bisoprolol  Therapeutic alternatives:  - atenolol* - carvedilol - metoprolol	  <b>Tablet:</b> 1.25 mg; 5 mg.  *atenolol should not be used as a first-line agent in uncomplicated hypertension in patients > 60 years
<input type="checkbox"/> enalapril  Therapeutic alternatives:  - 4 <sup>th</sup> level ATC chemical subgroup (C09AA ACE inhibitors, plain)	  <b>Tablet:</b> 2.5 mg; 5 mg (as hydrogen maleate).
<input type="checkbox"/> hydralazine*  	  <b>Powder for injection:</b> 20 mg (hydrochloride) in ampoule.  <b>Tablet:</b> 25 mg; 50 mg (hydrochloride).  *Hydralazine is listed for use only in the acute management of severe pregnancy-induced hypertension. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines.
<input type="checkbox"/> hydrochlorothiazide  Therapeutic alternatives:  - chlorothiazide - chlorthalidone - indapamide	  <b>Oral liquid:</b> 50 mg/5 mL.  <b>Solid oral dosage form:</b> 12.5 mg; 25 mg.
<input type="checkbox"/> lisinopril + <input type="checkbox"/> amlodipine  Therapeutic alternatives:  - 4 <sup>th</sup> level ATC chemical subgroup (C09AA ACE inhibitors, plain) (for lisinopril)  - 4 <sup>th</sup> level ATC chemical subgroup (C08CA Dihydropyridine derivatives) (for amlodipine)	  <b>Tablet:</b> 10 mg + 5 mg; 20 mg + 5 mg; 20 mg + 10 mg.
<input type="checkbox"/> lisinopril + <input type="checkbox"/> hydrochlorothiazide  Therapeutic alternatives:  - 4 <sup>th</sup> level ATC chemical subgroup (C09AA ACE inhibitors, plain) (for lisinopril)  - chlorthalidone, chlorothiazide, indapamide (for hydrochlorothiazide)	  <b>Tablet:</b> 10 mg + 12.5 mg; 20 mg + 12.5 mg; 20 mg + 25 mg.
<input type="checkbox"/> losartan  Therapeutic alternatives:  - 4 <sup>th</sup> level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain)	  <b>Tablet:</b> 25 mg; 50 mg; 100 mg.

# WHO Model List of Essential Medicines – 22nd List (2021)

methyldopa*	<p><b>Tablet:</b> 250 mg.</p> <p>*Methyldopa is listed for use only in the management of pregnancy-induced hypertension. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines.</p>
<input type="checkbox"/> telmisartan + <input type="checkbox"/> amlodipine Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain) (for telmisartan) - 4 <sup>th</sup> level ATC chemical subgroup (C08CA Dihydropyridine derivatives) (for amlodipine)	<p><b>Tablet:</b> 40 mg + 5 mg; 80 mg + 5 mg; 80 mg + 10 mg.</p>
<input type="checkbox"/> telmisartan + <input type="checkbox"/> hydrochlorothiazide Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain) (for telmisartan) - chlorthalidone, chlorothiazide, indapamide (for hydrochlorothiazide)	<p><b>Tablet:</b> 40 mg + 12.5 mg; 80 mg + 12.5 mg; 80 mg + 25 mg.</p>
<p><b>Complementary List</b></p>	
sodium nitroprusside	<b>Powder for infusion:</b> 50 mg in ampoule.
<h2>12.4 Medicines used in heart failure</h2>	
<input type="checkbox"/> bisoprolol Therapeutic alternatives: - carvedilol - metoprolol	<p><b>Tablet:</b> 1.25 mg; 5 mg.</p>
<input type="checkbox"/> digoxin	<p><b>Injection:</b> 250 micrograms/mL in 2 mL ampoule.  <b>Oral liquid:</b> 50 micrograms/mL.  <b>Tablet:</b> 62.5 micrograms; 250 micrograms.</p>
<input type="checkbox"/> enalapril Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (C09AA ACE inhibitors, plain)	<p><b>Tablet:</b> 2.5 mg; 5 mg (as hydrogen maleate).</p>
<input type="checkbox"/> furosemide Therapeutic alternatives: - bumetanide - torasemide	<p><b>Injection:</b> 10 mg/mL in 2 mL ampoule.  <b>Oral liquid:</b> 20 mg/5 mL [c].  <b>Tablet:</b> 40 mg.</p>
<input type="checkbox"/> hydrochlorothiazide Therapeutic alternatives: - chlorothiazide - chlorthalidone - indapamide	<p><b>Oral liquid:</b> 50 mg/5 mL.  <b>Solid oral dosage form:</b> 25 mg.</p>
<input type="checkbox"/> losartan Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain)	<p><b>Tablet:</b> 25 mg; 50 mg; 100 mg.</p>

# WHO Model List of Essential Medicines – 22nd List (2021)

spironolactone	Tablet: 25 mg.
<i>Complementary List</i>	
dopamine	<i>Injection: 40 mg/mL (hydrochloride) in 5 mL vial.</i>
12.5 Antithrombotic medicines	
12.5.1 Anti-platelet medicines	
acetylsalicylic acid	Tablet: 100 mg.
clopidogrel	Tablet: 75 mg; 300 mg
12.5.2 Thrombolytic medicines	
<i>Complementary List</i>	
alteplase	<i>Powder for injection: 10 mg; 20 mg; 50 mg in vial</i>
streptokinase	<i>Powder for injection: 1.5 million IU in vial.</i>
12.6 Lipid-lowering agents	
<input type="checkbox"/> simvastatin* Therapeutic alternatives: <ul style="list-style-type: none"> <li>- atorvastatin</li> <li>- fluvastatin</li> <li>- lovastatin</li> <li>- pravastatin</li> </ul>	Tablet: 5 mg; 10 mg; 20 mg; 40 mg. *For use in high-risk patients.
13. DERMATOLOGICAL MEDICINES (topical)	
13.1 Antifungal medicines	
<input type="checkbox"/> miconazole Therapeutic alternatives: <ul style="list-style-type: none"> <li>- 4<sup>th</sup> level ATC chemical subgroup (D01AC Imidazole and triazole derivatives) excluding combinations</li> </ul>	Cream or ointment: 2% (nitrate).
selenium sulfide	Detergent-based suspension: 2%.
sodium thiosulfate	Solution: 15%.
terbinafine	Cream or ointment: 1% (hydrochloride).

# WHO Model List of Essential Medicines – 22nd List (2021)

13.2 Anti-infective medicines	
mupirocin	Cream: 2% (as calcium). Ointment: 2%.
potassium permanganate	Aqueous solution: 1:10 000.
silver sulfadiazine <small>a</small>	Cream: 1%. <small>a</small> > 2 months.
13.3 Anti-inflammatory and antipruritic medicines	
<input type="checkbox"/> betamethasone <small>a</small> Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (D07AC Corticosteroids, potent (group III))	Cream or ointment: 0.1% (as valerate). <small>a</small> Hydrocortisone preferred in neonates.
calamine	Lotion.
<input type="checkbox"/> hydrocortisone Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (D07AA Corticosteroids, weak (group I))	Cream or ointment: 1% (acetate).
13.4 Medicines affecting skin differentiation and proliferation	
benzoyl peroxide	Cream or lotion: 5%.
<input type="checkbox"/> calcipotriol Therapeutic alternatives: - calcitriol - tacalcitol	Cream or ointment: 50 micrograms/mL (0.005%). Lotion: 50 micrograms/mL (0.005%).
coal tar	Solution: 5%.
fluorouracil	Ointment: 5%.
<input type="checkbox"/> podophyllum resin Therapeutic alternatives: - podophyllotoxin	Solution: 10% to 25%.
salicylic acid	Solution: 5%.
urea	Cream or ointment: 5%; 10%.
13.5 Scabicides and pediculicides	
<input type="checkbox"/> benzyl benzoate <small>a</small> Therapeutic alternatives: - precipitated sulfur topical ointment	Lotion: 25%. <small>a</small> > 2 years.
permethrin	Cream: 5%. Lotion: 1%.

# WHO Model List of Essential Medicines – 22nd List (2021)

14. DIAGNOSTIC AGENTS	
<b>14.1 Ophthalmic medicines</b>	
fluorescein	<b>Eye drops:</b> 1% (sodium salt).
<input type="checkbox"/> tropicamide Therapeutic alternatives: - atropine - cyclopentolate	 <b>Eye drops:</b> 0.5%.
<b>14.2 Radiocontrast media</b>	
<input type="checkbox"/> amidotrizoate Therapeutic alternatives to be reviewed (2023)	<b>Injection:</b> 140 mg to 420 mg iodine/mL (as sodium or meglumine salt) in 20 mL ampoule.
barium sulfate	<b>Aqueous suspension.</b>
<input type="checkbox"/> iohexol Therapeutic alternatives to be reviewed (2023)	<b>Injection:</b> 140 mg to 350 mg iodine/mL in 5 mL; 10 mL; 20 mL ampoules.
<i>Complementary List</i>	
<i>barium sulfate [c]</i>	<i>Aqueous suspension.</i>
<input type="checkbox"/> meglumine iotroxate Therapeutic alternatives to be reviewed (2023)	<b>Solution:</b> 5 g to 8 g iodine in 100 mL to 250 mL.
<b>15. ANTISEPTICS AND DISINFECTANTS</b>	
<b>15.1 Antiseptics</b>	
<input type="checkbox"/> chlorhexidine Therapeutic alternatives to be reviewed (2023)	<b>Solution:</b> 5% (digluconate).
<input type="checkbox"/> ethanol Therapeutic alternatives: - propanol	<b>Solution:</b> 70% (denatured).
<input type="checkbox"/> povidone iodine Therapeutic alternatives: - iodine	<b>Solution:</b> 10% (equivalent to 1% available iodine).
<b>15.2 Disinfectants</b>	
alcohol based hand rub	<b>Solution:</b> containing ethanol 80% volume/volume. <b>Solution:</b> containing isopropyl alcohol 75% volume/volume.
chlorine base compound	<b>Liquid:</b> (0.1% available chlorine) for solution. <b>Powder:</b> (0.1% available chlorine) for solution. <b>Solid:</b> (0.1% available chlorine) for solution.

# WHO Model List of Essential Medicines – 22nd List (2021)

<input type="checkbox"/> chloroxylenol Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (D08AE Phenol and derivatives)	<b>Solution:</b> 4.8%.
glutaral	<b>Solution:</b> 2%.
<b>16. DIURETICS</b>	
amiloride	<b>Tablet:</b> 5 mg (hydrochloride).
<input type="checkbox"/> furosemide Therapeutic alternatives: - bumetanide - torasemide	<b>Injection:</b> 10 mg/mL in 2 mL ampoule. <b>Oral liquid:</b> 20 mg/5 mL [c]. <b>Tablet:</b> 10 mg [c]; 20 mg [c]; 40 mg.
<input type="checkbox"/> hydrochlorothiazide Therapeutic alternatives: - chlorothiazide - chlortalidone - indapamide	<b>Solid oral dosage form:</b> 25 mg.
mannitol	<b>Injectable solution:</b> 10%; 20%.
spironolactone	<b>Tablet:</b> 25 mg.
<i>Complementary List</i>	
<input type="checkbox"/> hydrochlorothiazide[c] Therapeutic alternatives: - chlorothiazide - chlortalidone	<b>Tablet (scored):</b> 25 mg.
mannitol [c]	<b>Injectable solution:</b> 10%; 20%.
spironolactone[c]	<b>Oral liquid:</b> 5 mg/5 mL; 10 mg/5 mL; 25 mg/5 mL. <b>Tablet:</b> 25 mg.
<b>17. GASTROINTESTINAL MEDICINES</b>	
<i>Complementary List</i>	
pancreatic enzymes[c]	Age-appropriate formulations and doses including lipase, protease and amylase.
<b>17.1 Antiulcer medicines</b>	
<input type="checkbox"/> omeprazole Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (A02BC Proton pump inhibitors) excluding combinations	<b>Powder for injection:</b> 40 mg in vial <b>Powder for oral liquid:</b> 20 mg; 40 mg sachets. <b>Solid oral dosage form:</b> 10 mg; 20 mg; 40 mg.
<input type="checkbox"/> ranitidine Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (A02BA H <sub>2</sub> -receptor antagonists) excluding combinations	<b>Injection:</b> 25 mg/mL (as hydrochloride) in 2 mL ampoule. <b>Oral liquid:</b> 75 mg/5 mL (as hydrochloride). <b>Tablet:</b> 150 mg (as hydrochloride).

# WHO Model List of Essential Medicines – 22nd List (2021)

## 17.2 Antiemetic medicines

dexamethasone	<b>Injection:</b> 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule. <b>Oral liquid:</b> 0.5 mg/5 mL; 2 mg/5 mL. <b>Solid oral dosage form:</b> 0.5 mg; 0.75 mg; 1.5 mg; 4 mg.
metoclopramide <span style="border: 1px solid black; padding: 0 2px;">a</span>	<b>Injection:</b> 5 mg/mL (hydrochloride) in 2 mL ampoule. <b>Oral liquid:</b> 5 mg/5 mL <span style="border: 1px solid black; padding: 0 2px;">c</span> . <b>Tablet:</b> 10 mg (hydrochloride). <span style="border: 1px solid black; padding: 0 2px;">a</span> Not in neonates.
<input type="checkbox"/> ondansetron <span style="border: 1px solid black; padding: 0 2px;">a</span> Therapeutic alternatives: - dolasetron - granisetron - palonosetron - tropisetron	<b>Injection:</b> 2 mg base/mL in 2 mL ampoule (as hydrochloride). <b>Oral liquid:</b> 4 mg base/5 mL. <b>Solid oral dosage form:</b> Eq 4 mg base; Eq 8 mg base; Eq 24 mg base. <span style="border: 1px solid black; padding: 0 2px;">a</span> > 1 month.

### Complementary list

aprepitant	<b>Capsule:</b> 80 mg; 125 mg; 165 mg <b>Powder for oral susension:</b> 125 mg in sachet
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## 17.3 Anti-inflammatory medicines

<input type="checkbox"/> sulfasalazine Therapeutic alternatives: - mesalazine	<b>Retention enema.</b> <b>Suppository:</b> 500 mg. <b>Tablet:</b> 500 mg.
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### Complementary List

hydrocortisone	<b>Retention enema:</b> 100 mg/60 mL. <b>Suppository:</b> 25 mg (acetate).
prednisolone	<b>Retention enema:</b> 20 mg/100 mL (as sodium phosphate).

## 17.4 Laxatives

<input type="checkbox"/> senna Therapeutic alternatives: - bisacodyl	<b>Tablet:</b> 7.5 mg (sennosides) (or traditional dosage forms).
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## 17.5 Medicines used in diarrhoea

oral rehydration salts – zinc sulfate <span style="border: 1px solid black; padding: 0 2px;">c</span>	<b>Co-package containing:</b> <b>ORS powder for dilution</b> (see Section 17.5.1) – zinc sulfate <b>solid oral dosage form</b> 20 mg (see Section 17.5.2)
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# WHO Model List of Essential Medicines – 22nd List (2021)

## 17.5.1 Oral rehydration

	Powder for dilution in 200 mL; 500 mL; 1 L.
oral rehydration salts	glucose: 75 mEq sodium: 75 mEq or mmol/L chloride: 65 mEq or mmol/L potassium: 20 mEq or mmol/L citrate: 10 mmol/L osmolarity: 245 mOsm/L glucose: 13.5 g/L sodium chloride: 2.6 g/L potassium chloride: 1.5 g/L trisodium citrate dihydrate*: 2.9 g/L
	*trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/L. However, as the stability of this latter formulation is very poor under tropical conditions, it is recommended only when manufactured for immediate use.

## 17.5.2 Medicines for diarrhoea

zinc sulfate*	Solid oral dosage form: 20 mg.  *In acute diarrhoea zinc sulfate should be used as an adjunct to oral rehydration salts.
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## 18. MEDICINES FOR ENDOCRINE DISORDERS

### 18.1 Adrenal hormones and synthetic substitutes

fludrocortisone	Tablet: 100 micrograms (acetate).
hydrocortisone	Tablet: 5 mg; 10 mg; 20 mg.

### 18.2 Androgens

#### *Complementary List*

testosterone	Injection: 200 mg (enanthate) in 1 mL ampoule.
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### 18.3 Estrogens

### 18.4 Progestogens

<input type="checkbox"/> medroxyprogesterone acetate Therapeutic alternatives: - norethisterone	Tablet: 5 mg.
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# WHO Model List of Essential Medicines – 22nd List (2021)

<b>18.5 Medicines for diabetes</b>	
<b>18.5.1 Insulins</b>	
insulin injection (soluble)* <i>*including quality-assured biosimilars</i>	<b>Injection:</b> 40 IU/mL in 10 mL vial; 100 IU/mL in 10 mL vial.
intermediate-acting insulin* <i>*including quality-assured biosimilars</i>	<b>Injection:</b> 40 IU/mL in 10 mL vial; 100 IU/mL in 10 mL vial (as compound insulin zinc suspension or isophane insulin).
<input type="checkbox"/> long-acting insulin analogues* Therapeutic alternatives: - insulin degludec - insulin detemir - insulin glargine <i>*including quality-assured biosimilars</i>	<b>Injection:</b> 100 IU/mL in 3 mL cartridge or pre-filled pen.
<b>18.5.2 Oral hypoglycaemic agents</b>	
<input type="checkbox"/> empagliflozin Therapeutic alternatives: - canagliflozin - dapagliflozin	<b>Tablet:</b> 10 mg; 25 mg.
<input type="checkbox"/> gliclazide* Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (A10BB Sulfonylureas)	<b>Solid oral dosage form:</b> (controlled-release tablets) 30 mg; 60 mg; 80 mg. <i>*glibenclamide not suitable above 60 years.</i>
metformin	<b>Tablet:</b> 500 mg (hydrochloride).
<i>Complementary List</i>	
<i>metformin [c]</i>	<b>Tablet:</b> 500 mg (hydrochloride).
<b>18.6 Medicines for hypoglycaemia</b>	
glucagon	<b>Injection:</b> 1 mg/mL.
<i>Complementary List</i>	
<i>diazoxide [c]</i>	<b>Oral liquid:</b> 50 mg/mL. <b>Tablet:</b> 50 mg.
<b>18.7 Thyroid hormones and antithyroid medicines</b>	
levothyroxine	<b>Tablet:</b> 25 micrograms [c]; 50 micrograms; 100 micrograms (sodium salt).
potassium iodide	<b>Tablet:</b> 60 mg.
<input type="checkbox"/> methimazole Therapeutic alternatives: - carbimazole (depending on local availability)	<b>Tablet:</b> 5mg, 10mg, 20mg.
propylthiouracil*	<b>Tablet:</b> 50 mg. <i>*For use when alternative first-line treatment is not appropriate or available; and in patients during the first trimester of pregnancy.</i>

# WHO Model List of Essential Medicines – 22nd List (2021)

<i>Complementary List</i>	
<i>Lugol's solution [c]</i>	<i>Oral liquid:</i> about 130 mg total iodine/mL.
<input type="checkbox"/> <i>methimazole [c]</i>  <i>Therapeutic alternatives:</i> - carbimazole (depending on local availability)	<i>Tablet:</i> 5mg, 10mg, 20mg.
<i>potassium iodide [c]</i>	<i>Tablet:</i> 60 mg.
<i>propylthiouracil* [c]</i>	<i>Tablet:</i> 50 mg.  <i>*For use when alternative first-line treatment is not appropriate or available</i>
<b>19. IMMUNOLOGICALS</b>	
<b>19.1 Diagnostic agents</b>	
All tuberculins should comply with the WHO requirements for tuberculins.	
<i>tuberculin, purified protein derivative (PPD)</i>	<b>Injection.</b>
<b>19.2 Sera, immunoglobulins and monoclonal antibodies</b>	
All plasma fractions should comply with the WHO requirements.	
<i>anti-rabies virus monoclonal antibodies*</i>  <i>*including quality-assured biosimilars</i>	<b>Injection:</b> 40 IU/mL in 1.25 mL, 2.5 mL vial; 100 IU/mL in 2.5 mL vial (human).  <b>Injection:</b> 300 IU/mL in 10 mL vial; 600 IU/mL in 1 mL, 2.5 mL and 5 mL vial (murine).
<i>antivenom immunoglobulin*</i>	<b>Injection.</b>  <i>*Exact type to be defined locally.</i>
<i>diphtheria antitoxin</i>	<b>Injection:</b> 10 000 IU; 20 000 IU in vial.
<i>equine rabies immunoglobulin</i>	<b>Injection:</b> 150 IU/mL; 200 IU/mL; 300 IU/mL; 400 IU/mL in vial.

# WHO Model List of Essential Medicines – 22nd List (2021)

## 19.3 Vaccines

WHO immunization policy recommendations are published in vaccine position papers based on recommendations made by the Strategic Advisory Group of Experts on Immunization (SAGE).

WHO vaccine position papers are updated three to four times per year. The list below details the vaccines for which there is a recommendation from SAGE and a corresponding WHO position paper as at September 2020. The most recent versions of the WHO position papers, reflecting the current evidence related to a specific vaccine and the related recommendations, can be accessed at any time on the WHO website at:

<https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers>

Vaccine recommendations may be universal or conditional (e.g., in certain regions, in some high-risk populations or as part of immunization programmes with certain characteristics). Details are available in the relevant position papers, and in the Summary Tables of WHO Routine Immunization Recommendations available on the WHO website at:

<https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/who-recommendations-for-routine-immunization---summary-tables>

Selection of vaccines from the Model List will need to be determined by each country after consideration of international recommendations, epidemiology and national priorities.

All vaccines should comply with the WHO requirements for biological substances.

WHO noted the need for vaccines used in children to be polyvalent.

<i>Recommendations for all</i>	
BCG vaccine	
diphtheria vaccine	
Haemophilus influenzae type b vaccine	
hepatitis B vaccine	
human papilloma virus (HPV) vaccine	
measles vaccine	
pertussis vaccine	
pneumococcal vaccine	
poliomyelitis vaccine	
rotavirus vaccine	
rubella vaccine	
tetanus vaccine	
<i>Recommendations for certain regions</i>	
Japanese encephalitis vaccine	
tick-borne encephalitis vaccine	
yellow fever vaccine	
<i>Recommendations for some high-risk populations</i>	
cholera vaccine	
dengue vaccine	
hepatitis A vaccine	
meningococcal meningitis vaccine	

# WHO Model List of Essential Medicines – 22nd List (2021)

rabies vaccine	
typhoid vaccine	

## *Recommendations for immunization programmes with certain characteristics*

influenza vaccine (seasonal)	
mumps vaccine	
varicella vaccine	

## 20. MUSCLE RELAXANTS (PERIPHERALLY-ACTING) AND CHOLINESTERASE INHIBITORS

<input type="checkbox"/> atracurium Therapeutic alternatives to be reviewed (2023)	<b>Injection:</b> 10 mg/mL (besylate).
neostigmine	<b>Injection:</b> 500 micrograms/mL (methylsulfate) in 1 mL ampoule; 2.5 mg/mL (methylsulfate) in 1 mL ampoule. <b>Tablet:</b> 15 mg (bromide).
suxamethonium	<b>Injection:</b> 50 mg/mL (chloride) in 2 mL ampoule. <b>Powder for injection:</b> (chloride), in vial.
<input type="checkbox"/> vecuronium [c] Therapeutic alternatives to be reviewed (2023)	<b>Powder for injection:</b> 10 mg (bromide) in vial.

### *Complementary List*

pyridostigmine	<b>Injection:</b> 1 mg in 1 mL ampoule. <b>Tablet:</b> 60 mg (bromide).
<input type="checkbox"/> vecuronium Therapeutic alternatives to be reviewed (2023)	<b>Powder for injection:</b> 10 mg (bromide) in vial.

## 21. OPHTHALMOLOGICAL PREPARATIONS

### 21.1 Anti-infective agents

aciclovir	<b>Ointment:</b> 3% W/W.
azithromycin	<b>Solution (eye drops):</b> 1.5%. – <i>Trachoma</i>
erythromycin	<b>Ointment:</b> 0.5% [c] – <i>Infections due to Chlamydia trachomatis or Neisseria gonorrhoea.</i>
<input type="checkbox"/> gentamicin Therapeutic alternatives: - amikacin - kanamycin - netilmicin - tobramycin	<b>Solution (eye drops):</b> 0.3% (sulfate). – <i>Bacterial blepharitis</i> – <i>Bacterial conjunctivitis</i>

# WHO Model List of Essential Medicines – 22nd List (2021)

natamycin	Suspension (eye drops): 5% – <i>Fungal keratitis</i>
<input type="checkbox"/> ofloxacin  Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (S01AE Fluoroquinolones)	<b>Solution (eye drops):</b> 0.3%. – <i>Bacterial conjunctivitis</i> – <i>Bacterial keratitis</i>
<input type="checkbox"/> tetracycline  Therapeutic alternatives: - chlortetracycline - oxytetracycline	<b>Eye ointment:</b> 1% (hydrochloride). – <i>Bacterial blepharitis</i> – <i>Bacterial conjunctivitis</i> – <i>Bacterial keratitis</i> – <i>Trachoma</i>
<b>21.2 Anti-inflammatory agents</b>	
<input type="checkbox"/> prednisolone  Therapeutic alternatives to be reviewed (2023)	<b>Solution (eye drops):</b> 0.5% (sodium phosphate).
<b>21.3 Local anaesthetics</b>	
<input type="checkbox"/> tetracaine <sup>a</sup>  Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (S01HA Local anaesthetics) excluding cocaine and combinations	<b>Solution (eye drops):</b> 0.5% (hydrochloride). <sup>a</sup> Not in preterm neonates.
<b>21.4 Miotics and antiglaucoma medicines</b>	
acetazolamide	<b>Tablet:</b> 250 mg.
latanoprost	<b>Solution (eye drops):</b> 50 micrograms/mL
<input type="checkbox"/> pilocarpine  Therapeutic alternatives: - carbachol	<b>Solution (eye drops):</b> 2%; 4% (hydrochloride or nitrate).
<input type="checkbox"/> timolol  Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (S01ED Beta blocking agents) excluding combinations	<b>Solution (eye drops):</b> 0.25%; 0.5% (as hydrogen maleate).
<b>21.5 Mydriatics</b>	
<input type="checkbox"/> atropine <sup>a</sup>  Therapeutic alternatives*: - cyclopentolate hydrochloride - homatropine hydrobromide  *EMLc only	<b>Solution (eye drops):</b> 0.1%; 0.5%; 1% (sulfate). <sup>a</sup> > 3 months.
<i>Complementary List</i>	
epinephrine (adrenaline)	<b>Solution (eye drops):</b> 2% (as hydrochloride).
<b>21.6 Anti-vascular endothelial growth factor (VEGF) preparations</b>	
<i>Complementary List</i>	
bevacizumab*  *including quality-assured biosimilars	<b>Injection:</b> 25 mg/mL.

# WHO Model List of Essential Medicines – 22nd List (2021)

22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE	
22.1 Contraceptives	
22.1.1 <i>Oral hormonal contraceptives</i>	
<input type="checkbox"/> ethinylestradiol + <input type="checkbox"/> levonorgestrel Therapeutic alternatives to be reviewed (2023)	Tablet: 30 micrograms + 150 micrograms.
<input type="checkbox"/> ethinylestradiol + <input type="checkbox"/> norethisterone Therapeutic alternatives to be reviewed (2023)	Tablet: 35 micrograms + 1 mg.
levonorgestrel	Tablet: 30 micrograms; 750 micrograms (pack of two); 1.5 mg.
ulipristal	Tablet: 30 mg (as acetate)
22.1.2 <i>Injectable hormonal contraceptives</i>	
estradiol cypionate + medroxyprogesterone acetate	Injection: 5 mg + 25 mg.
medroxyprogesterone acetate	Injection (intramuscular): 150 mg/mL in 1 mL vial. Injection (subcutaneous): 104 mg/0.65 mL in pre-filled syringe or single-dose injection delivery system.
norethisterone enantate	Oily solution: 200 mg/mL in 1 mL ampoule.
22.1.3 <i>Intrauterine devices</i>	
copper-containing device	
levonorgestrel-releasing intrauterine system	Intrauterine system: with reservoir containing 52 mg of levonorgestrel
22.1.4 <i>Barrier methods</i>	
condoms	
diaphragms	
22.1.5 <i>Implantable contraceptives</i>	
etonogestrel-releasing implant	Single-rod etonogestrel-releasing implant: containing 68 mg of etonogestrel.
levonorgestrel-releasing implant	Two-rod levonorgestrel-releasing implant: each rod containing 75 mg of levonorgestrel (150 mg total).
22.1.6 <i>Intravaginal contraceptives</i>	
ethinylestradiol + etonogestrel	Vaginal ring: containing 2.7 mg + 11.7 mg
progesterone vaginal ring*	Progesterone-releasing vaginal ring: containing 2.074 g of micronized progesterone. *For use in women actively breastfeeding at least 4 times per day
22.2 Ovulation inducers	
<i>Complementary List</i>	
clomifene	Tablet: 50 mg (citrate).

# WHO Model List of Essential Medicines – 22nd List (2021)

22.3 Uterotonics																															
carbetocin	<b>Injection (heat stable):</b> 100 micrograms/mL																														
□ ergometrine Therapeutic alternatives: - methylergometrine	<b>Injection:</b> 200 micrograms (hydrogen maleate) in 1 mL ampoule.																														
mifepristone – misoprostol  Where permitted under national law and where culturally acceptable.	<b>Tablet 200 mg – tablet 200 micrograms.</b>  <b>Co-package containing:</b> mifepristone 200 mg tablet [1] and misoprostol 200 micrograms tablet [4]																														
misoprostol	<b>Tablet:</b> 200 micrograms. – Management of incomplete abortion and miscarriage; – Prevention and treatment of postpartum haemorrhage where oxytocin is not available or cannot be safely used  <b>Vaginal tablet:</b> 25 micrograms.*  *Only for use for induction of labour where appropriate facilities are available.																														
oxytocin	<b>Injection:</b> 10 IU in 1 mL.																														
22.4 Antioxytoxics (tocolytics)																															
nifedipine	<b>Immediate-release capsule:</b> 10 mg.																														
22.5 Other medicines administered to the mother																															
dexamethasone	<b>Injection:</b> 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule.																														
multiple micronutrient supplement*	<b>Tablet containing:</b> <table> <tbody> <tr> <td>Vitamin A (retinol acetate)</td> <td>800 micrograms retinol activity equivalent</td> </tr> <tr> <td>Vitamin C (ascorbic acid)</td> <td>70 mg</td> </tr> <tr> <td>Vitamin D (cholecalciferol)</td> <td>5 micrograms (200 IU)</td> </tr> <tr> <td>Vitamin E (alpha tocopherol succinate)</td> <td>10 mg alpha tocopherol equivalent</td> </tr> <tr> <td>Vitamin B1 (thiamine mononitrate)</td> <td>1.4 mg</td> </tr> <tr> <td>Vitamin B2 (riboflavin)</td> <td>1.4 mg</td> </tr> <tr> <td>Vitamin B3 (niacinamide)</td> <td>18 mg niacin equivalent</td> </tr> <tr> <td>Vitamin B6 (pyridoxine hydrochloride)</td> <td>1.9 mg</td> </tr> <tr> <td>Folic acid (folic acid)</td> <td>680 micrograms dietary folate equivalent (400 micrograms)</td> </tr> <tr> <td>Vitamin B12 (cyanocobalamin)</td> <td>2.6 micrograms</td> </tr> <tr> <td>Iron (ferrous fumarate)</td> <td>30 mg</td> </tr> <tr> <td>Iodine (potassium iodide)</td> <td>150 micrograms</td> </tr> <tr> <td>Zinc (zinc oxide)</td> <td>15 mg</td> </tr> <tr> <td>Selenium (sodium selenite)</td> <td>65 micrograms</td> </tr> <tr> <td>Copper (cupric oxide)</td> <td>2 mg</td> </tr> </tbody> </table> <p>*For use in specific contexts. Refer to current WHO recommendations.</p>	Vitamin A (retinol acetate)	800 micrograms retinol activity equivalent	Vitamin C (ascorbic acid)	70 mg	Vitamin D (cholecalciferol)	5 micrograms (200 IU)	Vitamin E (alpha tocopherol succinate)	10 mg alpha tocopherol equivalent	Vitamin B1 (thiamine mononitrate)	1.4 mg	Vitamin B2 (riboflavin)	1.4 mg	Vitamin B3 (niacinamide)	18 mg niacin equivalent	Vitamin B6 (pyridoxine hydrochloride)	1.9 mg	Folic acid (folic acid)	680 micrograms dietary folate equivalent (400 micrograms)	Vitamin B12 (cyanocobalamin)	2.6 micrograms	Iron (ferrous fumarate)	30 mg	Iodine (potassium iodide)	150 micrograms	Zinc (zinc oxide)	15 mg	Selenium (sodium selenite)	65 micrograms	Copper (cupric oxide)	2 mg
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Zinc (zinc oxide)	15 mg																														
Selenium (sodium selenite)	65 micrograms																														
Copper (cupric oxide)	2 mg																														
tranexamic acid	<b>Injection:</b> 100 mg/mL in 10 mL ampoule																														
22.6 Medicines administered to the neonate [c]																															
caffeine citrate [c]	<b>Injection:</b> 20 mg/mL (equivalent to 10 mg caffeine base/mL). <b>Oral liquid:</b> 20 mg/mL (equivalent to 10 mg caffeine base/mL).																														
chlorhexidine [c]	<b>Solution or gel:</b> 7.1% (digluconate) delivering 4% chlorhexidine (for umbilical cord care).																														

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<i>Complementary List</i>	
<input type="checkbox"/> ibuprofen [c] <i>Therapeutic alternatives:</i> - indometacin	<i>Solution for injection:</i> 5 mg/mL.
<input type="checkbox"/> prostaglandin E1 [c] <i>Therapeutic alternatives:</i> - prostaglandin E2	<i>Solution for injection:</i> 0.5 mg/mL in alcohol.
surfactant [c]	<i>Suspension for intratracheal instillation:</i> 25 mg/mL or 80 mg/mL.
23. PERITONEAL DIALYSIS SOLUTION	
<i>Complementary List</i>	
intraperitoneal dialysis solution (of appropriate composition)	<i>Parenteral solution.</i>
24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS	
24.1 Medicines used in psychotic disorders	
<input type="checkbox"/> chlorpromazine <i>Therapeutic alternatives to be reviewed (2023)</i>	<b>Injection:</b> 25 mg/mL (hydrochloride) in 2 mL ampoule. <b>Oral liquid:</b> 25 mg/5 mL (hydrochloride). <b>Tablet:</b> 100 mg (hydrochloride).
<input type="checkbox"/> fluphenazine <i>Therapeutic alternatives to be reviewed (2023)</i>	<b>Injection:</b> 25 mg (decanoate or enantate) in 1 mL ampoule.
<input type="checkbox"/> haloperidol <i>Therapeutic alternatives to be reviewed (2023)</i>	<b>Injection:</b> 5 mg in 1 mL ampoule. <b>Tablet:</b> 2 mg; 5 mg.
<input type="checkbox"/> paliperidone <i>Therapeutic alternatives:</i> - risperidone injection	<b>Injection (prolonged-release):</b> 25 mg; 50 mg; 75 mg; 100 mg; 150 mg (as palmitate) in pre-filled syringe
risperidone	<b>Solid oral dosage form:</b> 0.25 mg to 6.0 mg.
<i>Complementary List</i>	
chlorpromazine [c]	<b>Injection:</b> 25 mg/mL (hydrochloride) in 2 mL ampoule. <b>Oral liquid:</b> 25 mg/5 mL (hydrochloride). <b>Tablet:</b> 10 mg; 25 mg; 50 mg; 100 mg (hydrochloride).
clozapine	<b>Solid oral dosage form:</b> 25 to 200 mg.
haloperidol [c]	<b>Injection:</b> 5 mg in 1 mL ampoule. <b>Oral liquid:</b> 2 mg/mL. <b>Solid oral dosage form:</b> 0.5 mg; 2 mg; 5 mg.

# WHO Model List of Essential Medicines – 22nd List (2021)

<b>24.2 Medicines used in mood disorders</b>	
<b>24.2.1 Medicines used in depressive disorders</b>	
<input type="checkbox"/> amitriptyline Therapeutic alternatives to be reviewed (2023)	Tablet: 25 mg; 75mg. (hydrochloride).
<input type="checkbox"/> fluoxetine Therapeutic alternatives: - citalopram - escitalopram - fluvoxamine - paroxetine - sertraline	Solid oral dosage form: 20 mg (as hydrochloride).
<i>Complementary List</i>	
fluoxetine <input type="checkbox"/> [c]  [a] > 8 years.	<b>Solid oral dosage form:</b> 20 mg (as hydrochloride).  [a] > 8 years.
<b>24.2.2 Medicines used in bipolar disorders</b>	
carbamazepine	Tablet (scored): 100 mg; 200 mg.
lithium carbonate	Solid oral dosage form: 300 mg.
valproic acid (sodium valproate)*  <i>*avoid use in pregnancy and in women and girls of child-bearing potential, unless alternative treatments are ineffective or not tolerated because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb.</i>	Tablet (enteric-coated): 200 mg; 500 mg.
<b>24.3 Medicines for anxiety disorders</b>	
<input type="checkbox"/> diazepam Therapeutic alternatives to be reviewed (2023)	Tablet (scored): 2 mg; 5 mg.
<b>24.4 Medicines used for obsessive compulsive disorders</b>	
clomipramine	Capsule: 10 mg; 25 mg (hydrochloride).
<b>24.5 Medicines for disorders due to psychoactive substance use</b>	
bupropion	Tablet (sustained-release): 150 mg (hydrochloride)
nicotine replacement therapy (NRT)	<b>Chewing gum:</b> 2 mg; 4 mg (as polacrilex). <b>Transdermal patch:</b> 5 mg to 30 mg/16 hrs; 7 mg to 21 mg/24 hrs.
varenicline	Tablet: 0.5 mg, 1 mg
<i>Complementary List</i>	
<input type="checkbox"/> methadone* Therapeutic alternatives: - buprenorphine	<b>Concentrate for oral liquid:</b> 5 mg/mL; 10 mg/mL (hydrochloride). <b>Oral liquid:</b> 5 mg/5 mL; 10 mg/5 mL (hydrochloride). <i>*The medicines should only be used within an established support programme.</i>

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25. MEDICINES ACTING ON THE RESPIRATORY TRACT	
25.1 Antiasthmatic medicines and medicines for chronic obstructive pulmonary disease	
<input type="checkbox"/> budesonide Therapeutic alternatives: - beclometasone - ciclesonide - flunisolide - fluticasone - mometasone	<b>Inhalation (aerosol):</b> 100 micrograms per dose; 200 micrograms per dose.
<input type="checkbox"/> budesonide + <input type="checkbox"/> formoterol Therapeutic alternatives: - beclometasone + formoterol - budesonide + salmeterol - fluticasone + formoterol - fluticasone furoate + vilanterol - mometasone + formoterol	<b>Dry powder inhaler:</b> 100 micrograms + 6 micrograms per dose; 200 micrograms + 6 micrograms per dose
epinephrine (adrenaline)	<b>Injection:</b> 1 mg/mL (as hydrochloride or hydrogen tartrate) in 1 mL ampoule.
ipratropium bromide	<b>Inhalation (aerosol):</b> 20 micrograms/metered dose.
<input type="checkbox"/> salbutamol Therapeutic alternatives: - terbutaline	<b>Inhalation (aerosol):</b> 100 micrograms (as sulfate) per dose. <b>Injection:</b> 50 micrograms/mL (as sulfate) in 5 mL ampoule. <b>Metered dose inhaler (aerosol):</b> 100 micrograms (as sulfate) per dose. <b>Respirator solution for use in nebulizers:</b> 5 mg/mL (as sulfate).
<input type="checkbox"/> tiotropium Therapeutic alternatives: - aclidinium - glycopyrronium - umeclidinium	<b>Powder for inhalaton, capsule:</b> 18 micrograms <b>Inhalation solution:</b> 1.25 micrograms; 2.5 micrograms per actuation
26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID–BASE DISTURBANCES	
26.1 Oral	
oral rehydration salts	See section 17.5.1.
potassium chloride	<b>Powder for solution.</b>
26.2 Parenteral	
glucose	<b>Injectable solution:</b> 5% (isotonic); 10% (hypertonic); 50% (hypertonic).
glucose with sodium chloride	<b>Injectable solution:</b> 4% glucose, 0.18% sodium chloride (equivalent to Na <sup>+</sup> 30 mmol/L, Cl <sup>-</sup> 30 mmol/L). <b>Injectable solution:</b> 5% glucose, 0.9% sodium chloride (equivalent to Na <sup>+</sup> 150 mmol/L and Cl <sup>-</sup> 150 mmol/L); 5% glucose, 0.45% sodium chloride (equivalent to Na <sup>+</sup> 75 mmol/L and Cl <sup>-</sup> 75 mmol/L) [c].

## WHO Model List of Essential Medicines – 22nd List (2021)

potassium chloride	<b>Solution:</b> 11.2% in 20 mL ampoule (equivalent to K <sup>+</sup> 1.5 mmol/mL, Cl <sup>-</sup> 1.5 mmol/mL). <b>Solution for dilution:</b> 7.5% (equivalent to K 1 mmol/mL and Cl 1 mmol/mL) [c]; 15% (equivalent to K 2 mmol/mL and Cl 2 mmol/mL) [c].
sodium chloride	<b>Injectable solution:</b> 0.9% isotonic (equivalent to Na <sup>+</sup> 154 mmol/L, Cl <sup>-</sup> 154 mmol/L).
sodium hydrogen carbonate	<b>Injectable solution:</b> 1.4% isotonic (equivalent to Na <sup>+</sup> 167 mmol/L, HCO <sub>3</sub> <sup>-</sup> 167 mmol/L). <b>Solution:</b> 8.4% in 10 mL ampoule (equivalent to Na <sup>+</sup> 1000 mmol/L, HCO <sub>3</sub> <sup>-</sup> 1000 mmol/L).
sodium lactate, compound solution	<b>Injectable solution.</b>
<b>26.3 Miscellaneous</b>	
water for injection	2 mL; 5 mL; 10 mL ampoules.
<b>27. VITAMINS AND MINERALS</b>	
ascorbic acid	<b>Tablet:</b> 50 mg.
calcium	<b>Tablet:</b> 500 mg (elemental).
<input checked="" type="checkbox"/> colecalciferol [c] Therapeutic alternatives: - ergocalciferol	<b>Oral liquid:</b> 400 IU/mL. <b>Solid oral dosage form:</b> 400 IU; 1000 IU.
<input checked="" type="checkbox"/> ergocalciferol Therapeutic alternatives: - colecalciferol	<b>Oral liquid:</b> 250 micrograms/mL (10 000 IU/mL). <b>Solid oral dosage form:</b> 1.25 mg (50 000 IU).
iodine	<b>Capsule:</b> 190 mg. <b>Iodized oil:</b> 1 mL (480 mg iodine); 0.5 mL (240 mg iodine) in ampoule (oral or injectable); 0.57 mL (308 mg iodine) in dispenser bottle.
multiple micronutrient powder [c]	<b>Sachets containing:</b> <ul style="list-style-type: none"><li>- iron (elemental) 12.5 mg (as coated ferrous fumarate)</li><li>- zinc (elemental) 5 mg</li><li>- vitamin A 300 micrograms</li><li>- with or without other micronutrients at recommended daily values</li></ul>
nicotinamide	<b>Tablet:</b> 50 mg.
pyridoxine	<b>Tablet:</b> 25 mg (hydrochloride).
retinol	<b>Capsule:</b> 50 000 IU; 100 000 IU; 200 000 IU (as palmitate). <b>Oral oily solution:</b> 100 000 IU/mL (as palmitate) in multidose dispenser. <b>Tablet (sugar-coated):</b> 10 000 IU (as palmitate). <b>Water-miscible injection:</b> 100 000 IU (as palmitate) in 2 mL ampoule.
riboflavin	<b>Tablet:</b> 5 mg.
thiamine	<b>Tablet:</b> 50 mg (hydrochloride).

# WHO Model List of Essential Medicines – 22nd List (2021)

Complementary List	
calcium gluconate	<i>Injection:</i> 100 mg/mL in 10 mL ampoule.
28. EAR, NOSE AND THROAT MEDICINES	
acetic acid [c]	Topical: 2%, in alcohol.
<input type="checkbox"/> budesonide [c] Therapeutic alternatives to be reviewed (2023)	Nasal spray: 100 micrograms per dose.
<input type="checkbox"/> ciprofloxacin [c] Therapeutic alternatives: - ofloxacin	Solution (ear drops): 0.3% (as hydrochloride).
<input type="checkbox"/> xylometazoline <input type="checkbox"/> [c] Therapeutic alternatives to be reviewed (2023)	Nasal spray: 0.05%. <input type="checkbox"/> Not in children less than 3 months.
29. MEDICINES FOR DISEASES OF JOINTS	
29.1 Medicines used to treat gout	
allopurinol	Tablet: 100 mg.
29.2 Disease-modifying anti-rheumatic drugs (DMARDs)	
chloroquine	Tablet: 100 mg; 150 mg (as phosphate or sulfate).
Complementary List	
azathioprine	Tablet: 50 mg.
hydroxychloroquine	<i>Solid oral dosage form:</i> 200 mg (as sulfate).
methotrexate	Tablet: 2.5 mg (as sodium salt).
penicillamine	<i>Solid oral dosage form:</i> 250 mg.
sulfasalazine	Tablet: 500 mg.
29.3 Juvenile joint diseases	
Complementary List	
acetylsalicylic acid* (acute or chronic use)	<i>Suppository:</i> 50 mg to 150 mg. <i>Tablet:</i> 100 mg to 500 mg. *For use for rheumatic fever, juvenile arthritis, Kawasaki disease.
30. DENTAL PREPARATIONS	
fluoride	Paste, cream or gel: containing between 1000 and 1500 ppm fluoride (any type).  In other appropriate topical formulations.
glass ionomer cement	Single-use capsules: 0.4 g powder + 0.09 mL liquid.  Multi-use bottle: powder + liquid.  Powder (fluoro-alumino-silicate glass) contains: 25-50% silicate, 20-40% aluminium oxide, 1-20% fluoride, 15-40% metal oxide, 0-15% phosphate, remainder are polyacrylic acid powder and metals in minimal quantities. Liquid (aqueous) contains: 7-25% polybasic carboxylic acid, 45-60% polyacrylic acid.
silver diamine fluoride	<i>Solution:</i> 38% w/v.

Table 1.1: Medicines with age or weight restrictions

artesunate + pyronaridine tetraphosphate	> 5 kg
atropine	> 3 months
bedaquiline	≥ 5 years
benzyl benzoate	>2 years
betamethasone topical preparations	hydrocortisone preferred in neonates
cefazolin	> 1 month
ceftriaxone	> 41 weeks corrected gestational age
darunavir	> 3 years
delamanid	≥ 3 years (25 mg dispersible tablet) ≥ 6 years (50 mg tablet)
dihydroartemisinin + piperaquine phosphate	> 5 kg
diloxanide	>25 kg
dolutegravir	≥ 4 weeks and ≥ 3 kg (10 mg dispersible tablet) ≥ 25 kg (50 mg tablet)
doxycycline	> 8 years (except for serious infections e.g. cholera)
fluoxetine	> 8 years
ibuprofen	> 3 months (except IV form for patent ductus arteriosus)
mefloquine	> 5 kg or > 3 months
metoclopramide	Not in neonates
nevirapine	> 6 weeks
ondansetron	> 1 month
silver sulfadiazine	> 2 months
tetracaine	Not in preterm neonates
xylometazoline	> 3 months

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Table 1.2: Explanation of dosage forms

## A. Principal dosage forms used in EML – oral administration

Term	Definition
Solid oral dosage form	<p>Refers to tablets or capsules or other solid dosage forms such as 'melts' that are immediate-release preparations. It implies that there is no difference in clinical efficacy or safety between the available dosage forms, and countries should therefore choose the form(s) to be listed depending on quality and availability.</p> <p>The term 'solid oral dosage form' is <i>never</i> intended to allow any type of modified-release tablet.</p>
Tablets	<p>Refers to:</p> <ul style="list-style-type: none"> <li>• uncoated or coated (film-coated or sugar-coated) tablets that are intended to be swallowed whole;</li> <li>• unscored and scored*;</li> <li>• tablets that are intended to be chewed before being swallowed;</li> <li>• tablets that are intended to be dispersed or dissolved in water or another suitable liquid before being swallowed;</li> <li>• tablets that are intended to be crushed before being swallowed.</li> </ul> <p>The term 'tablet' without qualification is <i>never</i> intended to allow any type of modified-release tablet.</p>
Tablets (qualified)	<p>Refers to a specific type of tablet:</p> <p><b>chewable</b> - tablets that are intended to be chewed before being swallowed;</p> <p><b>dispersible</b> - tablets that are intended to be dispersed in water or another suitable liquid before being swallowed;</p> <p><b>soluble</b> - tablets that are intended to be dissolved in water or another suitable liquid before being swallowed;</p> <p><b>crushable</b> - tablets that are intended to be crushed before being swallowed;</p> <p><b>scored</b> - tablets bearing a break mark or marks where sub-division is intended in order to provide doses of less than one tablet;</p> <p><b>sublingual</b> - tablets that are intended to be placed beneath the tongue.</p> <p>The term 'tablet' is <i>always</i> qualified with an additional term (in parentheses) in entries where one of the following types of tablet is intended: <b>gastro-resistant</b> (such tablets may sometimes be described as enteric-coated or as delayed-release), <b>prolonged-release</b> or another modified-release form.</p>

\* Scored tablets may be divided for ease of swallowing, provided that dose is a whole number of tablets.

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Capsules	Refers to hard or soft capsules.  The term 'capsule' without qualification is <i>never</i> intended to allow any type of modified-release capsule.
Capsules (qualified)	The term 'capsule' with qualification refers to <b>gastro-resistant</b> (such capsules may sometimes be described as enteric-coated or as delayed-release), <b>prolonged-release</b> or another modified-release form.
Granules	Preparations that are issued to patient as granules to be swallowed without further preparation, to be chewed, or to be taken in or with water or another suitable liquid.  The term 'granules' without further qualification is <i>never</i> intended to allow any type of modified-release granules.
Oral powder	Preparations that are issued to patient as powder (usually as single-dose) to be taken in or with water or another suitable liquid.
Oral liquid	Liquid preparations intended to be <i>swallowed</i> i.e. oral solutions, suspensions, emulsions and oral drops, including those constituted from powders or granules, but <i>not</i> those preparations intended for <i>oromucosal administration</i> e.g. gargles and mouthwashes.  Oral liquids presented as powders or granules may offer benefits in the form of better stability and lower transport costs. If more than one type of oral liquid is available on the same market (e.g. solution, suspension, granules for reconstitution), they may be interchanged and in such cases should be bioequivalent. It is preferable that oral liquids do not contain sugar and that solutions for children do not contain alcohol.

### B. Principal dosage forms used in EML – parenteral administration

Term	Definition
Injection	Refers to solutions, suspensions and emulsions including those constituted from powders or concentrated solutions.
Injection (qualified)	Route of administration is indicated in parentheses where relevant.
Injection (oily)	The term 'injection' is qualified by '(oily)' in relevant entries.
Intravenous infusion	Refers to solutions and emulsions including those constituted from powders or concentrated solutions.

### C. Other dosage forms

Mode of administration	Term to be used
To the eye	Eye drops, eye ointments.
Topical	For liquids: lotions, paints. For semi-solids: cream, ointment.
Rectal	Suppositories, gel or solution.
Vaginal	Pessaries or vaginal tablets.
Inhalation	Powder for inhalation, pressurized inhalation, nebulizer.

