Country preparedness for the introduction and appropriate use of antibiotics

Operational guidance

World Health Organization

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Abbreviations

AMR CC	antimicrobial resistance coordination committee
AMR	antimicrobial resistance
AMRASI	Antimicrobial Resistance Access and Stewardship Initiative
AMS	antimicrobial stewardship
AMU	antimicrobial use
AST	antimicrobial susceptibility testing
AWaRe	access, watch and reserve
BIA	budget impact analysis
CHAI	Clinton Health Access Initiative
CRP	collaborative registration procedure
DTC	drug and therapeutics committee
EDL	Model Essential Diagnostic list
EML	Model Lists of Essential Medicines
FRP	facilitated registration pathway
GARDP	Global Antibiotic Research & Development Partnership
GETF	Global Environment & Technology Foundation
GLASS	Global antimicrobial resistance and use surveillance system
GMP	good manufacturing practice
HCW	health care worker
HIC	high-income country
HTA	health technology assessment
IP	intellectual property
IPC	infection prevention and control
LMICs	low- and middle-income countries
LMIS	logistics management information system
LPA	Local Production and Assistance
M&E	monitoring and evaluation
MDRO	multidrug-resistant organism
MPP	Medicines Patent Pool
NAP	national action plan
NDTC	national drug and therapeutics committee
nEML	national essential medicines list
nEMLC	national essential medicines list committee
NIH	national institute of health
NRA	national regulatory authority
NRL	national reference laboratory or national referral laboratory
PAHO	Pan American Health Organization
PPP	public–private partnership

PPS	point prevalence survey
R&D	research and development
SOP	standard operating procedure
SRA	stringent regulatory authority
STG	standard treatment guideline
TB	tuberculosis
TNAP	Thailand National Antidote Programme
TRIPS	Trade-Related Aspects of Intellectual Property Rights
TWG	technical working group
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
VMI	vendor-managed inventory
WASH	water, sanitation and hygiene
WHO CC	WHO Collaborating Centres
WHO	World Health Organization
WLA	WHO-listed authority
WLPF	World Local Production Forum
WTO	World Trade Organization

1 Introduction, background, scope, and guiding principles

This operational guidance supports countries to appropriately introduce an antibiotic for the first time. It aims to ensure timely access, appropriate use and optimal patient outcomes, while minimizing the potential of emerging resistance, by offering guidance on how to introduce an antibiotic into national health care systems. It primarily focuses on **Watch** and **Reserve** antibiotics, which are typically used as second- and third-line treatments in hospital settings. Such antibiotics are essential for treating multidrug-resistant organisms (MDROs), but often face specific access challenges, especially in low- and middle-income countries (LMICs). This guidance outlines an approach to planning the introduction and implementation of these products, considering their unique characteristics and associated needs, with the goal of enhancing treatment access for patients and promoting appropriate overall antibiotic use.

This operational guidance has been developed as part of the SECURE initiative *(1)* and with the leadership of a multidisciplinary World Health Organization (WHO) Taskforce. The SECURE initiative, led by WHO and the Global Antibiotic Research and Development Partnership (GARDP), aims to improve access to established and new antibiotics, particularly in LMICs. Desk research and key informant interviews were conducted to inform the guidance. Data sources that were leveraged to develop the guidance include: existing WHO (global, regional and country level) guidance; published and unpublished literature; key informant interviews including with global, regional and country level policy-makers, clinicians and procurement agencies; review of examples of product introduction guidance from specific disease areas including tuberculosis, HIV, malaria and vaccines; and collection of country case studies. A two-day technical consultation on the guidance was also held, bringing together key stakeholders, including country representatives, disease experts and partners with product introduction expertise, to gather inputs on an early draft and shape the content of the guidance. The consultation gathered specific technical inputs, lessons from existing resources, best practices and case studies for inclusion in the final publication. It also provided an opportunity to discuss potential complementary tools to accompany the guidance and scoped opportunities to pilot test its utility and acceptability.

For participants of the technical consultation and external reviewers, declarations of interest (DOIs) were collected and thoroughly reviewed following WHO standard operating procedures. All experts submitted written disclosures of competing interests relevant for consideration to participate in the technical consultation. Participants were primarily representatives of national agencies and institutions, intergovernmental and non-governmental organizations, as well as industry representatives, all participating as representatives of their organization. For fifteen participants, a DOI was collected and reviewed by the WHO technical unit; In all cases, it was determined that the interests disclosed were not directly relevant to the scope of work of the operational guidance, and as a result the WHO technical unit granted their participation in the technical consultation as well as a review of the final draft of the operational guidance.

The guidance works through the process of developing an antibiotic introduction plan, considering all necessary steps, activities and resources across the pharmaceutical value chain. The guidance provides a product introduction framework that can be applied to any antibiotic, and tailored to individual country contexts and specific antibiotics as they are introduced. Countries can utilize the guidance to develop detailed, costed plans for an antibiotic(s) being introduced, and ensure that these plans are integrated with existing national antimicrobial resistance (AMR) strategies, such as national AMR action plans.

This document provides a practical overview of the process for introducing antibiotics. The guidance aims to equip countries with the necessary tools and information to make informed decisions, develop effective plans, and successfully introduce antibiotics into their health systems, ultimately improving patient outcomes and contributing to the global fight against AMR.

More detailed information and guidance are provided as annexes.

1.1 Background

AMR has been on the rise for decades. An estimated 1.14 million global deaths were attributed to drug-resistant infections in 2021, and it is responsible for significant morbidity and disability *(2)*. AMR places a heavy burden on health systems and complicates the response to health emergencies. The global challenge of AMR stems from the widespread overuse and misuse of antibiotics. In many LMICs, poor access to some existing, established antibiotics that are needed to treat both susceptible and resistant infections persists. At the same time, access to novel antibiotics that are available and are effective in treating drug-resistant infections is limited, especially LMICs where the burden is often highest.

Providing access to essential antibiotics for treatment of both susceptible and drug-resistant bacterial infections, and preserving their activity through antibiotic stewardship measures, are both crucial aspects of combating AMR.

WHO has developed the **Access**, **Watch**, and **Reserve** (AWaRe) system (including the AWaRe classification, antibiotic book, and indicators and targets *(3–4)*) to support countries in monitoring antibiotic use and implementing antimicrobial stewardship (AMS) programmes.[1] The AWaRe classification categorizes antibiotics according to their spectrum of activity and their potential to develop resistance:

- **Access** antibiotics have a narrow spectrum, meaning they target a limited number of bacteria, and have a lower resistance potential than antibiotics in other groups. Such antibiotics are generally recommended as empiric first- and second-line treatment options for common infections.
- **Watch** antibiotics have a broader spectrum and have a higher potential of developing resistance. They are recommended as first-choice options only for patients with severe clinical presentations or for infections where the causative pathogens are likely to be resistant to **Access** antibiotics.
- **Reserve** antibiotics are last-resort agents used for infections due to multidrug-resistant infections.

[1] While this document focuses on antibiotics, stewardship programmes are focused on antimicrobials more broadly.

Improving the use of **Access** antibiotics remains essential. However, limited availability of certain **Reserve** and **Watch** antibiotics effective against MDROs, especially in low-resource settings, highlights the need for intensified efforts to ensure their equitable access and appropriate uses, and availability of related diagnostic and sensitivity tests.

Since most **Reserve** antibiotics are last-resort treatments that are primarily used in hospital settings, they often face restricted or limited demand making them commercially unviable for pharmaceutical investment. This contributes to limited registration/commercialization by companies, especially in LMICs. Where they are registered, they are priced highly for several reasons, including but not limited to: recouping of research and development (R&D) costs; covering cost of goods sold; and high operational costs. Other factors limiting their availability include registration costs and related complexities, as well as concerns over inappropriate use that could introduce and accelerate resistance.

While R&D efforts for new antibiotics to treat MDROs have accelerated in recent years and have yielded several novel **Reserve** antibiotics, there are still too few antibiotics in the development pipeline to meet the most critical and anticipated needs. At the same time, due in part to limited R&D incentives, only 16 antibacterials have been approved by any SRA/WHO-Listed Authority (WLA) since July 2017 *(5)*. Of the 25 antibiotics that were developed between 1999 and 2014, only 12 were registered in more than ten countries, and where their use is often prohibitively expensive *(6)*. On the demand side, there are few stewardship models that ensure timely access to quality treatments for MDROs while also safeguarding their use, ensuring they are only prescribed when other antibiotics have failed.

1.2 Global commitments to address AMR

In 2024, global leaders reinforced commitments to address AMR and reduce associated morbidity and mortality. At the 77th World Health Assembly in May 2024, Member States adopted the resolution Antimicrobial resistance: accelerating national and global responses *(7)*. Under the broad concept of the people-centred approach to addressing antimicrobial resistance in human health *(8)*, the resolution welcomed the *WHO Strategic and operational priorities to address drug-resistant bacterial infections in the human health sector 2025–2035 (9)*. This report outlines the urgent strategic and operational priorities for an accelerated programmatic response to AMR in the human health sector over the next ten years and includes four strategic priorities[2] to address drug-resistant infections in the human health sector. Moreover, in September 2024 global leaders approved a political declaration *(10)* at the United Nations General Assembly High-Level Meeting on Antimicrobial Resistance *(11)* committing to targets and actions to reduce the AMR burden, and called for sustainable financing so countries can appropriately respond to the threat.

Most recently, in November 2024, ministers and partners pledged action with the Jeddah Commitments on AMR *(12)* – a collective declaration to open a new chapter in global efforts to address AMR by a building a coalition for impact. The document provides clarity on specific mechanisms and agreements to translate the political declaration approved at the UNGA High-Level Meeting on AMR *(10)* into real-world action.

[2] The four priorities: Prevention of infections that give rise to the use of antibiotics; Universal access to affordable quality diagnosis and appropriate treatment of infections; Strategic information, science and innovation; Effective governance and financing.

Ensuring that diagnostics are included in global efforts to address AMR – and building on the *Strengthening diagnostics capacity* resolution *(13)* adopted by the 76th World Health Assembly in 2023 – WHO has launched the Antimicrobial Resistance Diagnostic Initiative which aims to bring diagnostics to the forefront of the global AMR response and support countries in strengthening microbiology laboratory capacity *(14)*.

Additionally, WHO has been supporting countries to plan for and respond to AMR, and has developed several guidance documents and tools to support countries to respond to the global AMR threat, and to guide a balanced approach to using antibiotics while preserving their effectiveness. These guidance documents and tools are aligned with the *Global action plan on antimicrobial resistance (15)*.

Relevant WHO guidance, reference documents and existing tools that can support antibiotic introduction can be found in Annex 1.

1.3 Scope

1.3.1 Areas and topics in scope

The scope of this document covers decision-making, planning and implementation steps (including monitoring, evaluation and quality improvements) to introduce an antibiotic**,** focusing on those used to treat MDROs. It does not include guidance for introducing other antimicrobials or related diagnostic tests, though many of the same principles and planning steps could apply. Additionally, the scope covers antibiotics that are included in WHO guidance documents and/or the WHO Model Lists of Essential Medicines (EML) *(16)* and have been classified through the WHO AWaRe classification.[3]

While all antibiotics are within the scope of this guidance – as introducing any antibiotic requires considered planning, especially for ensuring AMS and appropriate use – the focus is on introducing antibiotics that are active against MDROs (including newer antibiotics) and that are available on global markets. Antibiotics active against MDROs are generally classified as **Watch** and **Reserve** products in the WHO *AWaRe classification of antibiotics for evaluation and monitoring of use, 2023 (3)*. To increase access to **Watch** and **Reserve** antibiotics in LMICs, targeted measures are needed to address regulatory issues, overcome market challenges, facilitate robust stewardship programmes, and ensure operational diagnosis and surveillance systems that support their safe and appropriate use. The guidance focuses primarily on national planning for introducing **Watch** and **Reserve** antibiotics that are mostly used as second- and third-line treatments in hospital settings.