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artemether	21	<i>ciclosporin</i>	25
artemether + lumefantrine	21	ciprofloxacin	13, 55
artesunate	22	<i>cisplatin</i>	26
artesunate + amodiaquine	22	clarithromycin	13
artesunate + mefloquine	22	clindamycin	10
artesunate + pyronaridine tetraphosphate	22	clofazimine	15, 16
ascorbic acid	54	<i>clomifene</i>	49
<i>asparaginase</i>	25	clomipramine	52
atazanavir + ritonavir	18	clopidogrel	38
atracurium	47	clotrimazole	17
atropine	1, 4, 48	cloxacillin	10
<i>azathioprine</i>	25, 55	<i>clozapine</i>	51
azithromycin	12, 47	coagulation factor IX	35
barium sulfate	40	coagulation factor VIII	35
BCG vaccine	46	coal tar	39
<i>bedaquiline</i>	16	codeine	2
<i>bendamustine</i>	25	colecalciferol	54
benzathine benzylpenicillin	9	<i>colistin</i>	14
benznidazole	24	condoms	49
benzoyl peroxide	39	copper-containing device	49
benzyl benzoate	39	cyclizine	3
benzylpenicillin	9	<i>cyclophosphamide</i>	26
betamethasone	39	<i>cycloserine</i>	16
<i>bevacizumab</i>	48	<i>cytarabine</i>	26
<i>bicalutamide</i>	31	dabigatran	33
biperiden	33	<i>dacarbazine</i>	27
bisoprolol	35, 36, 37	daclatasvir	20

# WHO Model List of Essential Medicines – 22nd List (2021)

daclatasvir + sofosbuvir	20	fluconazole	17
<i>dactinomycin</i>	27	flucytosine	17
dapsone	15	<i>fludarabine</i>	27
darunavir	18	fludrocortisone	43
dasabuvir	20	fluorescein	40
<i>dasatinib</i>	30	fluoride	55
<i>daunorubicin</i>	27	<i>fluorouracil</i>	28, 39
<i>deferoxamine</i>	4, 34	fluoxetine	3, 52
<i>delamanid</i>	16	fluphenazine	51
dengue vaccine	46	folic acid	33
desmopressin	34	<i>fomepizole</i>	4
dexamethasone	3, 4, 31, 42, 50	<i>fosfomycin</i>	14
dextran 70	35	fresh-frozen plasma	34
diaphragms	49	furosemide	37, 41
diazepam	3, 5, 52	<i>gemcitabine</i>	28
<i>diazoxide</i>	44	gentamicin	10, 47
diethylcarbamazine	6	glass ionomer cement	55
digoxin	35, 37	glecaprevir + pibrentasvir	20
dihydroartemisinin + piperaquine phosphate	22	gliclazide	44
diloxanide	21	glucagon	44
<i>dimercaprol</i>	4	glucose	53
diphtheria antitoxin	45	glucose with sodium chloride	53
diphtheria vaccine	46	glutaral	41
<i>docetaxel</i>	27	glyceryl trinitrate	35
docusate sodium	3	griseofulvin	17
dolutegravir	19	Haemophilus influenzae type b vaccine	46
dolutegravir + lamivudine + tenofovir	19	haloperidol	3, 51
<i>dopamine</i>	38	halothane	1
<i>doxorubicin</i>	27	heparin sodium	33, 34
doxycycline	10, 22, 23	hepatitis A vaccine	46
efavirenz	18	hepatitis B vaccine	46
efavirenz + emtricitabine + tenofovir	19	human papilloma virus (HPV) vaccine	46
efavirenz + lamivudine + tenofovir	19	hydralazine	36
eflornithine	24	hydrochlorothiazide	36, 37, 41
empagliflozin	44	hydrocortisone	4, 31, 39, 42, 43
emtricitabine + tenofovir	19	hydroxocobalamin	33
enalapril	36, 37	<i>hydroxycarbamide</i>	28, 34
enoxaparin	33	<i>hydroxychloroquine</i>	55
entecavir	20	hyoscine butylbromide	3
<i>ephedrine</i>	1	hyoscine hydrobromide	3
epinephrine (adrenaline)	4, 35, 48, 53	<i>ibrutinib</i>	30
equine rabies immunoglobulin	45	ibuprofen	2, 24, 51
ergocalciferol	54	<i>ifosfamide</i>	28
ergometrine	50	<i>imatinib</i>	30
<i>erlotinib</i>	30	influenza vaccine	47
erythromycin	47	insulin injection (soluble)	44
<i>erythropoiesis-stimulating agents</i>	33	intermediate-acting insulin	44
estradiol cypionate + medroxyprogesterone acetate	49	<i>intraperitoneal dialysis solution (of appropriate composition)</i>	51
ethambutol	15	iodine	54
ethambutol + isoniazid + pyrazinamide + rifampicin	15	iohexol	40
ethambutol + isoniazid + rifampicin	15	ipratropium bromide	53
ethanol	40	<i>irinotecan</i>	28
ethinylestradiol + etonogestrel	49	isoflurane	1
ethinylestradiol + levonorgestrel	49	isoniazid	15
ethinylestradiol + norethisterone	49	isoniazid + pyrazinamide + rifampicin	15
<i>ethionamide</i>	16	isoniazid + pyridoxine + sulfamethoxazole + trimethoprim	19
<i>ethosuximide</i>	6	isoniazid + rifampicin	15
etonogestrel-releasing implant	49	isoniazid + rifapentine	15
<i>etoposide</i>	27	isosorbide dinitrate	35
<i>everolimus</i>	30	itraconazole	17
fentanyl	2	ivermectin	6, 24
ferrous salt	33	Japanese encephalitis vaccine	46
ferrous salt + folic acid	33	ketamine	1
fecinidazole	23		
<i>filgrastim</i>	31		

# WHO Model List of Essential Medicines – 22nd List (2021)

lactulose	3	natamycin	48
lamivudine	18	neostigmine	47
lamivudine + zidovudine	19	nevirapine	18
lamotrigine	5	niclosamide	6
latanoprost	48	nicotinamide	54
ledipasvir + sofosbuvir	20	nicotine replacement therapy (NRT)	52
<i>lenalidomide</i>	31	nifedipine	50
<i>leuprorelin</i>	32	nifurtimox	24
levamisole	6	<i>nilotinib</i>	30
levodopa + carbidopa	33	nitrofurantoin	11
<i>levofloxacin</i>	16	nitrous oxide	1
levonorgestrel	49	<i>nivolumab</i>	31
levonorgestrel-releasing implant	49	norethisterone enantate	49
levonorgestrel-releasing intrauterine system	49	<i>normal immunoglobulin</i>	35
levothyroxine	44	nystatin	17
lidocaine	1, 35	ofloxacin	48
lidocaine + epinephrine (adrenaline)	1	ombitasvir + paritaprevir + ritonavir	20
<i>linezolid</i>	14, 16	omeprazole	41
lisinopril + amlodipine	36	ondansetron	3, 42
lisinopril + hydrochlorothiazide	36	oral rehydration salts	43, 53
lithium carbonate	52	oral rehydration salts – zinc sulfate	42
long-acting insulin analogues	44	<i>oseltamivir</i>	20
loperamide	3	<i>oxaliplatin</i>	28
lopinavir + ritonavir	18	<i>oxamniquine</i>	6
loratadine	4	oxygen	1, 2
lorazepam	5	oxytocin	50
losartan	36, 37	<i>paclitaxel</i>	29
<i>Lugol's solution</i>	45	paliperidone	51
magnesium sulfate	5	<i>p-aminosalicylic acid</i>	16
mannitol	41	<i>pancreatic enzymes</i>	41
measles vaccine	46	paracetamol	2, 24
mebendazole	6	paromomycin	21
medroxyprogesterone acetate	43, 49	<i>pegaspargase</i>	29
mfloquine	22, 23	<i>pegylated interferon alfa 2a</i>	21
meglumine antimoniate	21	penicillamine	4, 55
<i>meglumine iotroxate</i>	40	<i>pentamidine</i>	23
melarsoprol	24	permethrin	39
<i>melphalan</i>	28	pertussis vaccine	46
meningococcal meningitis vaccine	46	phenobarbital	5
<i>mercaptopurine</i>	28	phenoxyethylpenicillin	11
<i>meropenem</i>	14, 16	phenytoin	5
<i>meropenem + vaborbactam</i>	14	<i>phytomenadione</i>	33
<i>mesna</i>	32	pilocarpine	48
metformin	44	piperacillin + tazobactam	14
<i>methadone</i>	2, 52	platelets	34
methimazole	44, 45	<i>plazomicin</i>	14
<i>methotrexate</i>	28, 55	pneumococcal vaccine	46
methylldopa	37	podophyllum resin	39
<i>methylprednisolone</i>	32	poliomyelitis vaccine	46
methylthioninium chloride (methylene blue)	4	<i>polymyxin B</i>	14
metoclopramide	3, 42	potassium chloride	53, 54
metronidazole	11, 21	potassium ferric hexacyano-ferrate(II) -2H <sub>2</sub> O (Prussian blue)	4
<i>micafungin</i>	17	<i>potassium iodide</i>	17, 44, 45
miconazole	38	potassium permanganate	39
midazolam	1, 3, 5	ovidone iodine	40
mifepristone – misoprostol	50	praziquantel	6
miltefosine	21	<i>prednisolone</i>	4, 32, 42, 48
misoprostol	50	primaquine	22
morphine	1, 2	procaine benzylpenicillin	11
moxifloxacin	15, 16	<i>procarbazine</i>	29
multiple micronutrient powder	54	progesterone vaginal ring	49
multiple micronutrient supplement	50	proguanil	23
mumps vaccine	47	propofol	1
mupirocin	39	propranolol	24
naloxone	4		

# WHO Model List of Essential Medicines – 22nd List (2021)

propylthiouracil	44, 45	sulfamethoxazole + trimethoprim	11, 23
<i>prostaglandin E1</i>	51	sulfasalazine	42, 55
protamine sulfate	33	sumatriptan	24
pyrantel	6	suramin sodium	23
pyrazinamide	15	<i>surfactant</i>	51
<i>pyridostigmine</i>	47	suxamethonium	47
pyridoxine	54	<i>tacrolimus</i>	25
pyrimethamine	23	<i>tamoxifen</i>	32
quinine	22	telmisartan + amlodipine	37
rabies vaccine	47	telmisartan + hydrochlorothiazide	37
raltegravir	19	tenofovir disoproxil fumarate	18, 20
ranitidine	41	terbinafine	38
<i>rasburicase</i>	32	<i>testosterone</i>	43
<i>realgar-Indigo naturalis formulation</i>	29	tetanus vaccine	46
red blood cells	34	tetracaine	48
retinol	54	tetracycline	48
ribavirin	19, 21	<i>thalidomide</i>	31
riboflavin	54	thiamine	54
rifabutin	15	tick-borne encephalitis vaccine	46
rifampicin	15	timolol	48
rifapentine	15	<i>tioguanine</i>	29
risperidone	51	tiotropium	53
ritonavir	18	tranexamic acid	34, 50
<i>rituximab</i>	30	<i>trastuzumab</i>	30
rotavirus vaccine	46	triclabendazole	6
rubella vaccine	46	trimethoprim	12
salbutamol	53	tropicamide	40
salicylic acid	39	tuberculin, purified protein derivative (PPD)	45
selenium sulfide	38	typhoid vaccine	47
senna	3, 42	ulipristal	49
silver diamine fluoride	55	urea	39
silver sulfadiazine	39	valganciclovir	19, 20
simvastatin	38	valproic acid (sodium valproate)	5, 6, 52
<i>sodium calcium edetate</i>	4	vancomycin	14
sodium chloride	54	varenicline	52
sodium hydrogen carbonate	54	varicella vaccine	47
sodium lactate	54	vecuronium	47
sodium nitrite	4	verapamil	35
<i>sodium nitroprusside</i>	37	<i>vinblastine</i>	29
sodium stibogluconate	21	<i>vincristine</i>	29
sodium thiosulfate	4, 38	<i>vinorelbine</i>	29
sofosbuvir	20	voriconazole	17
sofosbuvir + velpatasvir	20	warfarin	34
spectinomycin	11	water for injection	54
spironolactone	38, 41	whole blood	34
<i>streptokinase</i>	38	xylometazoline	55
<i>streptomycin</i>	16	yellow fever vaccine	46
<i>succimer</i>	4	zidovudine	18
sulfadiazine	23	zinc sulfate	43
sulfadoxine + pyrimethamine	22, 23	<i>zoledronic acid</i>	32



# The selection and use of essential medicines

## 2023

Web Annex A

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# World Health Organization

## Model List of Essential Medicines

23rd list  
(2023)



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# WHO Model List of Essential Medicines – 23rd List (2023)

## Explanatory notes

The **core list** presents a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

Where the [c] symbol is placed next to an individual medicine or strength of medicine on the core list it signifies that there is a specific indication for restricting its use to children.

The **complementary list** presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings.

Where the [c] symbol is placed next to an individual medicine or strength of medicine on the complementary list it signifies that the medicine(s) require(s) specialist diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training for their use in children.

The **square box symbol (□)** is intended to indicate therapeutic alternatives to the listed medicine that may be considered for selection in national essential medicines lists. Alternatives may be individual medicines, or multiple medicines within a pharmacological class or chemical subgroup, defined at the 4th level of the [Anatomical Therapeutic Chemical \(ATC\) classification](#), which have similar clinical effectiveness and safety. The listed medicine should be the example of the class or subgroup for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. Not all square box listings are applicable to medicine selection for children. A square box is not used to indicate alternative generic brands of the same small molecule medicines, nor alternative biosimilars of biological medicines. However, the selection and use of quality-assured generics and biosimilars of essential medicines at country level is recommended.

National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price.

The [a] symbol indicates that there is an age or weight restriction on use of the medicine; details for each medicine can be found in Table 1.1.

The presence of an entry on the Essential Medicines List carries no assurance as to pharmaceutical quality. It is the responsibility of the relevant national or regional drug regulatory authority to ensure that each product is of appropriate pharmaceutical quality (including stability) and that, when relevant, different products are interchangeable.

For recommendations and advice concerning all aspects of the quality assurance of medicines see the WHO website <https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/guidelines/quality-assurance>

Medicines and dosage forms are listed in alphabetical order within each section and the order of listing does not imply preference for one form over another. Standard treatment guidelines should be consulted for information on appropriate dosage forms.

The main terms used for dosage forms in the Essential Medicines List can be found in Table 1.2.

Definitions of many of these terms and pharmaceutical quality requirements applicable to the different categories are published in the current edition of *The International Pharmacopoeia*. <https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/pharmacopoeia>.

# WHO Model List of Essential Medicines – 23rd List (2023)

1. ANAESTHETICS, PREOPERATIVE MEDICINES AND MEDICAL GASES	
1.1 General anaesthetics and oxygen	
1.1.1 Inhalational medicines	
halothane	Inhalation.
isoflurane	Inhalation.
nitrous oxide	Inhalation.
oxygen	Inhalation (medical gas).
sevoflurane	Inhalation.
1.1.2 Injectable medicines	
ketamine	<b>Injection:</b> 50 mg/mL (as hydrochloride) in 10 mL vial.
<input type="checkbox"/> propofol Therapeutic alternatives: - thiopental	<b>Injection:</b> 10 mg/mL; 20 mg/mL.
1.2 Local anaesthetics	
<input type="checkbox"/> bupivacaine Therapeutic alternatives to be reviewed	<b>Injection:</b> 0.25%; 0.5% (hydrochloride) in vial. <b>Injection for spinal anaesthesia:</b> 0.5% (hydrochloride) in 4 mL ampoule to be mixed with 7.5% glucose solution.
<input type="checkbox"/> lidocaine Therapeutic alternatives to be reviewed	<b>Injection:</b> 1%; 2% (hydrochloride) in vial. <b>Injection for spinal anaesthesia:</b> 5% (hydrochloride) in 2 mL ampoule to be mixed with 7.5% glucose solution. <b>Topical forms:</b> 2% to 4% (hydrochloride).
lidocaine + epinephrine (adrenaline)	<b>Dental cartridge:</b> 2% (hydrochloride) + epinephrine 1:80 000. <b>Injection:</b> 1%; 2% (hydrochloride or sulfate) + epinephrine 1:200 000 in vial.
<i>Complementary List</i>	
ephedrine	<b>Injection:</b> 30 mg/mL (hydrochloride) in 1 mL ampoule. (For use in spinal anaesthesia during delivery, to prevent hypotension).
1.3 Preoperative medication and sedation for short-term procedures	
atropine	<b>Injection:</b> 1 mg (sulfate) in 1 mL ampoule.
<input type="checkbox"/> midazolam Therapeutic alternatives to be reviewed	<b>Injection:</b> 1 mg/mL. <b>Oral liquid:</b> 2 mg/mL [c]. <b>Tablet:</b> 7.5 mg; 15 mg.
morphine	<b>Injection:</b> 10 mg (sulfate or hydrochloride) in 1 mL ampoule.

# WHO Model List of Essential Medicines – 23rd List (2023)

1.4 Medical gases	
oxygen*	<b>Inhalation</b> For use in the management of hypoxaemia. *No more than 30% oxygen should be used to initiate resuscitation of neonates less than or equal to 32 weeks of gestation.
2. MEDICINES FOR PAIN AND PALLIATIVE CARE	
2.1 Non-opioids and non-steroidal anti-inflammatory medicines (NSAIDs)	
acetylsalicylic acid	<b>Suppository:</b> 50 mg to 150 mg. <b>Tablet:</b> 100 mg to 500 mg.
ibuprofen <sup>a</sup>	<b>Oral liquid:</b> 100 mg/5 mL [c], 200 mg/5 mL. <b>Tablet:</b> 200 mg; 400 mg; 600 mg. <sup>a</sup> Not in children less than 3 months.
paracetamol (acetaminophen)*	<b>Oral liquid:</b> 120 mg/5 mL or 125 mg/5 mL **, 250 mg/5 mL [c]. **The presence of both 120 mg/5 mL and 125 mg/5 mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided. <b>Suppository:</b> 100 mg, 250 mg [c]. <b>Tablet:</b> 250 mg, 325 mg, 500 mg. <b>Tablet (dispersible):</b> 100 mg, 250 mg [c]. *Not recommended for anti-inflammatory use due to lack of proven benefit to that effect.
2.2 Opioid analgesics	
codeine	<b>Tablet:</b> 30 mg (phosphate).
fentanyl*	<b>Transdermal patch:</b> 12 micrograms/hr; 25 micrograms/hr; 50 micrograms/hr; 75 micrograms/hr; 100 micrograms/hr. *For the management of cancer pain
<input type="checkbox"/> morphine Therapeutic alternatives: - hydromorphone - oxycodone	<b>Granules (slow release; to mix with water):</b> 20 mg to 200 mg (morphine sulfate). <b>Injection:</b> 10 mg (morphine hydrochloride or morphine sulfate) in 1 mL ampoule. <b>Oral liquid:</b> 10 mg/5 mL (morphine hydrochloride or morphine sulfate). <b>Tablet (slow release):</b> 10 mg to 200mg (morphine hydrochloride or morphine sulfate). <b>Tablet (immediate release):</b> 10 mg (morphine sulfate).
<i>Complementary list</i>	
methadone*	<b>Tablet:</b> 5 mg; 10 mg (hydrochloride) <b>Oral liquid:</b> 5 mg/5 mL; 10 mg/5 mL (hydrochloride) <b>Concentrate for oral liquid:</b> 5 mg/mL; 10 mg/mL (hydrochloride) *For the management of cancer pain.

## WHO Model List of Essential Medicines – 23rd List (2023)

2.3 Medicines for other common symptoms in palliative care	
amitriptyline	<b>Tablet:</b> 10 mg; 25 mg; 75 mg.
cyclizine [c]	<b>Injection:</b> 50 mg/mL. <b>Tablet:</b> 50 mg.
dexamethasone	<b>Injection:</b> 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule. <b>Oral liquid:</b> 2 mg/5 mL. <b>Tablet:</b> 2 mg [c]; 4 mg.
diazepam	<b>Injection:</b> 5 mg/mL. <b>Oral liquid:</b> 2 mg/5 mL. <b>Rectal gel:</b> 5 mg/mL in 0.5 mL, 2 mL, 4 mL rectal delivery system. <b>Rectal solution:</b> 2 mg/mL in 1.25 mL, 2.5 mL rectal tube; 4 mg/mL in 2.5 mL rectal tube. <b>Tablet:</b> 5 mg; 10 mg.
docosate sodium	<b>Capsule:</b> 100 mg. <b>Oral liquid:</b> 50 mg/5 mL.
fluoxetine	<b>Solid oral dosage form:</b> 20 mg (as hydrochloride).
haloperidol	<b>Injection:</b> 5 mg in 1 mL ampoule. <b>Oral liquid:</b> 2 mg/mL. <b>Solid oral dosage form:</b> 0.5 mg; 2mg; 5 mg.
hyoscine butylbromide	<b>Injection:</b> 20 mg/mL.
hyoscine hydrobromide [c]	<b>Injection:</b> 400 micrograms/mL; 600 micrograms/mL. <b>Transdermal patches:</b> 1 mg/72 hours.
lactulose [c]	<b>Oral liquid:</b> 3.1 to 3.7 g/5 mL.
loperamide	<b>Solid oral dosage form:</b> 2 mg.
metoclopramide	<b>Injection:</b> 5 mg/mL (hydrochloride) in 2 mL ampoule. <b>Oral liquid:</b> 5 mg/5 mL. <b>Solid oral form:</b> 10 mg (hydrochloride).
midazolam	<b>Injection:</b> 1 mg/mL; 5 mg/mL. <b>Oral liquid:</b> 2mg/mL [c]. <b>Solid oral dosage form:</b> 7.5 mg; 15 mg.
□ ondansetron <b>a</b> Therapeutic alternatives: - dolasetron - granisetron - palonosetron - tropisetron	<b>Injection:</b> 2 mg base/mL in 2 mL ampoule (as hydrochloride). <b>Oral liquid:</b> 4 mg base/5 mL. <b>Solid oral dosage form:</b> Eq 4 mg base; Eq 8 mg base. <b>a</b> > 1 month.
senna	<b>Oral liquid:</b> 7.5 mg/5 mL.

# WHO Model List of Essential Medicines – 23rd List (2023)

3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS	
dexamethasone	<b>Injection:</b> 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule.
epinephrine (adrenaline)	<b>Injection:</b> 1 mg/mL (as hydrochloride or hydrogen tartrate) in 1 mL ampoule.
hydrocortisone	<b>Powder for injection:</b> 100 mg (as sodium succinate) in vial.
<input type="checkbox"/> loratadine*	<b>Oral liquid:</b> 1 mg/mL. <b>Tablet:</b> 10 mg.  <i>*There may be a role for sedating antihistamines for limited indications (EMC).</i>
<input type="checkbox"/> prednisolone	<b>Oral liquid:</b> 5 mg/mL [c]. <b>Tablet:</b> 5 mg; 25 mg.
4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS	
4.1 Non-specific	
charcoal, activated	<b>Powder.</b>
4.2 Specific	
acetylcysteine	<b>Injection:</b> 200 mg/mL in 10 mL ampoule. <b>Oral liquid:</b> 10% [c]; 20% [c].
atropine	<b>Injection:</b> 1 mg (sulfate) in 1 mL ampoule.
calcium gluconate	<b>Injection:</b> 100 mg/mL in 10 mL ampoule.
methylthioninium chloride (methylene blue)	<b>Injection:</b> 10 mg/mL in 10 mL ampoule.
naloxone	<b>Injection:</b> 400 micrograms (hydrochloride) in 1 mL ampoule.
penicillamine	<b>Solid oral dosage form:</b> 250 mg.
potassium ferric hexacyano-ferrate(II) -2H <sub>2</sub> O (Prussian blue)	<b>Powder for oral administration.</b>
sodium nitrite	<b>Injection:</b> 30 mg/mL in 10 mL ampoule.
sodium thiosulfate	<b>Injection:</b> 250 mg/mL in 50 mL ampoule.
<i>Complementary List</i>	
deferoxamine	<b>Powder for injection:</b> 500 mg (mesilate) in vial.
dimercaprol	<b>Injection in oil:</b> 50 mg/mL in 2 mL ampoule.
fomepizole	<b>Injection:</b> 5 mg/mL (sulfate) in 20 mL ampoule or 1 g/mL (base) in 1.5 mL ampoule.
sodium calcium edetate	<b>Injection:</b> 200 mg/mL in 5 mL ampoule.
succimer	<b>Solid oral dosage form:</b> 100 mg.

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5. MEDICINES FOR DISEASES OF THE NERVOUS SYSTEM	
5.1 Antiseizure medicines	
carbamazepine	<p><b>Oral liquid:</b> 100 mg/5 mL.</p> <p><b>Tablet (chewable):</b> 100 mg; 200 mg.</p> <p><b>Tablet (scored):</b> 100 mg; 200 mg; 400 mg.</p>
diazepam	<p><b>Rectal gel:</b> 5 mg/mL in 0.5 mL, 2 mL, 4 mL rectal delivery system.</p> <p><b>Rectal solution:</b> 2 mg/mL in 1.25 mL, 2.5 mL rectal tube; 4 mg/mL in 2.5 mL rectal tube.</p>
lamotrigine*	<p><b>Tablet:</b> 25 mg; 50 mg; 100 mg; 200 mg.</p> <p><b>Tablet (chewable, dispersible):</b> 2 mg; 5 mg; 25 mg; 50 mg; 100 mg; 200 mg.</p> <p>*For use as adjunctive therapy for treatment-resistant partial or generalized seizures.</p>
levetiracetam	<p><b>Oral solution:</b> 100 mg/mL</p> <p><b>Tablet:</b> 250 mg; 500 mg; 750 mg; 1000 mg.</p>
<input type="checkbox"/> lorazepam Therapeutic alternatives: - diazepam (injection) - midazolam (injection)	<p><b>Injection:</b> 2 mg/mL in 1 mL ampoule; 4 mg/mL in 1 mL ampoule.</p>
magnesium sulfate*	<p><b>Injection:</b> 0.5 g/mL in 2 mL ampoule (equivalent to 1 g in 2 mL; 50% weight/volume); 0.5 g/mL in 10 mL ampoule (equivalent to 5 g in 10 mL; 50% weight/volume).</p> <p>*For use in eclampsia and severe pre-eclampsia and not for other convulsant disorders.</p>
midazolam	<p><b>Solution for oromucosal administration:</b> 5 mg/mL in 0.5 mL, 1 mL, 1.5 mL, 2 mL pre-filled syringe; 10 mg/mL in 0.25 mL, 0.5 mL, 0.75 mL, 1 mL pre-filled syringe.</p> <p><b>Injection*:</b> 1 mg/mL in 5 mL vial; 5 mg/mL in 1 mL or 3 mL vial.</p> <p>*For buccal administration when solution for oromucosal administration is not available.</p>
phenobarbital	<p><b>Injection:</b> 30 mg/mL or 60 mg/mL [c], 200 mg/mL (sodium).</p> <p><b>Oral liquid:</b> 15 mg/5 mL.</p> <p><b>Tablet:</b> 15 mg to 100 mg.</p>
phenytoin	<p><b>Injection:</b> 50 mg/mL (phenytoin sodium).</p> <p><b>Oral liquid:</b> 30 mg/5 mL (phenytoin).</p> <p><b>Solid oral dosage form:</b> 25 mg; 50 mg; 100 mg (phenytoin sodium).</p> <p><b>Tablet (chewable):</b> 50 mg (phenytoin).</p>
valproic acid (sodium valproate)*  <i>*Avoid use in pregnancy and in women and girls of child-bearing potential, unless alternative treatments are ineffective or not tolerated because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb.</i>	<p><b>Oral liquid:</b> 200 mg/5 mL.</p> <p><b>Tablet (crushable):</b> 100 mg.</p> <p><b>Tablet (enteric-coated):</b> 200 mg; 500 mg.</p>

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Complementary List	
ethosuximide	<b>Capsule:</b> 250 mg. <b>Oral liquid:</b> 250 mg/5 mL.
levetiracetam	<b>Concentrate solution for infusion:</b> 500 mg/5mL in 5 mL vial. <b>Solution for infusion:</b> 5 mg/mL; 10 mg/mL; 15 mg/mL in 100 mL bag.
valproic acid (sodium valproate)*  *Avoid use in pregnancy and in women and girls of child-bearing potential, unless alternative treatments are ineffective or not tolerated because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb.	<b>Injection:</b> 100 mg/mL in 3 mL, 4 mL, 10 mL ampoule.
5.2 Medicines for multiple sclerosis	
Complementary List	
cladribine	<b>Tablet:</b> 10 mg.
glatiramer acetate	<b>Injection (subcutaneous):</b> 20 mg/mL; 40 mg/mL in pre-filled syringe.
rituximab*  *including quality-assured biosimilars	<b>Injection (intravenous):</b> 500 mg/50 mL in 50 mL vial.
5.3 Medicines for parkinsonism	
<input type="checkbox"/> biperiden  Therapeutic alternatives: – trihexyphenidyl	<b>Injection:</b> 5 mg (lactate) in 1 mL ampoule. <b>Tablet:</b> 2 mg (hydrochloride).
levodopa + <input type="checkbox"/> carbidopa  Therapeutic alternatives: – benserazide (for carbidopa)	<b>Tablet:</b> 100 mg + 10 mg; 100 mg + 25 mg; 250 mg + 25 mg.

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6. ANTI-INFECTIVE MEDICINES	
6.1 Anthelmintics	
6.1.1 <i>Intestinal anthelmintics</i>	
albendazole	Tablet (chewable, scored): 400 mg.
ivermectin	Tablet: 3 mg.
levamisole	Tablet: 50 mg; 150 mg (as hydrochloride).
mebendazole	Tablet (chewable): 100 mg; 500 mg.
niclosamide	Tablet (chewable): 500 mg.
praziquantel	Tablet: 150 mg, 500 mg Tablet (scored): 600 mg.
pyrantel	Tablet (chewable): 250 mg (as embonate or pamoate).
6.1.2 <i>Antifilarials</i>	
albendazole	Tablet (chewable, scored): 400 mg.
diethylcarbamazine	Tablet: 50 mg; 100 mg (dihydrogen citrate).
ivermectin	Tablet: 3 mg.
6.1.3 <i>Antischistosomal and other antitrematode medicines</i>	
praziquantel	Tablet: 150 mg, 500 mg. Tablet (scored): 600 mg.
triclabendazole	Tablet (scored): 250 mg.
<i>Complementary List</i>	
oxamniquine*	Capsule: 250 mg. Oral liquid: 250 mg/5 mL. <i>*For use when praziquantel treatment fails.</i>
6.1.4 <i>Cysticidal medicines</i>	
<i>Complementary List</i>	
albendazole	Tablet (chewable): 200 mg [c]. Tablet (chewable, scored): 400 mg.
mebendazole	Tablet (chewable): 100 mg [c], 500 mg.
praziquantel	Tablet: 150 mg, 500 mg. Tablet (scored): 600 mg.

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## 6.2 Antibacterials

To assist in the development of tools for antibiotic stewardship at local, national and global levels and to reduce antimicrobial resistance, the Access, Watch, Reserve (AWaRe) classification of antibiotics was developed – where antibiotics are classified into different groups to emphasize the importance of their appropriate use.

### ACCESS GROUP ANTIBIOTICS

This group includes antibiotics that have activity against a wide range of commonly encountered susceptible pathogens while also showing lower resistance potential than antibiotics in the other groups. Selected Access group antibiotics are recommended as essential first or second choice empiric treatment options for infectious syndromes reviewed by the EML Expert Committee and are listed as individual medicines on the Model Lists to improve access and promote appropriate use. They are essential antibiotics that should be widely available, affordable and quality assured.

### WATCH GROUP ANTIBIOTICS

This group includes antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the [Critically Important Antimicrobials for Human Medicine](#) and/or antibiotics that are at relatively high risk of selection of bacterial resistance. These medicines should be prioritized as key targets of stewardship programs and monitoring. Selected Watch group antibiotics are recommended as essential first or second choice empiric treatment options for a limited number of specific infectious syndromes and are listed as individual medicines on the Model Lists.

### RESERVE GROUP ANTIBIOTICS

This group includes antibiotics and antibiotic classes that should be reserved for treatment of confirmed or suspected infections due to multi-drug-resistant organisms. Reserve group antibiotics should be treated as “last resort” options. Selected Reserve group antibiotics are listed as individual medicines on the Model Lists when they have a favourable risk-benefit profile and proven activity against “Critical Priority” or “High Priority” pathogens identified by the [WHO Priority Pathogens List](#), notably carbapenem resistant *Enterobacteriaceae*. These antibiotics should be accessible, but their use should be tailored to highly specific patients and settings, when all alternatives have failed or are not suitable. These medicines could be protected and prioritized as key targets of national and international stewardship programs involving monitoring and utilization reporting, to preserve their effectiveness.

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## 6.2.1 Access group antibiotics

	<b>Injection:</b> 50 mg/mL (as sulfate) [c]; 250 mg/mL (as sulfate) in 2 mL vial.	
amikacin	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>High-risk febrile neutropenia</i></li> <li>– <i>Pyelonephritis or prostatitis (severe)</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Sepsis in neonates and children</i> [c]</li> </ul>
	<b>Powder for injection:</b> 250 mg; 500 mg; 1 g (as sodium) in vial. <b>Powder for oral liquid:</b> 125 mg/5 mL; 250 mg/5 mL (as trihydrate) [c]. <b>Solid oral dosage form:</b> 250 mg; 500 mg; 1g (as trihydrate). <b>Tablet (dispersible, scored):</b> 250 mg; 500 mg (as trihydrate) [c].	
amoxicillin	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Community acquired pneumonia (mild to moderate)</i></li> <li>– <i>Community acquired pneumonia (severe)</i> [c]</li> <li>– <i>Complicated severe acute malnutrition</i> [c]</li> <li>– <i>Exacerbations of COPD</i></li> <li>– <i>Otitis media</i></li> <li>– <i>Pharyngitis</i></li> <li>– <i>Progressive apical dental abscess</i></li> <li>– <i>Sepsis in neonates and children</i> [c]</li> <li>– <i>Sinusitis</i></li> <li>– <i>Uncomplicated severe acute malnutrition</i> [c]</li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Acute bacterial meningitis</i></li> </ul>
amoxicillin + clavulanic acid	<b>Powder for injection:</b> 500 mg (as sodium) + 100 mg (as potassium salt); 1000 mg (as sodium) + 200 mg (as potassium salt) in vial. <b>Powder for oral liquid:</b> 125 mg (as trihydrate)+ 31.25 mg (as potassium salt)/5 mL; 250 mg (as trihydrate) + 62.5 mg (as potassium salt)/5mL [c]. <b>Tablet:</b> 500 mg (as trihydrate) + 125 mg (as potassium salt); 875 mg (as trihydrate) + 125 mg (as potassium salt). <b>Tablet (dispersible):</b> 200 mg (as trihydrate) + 28.5 mg (as potassium salt) [c]; 250 mg (as trihydrate) + 62.5 mg (as potassium salt) [c].	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Community acquired pneumonia (severe)</i> [c]</li> <li>– <i>Complicated intraabdominal infections (mild to moderate)</i></li> <li>– <i>Exacerbations of COPD</i></li> <li>– <i>Hospital acquired pneumonia</i></li> <li>– <i>Low-risk febrile neutropenia</i></li> <li>– <i>Lower urinary tract infections</i></li> <li>– <i>Sinusitis</i></li> <li>– <i>Skin and soft tissue infections</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Bone and joint infections</i></li> <li>– <i>Community-acquired pneumonia (mild to moderate)</i></li> <li>– <i>Community acquired pneumonia (severe)</i></li> <li>– <i>Otitis media</i></li> <li>– <i>Surgical prophylaxis</i></li> </ul>

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	Powder for injection: 500 mg; 1 g (as sodium) in vial.	
ampicillin	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Community acquired pneumonia (severe) [c]</i></li> <li>– <i>Complicated intraabdominal infections [c]</i></li> <li>– <i>Complicated severe acute malnutrition [c]</i></li> <li>– <i>Sepsis in neonates and children [c]</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Acute bacterial meningitis</i></li> </ul>
benzathine benzylpenicillin	<b>Powder for injection:</b> 1.2 million IU ( $\approx$ 900 mg) in vial [c]; 2.4 million IU ( $\approx$ 1.8 g) in vial.	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Syphilis</i></li> </ul>	<b>SECOND CHOICE</b>
benzylpenicillin	<b>Powder for injection:</b> 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial.	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Community acquired pneumonia (severe) [c]</i></li> <li>– <i>Complicated severe acute malnutrition [c]</i></li> <li>– <i>Sepsis in neonates and children [c]</i></li> <li>– <i>Syphilis</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Acute bacterial meningitis</i></li> </ul>
cefalexin	<b>Powder for oral liquid:</b> 125 mg/5 mL; 250 mg/5 mL (anhydrous). <b>Solid oral dosage form:</b> 250 mg; 500 mg (as monohydrate). <b>Tablet (dispersible):</b> 125 mg [c]; 250 mg [c].	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Skin and soft tissue infections</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Exacerbations of COPD</i></li> <li>– <i>Pharyngitis</i></li> </ul>
cefazolin <sup>a</sup>	<b>Powder for injection:</b> 1 g (as sodium salt) in vial. <span style="border: 1px solid black; padding: 2px;">a</span> > 1 month.	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Surgical prophylaxis</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Bone and joint infections</i></li> </ul>
chloramphenicol	<b>Oily suspension for injection*</b> : 0.5 g/mL (as sodium succinate) in 2 mL ampoule. *Only for the presumptive treatment of epidemic meningitis in children older than 2 years and in adults. <b>Powder for injection:</b> 1 g (as sodium succinate) in vial.	
	<b>FIRST CHOICE</b>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Acute bacterial meningitis</i></li> </ul>

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clindamycin	<p><b>Capsule:</b> 150 mg (as hydrochloride).</p> <p><b>Injection:</b> 150 mg/mL (as phosphate); 600 mg/4 mL (as phosphate); 900 mg/6 mL (as phosphate).</p> <p><b>Powder for oral liquid:</b> 75 mg/5 mL (as palmitate hydrochloride) [c].</p>	
	<b>FIRST CHOICE</b> – <i>Necrotizing fasciitis</i>	<b>SECOND CHOICE</b> – <i>Bone and joint infections</i>
<input checked="" type="checkbox"/> cloxacillin*  Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (J01CF Beta-lactamase resistant penicillins)	<p><b>Capsule:</b> 250 mg [c], 500 mg; 1 g (as sodium).</p> <p><b>Powder for injection:</b> 250 mg [c], 500 mg (as sodium) in vial.</p> <p><b>Powder for oral liquid:</b> 125 mg/5 mL, 250 mg/5 mL (as sodium) [c].</p> <p>*cloxacillin, dicloxacillin and flucloxacillin are preferred for oral administration due to better bioavailability.</p>	
	<b>FIRST CHOICE</b> – <i>Bone and joint infections</i> – <i>Skin and soft tissue infections</i>	<b>SECOND CHOICE</b> – <i>Sepsis in neonates and children</i> [c]
doxycycline <span style="border: 1px solid black; padding: 0 2px;">a</span>	<p><b>Oral liquid:</b> 50 mg/5 mL (calcium) [c].</p> <p><b>Powder for oral liquid:</b> 25 mg/5 mL (monohydrate) [c].</p> <p><b>Powder for injection:</b> 100 mg in vial.</p> <p><b>Solid oral dosage form:</b> 50 mg [c]; 100 mg (as hyclate).</p> <p><b>Tablet (dispersible):</b> 100 mg (as monohydrate) [c].</p> <p><span style="border: 1px solid black; padding: 0 2px;">a</span> Use in children &lt;8 years only for life-threatening infections when no alternative exists.</p>	
	<b>FIRST CHOICE</b> – <i>Cholera</i> – <i>Sexually transmitted infection due to Chlamydia trachomatis</i>	<b>SECOND CHOICE</b> – <i>Cholera</i> [c] – <i>Community acquired pneumonia (mild to moderate)</i> – <i>Exacerbations of COPD</i>
gentamicin	<p><b>Injection:</b> 10 mg/mL (as sulfate); 40 mg/mL (as sulfate) in 2 mL vial.</p>	
	<b>FIRST CHOICE</b> – <i>Acute bacterial meningitis in neonates</i> [c] – <i>Community acquired pneumonia (severe)</i> [c] – <i>Complicated intraabdominal infections</i> [c] – <i>Complicated severe acute malnutrition</i> [c] – <i>Sepsis in neonates and children</i> [c]	<b>SECOND CHOICE</b> – <i>Gonorrhoea</i> – <i>Surgical prophylaxis</i>

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	<b>Injection:</b> 500 mg in 100 mL vial. <b>Oral liquid:</b> 200 mg/5 mL (as benzoate). <b>Suppository:</b> 500 mg; 1 g. <b>Tablet:</b> 200 mg; 250 mg; 400 mg; 500 mg.	
metronidazole	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>C. difficile infection</i></li> <li>– <i>Complicated intraabdominal infections (mild to moderate)</i></li> <li>– <i>Complicated intrabdominal infections (severe)</i></li> <li>– <i>Necrotizing fasciitis</i></li> <li>– <i>Surgical prophylaxis</i></li> <li>– <i>Trichomoniasis</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Complicated intraabdominal infections (mild to moderate)</i></li> </ul>
	<b>Oral liquid:</b> 25 mg/5 mL [c]. <b>Solid oral dosage form:</b> 50 mg [c]; 100 mg.	
nitrofurantoin	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Lower urinary tract infections</i></li> </ul>	<b>SECOND CHOICE</b>
	<b>Powder for oral liquid:</b> 250 mg/5 mL (as potassium). <b>Solid oral dosage form:</b> 250 mg; 500 mg (as potassium).	
phenoxymethylenicillin	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Community acquired pneumonia (mild to moderate)</i></li> <li>– <i>Pharyngitis</i></li> <li>– <i>Progressive apical dental abscess</i></li> </ul>	<b>SECOND CHOICE</b>
procaine benzylpenicillin*	<b>Powder for injection:</b> 1 g (=1 million IU); 3 g (=3 million IU) in vial. *Procaine benzylpenicillin is not recommended as first-line treatment for neonatal sepsis except in settings with high neonatal mortality, when given by trained health workers in cases where hospital care is not achievable.	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Syphilis (congenital)</i> [c]</li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Syphilis</i></li> </ul>
	<b>Powder for injection:</b> 2 g (as hydrochloride) in vial.	
spectinomycin	<b>FIRST CHOICE</b>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Gonorrhoea</i></li> </ul>
	<b>Injection:</b> 80 mg + 16 mg/mL in 5 mL ampoule; 80 mg + 16 mg/mL in 10 mL ampoule. <b>Oral liquid:</b> 200 mg + 40 mg/5 mL. <b>Tablet:</b> 100 mg + 20 mg; 400 mg + 80 mg; 800 mg + 160 mg. <b>Tablet (dispersible):</b> 100 mg + 20 mg [c].	
sulfamethoxazole + trimethoprim	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Lower urinary tract infections</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Acute invasive diarrhoea / bacterial dysentery</i></li> </ul>

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trimethoprim	<b>Tablet:</b> 100 mg; 200 mg. <b>Oral liquid:</b> 50 mg/5 mL [c].	
	<b>FIRST CHOICE</b> – <i>Lower urinary tract infections</i>	<b>SECOND CHOICE</b>
<b>6.2.2 Watch group antibiotics</b>		
azithromycin	<b>Solid oral dosage form:</b> 250 mg; 500 mg (anhydrous). <b>Powder for oral liquid:</b> 200 mg/5 mL (anhydrous) [c].	
	<b>FIRST CHOICE</b> – <i>Cholera</i> – <i>Enteric fever</i> – <i>Gonorrhoea</i> – <i>Sexually transmitted infection due to Chlamydia trachomatis</i> – <i>Trachoma</i> – <i>Yaws</i>	<b>SECOND CHOICE</b> – <i>Acute invasive bacterial diarrhoea / dysentery</i> – <i>Gonorrhoea</i>
cefixime	<b>Powder for oral liquid:</b> 100 mg/5 mL [c]. <b>Solid oral dosage form:</b> 200 mg; 400 mg (as trihydrate).	
	<b>FIRST CHOICE</b>	<b>SECOND CHOICE</b> – <i>Acute invasive bacterial diarrhoea / dysentery</i> – <i>Gonorrhoea</i>
cefotaxime*	<b>Powder for injection:</b> 250 mg; 500 mg; 1 g; 2 g (as sodium) in vial. *3rd generation cephalosporin of choice for use in hospitalized neonates.	
	<b>FIRST CHOICE</b> – <i>Acute bacterial meningitis</i> – <i>Community acquired pneumonia (severe)</i> – <i>Complicated intraabdominal infections (mild to moderate)</i> – <i>Complicated intraabdominal infections (severe)</i> – <i>Hospital acquired pneumonia</i> – <i>Pyelonephritis or prostatitis (severe)</i>	<b>SECOND CHOICE</b> – <i>Bone and joint infections</i> – <i>Pyelonephritis or prostatitis (mild to moderate)</i> – <i>Sepsis in neonates and children [c]</i>

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ceftriaxone* <b>[a]</b>	<p><b>Powder for injection:</b> 250 mg; 500 mg; 1 g; 2 g (as sodium) in vial.</p> <p>*Do not administer with calcium and avoid in infants with hyperbilirubinaemia.</p> <p><b>[a]</b> &gt; 41 weeks corrected gestational age.</p>	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– Acute bacterial meningitis</li> <li>– Community acquired pneumonia (severe)</li> <li>– Complicated intraabdominal infections (mild to moderate)</li> <li>– Complicated intrabdominal infections (severe)</li> <li>– Endophthalmitis</li> <li>– Enteric fever</li> <li>– Gonorrhoea</li> <li>– Hospital acquired pneumonia</li> <li>– Necrotizing fasciitis</li> <li>– Pyelonephritis or prostatitis (severe)</li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– Acute invasive bacterial diarrhoea / dysentery</li> <li>– Bone and joint infections</li> <li>– Pyelonephritis or prostatitis (mild to moderate)</li> <li>– Sepsis in neonates and children <b>[c]</b></li> </ul>
cefuroxime	<p><b>Powder for injection:</b> 250 mg; 750 mg; 1.5 g (as sodium) in vial.</p>	
	<b>FIRST CHOICE</b>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– Surgical prophylaxis</li> </ul>
ciprofloxacin	<p><b>Oral liquid:</b> 250 mg/5 mL (anhydrous) <b>[c]</b>.</p> <p><b>Solution for IV infusion:</b> 2 mg/mL (as hydrate) <b>[c]</b>.</p> <p><b>Solid oral dosage form:</b> 100 mg <b>[c]</b>; 250 mg; 500 mg (as hydrochloride).</p>	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– Acute invasive bacterial diarrhoea / dysentery</li> <li>– Enteric fever</li> <li>– Low-risk febrile neutropenia</li> <li>– Pyelonephritis or prostatitis (mild to moderate)</li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– Cholera</li> <li>– Complicated intraabdominal infections (mild to moderate)</li> </ul>
□ clarithromycin† Therapeutic alternatives: - erythromycin*	<p><b>Powder for oral liquid:</b> 125 mg/5 mL; 250 mg/5 mL.</p> <p><b>Powder for injection:</b> 500 mg in vial.</p> <p><b>Solid oral dosage form:</b> 250 mg <b>[c]</b>; 500 mg.</p> <p>†clarithromycin is also listed for use in combination regimens for eradication of <i>H. pylori</i> in adults.</p>	
*as second choice treatment for pharyngitis in children (EMC only)	<b>FIRST CHOICE</b> <p>Community acquired pneumonia (severe)</p>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– Pharyngitis</li> </ul>

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piperacillin + tazobactam	<b>Powder for injection:</b> 2 g (as sodium) + 250 mg (as sodium); 4 g (as sodium) + 500 mg (as sodium) in vial.	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Complicated intraabdominal infections (severe)</i></li> <li>– <i>High-risk febrile neutropenia</i></li> <li>– <i>Hospital acquired pneumonia</i></li> <li>– <i>Necrotizing fasciitis</i></li> </ul>	<b>SECOND CHOICE</b>
vancomycin*	<b>Capsule:</b> 125 mg; 250 mg (as hydrochloride). *vancomycin powder for injection may also be used for oral administration	
	<b>FIRST CHOICE</b>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>C. difficile infection</i></li> </ul>
<b>Complementary List</b>		
ceftazidime	<b>Powder for injection:</b> 250 mg; 1 g (as pentahydrate) in vial.	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Endophthalmitis</i></li> </ul>	<b>SECOND CHOICE</b>
□ meropenem* [a]  Therapeutic alternatives*: - imipenem + cilastatin  *complicated intraabdominal infections and high-risk febrile neutropenia only. Meropenem is the preferred choice for acute bacterial meningitis in neonates.	<b>Powder for injection:</b> 500 mg (as trihydrate); 1 g (as trihydrate) in vial. [a] > 3 months.	
	<b>FIRST CHOICE</b>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Acute bacterial meningitis in neonates [c]</i></li> <li>– <i>Complicated intraabdominal infections (severe)</i></li> <li>– <i>High-risk febrile neutropenia</i></li> </ul>
vancomycin	<b>Powder for injection:</b> 250 mg; 500 mg; 1 g (as hydrochloride) in vial.	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Endophthalmitis</i></li> <li>– <i>Necrotizing fasciitis</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>High-risk febrile neutropenia</i></li> </ul>
<b>6.2.3 Reserve group antibiotics</b>		
<b>Complementary List</b>		
cefiderocol	<b>Powder for injection:</b> 1 g (as sulfate toxylate) in vial.	
ceftazidime + avibactam	<b>Powder for injection:</b> 2 g + 0.5 g in vial.	
ceftolozane + tazobactam	<b>Powder for injection:</b> 1 g + 0.5 g in vial.	
colistin	<b>Powder for injection:</b> 1 million IU (as colistemethate sodium) (equivalent to 34 mg colistin base activity) in vial.	
fosfomycin	<b>Powder for injection:</b> 2 g; 4 g (as sodium) in vial.	
o linezolid  Therapeutic alternatives: - tedizolid phosphate	<b>Injection for intravenous administration:</b> 2 mg/mL in 300 mL bag.	
	<b>Powder for oral liquid:</b> 100 mg/5 mL.	
	<b>Tablet:</b> 600 mg.	
	<b>Tablet (dispersible):</b> 150 mg [c].	

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<i>meropenem + vaborbactam</i>	<b>Powder for injection:</b> 1 g (as trihydrate) + 1 g in vial.
<i>plazomicin</i>	<b>Injection:</b> 500 mg/10 mL.
<i>polymyxin B</i>	<b>Powder for injection:</b> 500 000 IU (equivalent to 50 mg polymyxin B base) in vial.
<b>6.2.4 Antileprosy medicines</b>	
Medicines used in the treatment of leprosy should never be used except in combination. Combination therapy is essential to prevent the emergence of drug resistance. Colour-coded blister packs (MDT blister packs) containing standard two-medicine (paucibacillary leprosy) or three-medicine (multibacillary leprosy) combinations for adult and childhood leprosy should be used. MDT blister packs can be supplied free of charge through WHO.	
<i>clofazimine</i>	<b>Solid oral dosage form:</b> 50 mg; 100 mg.
<i>dapsone</i>	<b>Tablet:</b> 25 mg; 50 mg; 100 mg.
<i>rifampicin</i>	<b>Oral liquid:</b> 20 mg/mL [c]. <b>Solid oral dosage form:</b> 150 mg; 300 mg.
<b>6.2.5 Antituberculosis medicines</b>	
WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.	
<i>ethambutol</i>	<b>Tablet:</b> 100 mg; 400 mg (hydrochloride). <b>Tablet (dispersible):</b> 100 mg [c]
<i>ethambutol + isoniazid + pyrazinamide + rifampicin</i>	<b>Tablet:</b> 275 mg + 75 mg + 400 mg + 150 mg.
<i>ethambutol + isoniazid + rifampicin</i>	<b>Tablet:</b> 275 mg + 75 mg + 150 mg.
<i>ethionamide</i>	<b>Tablet:</b> 250 mg. <b>Tablet (dispersible):</b> 125 mg [c].
<i>isoniazid</i>	<b>Tablet:</b> 100 mg; 300 mg. <b>Tablet (dispersible):</b> 100 mg [c].
<i>isoniazid + pyrazinamide + rifampicin</i>	<b>Tablet (dispersible):</b> 50 mg + 150 mg + 75 mg [c].
<i>isoniazid + rifampicin</i>	<b>Tablet:</b> 75 mg + 150 mg; 150 mg + 300 mg. <b>Tablet (dispersible):</b> 50 mg + 75 mg [c].
<i>isoniazid + rifapentine</i>	<b>Tablet (scored):</b> 300 mg + 300 mg.
<i>moxifloxacin</i>	<b>Tablet:</b> 400 mg.
<i>pyrazinamide</i>	<b>Tablet:</b> 400 mg; 500 mg <b>Tablet (dispersible):</b> 150 mg.
<i>rifabutin</i>	<b>Solid oral dosage form:</b> 150 mg.* *For use only in patients with HIV receiving protease inhibitors.
<i>rifampicin</i>	<b>Oral liquid:</b> 20 mg/mL [c]. <b>Solid oral dosage form:</b> 150 mg; 300 mg.
<i>rifapentine</i>	<b>Tablet:</b> 150 mg; 300 mg.

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Complementary List	
Medicines for the treatment of multidrug-resistant tuberculosis (MDR-TB) should be used in specialized centres adhering to WHO standards for TB control.	
amikacin	<b>Injection:</b> 250 mg/mL (as sulfate) in 2 mL vial.
amoxicillin + clavulanic acid*	<b>Powder for oral liquid:</b> 250 mg (as trihydrate) + 62.5 mg (as potassium salt)/5mL [c]. <b>Tablet:</b> 500 mg (as trihydrate) + 125 mg (as potassium salt). *For use only in combination with meropenem or imipenem+cilastatin.
bedaquiline	<b>Tablet:</b> 20 mg [c]; 100 mg.
clofazimine	<b>Solid oral dosage form:</b> 50 mg; 100 mg.
<input checked="" type="checkbox"/> cycloserine Therapeutic alternatives: - terizidone	<b>Solid oral dosage form:</b> 125 mg [c]; 250 mg.
delamanid	<b>Tablet (dispersible):</b> 25 mg [c]. <b>Tablet:</b> 50 mg.
<input checked="" type="checkbox"/> ethionamide Therapeutic alternatives: - prontonamide	<b>Tablet:</b> 250 mg. <b>Tablet (dispersible):</b> 125 mg [c].
levofloxacin	<b>Tablet:</b> 250mg; 500 mg; 750 mg. <b>Tablet (dispersible):</b> 100 mg [c].
linezolid	<b>Tablet:</b> 600 mg. <b>Tablet (dispersible):</b> 150 mg [c].
<input checked="" type="checkbox"/> meropenem Therapeutic alternatives: - imipenem + cilastatin	<b>Powder for injection:</b> 500 mg (as trihydrate); 1 g (as trihydrate) in vial.
moxifloxacin	<b>Tablet:</b> 400 mg. <b>Tablet (dispersible):</b> 100 mg [c].
p-aminosalicylate sodium	<b>Powder for oral solution:</b> 5.52 g in sachet (equivalent to 4 g p-aminosalicylic acid).
pretomanid	<b>Tablet:</b> 200 mg.
streptomycin [c]	<b>Powder for injection:</b> 1 g (as sulfate) in vial.

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6.3 Antifungal medicines	
amphotericin B*	<p><b>Powder for injection:</b> 50 mg (liposomal complex) in vial.</p> <p><b>Powder for injection:</b> 50 mg (as sodium deoxycholate) in vial</p> <p>*Liposomal amphotericin B has a better safety profile than the sodium deoxycholate formulation and should be prioritized for selection and use depending on local availability and cost.</p>
clotrimazole	<p><b>Vaginal cream:</b> 1%; 10%.</p> <p><b>Vaginal tablet:</b> 100 mg; 500 mg.</p>
fluconazole	<p><b>Capsule:</b> 50 mg.</p> <p><b>Injection:</b> 2 mg/mL in vial.</p> <p><b>Oral liquid:</b> 50 mg/5 mL.</p> <p><b>Powder for oral liquid:</b> 50 mg/5 mL [c].</p>
flucytosine	<p><b>Capsule:</b> 250 mg.</p> <p><b>Infusion:</b> 2.5 g in 250 mL.</p>
griseofulvin	<p><b>Oral liquid:</b> 125 mg/5 mL [c].</p> <p><b>Solid oral dosage form:</b> 125 mg; 250 mg.</p>
itraconazole*	<p><b>Capsule:</b> 100 mg.</p> <p><b>Oral liquid:</b> 10 mg/mL.</p> <p>*For treatment of chronic pulmonary aspergillosis, histoplasmosis, sporotrichosis, paracoccidioidomycosis, mycoses caused by <i>T. marneffei</i> and chromoblastomycosis; and prophylaxis of histoplasmosis and infections caused by <i>T. marneffei</i> in AIDS patients.</p>
nystatin	<p><b>Lozenge:</b> 100 000 IU.</p> <p><b>Oral liquid:</b> 100 000 IU/mL [c].</p> <p><b>Pessary:</b> 100 000 IU.</p> <p><b>Solid oral dosage form:</b> 500 000 IU.</p>
voriconazole*	<p><b>Tablet:</b> 50 mg; 200 mg</p> <p><b>Powder for injection:</b> 200 mg in vial</p> <p><b>Powder for oral liquid:</b> 40 mg/mL</p> <p>*For treatment of chronic pulmonary aspergillosis and acute invasive aspergillosis.</p>
<i>Complementary List</i>	
<input type="checkbox"/> <i>micafungin</i> <i>Therapeutic alternatives:</i> - <i>anidulafungin</i> - <i>caspofungin</i>	<i>Powder for injection:</i> 50 mg (as sodium); 100 mg (as sodium) in vial.
<i>potassium iodide</i>	<i>Saturated solution.</i>

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<b>6.4 Antiviral medicines</b>	
<b>6.4.1 Antitherpes medicines</b>	
□ aciclovir Therapeutic alternatives: - valaciclovir (oral)	<b>Oral liquid:</b> 200 mg/5 mL [c]. <b>Powder for injection:</b> 250 mg (as sodium salt) in vial. <b>Tablet:</b> 200 mg.
<b>6.4.2 Antiretrovirals</b>	
Based on current evidence and experience of use, medicines in the following classes of antiretrovirals are included as essential medicines for treatment and prevention of HIV (prevention of mother-to-child transmission, pre-exposure prophylaxis (where indicated) and post-exposure prophylaxis). WHO emphasizes the importance of using these products in accordance with global and national guidelines. WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.	
Scored tablets can be used in children and therefore can be considered for inclusion in the listing of tablets, provided that adequate quality products are available.	
<b>6.4.2.1 Nucleoside/Nucleotide reverse transcriptase inhibitors</b>	
abacavir	<b>Tablet:</b> 300 mg (as sulfate).
lamivudine	<b>Oral liquid:</b> 50 mg/5 mL [c]. <b>Tablet:</b> 150 mg.
tenofovir disoproxil fumarate†	<b>Tablet:</b> 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil). †also indicated for pre-exposure prophylaxis.
zidovudine	<b>Capsule:</b> 250 mg. <b>Oral liquid:</b> 50 mg/5 mL. <b>Solution for IV infusion:</b> 10 mg/mL in 20 mL vial. <b>Tablet:</b> 300 mg.
<b>6.4.2.2 Non-nucleoside reverse transcriptase inhibitors</b>	
efavirenz	<b>Tablet:</b> 600 mg.
nevirapine [a]	<b>Oral liquid:</b> 50 mg/5 mL. <b>Tablet:</b> 50 mg (dispersible); 200 mg. [a] > 6 weeks
<b>6.4.2.3 Protease inhibitors</b>	
Selection of protease inhibitor(s) from the Model List will need to be determined by each country after consideration of international and national treatment guidelines and experience. Ritonavir is recommended for use in combination as a pharmacological booster, and not as an antiretroviral in its own right. All other protease inhibitors should be used in boosted forms (e.g. with ritonavir).	
atazanavir + ritonavir	<b>Tablet (heat stable):</b> 300 mg (as sulfate) + 100 mg.
darunavir [a]	<b>Tablet:</b> 75 mg; 400 mg; 600 mg; 800 mg [a] > 3 years
lopinavir + ritonavir	<b>Solid oral dosage form:</b> 40 mg + 10 mg [c]. <b>Tablet (heat stable):</b> 100 mg + 25 mg; 200 mg + 50 mg.
ritonavir	<b>Tablet (heat stable):</b> 25 mg; 100 mg.

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## 6.4.2.4 Integrase inhibitors

dolutegravir <small>a</small>	<p><b>Tablet (dispersible, scored):</b> 10 mg [c].</p> <p><b>[a]</b> ≥ 4 weeks and ≥ 3 kg</p> <p><b>Tablet:</b> 50 mg</p> <p><b>[a]</b> ≥ 25 kg</p>
raltegravir*	<p><b>Granules for oral suspension:</b> 100 mg in sachet.</p> <p><b>Tablet (chewable):</b> 25 mg.</p> <p><b>Tablet:</b> 400 mg.</p> <p>*For use in pregnant women and in second-line regimens in accordance with WHO treatment guidelines.</p>

## 6.4.2.5 Fixed-dose combinations of antiretroviral medicines

abacavir + lamivudine	<b>Tablet (dispersible, scored):</b> 120 mg (as sulfate) + 60 mg.
dolutegravir + lamivudine + tenofovir	<b>Tablet:</b> 50 mg + 300 mg + 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil)
efavirenz + <input type="checkbox"/> emtricitabine + tenofovir Therapeutic alternatives: - lamivudine (for emtricitabine)	<b>Tablet:</b> 600 mg + 200 mg + 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil).
efavirenz + lamivudine + tenofovir	<b>Tablet:</b> 400 mg + 300 mg + 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil)
<input type="checkbox"/> emtricitabine + tenofovir† Therapeutic alternatives: - lamivudine (for emtricitabine)	<b>Tablet:</b> 200 mg + 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil). † combination also indicated for pre-exposure prophylaxis
lamivudine + zidovudine	<b>Tablet:</b> 30 mg + 60 mg [c]; 150 mg + 300 mg.

## 6.4.2.6 Medicines for prevention of HIV-related opportunistic infections

isoniazid + pyridoxine + sulfamethoxazole + trimethoprim	<b>Tablet (scored):</b> 300 mg + 25 mg + 800 mg + 160 mg
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## 6.4.3 Other antivirals

ribavirin*	<p><b>Injection for intravenous administration:</b> 800 mg and 1 g in 10 mL phosphate buffer solution.</p> <p><b>Solid oral dosage form:</b> 200 mg; 400 mg; 600 mg.</p> <p>*For the treatment of viral haemorrhagic fevers</p>
valganciclovir*	<p><b>Tablet:</b> 450 mg.</p> <p>*For the treatment of cytomegalovirus retinitis (CMVr).</p>

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<i>Complementary list</i>	
oseltamivir*	<p><b>Capsule:</b> 30 mg; 45 mg; 75 mg (as phosphate).</p> <p>*Severe illness due to confirmed or suspected influenza virus infection in critically ill hospitalized patients</p>
valganciclovir*[c]	<p><b>Powder for oral solution:</b> 50 mg/mL</p> <p><b>Tablet:</b> 450 mg.</p> <p>*For the treatment of cytomegalovirus retinitis (CMVr).</p>
6.4.4 Antihepatitis medicines	
6.4.4.1 Medicines for hepatitis B	
6.4.4.1.1 Nucleoside/Nucleotide reverse transcriptase inhibitors	
entecavir	<p><b>Oral liquid:</b> 0.05 mg/mL</p> <p><b>Tablet:</b> 0.5 mg; 1 mg</p>
tenofovir disoproxil fumarate	<b>Tablet:</b> 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil).
6.4.4.2 Medicines for hepatitis C	
Pangenotypic direct-acting antivirals should be considered as therapeutic alternatives for the purposes of selection and procurement at national level.	
6.4.4.2.1 □ Pangenotypic direct-acting antiviral combinations	
daclatasvir*	<p><b>Tablet:</b> 30 mg; 60 mg (as hydrochloride).</p> <p>*Pangenotypic when used in combination with sofosbuvir</p>
daclatasvir + sofosbuvir	<b>Tablet:</b> 60 mg + 400 mg.
glecaprevir + pibrentasvir	<p><b>Tablet:</b> 100 mg + 40 mg.</p> <p><b>Granules:</b> 50 mg + 20 mg in sachet [c].</p>
ravidasvir*	<p><b>Tablet:</b> 200 mg.</p> <p>*Pangenotypic when used in combination with sofosbuvir</p>
sofosbuvir*	<p><b>Tablet:</b> 200 mg; 400 mg.</p> <p>*Pangenotypic when used in combination with daclatasvir or ravidasvir</p>
sofosbuvir + velpatasvir	<b>Tablet:</b> 200 mg + 50 mg [c]; 400 mg + 100 mg.
6.4.4.2.2 Non-pangenotypic direct-acting antiviral combinations	
ledipasvir + sofosbuvir	<b>Tablet:</b> 90 mg + 400 mg.
6.4.4.2.3 Other antivirals for hepatitis C	
ribavirin*	<p><b>Injection for intravenous administration:</b> 800 mg and 1 g in 10 mL phosphate buffer solution.</p> <p><b>Solid oral dosage form:</b> 200 mg; 400 mg; 600 mg.</p> <p>*For the treatment of hepatitis C, in combination with direct acting anti-viral medicines</p>

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<b>6.5 Antiprotozoal medicines</b>	
<b>6.5.1 Antiamoebic and antigiardiasis medicines</b>	
diloxanide <b>[a]</b>	<p><b>Tablet:</b> 500 mg (furoate).</p> <p><b>[a]</b> &gt; 25 kg.</p>
<input type="checkbox"/> metronidazole Therapeutic alternatives: - tinidazole	<p><b>Injection:</b> 500 mg in 100 mL vial.</p> <p><b>Oral liquid:</b> 200 mg/5 mL (as benzoate).</p> <p><b>Tablet:</b> 200 mg; 250 mg; 400 mg; 500 mg.</p>
<b>6.5.2 Antileishmaniasis medicines</b>	
amphotericin B*	<p><b>Powder for injection:</b> 50 mg (liposomal complex) in vial.</p> <p><b>Powder for injection:</b> 50 mg (as sodium deoxycholate) in vial.</p> <p>*Liposomal amphotericin B has a better safety profile than the sodium deoxycholate formulation and should be prioritized for selection and use depending on local availability and cost.</p>
meglumine antimoniate	<b>Injection:</b> 1.5 g/5 mL in 5 mL ampoule.
miltefosine	<b>Solid oral dosage form:</b> 10 mg; 50 mg.
paromomycin	<b>Solution for intramuscular injection:</b> 750 mg of paromomycin base (as sulfate).
sodium stibogluconate	<b>Injection:</b> 100 mg/mL in 30 mL vial.
<b>6.5.3 Antimalarial medicines</b>	
<b>6.5.3.1 For curative treatment</b>	
Medicines for the treatment of <i>P. falciparum</i> malaria cases should be used in combination. The list currently recommends combinations according to treatment guidelines. WHO recognizes that not all of the fixed dose combinations (FDCs) in the WHO treatment guidelines exist, and encourages their development and rigorous testing. WHO also encourages development and testing of rectal dosage formulations.	
amodiaquine*	<p><b>Tablet:</b> 153 mg or 200 mg (as hydrochloride).</p> <p>*To be used in combination with artesunate 50 mg.</p>
artemether*	<p><b>Oily injection:</b> 80 mg/mL in 1 mL ampoule.</p> <p>*For use in the management of severe malaria.</p>
artemether + lumefantrine*	<p><b>Tablet:</b> 20 mg + 120 mg.</p> <p><b>Tablet (dispersible):</b> 20 mg + 120 mg [c].</p> <p>*Not recommended in the first trimester of pregnancy or in children below 5 kg.</p>

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artesunate*	<p><b>Injection:</b> ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution. For use in the management of severe malaria.</p> <p><b>Rectal dosage form:</b> 50 mg [c]; 100 mg [c]; 200 mg capsules (for pre-referral treatment of severe malaria only; patients should be taken to an appropriate health facility for follow-up care) [c].</p> <p><b>Tablet:</b> 50 mg.</p> <p>*To be used in combination with either amodiaquine, mefloquine or sulfadoxine + pyrimethamine.</p>
artesunate + amodiaquine*	<p><b>Tablet:</b> 25 mg + 67.5 mg; 50 mg + 135 mg; 100 mg + 270 mg.</p> <p>*Other combinations that deliver the target doses required such as 153 mg or 200 mg (as hydrochloride) with 50 mg artesunate can be alternatives.</p>
artesunate + mefloquine	<p><b>Tablet:</b> 25 mg + 55 mg; 100 mg + 220 mg.</p>
artesunate + pyronaridine tetraphosphate [a]	<p><b>Granules:</b> 20 mg + 60 mg [c].</p> <p><b>Tablet:</b> 60 mg + 180 mg.</p> <p>[a] &gt; 5 kg</p>
chloroquine*	<p><b>Oral liquid:</b> 50 mg/5 mL (as phosphate or sulfate).</p> <p><b>Tablet:</b> 100 mg; 150 mg (as phosphate or sulfate).</p> <p>*For use only for the treatment of <i>Plasmodium vivax</i> infection.</p>
dihydroartemisinin + piperaquine phosphate [a]	<p><b>Tablet:</b> 20 mg + 160 mg; 40 mg + 320 mg.</p> <p>[a] &gt; 5 kg</p>
doxycycline*	<p><b>Capsule:</b> 100 mg (as hydrochloride or hyclate).</p> <p><b>Tablet (dispersible):</b> 100 mg (as monohydrate).</p> <p>*For use only in combination with quinine.</p>
mefloquine*	<p><b>Tablet:</b> 250 mg (as hydrochloride).</p> <p>*To be used in combination with artesunate 50 mg.</p>
primaquine*	<p><b>Tablet:</b> 7.5 mg; 15 mg (as diphosphate).</p> <p>*Only for use to achieve radical cure of <i>Plasmodium vivax</i> and <i>Plasmodium ovale</i> infections, given for 14 days.</p>
quinine*	<p><b>Injection:</b> 300 mg/mL (hydrochloride) in 2 mL ampoule.</p> <p><b>Tablet:</b> 300 mg (sulfate) or 300 mg (bisulfate).</p> <p>*For use only in the management of severe malaria and should be used in combination with doxycycline.</p>
sulfadoxine + pyrimethamine*	<p><b>Tablet:</b> 500 mg + 25 mg.</p> <p>*Only in combination with artesunate 50 mg.</p>

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## 6.5.3.2 For chemoprevention

amodiaquine – sulfadoxine + pyrimethamine [c]	<b>Co-packaged dispersible tablets:</b> amodiaquine 76.5 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 250 mg + 12.5 mg [1]; amodiaquine 153 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 500 mg + 25 mg [1].
chloroquine*	<b>Oral liquid:</b> 50 mg/5 mL (as phosphate or sulfate). <b>Tablet:</b> 150 mg (as phosphate or sulfate). *For use only in central American regions, for <i>Plasmodium vivax</i> infections.
doxycycline [a]	<b>Solid oral dosage form:</b> 100 mg (as hydrochloride or hyclate). [a] > 8 years.
mefloquine [a]	<b>Tablet:</b> 250 mg (as hydrochloride). [a] > 5 kg or > 3 months.
proguanil*	<b>Tablet:</b> 100 mg (as hydrochloride). *For use only in combination with chloroquine.
sulfadoxine + pyrimethamine	<b>Tablet:</b> 250 mg + 12.5 mg [c]; 500 mg + 25 mg.

## 6.5.4 Antipneumocystosis and antitoxoplasmosis medicines

pyrimethamine	<b>Tablet:</b> 25 mg.
sulfadiazine	<b>Tablet:</b> 500 mg.
sulfamethoxazole + trimethoprim	<b>Injection:</b> 80 mg + 16 mg/mL in 5 mL ampoule; 80 mg + 16 mg/mL in 10 mL ampoule. <b>Oral liquid:</b> 200 mg + 40 mg/5 mL [c]. <b>Tablet:</b> 100 mg + 20 mg; 400 mg + 80 mg [c]; 800 mg + 160 mg. <b>Tablet (dispersible):</b> 100 mg + 20 mg [c].

## Complementary List

pentamidine	<b>Tablet:</b> 200 mg; 300 mg (as isethionate).
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## 6.5.5 Antitrypanosomal medicines

### 6.5.5.1 African trypanosomiasis

fexinidazole*	<b>Tablet:</b> 600 mg *For the treatment of 1 <sup>st</sup> and 2 <sup>nd</sup> stage of human African trypanosomiasis due to <i>Trypanosoma brucei gambiense</i> infection.
<b>Medicines for the treatment of 1<sup>st</sup> stage African trypanosomiasis</b>	
pentamidine*	<b>Powder for injection:</b> 300 mg (as isetionate) in vial. *To be used for the treatment of <i>Trypanosoma brucei gambiense</i> infection.
suramin sodium*	<b>Powder for injection:</b> 1 g in vial. *To be used for the treatment of the initial phase of <i>Trypanosoma brucei rhodesiense</i> infection.

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Medicines for the treatment of 2 <sup>nd</sup> stage African trypanosomiasis	
eflornithine*	<b>Injection:</b> 200 mg/mL (hydrochloride) in 50 mL bottle. *To be used for the treatment of <i>Trypanosoma brucei gambiense</i> infection.
melarsoprol	<b>Injection:</b> 180 mg/5 mL in 5 mL ampoule (3.6% solution).
nifurtimox *	<b>Tablet (scored):</b> 30 mg; 120 mg. *Only to be used in combination with eflornithine, for the treatment of <i>Trypanosoma brucei gambiense</i> infection.
<i>Complementary List</i>	
melarsoprol [c]	<b>Injection:</b> 180 mg/5 mL in 5 mL ampoule (3.6% solution).
6.5.5.2 American trypanosomiasis	
benznidazole	<b>Tablet:</b> 12.5 mg [c] <b>Tablet (scored):</b> 50 mg; 100 mg.
nifurtimox	<b>Tablet (scored):</b> 30 mg; 120 mg.
6.6 Medicines for ectoparasitic infections	
ivermectin	<b>Tablet:</b> 3 mg
6.7 Medicines for Ebola virus disease	
ansuvimab	<b>Powder for injection:</b> 400 mg
atoltivimab + maftivimab + odesivimab	<b>Injection:</b> 241.7 mg + 241.7 mg + 241.7 mg in 14.5 mL vial
6.8 Medicines for COVID-19	
WHO recommends that effective and safe therapeutics for prevention and treatment of COVID-19 should be considered as essential medicines in the context of the public health emergency. WHO recommendations are revised and updated regularly in WHO living guidelines for therapeutics for the treatment and prevention of COVID-19.	
Selection of essential therapeutics for COVID-19 at the national level should be informed by recommendations in these guidelines, and consideration of the latest evidence, epidemiology and national priorities.	
The latest WHO Therapeutics and COVID-19: living guideline is available online at: <a href="https://app.magicapp.org/#/guideline/nBkO1E">https://app.magicapp.org/#/guideline/nBkO1E</a>	
The latest WHO Drugs to prevent COVID-19: living guideline is available online at: <a href="https://app.magicapp.org/#/guideline/L6RxYL">https://app.magicapp.org/#/guideline/L6RxYL</a>	

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7. ANTIMIGRAINE MEDICINES	
7.1 For treatment of acute attack	
acetylsalicylic acid	Tablet: 300 mg to 500 mg.
ibuprofen [c]	Oral liquid: 100 mg/5 mL [c]. Tablet: 200 mg; 400 mg.
paracetamol (acetaminophen)	Oral liquid: 120 mg/5 mL or 125 mg/5 mL*; 250 mg/5 mL [c]. *The presence of both 120 mg/5 mL and 125 mg/5mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided. Suppository: 250 mg [c]. Tablet: 250 mg; 325 mg; 500 mg. Tablet (dispersible): 100 mg, 250 mg [c].
sumatriptan	Tablet: 50 mg
7.2 For prophylaxis	
<input type="checkbox"/> propranolol Therapeutic alternatives to be reviewed	Tablet: 20 mg; 40 mg (hydrochloride).
8. IMMUNOMODULATORS AND ANTINEOPLASTICS	
8.1 Immunomodulators for non-malignant disease	
<i>Complementary List</i>	
<input type="checkbox"/> adalimumab*  <i>Therapeutic alternatives*:</i> - certolizumab pegol - etanercept - golimumab - infliximab  <i>*including quality-assured biosimilars</i>	<i>Injection:</i> 10 mg/0.2 mL [c]; 20 mg/0.4 mL [c]; 40 mg/0.8 mL; 40 mg/0.4 mL.
azathioprine	<i>Oral liquid:</i> 10 mg/mL [c]. <i>Powder for injection:</i> 50 mg [c]; 100 mg (as sodium salt) in vial. <i>Tablet:</i> 25 mg [c]. <i>Tablet (scored):</i> 50 mg.
ciclosporin	<i>Capsule:</i> 25 mg. <i>Concentrate for injection:</i> 50 mg/mL in 1 mL ampoule. <i>Oral liquid:</i> 100 mg/mL [c].
tacrolimus	<i>Capsule (immediate-release):</i> 0.5 mg; 0.75 mg; 1 mg; 2 mg; 5 mg. <i>Granules for oral suspension:</i> 0.2 mg; 1 mg. <i>Injection:</i> 5 mg/mL in 1 mL vial.

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8.2 Antineoplastics and supportive medicines	
Medicines listed below should be used according to protocols for treatment of the diseases.	
8.2.1 Cytotoxic medicines	
Complementary List	
<i>arsenic trioxide</i>	<p><b>Concentrate for solution for infusion:</b> 1 mg/mL; 2 mg/mL.</p> <ul style="list-style-type: none"> <li>– Acute promyelocytic leukaemia</li> </ul>
<i>asparaginase*</i> *including quality-assured biosimilars	<p><b>Powder for injection:</b> 10 000 IU in vial.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia.</li> </ul>
<i>bendamustine</i>	<p><b>Injection:</b> 45 mg/0.5 mL; 180 mg/2 mL.</p> <ul style="list-style-type: none"> <li>– Chronic lymphocytic leukaemia</li> <li>– Follicular lymphoma</li> </ul>
<i>bleomycin</i>	<p><b>Powder for injection:</b> 15 000 IU (as sulfate) in vial.</p> <ul style="list-style-type: none"> <li>– Hodgkin lymphoma</li> <li>– Kaposi sarcoma</li> <li>– Ovarian germ cell tumour</li> <li>– Testicular germ cell tumour</li> </ul>
<i>calcium folinate (leucovorin calcium)</i>	<p><b>Injection:</b> 3 mg/mL in 10 mL ampoule; 7.5 mg/mL in 2 mL ampoule; 10 mg/mL in 5 mL ampoule.</p> <p><b>Tablet:</b> 5 mg; 15 mg; 25 mg.</p> <ul style="list-style-type: none"> <li>– Burkitt lymphoma</li> <li>– Early stage colon cancer</li> <li>– Early stage rectal cancer</li> <li>– Gestational trophoblastic neoplasia</li> <li>– Metastatic colorectal cancer</li> <li>– Osteosarcoma</li> </ul>
<i>capecitabine</i>	<p><b>Tablet:</b> 150 mg; 500 mg.</p> <ul style="list-style-type: none"> <li>– Early stage colon cancer</li> <li>– Early stage rectal cancer</li> <li>– Metastatic breast cancer</li> <li>– Metastatic colorectal cancer</li> </ul>
<i>carboplatin</i>	<p><b>Injection:</b> 50 mg/5 mL; 150 mg/15 mL; 450 mg/45 mL; 600 mg/60 mL.</p> <ul style="list-style-type: none"> <li>– Cervical cancer</li> <li>– Early stage breast cancer</li> <li>– Epithelial ovarian cancer</li> <li>– Head and neck cancer (as a radio-sensitizer)</li> <li>– Low-grade glioma</li> <li>– Nasopharyngeal cancer</li> <li>– Nephroblastoma (Wilms tumour)</li> <li>– Non-small cell lung cancer</li> <li>– Osteosarcoma</li> <li>– Ovarian germ cell tumour</li> <li>– Retinoblastoma</li> <li>– Testicular germ cell tumour</li> </ul>
<i>chlorambucil</i>	<p><b>Tablet:</b> 2 mg.</p> <ul style="list-style-type: none"> <li>– Chronic lymphocytic leukaemia</li> </ul>

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<i>cisplatin</i>	<p><b>Injection:</b> 10 mg/10 mL; 20 mg/20 mL; 50 mg/50 mL; 100 mg/100 mL.</p> <ul style="list-style-type: none"> <li>– Cervical cancer</li> <li>– Head and neck cancer (as a radio-sensitizer)</li> <li>– Low-grade glioma</li> <li>– Nasopharyngeal cancer (as a radio-sensitizer)</li> <li>– Non-small cell lung cancer</li> <li>– Osteosarcoma</li> <li>– Ovarian germ cell tumour</li> <li>– Testicular germ cell tumour</li> </ul>
<i>cyclophosphamide</i>	<p><b>Powder for injection:</b> 500 mg; 1 g; 2 g in vial. <b>Solid oral dosage form:</b> 25 mg; 50 mg.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Anaplastic large cell lymphoma</li> <li>– Burkitt lymphoma</li> <li>– Chronic lymphocytic leukaemia</li> <li>– Diffuse large B-cell lymphoma</li> <li>– Early stage breast cancer</li> <li>– Ewing sarcoma</li> <li>– Follicular lymphoma</li> <li>– Gestational trophoblastic neoplasia</li> <li>– Hodgkin lymphoma</li> <li>– Low-grade glioma</li> <li>– Metastatic breast cancer</li> <li>– Multiple myeloma</li> <li>– Nephroblastoma (Wilms tumour)</li> <li>– Rhabdomyosarcoma</li> </ul>
<i>cytarabine</i>	<p><b>Injection:</b> 100 mg/mL in vial <b>Powder for injection:</b> 100 mg in vial.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Acute myeloid leukaemia</li> <li>– Acute promyelocytic leukaemia</li> <li>– Anaplastic large cell lymphoma</li> <li>– Burkitt lymphoma</li> <li>– Langerhans cell histiocytosis</li> </ul>
<i>dacarbazine</i>	<p><b>Powder for injection:</b> 100 mg; 200 mg in vial.</p> <ul style="list-style-type: none"> <li>– Hodgkin lymphoma</li> </ul>
<i>dactinomycin</i>	<p><b>Powder for injection:</b> 500 micrograms in vial.</p> <ul style="list-style-type: none"> <li>– Ewing sarcoma</li> <li>– Gestational trophoblastic neoplasia</li> <li>– Nephroblastoma (Wilms tumour)</li> <li>– Rhabdomyosarcoma</li> </ul>
<i>daunorubicin</i>	<p><b>Injection:</b> 2 mg/mL; 5 mg/mL (as hydrochloride) in vial. <b>Powder for injection:</b> 20 mg; 50 mg (as hydrochloride) in vial.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Acute myeloid leukaemia</li> <li>– Acute promyelocytic leukaemia</li> </ul>

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<i>docetaxel</i>	<p><b>Injection:</b> 20 mg/mL; 40 mg/mL.</p> <ul style="list-style-type: none"> <li>– Early stage breast cancer</li> <li>– Metastatic breast cancer</li> <li>– Metastatic prostate cancer</li> </ul>
<i>doxorubicin</i>	<p><b>Injection:</b> 2 mg/mL (hydrochloride) in vial.</p> <p><b>Powder for injection:</b> 10 mg; 50 mg (hydrochloride) in vial.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Anaplastic large cell lymphoma</li> <li>– Burkitt lymphoma</li> <li>– Diffuse large B-cell lymphoma</li> <li>– Early stage breast cancer</li> <li>– Ewing sarcoma</li> <li>– Follicular lymphoma</li> <li>– Hodgkin lymphoma</li> <li>– Kaposi sarcoma</li> <li>– Metastatic breast cancer</li> <li>– Multiple myeloma</li> <li>– Nephroblastoma (<i>Wilms tumour</i>)</li> <li>– Osteosarcoma</li> </ul>
<i>doxorubicin (as pegylated liposomal)</i>	<p><b>Injection:</b> 2 mg/mL (hydrochloride) in 10 mL, 25 mL vial</p> <ul style="list-style-type: none"> <li>– Kaposi sarcoma</li> </ul>
<i>etoposide</i>	<p><b>Capsule:</b> 50 mg, 100 mg.</p> <p><b>Injection:</b> 20 mg/mL in 5 mL ampoule.</p> <p><b>Powder for injection:</b> 100 mg (as phosphate) in vial</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Acute myeloid leukaemia</li> <li>– Anaplastic large cell lymphoma</li> <li>– Burkitt lymphoma</li> <li>– Ewing sarcoma</li> <li>– Gestational trophoblastic neoplasia</li> <li>– Hodgkin lymphoma</li> <li>– Nephroblastoma (<i>Wilms tumour</i>)</li> <li>– Non-small cell lung cancer</li> <li>– Osteosarcoma</li> <li>– Ovarian germ cell tumour</li> <li>– Retinoblastoma</li> <li>– Testicular germ cell tumour</li> </ul>
<i>fludarabine</i>	<p><b>Powder for injection:</b> 50 mg (phosphate) in vial.</p> <p><b>Tablet:</b> 10 mg</p> <ul style="list-style-type: none"> <li>– Chronic lymphocytic leukaemia.</li> </ul>
<i>fluorouracil</i>	<p><b>Injection:</b> 50 mg/mL in vial.</p> <ul style="list-style-type: none"> <li>– Early stage breast cancer</li> <li>– Early stage colon cancer</li> <li>– Early stage rectal cancer</li> <li>– Metastatic colorectal cancer</li> <li>– Nasopharyngeal cancer</li> </ul>
<i>gemcitabine</i>	<p><b>Powder for injection:</b> 200 mg; 1 g in vial.</p> <ul style="list-style-type: none"> <li>– Epithelial ovarian cancer</li> <li>– Non-small cell lung cancer</li> </ul>

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<i>hydroxycarbamide (hydroxyurea)</i>	<p><b>Solid oral dosage form:</b> 100 mg [c]; 200 mg; 300 mg; 400 mg; 500 mg; 1 g.</p> <ul style="list-style-type: none"> <li>– Chronic myeloid leukaemia</li> </ul>
<i>ifosfamide</i>	<p><b>Powder for injection:</b> 500 mg; 1 g; 2 g in vial.</p> <ul style="list-style-type: none"> <li>– Anaplastic large cell lymphoma</li> <li>– Burkitt lymphoma</li> <li>– Ewing sarcoma</li> <li>– Nephroblastoma (<i>Wilms tumour</i>)</li> <li>– Ovarian germ cell tumour</li> <li>– Osteosarcoma</li> <li>– Rhabdomyosarcoma</li> <li>– Testicular germ cell tumour</li> </ul>
<i>irinotecan</i>	<p><b>Injection:</b> 40 mg/2 mL in 2 mL vial; 100 mg/5 mL in 5 mL vial; 500 mg/25 mL in 25 mL vial.</p> <ul style="list-style-type: none"> <li>– Metastatic colorectal cancer</li> <li>– Nephroblastoma (<i>Wilms tumour</i>)</li> <li>– Rhabdomyosarcoma</li> </ul>
<i>melphalan</i>	<p><b>Tablet:</b> 2 mg</p> <p><b>Powder for injection:</b> 50 mg in vial</p> <ul style="list-style-type: none"> <li>– Multiple myeloma</li> </ul>
<i>mercaptopurine</i>	<p><b>Tablet:</b> 50 mg.</p> <p><b>Oral liquid:</b> 20 mg/mL [c].</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Acute promyelocytic leukaemia.</li> <li>– Langerhans cell histiocytosis</li> </ul>
<i>methotrexate</i>	<p><b>Concentrated injection:</b> 1000 mg/10 mL.</p> <p><b>Injection:</b> 50mg/2 mL.</p> <p><b>Powder for injection:</b> 50 mg (as sodium) in vial.</p> <p><b>Tablet:</b> 2.5 mg (as sodium).</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Acute promyelocytic leukaemia</li> <li>– Anaplastic large cell lymphoma</li> <li>– Burkitt lymphoma</li> <li>– Early stage breast cancer</li> <li>– Gestational trophoblastic neoplasia</li> <li>– Langerhans cell histiocytosis</li> <li>– Osteosarcoma</li> </ul>
<i>oxaliplatin</i>	<p><b>Injection:</b> 50 mg/10 mL in 10 mL vial; 100 mg/20 mL in 20 mL vial; 200 mg/40 mL in 40 mL vial.</p> <p><b>Powder for injection:</b> 50 mg; 100 mg in vial.</p> <ul style="list-style-type: none"> <li>– Early stage colon cancer</li> <li>– Metastatic colorectal cancer</li> </ul>

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paclitaxel	<p><i>Injection:</i> 6 mg/mL in vial.</p> <ul style="list-style-type: none"> <li>– Cervical cancer</li> <li>– Epithelial ovarian cancer</li> <li>– Early stage breast cancer</li> <li>– Metastatic breast cancer</li> <li>– Kaposi sarcoma</li> <li>– Nasopharyngeal cancer</li> <li>– Non-small cell lung cancer</li> <li>– Ovarian germ cell tumour</li> </ul>
<p>pegaspargase*</p> <p>*including quality-assured biosimilars</p>	<p><i>Injection:</i> 3750 units/5 mL in vial.</p> <p><i>Powder for injection:</i> 3750 units in vial.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> </ul>
procarbazine [c]	<p><i>Capsule:</i> 50 mg (as hydrochloride).</p> <ul style="list-style-type: none"> <li>– Hodgkin lymphoma</li> </ul>
realgar-Indigo naturalis formulation	<p><i>Tablet:</i> 270 mg (containing tetra-arsenic tetra-sulfide 30 mg).</p> <ul style="list-style-type: none"> <li>– Acute promyelocytic leukaemia</li> </ul>
tioguanine [c]	<p><i>Solid oral dosage form:</i> 40 mg.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> </ul>
vinblastine	<p><i>Injection:</i> 10 mg/10 mL (sulfate) in vial.</p> <p><i>Powder for injection:</i> 10 mg (sulfate) in vial.</p> <ul style="list-style-type: none"> <li>– Anaplastic large cell lymphoma</li> <li>– Hodgkin lymphoma</li> <li>– Kaposi sarcoma</li> <li>– Langerhans cell histiocytosis</li> <li>– Low-grade glioma</li> <li>– Ovarian germ cell tumour</li> <li>– Testicular germ cell tumour</li> </ul>
vincristine	<p><i>Injection:</i> 1 mg/mL (sulfate); 2 mg/2 mL (sulfate) in vial.</p> <p><i>Powder for injection:</i> 1 mg; 5 mg (sulfate) in vial.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Burkitt lymphoma</li> <li>– Diffuse large B-cell lymphoma</li> <li>– Ewing sarcoma</li> <li>– Follicular lymphoma</li> <li>– Gestational trophoblastic neoplasia</li> <li>– Hodgkin lymphoma</li> <li>– Kaposi sarcoma</li> <li>– Langerhans cell histiocytosis</li> <li>– Low-grade glioma</li> <li>– Nephroblastoma (Wilms tumour)</li> <li>– Retinoblastoma</li> <li>– Rhabdomyosarcoma</li> </ul>
vinorelbine	<p><i>Capsule:</i> 20 mg; 30 mg; 80 mg.</p> <p><i>Injection:</i> 10 mg/mL in 1 mL, 5 mL vial.</p> <ul style="list-style-type: none"> <li>– Non-small cell lung cancer</li> <li>– Metastatic breast cancer</li> <li>– Rhabdomyosarcoma</li> </ul>

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8.2.2 Targeted therapies	
Complementary List	
<i>all-trans retinoid acid (ATRA)</i>	<b>Capsule:</b> 10 mg. – Acute promyelocytic leukaemia.
<i>bortezomib</i>	<b>Powder for injection:</b> 3.5 mg in vial. – Multiple myeloma
<i>dasatinib</i>	<b>Tablet:</b> 20 mg; 50 mg; 70 mg; 80 mg; 100 mg; 140 mg. – Imatinib-resistant chronic myeloid leukaemia
<input checked="" type="checkbox"/> <i>erlotinib</i>  Therapeutic alternatives: - afatinib - gefitinib	<b>Tablet:</b> 100 mg, 150 mg. – EGFR mutation-positive advanced non-small cell lung cancer
<i>everolimus</i>	<b>Tablet:</b> 2.5 mg; 5 mg; 7.5 mg; 10 mg. <b>Tablet (dispersible):</b> 2 mg; 3 mg; 5 mg. – Subependymal giant cell astrocytoma
<i>ibrutinib</i>	<b>Capsule:</b> 140 mg. – Relapsed/refractory chronic lymphocytic leukaemia
<i>imatinib</i>	<b>Solid oral dosage form:</b> 100 mg; 400 mg. – Chronic myeloid leukaemia – Gastrointestinal stromal tumour – Philadelphia chromosome positive acute lymphoblastic leukaemia
<i>nilotinib</i>	<b>Capsule:</b> 150 mg; 200 mg. – Imatinib-resistant chronic myeloid leukaemia
<i>rituximab*</i>  *including quality-assured biosimilars	<b>Injection (intravenous):</b> 100 mg/10 mL in 10 mL vial; 500 mg/50 mL in 50 mL vial. – Burkitt lymphoma – Diffuse large B-cell lymphoma – Chronic lymphocytic leukaemia – Follicular lymphoma
<i>trastuzumab*</i>  *including quality-assured biosimilars	<b>Powder for injection:</b> 60 mg; 150 mg; 440 mg in vial. – Early stage HER2-positive breast cancer – Metastatic HER2-positive breast cancer

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8.2.3 Immunomodulators	
Complementary List	
<p><i>filgrastim*</i> *including quality-assured biosimilars</p>	<p><b>Injection:</b> 120 micrograms/0.2 mL; 300 micrograms/0.5 mL; 480 micrograms/0.8 mL in pre-filled syringe.</p> <p><b>Injection:</b> 300 micrograms/mL in 1 mL vial; 480 micrograms/1.6 mL in 1.6 mL vial.</p> <ul style="list-style-type: none"> <li>– Primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy.</li> <li>– Secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy</li> <li>– To facilitate administration of dose dense chemotherapy regimens</li> </ul>
<p><i>lenalidomide</i></p>	<p><b>Capsule:</b> 25 mg.</p> <ul style="list-style-type: none"> <li>– Multiple myeloma</li> </ul>
<p><input type="checkbox"/> <i>nivolumab*</i> Therapeutic alternatives*: - pembrolizumab *including quality-assured biosimilars</p>	<p><b>Concentrate solution for infusion:</b> 10 mg/mL.</p> <ul style="list-style-type: none"> <li>– Metastatic melanoma</li> </ul>
<p><i>pegfilgrastim*</i> *including quality-assured biosimilars</p>	<p><b>Injection:</b> 6 mg/0.6 mL in pre-filled syringe.</p> <ul style="list-style-type: none"> <li>– Primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy</li> <li>– Secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy</li> <li>– To facilitate administration of dose dense chemotherapy regimens</li> </ul>
<p><i>thalidomide</i></p>	<p><b>Capsule:</b> 50 mg.</p> <ul style="list-style-type: none"> <li>– Multiple myeloma</li> </ul>
8.2.4 Hormones and antihormones	
Complementary List	
<p><input type="checkbox"/> <i>abiraterone</i> Therapeutic alternatives: - enzalutamide</p>	<p><b>Tablet:</b> 250 mg; 500 mg.</p> <ul style="list-style-type: none"> <li>– Metastatic castration-resistant prostate cancer</li> </ul>
<p><input type="checkbox"/> <i>anastrozole</i> Therapeutic alternatives: - 4<sup>th</sup> level ATC chemical subgroup (L02BG Aromatase inhibitors)</p>	<p><b>Tablet:</b> 1 mg.</p> <ul style="list-style-type: none"> <li>– Early stage breast cancer</li> <li>– Metastatic breast cancer</li> </ul>
<p><input type="checkbox"/> <i>bicalutamide</i> Therapeutic alternatives: - flutamide - nilutamide</p>	<p><b>Tablet:</b> 50 mg.</p> <ul style="list-style-type: none"> <li>– Metastatic prostate cancer</li> </ul>

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<i>dexamethasone</i>	<p><b>Injection:</b> 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule.</p> <p><b>Oral liquid:</b> 2 mg/5 mL [c].</p> <p><b>Tablet:</b> 2 mg [c]; 4 mg.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Anaplastic large cell lymphoma</li> <li>– Burkitt lymphoma</li> <li>– Multiple myeloma</li> </ul>
<i>hydrocortisone</i>	<p><b>Powder for injection:</b> 100 mg (as sodium succinate) in vial.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Burkitt lymphoma</li> </ul>
<input type="checkbox"/> <i>leuprorelin</i> <i>Therapeutic alternatives:</i> - goserelin - triptorelin	<p><b>Injection:</b> 7.5 mg; 22.5 mg in pre-filled syringe.</p> <ul style="list-style-type: none"> <li>– Early stage breast cancer</li> <li>– Metastatic prostate cancer.</li> </ul>
<i>methylprednisolone [c]</i>	<p><b>Injection:</b> 40 mg/mL (as sodium succinate) in 1 mL single-dose vial and 5 mL multi-dose vials; 80 mg/mL (as sodium succinate) in 1 mL single-dose vial.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukamia</li> <li>– Burkitt lymphoma</li> </ul>
<input type="checkbox"/> <i>prednisolone</i> <i>Therapeutic alternatives:</i> - prednisone	<p><b>Oral liquid:</b> 5 mg/mL [c].</p> <p><b>Tablet:</b> 5 mg; 25 mg.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Anaplastic large cell lymphoma</li> <li>– Burkitt lymphoma</li> <li>– Chronic lymphocytic leukaemia</li> <li>– Diffuse large B-cell lymphoma</li> <li>– Follicular lymphoma</li> <li>– Hodgkin lymphoma</li> <li>– Langerhans cell histiocytosis</li> <li>– Metastatic castration-resistsnt prostate cancer</li> <li>– Multiple myeloma</li> </ul>
<i>tamoxifen</i>	<p><b>Tablet:</b> 10 mg; 20 mg (as citrate).</p> <ul style="list-style-type: none"> <li>– Early stage breast cancer</li> <li>– Metastatic breast cancer.</li> </ul>
<b>8.2.5 Supportive medicines</b>	
<i>Complementary List</i>	
<i>allopurinol [c]</i>	<p><b>Tablet:</b> 100 mg; 300 mg.</p> <ul style="list-style-type: none"> <li>– Tumour lysis syndrome</li> </ul>
<i>mesna</i>	<p><b>Injection:</b> 100 mg/mL in 4 mL and 10 mL ampoules.</p> <p><b>Tablet:</b> 400 mg; 600 mg.</p> <ul style="list-style-type: none"> <li>– Burkitt lymphoma</li> <li>– Ewing sarcoma</li> <li>– Nephroblastoma (Wilms tumour)</li> <li>– Ovarian germ cell tumour</li> <li>– Osteosarcoma</li> <li>– Rhabdomyosarcoma</li> <li>– Testicular germ cell tumour</li> </ul>

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<i>rasburicase</i>	<i>Powder and solvent for solution for infusion:</i> 1.5 mg; 7.5 mg in vial. – Tumour lysis syndrome
<i>zoledronic acid</i>	<i>Concentrate solution for infusion:</i> 4 mg/5 mL in 5 mL vial. <i>Solution for infusion:</i> 4 mg/100 mL in 100 mL bottle. – Malignancy-related bone disease

## 9. THERAPEUTIC FOODS

ready-to-use therapeutic food [c]	Biscuit or paste*. *of nutritional composition as determined by the UN joint statement on the community-based management of severe acute malnutrition and Codex alimentarius guidelines.
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## 10. MEDICINES AFFECTING THE BLOOD

### 10.1 Antianaemia medicines

ferrous salt	<b>Oral liquid:</b> equivalent to 25 mg iron (as sulfate)/mL. <b>Tablet:</b> equivalent to 60 mg iron.
ferrous salt + folic acid	<b>Tablet:</b> equivalent to 60 mg elemental iron + 400 micrograms folic acid.* *nutritional supplement for use during pregnancy <b>Tablet:</b> equivalent to 60 mg elemental iron + 2.8 mg folic acid.** **for weekly iron and folic acid supplementation
folic acid	<b>Tablet:</b> 400 micrograms*; 1 mg; 5 mg. *periconceptual use for prevention of first occurrence of neural tube defects
hydroxocobalamin	<b>Injection:</b> 1 mg/mL (as acetate, as hydrochloride or as sulfate) in 1 mL ampoule.

#### Complementary List

<input type="checkbox"/> erythropoiesis-stimulating agents*	<b>Injection: pre-filled syringe</b> 1000 IU/0.5 mL; 2000 IU/0.5 mL; 3000 IU/0.3 mL; 4000 IU/0.4 mL; 5000 IU/0.5 mL; 6000 IU/0.6 mL; 8000 IU/0.8mL; 10 000 IU/1 mL; 20 000 IU/0.5 mL; 40 000 IU/1 mL.
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### 10.2 Medicines affecting coagulation

<input type="checkbox"/> dabigatran	
Therapeutic alternatives: - apixaban - edoxaban - rivaroxaban	<b>Capsule:</b> 110 mg; 150 mg.

# WHO Model List of Essential Medicines – 23rd List (2023)

<p>o enoxaparin*</p> <p>Therapeutic alternatives*:</p> <ul style="list-style-type: none"> <li>- dalteparin</li> <li>- nadroparin</li> </ul> <p>*including quality-assured biosimilars</p>	<p><b>Injection: ampoule or pre-filled syringe</b></p> <p>20 mg/0.2 mL; 40 mg/0.4 mL; 60 mg/0.6 mL; 80 mg/0.8 mL; 100 mg/1 mL; 120 mg/0.8 mL; 150 mg/1 mL.</p>
heparin sodium	<p><b>Injection:</b> 1000 IU/mL; 5000 IU/mL; 20 000 IU/mL in 1 mL ampoule.</p>
phytomenadione	<p><b>Injection:</b> 1 mg/mL [c]; 10 mg/mL in ampoule.</p> <p><b>Tablet:</b> 10 mg.</p>
protamine sulfate	<p><b>Injection:</b> 10 mg/mL in 5 mL ampoule.</p>
tranexamic acid	<p><b>Injection:</b> 100 mg/mL in 10 mL ampoule.</p>
<input type="checkbox"/> warfarin Therapeutic alternatives to be reviewed	<p><b>Tablet:</b> 1 mg; 2 mg; 5 mg (sodium).</p>

## Complementary List

<p>desmopressin[c]</p>	<p><b>Injection:</b> 4 micrograms/mL (as acetate) in 1 mL ampoule.</p> <p><b>Nasal spray:</b> 10 micrograms (as acetate) per dose.</p>
heparin sodium [c]	<p><b>Injection:</b> 1000 IU/mL; 5000 IU/mL in 1 mL ampoule.</p>
protamine sulfate [c]	<p><b>Injection:</b> 10 mg/mL in 5 mL ampoule.</p>
<input type="checkbox"/> warfarin [c] Therapeutic alternatives to be reviewed	<p><b>Tablet:</b> 0.5 mg; 1 mg; 2 mg; 5 mg (sodium).</p>

## 10.3 Other medicines for haemoglobinopathies

<input type="checkbox"/> deferasirox Therapeutic alternatives: - deferiprone	<p><b>Tablet (dispersible):</b> 100 mg; 125 mg; 250 mg; 400 mg; 500 mg.</p> <p><b>Tablet (film-coated):</b> 90 mg; 180 mg; 360 mg.</p>
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## Complementary List

deferoxamine	<p><b>Powder for injection:</b> 500 mg (mesilate) in vial.</p>
hydroxycarbamide (hydroxyurea)	<p><b>Solid oral dosage form:</b> 100 mg [c]; 200 mg; 500 mg; 1 g.</p>

## 11. BLOOD PRODUCTS OF HUMAN ORIGIN AND PLASMA SUBSTITUTES

### 11.1 Blood and blood components

In accordance with the World Health Assembly resolution WHA63.12, WHO recognizes that achieving self-sufficiency, unless special circumstances preclude it, in the supply of safe blood components based on voluntary, non-remunerated blood donation, and the security of that supply are important national goals to prevent blood shortages and meet the transfusion requirements of the patient population. All preparations should comply with the WHO requirements.	
<input type="checkbox"/> cryoprecipitate, pathogen-reduced Therapeutic alternatives: - cryoprecipitate (not pathogen-reduced)	<p><b>Injection:</b> frozen liquid in bag or lyophilized powder in vial containing:</p> <ul style="list-style-type: none"> <li>- &gt; 50 IU Factor VIII</li> <li>- &gt; 100 IU vWF</li> <li>- &gt; 140 mg clottable fibrinogen per unit</li> </ul>

fresh-frozen plasma	
platelets	
red blood cells	

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whole blood	
<b>11.2 Plasma-derived medicines</b>	
All human plasma-derived medicines should comply with the WHO requirements.	
<b>11.2.1 Human immunoglobulins</b>	
anti-D immunoglobulin	<b>Injection:</b> 250 micrograms in single-dose vial.
anti-rabies immunoglobulin	<b>Injection:</b> 150 IU/mL in vial.
anti-tetanus immunoglobulin	<b>Injection:</b> 500 IU in vial.
<i>Complementary List</i>	
<i>normal immunoglobulin</i>	<p><b>Intramuscular administration:</b> 16% protein solution.</p> <p><b>Subcutaneous administration:</b> 15%; 16% protein solution.</p> <ul style="list-style-type: none"> <li>– Primary immune deficiency.</li> </ul> <p><b>Intravenous administration:</b> 5%; 10% protein solution.</p> <ul style="list-style-type: none"> <li>– Primary immune deficiency</li> <li>– Kawasaki disease</li> <li>– Langerhans cell histiocytosis</li> </ul>
<b>11.2.2 Blood coagulation factors</b>	
<i>Complementary List</i>	
coagulation factor VIII	<b>Powder for injection:</b> 250 IU; 500 IU; 1000 IU in vial.
<input type="checkbox"/> coagulation factor IX Therapeutic alternatives: - coagulation factor IX complex	<b>Powder for injection:</b> 500 IU; 1000 IU in vial.
<b>11.3 Plasma substitutes</b>	
<input type="checkbox"/> dextran 70 Therapeutic alternatives: - polygeline injectable solution 3.5%	<b>Injectable solution:</b> 6%.
<b>12. CARDIOVASCULAR MEDICINES</b>	
<b>12.1 Antianginal medicines</b>	
<input type="checkbox"/> bisoprolol Therapeutic alternatives: - carvedilol - metoprolol	<b>Tablet:</b> 1.25 mg; 5 mg.
glyceryl trinitrate	<b>Tablet (sublingual):</b> 500 micrograms.
isosorbide dinitrate	<b>Tablet (sublingual):</b> 5 mg.
verapamil	<b>Tablet:</b> 40 mg; 80 mg (hydrochloride).

# WHO Model List of Essential Medicines – 23rd List (2023)

12.2 Antiarrhythmic medicines	
<input type="checkbox"/> bisoprolol Therapeutic alternatives: - carvedilol - metoprolol	<b>Tablet:</b> 1.25 mg; 5 mg.
digoxin	<b>Injection:</b> 250 micrograms/mL in 2 mL ampoule. <b>Oral liquid:</b> 50 micrograms/mL. <b>Tablet:</b> 62.5 micrograms; 250 micrograms.
epinephrine (adrenaline)	<b>Injection:</b> 100 micrograms/mL (as acid tartrate or hydrochloride) in 10 mL ampoule.
lidocaine	<b>Injection:</b> 20 mg/mL (hydrochloride) in 5 mL ampoule.
verapamil	<b>Injection:</b> 2.5 mg/mL (hydrochloride) in 2 mL ampoule. <b>Tablet:</b> 40 mg; 80 mg (hydrochloride).
<b>Complementary List</b>	
amiodarone	<b>Injection:</b> 50 mg/mL (hydrochloride) in 3 mL ampoule. <b>Tablet:</b> 100 mg; 200 mg; 400 mg (hydrochloride).
12.3 Antihypertensive medicines	
<input type="checkbox"/> amlodipine Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (C08CA Dihydropyridine derivatives)	<b>Tablet:</b> 5 mg (as maleate, mesylate or besylate).
<input type="checkbox"/> bisoprolol Therapeutic alternatives: - atenolol* - carvedilol - metoprolol	<b>Tablet:</b> 1.25 mg; 5 mg. <small>*atenolol should not be used as a first-line agent in uncomplicated hypertension in patients &gt; 60 years</small>
<input type="checkbox"/> enalapril Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (C09AA ACE inhibitors, plain)	<b>Oral liquid:</b> 1 mg/mL (as hydrogen maleate) [c]. <b>Tablet:</b> 2.5 mg; 5 mg; 10 mg (as hydrogen maleate).
hydralazine*	<b>Powder for injection:</b> 20 mg (hydrochloride) in ampoule. <b>Tablet:</b> 25 mg; 50 mg (hydrochloride). <small>*Hydralazine is listed for use only in the acute management of severe pregnancy-induced hypertension. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines.</small>
<input type="checkbox"/> hydrochlorothiazide Therapeutic alternatives: - chlorothiazide - chlorthalidone - indapamide	<b>Oral liquid:</b> 50 mg/5 mL. <b>Solid oral dosage form:</b> 12.5 mg; 25 mg.