Furthermore, antibiotics within the scope includes those that contain active chemical ingredients, or related combination(s), that have not been previously registered in a given country. This may include products that are both on- and off-patent, and can include products not available, or not previously used in a country but are nevertheless available on global markets. This can also include products that may have been commercialized elsewhere but have never been registered or supplied in a country. For example, a ceftazidime–avibactam product may not be registered in a particular country – neither as the originator brand nor as a generic version. However, if the chemical is recognized as a priority public health need, the country may seek to introduce a suitable product, whether as the originator brand or a generic version.

[3] WHO updates the WHO EML and AWaRe classification every two years, so the latest version(s) should be accessed and reviewed prior to beginning the introduction planning process. WHO may also make product recommendations outside of EML updates and so a thorough check of the most recent WHO guidance is needed when selecting which antibiotics to introduce.

The guidance covers the human health sector, encompassing both public and private sectors. While it is focused on ensuring antibiotic availability in a country's public health system, it includes considerations on private sector engagement and approaches to ensuring appropriate antibiotic use in the private sector. The guidance emphasizes adapting plans to each country's unique circumstances, such as local capacities, health systems and available resources. It also allows for the guidance to be adapted for the introduction of a specific antibiotic and integrating the introduction plan with existing national AMR strategies, such as national action plans (NAPs) on AMR.

Antibiotic introduction in this document refers to an integrated set of activities aimed at preparing public health systems to effectively obtain, register, procure, deploy, distribute, deliver, appropriately use and monitor the use of an antibiotic that has not been previously available in the country (i.e. it has not yet obtained marketing authorization or registration approval by the relevant national regulatory authority (NRA)) *(17)*. This includes activities countries may need to consider prior to registration, activities for the registration process, and subsequent activities to ensure that the antibiotic is used appropriately.

National activities, as well as participation in global and regional activities that can accelerate access to antibiotics, are highlighted in the guidance. This includes the steps individual countries can take to plan for antibiotic introduction and tailoring these steps to the country context and setting. At the same time, the guidance acknowledges the potential linkages to global and regional initiatives aimed at addressing some of the major market and access hurdles limiting access to antibiotics. For example, the SECURE global access initiative, works to overcome global antibiotic access challenges, while responding to and working with regional initiatives *(1)*. Countries may choose to work with such initiatives as part of their plans to enable access to antibiotics. The guidance also considers variations across regions and includes considerations for regional approaches to antibiotic introduction. While these broader efforts go hand-in-hand with enabling access, this document focuses on ensuring that when a newer antibiotic emerges from the R&D pipeline, countries are prepared for market authorization and that – once it is registered – it can be introduced and appropriately used in countries. This includes ensuring that countries have AMS programmes in place and sufficient testing and surveillance capacities available and operating.

Further details on global and regional initiatives that are relevant for antibiotic introduction are included in Annex 2. It includes different supranational initiatives, strategies and collaboration opportunities for countries to consider as part of antibiotic introduction planning.

As countries integrate antibiotics into their health care systems, sustaining expanded access requires a strong focus on maintaining AMS programmes and practices. Additionally, ensuring adequate access to diagnostics, laboratory capacity and AMR surveillance is essential to meet ongoing needs. For this reason, steps towards establishing robust systems to consistently monitor and report AMR trends, sufficiently equipping laboratories with diagnostic tools and technologies, and providing adequate training for laboratory personnel to perform accurate testing, are all within the scope of this guidance. Strengthening these critical components enables timely identification of resistance patterns, supports informed decision-making for treatment guidelines, and enhances the ability to respond effectively to emerging AMR threats.

1.3.2 Areas and topics out of scope

The guidance does not cover introduction of other antimicrobials or diagnostics, though many of the same principles and planning steps may still apply.

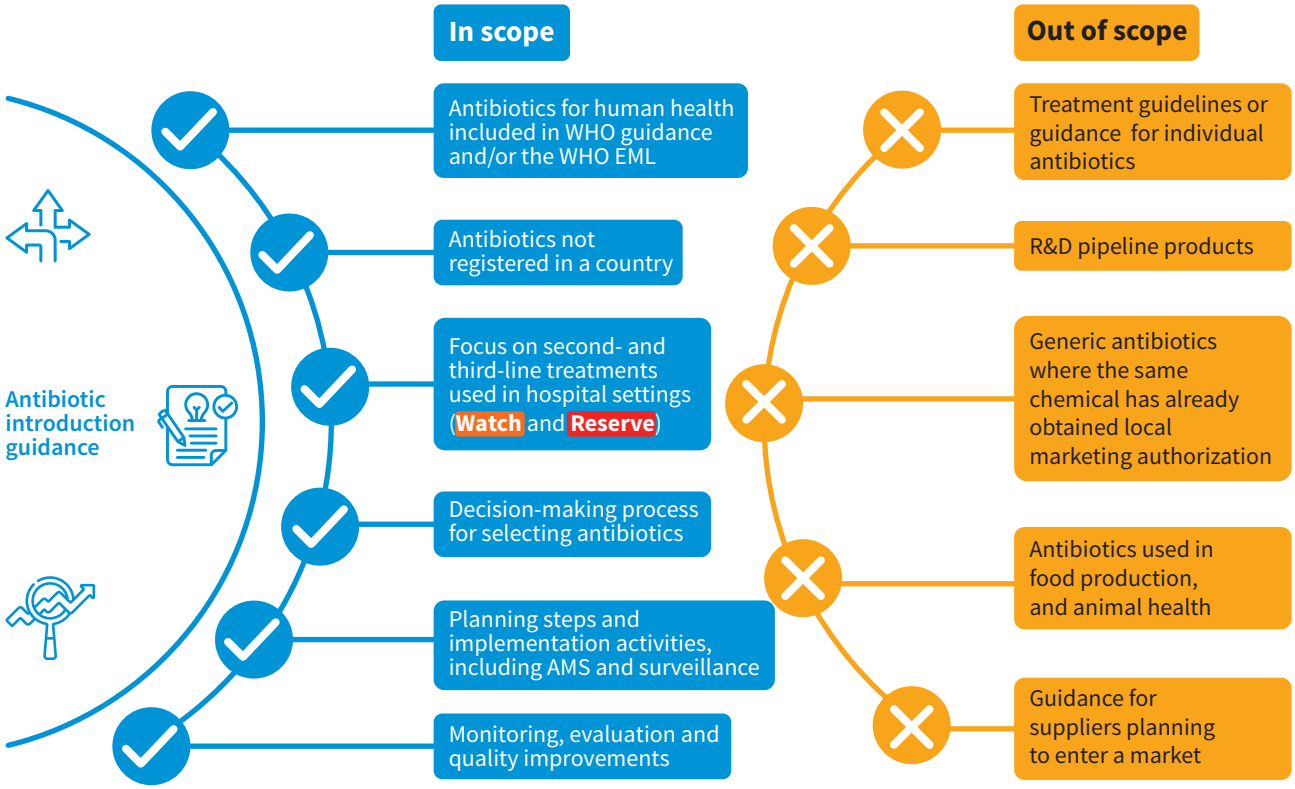
The guidance is not targeted at generic equivalents of existing antibiotic medications that are already registered in a country, or products that are still in development and not yet evaluated for safety, efficacy or quality (i.e. products that are still in the R&D pipeline). However, if a generic product is the first to be registered or used routinely in a country, such a scenario would be in scope.

The guidance does not provide specific guidance on individual products but may reference specific products as examples to illustrate diverse approaches. Plans should not be limited to the examples presented in the guidance.

The guidance has been developed from the perspective of the health system and delivering the best treatment outcomes for patients, rather than that of the supplier (i.e. it is not intended to inform a marketing authorization holder's product roll-out and/or marketing plans).

While NAPs should adopt a 'One Health' approach that incorporates sector-specific actions in the human health, food production, animal and environmental sectors, and a coordinated approach across these sectors, this guidance document only focuses on antibiotics for use in humans. Further information on a One Health approach can be found in the Global action plan on antimicrobial resistance *(15)* and the *One health joint plan of action (2022–2026): working together for the health of humans, animals, plants and the environment (18)*. Fig. 1 provides a quick reference to the scope of the guidance.

Fig. 1. Scope of the antibiotic introduction guidance



Note: WHO EML: WHO Model Lists of Essential Medicines; AMS: antimicrobial stewardship; R&D: research and development.

1.3.3 Target audience

This guidance is intended for various stakeholders involved in antibiotic introduction including: country-level decision-makers, AMR multisectoral coordination committees and AMR technical working groups (TWGs), facility-level AMS committees, programme managers, national regulatory authorities, national and hospital drug and therapeutics committees (DTCs), facility and clinic managers, health care professionals, partners including global procurement agencies, and donors supporting antibiotic introduction.

1.4 Guiding principles for introducing antibiotics

Introducing antibiotics should be part of plans to strengthen health systems and part of universal health coverage policies. Therefore, introducing antibiotics may impact a country's health care system across the entire value chain and should be a part of the NAP. Recognizing the potential impact on the health system, seven guiding principles have been developed for optimal antibiotic introduction. These principles serve to not only facilitate the smooth integration of a given antibiotic so it is available when patients need it, but also to strengthen overall AMS efforts.

i. Strong, country-led planning and coordination with:
   - evidence-based planning and decision-making processes; and
   - accountability and integration with other components of the health system.

ii. Sustained comprehensive access to antibiotics at the right level of the health service for everyone who needs them.

iii. Availability of a balanced national essential medicines list and/or antibiotic formulary list that:
   - is optimized based on local epidemiological and clinical needs;
   - aligns with the WHO EML and the WHO AWaRe classification and antibiotic book;
   - manages antibiotic use to prevent overuse, while ensuring access; and
   - preserves the efficacy of existing antibiotics.

iv. Safe and effective antibiotic supply and distribution with:
   - clear treatment guidelines and policies for appropriate use of antibiotics for at least common clinical infections (e.g. those included in the WHO AWaRe antibiotic book) and very severe infections (such as infections with antimicrobial-resistant pathogens that make infections harder to treat and increases the risk of disease spread, severe illness and death);
   - quality-assured products;
   - consistent supply without interruptions or shortages;
   - effective storage, logistics and drug management systems; and
   - sustainable local and/or regional production of quality antibiotics to ensure access health security for populations (if appropriate for the antibiotic and scenario).

v. Robust AMS policies and programmes that:
   - establishes programmes both nationally and in health facilities;
   - utilizes local knowledge and expertise to inform AMR trends, policies, treatment guidelines and protocols, and appropriate antibiotic use;
   - ensures robust functional, national AMR and AMU surveillance systems that are connected to all levels of care and are used to inform and monitor interventions;
   - has high-quality monitoring and evaluation systems to track introduction progress, and to support disease surveillance and monitor AMU patterns;
   - provides quality education and training to develop a competent, motivated and accountable health care workforce that has safe treatment practices and monitors/reports adverse events including treatment failures;
   - expands awareness on appropriate AMU across the health care workforce and in the public.

vi. Links to other AMR mitigation and control strategies such as: improved infection prevention and control (IPC) including health care-associated infection prevention, and water, sanitation and hygiene (WASH) and building diagnostic capacities, which:
   - ensure access to diagnostics alongside robust sustainable, quality-assured laboratory services;
   - strengthen microbiological laboratory infrastructure to ensure accurate and timely pathogen identification and antimicrobial susceptibility testing (AST);
   - enhance AMR routine surveillance and standardized data collection and analysis;

- routinely report AMR trends and antibiogram data; and
- link antibiotic use to diagnostic confirmation whenever possible.

vii. Adequate resource allocation that:

- provides sufficient human and financial resources for the introduction, sustained and appropriate use of antibiotics;
- is balanced across both antibiotics and the diagnostics and testing equipment needed to appropriately use antibiotics;
- avoids negatively impacting other health programmes and services;
- considers the budget impact and/or the value for money of introducing a given antibiotic.