# WHO Model List of Essential Medicines – 23rd List (2023)

<p><input type="checkbox"/> lisinopril + <input type="checkbox"/> amlodipine</p> <p>Therapeutic alternatives:</p> <ul style="list-style-type: none"> <li>- 4<sup>th</sup> level ATC chemical subgroup (C09AA ACE inhibitors, plain) (for lisinopril)</li> <li>- 4<sup>th</sup> level ATC chemical subgroup (C08CA Dihydropyridine derivatives) (for amlodipine)</li> </ul>	<p><b>Tablet:</b> 10 mg + 5 mg; 20 mg + 5 mg; 20 mg + 10 mg.</p>
<p><input type="checkbox"/> lisinopril + <input type="checkbox"/> hydrochlorothiazide</p> <p>Therapeutic alternatives:</p> <ul style="list-style-type: none"> <li>- 4<sup>th</sup> level ATC chemical subgroup (C09AA ACE inhibitors, plain) (for lisinopril)</li> <li>- chlorthalidone, chlorothiazide, indapamide (for hydrochlorothiazide)</li> </ul>	<p><b>Tablet:</b> 10 mg + 12.5 mg; 20 mg + 12.5 mg; 20 mg + 25 mg.</p>
<p><input type="checkbox"/> losartan</p> <p>Therapeutic alternatives:</p> <ul style="list-style-type: none"> <li>- 4<sup>th</sup> level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain)</li> </ul>	<p><b>Tablet:</b> 25 mg; 50 mg; 100 mg.</p>
<p><input type="checkbox"/> methyldopa*</p>	<p><b>Tablet:</b> 250 mg.</p> <p>*Methyldopa is listed for use only in the management of pregnancy-induced hypertension. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines.</p>
<p><input type="checkbox"/> telmisartan + <input type="checkbox"/> amlodipine</p> <p>Therapeutic alternatives:</p> <ul style="list-style-type: none"> <li>- 4<sup>th</sup> level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain) (for telmisartan)</li> <li>- 4<sup>th</sup> level ATC chemical subgroup (C08CA Dihydropyridine derivatives) (for amlodipine)</li> </ul>	<p><b>Tablet:</b> 40 mg + 5 mg; 80 mg + 5 mg; 80 mg + 10 mg.</p>
<p><input type="checkbox"/> telmisartan + <input type="checkbox"/> hydrochlorothiazide</p> <p>Therapeutic alternatives:</p> <ul style="list-style-type: none"> <li>- 4<sup>th</sup> level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain) (for telmisartan)</li> <li>- chlorthalidone, chlorothiazide, indapamide (for hydrochlorothiazide)</li> </ul>	<p><b>Tablet:</b> 40 mg + 12.5 mg; 80 mg + 12.5 mg; 80 mg + 25 mg.</p>
<p><b>Complementary List</b></p>	
<p><i>sodium nitroprusside</i></p>	<p><b>Powder for infusion:</b> 50 mg in ampoule.</p>

# WHO Model List of Essential Medicines – 23rd List (2023)

12.4 Medicines used in heart failure	
<input type="checkbox"/> bisoprolol Therapeutic alternatives: - carvedilol - metoprolol	<b>Tablet:</b> 1.25 mg; 5 mg.
<input type="checkbox"/> digoxin	<b>Injection:</b> 250 micrograms/mL in 2 mL ampoule. <b>Oral liquid:</b> 50 micrograms/mL. <b>Tablet:</b> 62.5 micrograms; 250 micrograms.
<input type="checkbox"/> enalapril Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (C09AA ACE inhibitors, plain)	<b>Tablet:</b> 2.5 mg; 5 mg; 10 mg (as hydrogen maleate).
<input type="checkbox"/> furosemide Therapeutic alternatives: - bumetanide - torasemide	<b>Injection:</b> 10 mg/mL in 2 mL, 5 mL ampoule. <b>Oral liquid:</b> 20 mg/5 mL; 50 mg/5 mL [c]. <b>Tablet:</b> 20 mg; 40 mg.
<input type="checkbox"/> hydrochlorothiazide Therapeutic alternatives: - chlorothiazide - chlorthalidone - indapamide	<b>Oral liquid:</b> 50 mg/5 mL. <b>Solid oral dosage form:</b> 25 mg.
<input type="checkbox"/> losartan Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain)	<b>Tablet:</b> 25 mg; 50 mg; 100 mg.
spironolactone	<b>Tablet:</b> 25 mg.
<i>Complementary List</i>	
<input type="checkbox"/> digoxin [c]	<b>Injection:</b> 100 micrograms/mL in 1 mL ampoule; 250 micrograms/mL in 2 mL ampoule. <b>Oral liquid:</b> 50 micrograms/mL. <b>Tablet:</b> 62.5 micrograms; 125 micrograms; 250 mg micrograms.
<input type="checkbox"/> dopamine	<b>Injection:</b> 40 mg/mL (hydrochloride) in 5 mL vial.
12.5 Antithrombotic medicines	
12.5.1 Anti-platelet medicines	
acetylsalicylic acid	<b>Tablet:</b> 100 mg.
clopidogrel	<b>Tablet:</b> 75 mg; 300 mg
12.5.2 Thrombolytic medicines	
<i>Complementary List</i>	
<input type="checkbox"/> alteplase	<b>Powder for injection:</b> 10 mg; 20 mg; 50 mg in vial
<input type="checkbox"/> streptokinase	<b>Powder for injection:</b> 1.5 million IU in vial.

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<b>12.6 Lipid-lowering agents</b>	
<input type="checkbox"/> simvastatin* Therapeutic alternatives: <ul style="list-style-type: none"> <li>- atorvastatin</li> <li>- fluvastatin</li> <li>- lovastatin</li> <li>- pravastatin</li> </ul>	<b>Tablet:</b> 5 mg; 10 mg; 20 mg; 40 mg. *For use in high-risk patients.
<b>12.7 Fixed-dose combinations for prevention of atherosclerotic cardiovascular disease</b>	
acetylsalicylic acid + <input type="checkbox"/> atorvastatin + <input type="checkbox"/> ramipril Therapeutic alternatives: <ul style="list-style-type: none"> <li>- fluvastatin, lovastatin, pravastatin, simvastatin (for atorvastatin)</li> <li>- 4<sup>th</sup> level ATC chemical subgroup (C09AA ACE inhibitors, plain) (for ramipril)</li> </ul>	<b>Tablet:</b> 100 mg + 20 mg + 2.5 mg; 100 mg + 20 mg + 5 mg; 100 mg + 20 mg + 10 mg; 100 mg + 40 mg + 2.5 mg; 100 mg + 40 mg + 5 mg; 100 mg + 40 mg + 10 mg.
acetylsalicylic acid + <input type="checkbox"/> simvastatin + <input type="checkbox"/> ramipril + <input type="checkbox"/> atenolol + <input type="checkbox"/> hydrochlorothiazide Therapeutic alternatives: <ul style="list-style-type: none"> <li>- atorvastatin, fluvastatin, lovastatin, pravastatin (for simvastatin)</li> <li>- 4<sup>th</sup> level ATC chemical subgroup (C09AA ACE inhibitors, plain) (for ramipril)</li> <li>- bisoprolol, carvedilol, metoprolol (for atenolol)</li> <li>- chlorthalidone, chlorothiazide, indapamide (for hydrochlorothiazide)</li> </ul>	<b>Tablet:</b> 100 mg + 20 mg + 5 mg + 50 mg + 12.5 mg.
<input type="checkbox"/> atorvastatin + <input type="checkbox"/> perindopril + <input type="checkbox"/> amlodipine Therapeutic alternatives: <ul style="list-style-type: none"> <li>- fluvastatin, lovastatin, pravastatin, simvastatin (for atorvastatin)</li> <li>- 4<sup>th</sup> level ATC chemical subgroup (C09AA ACE inhibitors, plain) (for perindopril)</li> <li>- 4<sup>th</sup> level ATC chemical subgroup (C08CA Dihydropyridine derivatives) (for amlodipine)</li> </ul>	<b>Tablet:</b> 20 mg + 5 mg + 5 mg; 20 mg + 10 mg + 10 mg; 40 mg + 5 mg + 5 mg; 40 mg + 10 mg + 10 mg.
<b>13. DERMATOLOGICAL MEDICINES</b>	
<b>13.1 Antifungal medicines</b>	
<input type="checkbox"/> miconazole Therapeutic alternatives: <ul style="list-style-type: none"> <li>- 4<sup>th</sup> level ATC chemical subgroup (D01AC Imidazole and triazole derivatives) excluding combinations</li> </ul>	<b>Cream or ointment:</b> 2% (nitrate).
selenium sulfide	Detergent-based suspension: 2%.
sodium thiosulfate	Solution: 15%.
terbinafine	Cream or ointment: 1% (hydrochloride).

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13.2 Anti-infective medicines	
mupirocin	<b>Cream:</b> 2% (as calcium). <b>Ointment:</b> 2%.
potassium permanganate	<b>Aqueous solution:</b> 1:10 000.
silver sulfadiazine <small>a</small>	<b>Cream:</b> 1%. <small>a</small> > 2 months.
13.3 Anti-inflammatory and antipruritic medicines	
<input type="checkbox"/> betamethasone <small>a</small> Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (D07AC Corticosteroids, potent (group III))	<b>Cream or ointment:</b> 0.1% (as valerate). <small>a</small> Hydrocortisone preferred in neonates.
calamine	<b>Lotion.</b>
<input type="checkbox"/> hydrocortisone Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (D07AA Corticosteroids, weak (group I))	<b>Cream or ointment:</b> 1% (acetate).
13.4 Medicines affecting skin differentiation and proliferation	
benzoyl peroxide	<b>Cream or lotion:</b> 5%.
<input type="checkbox"/> calcipotriol Therapeutic alternatives: - calcitriol - tacalcitol	<b>Cream or ointment:</b> 50 micrograms/mL (0.005%). <b>Lotion:</b> 50 micrograms/mL (0.005%).
coal tar	<b>Solution:</b> 5%.
fluorouracil	<b>Ointment:</b> 5%.
<input type="checkbox"/> podophyllum resin Therapeutic alternatives: - podophyllotoxin	<b>Solution:</b> 10% to 25%.
salicylic acid	<b>Solution:</b> 5%.
urea	<b>Cream or ointment:</b> 5%; 10%.
<i>Complementary List</i>	
<i>methotrexate</i>	<b>Tablet:</b> 2.5 mg; 10 mg (as sodium).
13.5 Scabicides and pediculicides	
<input type="checkbox"/> benzyl benzoate <small>a</small> Therapeutic alternatives: - precipitated sulfur topical ointment	<b>Lotion:</b> 25%. <small>a</small> > 2 years.
permethrin	<b>Cream:</b> 5%. <b>Lotion:</b> 1%.

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14. DIAGNOSTIC AGENTS	
<b>14.1 Ophthalmic medicines</b>	
fluorescein	<b>Eye drops:</b> 1% (sodium salt).
<input type="checkbox"/> tropicamide Therapeutic alternatives: - atropine - cyclopentolate	<b>Eye drops:</b> 0.5%.
<b>14.2 Radiocontrast media</b>	
<input type="checkbox"/> amidotrizoate Therapeutic alternatives to be reviewed	<b>Injection:</b> 140 mg to 420 mg iodine/mL (as sodium or meglumine salt) in 20 mL ampoule.
barium sulfate	<b>Aqueous suspension.</b>
<input type="checkbox"/> iohexol Therapeutic alternatives to be reviewed	<b>Injection:</b> 140 mg to 350 mg iodine/mL in 5 mL, 10 mL, 20 mL ampoules.
<i>Complementary List</i>	
barium sulfate [c]	<b>Aqueous suspension.</b>
<input type="checkbox"/> meglumine iotroxate Therapeutic alternatives to be reviewed	<b>Solution:</b> 5 g to 8 g iodine in 100 mL to 250 mL.
<b>15. ANTISEPTICS AND DISINFECTANTS</b>	
<b>15.1 Antiseptics</b>	
<input type="checkbox"/> chlorhexidine Therapeutic alternatives to be reviewed	<b>Solution:</b> 5% (digluconate).
<input type="checkbox"/> ethanol Therapeutic alternatives: - propanol	<b>Solution:</b> 70% (denatured).
<input type="checkbox"/> povidone iodine Therapeutic alternatives: - iodine	<b>Solution:</b> 10% (equivalent to 1% available iodine).
<b>15.2 Disinfectants</b>	
alcohol based hand rub	<b>Solution:</b> containing ethanol 80% volume/volume. <b>Solution:</b> containing isopropyl alcohol 75% volume/volume.
chlorine base compound	<b>Liquid:</b> (0.1% available chlorine) for solution. <b>Powder:</b> (0.1% available chlorine) for solution. <b>Solid:</b> (0.1% available chlorine) for solution.

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o chloroxylenol Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (D08AE Phenol and derivatives)	<b>Solution:</b> 4.8%.
glutaral	<b>Solution:</b> 2%.
<b>16. DIURETICS</b>	
amiloride	<b>Tablet:</b> 5 mg (hydrochloride).
<input type="checkbox"/> furosemide Therapeutic alternatives: - bumetanide - torasemide	<b>Injection:</b> 10 mg/mL in 2 mL, 5 mL ampoule. <b>Oral liquid:</b> 20 mg/5 mL; 50 mg/5 mL [c]. <b>Tablet:</b> 20 mg; 40 mg.
<input type="checkbox"/> hydrochlorothiazide Therapeutic alternatives: - chlorothiazide - chlortalidone - indapamide	<b>Solid oral dosage form:</b> 25 mg.
mannitol	<b>Injectable solution:</b> 10%; 20%.
spironolactone	<b>Tablet:</b> 25 mg.
<i>Complementary List</i>	
<input type="checkbox"/> hydrochlorothiazide[c] Therapeutic alternatives: - chlorothiazide - chlortalidone	<b>Tablet (scored):</b> 25 mg.
mannitol [c]	<b>Injectable solution:</b> 10%; 20%.
spironolactone[c]	<b>Oral liquid:</b> 5 mg/5 mL; 10 mg/5 mL; 25 mg/5 mL. <b>Tablet:</b> 25 mg.
<b>17. GASTROINTESTINAL MEDICINES</b>	
<i>Complementary List</i>	
pancreatic enzymes[c]	Age-appropriate formulations and doses including lipase, protease and amylase.
<b>17.1 Antiulcer medicines</b>	
<input type="checkbox"/> omeprazole Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (A02BC Proton pump inhibitors) excluding combinations	<b>Powder for injection:</b> 40 mg in vial <b>Powder for oral liquid:</b> 20 mg; 40 mg sachets. <b>Solid oral dosage form:</b> 10 mg; 20 mg; 40 mg.
<input type="checkbox"/> ranitidine Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (A02BA H <sub>2</sub> -receptor antagonists) excluding combinations	<b>Injection:</b> 25 mg/mL (as hydrochloride) in 2 mL ampoule. <b>Oral liquid:</b> 75 mg/5 mL (as hydrochloride). <b>Tablet:</b> 150 mg (as hydrochloride).

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17.2 Antiemetic medicines	
dexamethasone	<p><b>Injection:</b> 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule.</p> <p><b>Oral liquid:</b> 0.5 mg/5 mL; 2 mg/5 mL.</p> <p><b>Solid oral dosage form:</b> 0.5 mg; 0.75 mg; 1.5 mg; 4 mg.</p>
metoclopramide <span style="border: 1px solid black; padding: 0 2px;">a</span>	<p><b>Injection:</b> 5 mg/mL (hydrochloride) in 2 mL ampoule.</p> <p><b>Oral liquid:</b> 5 mg/5 mL <span style="border: 1px solid black; padding: 0 2px;">c</span>.</p> <p><b>Tablet:</b> 10 mg (hydrochloride).</p> <p><span style="border: 1px solid black; padding: 0 2px;">a</span> Not in neonates.</p>
<input type="checkbox"/> ondansetron <span style="border: 1px solid black; padding: 0 2px;">a</span> Therapeutic alternatives: - dolasetron - granisetron - palonosetron - tropisetron	<p><b>Injection:</b> 2 mg base/mL in 2 mL ampoule (as hydrochloride).</p> <p><b>Oral liquid:</b> 4 mg base/5 mL.</p> <p><b>Solid oral dosage form:</b> Eq 4 mg base; Eq 8 mg base; Eq 24 mg base.</p> <p><span style="border: 1px solid black; padding: 0 2px;">a</span> &gt; 1 month.</p>
<i>Complementary list</i>	
aprepitant	<p><b>Capsule:</b> 80 mg; 125 mg; 165 mg</p> <p><b>Powder for oral suspension:</b> 125 mg in sachet</p>
17.3 Anti-inflammatory medicines	
<input type="checkbox"/> sulfasalazine Therapeutic alternatives: - mesalazine	<p><b>Retention enema.</b></p> <p><b>Suppository:</b> 500 mg.</p> <p><b>Tablet:</b> 500 mg.</p>
<i>Complementary List</i>	
hydrocortisone	<p><b>Retention enema:</b> 100 mg/60 mL.</p> <p><b>Suppository:</b> 25 mg (acetate).</p>
prednisolone	<b>Retention enema:</b> 20 mg/100 mL (as sodium phosphate).
17.4 Laxatives	
<input type="checkbox"/> senna Therapeutic alternatives: - bisacodyl	<b>Tablet:</b> 7.5 mg (sennosides) (or traditional dosage forms).
17.5 Medicines used in diarrhoea	
oral rehydration salts – zinc sulfate <span style="border: 1px solid black; padding: 0 2px;">c</span>	<p><b>Co-package containing:</b></p> <p><b>ORS powder for dilution</b> (see Section 17.5.1) – zinc sulfate <b>solid oral dosage form</b> 20 mg (see Section 17.5.2)</p>

# WHO Model List of Essential Medicines – 23rd List (2023)

## 17.5.1 Oral rehydration

	Powder for dilution in 200 mL; 500 mL; 1 L.
oral rehydration salts	glucose: 75 mEq sodium: 75 mEq or mmol/L chloride: 65 mEq or mmol/L potassium: 20 mEq or mmol/L citrate: 10 mmol/L osmolarity: 245 mOsm/L glucose: 13.5 g/L sodium chloride: 2.6 g/L potassium chloride: 1.5 g/L trisodium citrate dihydrate*: 2.9 g/L
	*trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/L. However, as the stability of this latter formulation is very poor under tropical conditions, it is recommended only when manufactured for immediate use.

## 17.5.2 Medicines for diarrhoea

zinc sulfate*	Solid oral dosage form: 20 mg.  *In acute diarrhoea zinc sulfate should be used as an adjunct to oral rehydration salts.
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# 18. MEDICINES FOR ENDOCRINE DISORDERS

## 18.1 Adrenal hormones and synthetic substitutes

fludrocortisone	Tablet: 100 micrograms (acetate).
hydrocortisone	Tablet: 5 mg; 10 mg; 20 mg.

## 18.2 Androgens

### Complementary List

testosterone	Injection: 200 mg (enanthate) in 1 mL ampoule.
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## 18.3 Estrogens

## 18.4 Progestogens

<input type="checkbox"/> medroxyprogesterone acetate  Therapeutic alternatives: - norethisterone	Tablet: 5 mg.
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# WHO Model List of Essential Medicines – 23rd List (2023)

<b>18.5 Medicines for diabetes</b>	
<b>18.5.1 Insulins</b>	
insulin injection (soluble)* <i>*including quality-assured biosimilars</i>	<b>Injection:</b> 40 IU/mL in 10 mL vial; 100 IU/mL in 10 mL vial; 100 IU/mL in 3 mL cartridge or pre-filled pen.
intermediate-acting insulin* <i>*including quality-assured biosimilars</i>	<b>Injection:</b> 40 IU/mL in 10 mL vial; 100 IU/mL in 10 mL vial; 100 IU/mL in 3 mL cartridge or pre-filled pen (as compound insulin zinc suspension or isophane insulin).
<input type="checkbox"/> long-acting insulin analogues* Therapeutic alternatives: - insulin degludec - insulin detemir - insulin glargine <i>*including quality-assured biosimilars</i>	<b>Injection:</b> 100 IU/mL in 3 mL cartridge or pre-filled pen.
<b>18.5.2 Oral hypoglycaemic agents</b>	
<input type="checkbox"/> empagliflozin Therapeutic alternatives: - canagliflozin - dapagliflozin	<b>Tablet:</b> 10 mg; 25 mg.
<input type="checkbox"/> gliclazide* Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (A10BB Sulfonylureas)	<b>Solid oral dosage form:</b> (controlled-release tablets) 30 mg; 60 mg; 80 mg. <i>*glibenclamide not suitable above 60 years.</i>
metformin	<b>Tablet:</b> 500 mg (hydrochloride).
<i>Complementary List</i>	
metformin [c]	<b>Tablet:</b> 500 mg (hydrochloride).
<b>18.6 Medicines for hypoglycaemia</b>	
glucagon	<b>Injection:</b> 1 mg/mL.
<i>Complementary List</i>	
diazoxide [c]	<b>Oral liquid:</b> 50 mg/mL. <b>Tablet:</b> 50 mg.
<b>18.7 Thyroid hormones and antithyroid medicines</b>	
levothyroxine	<b>Tablet:</b> 25 micrograms [c]; 50 micrograms; 100 micrograms (sodium salt).
potassium iodide	<b>Tablet:</b> 60 mg.
<input type="checkbox"/> methimazole Therapeutic alternatives: - carbimazole (depending on local availability)	<b>Tablet:</b> 5mg, 10mg, 20mg.
propylthiouracil*	<b>Tablet:</b> 50 mg. <i>*For use when alternative first-line treatment is not appropriate or available; and in patients during the first trimester of pregnancy.</i>

# WHO Model List of Essential Medicines – 23rd List (2023)

Complementary List	
Lugol's solution [c]	<i>Oral liquid:</i> about 130 mg total iodine/mL.
<input type="checkbox"/> methimazole [c] Therapeutic alternatives: - carbimazole (depending on local availability)	Tablet: 5mg, 10mg, 20mg.
potassium iodide [c]	Tablet: 60 mg.
propylthiouracil* [c]	Tablet: 50 mg. <i>*For use when alternative first-line treatment is not appropriate or available</i>
18.8 Medicines for disorders of the pituitary hormone system	
<input type="checkbox"/> cabergoline Therapeutic alternatives: - bromocriptine	Tablet: 0.5 mg; 1 mg.
Complementary List	
octreotide	<i>Injection (immediate-release):</i> 0.05 mg/mL; 0.1 mg/mL; 0.5 mg/mL (as acetate) in 1 mL vial. <i>Injection (modified-release):</i> 20 mg (as acetate) in vial plus diluent.
19. IMMUNOLOGICALS	
19.1 Diagnostic agents	
All tuberculins should comply with the WHO requirements for tuberculins.	
tuberculin, purified protein derivative (PPD)	<b>Injection.</b>
19.2 Sera, immunoglobulins and monoclonal antibodies	
All plasma fractions should comply with the WHO requirements.	
anti-rabies virus monoclonal antibodies* <i>*including quality-assured biosimilars</i>	<b>Injection:</b> 40 IU/mL in 1.25 mL, 2.5 mL vial; 100 IU/mL in 2.5 mL vial (human). <b>Injection:</b> 300 IU/mL in 10 mL vial; 600 IU/mL in 1 mL, 2.5 mL and 5 mL vial (murine).
antivenom immunoglobulin*	<b>Injection.</b> <i>*Exact type to be defined locally.</i>
diphtheria antitoxin	<b>Injection:</b> 10 000 IU; 20 000 IU in vial.
equine rabies immunoglobulin	<b>Injection:</b> 150 IU/mL; 200 IU/mL; 300 IU/mL; 400 IU/mL in vial.

# WHO Model List of Essential Medicines – 23rd List (2023)

## 19.3 Vaccines

WHO immunization policy recommendations are published in vaccine position papers based on recommendations made by the Strategic Advisory Group of Experts on Immunization (SAGE).

WHO vaccine position papers are updated three to four times per year. The list below details the vaccines for which there is a recommendation from SAGE and a corresponding WHO position paper as at March 2023. The most recent versions of the WHO position papers, reflecting the current evidence related to a specific vaccine and the related recommendations, can be accessed at any time on the WHO website at:

<https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers>

Vaccine recommendations may be universal or conditional (e.g., in certain regions, in some high-risk populations or as part of immunization programmes with certain characteristics). Details are available in the relevant position papers, and in the Summary Tables of WHO Routine Immunization Recommendations available on the WHO website at:

<https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/who-recommendations-for-routine-immunization---summary-tables>

Selection of vaccines from the Model List will need to be determined by each country after consideration of international recommendations, epidemiology and national priorities.

All vaccines should comply with the WHO requirements for biological substances.

WHO noted the need for vaccines used in children to be polyvalent.

<i>Recommendations for all</i>	
BCG vaccine	
diphtheria vaccine	
Haemophilus influenzae type b vaccine	
hepatitis B vaccine	
human papilloma virus (HPV) vaccine	
measles vaccine	
pertussis vaccine	
pneumococcal vaccine	
poliomyelitis vaccine	
rotavirus vaccine	
rubella vaccine	
tetanus vaccine	
<i>Recommendations for certain regions</i>	
Japanese encephalitis vaccine	
tick-borne encephalitis vaccine	
yellow fever vaccine	
<i>Recommendations for some high-risk populations</i>	
cholera vaccine	
dengue vaccine	
hepatitis A vaccine	
meningococcal meningitis vaccine	

# WHO Model List of Essential Medicines – 23rd List (2023)

rabies vaccine	
typhoid vaccine	
<b>Recommendations for immunization programmes with certain characteristics</b>	
influenza vaccine (seasonal)	
mumps vaccine	
varicella vaccine	
<b>20. MUSCLE RELAXANTS (PERIPHERALLY-ACTING) AND CHOLINESTERASE INHIBITORS</b>	
<input type="checkbox"/> atracurium Therapeutic alternatives to be reviewed	<b>Injection:</b> 10 mg/mL (besylate).
neostigmine	<b>Injection:</b> 500 micrograms/mL (methylsulfate) in 1 mL ampoule; 2.5 mg/mL (methylsulfate) in 1 mL ampoule. <b>Tablet:</b> 15 mg (bromide).
suxamethonium	<b>Injection:</b> 50 mg/mL (chloride) in 2 mL ampoule. <b>Powder for injection:</b> (chloride), in vial.
<input type="checkbox"/> vecuronium [c] Therapeutic alternatives: -atracurium	<b>Powder for injection:</b> 10 mg (bromide) in vial.
<b>Complementary List</b>	
pyridostigmine	<b>Injection:</b> 1 mg in 1 mL ampoule. <b>Tablet:</b> 60 mg (bromide).
<input type="checkbox"/> vecuronium Therapeutic alternatives to be reviewed	<b>Powder for injection:</b> 10 mg (bromide) in vial.
<b>21. OPHTHALMOLOGICAL PREPARATIONS</b>	
<b>21.1 Anti-infective agents</b>	
aciclovir	<b>Ointment:</b> 3% w/w.
azithromycin	<b>Solution (eye drops):</b> 1.5%. – <i>Trachoma</i>
erythromycin	<b>Ointment:</b> 0.5% [c] – <i>Infections due to Chlamydia trachomatis or Neisseria gonorrhoea.</i>
<input type="checkbox"/> gentamicin Therapeutic alternatives: - amikacin - kanamycin - netilmicin - tobramycin	<b>Solution (eye drops):</b> 0.3% (sulfate). – <i>Bacterial blepharitis</i> – <i>Bacterial conjunctivitis</i>
natamycin	<b>Suspension (eye drops):</b> 5% – <i>Fungal keratitis</i>

# WHO Model List of Essential Medicines – 23rd List (2023)

<input type="checkbox"/> ofloxacin Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (S01AE Fluoroquinolones)	Solution (eye drops): 0.3%. – <i>Bacterial conjunctivitis</i> – <i>Bacterial keratitis</i>
<input type="checkbox"/> tetracycline Therapeutic alternatives: - chlortetracycline - oxytetracycline	Eye ointment: 1% (hydrochloride). – <i>Bacterial blepharitis</i> – <i>Bacterial conjunctivitis</i> – <i>Bacterial keratitis</i> – <i>Trachoma</i>
<b>21.2 Anti-inflammatory agents</b>	
<input type="checkbox"/> prednisolone Therapeutic alternatives to be reviewed	Solution (eye drops): 0.5% (sodium phosphate).
<b>21.3 Local anaesthetics</b>	
<input type="checkbox"/> tetracaine <small>a</small> Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (S01HA Local anaesthetics) excluding cocaine and combinations	Solution (eye drops): 0.5% (hydrochloride). <small>a</small> Not in preterm neonates.
<b>21.4 Miotics and antiglaucoma medicines</b>	
acetazolamide	Tablet: 250 mg.
latanoprost	Solution (eye drops): 50 micrograms/mL.
<input type="checkbox"/> pilocarpine Therapeutic alternatives: - carbachol	Solution (eye drops): 2%; 4% (hydrochloride or nitrate).
<input type="checkbox"/> timolol Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (S01ED Beta blocking agents) excluding combinations	Solution (eye drops): 0.25%; 0.5% (as hydrogen maleate).
<b>21.5 Mydriatics</b>	
<input type="checkbox"/> atropine <small>a</small> Therapeutic alternatives*: - cyclopentolate hydrochloride - homatropine hydrobromide <small>*EMLc only</small>	Solution (eye drops): 0.1%; 0.5%; 1% (sulfate). <small>a</small> > 3 months.
<i>Complementary List</i>	
epinephrine (adrenaline)	Solution (eye drops): 2% (as hydrochloride).
<b>21.6 Anti-vascular endothelial growth factor (VEGF) preparations</b>	
<i>Complementary List</i>	
bevacizumab* <small>*including quality-assured biosimilars</small>	Injection: 25 mg/mL.

# WHO Model List of Essential Medicines – 23rd List (2023)

22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE	
22.1 Contraceptives	
22.1.1 Oral hormonal contraceptives	
☐ ethinylestradiol + ☐ levonorgestrel Therapeutic alternatives to be reviewed	<b>Tablet:</b> 30 micrograms + 150 micrograms.
☐ ethinylestradiol + ☐ norethisterone Therapeutic alternatives to be reviewed	<b>Tablet:</b> 35 micrograms + 1 mg.
levonorgestrel	<b>Tablet:</b> 30 micrograms; 750 micrograms (pack of two); 1.5 mg.
ulipristal	<b>Tablet:</b> 30 mg (as acetate).
22.1.2 Injectable hormonal contraceptives	
estradiol cypionate + medroxyprogesterone acetate	<b>Injection:</b> 5 mg + 25 mg.
medroxyprogesterone acetate	<b>Injection (intramuscular):</b> 150 mg/mL in 1 mL vial. <b>Injection (subcutaneous):</b> 104 mg/0.65 mL in pre-filled syringe or single-dose injection delivery system.
norethisterone enantate	<b>Oily solution:</b> 200 mg/mL in 1 mL ampoule.
22.1.3 Intrauterine devices	
copper-containing device	
levonorgestrel-releasing intrauterine system	<b>Intrauterine system:</b> with reservoir containing 52 mg of levonorgestrel
22.1.4 Barrier methods	
condoms	
diaphragms	
22.1.5 Implantable contraceptives	
etonogestrel-releasing implant	<b>Single-rod etonogestrel-releasing implant:</b> containing 68 mg of etonogestrel.
levonorgestrel-releasing implant	<b>Two-rod levonorgestrel-releasing implant:</b> each rod containing 75 mg of levonorgestrel (150 mg total).
22.1.6 Intravaginal contraceptives	
ethinylestradiol + etonogestrel	<b>Vaginal ring:</b> containing 2.7 mg + 11.7 mg
progesterone vaginal ring*	<b>Progesterone-releasing vaginal ring:</b> containing 2.074 g of micronized progesterone. *For use in women actively breastfeeding at least 4 times per day

# WHO Model List of Essential Medicines – 23rd List (2023)

22.2 Ovulation inducers	
<i>Complementary List</i>	
clomifene	<i>Tablet:</i> 50 mg (citrate).
<input type="checkbox"/> letrozole Therapeutic alternatives: - anastrozole	<i>Solid oral dosage form:</i> 2.5 mg.
22.3 Uterotonics	
carbetocin	<i>Injection (heat stable):</i> 100 micrograms/mL.
<input type="checkbox"/> ergometrine Therapeutic alternatives: - methylergometrine	<i>Injection:</i> 200 micrograms (hydrogen maleate) in 1 mL ampoule.
mifepristone – misoprostol  Where permitted under national law and where culturally acceptable.	<i>Tablet</i> 200 mg – <i>tablet</i> 200 micrograms.  <b>Co-package containing:</b> mifepristone 200 mg tablet [1] and misoprostol 200 micrograms tablet [4] <ul style="list-style-type: none"><li>– Management of intrauterine fetal demise;</li><li>– Management of induced abortion</li></ul>
misoprostol	<i>Tablet:</i> 200 micrograms. <ul style="list-style-type: none"><li>– Management of incomplete abortion and miscarriage;</li><li>– Prevention and treatment of postpartum haemorrhage where oxytocin is not available or cannot be safely used</li></ul> <b>Vaginal tablet:</b> 25 micrograms.*  *Only for use for induction of labour where appropriate facilities are available.
oxytocin	<i>Injection:</i> 10 IU in 1 mL.
22.4 Antioxytocics (tocolytics)	
nifedipine	<b>Immediate-release capsule:</b> 10 mg.

# WHO Model List of Essential Medicines – 23rd List (2023)

22.5 Other medicines administered to the mother																															
dexamethasone	<b>Injection:</b> 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule.																														
multiple micronutrient supplement*	<p><b>Tablet containing:</b></p> <table> <tbody> <tr><td>Vitamin A (retinol acetate)</td><td>800 micrograms retinol activity equivalent</td></tr> <tr><td>Vitamin C (ascorbic acid)</td><td>70 mg</td></tr> <tr><td>Vitamin D (cholecalciferol)</td><td>5 micrograms (200 IU)</td></tr> <tr><td>Vitamin E (alpha tocopherol succinate)</td><td>10 mg alpha tocopherol equivalent</td></tr> <tr><td>Vitamin B1 (thiamine mononitrate)</td><td>1.4 mg</td></tr> <tr><td>Vitamin B2 (riboflavin)</td><td>1.4 mg</td></tr> <tr><td>Vitamin B3 (niacinamide)</td><td>18 mg niacin equivalent</td></tr> <tr><td>Vitamin B6 (pyridoxine hydrochloride)</td><td>1.9 mg</td></tr> <tr><td>Folic acid (folic acid)</td><td>680 micrograms dietary folate equivalent (400 micrograms)</td></tr> <tr><td>Vitamin B12 (cyanocobalamin)</td><td>2.6 micrograms</td></tr> <tr><td>Iron (ferrous fumarate)</td><td>30 mg</td></tr> <tr><td>Iodine (potassium iodide)</td><td>150 micrograms</td></tr> <tr><td>Zinc (zinc oxide)</td><td>15 mg</td></tr> <tr><td>Selenium (sodium selenite)</td><td>65 micrograms</td></tr> <tr><td>Copper (cupric oxide)</td><td>2 mg</td></tr> </tbody> </table> <p>*For use in specific contexts. Refer to current WHO recommendations.</p>	Vitamin A (retinol acetate)	800 micrograms retinol activity equivalent	Vitamin C (ascorbic acid)	70 mg	Vitamin D (cholecalciferol)	5 micrograms (200 IU)	Vitamin E (alpha tocopherol succinate)	10 mg alpha tocopherol equivalent	Vitamin B1 (thiamine mononitrate)	1.4 mg	Vitamin B2 (riboflavin)	1.4 mg	Vitamin B3 (niacinamide)	18 mg niacin equivalent	Vitamin B6 (pyridoxine hydrochloride)	1.9 mg	Folic acid (folic acid)	680 micrograms dietary folate equivalent (400 micrograms)	Vitamin B12 (cyanocobalamin)	2.6 micrograms	Iron (ferrous fumarate)	30 mg	Iodine (potassium iodide)	150 micrograms	Zinc (zinc oxide)	15 mg	Selenium (sodium selenite)	65 micrograms	Copper (cupric oxide)	2 mg
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Zinc (zinc oxide)	15 mg																														
Selenium (sodium selenite)	65 micrograms																														
Copper (cupric oxide)	2 mg																														
tranexamic acid	<b>Injection:</b> 100 mg/mL in 10 mL ampoule.																														
22.6 Medicines administered to the neonate [c]																															
caffeine citrate [c]	<b>Injection:</b> 20 mg/mL (equivalent to 10 mg caffeine base/mL). <b>Oral liquid:</b> 20 mg/mL (equivalent to 10 mg caffeine base/mL).																														
chlorhexidine [c]	<b>Solution or gel:</b> 7.1% (digluconate) delivering 4% chlorhexidine (for umbilical cord care).																														
<i>Complementary List</i>																															
<input type="checkbox"/> ibuprofen [c] <i>Therapeutic alternatives:</i> - indometacin	<b>Solution for injection:</b> 5 mg/mL.																														
<input type="checkbox"/> prostaglandin E1 [c] <i>Therapeutic alternatives:</i> - prostaglandin E2	<b>Solution for injection:</b> 0.5 mg/mL in alcohol.																														
surfactant [c]	<b>Suspension for intratracheal instillation:</b> 25 mg/mL or 80 mg/mL.																														
23. PERITONEAL DIALYSIS SOLUTION																															
<i>Complementary List</i>																															
intraperitoneal dialysis solution	<b>Parenteral solution:</b> of appropriate composition.																														

# WHO Model List of Essential Medicines – 23rd List (2023)

24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS	
24.1 Medicines for psychotic disorders	
<input type="checkbox"/> fluphenazine Therapeutic alternatives: - haloperidol decanoate - zuclopentixol decanoate	<b>Injection:</b> 25 mg (decanoate or enantate) in 1 mL ampoule.
<input type="checkbox"/> haloperidol Therapeutic alternatives: - chlorpromazine	<b>Tablet:</b> 2 mg; 5 mg.
haloperidol	<b>Injection:</b> 5 mg/mL in 1 mL ampoule.
olanzapine	<b>Powder for injection:</b> 10 mg in vial.
<input type="checkbox"/> paliperidone Therapeutic alternatives: - risperidone injection	<b>Injection (prolonged-release):</b> 25 mg; 50 mg; 75 mg; 100 mg; 150 mg (as palmitate) in pre-filled syringe.
<input type="checkbox"/> risperidone Therapeutic alternatives: - aripiprazole - olanzapine - paliperidone - quetiapine	<b>Solid oral dosage form:</b> 0.25 mg to 6.0 mg.
<i>Complementary List</i>	
clozapine	<b>Solid oral dosage form:</b> 25 to 200 mg.
24.2 Medicines for mood disorders	
24.2.1 Medicines for depressive disorders	
amitriptyline	<b>Tablet:</b> 25 mg; 75mg (hydrochloride).
<input type="checkbox"/> fluoxetine Therapeutic alternatives: - citalopram - escitalopram - fluvoxamine - paroxetine - sertraline	<b>Solid oral dosage form:</b> 20 mg (as hydrochloride).
24.2.2 Medicines for bipolar disorders	
carbamazepine	<b>Tablet (scored):</b> 100 mg; 200 mg; 400 mg.
lithium carbonate	<b>Solid oral dosage form:</b> 300 mg.
<input type="checkbox"/> quetiapine Therapeutic alternatives: - aripiprazole - olanzapine - paliperidone	<b>Tablet (immediate-release):</b> 25 mg; 100 mg; 150 mg; 200 mg; 300 mg. <b>Tablet (modified-release):</b> 50 mg; 150 mg; 200 mg; 300 mg; 400 mg.

# WHO Model List of Essential Medicines – 23rd List (2023)

<p>valproic acid (sodium valproate)*</p> <p><i>*avoid use in pregnancy and in women and girls of child-bearing potential, unless alternative treatments are ineffective or not tolerated because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb.</i></p>	<p><b>Tablet (enteric-coated):</b> 200 mg; 500 mg.</p>
<b>24.3 Medicines for anxiety disorders</b>	
<p><input type="checkbox"/> diazepam*</p> <p>Therapeutic alternatives: - lorazepam</p>	<p><b>Tablet (scored):</b> 2 mg; 5 mg.</p> <p>*For short-term emergency management of acute and severe anxiety symptoms only</p>
<p><input type="checkbox"/> fluoxetine</p> <p>Therapeutic alternatives: - citalopram - escitalopram - fluvoxamine - paroxetine - sertraline</p>	<p><b>Solid oral dosage form:</b> 20 mg (as hydrochloride).</p>
<b>24.4 Medicines for obsessive compulsive disorders</b>	
<p>clomipramine</p>	<p><b>Capsule:</b> 10 mg; 25 mg (hydrochloride).</p>
<p><input type="checkbox"/> fluoxetine</p> <p>Therapeutic alternatives: - citalopram - escitalopram - fluvoxamine - paroxetine - sertraline</p>	<p><b>Solid oral dosage form:</b> 20 mg (as hydrochloride).</p>
<b>24.5 Medicines for disorders due to psychoactive substance use</b>	
<b>24.5.1 Medicines for alcohol use disorders</b>	
<p>acamprosate calcium</p>	<p><b>Tablet:</b> 333 mg</p>
<p>naltrexone</p>	<p><b>Injection suspension (extended-release):</b> 380 mg in vial <b>Tablet:</b> 50 mg</p>
<b>24.5.2 Medicines for nicotine use disorders</b>	
<p>bupropion</p>	<p><b>Tablet (sustained-release):</b> 150 mg (hydrochloride).</p>
<p>nicotine replacement therapy (NRT)</p>	<p><b>Chewing gum:</b> 2 mg; 4 mg (as polacrilex). <b>Lozenge:</b> 2 mg; 4 mg. <b>Oral spray:</b> 1 mg per actuation. <b>Transdermal patch:</b> 5 mg to 30 mg/16 hrs; 7 mg to 21 mg/24 hrs.</p>
<p>varenicline</p>	<p><b>Tablet:</b> 0.5 mg, 1 mg</p>

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24.5.3 Medicines for opioid use disorders	
<i>Complementary List</i>	
<input type="checkbox"/> methadone* Therapeutic alternatives: <ul style="list-style-type: none"> <li>- buprenorphine</li> </ul>	<b>Concentrate for oral liquid:</b> 5 mg/mL; 10 mg/mL (hydrochloride). <b>Oral liquid:</b> 5 mg/5 mL; 10 mg/5 mL (hydrochloride). <i>*The medicines should only be used within an established support programme.</i>
<b>25. MEDICINES ACTING ON THE RESPIRATORY TRACT</b>	
<b>25.1 Antiasthmatic medicines and medicines for chronic obstructive pulmonary disease</b>	
<input type="checkbox"/> budesonide Therapeutic alternatives: <ul style="list-style-type: none"> <li>- beclometasone</li> <li>- ciclesonide</li> <li>- flunisolide</li> <li>- fluticasone</li> <li>- mometasone</li> </ul>	<b>Inhalation (aerosol):</b> 100 micrograms per dose; 200 micrograms per dose.
<input type="checkbox"/> budesonide + <input type="checkbox"/> formoterol Therapeutic alternatives: <ul style="list-style-type: none"> <li>- beclometasone + formoterol</li> <li>- budesonide + salmeterol</li> <li>- fluticasone + formoterol</li> <li>- fluticasone furoate + vilanterol</li> <li>- mometasone + formoterol</li> </ul>	<b>Dry powder inhaler:</b> 100 micrograms + 6 micrograms per dose; 200 micrograms + 6 micrograms per dose.
epinephrine (adrenaline)	<b>Injection:</b> 1 mg/mL (as hydrochloride or hydrogen tartrate) in 1 mL ampoule.
ipratropium bromide	<b>Inhalation (aerosol):</b> 20 micrograms/metered dose.
<input type="checkbox"/> salbutamol Therapeutic alternatives: <ul style="list-style-type: none"> <li>- terbutaline</li> </ul>	<b>Inhalation (aerosol):</b> 100 micrograms (as sulfate) per dose. <b>Injection:</b> 50 micrograms/mL (as sulfate) in 5 mL ampoule. <b>Metered dose inhaler (aerosol):</b> 100 micrograms (as sulfate) per dose. <b>Respirator solution for use in nebulizers:</b> 5 mg/mL (as sulfate).
<input type="checkbox"/> tiotropium Therapeutic alternatives: <ul style="list-style-type: none"> <li>- aclidinium</li> <li>- glycopyrronium</li> <li>- umeclidinium</li> </ul>	<b>Powder for inhalaton, capsule:</b> 18 micrograms. <b>Inhalation solution:</b> 1.25 micrograms; 2.5 micrograms per actuation.
<b>26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID–BASE DISTURBANCES</b>	
<b>26.1 Oral</b>	
oral rehydration salts	See section 17.5.1.
potassium chloride	<b>Powder for solution.</b>
<b>26.2 Parenteral</b>	
glucose	<b>Injectable solution:</b> 5% (isotonic); 10% (hypertonic); 50% (hypertonic).

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glucose with sodium chloride	<b>Injectable solution:</b> 4% glucose, 0.18% sodium chloride (equivalent to Na <sup>+</sup> 30 mmol/L, Cl <sup>-</sup> 30 mmol/L).  <b>Injectable solution:</b> 5% glucose, 0.9% sodium chloride (equivalent to Na <sup>+</sup> 150 mmol/L and Cl <sup>-</sup> 150 mmol/L); 5% glucose, 0.45% sodium chloride (equivalent to Na <sup>+</sup> 75 mmol/L and Cl <sup>-</sup> 75 mmol/L) [c].
potassium chloride	<b>Solution:</b> 11.2% in 20 mL ampoule (equivalent to K <sup>+</sup> 1.5 mmol/mL, Cl <sup>-</sup> 1.5 mmol/mL).  <b>Solution for dilution:</b> 7.5% (equivalent to K 1 mmol/mL and Cl 1 mmol/mL) [c]; 15% (equivalent to K 2 mmol/mL and Cl 2 mmol/mL) [c].
sodium chloride	<b>Injectable solution:</b> 0.9% isotonic (equivalent to Na <sup>+</sup> 154 mmol/L, Cl <sup>-</sup> 154 mmol/L).
sodium hydrogen carbonate	<b>Injectable solution:</b> 1.4% isotonic (equivalent to Na <sup>+</sup> 167 mmol/L, HCO <sub>3</sub> <sup>-</sup> 167 mmol/L).  <b>Solution:</b> 8.4% in 10 mL ampoule (equivalent to Na <sup>+</sup> 1000 mmol/L, HCO <sub>3</sub> <sup>-</sup> 1000 mmol/L).
sodium lactate, compound solution	<b>Injectable solution.</b>
<b>26.3 Miscellaneous</b>	
water for injection	2 mL; 5 mL; 10 mL ampoules.
<b>27. VITAMINS AND MINERALS</b>	
ascorbic acid	<b>Tablet:</b> 50 mg.
calcium	<b>Tablet:</b> 500 mg (elemental).
<input type="checkbox"/> colecalciferol [c] Therapeutic alternatives: - ergocalciferol	<b>Oral liquid:</b> 400 IU/mL.  <b>Solid oral dosage form:</b> 400 IU; 1000 IU.
<input type="checkbox"/> ergocalciferol Therapeutic alternatives: - colecalciferol	<b>Oral liquid:</b> 250 micrograms/mL (10 000 IU/mL).  <b>Solid oral dosage form:</b> 1.25 mg (50 000 IU).
iodine	<b>Capsule:</b> 190 mg.  <b>Iodized oil:</b> 1 mL (480 mg iodine); 0.5 mL (240 mg iodine) in ampoule (oral or injectable); 0.57 mL (308 mg iodine) in dispenser bottle.
multiple micronutrient powder [c]	<b>Sachets containing:</b> - iron (elemental) 12.5 mg (as coated ferrous fumarate) - zinc (elemental) 5 mg - vitamin A 300 micrograms - with or without other micronutrients at recommended daily values
nicotinamide	<b>Tablet:</b> 50 mg.
pyridoxine	<b>Tablet:</b> 25 mg (hydrochloride).

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retinol	<b>Capsule:</b> 50 000 IU; 100 000 IU; 200 000 IU (as palmitate). <b>Oral oily solution:</b> 100 000 IU/mL (as palmitate) in multidose dispenser. <b>Tablet (sugar-coated):</b> 10 000 IU (as palmitate). <b>Water-miscible injection:</b> 100 000 IU (as palmitate) in 2 mL ampoule.
riboflavin	<b>Tablet:</b> 5 mg.
thiamine	<b>Tablet:</b> 50 mg (hydrochloride).
<b>Complementary List</b>	
calcium gluconate	<b>Injection:</b> 100 mg/mL in 10 mL ampoule.
<b>28. EAR, NOSE AND THROAT MEDICINES</b>	
acetic acid [c]	<b>Topical:</b> 2%, in alcohol.
<input type="checkbox"/> budesonide [c] Therapeutic alternatives to be reviewed	<b>Nasal spray:</b> 100 micrograms per dose.
<input type="checkbox"/> ciprofloxacin [c] Therapeutic alternatives: - ofloxacin	<b>Solution (ear drops):</b> 0.3% (as hydrochloride).
<input type="checkbox"/> xylometazoline <input type="checkbox"/> [c] Therapeutic alternatives to be reviewed	<b>Nasal spray:</b> 0.05%. <input type="checkbox"/> Not in children less than 3 months.
<b>29. MEDICINES FOR DISEASES OF JOINTS</b>	
<b>29.1 Medicines used to treat gout</b>	
allopurinol	<b>Tablet:</b> 100 mg.
<b>29.2 Disease-modifying anti-rheumatic drugs (DMARDs)</b>	
chloroquine	<b>Tablet:</b> 100 mg; 150 mg (as phosphate or sulfate).
<b>Complementary List</b>	
azathioprine	<b>Tablet:</b> 50 mg.
hydroxychloroquine	<b>Solid oral dosage form:</b> 200 mg (as sulfate).
methotrexate	<b>Tablet:</b> 2.5 mg (as sodium).
penicillamine	<b>Solid oral dosage form:</b> 250 mg.
sulfasalazine	<b>Tablet:</b> 500 mg.
<b>29.3 Medicines for juvenile joint diseases</b>	
<b>Complementary List</b>	
acetylsalicylic acid* (acute or chronic use)	<b>Suppository:</b> 50 mg to 150 mg. <b>Tablet:</b> 100 mg to 500 mg. *For use for rheumatic fever, juvenile arthritis, Kawasaki disease.

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<p>o <i>adalimumab*</i></p> <p><i>Therapeutic alternatives*:</i></p> <ul style="list-style-type: none"> <li>- <i>certolizumab pegol</i></li> <li>- <i>etanercept</i></li> <li>- <i>golimumab</i></li> <li>- <i>infliximab</i></li> </ul> <p>*including quality-assured biosimilars</p>	<p><b>Injection:</b> 10 mg/0.2 mL [c]; 20 mg/0.4 mL [c]; 40 mg/0.8 mL; 40 mg/0.4 mL.</p>
<p><i>methotrexate</i></p>	<p><b>Tablet:</b> 2.5 mg (as sodium).</p>
<p><input type="checkbox"/> <i>triamicinolone hexacetonide</i></p> <p><i>Therapeutic alternatives:</i></p> <ul style="list-style-type: none"> <li>- <i>triamicinolone acetonide</i></li> </ul>	<p><b>Injection:</b> 20 mg/mL in vial.</p>

## 30. DENTAL MEDICINES AND PREPARATIONS

<p>fluoride</p>	<p><b>Gel:</b> containing 2500 to 12 500 ppm fluoride (any type).  <b>Mouthrinse:</b> containing 230 to 900 ppm fluoride (any type).  <b>Toothpaste, cream or gel:</b> containing 1000 to 1500 ppm fluoride (any type).  <b>Varnish:</b> containing 22 500 ppm fluoride (any type).</p>
<p>glass ionomer cement</p>	<p><b>Single-use capsules:</b> 0.4 g powder + 0.09 mL liquid.  <b>Multi-use bottle:</b> powder + liquid.            Powder (fluoro-alumino-silicate glass) contains: 25-50% silicate, 20-40% aluminium oxide, 1-20% fluoride, 15-40% metal oxide, 0-15% phosphate, remainder are polyacrylic acid powder and metals in minimal quantities. Liquid (aqueous) contains: 7-25% polybasic carboxylic acid, 45-60% polyacrylic acid.</p>
<p>resin-based composite (low-viscosity)*</p>	<p><b>Single-use applicator or multi-use bottle</b>            *of any type for use as dental sealant</p>
<p>resin-based composite (high-viscosity)*</p>	<p><b>Single-use capsule or multi-use syringe</b>            *of any type for use as dental filling material</p>
<p>silver diamine fluoride</p>	<p><b>Solution:</b> 38% w/v.</p>

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Table 1.1: Medicines with age or weight restrictions

artesunate + pyronaridine tetraphosphate	> 5 kg
atropine	> 3 months
benzyl benzoate	>2 years
betamethasone topical preparations	hydrocortisone preferred in neonates
cefazolin	> 1 month
ceftriaxone	> 41 weeks corrected gestational age
darunavir	> 3 years
dihydroartemisinin + piperaquine phosphate	> 5 kg
diloxanide	>25 kg
dolutegravir	≥ 4 weeks and ≥ 3 kg (10 mg dispersible tablet) ≥ 25 kg (50 mg tablet)
doxycycline	> 8 years (except for serious infections e.g. cholera)
ibuprofen	> 3 months (except IV form for patent ductus arteriosus)
mefloquine	> 5 kg or > 3 months
metoclopramide	Not in neonates
nevirapine	> 6 weeks
ondansetron	> 1 month
silver sulfadiazine	> 2 months
tetracaine	Not in preterm neonates
xylometazoline	> 3 months

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Table 1.2: Explanation of dosage forms

## A. Principal dosage forms used in EML – oral administration

Term	Definition
<b>Solid oral dosage form</b>	<p>Refers to tablets or capsules or other solid dosage forms such as 'melts' that are immediate-release preparations. It implies that there is no difference in clinical efficacy or safety between the available dosage forms, and countries should therefore choose the form(s) to be listed depending on quality and availability.</p> <p>The term 'solid oral dosage form' is <i>never</i> intended to allow any type of modified-release tablet.</p>
<b>Tablets</b>	<p>Refers to:</p> <ul style="list-style-type: none"> <li>• uncoated or coated (film-coated or sugar-coated) tablets that are intended to be swallowed whole;</li> <li>• unscored and scored*;</li> <li>• tablets that are intended to be chewed before being swallowed;</li> <li>• tablets that are intended to be dispersed or dissolved in water or another suitable liquid before being swallowed;</li> <li>• tablets that are intended to be crushed before being swallowed.</li> </ul> <p>The term 'tablet' without qualification is <i>never</i> intended to allow any type of modified-release tablet.</p>
<b>Tablets (qualified)</b>	<p>Refers to a specific type of tablet:</p> <p><b>chewable</b> - tablets that are intended to be chewed before being swallowed;</p> <p><b>dispersible</b> - tablets that are intended to be dispersed in water or another suitable liquid before being swallowed;</p> <p><b>soluble</b> - tablets that are intended to be dissolved in water or another suitable liquid before being swallowed;</p> <p><b>crushable</b> - tablets that are intended to be crushed before being swallowed;</p> <p><b>scored</b> - tablets bearing a break mark or marks where sub-division is intended in order to provide doses of less than one tablet;</p> <p><b>sublingual</b> - tablets that are intended to be placed beneath the tongue.</p> <p>The term 'tablet' is <i>always</i> qualified with an additional term (in parentheses) in entries where one of the following types of tablet is intended: <b>gastro-resistant</b> (such tablets may sometimes be described as enteric-coated or as delayed-release), <b>prolonged-release</b> or another modified-release form.</p>

\* Scored tablets may be divided for ease of swallowing, provided that dose is a whole number of tablets.

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Capsules	Refers to hard or soft capsules.  The term 'capsule' without qualification is <i>never</i> intended to allow any type of modified-release capsule.
Capsules (qualified)	The term 'capsule' with qualification refers to <b>gastro-resistant</b> (such capsules may sometimes be described as enteric-coated or as delayed-release), <b>prolonged-release</b> or another modified-release form.
Granules	Preparations that are issued to patient as granules to be swallowed without further preparation, to be chewed, or to be taken in or with water or another suitable liquid.  The term 'granules' without further qualification is <i>never</i> intended to allow any type of modified-release granules.
Oral powder	Preparations that are issued to patient as powder (usually as single-dose) to be taken in or with water or another suitable liquid.
Oral liquid	Liquid preparations intended to be <i>swallowed</i> i.e. oral solutions, suspensions, emulsions and oral drops, including those constituted from powders or granules, but <i>not</i> those preparations intended for <i>oromucosal administration</i> e.g. gargles and mouthwashes.  Oral liquids presented as powders or granules may offer benefits in the form of better stability and lower transport costs. If more than one type of oral liquid is available on the same market (e.g. solution, suspension, granules for reconstitution), they may be interchanged and in such cases should be bioequivalent. It is preferable that oral liquids do not contain sugar and that solutions for children do not contain alcohol.

### B. Principal dosage forms used in EML – parenteral administration

Term	Definition
Injection	Refers to solutions, suspensions and emulsions including those constituted from powders or concentrated solutions.
Injection (qualified)	Route of administration is indicated in parentheses where relevant.
Injection (oily)	The term 'injection' is qualified by '(oily)' in relevant entries.
Intravenous infusion	Refers to solutions and emulsions including those constituted from powders or concentrated solutions.

### C. Other dosage forms

Mode of administration	Term to be used
To the eye	Eye drops, eye ointments.
Topical	For liquids: lotions, paints. For semi-solids: cream, ointment.
Rectal	Suppositories, gel or solution.
Vaginal	Pessaries or vaginal tablets.
Inhalation	Powder for inhalation, pressurized inhalation, nebulizer.

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# World Health Organization Model List of Essential Medicines for Children

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8th List  
(2021)



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# WHO Model List of Essential Medicines for Children – 8th List (2021)

## Explanatory notes

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This Model List is intended for use for children up to and including 12 years of age.

The **core list** presents a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

The **complementary list** presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings.

The **square box symbol (□)** is intended to indicate therapeutic alternatives to the listed medicine that may be considered for selection in national essential medicines lists. Alternatives may be individual medicines, or multiple medicines within a pharmacological class or chemical subgroup, defined at the 4th level of the [Anatomical Therapeutic Chemical \(ATC\) classification](#), which have similar clinical effectiveness and safety. The listed medicine should be the example of the class or subgroup for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. A square box is not used to indicate alternative generic brands of the same small molecule medicines, nor alternative biosimilars of biological medicines. However, the selection and use of quality-assured generics and biosimilars of essential medicines at country level is recommended.

National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price.

The **[ ]** symbol indicates that there is an age or weight restriction on use of the medicine; details for each medicine are in Table 1.1 of Annex 1.

The presence of an entry on the Essential Medicines List for Children carries no assurance as to pharmaceutical quality. It is the responsibility of the relevant national or regional drug regulatory authority to ensure that each product is of appropriate pharmaceutical quality (including stability) and that when relevant, different products are interchangeable.

For recommendations and advice concerning all aspects of the quality assurance of medicines see the WHO Medicines website <https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/guidelines/quality-assurance>.

Medicines and dosage forms are listed in alphabetical order within each section and the order of listing does not imply preference for one form over another. Standard treatment guidelines should be consulted for information on appropriate dosage forms.

The main terms used for dosage forms in the Essential Medicines List can be found in Table 1.2 of Annex 1.

Definitions of many of these terms and pharmaceutical quality requirements applicable to the different categories are published in the current edition of *The International Pharmacopoeia*  
<https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/pharmacopoeia>.

# WHO Model List of Essential Medicines for Children – 8th List (2021)

1. ANAESTHETICS, PREOPERATIVE MEDICINES AND MEDICAL GASES	
1.1 General anaesthetics and oxygen	
1.1.1 Inhalational medicines	
halothane	Inhalation.
isoflurane	Inhalation.
nitrous oxide	Inhalation.
oxygen	Inhalation (medical gas).
1.1.2 Injectable medicines	
ketamine	Injection: 50 mg/mL (as hydrochloride) in 10 mL vial.
<input type="checkbox"/> propofol *	
Therapeutic alternatives: - thiopental	Injection: 10 mg/mL; 20 mg/mL.
1.2 Local anaesthetics	
<input type="checkbox"/> bupivacaine Therapeutic alternatives to be reviewed (2023)	Injection: 0.25%; 0.5% (hydrochloride) in vial. <b>Injection for spinal anaesthesia:</b> 0.5% (hydrochloride) in 4 mL ampoule to be mixed with 7.5% glucose solution.
<input type="checkbox"/> lidocaine Therapeutic alternatives to be reviewed (2023)	Injection: 1%; 2% (hydrochloride) in vial. <b>Injection for spinal anaesthesia:</b> 5% (hydrochloride) in 2 mL ampoule to be mixed with 7.5% glucose solution. <b>Topical forms:</b> 2% to 4% (hydrochloride).
lidocaine + epinephrine (adrenaline)	Dental cartridge: 2% (hydrochloride) + epinephrine 1:80 000. Injection: 1%; 2% (hydrochloride or sulfate) + epinephrine 1:200 000 in vial.
1.3 Preoperative medication and sedation for short-term procedures	
atropine	Injection: 1 mg (sulfate) in 1mL ampoule.
<input type="checkbox"/> midazolam Therapeutic alternatives to be reviewed (2023)	Injection: 1 mg/mL. Oral liquid: 2 mg/mL. Tablet: 7.5 mg; 15 mg.
morphine	Injection: 10 mg (sulfate or hydrochloride) in 1mL ampoule.
1.4 Medical gases	
oxygen*	<b>Inhalation</b> For use in the management of hypoxaemia. *No more than 30% oxygen should be used to initiate resuscitation of neonates less than or equal to 32 weeks of gestation.

# WHO Model List of Essential Medicines for Children – 8th List (2021)

2. MEDICINES FOR PAIN AND PALLIATIVE CARE	
2.1 Non-opioids and non-steroidal anti-inflammatory medicines (NSAIDs)	
ibuprofen <small>a</small>	<p><b>Oral liquid:</b> 200 mg/5 mL.</p> <p><b>Tablet:</b> 200 mg; 400 mg; 600 mg.</p> <p><small>a Not in children less than 3 months.</small></p>
paracetamol*	<p><b>Oral liquid:</b> 120 mg/5 mL; 125 mg/5 mL.</p> <p><b>Suppository:</b> 100 mg.</p> <p><b>Tablet:</b> 100 mg to 500 mg.</p> <p>*Not recommended for anti-inflammatory use due to lack of proven benefit to that effect.</p>
2.2 Opioid analgesics	
<input type="checkbox"/> morphine Therapeutic alternatives: - hydromorphone - oxycodone	<p><b>Granules (slow release; to mix with water):</b> 20 mg to 200 mg (morphine sulfate).</p> <p><b>Injection:</b> 10 mg (morphine hydrochloride or morphine sulfate) in 1 mL ampoule.</p> <p><b>Oral liquid:</b> 10 mg/5 mL (morphine hydrochloride or morphine sulfate).</p> <p><b>Tablet (slow release):</b> 10 mg to 200mg (morphine hydrochloride or morphine sulfate).</p> <p><b>Tablet (immediate release):</b> 10 mg (morphine sulfate).</p>
<i>Complementary list</i>	
methadone*	<p><b>Tablet:</b> 5 mg; 10 mg (hydrochloride).</p> <p><b>Oral liquid:</b> 5 mg/5 mL; 10 mg/5 mL (hydrochloride).</p> <p><b>Concentrate for oral liquid:</b> 5 mg/mL; 10 mg/mL (hydrochloride)</p> <p>*For the management of cancer pain.</p>
2.3 Medicines for other symptoms common in palliative care	
amitriptyline	<b>Tablet:</b> 10 mg; 25 mg.
cyclizine	<p><b>Injection:</b> 50 mg/mL.</p> <p><b>Tablet:</b> 50 mg.</p>
dexamethasone	<p><b>Injection:</b> 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule.</p> <p><b>Oral liquid:</b> 2 mg/5 mL.</p> <p><b>Tablet:</b> 2 mg.</p>
diazepam	<p><b>Injection:</b> 5 mg/mL.</p> <p><b>Oral liquid:</b> 2 mg/5 mL.</p> <p><b>Rectal solution:</b> 2.5 mg; 5 mg; 10 mg.</p> <p><b>Tablet:</b> 5 mg; 10 mg.</p>

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docusate sodium	Capsule: 100 mg. Oral liquid: 50 mg/5 mL.
fluoxetine <small>a</small>	Solid oral dosage form: 20 mg (as hydrochloride). <small>a</small> > 8 years.
hyoscine hydrobromide	Injection: 400 micrograms/mL; 600 micrograms/mL. Transdermal patches: 1 mg/72 hours.
lactulose	Oral liquid: 3.1 to 3.7 g/5 mL.
midazolam	Injection: 1 mg/mL; 5 mg/mL. Oral liquid: 2mg/mL. Solid oral dosage form: 7.5 mg; 15 mg.
<input type="checkbox"/> ondansetron <small>a</small> Therapeutic alternatives: - dolasetron - granisetron - palonosetron - tropisetron	Injection: 2 mg base/mL in 2 mL ampoule (as hydrochloride). Oral liquid: 4 mg base/5 mL. Solid oral dosage form: Eq 4 mg base; Eq 8 mg base. <small>a</small> > 1 month.
senna	Oral liquid: 7.5 mg/5 mL.
<b>3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS</b>	
dexamethasone	Injection: 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule.
epinephrine (adrenaline)	Injection: 1 mg/mL (as hydrochloride or hydrogen tartrate) in 1 mL ampoule.
hydrocortisone	Powder for injection: 100 mg (as sodium succinate) in vial.
<input type="checkbox"/> loratadine* Therapeutic alternatives: - cetirizine - fexofenadine	Oral liquid: 1 mg/mL. Tablet: 10 mg. <i>*There may be a role for sedating antihistamines for limited indications.</i>
<input type="checkbox"/> prednisolone Therapeutic alternatives: - prednisone	Oral liquid: 5 mg/mL. Tablet: 5 mg; 25 mg.
<b>4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS</b>	
<b>4.1 Non-specific</b>	
charcoal, activated	Powder.
<b>4.2 Specific</b>	
acetylcysteine	Injection: 200 mg/mL in 10 mL ampoule. Oral liquid: 10%; 20%.
atropine	Injection: 1 mg (sulfate) in 1 mL ampoule.
calcium gluconate	Injection: 100 mg/mL in 10 mL ampoule.
naloxone	Injection: 400 micrograms (hydrochloride) in 1 mL ampoule.
<i>Complementary List</i>	
deferoxamine	Powder for injection: 500 mg (mesilate) in vial.

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<i>dimercaprol</i>	<i>Injection in oil:</i> 50 mg/mL in 2 mL ampoule.
<i>fomepizole</i>	<i>Injection:</i> 5 mg/mL (sulfate) in 20 mL ampoule or 1 g/mL (base) in 1.5 mL ampoule.
<i>sodium calcium edetate</i>	<i>Injection:</i> 200 mg/mL in 5 mL ampoule.
<i>succimer</i>	<i>Solid oral dosage form:</i> 100 mg.
<b>5. ANTICONVULSANTS/ANTIEPILEPTICS</b>	
carbamazepine	<b>Oral liquid:</b> 100 mg/5 mL. <b>Tablet (chewable):</b> 100 mg; 200 mg. <b>Tablet (scored):</b> 100 mg; 200 mg.
diazepam	<b>Gel or rectal solution:</b> 5 mg/mL in 0.5 mL; 2 mL; 4 mL tubes.
lamotrigine*	<b>Tablet:</b> 25 mg; 50 mg; 100 mg; 200 mg. <b>Tablet (chewable, dispersible):</b> 2 mg; 5 mg; 25 mg; 50 mg; 100 mg; 200 mg. *For use as adjunctive therapy for treatment-resistant partial or generalized seizures.
<input type="checkbox"/> lorazepam Therapeutic alternatives: - diazepam (injection) - midazolam (injection)	<b>Injection:</b> 2 mg/mL in 1 mL ampoule; 4 mg/mL in 1 mL ampoule.
midazolam	<b>Solution for oromucosal administration:</b> 5 mg/mL; 10 mg/mL <b>Ampoule*:</b> 1 mg/mL; 10 mg/mL *For buccal administration when solution for oromucosal administration is not available
phenobarbital	<b>Injection:</b> 200 mg/mL (sodium). <b>Oral liquid:</b> 15 mg/5 mL. <b>Tablet:</b> 15 mg to 100 mg.
phenytoin	<b>Injection:</b> 50 mg/mL (sodium) in 5 mL vial. <b>Oral liquid:</b> 25 mg to 30 mg/5 mL.* <b>Solid oral dosage form:</b> 25 mg; 50 mg; 100 mg (sodium). <b>Tablet (chewable):</b> 50 mg. *The presence of both 25 mg/5 mL and 30 mg/5 mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided.
valproic acid (sodium valproate)* <i>*avoid use in pregnancy and in women and girls of child-bearing potential, unless alternative treatments are ineffective or not tolerated because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb.</i>	<b>Oral liquid:</b> 200 mg/5 mL. <b>Tablet (crushable):</b> 100 mg. <b>Tablet (enteric-coated):</b> 200 mg; 500 mg.

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<i>Complementary List</i>	
ethosuximide	<b>Capsule:</b> 250 mg. <b>Oral liquid:</b> 250 mg/5 mL.
valproic acid (sodium valproate)*  *avoid use in pregnancy and in women and girls of child-bearing potential, unless alternative treatments are ineffective or not tolerated because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb.	  <b>Injection:</b> 100 mg/mL in 4 mL ampoule; 100 mg/mL in 10 mL ampoule.
6. ANTI-INFECTIVE MEDICINES	
6.1 Anthelmintics	
6.1.1 <i>Intestinal anthelmintics</i>	
albendazole	<b>Tablet (chewable):</b> 400 mg.
ivermectin	<b>Tablet (scored):</b> 3 mg.
levamisole	<b>Tablet:</b> 50 mg; 150 mg (as hydrochloride).
mebendazole	<b>Tablet (chewable):</b> 100 mg; 500 mg.
niclosamide	<b>Tablet (chewable):</b> 500 mg.
praziquantel	<b>Tablet:</b> 150 mg; 600 mg.
pyrantel	<b>Oral liquid:</b> 50 mg (as embonate or pamoate)/mL. <b>Tablet (chewable):</b> 250 mg (as embonate or pamoate).
6.1.2 <i>Antifilarials</i>	
albendazole	<b>Tablet (chewable):</b> 400 mg.
diethylcarbamazine	<b>Tablet:</b> 50 mg; 100 mg (dihydrogen citrate).
ivermectin	<b>Tablet (scored):</b> 3 mg.
6.1.3 <i>Antischistosomal and other antitrematode medicines</i>	
praziquantel	<b>Tablet:</b> 600 mg.
triclabendazole	<b>Tablet:</b> 250 mg.
<i>Complementary List</i>	
oxamniquine*	<b>Capsule:</b> 250 mg. <b>Oral liquid:</b> 250 mg/5 mL.  *For use when praziquantel treatment fails.
6.1.4 <i>Cysticidal medicines</i>	
<i>Complementary List</i>	
albendazole	<b>Tablet (chewable):</b> 400 mg.
mebendazole	<b>Tablet (chewable):</b> 500 mg.
praziquantel	<b>Tablet:</b> 500 mg; 600 mg

# WHO Model List of Essential Medicines for Children – 8th List (2021)

## 6.2 Antibacterials

To assist in the development of tools for antibiotic stewardship at local, national and global levels and to reduce antimicrobial resistance, the Access, Watch, Reserve (AWaRe) classification of antibiotics has been developed by WHO – where antibiotics are classified into different groups to emphasize the importance of their appropriate use.

### ACCESS GROUP ANTIBIOTICS

This group includes antibiotics that have activity against a wide range of commonly encountered susceptible pathogens while also showing lower resistance potential than antibiotics in the other groups. Selected Access group antibiotics are recommended as essential first or second choice empiric treatment options for infectious syndromes reviewed by the EML Expert Committee and are listed as individual medicines on the Model Lists to improve access and promote appropriate use. They are essential antibiotics that should be widely available, affordable and quality assured.

### WATCH GROUP ANTIBIOTICS

This group includes antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the [Critically Important Antimicrobials for Human Medicine](#) and/or antibiotics that are at relatively high risk of selection of bacterial resistance. These medicines should be prioritized as key targets of stewardship programs and monitoring. Selected Watch group antibiotics are recommended as essential first or second choice empiric treatment options for a limited number of specific infectious syndromes and are listed as individual medicines on the Model Lists.

### RESERVE GROUP ANTIBIOTICS

This group includes antibiotics and antibiotic classes that should be reserved for treatment of confirmed or suspected infections due to multi-drug-resistant organisms. Reserve group antibiotics should be treated as “last resort” options. Selected Reserve group antibiotics are listed as individual medicines on the Model Lists when they have a favourable risk-benefit profile and proven activity against “Critical Priority” or “High Priority” pathogens identified by the [WHO Priority Pathogens List](#), notably carbapenem resistant *Enterobacteriaceae*. These antibiotics should be accessible, but their use should be tailored to highly specific patients and settings, when all alternatives have failed or are not suitable. These medicines could be protected and prioritized as key targets of national and international stewardship programs involving monitoring and utilization reporting, to preserve their effectiveness.

# WHO Model List of Essential Medicines for Children – 8th List (2021)

6.2.1 Access group antibiotics						
amikacin		<p><b>Injection:</b> 250 mg/mL (as sulfate) in 2 mL vial.</p> <table> <tr> <td><b>FIRST CHOICE</b></td><td><b>SECOND CHOICE</b></td></tr> <tr> <td> <ul style="list-style-type: none"> <li>– <i>High-risk febrile neutropenia-pyelonephritis (severe)</i></li> </ul> </td><td> <ul style="list-style-type: none"> <li>– <i>Sepsis in neonates and children</i></li> </ul> </td></tr> </table>	<b>FIRST CHOICE</b>	<b>SECOND CHOICE</b>	<ul style="list-style-type: none"> <li>– <i>High-risk febrile neutropenia-pyelonephritis (severe)</i></li> </ul>	<ul style="list-style-type: none"> <li>– <i>Sepsis in neonates and children</i></li> </ul>
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amoxicillin		<p><b>Powder for injection:</b> 250 mg; 500 mg; 1 g (as sodium) in vial.</p> <p><b>Powder for oral liquid:</b> 125 mg/5 mL; 250 mg/5 mL (as trihydrate).</p> <p><b>Solid oral dosage form:</b> 250 mg; 500 mg (as trihydrate).</p> <table> <tr> <td><b>FIRST CHOICE</b></td><td><b>SECOND CHOICE</b></td></tr> <tr> <td> <ul style="list-style-type: none"> <li>– <i>Community acquired pneumonia (mild to moderate)</i></li> <li>– <i>Community acquired pneumonia (severe)</i></li> <li>– <i>Complicated severe acute malnutrition</i></li> <li>– <i>Otitis media</i></li> <li>– <i>Pharyngitis</i></li> <li>– <i>Progressive apical dental abscess</i></li> <li>– <i>Sepsis in neonates and children</i></li> <li>– <i>Sinusitis</i></li> <li>– <i>Uncomplicated severe acute malnutrition</i></li> </ul> </td><td> <ul style="list-style-type: none"> <li>– <i>Acute bacterial meningitis</i></li> </ul> </td></tr> </table>	<b>FIRST CHOICE</b>	<b>SECOND CHOICE</b>	<ul style="list-style-type: none"> <li>– <i>Community acquired pneumonia (mild to moderate)</i></li> <li>– <i>Community acquired pneumonia (severe)</i></li> <li>– <i>Complicated severe acute malnutrition</i></li> <li>– <i>Otitis media</i></li> <li>– <i>Pharyngitis</i></li> <li>– <i>Progressive apical dental abscess</i></li> <li>– <i>Sepsis in neonates and children</i></li> <li>– <i>Sinusitis</i></li> <li>– <i>Uncomplicated severe acute malnutrition</i></li> </ul>	<ul style="list-style-type: none"> <li>– <i>Acute bacterial meningitis</i></li> </ul>
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amoxicillin + clavulanic acid		<p><b>Powder for injection:</b> 500 mg (as sodium) + 100 mg (as potassium salt); 1000 mg (as sodium) + 200 mg (as potassium salt) in vial.</p> <p><b>Powder for oral liquid:</b> 125 mg (as trihydrate)+ 31.25 mg (as potassium salt)/5 mL; 250 mg (as trihydrate) + 62.5 mg (as potassium salt)/5mL.</p> <p><b>Tablet:</b> 500 mg (as trihydrate) + 125 mg (as potassium salt).</p> <table> <tr> <td><b>FIRST CHOICE</b></td><td><b>SECOND CHOICE</b></td></tr> <tr> <td> <ul style="list-style-type: none"> <li>– <i>Community acquired pneumonia (severe)</i></li> <li>– <i>Complicated intraabdominal infections (mild to moderate)</i></li> <li>– <i>Hospital acquired pneumonia</i></li> <li>– <i>Low-risk febrile neutropenia</i></li> <li>– <i>Lower urinary tract infections</i></li> <li>– <i>Sinusitis</i></li> <li>– <i>Skin and soft tissue infections</i></li> </ul> </td><td> <ul style="list-style-type: none"> <li>– <i>Bone and joint infections</i></li> <li>– <i>Community acquired pneumonia (mild to moderate)</i></li> <li>– <i>Community acquired pneumonia (severe)</i></li> <li>– <i>Otitis media</i></li> <li>– <i>Surgical prophylaxis</i></li> </ul> </td></tr> </table>	<b>FIRST CHOICE</b>	<b>SECOND CHOICE</b>	<ul style="list-style-type: none"> <li>– <i>Community acquired pneumonia (severe)</i></li> <li>– <i>Complicated intraabdominal infections (mild to moderate)</i></li> <li>– <i>Hospital acquired pneumonia</i></li> <li>– <i>Low-risk febrile neutropenia</i></li> <li>– <i>Lower urinary tract infections</i></li> <li>– <i>Sinusitis</i></li> <li>– <i>Skin and soft tissue infections</i></li> </ul>	<ul style="list-style-type: none"> <li>– <i>Bone and joint infections</i></li> <li>– <i>Community acquired pneumonia (mild to moderate)</i></li> <li>– <i>Community acquired pneumonia (severe)</i></li> <li>– <i>Otitis media</i></li> <li>– <i>Surgical prophylaxis</i></li> </ul>
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ampicillin		<p><b>Powder for injection:</b> 500 mg; 1 g (as sodium) in vial.</p> <table> <tr> <td><b>FIRST CHOICE</b></td><td><b>SECOND CHOICE</b></td></tr> <tr> <td> <ul style="list-style-type: none"> <li>– <i>Community acquired pneumonia (severe)</i></li> <li>– <i>Complicated intraabdominal infections</i></li> <li>– <i>Complicated severe acute malnutrition</i></li> <li>– <i>Sepsis in neonates and children</i></li> </ul> </td><td> <ul style="list-style-type: none"> <li>– <i>Acute bacterial meningitis</i></li> </ul> </td></tr> </table>	<b>FIRST CHOICE</b>	<b>SECOND CHOICE</b>	<ul style="list-style-type: none"> <li>– <i>Community acquired pneumonia (severe)</i></li> <li>– <i>Complicated intraabdominal infections</i></li> <li>– <i>Complicated severe acute malnutrition</i></li> <li>– <i>Sepsis in neonates and children</i></li> </ul>	<ul style="list-style-type: none"> <li>– <i>Acute bacterial meningitis</i></li> </ul>
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benzathine benzylpenicillin	<b>Powder for injection:</b> 1.2 million IU ( $\approx$ 900 mg) in vial; 2.4 million IU ( $\approx$ 1.8 g) in vial.	
	<b>FIRST CHOICE</b> – <i>Syphilis (congenital)</i>	<b>SECOND CHOICE</b>
benzylpenicillin	<b>Powder for injection:</b> 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial.	
	<b>FIRST CHOICE</b> – <i>Community acquired pneumonia (severe)</i> – <i>Complicated severe acute malnutrition</i> – <i>Sepsis in neonates and children</i> – <i>Syphilis (congenital)</i>	<b>SECOND CHOICE</b> – <i>Acute bacterial meningitis</i>
cefalexin	<b>Powder for oral liquid:</b> 125 mg/5 mL; 250 mg/5 mL (anhydrous). <b>Solid oral dosage form:</b> 250 mg (as monohydrate).	
	<b>FIRST CHOICE</b> – <i>Skin and soft tissue infections</i>	<b>SECOND CHOICE</b> – <i>Pharyngitis</i>
cefazolin <small>a</small>	<b>Powder for injection:</b> 1 g (as sodium salt) in vial. <small>a</small> > 1 month.	
	<b>FIRST CHOICE</b> – <i>Surgical prophylaxis</i>	<b>SECOND CHOICE</b> – <i>Bone and joint infections</i>
chloramphenicol	<b>Capsule:</b> 250 mg. <b>Oily suspension for injection*</b> : 0.5 g/mL (as sodium succinate) in 2 mL ampoule. *Only for the presumptive treatment of epidemic meningitis in children older than 2 years. <b>Oral liquid:</b> 150 mg/5 mL (as palmitate). <b>Powder for injection:</b> 1 g (sodium succinate) in vial.	
	<b>FIRST CHOICE</b>	<b>SECOND CHOICE</b> – <i>Acute bacterial meningitis</i>
clindamycin	<b>Capsule:</b> 150 mg (as hydrochloride). <b>Injection:</b> 150 mg/mL (as phosphate). <b>Oral liquid:</b> 75 mg/5 mL (as palmitate).	
	<b>FIRST CHOICE</b> – <i>Necrotizing fasciitis</i>	<b>SECOND CHOICE</b> – <i>Bone and joint infections</i>

# WHO Model List of Essential Medicines for Children – 8th List (2021)

<input type="checkbox"/> cloxacillin* <p>Therapeutic alternatives:</p> <ul style="list-style-type: none"> <li>- 4<sup>th</sup> level ATC chemical subgroup (J01CF Beta-lactamase resistant penicillins)</li> </ul>	<p><b>Capsule:</b> 500 mg; 1 g (as sodium).</p> <p><b>Powder for injection:</b> 500 mg (as sodium) in vial.</p> <p><b>Powder for oral liquid:</b> 125 mg/5 mL (as sodium).</p> <p>*cloxacillin, dicloxacillin and flucloxacillin are preferred for oral administration due to better bioavailability.</p>	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Bone and joint infections</i></li> <li>– <i>Skin and soft tissue infections</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Sepsis in neonates and children</i></li> </ul>
doxycycline <input checked="" type="checkbox"/> a	<p><b>Oral liquid:</b> 25 mg/5 mL; 50 mg/5 mL (anhydrous).</p> <p><b>Powder for injection:</b> 100 mg in vial.</p> <p><b>Solid oral dosage form:</b> 50 mg; 100 mg (as hyclate).</p> <p><input checked="" type="checkbox"/> Use in children &lt;8 years only for life-threatening infections when no alternative exists.</p>	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Cholera</i></li> <li>– <i>Community acquired pneumonia (mild to moderate)</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Surgical prophylaxis</i></li> </ul>
gentamicin	<p><b>Injection:</b> 10 mg/mL (as sulfate); 40 mg/mL (as sulfate) in 2 mL vial.</p>	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Acute bacterial meningitis in neonates</i></li> <li>– <i>Community acquired pneumonia (severe)</i></li> <li>– <i>Complicated intraabdominal infections</i></li> <li>– <i>Complicated severe acute malnutrition</i></li> <li>– <i>Sepsis in neonates and children</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Surgical prophylaxis</i></li> </ul>
metronidazole	<p><b>Injection:</b> 500 mg in 100 mL vial.</p> <p><b>Oral liquid:</b> 200 mg/5 mL (as benzoate).</p> <p><b>Tablet:</b> 200 mg to 500 mg.</p>	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>C. difficile infection</i></li> <li>– <i>Complicated intra-abdominal infections (mild to moderate)</i></li> <li>– <i>Complicated intra-abdominal infections (severe)</i></li> <li>– <i>Necrotizing fasciitis</i></li> <li>– <i>Surgical prophylaxis</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Complicated intra-abdominal infections (mild to moderate)</i></li> </ul>
nitrofurantoin	<p><b>Oral liquid:</b> 25 mg/5 mL.</p> <p><b>Tablet:</b> 100 mg.</p>	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Lower urinary tract infections</i></li> </ul>	<b>SECOND CHOICE</b>

## WHO Model List of Essential Medicines for Children – 8th List (2021)

phenoxycephalothin	<b>Powder for oral liquid:</b> 250 mg/5 mL (as potassium). <b>Tablet:</b> 250 mg (as potassium).	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Community acquired pneumonia (mild to moderate)</i></li> <li>– <i>Pharyngitis</i></li> <li>– <i>Progressive apical dental abscess</i></li> </ul>	<b>SECOND CHOICE</b>
procaine benzylpenicillin*	<b>Powder for injection:</b> 1 g (=1 million IU); 3 g (=3 million IU) in vial.  *Procaine benzylpenicillin is not recommended as first-line treatment for neonatal sepsis / sepsis except in settings with high neonatal mortality, when given by trained health workers in cases where hospital care is not achievable.	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Syphilis (congenital)</i></li> </ul>	<b>SECOND CHOICE</b>
sulfamethoxazole + trimethoprim	<b>Injection:</b> 80 mg + 16 mg/ mL in 5 mL ampoule; 80 mg + 16 mg/ mL in 10 mL ampoule.  <b>Oral liquid:</b> 200 mg + 40 mg/5 mL.  <b>Tablet:</b> 100 mg + 20 mg; 400 mg + 80 mg.	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Lower urinary tract infections</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Acute invasive bacterial diarrhoea / dysentery</i></li> </ul>
trimethoprim	<b>Tablet:</b> 100 mg; 200 mg.  <b>Oral liquid:</b> 50 mg/5 mL.	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Lower urinary tract infections</i></li> </ul>	<b>SECOND CHOICE</b>
<b>6.2.2 Watch group antibiotics</b>		
azithromycin	<b>Capsule:</b> 250 mg; 500 mg (anhydrous).  <b>Oral liquid:</b> 200 mg/5 mL.	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Cholera</i></li> <li>– <i>Enteric fever</i></li> <li>– <i>Trachoma</i></li> <li>– <i>Yaws</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Acute invasive bacterial diarrhoea / dysentery</i></li> </ul>
ceftriaxone	<b>Powder for oral liquid:</b> 100 mg/5 mL.  <b>Solid oral dosage form:</b> 200 mg; 400 mg (as trihydrate).	
	<b>FIRST CHOICE</b>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Acute invasive bacterial diarrhoea / dysentery</i></li> </ul>

## WHO Model List of Essential Medicines for Children – 8th List (2021)

cefotaxime*	<p><b>Powder for injection:</b> 250 mg (as sodium) in vial.</p> <p>*3rd generation cephalosporin of choice for use in hospitalized neonates.</p>	
	<p><b>FIRST CHOICE</b></p> <ul style="list-style-type: none"> <li>– <i>Acute bacterial meningitis</i></li> <li>– <i>Community acquired pneumonia (severe)</i></li> <li>– <i>Complicated intraabdominal infections (mild to moderate)</i></li> <li>– <i>Complicated intraabdominal infections (severe)</i></li> <li>– <i>Hospital acquired pneumonia</i></li> <li>– <i>Pyelonephritis (severe)</i></li> </ul>	<p><b>SECOND CHOICE</b></p> <ul style="list-style-type: none"> <li>– <i>Bone and joint infections</i></li> <li>– <i>Pyelonephritis (mild to moderate)</i></li> <li>– <i>Sepsis in neonates and children</i></li> </ul>
ceftriaxone* <sup>a</sup>	<p><b>Powder for injection:</b> 250 mg; 1 g (as sodium) in vial.</p> <p>*Do not administer with calcium and avoid in infants with hyperbilirubinaemia.</p> <p>[a] &gt; 41 weeks corrected gestational age.</p>	
	<p><b>FIRST CHOICE</b></p> <ul style="list-style-type: none"> <li>– <i>Acute bacterial meningitis</i></li> <li>– <i>Community acquired pneumonia (severe)</i></li> <li>– <i>Complicated intraabdominal infections (mild to moderate)</i></li> <li>– <i>Complicated intraabdominal infections (severe)</i></li> <li>– <i>Endophthalmitis</i></li> <li>– <i>Enteric fever</i></li> <li>– <i>Hospital acquired pneumonia</i></li> <li>– <i>Necrotizing fasciitis</i></li> <li>– <i>Pyelonephritis (severe)</i></li> </ul>	<p><b>SECOND CHOICE</b></p> <ul style="list-style-type: none"> <li>– <i>Acute invasive bacterial diarrhoea / dysentery</i></li> <li>– <i>Bone and joint infections</i></li> <li>– <i>Pyelohepnitis or prostatitis (mild to moderate)</i></li> <li>– <i>Sepsis in neonates and children</i></li> </ul>
cefuroxime	<p><b>Powder for injection:</b> 250 mg; 750 mg; 1.5 g (as sodium) in vial.</p>	
	<p><b>FIRST CHOICE</b></p>	<p><b>SECOND CHOICE</b></p> <ul style="list-style-type: none"> <li>– <i>Surgical prophylaxis</i></li> </ul>
ciprofloxacin	<p><b>Oral liquid:</b> 250 mg/5 mL (anhydrous) .</p> <p><b>Solution for IV infusion:</b> 2 mg/ mL (as hyclate) .</p> <p><b>Solid oral dosage form:</b> 250 mg (as hydrochloride).</p>	
	<p><b>FIRST CHOICE</b></p> <ul style="list-style-type: none"> <li>– <i>Acute invasive bacterial diarrhoea / dysentery</i></li> <li>– <i>Enteric fever</i></li> <li>– <i>Low-risk febrile neutropenia</i></li> <li>– <i>Pyelonephritis (mild to moderate)</i></li> </ul>	<p><b>SECOND CHOICE</b></p> <ul style="list-style-type: none"> <li>– <i>Cholera</i></li> <li>– <i>Complicated intraabdominal infections (mild to moderate)</i></li> </ul>

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<input type="checkbox"/> clarithromycin Therapeutic alternatives: - erythromycin	<b>Powder for oral liquid:</b> 125 mg/5 mL; 250 mg/5 mL. <b>Powder for injection:</b> 500 mg in vial. <b>Solid oral dosage form:</b> 500 mg.	
	<b>FIRST CHOICE</b>	<b>SECOND CHOICE</b> – <i>Pharyngitis</i>
<b>piperacillin + tazobactam</b>		<b>Powder for injection:</b> 2 g (as sodium) + 250 mg (as sodium); 4 g (as sodium) + 500 mg (as sodium) in vial.
<b>FIRST CHOICE</b> – <i>Complicated intraabdominal infections (severe)</i> – <i>High-risk febrile neutropenia</i> – <i>Hospital acquired pneumonia</i> – <i>Necrotizing fasciitis</i>		<b>SECOND CHOICE</b>
<b>vancomycin</b>		<b>Capsule:</b> 125 mg; 250 mg (as hydrochloride).
<b>FIRST CHOICE</b>		<b>SECOND CHOICE</b> – <i>C. difficile infection</i>
<i>Complementary List</i>		
<b>ceftazidime</b>	<b>Powder for injection:</b> 250 mg; 1 g (as pentahydrate) in vial.	
	<b>FIRST CHOICE</b> – <i>Endophthalmitis</i>	<b>SECOND CHOICE</b>
<input type="checkbox"/> <b>meropenem*</b> <sup>a</sup> Therapeutic alternatives*: - imipenem + cilastatin  <i>*complicated intraabdominal infections and high-risk febrile neutropenia only. Meropenem is the preferred choice for acute bacterial meningitis in neonates.</i>	<b>Powder for injection:</b> 500 mg (as trihydrate); 1 g (as trihydrate) in vial <small>[a] &gt; 3 months.</small>	
	<b>FIRST CHOICE</b>	<b>SECOND CHOICE</b> – <i>Acute bacterial meningitis in neonates</i> – <i>Complicated intraabdominal infections (severe)</i> – <i>High-risk febrile neutropenia</i>
<b>vancomycin</b>	<b>Powder for injection:</b> 250 mg (as hydrochloride) in vial.	
	<b>FIRST CHOICE</b> – <i>Endophthalmitis</i> – <i>Necrotizing fasciitis</i>	<b>SECOND CHOICE</b> – <i>High-risk febrile neutropenia</i>

# WHO Model List of Essential Medicines for Children – 8th List (2021)

<b>6.2.3 Reserve group antibiotics</b>	
<b>Complementary List</b>	
ceftazidime + avibactam	<b>Powder for injection:</b> 2 g + 0.5 g in vial
colistin	<b>Powder for injection:</b> 1 million IU (as colistemethate sodium) in vial
fosfomycin	<b>Powder for injection:</b> 2 g; 4 g (as sodium) in vial
linezolid	<b>Injection for intravenous administration:</b> 2 mg/mL in 300 mL bag. <b>Powder for oral liquid:</b> 100 mg/5 mL. <b>Tablet:</b> 400 mg; 600 mg.
polymyxin B	<b>Powder for injection:</b> 500,000 IU in vial
<b>6.2.4 Antileprosy medicines</b>	
Medicines used in the treatment of leprosy should never be used except in combination. Combination therapy is essential to prevent the emergence of drug resistance. Colour-coded blister packs (MDT blister packs) containing standard two-medicine (paucibacillary leprosy) or three-medicine (multibacillary leprosy) combinations for adult and childhood leprosy should be used. MDT blister packs can be supplied free of charge through WHO.	
clofazimine	<b>Capsule:</b> 50 mg; 100 mg.
dapsone	<b>Tablet:</b> 25 mg; 50 mg; 100 mg.
rifampicin	<b>Solid oral dosage form:</b> 150 mg; 300 mg.
<b>6.2.5 Antituberculosis medicines</b>	
WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.	
ethambutol	<b>Oral liquid:</b> 25 mg/mL. <b>Tablet:</b> 100 mg; 400 mg (hydrochloride). <b>Tablet (dispersible):</b> 100 mg.
isoniazid	<b>Oral liquid:</b> 50 mg/5 mL. <b>Tablet:</b> 100 mg; 300 mg. <b>Tablet (dispersible):</b> 100 mg.
isoniazid + pyrazinamide + rifampicin	<b>Tablet (dispersible):</b> 50 mg + 150 mg + 75 mg.
isoniazid + rifampicin	<b>Tablet (dispersible):</b> 50 mg + 75 mg.
isoniazid + rifapentine	<b>Tablet (scored):</b> 300 mg + 300 mg.
pyrazinamide	<b>Oral liquid:</b> 30 mg/mL. <b>Tablet:</b> 400 mg; 500 mg. <b>Tablet (dispersible):</b> 150 mg.
rifampicin	<b>Oral liquid:</b> 20 mg/mL. <b>Solid oral dosage form:</b> 150 mg; 300 mg.
rifapentine	<b>Tablet:</b> 150 mg; 300 mg.

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Complementary List	
Medicines for the treatment of multidrug-resistant tuberculosis (MDR-TB) should be used in specialized centres adhering to WHO standards for TB control.	
<i>amikacin</i>	<b>Injection:</b> 100 mg/2 mL (as sulfate) in 2 mL vial; 250 mg/mL (as sulfate) in 2 mL vial.
<i>amoxicillin + clavulanic acid*</i>	<b>Powder for oral liquid:</b> 250 mg (as trihydrate) + 62.5 mg (as potassium salt)/5mL. <b>Tablet:</b> 500 mg (as trihydrate) + 125 mg (as potassium salt). *For use only in combination with meropenem.
<i>bedaquiline a</i>	<b>Tablet:</b> 20 mg;100 mg. a ≥ 5 years
<i>clofazimine</i>	<b>Solid oral dosage form:</b> 50 mg; 100 mg.
<i>cycloserine</i>	<b>Solid oral dosage form:</b> 125 mg; 250 mg.
<i>delamanid a</i>	<b>Tablet (dispersible):</b> 25 mg. a ≥3 years <b>Tablet:</b> 50 mg. a ≥6 years
<input type="checkbox"/> <i>ethionamide</i> Therapeutic alternatives: - <i>prionamide</i>	<b>Tablet:</b> 125 mg; 250 mg. <b>Tablet (dispersible):</b> 125 mg.
<i>levofloxacin</i>	<b>Tablet:</b> 250 mg; 500 mg. <b>Tablet (dispersible):</b> 100 mg.
<i>linezolid</i>	<b>Powder for oral liquid:</b> 100 mg/5 mL. <b>Tablet:</b> 600 mg. <b>Tablet (dispersible):</b> 150 mg.
<i>meropenem</i>	<b>Powder for injection:</b> 500 mg (as trihydrate); 1 g (as trihydrate) in vial.
<i>moxifloxacin</i>	<b>Tablet:</b> 400 mg. <b>Tablet (dispersible):</b> 100 mg.
<i>p-aminosalicylic acid</i>	<b>Granules:</b> 4 g in sachet.
<i>streptomycin</i>	<b>Powder for injection:</b> 1 g (as sulfate) in vial.
<b>6.3 Antifungal medicines</b>	
<i>amphotericin B</i>	<b>Powder for injection:</b> 50 mg in vial (as sodium deoxycholate or liposomal complex).
<i>fluconazole</i>	<b>Capsule:</b> 50 mg. <b>Injection:</b> 2 mg/mL in vial. <b>Oral liquid:</b> 50 mg/5 mL.
<i>flucytosine</i>	<b>Capsule:</b> 250 mg. <b>Infusion:</b> 2.5 g in 250 mL.
<i>griseofulvin</i>	<b>Oral liquid:</b> 125 mg/5 mL. <b>Solid oral dosage form:</b> 125 mg; 250 mg.

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itraconazole*	<p><b>Capsule:</b> 100 mg.</p> <p><b>Oral liquid:</b> 10 mg/mL.</p> <p>*For treatment of chronic pulmonary aspergillosis, acute invasive aspergillosis, histoplasmosis, sporotrichosis, paracoccidioidomycosis, mycoses caused by <i>T. marneffei</i> and chromoblastomycosis; and prophylaxis of histoplasmosis and infections caused by <i>T. marneffei</i> in AIDS patients.</p>
nystatin	<p><b>Lozenge:</b> 100 000 IU.</p> <p><b>Oral liquid:</b> 50 mg/5 mL; 100 000 IU/mL.</p> <p><b>Tablet:</b> 100 000 IU; 500 000 IU.</p>
voriconazole*	<p><b>Tablet:</b> 50 mg; 200 mg.</p> <p><b>Powder for injection:</b> 200 mg in vial.</p> <p><b>Powder for oral liquid:</b> 40 mg/mL.</p> <p>*For treatment of chronic pulmonary aspergillosis and acute invasive aspergillosis.</p>

## Complementary List

<input type="checkbox"/> <i>micafungin</i> Therapeutic alternatives: - <i>anidulafungin</i> - <i>caspofungin</i>	<b>Powder for injection:</b> 50 mg (as sodium); 100 mg (as sodium) in vial.
potassium iodide	<b>Saturated solution.</b>

## 6.4 Antiviral medicines

### 6.4.1 Antiherpes medicines

aciclovir	<b>Oral liquid:</b> 200 mg/5 mL. <b>Powder for injection:</b> 250 mg (as sodium salt) in vial. <b>Tablet:</b> 200 mg.
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### 6.4.2 Antiretrovirals

Based on current evidence and experience of use, medicines in the following classes of antiretrovirals are included as essential medicines for treatment and prevention of HIV (prevention of mother-to-child transmission and post-exposure prophylaxis). WHO emphasizes the importance of using these products in accordance with global and national guidelines. WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

Scored tablets can be used in children and therefore can be considered for inclusion in the listing of tablets, provided that adequate quality products are available.

#### 6.4.2.1 Nucleoside/Nucleotide reverse transcriptase inhibitors

lamivudine	<b>Oral liquid:</b> 50 mg/5 mL.
zidovudine	<b>Oral liquid:</b> 50 mg/5 mL.

#### 6.4.2.2 Non-nucleoside reverse transcriptase inhibitors

nevirapine <sup>a</sup>	<b>Oral liquid:</b> 50 mg/5 mL. <b>Tablet (dispersible):</b> 50 mg. <sup>a</sup> > 6 weeks
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# WHO Model List of Essential Medicines for Children – 8th List (2021)

## 6.4.2.3 Protease inhibitors

Selection of protease inhibitor(s) from the Model List will need to be determined by each country after consideration of international and national treatment guidelines and experience. Ritonavir is recommended for use in combination as a pharmacological booster, and not as an antiretroviral in its own right. All other protease inhibitors should be used in boosted forms (e.g. with ritonavir).

darunavir <b>a</b>	<b>Tablet:</b> 75 mg.  <b>a</b> > 3 years
lopinavir + ritonavir	<b>Solid oral dosage form:</b> 40 mg + 10 mg. <b>Tablet (heat stable):</b> 100 mg + 25 mg.
ritonavir	<b>Tablet (heat stable):</b> 25 mg; 100 mg.

## 6.4.2.4 Integrase inhibitors

dolutegravir <b>a</b>	<b>Tablet (dispersible, scored):</b> 10 mg.  <b>a</b> ≥4 weeks and ≥3 kg  <b>Tablet:</b> 50 mg.  <b>a</b> ≥ 25 kg
raltegravir*	<b>Granules for oral suspension:</b> 100 mg in sachet.  <b>Tablet (chewable):</b> 25 mg.  *For use in second-line regimens in accordance with WHO treatment guidelines

## 6.4.2.5 Fixed-dose combinations of antiretroviral medicines

abacavir + lamivudine	<b>Tablet (dispersible, scored):</b> 120 mg (as sulfate) + 60 mg.
lamivudine + zidovudine	<b>Tablet:</b> 30 mg + 60 mg.

## 6.4.2.6 Medicines for prevention of HIV-related opportunistic infections

isoniazid + pyridoxine + sulfamethoxazole + trimethoprim	<b>Tablet (scored):</b> 300 mg + 25 mg + 800 mg + 160 mg
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## 6.4.3 Other antivirals

ribavirin*	<b>Injection for intravenous administration:</b> 800 mg and 1 g in 10 mL phosphate buffer solution.  <b>Solid oral dosage form:</b> 200 mg; 400 mg; 600 mg.  *For the treatment of viral haemorrhagic fevers only.
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## Complementary List

oseltamivir*	<b>Capsule:</b> 30 mg; 45 mg; 75 mg (as phosphate).  *Severe illness due to confirmed or suspected influenza virus infection in critically ill hospitalized patients
valganciclovir*	<b>Powder for oral solution:</b> 50 mg/mL  <b>Tablet:</b> 450 mg.  *For the treatment of cytomegalovirus retinitis (CMVr).

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<b>6.4.4 Antihepatitis medicines</b>	
<b>6.4.4.1 Medicines for hepatitis B</b>	
<b>6.4.4.1.1 Nucleoside/Nucleotide reverse transcriptase inhibitors</b>	
entecavir	<p><b>Oral liquid:</b> 0.05 mg/ mL</p> <p><b>Tablet:</b> 0.5 mg; 1 mg</p>
<b>6.4.4.2 Medicines for hepatitis C</b>	
Pangenotypic direct-acting antivirals should be considered as therapeutically equivalent for the purposes of selection and procurement at national level.	
<b>6.4.4.2.1 □ Pangenotypic direct-acting antiviral combinations</b>	
daclatasvir*	<p><b>Tablet:</b> 30 mg; 60 mg (as hydrochloride).</p> <p>*Pangenotypic when used in combination with sofosbuvir</p>
daclatasvir + sofosbuvir	<b>Tablet:</b> 60 mg + 400 mg.
glecaprevir + pibrentasvir	<p><b>Granules:</b> 50 mg + 20 mg in sachet.</p> <p><b>Tablet:</b> 100 mg + 40 mg.</p>
sofosbuvir*	<p><b>Tablet:</b> 200 mg; 400 mg.</p> <p>*Pangenotypic when used in combination with daclatasvir</p>
sofosbuvir + velpatasvir	<b>Tablet:</b> 200 mg + 50 mg; 400 mg + 100 mg
<b>6.4.4.2.2 Non-pangenotypic direct-acting antiviral combinations</b>	
<b>6.4.4.2.3 Other antivirals for hepatitis C</b>	
<b>6.5 Antiprotozoal medicines</b>	
<b>6.5.1 Antiamoebic and antiangiardiasis medicines</b>	
diloxanide 	<p><b>Tablet:</b> 500 mg (furoate).</p> <p> &gt; 25 kg.</p>
□ metronidazole Therapeutic alternatives: - tinidazole	<p><b>Injection:</b> 500 mg in 100 mL vial.</p> <p><b>Oral liquid:</b> 200 mg/5 mL (as benzoate).</p> <p><b>Tablet:</b> 200 mg to 500 mg.</p>
<b>6.5.2 Antileishmaniasis medicines</b>	
amphotericin B	<b>Powder for injection:</b> 50 mg in vial (as sodium deoxycholate or liposomal complex).
miltefosine	<b>Solid oral dosage form:</b> 10 mg; 50 mg.
paromomycin	<b>Solution for intramuscular injection:</b> 750 mg of paromomycin base (as sulfate).
sodium stibogluconate <b>or</b> meglumine antimoniate	<b>Injection:</b> 100 mg/mL, 1 vial = 30 mL <b>or</b> 30%, equivalent to approximately 8.1% antimony (pentavalent) in 5 mL ampoule.