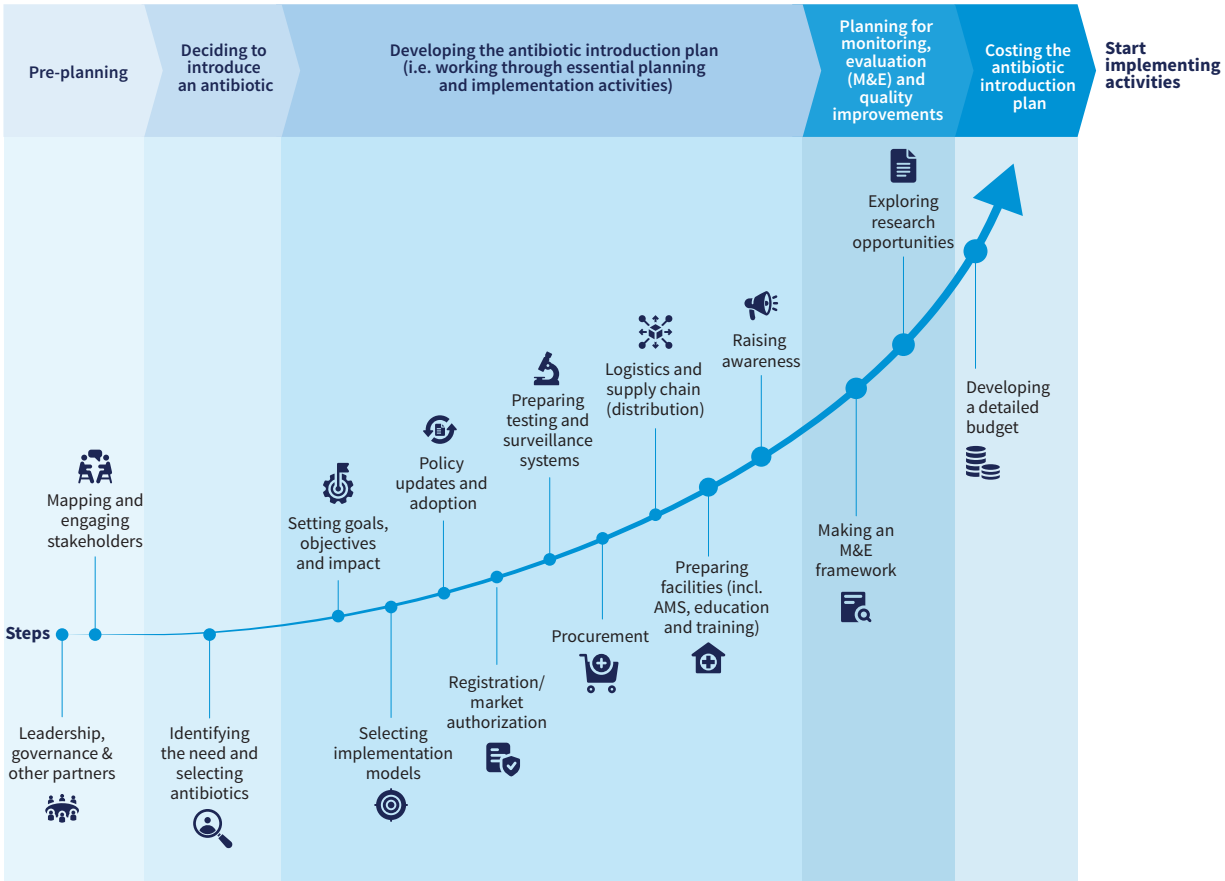
2 Structure of the operational guidance

This operational guidance is designed around five elements of the antibiotic introduction process:

i. Pre-planning.
ii. Deciding to introduce an antibiotic.
iii. Developing the antibiotic introduction plan (i.e. working through essential planning and implementation activities).
iv. Planning for monitoring and evaluation (M&E), and ongoing quality improvements.
v. Costing the antibiotic introduction plan

For each element, the key steps, activities, considerations and resources are outlined (**Fig. 2**). Working through the steps outlined in this guidance should result in a clear, stepwise antibiotic introduction plan.

Fig. 2. Key steps within each element of the antibiotic introduction process

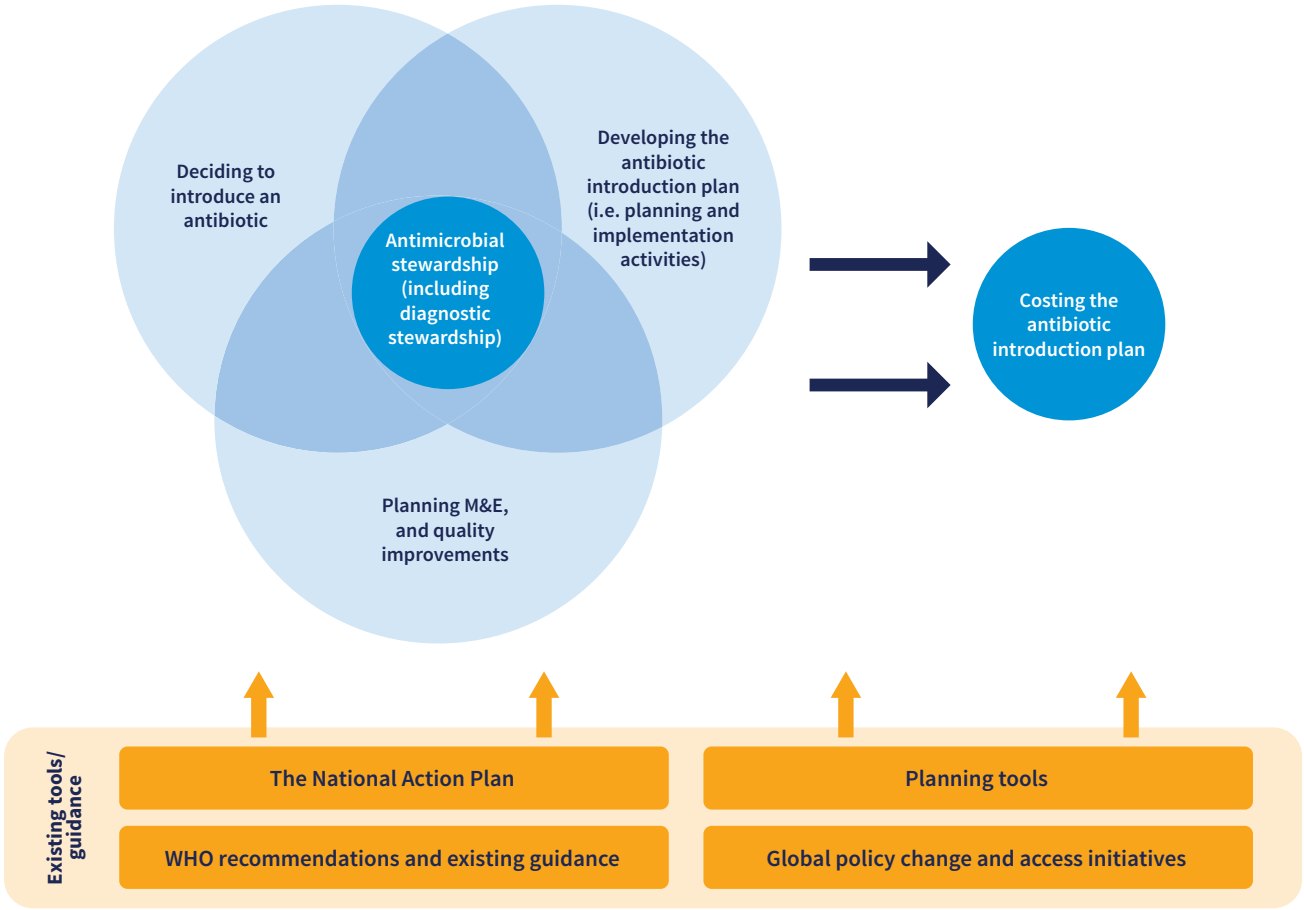


The process is flexible, and it may not always be implemented sequentially or require every step. The antibiotic introduction process should be tailored to the unique country situation, and the planning process should start based on the context and antibiotic availability status. For instance, product introduction usually starts with product registration/market authorization. But, given that this guidance focuses on **Watch** and **Reserve** antibiotics – and that some **Reserve** antibiotic suppliers may be reluctant to register products in unclear or small markets – this guidance starts with "deciding to introduce an antibiotic". This is because demonstrating a willingness to make an antibiotic available nationally may signal to companies that there is a viable market for engagement. In some countries, companies may see a viable market and independently register antibiotics – in such contexts the process will start with registration followed by policy adoption. There are also some settings and contexts in which deciding to introduce an antibiotic may come before the steps involved in pre-planning. This could include settings with established warning and surveillance systems, and processes to inform the need for a specific antibiotic, or when countries are working with donors to introduce a specific antibiotic.

To design and develop context-specific solutions, countries are encouraged to work with existing medicine introduction processes, with reference or linked to national efforts to address AMR (such as the NAP), and use as much locally-driven information and expertise as possible. When tailoring plans, countries should note that the process includes considerations for building stewardship activities into plans, which may not be needed for the introduction of other types of medicines.

All elements of the antibiotic introduction process are interconnected, with AMS, including diagnostic stewardship, at the centre. Ideally, the process should utilize existing tools such as the *WHO costing and budgeting tool for national action plans on antimicrobial resistance (19)*(a flexible budgeting tool that can be adapted for budgeting the antibiotic introduction plan), existing guidance such as the WHO EML and the WHO AWaRe antibiotic book, and regional or global initiatives to support antibiotic access (Fig. 3). Lists of available WHO tools and guidance are provided in Annexes 2 (global and regional initiatives) and 3.

Fig. 3. Antimicrobial stewardship and the main elements of the antibiotic introduction process



Note: Adapted from (20).

The next section outlines the steps involved in developing an antibiotic introduction plan, with each step presented in the following format:

Purpose

Explains the objective of the step and what should be achieved.

Actions

Provides a simplified outline of the most important actions involved within each step.

Key considerations

Provides a summary of different aspects of the step that may need to be considered, especially areas where adaptation is needed for the local context.

Relevant resources and tools.

Presents a list of resources and tools that can be used to support completion of the step. It also references specific annexes where the user can find a more detailed explanation of the content or considerations for each step.

Before starting the process, two key pre-planning steps are proposed to ensure smooth planning and successful implementation of the plan.

2.1 Pre-planning to start the antibiotic introduction process

Purpose

To ensure that the right individuals, support, stakeholders and resources are identified, engaged and/or involved from the beginning of the process.

Important!

Resources, support and stakeholders required for every step of the introduction process should be mapped at the beginning of each step. Therefore, the stakeholder mapping exercise included in this step is a continuous process and should be cross-checked and revised for each step.