# WHO Model List of Essential Medicines for Children – 8th List (2021)

<b>6.5.3 Antimalarial medicines</b>	
<b>6.5.3.1 For curative treatment</b>	
Medicines for the treatment of <i>P. falciparum</i> malaria cases should be used in combination. The list currently recommends combinations according to treatment guidelines. WHO recognizes that not all of the fixed dose combinations (FDCs in the WHO treatment guidelines exist, and encourages their development and rigorous testing. WHO also encourages development and testing of rectal dosage formulations.	
amodiaquine*	<p><b>Tablet:</b> 153 mg or 200 mg (as hydrochloride).</p> <p>*To be used in combination with artesunate 50 mg.</p>
artemether*	<p><b>Oily injection:</b> 80 mg/mL in 1 mL ampoule.</p> <p>*For use in the management of severe malaria.</p>
artemether + lumefantrine*	<p><b>Tablet:</b> 20 mg + 120 mg.</p> <p><b>Tablet (dispersible):</b> 20 mg + 120 mg.</p> <p>*Not recommended in the first trimester of pregnancy or in children below 5 kg.</p>
artesunate*	<p><b>Injection:</b> ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution.</p> <p>For use in the management of severe malaria.</p> <p><b>Rectal dosage form:</b> 50 mg; 100 mg; 200 mg capsules (for pre-referral treatment of severe malaria only; patients should be taken to an appropriate health facility for follow-up care).</p> <p><b>Tablet:</b> 50 mg.</p> <p>*To be used in combination with either amodiaquine, mefloquine or sulfadoxine + pyrimethamine.</p>
artesunate + amodiaquine *	<p><b>Tablet:</b> 25 mg + 67.5 mg; 50 mg + 135 mg; 100 mg + 270 mg.</p> <p>*Other combinations that deliver the target doses required such as 153 mg or 200 mg (as hydrochloride) with 50 mg artesunate can be alternatives.</p>
artesunate + mefloquine	<p><b>Tablet:</b> 25 mg + 55 mg; 100 mg + 220 mg.</p>
artesunate + pyronaridine tetraphosphate <sup>a</sup>	<p><b>Granules:</b> 20 mg + 60 mg.</p> <p><b>Tablet:</b> 60 mg + 180 mg.</p> <p><sup>a</sup>&gt; 5 kg</p>
chloroquine*	<p><b>Oral liquid:</b> 50 mg/5 mL (as phosphate or sulfate).</p> <p><b>Tablet:</b> 100 mg; 150 mg (as phosphate or sulfate).</p> <p>*For use only for the treatment of <i>Plasmodium vivax</i> infection.</p>
dihydroartemisinin + piperaquine phosphate <sup>a</sup>	<p><b>Tablet:</b> 20 mg + 160 mg; 40 mg + 320 mg.</p> <p><sup>a</sup>&gt; 5 kg</p>
doxycycline*	<p><b>Capsule:</b> 100 mg (as hydrochloride or hyclate).</p> <p><b>Tablet (dispersible):</b> 100 mg (as monohydrate).</p> <p>*For use only in combination with quinine.</p>

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mefloquine*	<b>Tablet:</b> 250 mg (as hydrochloride). *To be used in combination with artesunate 50 mg.
primaquine*	<b>Tablet:</b> 7.5 mg; 15 mg (as diphosphate). *Only for use to achieve radical cure of <i>Plasmodium vivax</i> and <i>Plasmodium ovale</i> infections, given for 14 days.
quinine*	<b>Injection:</b> 300 mg/mL (hydrochloride) in 2 mL ampoule. <b>Tablet:</b> 300 mg (sulfate) or 300 mg (bisulfate). *For use only in the management of severe malaria and should be used in combination with doxycycline.
sulfadoxine + pyrimethamine*	<b>Tablet:</b> 500 mg + 25 mg. *Only in combination with artesunate 50 mg.
<b>6.5.3.2 For chemoprevention</b>	
amodiaquine – sulfadoxine + pyrimethamine	<b>Co-packaged dispersible tablets:</b> amodiaquine 76.5 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 250 mg + 12.5 mg [1]; amodiaquine 153 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 500 mg + 25 mg [1].
chloroquine*	<b>Oral liquid:</b> 50 mg/5 mL (as phosphate or sulfate). <b>Tablet:</b> 150 mg (as phosphate or sulfate). *For use only for the treatment of <i>Plasmodium vivax</i> infection.
doxycycline <small>[a]</small>	<b>Solid oral dosage form:</b> 100 mg (as hydrochloride or hyclate). <small>[a]</small> > 8 years.
mefloquine <small>[a]</small>	<b>Tablet:</b> 250 mg (as hydrochloride). <small>[a]</small> > 5 kg or > 3 months.
proguanil*	<b>Tablet:</b> 100 mg (as hydrochloride). *For use only in combination with chloroquine.
sulfadoxine + pyrimethamine	<b>Tablet:</b> 250 mg + 12.5 mg.
<b>6.5.4 Antipneumocystosis and antitoxoplasmosis medicines</b>	
pyrimethamine	<b>Tablet:</b> 25 mg.
sulfadiazine	<b>Tablet:</b> 500 mg.
sulfamethoxazole + trimethoprim	<b>Injection:</b> 80 mg + 16 mg/mL in 5 mL ampoule; 80 mg + 16 mg/mL in 10 mL ampoule. <b>Oral liquid:</b> 200 mg + 40 mg/5 mL. <b>Tablet:</b> 100 mg + 20 mg; 400 mg + 80 mg.
<b>6.5.5 Antitrypanosomal medicines</b>	
<b>6.5.5.1 African trypanosomiasis</b>	
fexinidazole*	<b>Tablet:</b> 600 mg *For the treatment of 1 <sup>st</sup> and 2 <sup>nd</sup> stage of human African trypanosomiasis due to <i>Trypanosoma brucei gambiense</i> infection.

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Medicines for the treatment of 1<sup>st</sup> stage African trypanosomiasis.

pentamidine*	<b>Powder for injection:</b> 200 mg (as isetionate) in vial. *To be used for the treatment of <i>Trypanosoma brucei gambiense</i> infection.
suramin sodium*	<b>Powder for injection:</b> 1 g in vial. *To be used for the treatment of the initial phase of <i>Trypanosoma brucei rhodesiense</i> infection.

Medicines for the treatment of 2<sup>nd</sup> stage African trypanosomiasis

eflornithine*	<b>Injection:</b> 200 mg/mL (hydrochloride) in 100 mL bottle. *To be used for the treatment of <i>Trypanosoma brucei gambiense</i> infection.
nifurtimox*	<b>Tablet:</b> 120 mg. *Only to be used in combination with eflornithine, for the treatment of <i>Trypanosoma brucei gambiense</i> infection.

### Complementary List

melarsoprol	<b>Injection:</b> 180 mg/5 mL in 5 mL ampoule (3.6% solution).
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### 6.5.5.2 American trypanosomiasis

benznidazole	<b>Tablet:</b> 12.5 mg; 100 mg. <b>Tablet (scored):</b> 50 mg.
nifurtimox	<b>Tablet:</b> 30 mg; 120 mg; 250 mg.

### 6.6 Medicines for ectoparasitic infections

ivermectin	<b>Tablet (scored):</b> 3 mg
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## 7. ANTIMIGRAINE MEDICINES

### 7.1 For treatment of acute attack

ibuprofen	<b>Tablet:</b> 200 mg; 400 mg.
paracetamol	<b>Oral liquid:</b> 120 mg/5 mL; 125 mg/5 mL. <b>Tablet:</b> 300 mg to 500 mg.

### 7.2 For prophylaxis

propranolol	<b>Tablet:</b> 20 mg; 40 mg (hydrochloride).
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8. IMMUNOMODULATORS AND ANTINEOPLASTICS	
8.1 Immunomodulators for non-malignant disease	
<i>Complementary List</i>	
<input type="checkbox"/> <i>adalimumab*</i> <i>Therapeutic alternatives*:</i> - <i>etanercept</i> - <i>infliximab</i>  <i>*including quality-assured biosimilars</i>	<i>Injection:</i> 40 mg/0.8 mL; 40 mg/0.4 mL.
<i>azathioprine</i>	<i>Powder for injection:</i> 100 mg (as sodium salt) in vial. <i>Tablet (scored):</i> 50 mg.
<i>ciclosporin</i>	<i>Capsule:</i> 25 mg. <i>Concentrate for injection:</i> 50 mg/mL in 1 mL ampoule.
<i>tacrolimus</i>	<i>Capsule (immediate-release):</i> 0.5 mg; 0.75 mg; 1 mg; 2 mg; 5 mg. <i>Granules for oral suspension:</i> 0.2 mg; 1 mg. <i>Injection:</i> 5 mg/mL in 1 mL vial.
8.2 Antineoplastic and supportive medicines	
Medicines listed below should be used according to protocols for treatment of the diseases.	
8.2.1 Cytotoxic medicines	
<i>Complementary List</i>	
<i>arsenic trioxide</i>	<i>Concentrate for solution for infusion:</i> 1 mg/mL – Acute promyelocytic leukaemia
<i>asparaginase*</i> <i>*including quality-assured biosimilars</i>	<i>Powder for injection:</i> 10 000 IU in vial. – Acute lymphoblastic leukaemia
<i>bleomycin</i>	<i>Powder for injection:</i> 15 mg (as sulfate) in vial. – Hodgkin lymphoma – Kaposi sarcoma – Testicular germ cell tumours – Ovarian germ cell tumours
<i>calcium folinate</i>	<i>Injection:</i> 3 mg/mL in 10 mL ampoule. <i>Tablet:</i> 5 mg; 15 mg; 25 mg. – Burkitt lymphoma – Osteosarcoma
<i>carboplatin</i>	<i>Injection:</i> 50 mg/5 mL; 150 mg/15 mL; 450 mg/45 mL; 600 mg/60 mL. – Low-grade glioma – Nephroblastoma ( <i>Wilms tumour</i> ) – Osteosarcoma – Ovarian germ cell tumour – Retinoblastoma – Testicular germ cell tumour

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<i>cisplatin</i>	<p><b>Injection:</b> 10 mg/10 mL; 20 mg/20 mL; 50 mg/50 mL; 100 mg/100mL.</p> <ul style="list-style-type: none"> <li>– Low-grade glioma</li> <li>– Nasopharyngeal cancer</li> <li>– Osteosarcoma</li> <li>– Ovarian germ cell tumours</li> <li>– Testicular germ cell tumours</li> </ul>
<i>cyclophosphamide</i>	<p><b>Powder for injection:</b> 500 mg; 1 g; 2 g in vial. <b>Tablet:</b> 25 mg; 50 mg.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Burkitt lymphoma</li> <li>– Diffuse large B-cell lymphoma</li> <li>– Ewing sarcoma</li> <li>– Hodgkin lymphoma</li> <li>– Low-grade glioma</li> <li>– Nephroblastoma (<i>Wilms tumour</i>)</li> <li>– Rhabdomyosarcoma</li> </ul>
<i>cytarabine</i>	<p><b>Powder for injection:</b> 100 mg in vial.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Acute myeloid leukaemia</li> <li>– Acute promyelocytic leukaemia</li> <li>– Burkitt lymphoma</li> </ul>
<i>dacarbazine</i>	<p><b>Powder for injection:</b> 100 mg in vial.</p> <ul style="list-style-type: none"> <li>– Hodgkin lymphoma</li> </ul>
<i>dactinomycin</i>	<p><b>Powder for injection:</b> 500 micrograms in vial.</p> <ul style="list-style-type: none"> <li>– Ewing sarcoma</li> <li>– Nephroblastoma (<i>Wilms tumour</i>)</li> <li>– Rhabdomyosarcoma</li> </ul>
<i>daunorubicin</i>	<p><b>Powder for injection:</b> 50 mg (hydrochloride) in vial.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Acute promyelocytic leukaemia.</li> </ul>
<i>doxorubicin</i>	<p><b>Powder for injection:</b> 10 mg; 50 mg (hydrochloride) in vial.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Burkitt lymphoma</li> <li>– Diffuse large B-cell lymphoma</li> <li>– Ewing sarcoma</li> <li>– Hodgkin lymphoma</li> <li>– Kaposi sarcoma</li> <li>– Nephroblastoma (<i>Wilms tumour</i>)</li> <li>– Osteosarcoma</li> </ul>

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<i>etoposide</i>	<p><b>Capsule:</b> 50 mg; 100 mg.</p> <p><b>Injection:</b> 20 mg/mL in 5 mL ampoule.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Acute myeloid leukaemia</li> <li>– Burkitt lymphoma</li> <li>– Ewing sarcoma</li> <li>– Hodgkin lymphoma</li> <li>– Nephroblastoma (<i>Wilms tumour</i>)</li> <li>– Osteosarcoma</li> <li>– Ovarian germ cell tumours</li> <li>– Retinoblastoma</li> <li>– Testicular germ cell tumours</li> </ul>
<i>fluorouracil</i>	<p><b>Injection:</b> 50 mg/mL in 5 mL ampoule.</p> <ul style="list-style-type: none"> <li>– Early stage colon cancer</li> <li>– Early stage rectal cancer</li> <li>– Nasopharyngeal cancer</li> <li>– Metastatic colorectal cancer</li> </ul>
<i>hydroxycarbamide</i>	<p><b>Solid oral dosage form:</b> 200 mg; 250 mg; 300 mg; 400 mg; 500 mg; 1 g.</p> <ul style="list-style-type: none"> <li>– Chronic myeloid leukaemia</li> </ul>
<i>ifosfamide</i>	<p><b>Powder for injection:</b> 500 mg; 1 g; 2 g in vial.</p> <ul style="list-style-type: none"> <li>– Burkitt lymphoma</li> <li>– Ewing sarcoma</li> <li>– Nephroblastoma (<i>Wilms tumour</i>)</li> <li>– Osteosarcoma</li> <li>– Ovarian germ cell tumours</li> <li>– Rhabdomyosarcoma</li> <li>– Testicular germ cell tumours</li> </ul>
<i>irinotecan</i>	<p><b>Injection:</b> 40 mg/2 mL in 2 mL vial; 100 mg/5 mL in 5 mL vial; 500 mg/25 mL in 25 mL vial.</p> <ul style="list-style-type: none"> <li>– Metastatic colorectal cancer</li> <li>– Nephroblastoma (<i>Wilms tumour</i>)</li> <li>– Rhabdomyosarcoma</li> </ul>
<i>mercaptopurine</i>	<p><b>Tablet:</b> 50 mg.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Acute promyelocytic leukaemia</li> </ul>
<i>methotrexate</i>	<p><b>Powder for injection:</b> 50 mg (as sodium salt) in vial.</p> <p><b>Tablet:</b> 2.5 mg (as sodium salt).</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Acute promyelocytic leukaemia</li> <li>– Burkitt lymphoma</li> <li>– Osteosarcoma</li> </ul>
<i>oxaliplatin</i>	<p><b>Injection:</b> 50 mg/10 mL in 10 mL vial; 100 mg/20 mL in 20 mL vial; 200 mg/40 mL in 40 mL vial.</p> <p><b>Powder for injection:</b> 50 mg; 100 mg in vial.</p> <ul style="list-style-type: none"> <li>– Early stage colon cancer</li> <li>– Metastatic colorectal cancer</li> </ul>

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<i>paclitaxel</i>	<b>Injection:</b> 6 mg/mL in vial. – Ovarian germ cell tumours
<i>pegaspargase*</i> *including quality-assured biosimilars	<b>Injection:</b> 3,750 units/5 mL in vial – Acute lymphoblastic leukaemia.
<i>procarbazine</i>	<b>Capsule:</b> 50 mg (as hydrochloride). – Hodgkin lymphoma
<i>realgar-Indigo naturalis formulation</i>	<b>Tablet:</b> 270 mg (containing tetra-arsenic tetra-sulfide 30 mg) – Acute promyelocytic leukaemia
<i>tioguanine</i>	<b>Solid oral dosage form:</b> 40 mg. – Acute lymphoblastic leukaemia.
<i>vinblastine</i>	<b>Injection:</b> 10 mg/10 mL (sulfate) in vial. <b>Powder for injection:</b> 10 mg (sulfate) in vial. – Hodgkin lymphoma – Low-grade glioma – Ovarian germ cell tumours – Testicular germ cell tumours
<i>vincristine</i>	<b>Injection:</b> 1 mg/mL (sulfate); 2 mg/2 mL (sulfate) in vial. <b>Powder for injection:</b> 1 mg; 5 mg (sulfate) in vial. – Acute lymphoblastic leukaemia – Burkitt lymphoma. – Diffuse large B-cell lymphoma – Ewing sarcoma – Hodgkin lymphoma – Kaposi sarcoma – Low-grade glioma – Nephroblastoma (Wilms tumour) – Retinoblastoma – Rhabdomyosarcoma
<i>vinorelbine</i>	<b>Capsule:</b> 20 mg; 30 mg; 80 mg. <b>Injection:</b> 10 mg/mL in 1 mL vial; 50 mg/5 mL in 5 mL vial. – Rhabdomyosarcoma

### 8.2.2 Targeted therapies

#### Complementary List

<i>all-trans retinoid acid (ATRA)</i>	<b>Capsule:</b> 10 mg. – Acute promyelocytic leukaemia
<i>dasatinib</i>	<b>Tablet:</b> 20 mg; 50 mg; 70 mg; 80 mg; 100 mg; 140 mg. – Imatinib-resistant chronic myeloid leukaemia
<i>everolimus</i>	<b>Tablet:</b> 2.5 mg; 5 mg; 7.5 mg; 10 mg. <b>Tablet (dispersible):</b> 2 mg; 3 mg; 5 mg. – Subependymal giant cell astrocytoma

# WHO Model List of Essential Medicines for Children – 8th List (2021)

<i>imatinib</i>	<p><b>Solid oral dosage form:</b> 100 mg; 400 mg.</p> <ul style="list-style-type: none"> <li>– Chronic myeloid leukaemia</li> <li>– Gastrointestinal stromal tumour</li> <li>– Philadelphia chromosome positive acute lymphoblastic leukaemia</li> </ul>
<i>nilotinib</i>	<p><b>Capsule:</b> 150 mg; 200 mg.</p> <ul style="list-style-type: none"> <li>– Imatinib-resistant chronic myeloid leukaemia</li> </ul>
<i>rituximab*</i> <small>*including quality-assured biosimilars</small>	<p><b>Injection (intravenous):</b> 100 mg/10 mL in 10 mL vial; 500 mg/50 mL in 50 mL vial.</p> <ul style="list-style-type: none"> <li>– Diffuse large B-cell lymphoma</li> </ul>

## 8.2.3 Immunomodulators

### Complementary List

<i>filgrastim*</i> <small>*including quality-assured biosimilars</small>	<p><b>Injection:</b> 120 micrograms/0.2 mL; 300 micrograms/0.5 mL; 480 micrograms/0.8 mL in pre-filled syringe.</p> <p><b>Injection:</b> 300 micrograms/mL in 1 mL vial; 480 micrograms/1.6 mL in 1.6 mL vial.</p> <ul style="list-style-type: none"> <li>– Primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy.</li> <li>– Secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy</li> <li>– To facilitate administration of dose dense chemotherapy regimens</li> </ul>
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## 8.2.4 Hormones and antihormones

### Complementary List

<i>dexamethasone</i>	<p><b>Injection:</b> 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule.</p> <p><b>Oral liquid:</b> 2 mg/5 mL.</p> <p><b>Tablet:</b> 2 mg; 4 mg.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Burkitt lymphoma</li> </ul>
<i>hydrocortisone</i>	<p><b>Powder for injection:</b> 100 mg (as sodium succinate) in vial.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Burkitt lymphoma</li> </ul>
<i>methylprednisolone</i>	<p><b>Injection:</b> 40 mg/mL (as sodium succinate) in 1 mL single-dose vial and 5 mL multi-dose vials; 80 mg/mL (as sodium succinate) in 1 mL single-dose vial.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukemia</li> <li>– Burkitt lymphoma</li> </ul>

# WHO Model List of Essential Medicines for Children – 8th List (2021)

<input type="checkbox"/> prednisolone <i>Therapeutic alternatives:</i> - prednisone	<b>Oral liquid:</b> 5 mg/mL. <b>Tablet:</b> 5 mg; 25 mg. <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Burkitt lymphoma</li> <li>– Diffuse large B-cell lymphoma</li> <li>– Hodgkin lymphoma</li> </ul>
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## 8.2.5 Supportive medicines

### Complementary List

<i>allopurinol</i>	<b>Tablet:</b> 100 mg; 300 mg. <ul style="list-style-type: none"> <li>– Tumour lysis syndrome</li> </ul>
<i>mesna</i>	<b>Injection:</b> 100 mg/mL in 4 mL and 10 mL ampoules. <b>Tablet:</b> 400 mg; 600 mg. <ul style="list-style-type: none"> <li>– Burkitt lymphoma</li> <li>– Ewing sarcoma</li> <li>– Nephroblastoma (<i>Wilms tumour</i>)</li> <li>– Osteosarcoma</li> <li>– Ovarian germ cell tumours</li> <li>– Rhabdomyosarcoma</li> <li>– Testicular germ cell tumours</li> </ul>
<i>rasburicase</i>	<b>Powder and solvent for solution for infusion:</b> 1.5 mg; 7.5 mg in vial <ul style="list-style-type: none"> <li>– Tumour lysis syndrome</li> </ul>

## 9. ANTIPARKINSONISM MEDICINES

## 10. MEDICINES AFFECTING THE BLOOD

### 10.1 Antianaemia medicines

<i>ferrous salt</i>	<b>Oral liquid:</b> equivalent to 25 mg iron (as sulfate)/mL. <b>Tablet:</b> equivalent to 60 mg iron.
<i>folic acid</i>	<b>Tablet:</b> 1 mg; 5 mg.
<i>hydroxocobalamin</i>	<b>Injection:</b> 1 mg (as acetate, as hydrochloride or as sulfate) in 1 mL ampoule.

### Complementary List

<input type="checkbox"/> erythropoiesis-stimulating agents <i>Therapeutic alternatives:</i> - epoetin alfa, beta and theta - darbepoetin alfa <i>*including quality-assured biosimilars</i>	<b>Injection: pre-filled syringe</b> 1000 IU/0.5 mL; 2000 IU/0.5 mL; 3000 IU/0.3 mL; 4000 IU/0.4 mL; 5000 IU/0.5 mL; 6000 IU/0.6 mL; 8000 IU/0.8mL; 10 000 IU/1 mL; 20 000 IU/0.5 mL; 40 000 IU/1 mL.
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### 10.2 Medicines affecting coagulation

<input type="checkbox"/> enoxaparin <i>Therapeutic alternatives:</i> - dalteparin - nadroparin <i>*including quality-assured biosimilars</i>	<b>Injection: ampoule or pre-filled syringe</b> 20 mg/0.2 mL; 40 mg/0.4 mL; 60 mg/0.6 mL; 80 mg/0.8 mL; 100 mg/1 mL; 120 mg/0.8 mL; 150 mg/1 mL.
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# WHO Model List of Essential Medicines for Children – 8th List (2021)

phytomenadione	<b>Injection:</b> 1 mg/mL; 10 mg/mL in ampoule. <b>Tablet:</b> 10 mg.
<b>Complementary List</b>	
desmopressin	<b>Injection:</b> 4 micrograms/mL (as acetate) in 1 mL ampoule. <b>Nasal spray:</b> 10 micrograms (as acetate) per dose.
heparin sodium	<b>Injection:</b> 1000 IU/mL; 5000 IU/mL in 1 mL ampoule.
protamine sulfate	<b>Injection:</b> 10 mg/mL in 5 mL ampoule.
<input type="checkbox"/> warfarin Therapeutic alternatives to be reviewed (2023)	<b>Tablet:</b> 0.5 mg; 1 mg; 2 mg; 5 mg (sodium).
<b>10.3 Other medicines for haemoglobinopathies</b>	
<b>Complementary list</b>	
<input type="checkbox"/> deferoxamine* Therapeutic alternatives: - deferasirox (oral)	<b>Powder for injection:</b> 500 mg (mesilate) in vial.
hydroxycarbamide	<b>Solid oral dosage form:</b> 200 mg; 500 mg; 1 g.
<b>11. BLOOD PRODUCTS OF HUMAN ORIGIN AND PLASMA SUBSTITUTES</b>	
<b>11.1 Blood and blood components</b>	
In accordance with the World Health Assembly resolution WHA63.12, WHO recognizes that achieving self-sufficiency, unless special circumstances preclude it, in the supply of safe blood components based on voluntary, non-remunerated blood donation, and the security of that supply are important national goals to prevent blood shortages and meet the transfusion requirements of the patient population. All preparations should comply with the WHO requirements.	
fresh-frozen plasma	
platelets	
red blood cells	
whole blood	
<b>11.2 Plasma-derived medicines</b>	
All human plasma-derived medicines should comply with the WHO requirements.	
<b>11.2.1 Human immunoglobulins</b>	
anti-rabies immunoglobulin	<b>Injection:</b> 150 IU/mL in vial.
anti-tetanus immunoglobulin	<b>Injection:</b> 500 IU in vial.
<b>Complementary List</b>	
normal immunoglobulin	<b>Intramuscular administration:</b> 16% protein solution.* <b>Intravenous administration:</b> 5%; 10% protein solution.** <b>Subcutaneous administration:</b> 15%; 16% protein solution.* *Indicated for primary immune deficiency. **Indicated for primary immune deficiency and Kawasaki disease.

# WHO Model List of Essential Medicines for Children – 8th List (2021)

<b>11.2.2 Blood coagulation factors</b>	
<i>Complementary List</i>	
<input type="checkbox"/> coagulation factor VIII Therapeutic alternatives to be reviewed (2023)	<b>Powder for injection:</b> 500 IU/vial.
<input type="checkbox"/> coagulation factor IX Therapeutic alternatives to be reviewed (2023)	<b>Powder for injection:</b> 500 IU/vial, 1000 IU/vial.
<b>11.3 Plasma substitutes</b>	
<input type="checkbox"/> dextran 70 Therapeutic alternatives: - Polygeline injectable solution 3.5%	<b>Injectable solution:</b> 6%.
<b>12. CARDIOVASCULAR MEDICINES</b>	
<b>12.1 Antianginal medicines</b>	
<b>12.2 Antiarrhythmic medicines</b>	
<b>12.3 Antihypertensive medicines</b>	
<input type="checkbox"/> enalapril Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (C09AA ACE inhibitors, plain)	<b>Tablet:</b> 2.5 mg; 5 mg (as hydrogen maleate).
<b>12.4 Medicines used in heart failure</b>	
digoxin	<b>Injection:</b> 250 micrograms/mL in 2 mL ampoule. <b>Oral liquid:</b> 50 micrograms/mL. <b>Tablet:</b> 62.5 micrograms; 250 micrograms.
furosemide	<b>Injection:</b> 10 mg/mL in 2 mL ampoule. <b>Oral liquid:</b> 20 mg/5 mL. <b>Tablet:</b> 40 mg.
<i>Complementary List</i>	
dopamine	<b>Injection:</b> 40 mg/mL (hydrochloride) in 5 mL vial.
<b>12.5 Antithrombotic medicines</b>	
<b>12.6 Lipid-lowering agents</b>	

# WHO Model List of Essential Medicines for Children – 8th List (2021)

<b>13. DERMATOLOGICAL MEDICINES (topical)</b>	
<b>13.1 Antifungal medicines</b>	
<input type="checkbox"/> miconazole Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (D01AC Imidazole and triazole derivatives) excluding combinations	<b>Cream or ointment:</b> 2% (nitrate).
terbinafine	<b>Cream or ointment:</b> 1% (hydrochloride).
<b>13.2 Anti-infective medicines</b>	
mupirocin	<b>Cream:</b> 2% (as calcium). <b>Ointment:</b> 2%.
potassium permanganate	<b>Aqueous solution:</b> 1:10 000.
silver sulfadiazine <sup>a</sup>	<b>Cream:</b> 1%. <sup>a</sup> > 2 months.
<b>13.3 Anti-inflammatory and antipruritic medicines</b>	
<input type="checkbox"/> betamethasone <sup>a</sup> Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (D07AC Corticosteroids, potent (group III))	<b>Cream or ointment:</b> 0.1% (as valerate). <sup>a</sup> Hydrocortisone preferred in neonates.
calamine	<b>Lotion.</b>
hydrocortisone	<b>Cream or ointment:</b> 1% (acetate).
<b>13.4 Medicines affecting skin differentiation and proliferation</b>	
benzoyl peroxide	<b>Cream or lotion:</b> 5%.
<input type="checkbox"/> calcipotriol Therapeutic alternatives: - calcitriol - tacalcitol	<b>Cream or ointment:</b> 50 micrograms/mL (0.005%). <b>Lotion:</b> 50 micrograms/mL (0.005%).
coal tar	<b>Solution:</b> 5%.
<input type="checkbox"/> podophyllum resin Therapeutic alternatives: - podophyllotoxin	<b>Solution:</b> 10% to 25%.
salicylic acid	<b>Solution:</b> 5%.
urea	<b>Cream or ointment:</b> 5%; 10%.
<b>13.5 Scabicides and pediculicides</b>	
<input type="checkbox"/> benzyl benzoate <sup>a</sup> Therapeutic alternatives: - precipitated sulfur topical ointment	<b>Lotion:</b> 25%. <sup>a</sup> > 2 years.
permethrin	<b>Cream:</b> 5%. <b>Lotion:</b> 1%.

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14. DIAGNOSTIC AGENTS	
14.1 Ophthalmic medicines	
fluorescein	<b>Eye drops:</b> 1% (sodium salt).
<input type="checkbox"/> tropicamide Therapeutic alternatives: - atropine - cyclopentolate	<b>Eye drops:</b> 0.5%.
14.2 Radiocontrast media	
<i>Complementary List</i>	
barium sulfate	<b>Aqueous suspension.</b>
15. ANTISEPTICS AND DISINFECTANTS	
15.1 Antiseptics	
<input type="checkbox"/> chlorhexidine Therapeutic alternatives to be reviewed (2023)	<b>Solution:</b> 5% (digluconate).
<input type="checkbox"/> ethanol Therapeutic alternatives: - propanol	<b>Solution:</b> 70% (denatured).
<input type="checkbox"/> povidone iodine Therapeutic alternatives - iodine	<b>Solution:</b> 10% (equivalent to 1% available iodine).
15.2 Disinfectants	
alcohol based hand rub	<b>Solution</b> containing ethanol 80% volume /volume. <b>Solution</b> containing isopropyl alcohol 75% volume/volume.
chlorine base compound	<b>Liquid:</b> (0.1% available chlorine) for solution. <b>Powder:</b> (0.1% available chlorine) for solution. <b>Solid:</b> (0.1% available chlorine) for solution.
<input type="checkbox"/> chloroxylenol Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (D08AE Phenol and derivatives)	<b>Solution:</b> 4.8%.
glutaral	<b>Solution:</b> 2%.

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## 16. DIURETICS

furosemide	<b>Injection:</b> 10 mg/mL in 2 mL ampoule. <b>Oral liquid:</b> 20 mg/5 mL. <b>Tablet:</b> 10 mg; 20 mg; 40 mg.
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### Complementary List

<input type="checkbox"/> hydrochlorothiazide Therapeutic alternatives: - chlorothiazide - chlortalidone	<b>Tablet (scored):</b> 25 mg.
mannitol	<b>Injectable solution:</b> 10%; 20%.
spironolactone	<b>Oral liquid:</b> 5 mg/5 mL; 10 mg/5 mL; 25 mg/5 mL. <b>Tablet:</b> 25 mg.

## 17. GASTROINTESTINAL MEDICINES

### Complementary List

pancreatic enzymes	Age-appropriate formulations and doses including lipase, protease and amylase.
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### 17.1 Antiulcer medicines

<input type="checkbox"/> omeprazole Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (A02BC Proton pump inhibitors) excluding combinations	<b>Powder for oral liquid:</b> 20 mg; 40 mg sachets. <b>Solid oral dosage form:</b> 10 mg; 20 mg; 40 mg.
<input type="checkbox"/> ranitidine - 4 <sup>th</sup> level ATC chemical subgroup (A02BA H <sub>2</sub> -receptor antagonists) excluding combinations	<b>Injection:</b> 25 mg/mL (as hydrochloride) in 2 mL ampoule. <b>Oral liquid:</b> 75 mg/5 mL (as hydrochloride). <b>Tablet:</b> 150 mg (as hydrochloride).

### 17.2 Antiemetic medicines

dexamethasone	<b>Injection:</b> 4 mg/mL in 1 mL ampoule (as disodium phosphate salt). <b>Oral liquid:</b> 0.5 mg/5 mL; 2 mg/5 mL. <b>Solid oral dosage form:</b> 0.5 mg; 0.75 mg; 1.5 mg; 4 mg.
metoclopramide <sup>a</sup>	<b>Injection:</b> 5 mg/mL (hydrochloride) in 2 mL ampoule. <b>Oral liquid:</b> 5 mg/5 mL. <b>Tablet:</b> 10 mg (hydrochloride). <sup>a</sup> Not in neonates.
<input type="checkbox"/> ondansetron <sup>a</sup> Therapeutic alternatives: - dolasetron - granisetron - palonosetron - tropisetron	<b>Injection:</b> 2 mg base/mL in 2 mL ampoule (as hydrochloride). <b>Oral liquid:</b> 4 mg base/5 mL. <b>Solid oral dosage form:</b> Eq 4 mg base; Eq 8 mg base. <sup>a</sup> > 1 month.

# WHO Model List of Essential Medicines for Children – 8th List (2021)

<i>Complementary list</i>																					
aprepitant	<p><b>Capsule:</b> 80 mg; 125 mg; 165 mg</p> <p><b>Powder for oral susension:</b> 125 mg in sachet</p>																				
17.3 Anti-inflammatory medicines																					
17.4 Laxatives																					
17.5 Medicines used in diarrhoea																					
oral rehydration salts – zinc sulfate	<p><b>Co-package containing:</b></p> <p>ORS powder for dilution (see Section 17.5.1) – zinc sulfate <b>solid oral dosage form</b> 20 mg (see Section 17.5.2)</p>																				
17.5.1 Oral rehydration																					
oral rehydration salts	<p><b>Powder for dilution</b> in 200 mL; 500 mL; 1 L.</p> <table> <tbody> <tr> <td>glucose:</td> <td>75 mEq</td> </tr> <tr> <td>sodium:</td> <td>75 mEq or mmol/L</td> </tr> <tr> <td>chloride:</td> <td>65 mEq or mmol/L</td> </tr> <tr> <td>potassium:</td> <td>20 mEq or mmol/L</td> </tr> <tr> <td>citrate:</td> <td>10 mmol/L</td> </tr> <tr> <td>osmolarity:</td> <td>245 mOsm/L</td> </tr> <tr> <td>glucose:</td> <td>13.5 g/L</td> </tr> <tr> <td>sodium chloride:</td> <td>2.6 g/L</td> </tr> <tr> <td>potassium chloride:</td> <td>1.5 g/L</td> </tr> <tr> <td>trisodium citrate dihydrate*:</td> <td>2.9 g/L</td> </tr> </tbody> </table> <p>*trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/L. However, as the stability of this latter formulation is very poor under tropical conditions, it is recommended only when manufactured for immediate use.</p>	glucose:	75 mEq	sodium:	75 mEq or mmol/L	chloride:	65 mEq or mmol/L	potassium:	20 mEq or mmol/L	citrate:	10 mmol/L	osmolarity:	245 mOsm/L	glucose:	13.5 g/L	sodium chloride:	2.6 g/L	potassium chloride:	1.5 g/L	trisodium citrate dihydrate*:	2.9 g/L
glucose:	75 mEq																				
sodium:	75 mEq or mmol/L																				
chloride:	65 mEq or mmol/L																				
potassium:	20 mEq or mmol/L																				
citrate:	10 mmol/L																				
osmolarity:	245 mOsm/L																				
glucose:	13.5 g/L																				
sodium chloride:	2.6 g/L																				
potassium chloride:	1.5 g/L																				
trisodium citrate dihydrate*:	2.9 g/L																				
17.5.2 Medicines for diarrhoea																					
zinc sulfate*	<p><b>Solid oral dosage form:</b> 20 mg.</p> <p>*In acute diarrhoea, zinc sulfate should be used as an adjunct to oral rehydration salts.</p>																				
18. MEDICINES FOR ENDOCRINE DISORDERS																					
18.1 Adrenal hormones and synthetic substitutes																					
fludrocortisone	<b>Tablet:</b> 100 micrograms (acetate).																				
hydrocortisone	<b>Tablet:</b> 5 mg; 10 mg; 20 mg.																				
18.2 Androgens																					
18.3 Estrogens																					
18.4 Progestogens																					

# WHO Model List of Essential Medicines for Children – 8th List (2021)

<b>18.5 Medicines for diabetes</b>	
<b>18.5.1 Insulins</b>	
insulin injection (soluble)* <i>*including quality-assured biosimilars</i>	<b>Injection:</b> 100 IU/mL in 10 mL vial.
intermediate-acting insulin* <i>*including quality-assured biosimilars</i>	<b>Injection:</b> 100 IU/mL in 10 mL vial (as compound insulin zinc suspension or isophane insulin).
<input type="checkbox"/> long-acting insulin analogues*  Therapeutic alternatives:  - insulin detemir - insulin degludec - insulin glargine  <i>*including quality-assured biosimilars</i>	  <b>Injection:</b> 100 IU/mL in 3 mL cartridge or pre-filled pen.
<b>18.5.2 Oral hypoglycaemic agents</b>	
<i>Complementary List</i>	
metformin	<b>Tablet:</b> 500 mg (hydrochloride).
<b>18.6 Medicines for hypoglycaemia</b>	
glucagon	<b>Injection:</b> 1 mg/mL.
<i>Complementary List</i>	
diazoxide	<b>Oral liquid:</b> 50 mg/mL <b>Tablet:</b> 50 mg
<b>18.7 Thyroid hormones and antithyroid medicines</b>	
levothyroxine	<b>Tablet:</b> 25 micrograms; 50 micrograms; 100 micrograms (sodium salt).
<i>Complementary List</i>	
Lugol's solution	<b>Oral liquid:</b> about 130 mg total iodine/mL.
<input type="checkbox"/> methimazole  Therapeutic alternatives:  - carbimazole (depending on local availability)	<b>Tablet:</b> 5mg, 10mg, 20mg.
potassium iodide	<b>Tablet:</b> 60 mg.
propylthiouracil*	<b>Tablet:</b> 50 mg.  <i>*For use when alternative first-line treatment is not appropriate or available</i>

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19. IMMUNOLOGICALS	
<b>19.1 Diagnostic agents</b>	
All tuberculins should comply with the WHO requirements for tuberculins.	
tuberculin, purified protein derivative (PPD)	<b>Injection.</b>
<b>19.2 Sera, immunoglobulins and monoclonal antibodies</b>	
All plasma fractions should comply with the WHO requirements.	
anti-rabies virus monoclonal antibodies*	<b>Injection:</b> 40 IU/mL in 1.25 mL, 2.5 mL vial; 100 IU/mL in 2.5 mL vial (human).
*including quality-assured biosimilars	<b>Injection:</b> 300 IU/mL in 10 mL vial; 600 IU/mL in 1 mL, 2.5 mL and 5 mL vial (murine).
antivenom immunoglobulin*	<b>Injection.</b> *Exact type to be defined locally.
diphtheria antitoxin	<b>Injection:</b> 10 000 IU; 20 000 IU in vial.
equine rabies immunoglobulin	<b>Injection:</b> 150 IU/mL; 200 IU/mL; 300 IU/mL; 400 IU/mL in vial
<b>19.3 Vaccines</b>	
WHO immunization policy recommendations are published in vaccine position papers on the basis of recommendations made by the Strategic Advisory Group of Experts on Immunization (SAGE).	
WHO vaccine position papers are updated three to four times per year. The list below details the vaccines for which there is a recommendation from SAGE and a corresponding WHO position paper as at September 2020. The most recent versions of the WHO position papers, reflecting the current evidence related to a specific vaccine and the related recommendations, can be accessed at any time on the WHO website at:	
<p><a href="https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers">https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers</a></p> <p>Vaccine recommendations may be universal or conditional (e.g., in certain regions, in some high-risk populations or as part of immunization programmes with certain characteristics). Details are available in the relevant position papers, and in the Summary Tables of WHO Routine Immunization Recommendations available on the WHO website at:</p> <p><a href="https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/who-recommendations-for-routine-immunization---summary-tables">https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/who-recommendations-for-routine-immunization---summary-tables</a></p> <p>Selection of vaccines from the Model List will need to be determined by each country after consideration of international recommendations, epidemiology and national priorities.</p> <p>All vaccines should comply with the WHO requirements for biological substances.</p> <p>WHO noted the need for vaccines used in children to be polyvalent.</p>	
<b>Recommendations for all</b>	
BCG vaccine	
diphtheria vaccine	
Haemophilus influenzae type b vaccine	
hepatitis B vaccine	
human papilloma virus (HPV) vaccine	
measles vaccine	
pertussis vaccine	
pneumococcal vaccine	
poliomyelitis vaccine	

## WHO Model List of Essential Medicines for Children – 8th List (2021)

rotavirus vaccine	
rubella vaccine	
tetanus vaccine	
<i>Recommendations for certain regions</i>	
Japanese encephalitis vaccine	
tick-borne encephalitis vaccine	
yellow fever vaccine	
<i>Recommendations for some high-risk populations</i>	
cholera vaccine	
dengue vaccine	
hepatitis A vaccine	
meningococcal meningitis vaccine	
rabies vaccine	
typhoid vaccine	
<i>Recommendations for immunization programmes with certain characteristics</i>	
influenza vaccine (seasonal)	
mumps vaccine	
varicella vaccine	

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20. MUSCLE RELAXANTS (PERIPHERALLY-ACTING) AND CHOLINESTERASE INHIBITORS	
neostigmine	<p><b>Injection:</b> 500 micrograms/mL (methylsulfate) in 1 mL ampoule; 2.5 mg/mL (methylsulfate) in 1 mL ampoule.</p> <p><b>Tablet:</b> 15 mg (bromide).</p>
suxamethonium	<p><b>Injection:</b> 50 mg/mL (chloride) in 2 mL ampoule.</p> <p><b>Powder for injection:</b> (chloride), in vial.</p>
<input type="checkbox"/> vecuronium Therapeutic alternatives to be reviewed (2023)	<b>Powder for injection:</b> 10 mg (bromide) in vial.
<i>Complementary List</i>	
pyridostigmine	<p><b>Injection:</b> 1 mg in 1 mL ampoule.</p> <p><b>Tablet:</b> 60 mg (bromide).</p>
21. OPHTHALMOLOGICAL PREPARATIONS	
21.1 Anti-infective agents	
aciclovir	<b>Ointment:</b> 3% w/w.
azithromycin	<p><b>Solution (eye drops):</b> 1.5%</p> <ul style="list-style-type: none"> <li>– Trachoma</li> </ul>
erythromycin	<p><b>Ointment:</b> 0.5%</p> <ul style="list-style-type: none"> <li>– <i>Infections due to Chlamydia trachomatis or Neisseria gonorrhoeae.</i></li> </ul>
<input type="checkbox"/> gentamicin Therapeutic alternatives: - amikacin - kanamycin - netilmicin - tobramycin	<p><b>Solution (eye drops):</b> 0.3% (sulfate).</p> <ul style="list-style-type: none"> <li>– <i>Bacterial blepharitis</i></li> <li>– <i>Bacterial conjunctivitis</i></li> </ul>
natamycin	<p><b>Suspension (eye drops):</b> 5%</p> <ul style="list-style-type: none"> <li>– <i>Fungal keratitis</i></li> </ul>
<input type="checkbox"/> ofloxacin Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (S01AE Fluoroquinolones)	<p><b>Solution (eye drops):</b> 0.3%.</p> <ul style="list-style-type: none"> <li>– <i>Bacterial conjunctivitis</i></li> <li>– <i>Bacterial keratitis</i></li> </ul>
<input type="checkbox"/> tetracycline Therapeutic alternatives: - chlortetracycline - oxytetracycline	<p><b>Eye ointment:</b> 1% (hydrochloride).</p> <ul style="list-style-type: none"> <li>– <i>Bacterial blepharitis</i></li> <li>– <i>Bacterial conjunctivitis</i></li> <li>– <i>Bacterial keratitis</i></li> <li>– <i>Trachoma</i></li> </ul>
21.2 Anti-inflammatory agents	
<input type="checkbox"/> prednisolone Therapeutic alternatives to be reviewed (2023)	<b>Solution (eye drops):</b> 0.5% (sodium phosphate).

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<b>21.3 Local anaesthetics</b>	
<input type="checkbox"/> tetracaine <small>a</small> Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (S01HA Local anaesthetics) excluding cocaine and combinations	<b>Solution (eye drops):</b> 0.5% (hydrochloride). <small>a</small> Not in preterm neonates.
<b>21.4 Miotics and antiglaucoma medicines</b>	
<b>21.5 Mydriatics</b>	
<input type="checkbox"/> atropine <small>a</small> Therapeutic alternatives: - homatropine hydrobromide - cyclopentolate hydrochloride	<b>Solution (eye drops):</b> 0.1%; 0.5%; 1% (sulfate). <small>a</small> > 3 months.
<i>Complementary List</i> epinephrine (adrenaline)	
epinephrine (adrenaline)	<b>Solution (eye drops):</b> 2% (as hydrochloride).
<b>21.6 Anti-vascular endothelial growth factor (VEGF) preparations</b>	
<b>22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE</b>	
<b>22.1 Contraceptives</b>	
<b>22.2 Ovulation inducers</b>	
<b>22.3 Uterotonics</b>	
<b>22.4 Antioxytocics (tocolytics)</b>	
<b>22.5 Other medicines administered to the mother</b>	
<b>22.6 Medicines administered to the neonate</b>	
caffeine citrate	<b>Injection:</b> 20 mg/mL (equivalent to 10 mg caffeine base/mL). <b>Oral liquid:</b> 20 mg/mL (equivalent to 10 mg caffeine base/mL).
chlorhexidine	<b>Solution or gel:</b> 7.1% (digluconate) delivering 4% chlorhexidine (for umbilical cord care).
<i>Complementary List</i> <input type="checkbox"/> ibuprofen Therapeutic alternatives: - indometacin	
	<b>Solution for injection:</b> 5 mg/mL.
<input type="checkbox"/> prostaglandin E1 Therapeutic alternatives: - prostaglandin E2	<b>Solution for injection:</b> 0.5 mg/mL in alcohol.
surfactant	<b>Suspension for intratracheal instillation:</b> 25 mg/mL or 80 mg/mL
<b>23. PERITONEAL DIALYSIS SOLUTION</b>	
<i>Complementary List</i> intraperitoneal dialysis solution (of appropriate composition)	
intraperitoneal dialysis solution (of appropriate composition)	<b>Parenteral solution.</b>

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<b>24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS</b>	
24.1 Medicines used in psychotic disorders	
<i>Complementary List</i>	
chlorpromazine	<p><i>Injection:</i> 25 mg/mL (hydrochloride) in 2 mL ampoule.</p> <p><i>Oral liquid:</i> 25 mg/5 mL (hydrochloride).</p> <p><i>Tablet:</i> 10 mg; 25 mg; 50 mg; 100 mg (hydrochloride).</p>
haloperidol	<p><i>Injection:</i> 5 mg in 1 mL ampoule.</p> <p><i>Oral liquid:</i> 2 mg/mL.</p> <p><i>Solid oral dosage form:</i> 0.5 mg; 2 mg; 5 mg.</p>
24.2 Medicines used in mood disorders	
24.2.1 Medicines used in depressive disorders	
<i>Complementary List</i>	
fluoxetine <small>a</small>	<p><i>Solid oral dosage form:</i> 20 mg (as hydrochloride).</p> <p><small>a</small> &gt; 8 years.</p>
24.2.2 Medicines used in bipolar disorders	
24.3 Medicines for anxiety disorders	
24.4 Medicines used for obsessive compulsive disorders	
24.5 Medicines for disorders due to psychoactive substance use	
<b>25. MEDICINES ACTING ON THE RESPIRATORY TRACT</b>	
25.1 Antiasthmatic medicines	
<input type="checkbox"/> budesonide Therapeutic alternatives: - beclometasone - ciclesonide - flunisolide - fluticasone - mometasone	<p><i>Inhalation (aerosol):</i> 100 micrograms per dose; 200 micrograms per dose.</p>
epinephrine (adrenaline)	<p><i>Injection:</i> 1 mg/mL (as hydrochloride or hydrogen tartrate) in 1 mL ampoule.</p>
<input type="checkbox"/> salbutamol Therapeutic alternatives: - terbutaline	<p><i>Injection:</i> 50 micrograms/mL (as sulfate) in 5 mL ampoule.</p> <p><i>Metered dose inhaler (aerosol):</i> 100 micrograms (as sulfate) per dose.</p> <p><i>Respirator solution for use in nebulizers:</i> 5 mg/mL (as sulfate).</p>
<b>26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID-BASE DISTURBANCES</b>	
26.1 Oral	
oral rehydration salts	See section 17.5.1.
potassium chloride	Powder for solution.

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26.2 Parenteral	
glucose	<b>Injectable solution:</b> 5% (isotonic); 10% (hypertonic); 50% (hypertonic).
glucose with sodium chloride	<b>Injectable solution:</b> 5% glucose, 0.9% sodium chloride (equivalent to Na <sup>+</sup> 150 mmol/L and Cl <sup>-</sup> 150 mmol/L); 5% glucose, 0.45% sodium chloride (equivalent to Na <sup>+</sup> 75 mmol/L and Cl <sup>-</sup> 75 mmol/L).
potassium chloride	<b>Solution for dilution:</b> 7.5% (equivalent to K <sup>+</sup> 1 mmol/mL and Cl <sup>-</sup> 1 mmol/mL); 15% (equivalent to K <sup>+</sup> 2 mmol/mL and Cl <sup>-</sup> 2 mmol/mL).
sodium chloride	<b>Injectable solution:</b> 0.9% isotonic (equivalent to Na <sup>+</sup> 154 mmol/L, Cl <sup>-</sup> 154 mmol/L).
sodium hydrogen carbonate	<b>Injectable solution:</b> 1.4% isotonic (equivalent to Na <sup>+</sup> 167 mmol/L, HCO <sub>3</sub> <sup>-</sup> 167 mmol/L). <b>Solution:</b> 8.4% in 10 mL ampoule (equivalent to Na <sup>+</sup> 1000 mmol/L, HCO <sub>3</sub> <sup>-</sup> 1000 mmol/L).
sodium lactate, compound solution	<b>Injectable solution.</b>
26.3 Miscellaneous	
water for injection	2 mL; 5 mL; 10 mL ampoules.
27. VITAMINS AND MINERALS	
ascorbic acid	<b>Tablet:</b> 50 mg.
<input type="checkbox"/> colecalciferol Therapeutic alternatives: - ergocalciferol	<b>Oral liquid:</b> 400 IU/mL. <b>Solid oral dosage form:</b> 400 IU; 1000 IU.
iodine	<b>Capsule:</b> 190 mg. <b>Iodized oil:</b> 1 mL (480 mg iodine); 0.5 mL (240 mg iodine) in ampoule (oral or injectable); 0.57 mL (308 mg iodine) in dispenser bottle.
multiple micronutrient powder	<b>Sachets containing:</b> - iron (elemental) 12.5 mg (as coated ferrous fumarate) - zinc (elemental) 5 mg - vitamin A 300 micrograms - with or without other micronutrients at recommended daily values
pyridoxine	<b>Tablet:</b> 25 mg (hydrochloride).
retinol	<b>Capsule:</b> 100 000 IU; 200 000 IU (as palmitate). <b>Oral oily solution:</b> 100 000 IU/mL (as palmitate) in multidose dispenser. <b>Tablet (sugar-coated):</b> 10 000 IU (as palmitate). <b>Water-miscible injection:</b> 100 000 IU (as palmitate) in 2 mL ampoule.
riboflavin	<b>Tablet:</b> 5 mg.
thiamine	<b>Tablet:</b> 50 mg (hydrochloride).
<i>Complementary List</i>	
calcium gluconate	<b>Injection:</b> 100 mg/mL in 10 mL ampoule.

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28. EAR, NOSE AND THROAT MEDICINES	
acetic acid	<b>Topical:</b> 2%, in alcohol.
<input type="checkbox"/> budesonide Therapeutic alternatives to be reviewed (2023)	<b>Nasal spray:</b> 100 micrograms per dose.
<input type="checkbox"/> ciprofloxacin Therapeutic alternatives: - ofloxacin	<b>Solution (ear drops):</b> 0.3% (as hydrochloride).
<input type="checkbox"/> xylometazoline <sup>a</sup> Therapeutic alternatives to be reviewed (2023)	<b>Nasal spray:</b> 0.05%. <sup>a</sup> Not in children less than 3 months.
29. MEDICINES FOR DISEASES OF JOINTS	
29.1 Medicines used to treat gout	
29.2 Disease-modifying anti-rheumatic drugs (DMARDs)	
<i>Complementary List</i>	
hydroxychloroquine	<b>Solid oral dosage form:</b> 200 mg (as sulfate).
methotrexate	<b>Tablet:</b> 2.5 mg (as sodium salt).
29.3 Juvenile joint diseases	
<i>Complementary List</i>	
acetylsalicylic acid*(acute or chronic use)	<b>Suppository:</b> 50 mg to 150 mg. <b>Tablet:</b> 100 mg to 500 mg. *For use for rheumatic fever, juvenile arthritis, Kawasaki disease.
30. DENTAL PREPARATIONS	
fluoride	<b>Paste, cream or gel:</b> containing between 1000 and 1500 ppm fluoride (any type). <b>In other appropriate topical formulations.</b>
glass ionomer cement	<b>Single-use capsules:</b> 0.4 g powder + 0.09 mL liquid <b>Multi-use bottle:</b> powder + liquid Powder (fluoro-alumino-silicate glass) contains: 25-50% silicate, 20-40% aluminium oxide, 1-20% fluoride, 15-40% metal oxide, 0-15% phosphate, remainder are polyacrylic acid powder and metals in minimal quantities. Liquid (aqueous) contains: 7-25% polybasic carboxylic acid, 45-60% polyacrylic acid.
silver diamine fluoride	<b>Solution:</b> 38% w/v

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# The selection and use of essential medicines 2023

Web Annex B

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## World Health Organization Model List of Essential Medicines for Children

9th list  
(2023)



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# WHO Model List of Essential Medicines for Children – 9th List (2023)

## Explanatory notes

This Model List is intended for use for children up to and including 12 years of age.

The **core list** presents a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

The **complementary list** presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings.

The **square box symbol (□)** is intended to indicate therapeutic alternatives to the listed medicine that may be considered for selection in national essential medicines lists. Alternatives may be individual medicines, or multiple medicines within a pharmacological class or chemical subgroup, defined at the 4th level of the [Anatomical Therapeutic Chemical \(ATC\) classification](#), which have similar clinical effectiveness and safety. The listed medicine should be the example of the class or subgroup for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. A square box is not used to indicate alternative generic brands of the same small molecule medicines, nor alternative biosimilars of biological medicines. However, the selection and use of quality-assured generics and biosimilars of essential medicines at country level is recommended.

National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price.

The format and numbering of the 22nd WHO Model List of Essential Medicines is used for the 8th WHO Model Essential List for Children. Some sections have been deleted because they contain medicines that are not relevant for children.

The **a** symbol indicates that there is an age or weight restriction on use of the medicine; details for each medicine are in Table 1.1 of Annex 1.

The presence of an entry on the Essential Medicines List for Children carries no assurance as to pharmaceutical quality. It is the responsibility of the relevant national or regional drug regulatory authority to ensure that each product is of appropriate pharmaceutical quality (including stability) and that when relevant, different products are interchangeable.

For recommendations and advice concerning all aspects of the quality assurance of medicines see the WHO Medicines website <https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/guidelines/quality-assurance>.

Medicines and dosage forms are listed in alphabetical order within each section and the order of listing does not imply preference for one form over another. Standard treatment guidelines should be consulted for information on appropriate dosage forms.

The main terms used for dosage forms in the Essential Medicines List can be found in Table 1.2 of Annex 1.

Definitions of many of these terms and pharmaceutical quality requirements applicable to the different categories are published in the current edition of *The International Pharmacopoeia* <https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/pharmacopoeia>.

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1. ANAESTHETICS, PREOPERATIVE MEDICINES AND MEDICAL GASES	
1.1 General anaesthetics and oxygen	
1.1.1 Inhalational medicines	
halothane	Inhalation.
isoflurane	Inhalation.
nitrous oxide	Inhalation.
oxygen	Inhalation (medical gas).
sevoflurane	Inhalation.
1.1.2 Injectable medicines	
ketamine	Injection: 50 mg/mL (as hydrochloride) in 10 mL vial.
<input type="checkbox"/> propofol *	
Therapeutic alternatives: - thiopental	Injection: 10 mg/mL; 20 mg/mL.
1.2 Local anaesthetics	
<input type="checkbox"/> bupivacaine Therapeutic alternatives to be reviewed	Injection: 0.25%; 0.5% (hydrochloride) in vial. <b>Injection for spinal anaesthesia:</b> 0.5% (hydrochloride) in 4 mL ampoule to be mixed with 7.5% glucose solution.
<input type="checkbox"/> lidocaine Therapeutic alternatives to be reviewed	Injection: 1%; 2% (hydrochloride) in vial. <b>Injection for spinal anaesthesia:</b> 5% (hydrochloride) in 2 mL ampoule to be mixed with 7.5% glucose solution. <b>Topical forms:</b> 2% to 4% (hydrochloride).
lidocaine + epinephrine (adrenaline)	Dental cartridge: 2% (hydrochloride) + epinephrine 1:80 000. <b>Injection:</b> 1%; 2% (hydrochloride or sulfate) + epinephrine 1:200 000 in vial.
1.3 Preoperative medication and sedation for short-term procedures	
atropine	Injection: 1 mg (sulfate) in 1mL ampoule.
<input type="checkbox"/> midazolam Therapeutic alternatives to be reviewed	Injection: 1 mg/mL. <b>Oral liquid:</b> 2 mg/mL. <b>Tablet:</b> 7.5 mg; 15 mg.
morphine	Injection: 10 mg (sulfate or hydrochloride) in 1mL ampoule.
1.4 Medical gases	
oxygen*	Inhalation For use in the management of hypoxaemia. *No more than 30% oxygen should be used to initiate resuscitation of neonates less than or equal to 32 weeks of gestation.

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2. MEDICINES FOR PAIN AND PALLIATIVE CARE	
2.1 Non-opioids and non-steroidal anti-inflammatory medicines (NSAIDs)	
ibuprofen <sup>a</sup>	<p><b>Oral liquid:</b> 100 mg/5 mL; 200 mg/5 mL.  <b>Tablet:</b> 200 mg; 400 mg; 600 mg.</p> <p><sup>a</sup> Not in children less than 3 months.</p>
paracetamol (acetaminophen) *	<p><b>Oral liquid:</b> 120 mg/5 mL or 125 mg/5 mL**; 250 mg/5 mL.  **The presence of both 120 mg/5 mL and 125 mg/5 mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided.</p> <p><b>Suppository:</b> 100 mg; 250 mg.  <b>Tablet:</b> 250 mg; 325 mg; 500 mg.  <b>Tablet (dispersible):</b> 100 mg; 250 mg</p> <p>*Not recommended for anti-inflammatory use due to lack of proven benefit to that effect.</p>
2.2 Opioid analgesics	
<input type="checkbox"/> morphine Therapeutic alternatives: - hydromorphone - oxycodone	<p><b>Granules (slow release; to mix with water):</b> 20 mg to 200 mg (morphine sulfate).</p> <p><b>Injection:</b> 10 mg (morphine hydrochloride or morphine sulfate) in 1 mL ampoule.</p> <p><b>Oral liquid:</b> 10 mg/5 mL (morphine hydrochloride or morphine sulfate).</p> <p><b>Tablet (slow release):</b> 10 mg to 200mg (morphine hydrochloride or morphine sulfate).</p> <p><b>Tablet (immediate release):</b> 10 mg (morphine sulfate).</p>
<i>Complementary list</i>	
methadone*	<p><b>Tablet:</b> 5 mg; 10 mg (hydrochloride).</p> <p><b>Oral liquid:</b> 5 mg/5 mL; 10 mg/5 mL (hydrochloride).</p> <p><b>Concentrate for oral liquid:</b> 5 mg/mL; 10 mg/mL (hydrochloride)</p> <p>*For the management of cancer pain.</p>
2.3 Medicines for other symptoms common in palliative care	
amitriptyline	<b>Tablet:</b> 10 mg; 25 mg.
cyclizine	<p><b>Injection:</b> 50 mg/mL.</p> <p><b>Tablet:</b> 50 mg.</p>
dexamethasone	<p><b>Injection:</b> 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule.</p> <p><b>Oral liquid:</b> 2 mg/5 mL.</p> <p><b>Tablet:</b> 2 mg.</p>
diazepam	<p><b>Injection:</b> 5 mg/mL.</p> <p><b>Oral liquid:</b> 2 mg/5 mL.</p> <p><b>Rectal gel:</b> 5 mg/mL in 0.5 mL, 2 mL, 4 mL rectal delivery system.</p> <p><b>Rectal solution:</b> 2 mg/mL in 1.25 mL, 2.5 mL rectal tubes; 4 mg/mL in 2.5 mL rectal tube.</p> <p><b>Tablet:</b> 5 mg; 10 mg.</p>

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docusate sodium	<b>Capsule:</b> 100 mg. <b>Oral liquid:</b> 50 mg/5 mL.
hyoscine hydrobromide	<b>Injection:</b> 400 micrograms/mL; 600 micrograms/mL. <b>Transdermal patches:</b> 1 mg/72 hours.
lactulose	<b>Oral liquid:</b> 3.1 to 3.7 g/5 mL.
midazolam	<b>Injection:</b> 1 mg/mL; 5 mg/mL. <b>Oral liquid:</b> 2mg/mL. <b>Solid oral dosage form:</b> 7.5 mg; 15 mg.
<input type="checkbox"/> ondansetron <small>a</small> Therapeutic alternatives - dolasetron - granisetron - palonosetron - tropisetron	<b>Injection:</b> 2 mg base/mL in 2 mL ampoule (as hydrochloride). <b>Oral liquid:</b> 4 mg base/5 mL. <b>Solid oral dosage form:</b> Eq 4 mg base; Eq 8 mg base. <small>a</small> > 1 month.
senna	<b>Oral liquid:</b> 7.5 mg/5 mL.
<b>3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS</b>	
dexamethasone	<b>Injection:</b> 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule.
epinephrine (adrenaline)	<b>Injection:</b> 1 mg/mL (as hydrochloride or hydrogen tartrate) in 1 mL ampoule.
hydrocortisone	<b>Powder for injection:</b> 100 mg (as sodium succinate) in vial.
<input type="checkbox"/> loratadine* Therapeutic alternatives: - cetirizine - fexofenadine	<b>Oral liquid:</b> 1 mg/mL. <b>Tablet:</b> 10 mg. <i>*There may be a role for sedating antihistamines for limited indications.</i>
<input type="checkbox"/> prednisolone Therapeutic alternatives: - prednisone	<b>Oral liquid:</b> 5 mg/mL. <b>Tablet:</b> 5 mg; 25 mg.

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4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS	
<b>4.1 Non-specific</b>	
charcoal, activated	Powder.
<b>4.2 Specific</b>	
acetylcysteine	<b>Injection:</b> 200 mg/mL in 10 mL ampoule. <b>Oral liquid:</b> 10%; 20%.
atropine	<b>Injection:</b> 1 mg (sulfate) in 1 mL ampoule.
calcium gluconate	<b>Injection:</b> 100 mg/mL in 10 mL ampoule.
naloxone	<b>Injection:</b> 400 micrograms (hydrochloride) in 1 mL ampoule.
<i>Complementary List</i>	
deferoxamine	<b>Powder for injection:</b> 500 mg (mesilate) in vial.
dimercaprol	<b>Injection in oil:</b> 50 mg/mL in 2 mL ampoule.
fomepizole	<b>Injection:</b> 5 mg/mL (sulfate) in 20 mL ampoule or 1 g/mL (base) in 1.5 mL ampoule.
sodium calcium edetate	<b>Injection:</b> 200 mg/mL in 5 mL ampoule.
succimer	<b>Solid oral dosage form:</b> 100 mg.
5. MEDICINES FOR DISEASES OF THE NERVOUS SYSTEM	
<b>5.1 Antiseizure medicines</b>	
carbamazepine	<b>Oral liquid:</b> 100 mg/5 mL. <b>Tablet (chewable):</b> 100 mg; 200 mg. <b>Tablet (scored):</b> 100 mg; 200 mg; 400 mg.
diazepam	<b>Rectal gel:</b> 5 mg/mL in 0.5 mL, 2 mL, 4 mL rectal delivery system. <b>Rectal solution:</b> 2 mg/mL in 1.25 mL, 2.5 mL rectal tubes; 4 mg/mL in 2.5 mL rectal tube.
lamotrigine*	<b>Tablet:</b> 25 mg; 50 mg; 100 mg; 200 mg. <b>Tablet (chewable, dispersible):</b> 2 mg; 5 mg; 25 mg; 50 mg; 100 mg; 200 mg. *For use as adjunctive therapy for treatment-resistant partial or generalized seizures.
levetiracetam	<b>Oral solution:</b> 100 mg/mL. <b>Tablet:</b> 250 mg; 500 mg; 750 mg; 1000 mg.
<input type="checkbox"/> lorazepam Therapeutic alternatives: - diazepam (injection) - midazolam (injection)	<b>Injection:</b> 2 mg/mL in 1 mL ampoule; 4 mg/mL in 1 mL ampoule.

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midazolam	<p><b>Solution for oromucosal administration:</b> 5 mg/mL in 0.5 mL, 1 mL, 1.5 mL, 2 mL pre-filled syringe; 10 mg/mL in 0.25 mL, 0.5 mL, 0.75 mL, 1 mL pre-filled syringe.</p> <p><b>Injection*</b>: 1 mg/mL in 5 mL vial; 5 mg/mL in 1 mL or 3 mL vial.</p> <p>*For buccal administration when solution for oromucosal administration is not available.</p>
phenobarbital	<p><b>Injection:</b> 30 mg/mL or 60 mg/mL; 200 mg/mL (sodium).</p> <p><b>Oral liquid:</b> 15 mg/5 mL.</p> <p><b>Tablet:</b> 15 mg to 100 mg.</p>
phenytoin	<p><b>Injection:</b> 50 mg/mL (phenytoin sodium).</p> <p><b>Oral liquid:</b> 30 mg/5 mL (phenytoin).</p> <p><b>Solid oral dosage form:</b> 25 mg; 50 mg; 100 mg (phenytoin sodium).</p> <p><b>Tablet (chewable):</b> 50 mg (phenytoin).</p>
valproic acid (sodium valproate)*  <i>*avoid use in pregnancy and in women and girls of child-bearing potential, unless alternative treatments are ineffective or not tolerated because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb.</i>	<p><b>Oral liquid:</b> 200 mg/5 mL.</p> <p><b>Tablet (crushable):</b> 100 mg.</p> <p><b>Tablet (enteric-coated):</b> 200 mg; 500 mg.</p>
<b>Complementary List</b>	
ethosuximide	<p><b>Capsule:</b> 250 mg.</p> <p><b>Oral liquid:</b> 250 mg/5 mL.</p>
levetiracetam	<p><b>Concentrate solution for infusion:</b> 500 mg/5mL in 5 mL vial.</p> <p><b>Solution for infusion:</b> 5 mg/mL; 10 mg/mL; 15 mg/mL in 100 mL bag.</p>
valproic acid (sodium valproate)*  <i>*avoid use in pregnancy and in women and girls of child-bearing potential, unless alternative treatments are ineffective or not tolerated because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb.</i>	<p><b>Injection:</b> 100 mg/mL in 3 mL, 4 mL, 10 mL ampoule.</p>
<b>5.2 Medicines for multiple sclerosis</b>	
<b>5.3 Medicines for parkinsonism</b>	

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6. ANTI-INFECTIVE MEDICINES	
6.1 Anthelmintics	
6.1.1 <i>Intestinal anthelmintics</i>	
albendazole	Tablet (chewable, scored): 400 mg.
ivermectin	Tablet: 3 mg.
levamisole	Tablet: 50 mg (as hydrochloride).
mebendazole	Tablet (chewable): 100 mg; 500 mg.
niclosamide	Tablet (chewable): 500 mg.
praziquantel	Tablet: 150 mg; 500 mg. Tablet (scored): 600 mg.
pyrantel	Tablet (chewable): 250 mg (as embonate or pamoate).
6.1.2 <i>Antifilarials</i>	
albendazole	Tablet (chewable, scored): 400 mg.
diethylcarbamazine	Tablet: 50 mg; 100 mg (dihydrogen citrate).
ivermectin	Tablet: 3 mg.
6.1.3 <i>Antischistosomals and other antitrematode medicines</i>	
praziquantel	Tablet: 150 mg; 500 mg. Tablet (scored): 600 mg.
triclabendazole	Tablet (scored): 250 mg.
<i>Complementary List</i>	
oxamniquine*	Capsule: 250 mg. Oral liquid: 250 mg/5 mL. <i>*For use when praziquantel treatment fails.</i>
6.1.4 <i>Cysticidal medicines</i>	
<i>Complementary List</i>	
albendazole	Tablet (chewable): 200 mg. Tablet (chewable, scored): 400 mg.
mebendazole	Tablet (chewable): 100 mg; 500 mg.
praziquantel	Tablet: 150 mg; 500 mg. Tablet (scored): 600 mg

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## 6.2 Antibacterials

To assist in the development of tools for antibiotic stewardship at local, national and global levels and to reduce antimicrobial resistance, the Access, Watch, Reserve (AWaRe) classification of antibiotics has been developed by WHO – where antibiotics are classified into different groups to emphasize the importance of their appropriate use.

### ACCESS GROUP ANTIBIOTICS

This group includes antibiotics that have activity against a wide range of commonly encountered susceptible pathogens while also showing lower resistance potential than antibiotics in the other groups. Selected Access group antibiotics are recommended as essential first or second choice empiric treatment options for infectious syndromes reviewed by the EML Expert Committee and are listed as individual medicines on the Model Lists to improve access and promote appropriate use. They are essential antibiotics that should be widely available, affordable and quality assured.

### WATCH GROUP ANTIBIOTICS

This group includes antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the [Critically Important Antimicrobials for Human Medicine](#) and/or antibiotics that are at relatively high risk of selection of bacterial resistance. These medicines should be prioritized as key targets of stewardship programs and monitoring. Selected Watch group antibiotics are recommended as essential first or second choice empiric treatment options for a limited number of specific infectious syndromes and are listed as individual medicines on the Model Lists.

### RESERVE GROUP ANTIBIOTICS

This group includes antibiotics and antibiotic classes that should be reserved for treatment of confirmed or suspected infections due to multi-drug-resistant organisms. Reserve group antibiotics should be treated as “last resort” options. Selected Reserve group antibiotics are listed as individual medicines on the Model Lists when they have a favourable risk-benefit profile and proven activity against “Critical Priority” or “High Priority” pathogens identified by the [WHO Priority Pathogens List](#), notably carbapenem resistant *Enterobacteriaceae*. These antibiotics should be accessible, but their use should be tailored to highly specific patients and settings, when all alternatives have failed or are not suitable. These medicines could be protected and prioritized as key targets of national and international stewardship programs involving monitoring and utilization reporting, to preserve their effectiveness.

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6.2.1 Access group antibiotics		
		<b>Injection:</b> 50 mg/mL (as sulfate); 250 mg/mL (as sulfate) in 2 mL vial.
amikacin	<b>FIRST CHOICE</b> <ul style="list-style-type: none"><li>– <i>High-risk febrile neutropenia-pyelonephritis (severe)</i></li></ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"><li>– <i>Sepsis in neonates and children</i></li></ul>
		<b>Powder for injection:</b> 250 mg; 500 mg; 1 g (as sodium) in vial. <b>Powder for oral liquid:</b> 125 mg/5 mL; 250 mg/5 mL (as trihydrate). <b>Solid oral dosage form:</b> 250 mg; 500 mg (as trihydrate). <b>Tablet (dispersible, scored):</b> 250 mg; 500 mg (as trihydrate).
amoxicillin	<b>FIRST CHOICE</b> <ul style="list-style-type: none"><li>– <i>Community acquired pneumonia (mild to moderate)</i></li><li>– <i>Community acquired pneumonia (severe)</i></li><li>– <i>Complicated severe acute malnutrition</i></li><li>– <i>Otitis media</i></li><li>– <i>Pharyngitis</i></li><li>– <i>Progressive apical dental abscess</i></li><li>– <i>Sepsis in neonates and children</i></li><li>– <i>Sinusitis</i></li><li>– <i>Uncomplicated severe acute malnutrition</i></li></ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"><li>– <i>Acute bacterial meningitis</i></li></ul>
		<b>Powder for injection:</b> 500 mg (as sodium) + 100 mg (as potassium salt); 1000 mg (as sodium) + 200 mg (as potassium salt) in vial. <b>Powder for oral liquid:</b> 125 mg (as trihydrate)+ 31.25 mg (as potassium salt)/5 mL; 250 mg (as trihydrate) + 62.5 mg (as potassium salt)/5mL. <b>Tablet:</b> 500 mg (as trihydrate) + 125 mg (as potassium salt). <b>Tablet (dispersible):</b> 200 mg (as trihydrate) + 28.5 mg (as potassium salt); 250 mg (as trihydrate) + 62.5 mg (as potassium salt).
amoxicillin + clavulanic acid	<b>FIRST CHOICE</b> <ul style="list-style-type: none"><li>– <i>Community acquired pneumonia (severe)</i></li><li>– <i>Complicated intraabdominal infections (mild to moderate)</i></li><li>– <i>Hospital acquired pneumonia</i></li><li>– <i>Low-risk febrile neutropenia</i></li><li>– <i>Lower urinary tract infections</i></li><li>– <i>Sinusitis</i></li><li>– <i>Skin and soft tissue infections</i></li></ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"><li>– <i>Bone and joint infections</i></li><li>– <i>Community acquired pneumonia (mild to moderate)</i></li><li>– <i>Community acquired pneumonia (severe)</i></li><li>– <i>Otitis media</i></li><li>– <i>Surgical prophylaxis</i></li></ul>

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	Powder for injection: 500 mg; 1 g (as sodium) in vial.	
ampicillin	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Community acquired pneumonia (severe)</i></li> <li>– <i>Complicated intraabdominal infections</i></li> <li>– <i>Complicated severe acute malnutrition</i></li> <li>– <i>Sepsis in neonates and children</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Acute bacterial meningitis</i></li> </ul>
benzathine benzylpenicillin	<b>Powder for injection:</b> 1.2 million IU ( $\approx$ 900 mg) in vial; 2.4 million IU ( $\approx$ 1.8 g) in vial.	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Syphilis (congenital)</i></li> </ul>	<b>SECOND CHOICE</b>
benzylpenicillin	<b>Powder for injection:</b> 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial.	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Community acquired pneumonia (severe)</i></li> <li>– <i>Complicated severe acute malnutrition</i></li> <li>– <i>Sepsis in neonates and children</i></li> <li>– <i>Syphilis (congenital)</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Acute bacterial meningitis</i></li> </ul>
cefalexin	<b>Powder for oral liquid:</b> 125 mg/5 mL; 250 mg/5 mL (anhydrous). <b>Solid oral dosage form:</b> 250 mg (as monohydrate). <b>Tablet (dispersible):</b> 125 mg; 250 mg.	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Skin and soft tissue infections</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Pharyngitis</i></li> </ul>
cefazolin <sup>a</sup>	<b>Powder for injection:</b> 1 g (as sodium salt) in vial. <small>[a] &gt; 1 month.</small>	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Surgical prophylaxis</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Bone and joint infections</i></li> </ul>
chloramphenicol	<b>Oily suspension for injection*</b> : 0.5 g/mL (as sodium succinate) in 2 mL ampoule. <small>*Only for the presumptive treatment of epidemic meningitis in children older than 2 years.</small> <b>Powder for injection:</b> 1 g (sodium succinate) in vial.	
	<b>FIRST CHOICE</b>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Acute bacterial meningitis</i></li> </ul>

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clindamycin	<b>Capsule:</b> 150 mg (as hydrochloride). <b>Injection:</b> 150 mg/mL (as phosphate). <b>Powder for oral liquid:</b> 75 mg/5 mL (as palmitate hydrochloride).	
	<b>FIRST CHOICE</b> – <i>Necrotizing fasciitis</i>	<b>SECOND CHOICE</b> – <i>Bone and joint infections</i>
<input checked="" type="checkbox"/> cloxacillin* Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (J01CF Beta-lactamase resistant penicillins)		<b>Capsule:</b> 250 mg; 500 mg; 1 g (as sodium). <b>Powder for injection:</b> 250 mg; 500 mg (as sodium) in vial. <b>Powder for oral liquid:</b> 125 mg/5 mL; 250 mg/5 mL (as sodium). *cloxacillin, dicloxacillin and flucloxacillin are preferred for oral administration due to better bioavailability.
<b>FIRST CHOICE</b> – <i>Bone and joint infections</i> – <i>Skin and soft tissue infections</i>		<b>SECOND CHOICE</b> – <i>Sepsis in neonates and children</i>
doxycycline <span style="border: 1px solid black; padding: 0 2px;">a</span>		<b>Oral liquid:</b> 50 mg/5 mL (calcium). <b>Powder for oral liquid:</b> 25 mg/5 mL (monohydrate). <b>Powder for injection:</b> 100 mg in vial. <b>Solid oral dosage form:</b> 50 mg; 100 mg (as hydiate). <b>Tablet (dispersible):</b> 100 mg (as monohydrate). <span style="border: 1px solid black; padding: 0 2px;">a</span> Use in children <8 years only for life-threatening infections when no alternative exists.
<b>FIRST CHOICE</b>		<b>SECOND CHOICE</b> – <i>Cholera</i> – <i>Community acquired pneumonia (mild to moderate)</i>
gentamicin		<b>Injection:</b> 10 mg/mL (as sulfate); 40 mg/mL (as sulfate) in 2 mL vial.
<b>FIRST CHOICE</b> – <i>Acute bacterial meningitis in neonates</i> – <i>Community acquired pneumonia (severe)</i> – <i>Complicated intraabdominal infections</i> – <i>Complicated severe acute malnutrition</i> – <i>Sepsis in neonates and children</i>		<b>SECOND CHOICE</b> – <i>Surgical prophylaxis</i>

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	<b>Injection:</b> 500 mg in 100 mL vial. <b>Oral liquid:</b> 200 mg/5 mL (as benzoate). <b>Tablet:</b> 200 mg; 250 mg; 400 mg; 500 mg.	
metronidazole	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>C. difficile infection</i></li> <li>– <i>Complicated intra-abdominal infections (mild to moderate)</i></li> <li>– <i>Complicated intra-abdominal infections (severe)</i></li> <li>– <i>Necrotizing fasciitis</i></li> <li>– <i>Surgical prophylaxis</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Complicated intra-abdominal infections (mild to moderate)</i></li> </ul>
nitrofurantoin	<b>Oral liquid:</b> 25 mg/5 mL. <b>Solid oral dosage form:</b> 50 mg; 100 mg.	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Lower urinary tract infections</i></li> </ul>	<b>SECOND CHOICE</b>
phenoxyethylpenicillin	<b>Powder for oral liquid:</b> 250 mg/5 mL (as potassium). <b>Solid oral dosage form:</b> 250 mg (as potassium).	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Community acquired pneumonia (mild to moderate)</i></li> <li>– <i>Pharyngitis</i></li> <li>– <i>Progressive apical dental abscess</i></li> </ul>	<b>SECOND CHOICE</b>
procaine benzylpenicillin*	<b>Powder for injection:</b> 1 g (=1 million IU); 3 g (=3 million IU) in vial. <small>*Procaine benzylpenicillin is not recommended as first-line treatment for neonatal sepsis / sepsis except in settings with high neonatal mortality, when given by trained health workers in cases where hospital care is not achievable.</small>	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Syphilis (congenital)</i></li> </ul>	<b>SECOND CHOICE</b>
sulfamethoxazole + trimethoprim	<b>Injection:</b> 80 mg + 16 mg/ mL in 5 mL ampoule; 80 mg + 16 mg/ mL in 10 mL ampoule. <b>Oral liquid:</b> 200 mg + 40 mg/5 mL. <b>Tablet:</b> 100 mg + 20 mg; 400 mg + 80 mg. <b>Tablet (dispersible):</b> 100 mg + 20 mg.	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Lower urinary tract infections</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Acute invasive bacterial diarrhoea / dysentery</i></li> </ul>
trimethoprim	<b>Tablet:</b> 100 mg; 200 mg. <b>Oral liquid:</b> 50 mg/5 mL.	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Lower urinary tract infections</i></li> </ul>	<b>SECOND CHOICE</b>

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## 6.2.2 Watch group antibiotics

	<p><b>Solid oral dosage form:</b> 250 mg; 500 mg (anhydrous).</p> <p><b>Powder for oral liquid:</b> 200 mg/5 mL (anhydrous).</p>	
azithromycin	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Cholera</i></li> <li>– <i>Enteric fever</i></li> <li>– <i>Trachoma</i></li> <li>– <i>Yaws</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Acute invasive bacterial diarrhoea / dysentery</i></li> </ul>
	<p><b>Powder for oral liquid:</b> 100 mg/5 mL.</p> <p><b>Solid oral dosage form:</b> 200 mg; 400 mg (as trihydrate).</p>	
cefixime	<b>FIRST CHOICE</b>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Acute invasive bacterial diarrhoea / dysentery</i></li> </ul>
	<p><b>Powder for injection:</b> 250 mg; 500 mg; 1 g; 2 g (as sodium) in vial.</p> <p>*3rd generation cephalosporin of choice for use in hospitalized neonates.</p>	
cefotaxime*	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Acute bacterial meningitis</i></li> <li>– <i>Community acquired pneumonia (severe)</i></li> <li>– <i>Complicated intraabdominal infections (mild to moderate)</i></li> <li>– <i>Complicated intraabdominal infections (severe)</i></li> <li>– <i>Hospital acquired pneumonia</i></li> <li>– <i>Pyelonephritis (severe)</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Bone and joint infections</i></li> <li>– <i>Pyelonephritis (mild to moderate)</i></li> <li>– <i>Sepsis in neonates and children</i></li> </ul>
	<p><b>Powder for injection:</b> 250 mg; 500 mg; 1 g (as sodium) in vial.</p> <p>*Do not administer with calcium and avoid in infants with hyperbilirubinaemia.</p> <p><b>[a]</b> &gt; 41 weeks corrected gestational age.</p>	
ceftriaxone*[a]	<b>FIRST CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Acute bacterial meningitis</i></li> <li>– <i>Community acquired pneumonia (severe)</i></li> <li>– <i>Complicated intraabdominal infections (mild to moderate)</i></li> <li>– <i>Complicated intraabdominal infections (severe)</i></li> <li>– <i>Endophthalmitis</i></li> <li>– <i>Enteric fever</i></li> <li>– <i>Hospital acquired pneumonia</i></li> <li>– <i>Necrotizing fasciitis</i></li> <li>– <i>Pyelonephritis (severe)</i></li> </ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Acute invasive bacterial diarrhoea / dysentery</i></li> <li>– <i>Bone and joint infections</i></li> <li>– <i>Pyelonephritis (mild to moderate)</i></li> <li>– <i>Sepsis in neonates and children</i></li> </ul>
	<p><b>Powder for injection:</b> 250 mg; 750 mg; 1.5 g (as sodium) in vial.</p>	
cefuroxime	<b>FIRST CHOICE</b>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"> <li>– <i>Surgical prophylaxis</i></li> </ul>

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	Oral liquid: 250 mg/5 mL (anhydrous). Solution for IV infusion: 2 mg/ mL (as hyclate). Solid oral dosage form: 100 mg; 250 mg (as hydrochloride).	
ciprofloxacin	<b>FIRST CHOICE</b> <ul style="list-style-type: none"><li>– <i>Acute invasive bacterial diarrhoea / dysentery</i></li><li>– <i>Enteric fever</i></li><li>– <i>Low-risk febrile neutropenia</i></li><li>– <i>Pyelonephritis (mild to moderate)</i></li></ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"><li>– <i>Cholera</i></li><li>– <i>Complicated intraabdominal infections (mild to moderate)</i></li></ul>
<input type="checkbox"/> clarithromycin  Therapeutic alternatives: - erythromycin	<b>Powder for oral liquid:</b> 125 mg/5 mL; 250 mg/5 mL.  <b>Powder for injection:</b> 500 mg in vial.  <b>Solid oral dosage form:</b> 250 mg.	
	<b>FIRST CHOICE</b>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"><li>– <i>Pharyngitis</i></li></ul>
piperacillin + tazobactam	<b>Powder for injection:</b> 2 g (as sodium) + 250 mg (as sodium); 4 g (as sodium) + 500 mg (as sodium) in vial.	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"><li>– <i>Complicated intraabdominal infections (severe)</i></li><li>– <i>High-risk febrile neutropenia</i></li><li>– <i>Hospital acquired pneumonia</i></li><li>– <i>Necrotizing fasciitis</i></li></ul>	<b>SECOND CHOICE</b>
vancomycin*	<b>Capsule:</b> 125 mg; 250 mg (as hydrochloride).  *vancomycin powder for injection may also be used for oral administration.	
	<b>FIRST CHOICE</b>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"><li>– <i>C. difficile infection</i></li></ul>
<b>Complementary List</b>		
ceftazidime	<b>Powder for injection:</b> 250 mg; 1 g (as pentahydrate) in vial.	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"><li>– <i>Endophthalmitis</i></li></ul>	<b>SECOND CHOICE</b>
<input type="checkbox"/> meropenem* <span style="border: 1px solid black; padding: 2px;">a</span>  Therapeutic alternatives*: - imipenem + cilastatin  *complicated intraabdominal infections and high-risk febrile neutropenia only. Meropenem is the preferred choice for acute bacterial meningitis in neonates.	<b>Powder for injection:</b> 500 mg (as trihydrate); 1 g (as trihydrate) in vial  <span style="border: 1px solid black; padding: 2px;">a</span> > 3 months.	
	<b>FIRST CHOICE</b>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"><li>– <i>Acute bacterial meningitis in neonates</i></li><li>– <i>Complicated intraabdominal infections (severe)</i></li><li>– <i>High-risk febrile neutropenia</i></li></ul>
vancomycin	<b>Powder for injection:</b> 250 mg; 500 mg; 1 g (as hydrochloride) in vial.	
	<b>FIRST CHOICE</b> <ul style="list-style-type: none"><li>– <i>Endophthalmitis</i></li><li>– <i>Necrotizing fasciitis</i></li></ul>	<b>SECOND CHOICE</b> <ul style="list-style-type: none"><li>– <i>High-risk febrile neutropenia</i></li></ul>

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<b>6.2.3 Reserve group antibiotics</b>	
<b>Complementary List</b>	
ceftazidime + avibactam	<b>Powder for injection:</b> 2 g + 0.5 g in vial
ceftolozane + tazobactam	<b>Powder for injection:</b> 1 g + 0.5 g in vial.
colistin	<b>Powder for injection:</b> 1 million IU (as colistemethate sodium) (equivalent to 34 mg colistin base activity) in vial
fosfomycin	<b>Powder for injection:</b> 2 g; 4 g (as sodium) in vial
linezolid	<b>Injection for intravenous administration:</b> 2 mg/mL in 300 mL bag. <b>Powder for oral liquid:</b> 100 mg/5 mL. <b>Tablet (dispersible):</b> 150 mg.
polymyxin B	<b>Powder for injection:</b> 500,000 IU (equivalent to 50 mg polymyxin B base) in vial.
<b>6.2.4 Antileprosy medicines</b>	
Medicines used in the treatment of leprosy should never be used except in combination. Combination therapy is essential to prevent the emergence of drug resistance. Colour-coded blister packs (MDT blister packs) containing standard two-medicine (paucibacillary leprosy) or three-medicine (multibacillary leprosy) combinations for adult and childhood leprosy should be used. MDT blister packs can be supplied free of charge through WHO.	
clofazimine	<b>Solid oral dosage form:</b> 50 mg; 100 mg.
dapsone	<b>Tablet:</b> 25 mg; 50 mg; 100 mg.
rifampicin	<b>Oral liquid:</b> 20 mg/mL. <b>Solid oral dosage form:</b> 150 mg; 300 mg.
<b>6.2.5 Antituberculosis medicines</b>	
WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.	
ethambutol	<b>Tablet:</b> 100 mg; 400 mg (hydrochloride). <b>Tablet (dispersible):</b> 100 mg.
ethionamide	<b>Tablet:</b> 250 mg <b>Tablet (dispersible):</b> 125 mg.
isoniazid	<b>Tablet:</b> 100 mg; 300 mg. <b>Tablet (dispersible):</b> 100 mg.
isoniazid + pyrazinamide + rifampicin	<b>Tablet (dispersible):</b> 50 mg + 150 mg + 75 mg.
isoniazid + rifampicin	<b>Tablet (dispersible):</b> 50 mg + 75 mg.
isoniazid + rifapentine	<b>Tablet (scored):</b> 300 mg + 300 mg.
pyrazinamide	<b>Tablet:</b> 400 mg; 500 mg. <b>Tablet (dispersible):</b> 150 mg.
rifampicin	<b>Oral liquid:</b> 20 mg/mL. <b>Solid oral dosage form:</b> 150 mg; 300 mg.
rifapentine	<b>Tablet:</b> 150 mg; 300 mg.

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<i>Complementary List</i>	
Medicines for the treatment of multidrug-resistant tuberculosis (MDR-TB) should be used in specialized centres adhering to WHO standards for TB control.	
amikacin	<b>Injection:</b> 250 mg/mL (as sulfate) in 2 mL vial.
amoxicillin + clavulanic acid*	<b>Powder for oral liquid:</b> 250 mg (as trihydrate) + 62.5 mg (as potassium salt)/5mL. <b>Tablet:</b> 500 mg (as trihydrate) + 125 mg (as potassium salt). *For use only in combination with meropenem.
bedaquiline	<b>Tablet:</b> 20 mg; 100 mg.
clofazimine	<b>Solid oral dosage form:</b> 50 mg; 100 mg.
cycloserine	<b>Solid oral dosage form:</b> 125 mg; 250 mg.
delamanid	<b>Tablet (dispersible):</b> 25 mg. <b>Tablet:</b> 50 mg.
□ ethionamide Therapeutic alternatives: - prontosilamide	<b>Tablet:</b> 250 mg. <b>Tablet (dispersible):</b> 125 mg.
levofloxacin	<b>Tablet:</b> 250 mg; 500 mg. <b>Tablet (dispersible):</b> 100 mg.
linezolid	<b>Tablet:</b> 600 mg. <b>Tablet (dispersible):</b> 150 mg.
meropenem	<b>Powder for injection:</b> 500 mg (as trihydrate); 1 g (as trihydrate) in vial.
moxifloxacin	<b>Tablet:</b> 400 mg. <b>Tablet (dispersible):</b> 100 mg.
p-aminosalicylate sodium	<b>Powder for oral solution:</b> 5.52 g in sachet (equivalent to 4 g p-aminosalicylic acid).
streptomycin	<b>Powder for injection:</b> 1 g (as sulfate) in vial.
6.3 Antifungal medicines	
amphotericin B*	<b>Powder for injection:</b> 50 mg (liposomal complex) in vial. <b>Powder for injection:</b> 50 mg (as sodium deoxycholate) in vial. *Liposomal amphotericin B has a better safety profile than the sodium deoxycholate formulation and should be prioritized for selection and use depending on local availability and cost.
fluconazole	<b>Capsule:</b> 50 mg. <b>Injection:</b> 2 mg/mL in vial. <b>Oral liquid:</b> 50 mg/5 mL. <b>Powder for oral liquid:</b> 50 mg/5 mL.
flucytosine	<b>Capsule:</b> 250 mg. <b>Infusion:</b> 2.5 g in 250 mL.
griseofulvin	<b>Oral liquid:</b> 125 mg/5 mL. <b>Solid oral dosage form:</b> 125 mg; 250 mg.

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itraconazole*	<p><b>Capsule:</b> 100 mg.</p> <p><b>Oral liquid:</b> 10 mg/mL.</p> <p>*For treatment of chronic pulmonary aspergillosis, acute invasive aspergillosis, histoplasmosis, sporotrichosis, paracoccidioidomycosis, mycoses caused by <i>T. marneffei</i> and chromoblastomycosis; and prophylaxis of histoplasmosis and infections caused by <i>T. marneffei</i> in AIDS patients.</p>
nystatin	<p><b>Lozenge:</b> 100 000 IU.</p> <p><b>Oral liquid:</b> 100 000 IU/mL.</p> <p><b>Solid oral dosage form:</b> 500 000 IU.</p>
voriconazole*	<p><b>Tablet:</b> 50 mg; 200 mg.</p> <p><b>Powder for injection:</b> 200 mg in vial.</p> <p><b>Powder for oral liquid:</b> 40 mg/mL.</p> <p>*For treatment of chronic pulmonary aspergillosis and acute invasive aspergillosis.</p>

### Complementary List

<input type="checkbox"/> <i>micafungin</i>  Therapeutic alternatives: - <i>anidulafungin</i> - <i>caspofungin</i>	<b>Powder for injection:</b> 50 mg (as sodium); 100 mg (as sodium) in vial.
<i>potassium iodide</i>	<b>Saturated solution.</b>

### 6.4 Antiviral medicines

#### 6.4.1 Antitherpes medicines

aciclovir	<p><b>Oral liquid:</b> 200 mg/5 mL.</p> <p><b>Powder for injection:</b> 250 mg (as sodium salt) in vial.</p> <p><b>Tablet:</b> 200 mg.</p>
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## 6.4.2 Antiretrovirals

Based on current evidence and experience of use, medicines in the following classes of antiretrovirals are included as essential medicines for treatment and prevention of HIV (prevention of mother-to-child transmission and post-exposure prophylaxis). WHO emphasizes the importance of using these products in accordance with global and national guidelines. WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

Scored tablets can be used in children and therefore can be considered for inclusion in the listing of tablets, provided that adequate quality products are available.

### 6.4.2.1 Nucleoside/Nucleotide reverse transcriptase inhibitors

lamivudine	<b>Oral liquid:</b> 50 mg/5 mL.
zidovudine	<b>Oral liquid:</b> 50 mg/5 mL.

### 6.4.2.2 Non-nucleoside reverse transcriptase inhibitors

nevirapine <b>[a]</b>	<b>Oral liquid:</b> 50 mg/5 mL. <b>Tablet (dispersible):</b> 50 mg. <b>[a]</b> > 6 weeks
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### 6.4.2.3 Protease inhibitors

Selection of protease inhibitor(s) from the Model List will need to be determined by each country after consideration of international and national treatment guidelines and experience. Ritonavir is recommended for use in combination as a pharmacological booster, and not as an antiretroviral in its own right. All other protease inhibitors should be used in boosted forms (e.g. with ritonavir).

darunavir <b>[a]</b>	<b>Tablet:</b> 75 mg. <b>[a]</b> > 3 years
lopinavir + ritonavir	<b>Solid oral dosage form:</b> 40 mg + 10 mg. <b>Tablet (heat stable):</b> 100 mg + 25 mg.
ritonavir	<b>Tablet (heat stable):</b> 25 mg; 100 mg.

### 6.4.2.4 Integrase inhibitors

dolutegravir <b>[a]</b>	<b>Tablet (dispersible, scored):</b> 10 mg. <b>[a]</b> ≥ 4 weeks and ≥ 3 kg <b>Tablet:</b> 50 mg. <b>[a]</b> ≥ 25 kg
raltegravir*	<b>Granules for oral suspension:</b> 100 mg in sachet. <b>Tablet (chewable):</b> 25 mg. *For use in second-line regimens in accordance with WHO treatment guidelines

### 6.4.2.5 Fixed-dose combinations of antiretroviral medicines

abacavir + lamivudine	<b>Tablet (dispersible, scored):</b> 120 mg (as sulfate) + 60 mg.
lamivudine + zidovudine	<b>Tablet:</b> 30 mg + 60 mg.

### 6.4.2.6 Medicines for prevention of HIV-related opportunistic infections

isoniazid + pyridoxine + sulfamethoxazole + trimethoprim	<b>Tablet (scored):</b> 300 mg + 25 mg + 800 mg + 160 mg
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<b>6.4.3 Other antivirals</b>	
ribavirin*	<p><b>Injection for intravenous administration:</b> 800 mg and 1 g in 10 mL phosphate buffer solution.</p> <p><b>Solid oral dosage form:</b> 200 mg; 400 mg; 600 mg.</p> <p>*For the treatment of viral haemorrhagic fevers only.</p>
<b>Complementary List</b>	
oseltamivir*	<p><b>Capsule:</b> 30 mg; 45 mg; 75 mg (as phosphate).</p> <p>*Severe illness due to confirmed or suspected influenza virus infection in critically ill hospitalized patients</p>
valganciclovir*	<p><b>Powder for oral solution:</b> 50 mg/mL</p> <p><b>Tablet:</b> 450 mg.</p> <p>*For the treatment of cytomegalovirus retinitis (CMVr).</p>
<b>6.4.4 Antihepatitis medicines</b>	
<b>6.4.4.1 Medicines for hepatitis B</b>	
<b>6.4.4.1.1 Nucleoside/Nucleotide reverse transcriptase inhibitors</b>	
entecavir	<p><b>Oral liquid:</b> 0.05 mg/ mL</p> <p><b>Tablet:</b> 0.5 mg; 1 mg</p>
<b>6.4.4.2 Medicines for hepatitis C</b>	
Pangenotypic direct-acting antivirals should be considered as therapeutically equivalent for the purposes of selection and procurement at national level.	
<b>6.4.4.2.1 □ Pangenotypic direct-acting antiviral combinations</b>	
daclatasvir*	<p><b>Tablet:</b> 30 mg; 60 mg (as hydrochloride).</p> <p>*Pangenotypic when used in combination with sofosbuvir</p>
daclatasvir + sofosbuvir	<b>Tablet:</b> 60 mg + 400 mg.
glecaprevir + pibrentasvir	<p><b>Granules:</b> 50 mg + 20 mg in sachet.</p> <p><b>Tablet:</b> 100 mg + 40 mg.</p>
sofosbuvir*	<p><b>Tablet:</b> 200 mg; 400 mg.</p> <p>*Pangenotypic when used in combination with daclatasvir</p>
sofosbuvir + velpatasvir	<b>Tablet:</b> 200 mg + 50 mg; 400 mg + 100 mg
<b>6.4.4.2.2 Non-pangenotypic direct-acting antiviral combinations</b>	
<b>6.4.4.2.3 Other antivirals for hepatitis C</b>	

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<b>6.5 Antiprotozoal medicines</b>	
<b>6.5.1 Antiamoebic and anti<i>giardiasis</i> medicines</b>	
diloxanide <small>a</small>	<p><b>Tablet:</b> 500 mg (furoate).</p> <p><small>a &gt; 25 kg.</small></p>
<input type="checkbox"/> metronidazole Therapeutic alternatives: - tinidazole	<p><b>Injection:</b> 500 mg in 100 mL vial.</p> <p><b>Oral liquid:</b> 200 mg/5 mL (as benzoate).</p> <p><b>Tablet:</b> 200 mg; 250 mg; 400 mg; 500 mg</p>
<b>6.5.2 Antileishmaniasis medicines</b>	
amphotericin B*	<p><b>Powder for injection:</b> 50 mg (liposomal complex) in vial.</p> <p><b>Powder for injection:</b> 50 mg (as sodium deoxycholate) in vial.</p> <p>*Liposomal amphotericin B has a better safety profile than the sodium deoxycholate formulation and should be prioritized for selection and use depending on local availability and cost.</p>
meglumine antimoniate	<b>Injection:</b> 1.5 g/5 mL in 5 mL ampoule.
miltefosine	<b>Solid oral dosage form:</b> 10 mg; 50 mg.
paromomycin	<b>Solution for intramuscular injection:</b> 750 mg of paromomycin base (as sulfate).
sodium stibogluconate	<b>Injection:</b> 100 mg/mL in 30 mL vial.
<b>6.5.3 Antimalarial medicines</b>	
<b>6.5.3.1 For curative treatment</b>	
Medicines for the treatment of <i>P. falciparum</i> malaria cases should be used in combination. The list currently recommends combinations according to treatment guidelines. WHO recognizes that not all of the fixed dose combinations (FDCs in the WHO treatment guidelines exist, and encourages their development and rigorous testing. WHO also encourages development and testing of rectal dosage formulations.	
amodiaquine*	<p><b>Tablet:</b> 153 mg or 200 mg (as hydrochloride).</p> <p>*To be used in combination with artesunate 50 mg.</p>
artemether*	<p><b>Oily injection:</b> 80 mg/mL in 1 mL ampoule.</p> <p>*For use in the management of severe malaria.</p>
artemether + lumefantrine*	<p><b>Tablet:</b> 20 mg + 120 mg.</p> <p><b>Tablet (dispersible):</b> 20 mg + 120 mg.</p> <p>*Not recommended in the first trimester of pregnancy or in children below 5 kg.</p>
artesunate*	<p><b>Injection:</b> ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution.</p> <p>For use in the management of severe malaria.</p> <p><b>Rectal dosage form:</b> 50 mg; 100 mg; 200 mg capsules</p> <p>For pre-referral treatment of severe malaria only; patients should be taken to an appropriate health facility for follow-up care.</p> <p><b>Tablet:</b> 50 mg.</p> <p>*To be used in combination with either amodiaquine, mefloquine or sulfadoxine + pyrimethamine.</p>

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artesunate + amodiaquine *	<b>Tablet:</b> 25 mg + 67.5 mg; 50 mg + 135 mg; 100 mg + 270 mg. *Other combinations that deliver the target doses required such as 153 mg or 200 mg (as hydrochloride) with 50 mg artesunate can be alternatives.
artesunate + mefloquine	<b>Tablet:</b> 25 mg + 55 mg; 100 mg + 220 mg.
artesunate + pyronaridine tetraphosphate <span style="border: 1px solid black; padding: 0 2px;">a</span>	<b>Granules:</b> 20 mg + 60 mg. <b>Tablet:</b> 60 mg + 180 mg. <span style="border: 1px solid black; padding: 0 2px;">a</span> > 5 kg
chloroquine*	<b>Oral liquid:</b> 50 mg/5 mL (as phosphate or sulfate). <b>Tablet:</b> 100 mg; 150 mg (as phosphate or sulfate). *For use only for the treatment of <i>Plasmodium vivax</i> infection.
dihydroartemisinin + piperaquine phosphate <span style="border: 1px solid black; padding: 0 2px;">a</span>	<b>Tablet:</b> 20 mg + 160 mg; 40 mg + 320 mg. <span style="border: 1px solid black; padding: 0 2px;">a</span> > 5 kg
doxycycline*	<b>Capsule:</b> 100 mg (as hydrochloride or hyclate). <b>Tablet (dispersible):</b> 100 mg (as monohydrate). *For use only in combination with quinine.
mefloquine*	<b>Tablet:</b> 250 mg (as hydrochloride). *To be used in combination with artesunate 50 mg.
primaquine*	<b>Tablet:</b> 7.5 mg; 15 mg (as diphosphate). *Only for use to achieve radical cure of <i>Plasmodium vivax</i> and <i>Plasmodium ovale</i> infections, given for 14 days.
quinine*	<b>Injection:</b> 300 mg/mL (hydrochloride) in 2 mL ampoule. <b>Tablet:</b> 300 mg (sulfate) or 300 mg (bisulfate). *For use only in the management of severe malaria and should be used in combination with doxycycline.
sulfadoxine + pyrimethamine*	<b>Tablet:</b> 500 mg + 25 mg. *Only in combination with artesunate 50 mg.
<b>6.5.3.2 For chemoprevention</b>	
amodiaquine – sulfadoxine + pyrimethamine	<b>Co-packaged dispersible tablets:</b> amodiaquine 76.5 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 250 mg + 12.5 mg [1]; amodiaquine 153 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 500 mg + 25 mg [1].
chloroquine*	<b>Oral liquid:</b> 50 mg/5 mL (as phosphate or sulfate). <b>Tablet:</b> 150 mg (as phosphate or sulfate). *For use only for the treatment of <i>Plasmodium vivax</i> infection.
doxycycline <span style="border: 1px solid black; padding: 0 2px;">a</span>	<b>Solid oral dosage form:</b> 100 mg (as hydrochloride or hyclate). <span style="border: 1px solid black; padding: 0 2px;">a</span> > 8 years.
mefloquine <span style="border: 1px solid black; padding: 0 2px;">a</span>	<b>Tablet:</b> 250 mg (as hydrochloride). <span style="border: 1px solid black; padding: 0 2px;">a</span> > 5 kg or > 3 months.
proguanil*	<b>Tablet:</b> 100 mg (as hydrochloride). *For use only in combination with chloroquine.

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sulfadoxine + pyrimethamine	Tablet: 250 mg + 12.5 mg.
<b>6.5.4 Antipneumocystosis and antitoxoplasmosis medicines</b>	
pyrimethamine	Tablet: 25 mg.
sulfadiazine	Tablet: 500 mg.
sulfamethoxazole + trimethoprim	<p><b>Injection:</b> 80 mg + 16 mg/mL in 5 mL ampoule; 80 mg + 16 mg/mL in 10 mL ampoule.</p> <p><b>Oral liquid:</b> 200 mg + 40 mg/5 mL.</p> <p><b>Tablet:</b> 100 mg + 20 mg; 400 mg + 80 mg.</p> <p><b>Tablet (dispersible):</b> 100 mg + 20 mg.</p>
<b>6.5.5 Antitrypanosomal medicines</b>	
<b>6.5.5.1 African trypanosomiasis</b>	
fexinidazole*	<p><b>Tablet:</b> 600 mg</p> <p>*For the treatment of 1<sup>st</sup> and 2<sup>nd</sup> stage of human African trypanosomiasis due to <i>Trypanosoma brucei gambiense</i> infection.</p>
Medicines for the treatment of 1 <sup>st</sup> stage African trypanosomiasis.	
pentamidine*	<p><b>Powder for injection:</b> 300 mg (as isetionate) in vial.</p> <p>*To be used for the treatment of <i>Trypanosoma brucei gambiense</i> infection.</p>
suramin sodium*	<p><b>Powder for injection:</b> 1 g in vial.</p> <p>*To be used for the treatment of the initial phase of <i>Trypanosoma brucei rhodesiense</i> infection.</p>
Medicines for the treatment of 2 <sup>nd</sup> stage African trypanosomiasis	
eflornithine*	<p><b>Injection:</b> 200 mg/mL (hydrochloride) in 50 mL bottle.</p> <p>*To be used for the treatment of <i>Trypanosoma brucei gambiense</i> infection.</p>
nifurtimox*	<p><b>Tablet (scored):</b> 30 mg; 120 mg.</p> <p>*Only to be used in combination with eflornithine, for the treatment of <i>Trypanosoma brucei gambiense</i> infection.</p>
<i>Complementary List</i>	
melarsoprol	<b>Injection:</b> 180 mg/5 mL in 5 mL ampoule (3.6% solution).
<b>6.5.5.2 American trypanosomiasis</b>	
benznidazole	<p><b>Tablet:</b> 12.5 mg.</p> <p><b>Tablet (scored):</b> 50 mg; 100 mg.</p>
nifurtimox	<b>Tablet (scored):</b> 30 mg; 120 mg.
<b>6.6 Medicines for ectoparasitic infections</b>	
ivermectin	<b>Tablet:</b> 3 mg.