Steps involved

1. Identifying leadership and governance for the entire antibiotic introduction process
2. Mapping stakeholders, and planning engagement for the entire antibiotic introduction process

2.1.1 Identifying leadership, governance, and other partners for the entire process

Purpose

To have strong leadership and governance with the right functions and partners that can support decision-making and can design and implement the plan. To ensure that the governance structure is fit-for-purpose, that any gaps are addressed before planning starts, and that there is accountability with clear roles and responsibilities throughout the entire process.

Actions

1. Identify who is, or will be, responsible for leading decision-making related to antibiotic introduction and accountable for implementation within the ministry of health, NRA or other ministry or government department. In some countries this may be an AMR focal person (their role could be expanded to include this work if needed), or another responsible officer. In some countries this may be within a non-health ministry that is responsible for the introduction of medicines or AMR related activities.
2. It is important to identify and know who will drive the process for deciding to introduce an antibiotic.
    a. Know what AMR response or infectious disease coordination is already in place (e.g. what has been established as part of the NAP?) What One Health platforms exist? And are there existing technical groups/advisors supporting the national AMR response and infectious disease management that can support antibiotic selection and implementation?
    b. Understand how medicine introduction is currently governed and implemented nationally (e.g. what policy-making and regulatory processes need to be considered and what departments and/or agencies need to be engaged? Are there existing committees that manage and update national essential medicines lists (nEML), or other medicine evaluation committees in place that can support antibiotic selection?)
3. Once the AMR focal person or another responsible officer is identified, it is recommended that they plan a meeting with senior leadership in the ministry of health to secure their commitment and support.
4. Form links with existing governance and other relevant processes. Communicate the rationale for initiating the decision-making process (see Section 3) for antibiotic introduction and for developing an introduction plan.
5. Identify who is needed to make decisions, as well as who is needed to design, implement and evaluate the plan. This can include individuals, agencies, committees, groups or organizations that can support different activities throughout the introduction plan. Map out how they will interact (i.e. coordinate and collaborate, for decision-making, implementation and evaluation).
6. Identify any governance gaps related to the antibiotic introduction process and take steps to close the gaps (e.g. are there relevant TWGs that can articulate the public health need and inform selecting an antibiotic?) Does national health governance connect to facility level implementation – which may be important to implementation of antibiotic stewardship programmes – or do those links need to be made?

Key considerations

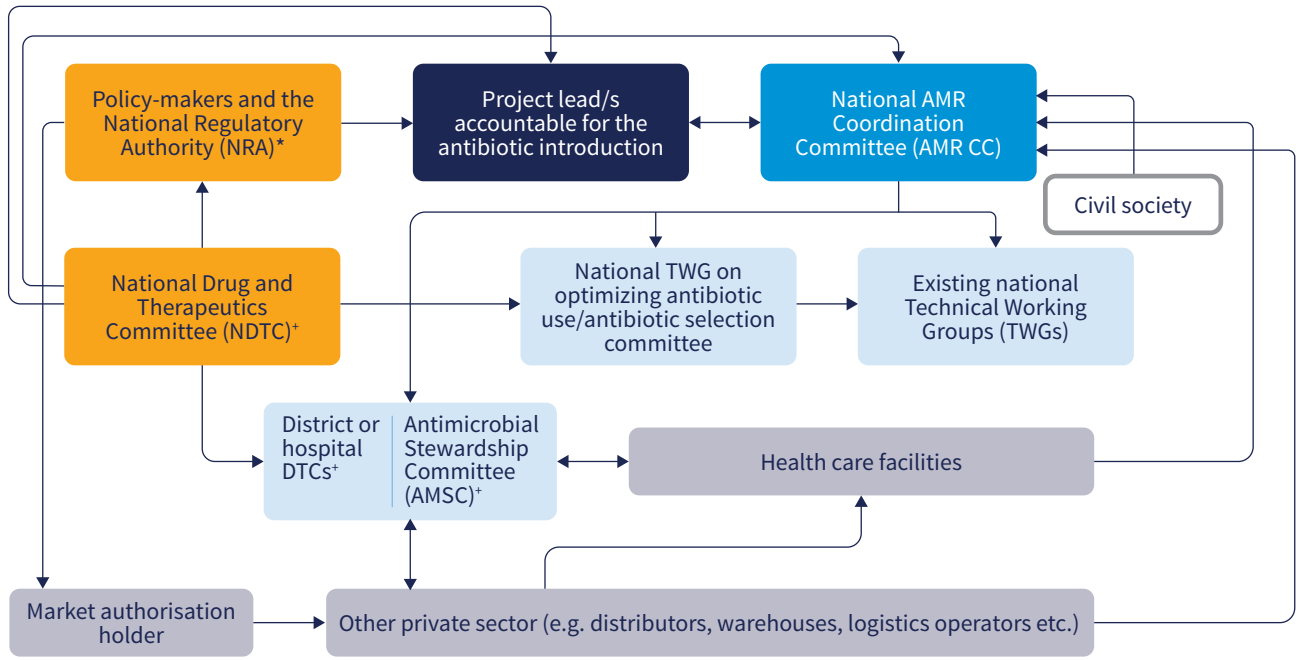
- In some settings and contexts, deciding to introduce an antibiotic (see Section 3) may come before the steps outlined under pre-planning. This could include, but is not limited to, settings with established warning and surveillance systems, and processes to inform the need for a specific antibiotic, or when countries are working with donors to introduce a specific antibiotic.
- Antibiotic introduction requires strong governance that is inclusive of stakeholders at all levels.

- Leadership, accountability and an inclusive decision-making process is central to securing stakeholder buy-in and successful implementation of the plan.
- In some settings with limited resources, a project lead may have both a leadership and national coordination role. A project lead may also have multiple roles when existing national coordination efforts are nascent or not yet fit-for-purpose, or do not have additional capacity to support antibiotic introduction.
- Key governance functions include:
  - National coordination.
  - Policy and regulatory oversight.
  - Technical expertise and advice.
- Key partners include:
  - Implementers, including the private sector.
  - Civil society organizations.
- The formality of country governance for introducing medicines vary between countries. Governance for antibiotic introduction should work within existing governance structures for all medicines, and be adapted so it is fit-for-purpose to govern antibiotic introduction, especially for the **Watch** and **Reserve** categories. This includes processes to work with specific technical experts and advisors on antibiotic selection and use, processes to ensure AMS programmes and policies are developed and implemented, and to ensure that the private sector is part of governance to work through delivery bottlenecks or market issues. Examples of existing structures could include a national essential medicines list committee (nEMLC) or a national drug and therapeutics committee (NDTC) that can support decision-making components of the introduction plan. In some settings, national working groups or subcommittees that focus on specific areas (e.g. review of new medicines, update of treatment guidelines, cost-effectiveness analyses) provide specialized expertise and support the nEMLC in its decision-making process. An existing antibiotic working group might also be relevant to provide specialized expertise and recommendations on the selection and use of antibiotics.
- Countries should ensure the governance structure is relevant to the local setting and can work based on available capacity.
- The NAP on AMR may include leadership and governance frameworks that can be adapted or followed to support antibiotic introduction.
- Ideally, governance should integrate with the NAP and One Health platforms if possible, so there is a unified approach to addressing AMR across different sectors.
- Fig. 4 is an illustration of how project leadership alongside national coordination, decision-makers, policy-makers, regulators, implementers including the private sector, and civil society could be organized. The figure reflects that establishing governance structures for antibiotic introduction is complex due to numerous stakeholder interactions, but countries should adapt and simplify governance and interactions to fit local contexts.
- If the right governance is not in place, a country may choose to follow a governance model as presented in Fig. 4, or adapt existing governance mechanisms to reflect their own country situation, or develop a new governance structure.
- The role of the private sector in the governance structure needs to be carefully considered and engagement should depend on each country's individual setting and health system.

Relevant resources and tools

- Refer to Annex 5 for detailed considerations and roles and responsibilities of key governance functions in the antibiotic introduction process.
- Step 1 of the six steps for sustainable implementation of NAPs on AMR (i.e. Strengthen coordination, collaboration and governance for NAP on AMR implementation) *(21,22)*
- WHO has developed sample terms of reference for national multisectoral coordination for AMR NAPs *(22)*.
- Guidance on facility-level implementation can be found in the WHO *Antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries: a WHO practical toolkit (23)*.

Fig. 4. An illustrative example of how governance for antibiotic introduction can be structured



Notes: Civil society organizations have technical expertise to support implementers, technical working groups and AMR CC activities at all levels. * = Policy-makers and NRA representatives are usually part of the AMR CC. In some countries AMR CC TWG's may play the role of the NDTC for antimicrobials (as part of AMR NAPs), or both the NDTC and AMR CC may work together. + = DTCs can operate at a national, district or hospital level. The AMSC operate at the facility level. In countries where the DTC established and functioning, the AMSC work in tandem to or form part of the DTC. Where DTCs are less established, the AMSC could operate in place of the DTC for antibiotics, or more independently from the DTC.

2.1.2 Mapping stakeholders and planning engagement

Purpose

To map stakeholders to their roles and responsibilities across the entire pharmaceutical value chain. That is, to identify **who** to engage, **why** they are being engaged and for what purpose, and **how** to engage them.

Important!

Resources, support and stakeholders required for every step of the introduction process should be mapped at the beginning of each step. Therefore, the stakeholder mapping exercise included in this step is a continuous process and should be cross-checked and revised for each step.

Actions

1. Develop a stakeholder map to identify **who** needs to be engaged and **why**. This should include outlining their level of awareness and influence, and their priority level for engagement.
   a. Who are the decision-makers? (i.e. those with authority and accountability to make decisions).
   b. Who are the informers? (i.e. those who will inform decisions and activities). These may be decision-makers, but also may only have a remit limited to providing technical expertise and advice
   c. Who are the implementers?
2. Include details in the stakeholder map about **how** each stakeholder will be engaged. This includes:
   a. interaction frequency and who will be responsible or the lead for the engagement;
   b. developing key messages;
   c. identifying the engagement channel.
3. Consider linking the stakeholder map to a communication and action plan that lists priority activities for each stakeholder and maps them along a timeline.

Key considerations

- Stakeholders include those that will be involved in the antibiotic introduction process and have a role in planning, implementation and evaluation.
- Stakeholders are multisectoral and include civil society organizations and representatives. They may also include the private sector, depending on a country's health care system.
- A stakeholder map should be simple and capture key information about individuals and groups.

- The stakeholder map may indicate if there are skills or resources missing, or whether specific committees or groups could streamline decision-making, planning and implementation. In these instances, refer to governance structures and set up optimal governance mechanisms that are fit-for-purpose.
- Some parts of the stakeholder map will likely need to be completed and/or updated as the antibiotic introduction progresses.
- Stakeholder mapping and engagement is a continuous activity that should take place at the beginning of each step in the introduction process.
- Stakeholders to consider through the antibiotic introduction process include (non-exhaustive):
  - Ministries and departments (i.e. government officials including within the ministry of health and other relevant departments, e.g. ministry of finance)
  - Politicians and/or parliamentarians.
  - Relevant policy-makers and regulators (e.g. NRAs and NDTCs)
  - Existing national AMR committees (e.g. an antimicrobial resistance coordination committee (AMR CC)).
  - Implementers of the AMR NAP.
  - Department of pharmaceutical services (or equivalent based on the local context).
  - Technical experts and advisors (including technical experts such as TWGs of AMR CCs).
  - National reference laboratory (NRL), the national institute of health (NIH), or national coordination body of laboratories.
  - Professionals (e.g. infectious disease doctors, clinicians, pharmacists, microbiologists, epidemiologists, etc; facility-level stakeholders including DTCs, AMS committees, clinicians, prescribers, pharmacists, nurses, and other health care workers; community health workers; laboratory managers and laboratory technicians).
  - Professional associations (e.g. medical professional associations, pharmacy associations, laboratory and microbiology associations).
  - Academic staff and institutions.
  - United Nations and other international agencies.
  - Donor organizations and foundations.
  - Regional partners and bodies.
  - Health insurance agencies.
  - Non-governmental organizations.
  - Civil society organizations and representatives.
  - Community groups and representatives.
  - Faith-based groups.
  - Pharmaceutical companies and manufacturers.
  - Diagnostics stakeholders.
  - Market authorization holders.
  - Relevant suppliers and/or importers.
  - Distributors and warehouse/supply chain managers.
  - Other implementing partners.

Relevant resources and tools

- Suggested stakeholder map template (Table 1).

Table 1. Illustrative example of a stakeholder map (non-exhaustive)

Stakeholder: AMR CC and existing AMR TWGs (including policy makers and regulators)									
Type (decision-maker, informer/ implementer)	Group/ individual	Current engagement level and role	Influence level	Priority	Notes	Key interaction messages	Interaction channel	Frequency	Relationship lead
Stakeholder: Additional policy makers e.g. Department of Pharmaceutical Services (or equivalent based on the local context), national EML committees etc									
Stakeholder: Additional regulators									
Stakeholder: Facility DTCs, AMS committees, and/or AMS teams									
Stakeholder: National Referral Laboratory (NRL), the National Institute of Health (NIH), or microbiology laboratories									
Stakeholder: Implementing partners									
Stakeholder: Healthcare workers									
Stakeholder: Private sector stakeholders									
Stakeholder: Civil society: professional organisations									
Stakeholder: Civil society: patient organisations									
Stakeholder: Civil society: communities									
Stakeholder: Civil society: NGOs									
Stakeholder: Civil society: FBOs									
Stakeholder: Supply chain (e.g. market authorisation holders, manufacturers, suppliers, importers, warehousing and distributors)									

3 Deciding to introduce an antibiotic

Purpose

To identify a clear, evidence-based public health and clinical need to introduce an antibiotic, and to secure political buy-in and financing needed to support its introduction into the health system.

Steps involved

1. Developing and implementing a decision-making process to prioritize and select antibiotic(s).
2. Linking decision-making to demand from health care facilities and providers.
3. Securing political buy-in and financing.

Reminder!

Identify and engage stakeholders required to support and implement decision-making activities (refer to the stakeholder map developed during pre-planning)

Key considerations

- Decision-making should be adapted to the local context and leverage existing capacity. Existing capacity, resources and processes should support the decision-making process, with adaptations and/or expansions as needed to support decision-making, implementation and M&E.
- Engagement with all stakeholders – especially with communities, civil society organizations, national reference laboratories and national institutes of health, health care workers and supply chain stakeholders – is key from the beginning and throughout the entire process.
- Decisions should be made on the best available local, regional or global evidence.
- Data and insights from prescription audits and clinician, pharmacist or professional association reports can also be useful in identifying the need, especially in areas where laboratory capacity is limited. These reports give a perspective on clinical experiences and could include data and trends on resistance patterns in local facilities.

- The decision to introduce an antibiotic should also consider whether there is adequate capacity to implement activities to ensure appropriate use, and if there is appropriate laboratory and surveillance capacity, or available resources to strengthen capacity before the antibiotic is introduced.

Before moving to planning and implementation, a clear public health need should be identified that has stakeholder buy-in, as well as agreed political and financial support for antibiotic introduction.

Relevant tools and resources

The antibiotic introduction checklist (Annex 4).

3.1 Developing and implementing a decision-making process to prioritize and select antibiotics

Purpose

To apply a systematic, transparent evidence-based process to guide and make decisions on which antibiotics are needed (i.e. which antibiotics to prioritize for introduction), and to guide those tasked with making recommendations and decisions on identifying and selecting priority antibiotics.

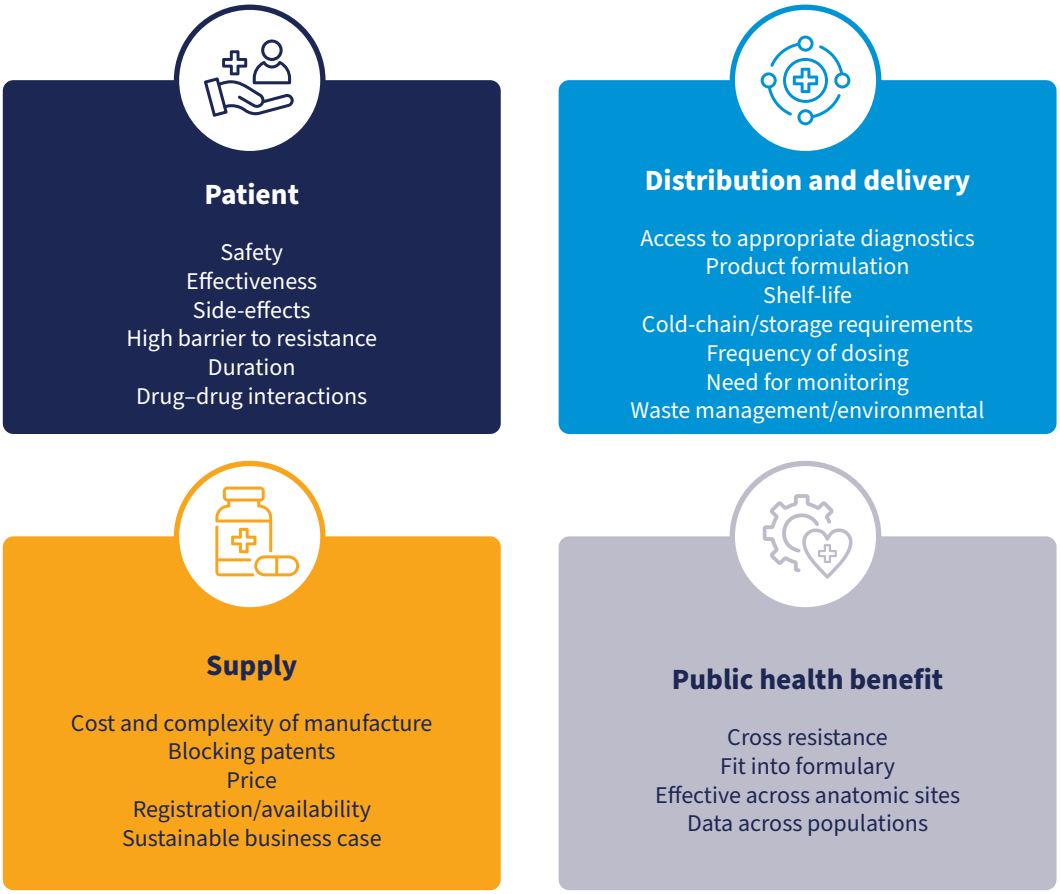
Actions

1. Prioritize antibiotics based on the public health and clinical need:
    a. Consult and engage stakeholders (using the stakeholder map developed in the previous section).
    b. Review and assess existing AMR and antibiotic-relevant policies and guidance, including global guidance such as the WHO EML and WHO AWaRe antibiotic book.
    c. Gather, review and analyse available data (e.g. local epidemiology, resistance patterns, current formularies and antibiotic use data of antibiotics currently being used nationally, antibiotic production/importation data etc.) to assess the prevalence and AMR trends of priority pathogens. This will help to identify whether currently used antibiotics can address the clinical need and if alternative options are needed. High resistance rates to existing antibiotics may justify introducing an antibiotic that targets multidrug-resistant organisms.
2. Select antibiotics matched to public health and clinical needs:
    a. Assess product characteristics in relation to the local epidemiology, resistance patterns, current formularies, antibiotic use data, patient population, supply, distribution, delivery, the ability of health care infrastructure to support product requirements including administration and treatment regime (e.g. dosing frequency), and the potential public health benefit (Fig. 5). This should also include an assessment of the testing, diagnostics and monitoring requirements to use the antibiotic and whether access to appropriate testing is available, or if new or additional capacity is required.

b. Ensure appropriate AMU and AMR surveillance and/or reporting systems are working effectively, and that the selected antibiotic can be integrated into existing systems, or capacity can be expanded to meet additional needs.
c. Ensure surveillance systems are in place to enhance the monitoring and management of antibiotic use, improve patient safety and inform stewardship activities.

3. Explore conducting health technology assessment(s) (HTA) to support decision-making.
4. Re-engage stakeholders to validate and communicate outcomes of prioritization and selection steps.
5. Decide whether to move forward and make the case to introduce an antibiotic.

Fig. 5. Product characteristics to consider when selecting antibiotics



Note: Adapted from GARDP (unpublished presentation, 2024).

Key considerations

The decision to introduce an antibiotic requires a thorough understanding of the related public health and clinical needs.

- The prioritization and selection process should safeguard that first- and second-line options are available and are being used, and **Reserve** classified products are introduced only as a last resort. During the process, consideration should be given to whether there is capacity and infrastructure to implement AMS activities to safeguard the use of a **Reserve** antibiotic, including if there is access to the tests needed to inform appropriate treatment.
- Existing medicines prioritization and selection processes may be active through the nEML process or NDTCs, and these should be leveraged where possible. In the absence of an existing process, leverage other health care advisory bodies that support the selection of products for nEMLs, or relevant technical experts and advisors.
- Technical experts and advisors can be engaged to support reviewing and assessing data, and making recommendations on priority antibiotics.
- The selection process should be based on a country's AMR/AMU situation, products on the WHO EML, in the WHO AWaRE antibiotic book, or other recent guidance. nEMLs are also relevant depending on their focus (e.g. some nEMLs focus on primary health care and so **Reserve** and **Watch** antibiotics that are used in hospital settings may be out of scope).
- Needs can be identified by assessing:
  - the current AMR situation (considering local, regional and global trends and threats);
  - the underlying need i.e. the local burden of infectious diseases, the local burden of MDROs and resistance rates;
  - current patterns of antibiotic use for the indication being targeted, delivery channels (i.e. public, private or unregulated sectors), and treatment gaps (e.g. consider use patterns and delivery channels for recommended and registered antibiotics that are currently available). Consider current treatment gaps for recommended but unavailable antibiotics, and the cause for the treatment gaps. Also consider antibiotic use patterns and delivery channels for antibiotics that are not recommended but available.
- The epidemiological and clinical 'real need' for an antibiotic should be rationalized so it is relative to context, including the urgency of accessing an antibiotic to respond to an urgent threat.
- Once the need has been established, select an antibiotic that best addresses the treatment gap and matches needs.
- Product characteristics criteria can also be used to guide antibiotic selection (Fig. 5).
- Available data for decision-making will vary across countries. In settings with limited data, an estimate of disease prevalence can be used to guide decisions alongside situation insights from clinicians and health care professionals (e.g. from medical professional associations/pharmaceutical associations) based on current clinical practice. Likewise, external global and regional data sources can be used to guide decision-making, including from neighbouring countries.