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6.7 Medicines for Ebola virus disease	
ansuvimab	Powder for injection: 400 mg.
atoltivimab + maftivimab + odesivimab	Injection: 241.7 mg + 241.7 mg + 241.7 mg in 14.5 mL vial.
6.8 Medicines for COVID-19	
WHO recommends that effective and safe therapeutics for prevention and treatment of COVID-19 should be considered as essential medicines in the context of the public health emergency. WHO recommendations are revised and updated regularly in WHO living guidelines for therapeutics for the treatment and prevention of COVID-19.	
Selection of essential therapeutics for COVID-19 at the national level should be informed by recommendations in these guidelines, and consideration of the latest evidence, epidemiology and national priorities.	
The latest WHO Therapeutics and COVID-19: living guideline is available online at: <a href="https://app.magicapp.org/#/guideline/nBkO1E">https://app.magicapp.org/#/guideline/nBkO1E</a>	
The latest WHO Drugs to prevent COVID-19: living guideline is available online at: <a href="https://app.magicapp.org/#/guideline/L6RxYL">https://app.magicapp.org/#/guideline/L6RxYL</a>	
7. ANTIMIGRAINE MEDICINES	
7.1 For treatment of acute attack	
ibuprofen	<b>Oral liquid:</b> 100 mg/5 mL. <b>Tablet:</b> 200 mg; 400 mg.
paracetamol (acetaminophen)	<b>Oral liquid:</b> 120 mg/5 mL or 125 mg/5 mL*; 250 mg/5 mL. *The presence of both 120 mg/5 mL and 125 mg/5mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided. <b>Suppository:</b> 250 mg. <b>Tablet:</b> 250 mg; 325 mg; 500 mg. <b>Tablet (dispersible):</b> 100 mg; 250 mg.
7.2 For prophylaxis	
propranolol	<b>Tablet:</b> 20 mg; 40 mg (hydrochloride).

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8. IMMUNOMODULATORS AND ANTINEOPLASTICS	
8.1 Immunomodulators for non-malignant disease	
<i>Complementary List</i>	
<input checked="" type="checkbox"/> <i>adalimumab*</i> <i>Therapeutic alternatives*:</i> - <i>etanercept</i> - <i>infliximab</i>  <i>*including quality-assured biosimilars</i>	<b>Injection:</b> 10 mg/0.2 mL; 20 mg/0.4 mL; 40 mg/0.8 mL; 40 mg/0.4 mL.
<i>azathioprine</i>	<b>Oral liquid:</b> 10 mg/mL. <b>Powder for injection:</b> 50 mg; 100 mg (as sodium salt) in vial. <b>Tablet:</b> 25 mg. <b>Tablet (scored):</b> 50 mg.
<i>ciclosporin</i>	<b>Capsule:</b> 25 mg. <b>Concentrate for injection:</b> 50 mg/mL in 1 mL ampoule. <b>Oral liquid:</b> 100 mg/mL.
<i>tacrolimus</i>	<b>Capsule (immediate-release):</b> 0.5 mg; 0.75 mg; 1 mg; 2 mg; 5 mg. <b>Granules for oral suspension:</b> 0.2 mg; 1 mg. <b>Injection:</b> 5 mg/mL in 1 mL vial.
8.2 Antineoplastic and supportive medicines	
Medicines listed below should be used according to protocols for treatment of the diseases.	
<i>8.2.1 Cytotoxic medicines</i>	
<i>Complementary List</i>	
<i>arsenic trioxide</i>	<b>Concentrate for solution for infusion:</b> 1 mg/mL; 2 mg/mL. – Acute promyelocytic leukaemia
<i>asparaginase*</i>  <i>*including quality-assured biosimilars</i>	<b>Powder for injection:</b> 10 000 IU in vial. – Acute lymphoblastic leukaemia
<i>bleomycin</i>	<b>Powder for injection:</b> 15 000 IU (as sulfate) in vial. – Hodgkin lymphoma – Kaposi sarcoma – Testicular germ cell tumours – Ovarian germ cell tumours
<i>calcium folinate (leucovorin calcium)</i>	<b>Injection:</b> 3 mg/mL in 10 mL ampoule; 7.5 mg/mL in 2 mL ampoule; 10 mg/mL in 5 mL ampoule. <b>Tablet:</b> 5 mg; 15 mg; 25 mg. – Burkitt lymphoma – Osteosarcoma

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carboplatin	<p><b>Injection:</b> 50 mg/5 mL; 150 mg/15 mL; 450 mg/45 mL; 600 mg/60 mL.</p> <ul style="list-style-type: none"> <li>– Low-grade glioma</li> <li>– Nephroblastoma (<i>Wilms tumour</i>)</li> <li>– Osteosarcoma</li> <li>– Ovarian germ cell tumours</li> <li>– Retinoblastoma</li> <li>– Testicular germ cell tumours</li> </ul>
cisplatin	<p><b>Injection:</b> 10 mg/10 mL; 20 mg/20 mL; 50 mg/50 mL; 100 mg/100mL.</p> <ul style="list-style-type: none"> <li>– Low-grade glioma</li> <li>– Nasopharyngeal cancer</li> <li>– Osteosarcoma</li> <li>– Ovarian germ cell tumours</li> <li>– Testicular germ cell tumours</li> </ul>
cyclophosphamide	<p><b>Powder for injection:</b> 500 mg; 1 g; 2 g in vial.  <b>Solid oral dosage form:</b> 25 mg; 50 mg.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Anaplastic large cell lymphoma</li> <li>– Burkitt lymphoma</li> <li>– Diffuse large B-cell lymphoma</li> <li>– Ewing sarcoma</li> <li>– Hodgkin lymphoma</li> <li>– Low-grade glioma</li> <li>– Nephroblastoma (<i>Wilms tumour</i>)</li> <li>– Rhabdomyosarcoma</li> </ul>
cytarabine	<p><b>Injection:</b> 100 mg/mL in vial.  <b>Powder for injection:</b> 100 mg in vial.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Acute myeloid leukaemia</li> <li>– Acute promyelocytic leukaemia</li> <li>– Anaplastic large cell lymphoma</li> <li>– Burkitt lymphoma</li> <li>– Langerhans cell histiocytosis</li> </ul>
dacarbazine	<p><b>Powder for injection:</b> 100 mg; 200 mg in vial.</p> <ul style="list-style-type: none"> <li>– Hodgkin lymphoma</li> </ul>
dactinomycin	<p><b>Powder for injection:</b> 500 micrograms in vial.</p> <ul style="list-style-type: none"> <li>– Ewing sarcoma</li> <li>– Nephroblastoma (<i>Wilms tumour</i>)</li> <li>– Rhabdomyosarcoma</li> </ul>
daunorubicin	<p><b>Injection:</b> 2 mg/mL; 5 mg/mL (as hydrochloride) in vial.  <b>Powder for injection:</b> 20 mg; 50 mg (as hydrochloride) in vial.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Acute promyelocytic leukaemia</li> </ul>

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doxorubicin	<p><b>Injection:</b> 2 mg/mL (hydrochloride) in 5 mL, 25 mL vial.</p> <p><b>Powder for injection:</b> 10 mg; 50 mg (hydrochloride) in vial.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Anaplastic large cell lymphoma</li> <li>– Burkitt lymphoma</li> <li>– Diffuse large B-cell lymphoma</li> <li>– Ewing sarcoma</li> <li>– Hodgkin lymphoma</li> <li>– Kaposi sarcoma</li> <li>– Nephroblastoma (<i>Wilms tumour</i>)</li> <li>– Osteosarcoma</li> </ul>
doxorubicin (as pegylated liposomal)	<p><b>Injection:</b> 2 mg/mL (hydrochloride) in 10 mL, 25 mL vial.</p> <ul style="list-style-type: none"> <li>– Kaposi sarcoma</li> </ul>
etoposide	<p><b>Capsule:</b> 50 mg; 100 mg.</p> <p><b>Injection:</b> 20 mg/mL in 5 mL ampoule.</p> <p><b>Powder for injection:</b> 100 mg (as phosphate) in vial.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Acute myeloid leukaemia</li> <li>– Anaplastic large cell lymphoma</li> <li>– Burkitt lymphoma</li> <li>– Ewing sarcoma</li> <li>– Hodgkin lymphoma</li> <li>– Nephroblastoma (<i>Wilms tumour</i>)</li> <li>– Osteosarcoma</li> <li>– Ovarian germ cell tumours</li> <li>– Retinoblastoma</li> <li>– Testicular germ cell tumours</li> </ul>
fluorouracil	<p><b>Injection:</b> 50 mg/mL in vial.</p> <ul style="list-style-type: none"> <li>– Early stage colon cancer</li> <li>– Early stage rectal cancer</li> <li>– Nasopharyngeal cancer</li> <li>– Metastatic colorectal cancer</li> </ul>
hydroxycarbamide (hydroxyurea)	<p><b>Solid oral dosage form:</b> 100 mg; 200 mg; 300 mg; 400 mg; 500 mg; 1 g.</p> <ul style="list-style-type: none"> <li>– Chronic myeloid leukaemia</li> </ul>
ifosfamide	<p><b>Powder for injection:</b> 500 mg; 1 g; 2 g in vial.</p> <ul style="list-style-type: none"> <li>– Anaplastic large cell lymphoma</li> <li>– Burkitt lymphoma</li> <li>– Ewing sarcoma</li> <li>– Nephroblastoma (<i>Wilms tumour</i>)</li> <li>– Osteosarcoma</li> <li>– Ovarian germ cell tumours</li> <li>– Rhabdomyosarcoma</li> <li>– Testicular germ cell tumours</li> </ul>
irinotecan	<p><b>Injection:</b> 40 mg/2 mL in 2 mL vial; 100 mg/5 mL in 5 mL vial; 500 mg/25 mL in 25 mL vial.</p> <ul style="list-style-type: none"> <li>– Metastatic colorectal cancer</li> <li>– Nephroblastoma (<i>Wilms tumour</i>)</li> <li>– Rhabdomyosarcoma</li> </ul>

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<i>mercaptopurine</i>	<p><b>Tablet:</b> 50 mg.</p> <p><b>Oral liquid:</b> 20 mg/mL.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Acute promyelocytic leukaemia</li> <li>– Langerhans cell histiocytosis</li> </ul>
<i>methotrexate</i>	<p><b>Concentrated injection:</b> 1000 mg/10 mL.</p> <p><b>Injection:</b> 50 mg/2 mL.</p> <p><b>Powder for injection:</b> 50 mg (as sodium) in vial.</p> <p><b>Tablet:</b> 2.5 mg (as sodium).</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Acute promyelocytic leukaemia</li> <li>– Anaplastic large cell lymphoma</li> <li>– Burkitt lymphoma</li> <li>– Langerhans cell histiocytosis</li> <li>– Osteosarcoma</li> </ul>
<i>oxaliplatin</i>	<p><b>Injection:</b> 50 mg/10 mL in 10 mL vial; 100 mg/20 mL in 20 mL vial; 200 mg/40 mL in 40 mL vial.</p> <p><b>Powder for injection:</b> 50 mg; 100 mg in vial.</p> <ul style="list-style-type: none"> <li>– Early stage colon cancer</li> <li>– Metastatic colorectal cancer</li> </ul>
<i>paclitaxel</i>	<p><b>Injection:</b> 6 mg/mL in vial.</p> <ul style="list-style-type: none"> <li>– Ovarian germ cell tumours</li> </ul>
<i>pegaspargase*</i> <small>*including quality-assured biosimilars</small>	<p><b>Injection:</b> 3750 units/5 mL in vial</p> <p><b>Powder for injection:</b> 3750 units in vial.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia.</li> </ul>
<i>procarbazine</i>	<p><b>Capsule:</b> 50 mg (as hydrochloride).</p> <ul style="list-style-type: none"> <li>– Hodgkin lymphoma</li> </ul>
<i>realgar-Indigo naturalis formulation</i>	<p><b>Tablet:</b> 270 mg (containing tetra-arsenic tetra-sulfide 30 mg)</p> <ul style="list-style-type: none"> <li>– Acute promyelocytic leukaemia</li> </ul>
<i>tioguanine</i>	<p><b>Solid oral dosage form:</b> 40 mg.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia.</li> </ul>
<i>vinblastine</i>	<p><b>Injection:</b> 10 mg/10 mL (sulfate) in vial.</p> <p><b>Powder for injection:</b> 10 mg (sulfate) in vial.</p> <ul style="list-style-type: none"> <li>– Anaplastic large cell lymphoma</li> <li>– Hodgkin lymphoma</li> <li>– Langerhans cell histiocytosis</li> <li>– Low-grade glioma</li> <li>– Ovarian germ cell tumours</li> <li>– Testicular germ cell tumours</li> </ul>

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<i>vincristine</i>	<p><b>Injection:</b> 1 mg/mL (sulfate); 2 mg/2 mL (sulfate) in vial.</p> <p><b>Powder for injection:</b> 1 mg; 5 mg (sulfate) in vial.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Burkitt lymphoma.</li> <li>– Diffuse large B-cell lymphoma</li> <li>– Ewing sarcoma</li> <li>– Hodgkin lymphoma</li> <li>– Kaposi sarcoma</li> <li>– Langerhans cell histiocytosis</li> <li>– Low-grade glioma</li> <li>– Nephroblastoma (<i>Wilms tumour</i>)</li> <li>– Retinoblastoma</li> <li>– Rhabdomyosarcoma</li> </ul>
<i>vinorelbine</i>	<p><b>Capsule:</b> 20 mg; 30 mg.</p> <p><b>Injection:</b> 10 mg/mL in 1 mL, 5 mL vial.</p> <ul style="list-style-type: none"> <li>– Rhabdomyosarcoma</li> </ul>

## 8.2.2 Targeted therapies

Complementary List	
<i>all-trans retinoid acid (ATRA)</i>	<p><b>Capsule:</b> 10 mg.</p> <ul style="list-style-type: none"> <li>– Acute promyelocytic leukaemia</li> </ul>
<i>dasatinib</i>	<p><b>Tablet:</b> 20 mg; 50 mg; 70 mg; 80 mg.</p> <ul style="list-style-type: none"> <li>– Imatinib-resistant chronic myeloid leukaemia</li> </ul>
<i>everolimus</i>	<p><b>Tablet:</b> 2.5 mg; 5 mg; 7.5 mg; 10 mg.</p> <p><b>Tablet (dispersible):</b> 2 mg; 3 mg; 5 mg.</p> <ul style="list-style-type: none"> <li>– Subependymal giant cell astrocytoma</li> </ul>
<i>imatinib</i>	<p><b>Solid oral dosage form:</b> 100 mg; 400 mg.</p> <ul style="list-style-type: none"> <li>– Chronic myeloid leukaemia</li> <li>– Gastrointestinal stromal tumour</li> <li>– Philadelphia chromosome positive acute lymphoblastic leukaemia</li> </ul>
<i>nilotinib</i>	<p><b>Capsule:</b> 150 mg; 200 mg.</p> <ul style="list-style-type: none"> <li>– Imatinib-resistant chronic myeloid leukaemia</li> </ul>
<i>rituximab*</i> <small>*including quality-assured biosimilars</small>	<p><b>Injection (intravenous):</b> 100 mg/10 mL in 10 mL vial; 500 mg/50 mL in 50 mL vial.</p> <ul style="list-style-type: none"> <li>– Burkitt lymphoma</li> <li>– Diffuse large B-cell lymphoma</li> </ul>

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8.2.3 Immunomodulators	
Complementary List	
filgrastim*  *including quality-assured biosimilars	<p><b>Injection:</b> 120 micrograms/0.2 mL; 300 micrograms/0.5 mL; 480 micrograms/0.8 mL in pre-filled syringe.</p> <p><b>Injection:</b> 300 micrograms/mL in 1 mL vial; 480 micrograms/1.6 mL in 1.6 mL vial.</p> <ul style="list-style-type: none"> <li>– Primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy.</li> <li>– Secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy</li> <li>– To facilitate administration of dose dense chemotherapy regimens</li> </ul>
pegfilgrastim*  *including quality-assured biosimilars	<p><b>Injection:</b> 6 mg/0.6 mL in pre-filled syringe.</p> <ul style="list-style-type: none"> <li>– Primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy</li> <li>– Secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy</li> <li>– To facilitate administration of dose dense chemotherapy regimens</li> </ul>
8.2.4 Hormones and antihormones	
Complementary List	
dexamethasone	<p><b>Injection:</b> 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule.</p> <p><b>Oral liquid:</b> 2 mg/5 mL.</p> <p><b>Tablet:</b> 2 mg; 4 mg.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Anaplastic large cell lymphoma</li> <li>– Burkitt lymphoma</li> </ul>
hydrocortisone	<p><b>Powder for injection:</b> 100 mg (as sodium succinate) in vial.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Burkitt lymphoma</li> </ul>
methylprednisolone	<p><b>Injection:</b> 40 mg/mL (as sodium succinate) in 1 mL single-dose vial and 5 mL multi-dose vials; 80 mg/mL (as sodium succinate) in 1 mL single-dose vial.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukemia</li> <li>– Burkitt lymphoma</li> </ul>
□ prednisolone  Therapeutic alternatives: - prednisone	<p><b>Oral liquid:</b> 5 mg/mL.</p> <p><b>Tablet:</b> 5 mg; 25 mg.</p> <ul style="list-style-type: none"> <li>– Acute lymphoblastic leukaemia</li> <li>– Anaplastic large cell lymphoma</li> <li>– Burkitt lymphoma</li> <li>– Diffuse large B-cell lymphoma</li> <li>– Hodgkin lymphoma</li> <li>– Langerhans cell histiocytosis</li> </ul>

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8.2.5 Supportive medicines	
<i>Complementary List</i>	
allopurinol	<p><b>Tablet:</b> 100 mg; 300 mg.</p> <ul style="list-style-type: none"> <li>– Tumour lysis syndrome</li> </ul>
mesna	<p><b>Injection:</b> 100 mg/mL in 4 mL and 10 mL ampoules.</p> <p><b>Tablet:</b> 400 mg; 600 mg.</p> <ul style="list-style-type: none"> <li>– Burkitt lymphoma</li> <li>– Ewing sarcoma</li> <li>– Nephroblastoma (<i>Wilms tumour</i>)</li> <li>– Osteosarcoma</li> <li>– Ovarian germ cell tumours</li> <li>– Rhabdomyosarcoma</li> <li>– Testicular germ cell tumours</li> </ul>
rasburicase	<p><b>Powder and solvent for solution for infusion:</b> 1.5 mg; 7.5 mg in vial</p> <ul style="list-style-type: none"> <li>– Tumour lysis syndrome</li> </ul>
9. THERAPEUTIC FOODS	
ready-to-use therapeutic food	<p><b>Biscuit or paste*.</b></p> <p>*of nutritional composition as determined by the UN joint statement on the community-based management of severe acute malnutrition and Codex alimentarius guidelines.</p>
10. MEDICINES AFFECTING THE BLOOD	
10.1 Antianaemia medicines	
ferrous salt	<p><b>Oral liquid:</b> equivalent to 25 mg iron (as sulfate)/mL.</p> <p><b>Tablet:</b> equivalent to 60 mg iron.</p>
folic acid	<p><b>Tablet:</b> 1 mg; 5 mg.</p>
hydroxocobalamin	<p><b>Injection:</b> 1 mg (as acetate, as hydrochloride or as sulfate) in 1 mL ampoule.</p>
<i>Complementary List</i>	
<input type="checkbox"/> <i>erythropoiesis-stimulating agents</i> Therapeutic alternatives: - epoetin alfa, beta and theta - darbepoetin alfa <small>*including quality-assured biosimilars</small>	<p><b>Injection: pre-filled syringe</b></p> <p>1000 IU/0.5 mL; 2000 IU/0.5 mL; 3000 IU/0.3 mL;            4000 IU/0.4 mL; 5000 IU/0.5 mL; 6000 IU/0.6 mL;            8000 IU/0.8mL; 10 000 IU/1 mL; 20 000 IU/0.5 mL;            40 000 IU/1 mL.</p>
10.2 Medicines affecting coagulation	
<input type="checkbox"/> enoxaparin Therapeutic alternatives: - dalteparin - nadroparin <small>*including quality-assured biosimilars</small>	<p><b>Injection: ampoule or pre-filled syringe</b></p> <p>20 mg/0.2 mL; 40 mg/0.4 mL; 60 mg/0.6 mL; 80 mg/0.8 mL;            100 mg/1 mL; 120 mg/0.8 mL; 150 mg/1 mL.</p>
phytomenadione	<p><b>Injection:</b> 1 mg/mL; 10 mg/mL in ampoule.</p> <p><b>Tablet:</b> 10 mg.</p>

# WHO Model List of Essential Medicines for Children – 9th List (2023)

<i>Complementary List</i>	
desmopressin	<b>Injection:</b> 4 micrograms/mL (as acetate) in 1 mL ampoule. <b>Nasal spray:</b> 10 micrograms (as acetate) per dose.
heparin sodium	<b>Injection:</b> 1000 IU/mL; 5000 IU/mL in 1 mL ampoule.
protamine sulfate	<b>Injection:</b> 10 mg/mL in 5 mL ampoule.
<input type="checkbox"/> warfarin Therapeutic alternatives to be reviewed	<b>Tablet:</b> 0.5 mg; 1 mg; 2 mg; 5 mg (sodium).
10.3 Other medicines for haemoglobinopathies	
<input type="checkbox"/> deferasirox Therapeutic alternatives: - deferiprone	<b>Tablet (dispersible):</b> 100 mg; 125 mg; 250 mg; 400 mg; 500 mg. <b>Tablet (film-coated):</b> 90 mg; 180 mg; 360 mg.
<i>Complementary list</i>	
deferoxamine	<b>Powder for injection:</b> 500 mg (mesilate) in vial.
hydroxycarbamide (hydroxyurea)	<b>Solid oral dosage form:</b> 100 mg; 200 mg; 500 mg; 1 g.
11. BLOOD PRODUCTS OF HUMAN ORIGIN AND PLASMA SUBSTITUTES	
11.1 Blood and blood components	
In accordance with the World Health Assembly resolution WHA63.12, WHO recognizes that achieving self-sufficiency, unless special circumstances preclude it, in the supply of safe blood components based on voluntary, non-remunerated blood donation, and the security of that supply are important national goals to prevent blood shortages and meet the transfusion requirements of the patient population. All preparations should comply with the WHO requirements.	
<input type="checkbox"/> cryoprecipitate, pathogen-reduced Therapeutic alternatives: - cryoprecipitate (not pathogen-reduced)	<b>Injection:</b> frozen liquid in bag or lyophilized powder in vial containing: - > 50 IU Factor VIII - > 100 IU vWF - > 140 mg clottable fibrinogen per unit
fresh-frozen plasma	
platelets	
red blood cells	
whole blood	
11.2 Plasma-derived medicines	
All human plasma-derived medicines should comply with the WHO requirements.	
11.2.1 Human immunoglobulins	
anti-rabies immunoglobulin	<b>Injection:</b> 150 IU/mL in vial.
anti-tetanus immunoglobulin	<b>Injection:</b> 500 IU in vial.

# WHO Model List of Essential Medicines for Children – 9th List (2023)

<i>Complementary List</i>	
<i>normal immunoglobulin</i>	<p><b>Intramuscular administration:</b> 16% protein solution.</p> <p><b>Subcutaneous administration:</b> 15%; 16% protein solution.</p> <ul style="list-style-type: none"> <li>– Primary immune deficiency.</li> </ul> <p><b>Intravenous administration:</b> 5%; 10% protein solution.</p> <ul style="list-style-type: none"> <li>– Primary immune deficiency</li> <li>– Kawasaki disease</li> <li>– Langerhans cell histiocytosis</li> </ul>
11.2.2 Blood coagulation factors	
<i>Complementary List</i>	
<i>coagulation factor VIII</i>	<b>Powder for injection:</b> 250 IU; 500 IU; 1000 IU in vial.
<input type="checkbox"/> <i>coagulation factor IX</i> Therapeutic alternatives: - <i>coagulation factor IX complex</i>	<b>Powder for injection:</b> 500 IU; 1000 IU in vial.
11.3 Plasma substitutes	
<input type="checkbox"/> <i>dextran 70</i> Therapeutic alternatives: - <i>Polygeline injectable solution 3.5%</i>	<b>Injectable solution:</b> 6%.
12. CARDIOVASCULAR MEDICINES	
12.1 Antianginal medicines	
12.2 Antiarrhythmic medicines	
12.3 Antihypertensive medicines	
<input type="checkbox"/> <i>enalapril</i> Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (C09AA ACE inhibitors, plain)	<b>Oral liquid:</b> 1 mg/mL (as hydrogen maleate). <b>Tablet:</b> 2.5 mg; 5 mg; 10 mg (as hydrogen maleate).
12.4 Medicines used in heart failure	
<i>furosemide</i>	<b>Injection:</b> 10 mg/mL in 2 mL, 5 mL ampoule. <b>Oral liquid:</b> 20 mg/5 mL; 50 mg/5 mL. <b>Tablet:</b> 20 mg; 40 mg.
<i>Complementary List</i>	
<i>digoxin</i>	<b>Injection:</b> 100 micrograms/mL in 1 mL ampoule; 250 micrograms/mL in 2 mL ampoule. <b>Oral liquid:</b> 50 micrograms/mL. <b>Tablet:</b> 62.5 micrograms; 125 micrograms; 250 mg micrograms.
<i>dopamine</i>	<b>Injection:</b> 40 mg/mL (hydrochloride) in 5 mL vial.
12.5 Antithrombotic medicines	
12.6 Lipid-lowering agents	

# WHO Model List of Essential Medicines for Children – 9th List (2023)

12.7 Fixed-dose combinations for prevention of atherosclerotic cardiovascular disease	
<b>13. DERMATOLOGICAL MEDICINES</b>	
<b>13.1 Antifungal medicines</b>	
<input type="checkbox"/> miconazole Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (D01AC Imidazole and triazole derivatives) excluding combinations	Cream or ointment: 2% (nitrate).
selenium sulfide	Detergent-based suspension: 2%.
terbinafine	Cream or ointment: 1% (hydrochloride).
<b>13.2 Anti-infective medicines</b>	
mupirocin	Cream: 2% (as calcium). Ointment: 2%.
potassium permanganate	Aqueous solution: 1:10 000.
silver sulfadiazine <sup>a</sup>	Cream: 1%. <sup>a</sup> > 2 months.
<b>13.3 Anti-inflammatory and antipruritic medicines</b>	
<input type="checkbox"/> betamethasone <sup>a</sup> Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (D07AC Corticosteroids, potent (group III))	Cream or ointment: 0.1% (as valerate). <sup>a</sup> Hydrocortisone preferred in neonates.
calamine	Lotion.
hydrocortisone	Cream or ointment: 1% (acetate).
<b>13.4 Medicines affecting skin differentiation and proliferation</b>	
benzoyl peroxide	Cream or lotion: 5%.
<input type="checkbox"/> calcipotriol Therapeutic alternatives: - calcitriol - tacalcitol	Cream or ointment: 50 micrograms/mL (0.005%). Lotion: 50 micrograms/mL (0.005%).
coal tar	Solution: 5%.
<input type="checkbox"/> podophyllum resin Therapeutic alternatives: - podophyllotoxin	Solution: 10% to 25%.
salicylic acid	Solution: 5%.
urea	Cream or ointment: 5%; 10%.
<i>Complementary List</i>	
<i>methotrexate</i>	<i>Tablet:</i> 2.5 mg; 10 mg (as sodium).

# WHO Model List of Essential Medicines for Children – 9th List (2023)

<b>13.5 Scabicides and pediculicides</b>	
<input type="checkbox"/> benzyl benzoate <small>a</small>	<b>Lotion:</b> 25%. <small>a &gt; 2 years.</small>
Therapeutic alternatives: - precipitated sulfur topical ointment	
<input type="checkbox"/> permethrin	<b>Cream:</b> 5%. <b>Lotion:</b> 1%.
<b>14. DIAGNOSTIC AGENTS</b>	
<b>14.1 Ophthalmic medicines</b>	
fluorescein	<b>Eye drops:</b> 1% (sodium salt).
<input type="checkbox"/> tropicamide	
Therapeutic alternatives: - atropine - cyclopentolate	<b>Eye drops:</b> 0.5%.
<b>14.2 Radiocontrast media</b>	
<i>Complementary List</i>	
<input type="checkbox"/> barium sulfate	<b>Aqueous suspension.</b>
<b>15. ANTISEPTICS AND DISINFECTANTS</b>	
<b>15.1 Antiseptics</b>	
<input type="checkbox"/> chlorhexidine	<b>Solution:</b> 5% (digluconate).
Therapeutic alternatives to be reviewed	
<input type="checkbox"/> ethanol	
Therapeutic alternatives: - propanol	<b>Solution:</b> 70% (denatured).
<input type="checkbox"/> povidone iodine	
Therapeutic alternatives: - iodine	<b>Solution:</b> 10% (equivalent to 1% available iodine).
<b>15.2 Disinfectants</b>	
alcohol based hand rub	<b>Solution</b> containing ethanol 80% volume /volume. <b>Solution</b> containing isopropyl alcohol 75% volume/volume.
chlorine base compound	<b>Liquid:</b> (0.1% available chlorine) for solution. <b>Powder:</b> (0.1% available chlorine) for solution. <b>Solid:</b> (0.1% available chlorine) for solution.
<input type="checkbox"/> chloroxylenol	
Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (D08AE Phenol and derivatives)	<b>Solution:</b> 4.8%.
glutaral	<b>Solution:</b> 2%.

# WHO Model List of Essential Medicines for Children – 9th List (2023)

16. DIURETICS	
furosemide	<p><b>Injection:</b> 10 mg/mL in 2 mL, 5 mL ampoule.</p> <p><b>Oral liquid:</b> 20 mg/5 mL; 50 mg/5 mL.</p> <p><b>Tablet:</b> 20 mg; 40 mg.</p>
<i>Complementary List</i>	
<input type="checkbox"/> hydrochlorothiazide Therapeutic alternatives: - chlorothiazide - chlortalidone	<p><b>Tablet (scored):</b> 25 mg.</p>
mannitol	<p><b>Injectable solution:</b> 10%; 20%.</p>
spironolactone	<p><b>Oral liquid:</b> 5 mg/5 mL; 10 mg/5 mL; 25 mg/5 mL.</p> <p><b>Tablet:</b> 25 mg.</p>
17. GASTROINTESTINAL MEDICINES	
<i>Complementary List</i>	
pancreatic enzymes	<p>Age-appropriate formulations and doses including lipase, protease and amylase.</p>
17.1 Antiulcer medicines	
<input type="checkbox"/> omeprazole Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (A02BC Proton pump inhibitors) excluding combinations	<p><b>Powder for oral liquid:</b> 20 mg; 40 mg sachets.</p> <p><b>Solid oral dosage form:</b> 10 mg; 20 mg; 40 mg.</p>
<input type="checkbox"/> ranitidine Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (A02BA H <sub>2</sub> -receptor antagonists) excluding combinations	<p><b>Injection:</b> 25 mg/mL (as hydrochloride) in 2 mL ampoule.</p> <p><b>Oral liquid:</b> 75 mg/5 mL (as hydrochloride).</p> <p><b>Tablet:</b> 150 mg (as hydrochloride).</p>
17.2 Antiemetic medicines	
dexamethasone	<p><b>Injection:</b> 4 mg/mL in 1 mL ampoule (as disodium phosphate salt).</p> <p><b>Oral liquid:</b> 0.5 mg/5 mL; 2 mg/5 mL.</p> <p><b>Solid oral dosage form:</b> 0.5 mg; 0.75 mg; 1.5 mg; 4 mg.</p>
metoclopramide <sup>a</sup>	<p><b>Injection:</b> 5 mg/mL (hydrochloride) in 2 mL ampoule.</p> <p><b>Oral liquid:</b> 5 mg/5 mL.</p> <p><b>Tablet:</b> 10 mg (hydrochloride).</p> <p><sup>a</sup> Not in neonates.</p>
<input type="checkbox"/> ondansetron <sup>a</sup> Therapeutic alternatives: - dolasetron - granisetron - palonosetron - tropisetron	<p><b>Injection:</b> 2 mg base/mL in 2 mL ampoule (as hydrochloride).</p> <p><b>Oral liquid:</b> 4 mg base/5 mL.</p> <p><b>Solid oral dosage form:</b> Eq 4 mg base; Eq 8 mg base.</p> <p><sup>a</sup> &gt; 1 month.</p>

# WHO Model List of Essential Medicines for Children – 9th List (2023)

<i>Complementary list</i>																					
<i>aprepitant</i>	<b>Capsule:</b> 80 mg; 125 mg; 165 mg <b>Powder for oral susension:</b> 125 mg in sachet																				
<b>17.3 Anti-inflammatory medicines</b>																					
<b>17.4 Laxatives</b>																					
<b>17.5 Medicines used in diarrhoea</b>																					
oral rehydration salts – zinc sulfate	Co-package containing: ORS powder for dilution (see Section 17.5.1) – zinc sulfate <b>solid oral dosage form</b> 20 mg (see Section 17.5.2)																				
<b>17.5.1 Oral rehydration</b>																					
oral rehydration salts	<p><b>Powder for dilution</b> in 200 mL; 500 mL; 1 L.</p> <table> <tbody> <tr><td>glucose:</td><td>75 mEq</td></tr> <tr><td>sodium:</td><td>75 mEq or mmol/L</td></tr> <tr><td>chloride:</td><td>65 mEq or mmol/L</td></tr> <tr><td>potassium:</td><td>20 mEq or mmol/L</td></tr> <tr><td>citrate:</td><td>10 mmol/L</td></tr> <tr><td>osmolarity:</td><td>245 mOsm/L</td></tr> <tr><td>glucose:</td><td>13.5 g/L</td></tr> <tr><td>sodium chloride:</td><td>2.6 g/L</td></tr> <tr><td>potassium chloride:</td><td>1.5 g/L</td></tr> <tr><td>trisodium citrate dihydrate*:</td><td>2.9 g/L</td></tr> </tbody> </table> <p>*trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/L. However, as the stability of this latter formulation is very poor under tropical conditions, it is recommended only when manufactured for immediate use.</p>	glucose:	75 mEq	sodium:	75 mEq or mmol/L	chloride:	65 mEq or mmol/L	potassium:	20 mEq or mmol/L	citrate:	10 mmol/L	osmolarity:	245 mOsm/L	glucose:	13.5 g/L	sodium chloride:	2.6 g/L	potassium chloride:	1.5 g/L	trisodium citrate dihydrate*:	2.9 g/L
glucose:	75 mEq																				
sodium:	75 mEq or mmol/L																				
chloride:	65 mEq or mmol/L																				
potassium:	20 mEq or mmol/L																				
citrate:	10 mmol/L																				
osmolarity:	245 mOsm/L																				
glucose:	13.5 g/L																				
sodium chloride:	2.6 g/L																				
potassium chloride:	1.5 g/L																				
trisodium citrate dihydrate*:	2.9 g/L																				
<b>17.5.2 Medicines for diarrhoea</b>																					
zinc sulfate*	<p><b>Solid oral dosage form:</b> 20 mg.</p> <p>*In acute diarrhoea, zinc sulfate should be used as an adjunct to oral rehydration salts.</p>																				
<b>18. MEDICINES FOR ENDOCRINE DISORDERS</b>																					
<b>18.1 Adrenal hormones and synthetic substitutes</b>																					
fludrocortisone	<b>Tablet:</b> 100 micrograms (acetate).																				
hydrocortisone	<b>Tablet:</b> 5 mg; 10 mg; 20 mg.																				
<b>18.2 Androgens</b>																					
<b>18.3 Estrogens</b>																					
<b>18.4 Progestogens</b>																					

# WHO Model List of Essential Medicines for Children – 9th List (2023)

<b>18.5 Medicines for diabetes</b>	
<b>18.5.1 Insulins</b>	
insulin injection (soluble)* <i>*including quality-assured biosimilars</i>	<b>Injection:</b> 100 IU/mL in 10 mL vial; 100 IU/mL in 3 mL cartridge or pre-filled pen.
intermediate-acting insulin* <i>*including quality-assured biosimilars</i>	<b>Injection:</b> 100 IU/mL in 10 mL vial; 100 IU/mL in 3 mL cartridge or pre-filled pen (as compound insulin zinc suspension or isophane insulin).
<input type="checkbox"/> long-acting insulin analogues* Therapeutic alternatives: - insulin detemir - insulin degludec - insulin glargine <i>*including quality-assured biosimilars</i>	<b>Injection:</b> 100 IU/mL in 3 mL cartridge or pre-filled pen.
<b>18.5.2 Oral hypoglycaemic agents</b>	
<i>Complementary List</i>	
metformin	<b>Tablet:</b> 500 mg (hydrochloride).
<b>18.6 Medicines for hypoglycaemia</b>	
glucagon	<b>Injection:</b> 1 mg/mL.
<i>Complementary List</i>	
diazoxide	<b>Oral liquid:</b> 50 mg/mL <b>Tablet:</b> 50 mg
<b>18.7 Thyroid hormones and antithyroid medicines</b>	
levothyroxine	<b>Tablet:</b> 25 micrograms; 50 micrograms; 100 micrograms (sodium salt).
<i>Complementary List</i>	
Lugol's solution	<b>Oral liquid:</b> about 130 mg total iodine/mL.
<input type="checkbox"/> methimazole Therapeutic alternatives: - carbimazole (depending on local availability)	<b>Tablet:</b> 5mg, 10mg, 20mg.
potassium iodide	<b>Tablet:</b> 60 mg.
propylthiouracil*	<b>Tablet:</b> 50 mg. <i>*For use when alternative first-line treatment is not appropriate or available</i>
<b>18.8 Medicines for disorders of the pituitary hormone system</b>	

# WHO Model List of Essential Medicines for Children – 9th List (2023)

19. IMMUNOLOGICALS	
<b>19.1 Diagnostic agents</b>	
All tuberculins should comply with the WHO requirements for tuberculins.	
tuberculin, purified protein derivative (PPD)	<b>Injection.</b>
<b>19.2 Sera, immunoglobulins and monoclonal antibodies</b>	
All plasma fractions should comply with the WHO requirements.	
anti-rabies virus monoclonal antibodies* <i>*including quality-assured biosimilars</i>	<b>Injection:</b> 40 IU/mL in 1.25 mL, 2.5 mL vial; 100 IU/mL in 2.5 mL vial (human). <b>Injection:</b> 300 IU/mL in 10 mL vial; 600 IU/mL in 1 mL, 2.5 mL and 5 mL vial (murine).
antivenom immunoglobulin*	<b>Injection.</b> *Exact type to be defined locally.
diphtheria antitoxin	<b>Injection:</b> 10 000 IU; 20 000 IU in vial.
equine rabies immunoglobulin	<b>Injection:</b> 150 IU/mL; 200 IU/mL; 300 IU/mL; 400 IU/mL in vial
<b>19.3 Vaccines</b>	
WHO immunization policy recommendations are published in vaccine position papers on the basis of recommendations made by the Strategic Advisory Group of Experts on Immunization (SAGE).	
WHO vaccine position papers are updated three to four times per year. The list below details the vaccines for which there is a recommendation from SAGE and a corresponding WHO position paper as at March 2023. The most recent versions of the WHO position papers, reflecting the current evidence related to a specific vaccine and the related recommendations, can be accessed at any time on the WHO website at:	
<p><a href="https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers">https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers</a></p> <p>Vaccine recommendations may be universal or conditional (e.g., in certain regions, in some high-risk populations or as part of immunization programmes with certain characteristics). Details are available in the relevant position papers, and in the Summary Tables of WHO Routine Immunization Recommendations available on the WHO website at:</p> <p><a href="https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/who-recommendations-for-routine-immunization---summary-tables">https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/who-recommendations-for-routine-immunization---summary-tables</a></p> <p>Selection of vaccines from the Model List will need to be determined by each country after consideration of international recommendations, epidemiology and national priorities.</p> <p>All vaccines should comply with the WHO requirements for biological substances.</p> <p>WHO noted the need for vaccines used in children to be polyvalent.</p>	
<b>Recommendations for all</b>	
BCG vaccine	
diphtheria vaccine	
Haemophilus influenzae type b vaccine	
hepatitis B vaccine	
human papilloma virus (HPV) vaccine	
measles vaccine	
pertussis vaccine	
pneumococcal vaccine	
poliomyelitis vaccine	

## WHO Model List of Essential Medicines for Children – 9th List (2023)

rotavirus vaccine	
rubella vaccine	
tetanus vaccine	
<i>Recommendations for certain regions</i>	
Japanese encephalitis vaccine	
tick-borne encephalitis vaccine	
yellow fever vaccine	
<i>Recommendations for some high-risk populations</i>	
cholera vaccine	
dengue vaccine	
hepatitis A vaccine	
meningococcal meningitis vaccine	
rabies vaccine	
typhoid vaccine	
<i>Recommendations for immunization programmes with certain characteristics</i>	
influenza vaccine (seasonal)	
mumps vaccine	
varicella vaccine	

# WHO Model List of Essential Medicines for Children – 9th List (2023)

20. MUSCLE RELAXANTS (PERIPHERALLY-ACTING) AND CHOLINESTERASE INHIBITORS	
neostigmine	<p><b>Injection:</b> 500 micrograms/mL (methylsulfate) in 1 mL ampoule; 2.5 mg/mL (methylsulfate) in 1 mL ampoule.</p> <p><b>Tablet:</b> 15 mg (bromide).</p>
suxamethonium	<p><b>Injection:</b> 50 mg/mL (chloride) in 2 mL ampoule.</p> <p><b>Powder for injection:</b> (chloride), in vial.</p>
<input type="checkbox"/> vecuronium Therapeutic alternatives: - atracurium	<b>Powder for injection:</b> 10 mg (bromide) in vial.
<i>Complementary List</i>	
pyridostigmine	<p><b>Injection:</b> 1 mg in 1 mL ampoule.</p> <p><b>Tablet:</b> 60 mg (bromide).</p>
21. OPHTHALMOLOGICAL PREPARATIONS	
21.1 Anti-infective agents	
aciclovir	<b>Ointment:</b> 3% w/w.
azithromycin	<b>Solution (eye drops):</b> 1.5% – <i>Trachoma</i>
erythromycin	<b>Ointment:</b> 0.5% – <i>Infections due to Chlamydia trachomatis or Neisseria gonorrhoeae.</i>
<input type="checkbox"/> gentamicin Therapeutic alternatives: - amikacin - kanamycin - netilmicin - tobramycin	<b>Solution (eye drops):</b> 0.3% (sulfate). – <i>Bacterial blepharitis</i> – <i>Bacterial conjunctivitis</i>
natamycin	<b>Suspension (eye drops):</b> 5% – <i>Fungal keratitis</i>
<input type="checkbox"/> ofloxacin Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (S01AE Fluoroquinolones)	<b>Solution (eye drops):</b> 0.3%. – <i>Bacterial conjunctivitis</i> – <i>Bacterial keratitis</i>
<input type="checkbox"/> tetracycline Therapeutic alternatives: - chlortetracycline - oxytetracycline	<b>Eye ointment:</b> 1% (hydrochloride). – <i>Bacterial blepharitis</i> – <i>Bacterial conjunctivitis</i> – <i>Bacterial keratitis</i> – <i>Trachoma</i>
21.2 Anti-inflammatory agents	
<input type="checkbox"/> prednisolone Therapeutic alternatives to be reviewed	<b>Solution (eye drops):</b> 0.5% (sodium phosphate).

# WHO Model List of Essential Medicines for Children – 9th List (2023)

<b>21.3 Local anaesthetics</b>	
<input type="checkbox"/> tetracaine <small>a</small>	<b>Solution (eye drops):</b> 0.5% (hydrochloride). <small>a</small> Not in preterm neonates.
Therapeutic alternatives: - 4 <sup>th</sup> level ATC chemical subgroup (S01HA Local anaesthetics) excluding cocaine and combinations	
<b>21.4 Miotics and antiglaucoma medicines</b>	
<b>21.5 Mydriatics</b>	
<input type="checkbox"/> atropine <small>a</small>	<b>Solution (eye drops):</b> 0.1%; 0.5%; 1% (sulfate). <small>a</small> > 3 months.
Therapeutic alternatives: - homatropine hydrobromide - cyclopentolate hydrochloride	
<i>Complementary List</i>	
<i>epinephrine (adrenaline)</i>	<i>Solution (eye drops):</i> 2% (as hydrochloride).
<b>21.6 Anti-vascular endothelial growth factor (VEGF) preparations</b>	
<b>22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE</b>	
<b>22.1 Contraceptives</b>	
<b>22.2 Ovulation inducers</b>	
<b>22.3 Uterotonics</b>	
<b>22.4 Antioxytocics (tocolytics)</b>	
<b>22.5 Other medicines administered to the mother</b>	
<b>22.6 Medicines administered to the neonate</b>	
caffeine citrate	<b>Injection:</b> 20 mg/mL (equivalent to 10 mg caffeine base/mL). <b>Oral liquid:</b> 20 mg/mL (equivalent to 10 mg caffeine base/mL).
chlorhexidine	<b>Solution or gel:</b> 7.1% (digluconate) delivering 4% chlorhexidine (for umbilical cord care).
<i>Complementary List</i>	
<input type="checkbox"/> ibuprofen	
Therapeutic alternatives: - indometacin	<b>Solution for injection:</b> 5 mg/mL.
<input type="checkbox"/> prostaglandin E1	
Therapeutic alternatives: - prostaglandin E2	<b>Solution for injection:</b> 0.5 mg/mL in alcohol.
surfactant	<b>Suspension for intratracheal instillation:</b> 25 mg/mL or 80 mg/mL
<b>23. PERITONEAL DIALYSIS SOLUTION</b>	
<i>Complementary List</i>	
<i>intraperitoneal dialysis solution</i>	<b>Parenteral solution:</b> of appropriate composition

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<b>24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS</b>	
24.1 Medicines for psychotic disorders	
24.2 Medicines for mood disorders	
24.2.1 Medicines for depressive disorders	
24.2.2 Medicines for bipolar disorders	
24.3 Medicines for anxiety disorders	
24.4 Medicines for obsessive compulsive disorders	
24.5 Medicines for disorders due to psychoactive substance use	
24.5.1 Medicines for alcohol use disorders	
24.5.2 Medicines for nicotine use disorders	
24.5.3 Medicines for opioid use disorders	
<b>25. MEDICINES ACTING ON THE RESPIRATORY TRACT</b>	
25.1 Antiasthmotic medicines	
<input type="checkbox"/> budesonide Therapeutic alternatives: - beclometasone - ciclesonide - flunisolide - fluticasone - mometasone	<b>Inhalation (aerosol):</b> 100 micrograms per dose; 200 micrograms per dose.
epinephrine (adrenaline)	<b>Injection:</b> 1 mg/mL (as hydrochloride or hydrogen tartrate) in 1 mL ampoule.
<input type="checkbox"/> salbutamol Therapeutic alternatives: - terbutaline	<b>Injection:</b> 50 micrograms/mL (as sulfate) in 5 mL ampoule. <b>Metered dose inhaler (aerosol):</b> 100 micrograms (as sulfate) per dose. <b>Respirator solution for use in nebulizers:</b> 5 mg/mL (as sulfate).
<b>26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID–BASE DISTURBANCES</b>	
26.1 Oral	
oral rehydration salts	See section 17.5.1.
potassium chloride	Powder for solution.
26.2 Parenteral	
glucose	<b>Injectable solution:</b> 5% (isotonic); 10% (hypertonic); 50% (hypertonic).
glucose with sodium chloride	<b>Injectable solution:</b> 5% glucose, 0.9% sodium chloride (equivalent to Na <sup>+</sup> 150 mmol/L and Cl <sup>-</sup> 150 mmol/L); 5% glucose, 0.45% sodium chloride (equivalent to Na <sup>+</sup> 75 mmol/L and Cl <sup>-</sup> 75 mmol/L).
potassium chloride	<b>Solution for dilution:</b> 7.5% (equivalent to K <sup>+</sup> 1 mmol/mL and Cl <sup>-</sup> 1 mmol/mL); 15% (equivalent to K <sup>+</sup> 2 mmol/mL and Cl <sup>-</sup> 2 mmol/mL).
sodium chloride	<b>Injectable solution:</b> 0.9% isotonic (equivalent to Na <sup>+</sup> 154 mmol/L, Cl <sup>-</sup> 154 mmol/L).
sodium hydrogen carbonate	<b>Injectable solution:</b> 1.4% isotonic (equivalent to Na <sup>+</sup> 167 mmol/L, HCO <sub>3</sub> <sup>-</sup> 167 mmol/L). <b>Solution:</b> 8.4% in 10 mL ampoule (equivalent to Na <sup>+</sup> 1000 mmol/L, HCO <sub>3</sub> <sup>-</sup> 1000 mmol/L).

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sodium lactate, compound solution	<b>Injectable solution.</b>
<b>26.3 Miscellaneous</b>	
water for injection	2 mL; 5 mL; 10 mL ampoules.
<b>27. VITAMINS AND MINERALS</b>	
ascorbic acid	<b>Tablet:</b> 50 mg.
<input type="checkbox"/> colecalciferol Therapeutic alternatives: - ergocalciferol	<b>Oral liquid:</b> 400 IU/mL. <b>Solid oral dosage form:</b> 400 IU; 1000 IU.
iodine	<b>Capsule:</b> 190 mg. <b>Iodized oil:</b> 1 mL (480 mg iodine); 0.5 mL (240 mg iodine) in ampoule (oral or injectable); 0.57 mL (308 mg iodine) in dispenser bottle.
multiple micronutrient powder	<b>Sachets containing:</b> - iron (elemental) 12.5 mg (as coated ferrous fumarate) - zinc (elemental) 5 mg - vitamin A 300 micrograms - with or without other micronutrients at recommended daily values
pyridoxine	<b>Tablet:</b> 25 mg (hydrochloride).
retinol	<b>Capsule:</b> 100 000 IU; 200 000 IU (as palmitate). <b>Oral oily solution:</b> 100 000 IU/mL (as palmitate) in multidose dispenser. <b>Tablet (sugar-coated):</b> 10 000 IU (as palmitate). <b>Water-miscible injection:</b> 100 000 IU (as palmitate) in 2 mL ampoule.
riboflavin	<b>Tablet:</b> 5 mg.
thiamine	<b>Tablet:</b> 50 mg (hydrochloride).
<i>Complementary List</i>	
calcium gluconate	<b>Injection:</b> 100 mg/mL in 10 mL ampoule.
<b>28. EAR, NOSE AND THROAT MEDICINES</b>	
acetic acid	<b>Topical:</b> 2%, in alcohol.
<input type="checkbox"/> budesonide Therapeutic alternatives to be reviewed	<b>Nasal spray:</b> 100 micrograms per dose.
<input type="checkbox"/> ciprofloxacin Therapeutic alternatives: - ofloxacin	<b>Solution (ear drops):</b> 0.3% (as hydrochloride).
<input type="checkbox"/> xylometazoline <sup>a</sup> Therapeutic alternatives to be reviewed	<b>Nasal spray:</b> 0.05%. <sup>a</sup> Not in children less than 3 months.

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29. MEDICINES FOR DISEASES OF JOINTS	
29.1 Medicines used to treat gout	
29.2 Disease-modifying anti-rheumatic drugs (DMARDs)	
<p><b>Complementary List</b></p>	
hydroxychloroquine	<b>Solid oral dosage form:</b> 200 mg (as sulfate).
methotrexate	<b>Tablet:</b> 2.5 mg (as sodium).
29.3 Medicines for juvenile joint diseases	
<p><b>Complementary List</b></p>	
acetylsalicylic acid*(acute or chronic use)	<b>Suppository:</b> 50 mg to 150 mg. <b>Tablet:</b> 100 mg to 500 mg. <small>*For use for rheumatic fever, juvenile arthritis, Kawasaki disease.</small>
<input type="checkbox"/> adalimumab* <i>Therapeutic alternatives*:</i> - etanercept - infliximab  <small>*including quality-assured biosimilars</small>	<b>Injection:</b> 10 mg/0.2 mL; 20 mg/0.4 mL; 40 mg/0.8 mL; 40 mg/0.4 mL.
methotrexate	<b>Tablet:</b> 2.5 mg (as sodium).
<input type="checkbox"/> triamcinolone hexacetonide <i>Therapeutic alternatives:</i> - triamcinolone acetonide	<b>Injection:</b> 20 mg/mL in vial.
30. DENTAL MEDICINES AND PREPARATIONS	
fluoride	<b>Gel:</b> containing 2500 to 12 500 ppm fluoride (any type). <b>Mouthrinse:</b> containing 230 to 900 ppm fluoride (any type). <b>Toothpaste: cream or gel:</b> containing 1000 to 1500 ppm fluoride (any type). <b>Varnish:</b> containing 22 500 ppm fluoride (any type).
glass ionomer cement	<b>Single-use capsules:</b> 0.4 g powder + 0.09 mL liquid <b>Multi-use bottle:</b> powder + liquid  Powder (fluoro-alumino-silicate glass) contains: 25-50% silicate, 20-40% aluminium oxide, 1-20% fluoride, 15-40% metal oxide, 0-15% phosphate, remainder are polyacrylic acid powder and metals in minimal quantities. Liquid (aqueous) contains: 7-25% polybasic carboxylic acid, 45-60% polyacrylic acid.
resin-based composite (low-viscosity)*	<b>Single-use applicator or multi-use bottle</b> <small>*of any type for use as dental sealant</small>
resin-based composite (high-viscosity)*	<b>Single-use capsule or multi-use syringe</b> <small>*of any type for use as dental filling material</small>
silver diamine fluoride	<b>Solution:</b> 38% w/v

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