- Gathering data can be an opportunity to capture and document data gaps, and corresponding infrastructure/capacity limitations with data collection and routine AMR surveillance.
- HTA is recommended but should be applied based on local capacity. Complex analyses are not always necessary. Countries with less developed HTA processes, or where data is limited, can consider an overall budget impact assessment that assesses affordability rather than value for money. For **Reserve** antibiotics, and any low volume antibiotic, a budget impact assessment should take into account the patient population size – while **Reserve** antibiotic volumes are likely to be low (even though they are generally expensive per unit), introducing them for a small patient population may still be financially acceptable. Other analyses and HTA approaches to consider include:
  - Conducting a comparative cost-evaluation (if data are available).
  - Leveraging regional HTA collaborations, or HTA conducted by other countries, can also be considered in countries where there is limited capacity to conduct HTA locally.
  - Planning a re-evaluation once more data is available.
- There should also be demonstrated commitment and resources to ensure the appropriate use of the selected antibiotic.
- Additional considerations for prioritizing and selecting an antibiotic include:
  - Alignment with national, regional and global priorities. For example, if a country is in the African region, consider whether introducing the antibiotic aligns with the priorities described in Voicing African priorities on the active pandemic: Accelerating the continental response to antimicrobial resistance *(24).*
  - If introducing the antibiotic will improve equity of access (e.g. can the antibiotic be used in vulnerable populations such as children <5 years of age?).
  - If the antibiotic is considered a priority by the medical and broader community (e.g. have clinicians voiced a need for an antibiotic to address a problem they are facing with treating bacterial infections?).
  - If introducing an antibiotic requires laboratory strengthening for diagnosis, susceptibility testing and therapeutic dose monitoring, along with enhancing surveillance systems to track resistance trends and usage patterns effectively.
  - If there is a supplier likely to register the antibiotic locally, or if the antibiotic has approval from a stringent regulatory authority or a WHO-listed authority, or has WHO prequalification.

Relevant resources and tools

- Refer to Annex 6 for detailed considerations for prioritizing and selecting antibiotics.
- Refer to Annex 7 for detailed considerations for conducting HTA, including data needs for a budget impact assessment.
- Completed stakeholder map to plan and engage stakeholders.
- WHO Model List of Essential Medicines *(16)*.
- AWaRe classification of antibiotics for evaluation and monitoring of use, 2023 *(3).*
- People-centred approach to addressing antimicrobial resistance in human health: WHO core package of interventions to support national action plans *(8)*.

- Globally available data sources in the public domain to support prioritizing antibiotics and assessing product characteristics:
  - Global Research on Antimicrobial Resistance project *(25)*.
  - Global antimicrobial resistance and use surveillance system *(26)*.
  - Global database for tracking AMR: Country self-assessment surveys *(27)*.
  - Product information labels: company websites or labels published by stringent regulatory authorities (e.g. United States Food and Drug Administration and European Medicines Agency).
- WHO guidance to countries to institutionalise HTA mechanisms *(28)*.
- Resource guide on the use of health technology assessment in health benefit package design processes *(29)*.
- OneHealth Tool *(30)* that attempts to link strategic objectives and targets of disease control and prevention programmes to the required investments in health systems.
- Generalized cost-effectiveness analysis *(31)* – part of the WHO CHOosing Interventions that are Cost-Effective (CHOICE) project.
- Medicine prices and other market information sources (for sources to conduct cost comparisons) *(32)*.

3.2 Linking decision-making to demand from health care facilities and providers

Purpose

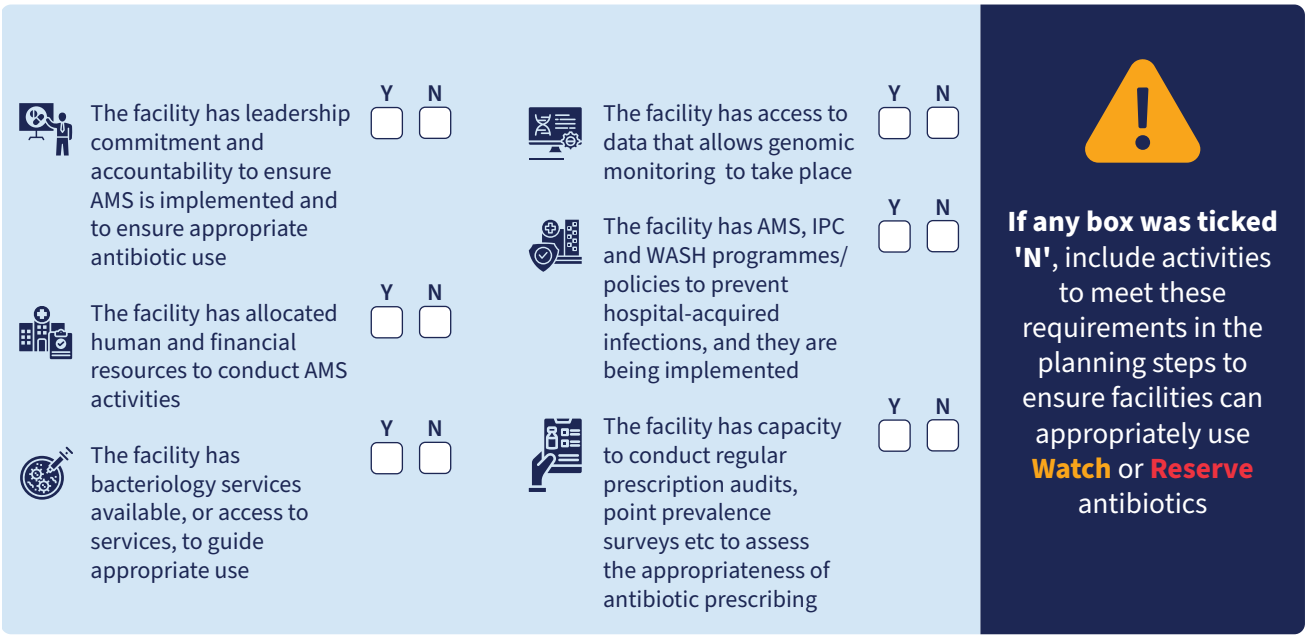
To ensure that there is capacity, need and willingness to use the selected antibiotic in relevant health care facilities (i.e. ensuring it can be and will be used at the point of care).

Actions

1. As part of continuous stakeholder engagement, re-engage facility-level decision-makers and providers and communicate the outcome of the antibiotic selection process.
2. Opportunistically leverage this engagement to capture information on facility capacity for planning and implementation focusing on:
   a. patient population and catchment area;
   b. human resource capacity and potential scope to upskill health care workers;
   c. current AMS policies/programmes and how these are being implemented (i.e. if facilities needing to use the selected antibiotic are not implementing AMS programmes, consider how to introduce AMS activities at the facility and what additional capacity is needed);
   d. facility infrastructure including intravenous pumps and ability to store products requiring cold chain/refrigeration etc;
   e. laboratory capacity and existence of, or linked to microbiology laboratories/ diagnostic networks.

3. Refer to the Facility readiness checklist (Fig. 6) to check if facilities have current capacity to appropriately use antibiotics.
4. Re-engage with supply chain stakeholders to identify any major challenges or potential bottlenecks to delivering the selected antibiotic, as well as other health care commodities including the required diagnostics, to facilities.
5. Refer to:
    a. Section 4.2. Deciding the antibiotic introduction approach for guidance on assessing the capacity of facilities and selecting those with the lowest risk of inappropriate use.
    b. Section 4.8. Preparing facilities: health care worker readiness and promoting antimicrobial stewardship for guidance on translating national antibiotic policy into practice at treating facilities.

Fig. 6. Facility readiness checklist



Key considerations

- Facility representatives, including those that have a lead role in managing and implementing AMS programmes in facilities, should be engaged from the beginning of the decision-making process. This step is to ensure that at the end of the process, a connection is made between those making decisions and those using the antibiotic.
- Efforts should be made to target facilities with the potential to safely and appropriately use the antibiotic being introduced. However, there may be instances where representatives from a health facility participates in the decision-making process, but their facility may not be eligible to use the antibiotic once it is made available.

Relevant resources and tools

- Completed stakeholder map to plan and engage stakeholders (see Table 1).

3.3 High-level cost estimates, political alignment and securing financing

Purpose

To secure political support and financial resources to allow for full planning and implementation by presenting the case for public health and clinal needs, and providing estimates on planning, implementation and M&E costs.

Important!

Developing a detailed budget is the last step of the process once all activities have been planned (see Section 6). The following steps are for developing high-level costing estimates to support making the case for introducing an antibiotic and securing support and alignment with the right government departments. Whereas the detailed budgeting comes after all activities of the introduction plan have been considered and planned to allow for developing a more realistic budget and can also support prioritising activities within budget limits.

Actions

1. Estimate high-level costs using benchmark estimates for assumed antibiotic introduction activities. For example, include (non-exhaustive):
   a. antibiotic procurement;
   b. other health care commodities procurement, including diagnostics and laboratory supplies;
   c. infrastructure and other equipment;
   d. supply chain warehousing and distribution;
   e. training, awareness and communication (i.e. human resources and materials);
   f. monitoring and evaluation (i.e. human resources and materials);
   g. operational research (i.e. human resources and materials);
   h. personnel for planning and implementing the antibiotic introduction plan (based on level of effort and costs to manage and implement similar projects).

2. Using the outputs from assessing the public health and clinical needs, and assessing antibiotic characteristics, develop a policy brief to make the case for introducing an antibiotic. Include at least the following elements in a 1–2-page policy brief:
   a. Title of the planned project.
   b. Purpose of the request (e.g. seeking approval to introduce an antibiotic to treat multi-drug-resistant infections nationally).
   c. The recommendations (including the expected funding need and budget impact).
   d. Expected impact of the recommendations.
   e. Key issues and risks.
   f. Background on the public health and clinical needs (i.e. the rationale).
   g. Consultation process (i.e. who has been engaged).
3. Brief relevant stakeholders to secure political alignment and financing to start planning and implementation for the selected antibiotic. Relevant stakeholders may include those responsible for making budgetary and technical decisions (e.g. ministers in the health or financing departments, or in some countries this may be a permanent secretary or deputy secretary).
4. Complete the antibiotic introduction checklist (Annex 4) to ensure that steps on 'Deciding to introduce an antibiotic' have been completed before moving to planning and implementation.

Key considerations

- This is a necessary step to ensure that there is politic will, buy-in and financing, including available financing in other budgets (e.g. pharmaceutical products budget), to realize the anticipated impact from the plan.
- This step can also be useful to identify any major funding gaps and to ensure that introducing an antibiotic is financially sustainable over the long-term.
- Each country will have local processes in place for seeking approval before planning and implementing a project like introducing an antibiotic. Existing processes should be followed.

Relevant resources and tools

- Refer to Annex 8 for detailed considerations for developing high-level cost estimates, political engagement and securing financing.
- Example policy brief template (see Annex 9).
- The antibiotic introduction checklist (Annex 4).

4 Developing the antibiotic introduction plan

Purpose

To develop 10–20 page costed antibiotic introduction plan that is actionable and measurable, and includes all planning and implementation activities needed to ensure successful introduction of an antibiotic, over a defined time-period.

Steps involved

1. Defining goals, objectives and expected impact(s).
2. Deciding on the antibiotic introduction approach.
3. Updating and adopting policies for introducing the antibiotic.
4. Preparing for antibiotic registration/market authorization.
5. Preparing testing and surveillance systems.
6. Procurement planning.
7. Preparing logistics and supply chain management.
8. Preparing facilities – health care worker readiness and promoting antimicrobial stewardship.
9. Developing a communication plan to raise awareness for the appropriate use of all antibiotics.

Reminder!

Identify and engage stakeholders required to support the development and implementation of the antibiotic introduction plan (refer to the stakeholder map developed during pre-planning)

Key considerations

- This step should only start after political support and financing is secured in the previous step (section 3.3).
- Successful antibiotic introduction involves careful consideration of various strategic, policy, infrastructure and resourcing aspects.
- Activities should refer to the goals in the NAP.

- A plan should span a defined time-period (e.g. three to five years – ideally spanning across one political cycle), delineating the goals, objectives, strategies, indicators and activities aimed at achieving milestones.
- Develop a detailed plan, outlining all activities and then cost the plan at the end of the process. The WHO costing and budgeting tool for national action plans on antimicrobial resistance *(19)* can be used to cost the introduction plan. It is flexible and adaptable so all types of activities can be costed using the tool.

Relevant resources and tools

- The antibiotic introduction checklist (Annex 4).

4.1 Defining goals, objectives, and expected impact(s)

Purpose

To define programmatic objectives, goals and targets and indicators that will guide implementation plans, measure success and capture lessons.

Actions

1. Define goals and objectives for introducing the selected antibiotic. These should be measurable and can be used to track progress throughout implementation.
2. Draft high-level measurable goals, impact, outcomes and outputs linked to assumed activities and inputs (i.e. available financing) (with consideration to using a theory of change).
3. Articulate feedback mechanism/process to assess progress and course correct as needed (see Annex 5).

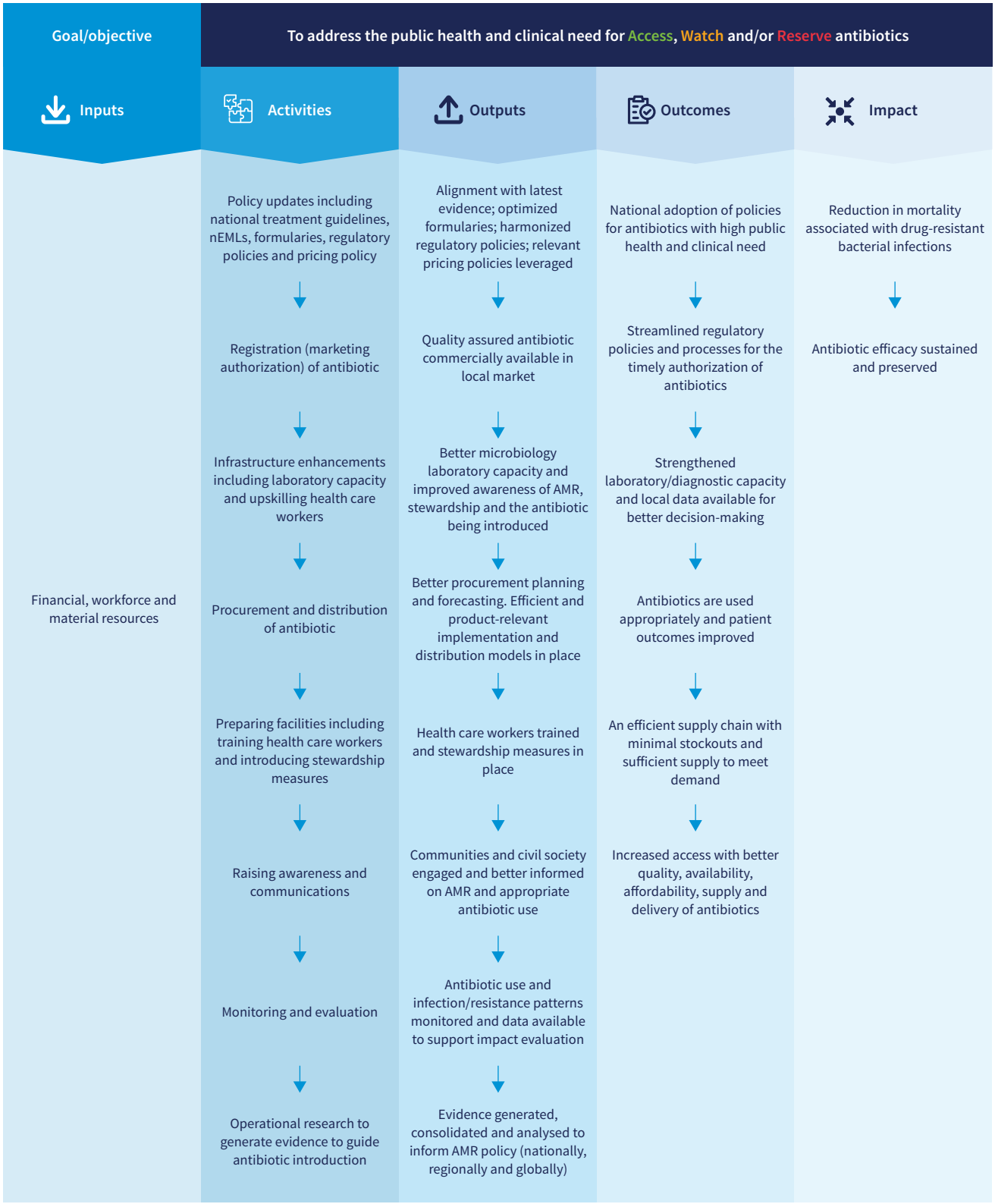
Key considerations

- Consider how the introduction of the selected antibiotic will improve patient outcomes, reduce the morbidity and mortality caused by drug-resistant infections, and help control and prevent AMR.
- Consider how the introduction of an antibiotic can be leveraged to reinforce or improve overall appropriate use, including strengthening testing platforms and surveillance systems. This is important for conserving the efficacy and effectiveness of the antibiotic and minimizing the risk of emerging resistance.
- Goals and objectives should refer to the NAP and include how introducing the antibiotic will improve equity.
- Goals through to expected impact can be organized using a theory of change *(33)* that organizes progress measurements into the goal, inputs, activities, outputs, outcomes and impact (Fig. 7).
- Goals/objectives, activities, outputs, outcomes and expected impacts need to be linked to targets, and indicators that are set when planning M&E for the antibiotic introduction plan (see Annex 19).

Relevant resources and tools

- A theory of change template (Annex 10).

Fig. 7. Illustrative example of a theory of change for antibiotic introduction



4.2 Deciding on the antibiotic introduction approach

Purpose

To decide on an introduction approach that best suits the local infrastructure, health care worker capacity and characteristics of the antibiotic. Approaches could include: phased-and-monitored (or pilot approach); simultaneous roll-out of an antibiotic nationally; existing or potential public–private partnerships, especially where access and availability are high in the private sector; a mix of different sub-national approaches.

Actions

1. Conduct a preliminary health care facility capacity assessment to identify facilities that need, and can appropriately use, the antibiotic (refer to facility readiness checklist (Fig. 6)). This includes having appropriate AMS programmes, or capacity to design and implement AMS programmes, along with diagnostic and microbiological services capable of reporting antibiotic susceptibility results.
2. Consult with stakeholders, including technical experts and advisors, and decide on the optimal introduction approach.
3. If an optimal approach is not apparent, a new introduction approach can be co-designed through a multi-stakeholder approach. This could include designing a structured programme specifically for last-resort antibiotic treatments such as vertical programmes that have been implemented for malaria, HIV and tuberculosis in LMICs.

Key considerations

- Different introduction approaches will likely have different financial implications, so decision-making should also consider potential costs.
- There are multiple possible approaches to introducing an antibiotic. The chosen approach should be tailored to the country context and health system, to local capacity, and to logistics and supply chain infrastructure.
- The introduction approach should align with and integrate into routine practices for all antibiotics, foster the appropriate use of antibiotics, and promote continuous and equitable access.
- Health care facility capacity assessments might consider the following factors:
  - Number of facilities that need the antibiotic.
  - Facility readiness i.e. those with current and/or potential capacity.
  - National and sub-national testing and diagnostic capacity.
  - Ability to manage the introduction of an antibiotic (e.g. staffing and beds to account for any anticipated changes in patient volume).
  - Current implementation of AMS programmes.
  - Current use and availability of first- and second- line antibiotics.
  - Adequate refrigeration and energy supplies, water, sanitation and hygiene and IPC capacity.

- The capacity assessment should also help highlight if there is a need to strengthen existing infrastructure to safely introduce the antibiotic.
- Key factors to consider when deciding the introduction approach include (Annex 11):
  - Number of antibiotics being introduced.
  - Urgency based on the volume of patients with MDROs needing treatment.
  - Level of care where the treatment should be made available.
  - Location of facilities and links to other services (e.g. NRL, NIH, or microbiology laboratories).
  - Implementation of AMS programmes, processes, policies and sufficient capacity to use the antibiotic appropriately.
  - Current and potential infrastructure and capacity.
  - Costs of the different approaches.

Relevant resources and tools

- Refer to Annex 11 for detailed considerations for deciding the antibiotic introduction approach.
- Antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries. A WHO practical toolkit *(23)*. Includes a checklist of essential health care facility core elements for AMS programmes in LMICs as well as a checklist of essential national core elements for AMS programmes in LMICs. It also includes guidance on assessing AMS programmes.

4.3 Updating and adopting policies to support introducing antibiotics

Purpose

To integrate the selected antibiotic into national policies, ensuring that it is available and appropriately used. To ensure that policies aim to expand health coverage by considering the cost of the antibiotic being introduced and that it is affordable and accessible (e.g. setting fair prices and providing financial support to reduce out-of-pocket costs for patients).

Actions

1. Linked to the review and assessment of existing AMR and antibiotic-relevant policies (see Section 3.1), update nEMLs, national treatment guidelines and formularies, pricing, insurance and reimbursement policies, and regulatory policies. Ensure alignment across all relevant policies. Policy alignment is important for successful nEML implementation and to ensure equitable access (i.e. policies are aligned to minimize out-of-pocket costs and the risk of catastrophic payments).
2. Starting with the nEML, adopt a multi-stakeholder approach (i.e. collaboration across leaders, national coordinators, nEML committees, technical experts/advisors, policy-makers, national regulatory authorities, and NDTCs etc) to support the process that will consider including the selected antibiotic on the list.

3. If local processes allow, and the NAP has been developed, is being implemented, and has a relevant section for priority antibiotics, include the selected antibiotic into the NAP.
4. Develop or update treatment guidelines/protocols with the selected antibiotic. These should be in line with testing/diagnostic capacity, and stewardship and AWaRe principles:
    a. it is paramount to ensure that treatment guidelines/protocols are updated to reflect different scenarios and the local health care system (i.e. that they are developed based on the local laboratory and diagnostic capacity for the antibiotic being introduced).
5. Identify and apply pricing policies for the selected antibiotic and integrate the antibiotic into social health insurance or reimbursement schemes, if applicable. This is especially important for ensuring equitable access for the entire population to the antibiotic being introduced. Consider (Annex 12):
    a. Referring to the work of the WHO Fair Pricing Forum *(34)* for approaches and emerging policies on market transparency and affordability, as well as the *WHO guideline on country pharmaceutical pricing policies (35)*.
    b. Pooled procurement as a pricing strategy for **Reserve** and some **Watch** antibiotics.
    c. Medicine access policies, such as reimbursement and subscription-based models.
    d. Intellectual property laws (Annex 2.2.1).
    e. Currency fluctuations.
6. Incorporate the antibiotic into surveillance systems and policies to monitor patterns of use and the emergence of resistance (see Section 4.5 Preparing testing and surveillance systems).
7. Identify, streamline and apply regulatory policies and processes for timely market authorization (see Section 4.4 Preparing for antibiotic registration/market authorization).
8. Develop a plan to communicate policy changes, including new treatment guidelines to facilities.

Key considerations

- For a product to be included on a nEML, nEML committees usually require the most recent evidence demonstrating safety and efficacy.
- nEMLs can be used to streamline and guide procurement planning, and can include limitations around antibiotic use to support AMS programmes.
- Not all nEMLs are fit-for-purpose for including second- and/or third-line antibiotics. In cases where nEMLs only target medicines used in primary health care, consider developing sub-lists to complement the nEML that include medicines only for use in specialized health settings or higher-level health facilities, such as **Reserve** antibiotics.
- Depending on country nEML cycles, it might not be possible to add an antibiotic to an nEML immediately, so plans should be developed around national schedules for updating nEMLs and timing activities so that the focus antibiotic/s are included in the next update round.

- The high cost of **Reserve** and some **Watch** antibiotics generally limits their availability in LMICs. For this reason, consideration should be given to pricing policies that may address the tension between price and volumes such as pooled procurement. Countries should also consider including antibiotics for multidrug-resistant infections in social health insurance and reimbursement schemes if applicable.
- The benefits and risks of different pricing strategies for antibiotics should be thoroughly assessed, as not all policies may have the desired intent. For example, external reference pricing may be a solution for overcoming data limitations with value-based pricing, but price accuracy can be difficult to obtain and requires a high-level of skill (i.e. prices collected from publicly available sources in comparison countries may not be accurate and might not reflect the final net price accounting for discounts, rebates and taxes etc.)*(36)*.
- Once policies are updated, consideration needs to be given to how these policies will be translated into practice.

Relevant resources and tools

- Refer to Annex 12 for detailed considerations for updating and adopting policies to support introducing antibiotics.
- Refer to Annex 13 for detailed considerations for streamlining regulatory policies and processes for timely market authorization.
- The corresponding NAP, where one exists.
- WHO Model List of Essential Medicines *(16)*.
- AWaRe classification of antibiotics for evaluation and monitoring of use, 2023 *(3)*.
- People-centred approach to addressing antimicrobial resistance in human health: WHO core package of interventions to support national action plans *(8)*.
- WHO guideline on country pharmaceutical pricing policies *(35)*.

4.4 Preparing for antibiotic registration/market authorization

Purpose

To ensure the introduction plan considers regulatory policies and processes that can facilitate market authorization of the selected antibiotic, and that the plan includes a clear, collaborative partnership with the NRA to prevent regulatory delays. Additionally, to ensure that products are quality assured through streamlined regulatory processes that facilitate the approval and introduction of antibiotics, ensuring they meet safety and efficacy standards.

Actions

1. Work with the NRA to identify existing policies and processes that apply to the selected antibiotic (e.g. accelerated registration pathways for orphan drugs, or urgent life-saving treatments, or emergency use waivers etc.).

2. Work with the NRA to leverage available facilitated registration pathways (e.g. the Collaborative Registration Procedure, Regional Joint Assessments, and referencing WHO-listed authorities).
3. With the NRA, decide on the regulatory policies and pathways for registering the selected antibiotic. Communicate the decision so that the appropriate registration pathway is clear to companies submitting a dossier for market authorization.

Key considerations

- Activities in this step should be centred on facilitating a strong regulatory environment for the appropriate use of all antibiotics.
- Companies have often been reluctant to apply for marketing authorization in LMICs because demand for **Reserve** and some **Watch** antibiotics is too low, or the market is too opaque. This lowers the companies' confidence that registering a product will yield a positive return *(37,38)*. For these antibiotics, registration is likely to follow policy adoption.
- Close collaboration between leadership, national coordination, nEMLCs, the NDTC and the NRA is essential for defining, informing and enforcing regulations on the prescription and delivery of antibiotics. This cooperation helps establish streamlined regulatory pathways that ensure antibiotic quality, and supports development and implementation of policies, such as accelerated approval for use.
- NRAs can play a role in enforcing marketing restrictions (i.e. prohibiting marketing authorization holders from marketing **Reserve** antibiotics at lower levels of care and/or restricting who they can market to). NRAs can also support active pharmacovigilance activities through collaboration with public health programmes, to strengthen the monitoring of the safety of these antibiotics in the general population.
- Recently, there have been global supply shortages of antibiotics. While NRAs are not officially mandated to address antibiotic shortages, various measures to prevent major shortages in health care systems have been taken in LMICs by NRAs and other stakeholders, including ministries of health and procurement agencies. These measures have been detailed in a recent WHO and GARDP report *Policy and regulatory interventions to address antibiotic shortages in low and middle-income countries (39)*. For example, NRAs, ministries of health or procurement officers can work to ensure that there are the required buffer stocks, collaborate with manufacturers to increase the supply of products or create incentives for manufacturers to register such products.

Below is an overview of regulatory strategies and approaches that could be considered by an NRA for **Watch** and **Reserve** antibiotics.

- Incentivize antibiotic registration through adequate implementation and use of facilitated registration pathways. This can accelerate the approval of antibiotics, minimize registration fees and, if appropriate, reduce the resources, time and workload required for the registration of an antibiotic.
- Implement reliance mechanisms to leverage outputs of other regulators and organizations (e.g. WHO Collaborative Registration Procedure and WHO-listed authorities) whenever possible. This will allow for greater focus on national level value-added regulatory activities.

- Incentivize registration by explicitly recognizing new antibiotic chemical entities targeting serious or life-threatening infections as a critical unmet medical need, and formalize their inclusion in regulatory frameworks for accelerated drug approvals.
- Consider allowing fee waivers/reductions and build in pre-submission meetings in the early stages of dossier preparation and rolling submissions that allows applicants to submit dossier sections in a staged process, rather than all at once.
- Participate in regulatory harmonization and convergence initiatives for accelerated approval and registration of antibiotics as part of the global and regional coordination in the fight against AMR:
  - Advocate that regional harmonization initiatives should add **Reserve** and **Watch** antibiotics to their priority list of products considered for regional review.
  - Establish memoranda of understanding to facilitate collaboration, trust building and exchange of information between NRAs.
  - Follow national processes to expedite registration of antibiotics approved through regulatory harmonization and convergence initiatives.
- Support appropriate use by incorporating data monitoring and reporting requirements into dossier submissions, and/or including labelling requirements that manage or restrict prescribing antibiotics.
- Foster the use of pharmacovigilance measures by facilitating integration between the pharmacovigilance and public health/disease control programmes, and consider the needs for active pharmacovigilance activities.
- Enhance reporting of adverse drug reactions from the facilities where new antibiotics are introduced through regular monitoring and oversight.
- Ensure regulatory systems are based on well-defined and strengthened market surveillance and regulatory processes capable of identifying and rejecting sub-standard or non-recommended antibiotics.

Relevant resources and tools

- Refer to Annex 13 for detailed considerations for streamlining regulatory policies and processes for timely market authorization. This Annex also includes a summary of strategies to consider to create a strong regulatory environment for medicines in general.
- Policy and regulatory interventions to address antibiotic shortages in low and middle-income countries *(39)*.
- WHO-prequalified Cefidericol *(40)*.
- The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) *(41)*.
- WHO Collaborative Procedure for Accelerated Registration *(42)*.
- WHO Facilitated Product Introduction Website *(43)*.
- WHO-Listed Authority *(44)*.
- Product assessment and manufacturing site good manufacturing inspection outputs produced by the WHO Prequalification Programme *(45)* and by stringent regulatory authorities *(46)*.

4.5 Preparing testing and surveillance systems

Purpose

To ensure that there is a national laboratory body/system in place that allows for appropriate and sufficient testing and diagnosis of bacterial infections, including multidrug-resistant organisms and regular reporting of AMR trends and antibiogram data, across different settings. This step also aims to emphasize the importance of an active national laboratory mechanism, body or committee (e.g. in many countries the NRL or a Laboratory Directorate) to coordinate and provide national guidance and procedures on diagnostic, testing and surveillance

Actions

1. Determine both the national and facility level diagnostic and microbiology capacity and assess whether that capacity is sufficient, or that resources are available to strengthen capacity, to introduce the selected antibiotic. This can be done through stakeholder engagements or capacity assessment surveys. Minimum capacity requirements include:
    a. Diagnostic stewardship policies at the health facility level.
    b. Well-trained staff.
    c. Adequate equipment and diagnostic supplies.
    d. Standard operation procedures.
        i. AST standards (e.g. refer to established guidelines such as those of the Clinical and Laboratory Standards Institute or the European Committee on Antimicrobial Susceptibility Testing).
    e. An established laboratory information system.
    f. Quality assurance system (such as participation in proficiency testing).
2. Select a diagnostic approach for the antibiotic being introduced that best reflects the local scenario:

Scenario 1. No laboratory capacities in place

- Countries with a weak or no laboratory and/or without NRL/NIH can be supported by regional or supranational reference centres (e.g. WHO Collaborating Centres).

Scenario 2. Weak Laboratory capacities

- Countries with weak laboratory capacities can be supported by the NRL/NIH. The NRL/NIH can implement AST for all health care facilities and provide the information to monitor the newly introduced antibiotic, while capacity to perform targeted AST is being strengthened in a stepwise manner. The NRL/NIH can also develop and implement a strategy to support testing of isolates from health care facilities.

Scenario 3. Laboratory capacity in place

- Countries with capacities in place should implement standard AST and include the newly introduced antibiotic as part of the routine surveillance system.

IMPORTANT!

All antibiotics should be prescribed based on local treatment protocols (standard treatment guidelines) that support good antibiotic stewardship practices. As the availability of diagnostic tools varies considerably in different settings, the WHO AWaRE antibiotic book *(3)* includes empiric antibiotic recommendations that are based on clinical signs and symptoms. Relevant diagnostic tests (including imaging and laboratory tests) are suggested based on WHO Model List of Essential In Vitro Diagnostics *(47)*. The list of tests provided in the AWaRE antibiotic book for each infection is not based on a formal assessment of their predictive value, but as a general guide of tests that could be clinically helpful, where available *(3)*.

A general exception to empiric treatment is for the use of Reserve antibiotics, where use should ideally follow test results. However, it is important to highlight that in cases of severe, life-threatening infections with a MDRO, Reserve antibiotics may be used based on empirical knowledge or in combination with other treatments prior to – or in the absence of – AST results. This is because early treatment of MDROs with a Reserve antibiotic has the greatest benefit and delaying use until after AST results are available may decrease health benefits. After treatment initiation, laboratory and diagnostic capacity is also important to support treatment modification if needed. For example, culture testing and results may indicate a need to either step-up or step-down use (e.g. de-escalating treatment based on clinical progress and with susceptibility results). For these reasons, it is paramount to ensure that treatment protocols are updated to reflect different scenarios and settings, and that they are based on the local laboratory and diagnostic capacity for the antibiotic being introduced (see Annex 12).

Key considerations

- Countries should consider the laboratory capacity needed to perform AST based on the availability of clinical breakpoints of new antimicrobials:
  - For antibiotics with standardized breakpoints, countries should implement the methodology based on their capacities and the availability of resources. In case of no available resources, countries can be supported by regional or supranational centres (e.g. WHO Collaborating Centres).

  - For antibiotics without standardized breakpoints, countries should consider the revision of existing scientific evidence or contact regional or supranational centres, such as WHO Collaborating Centres, for support.

- Some **Reserve** antibiotics and other antibiotics listed on the WHO EML require specialized testing for confirmation of antimicrobial susceptibility of resistant isolates. Despite this important need, many LMICs lack the necessary infrastructure or have not established the protocols needed to conduct specialized testing, deliver time-appropriate results and/or track antibiotic resistance and susceptibility (although laboratory capacity can vary widely from country to country, or even within a country). Countries can seek support to build capacity based on the local scenario. Additionally, as mentioned, the WHO AWaRe antibiotic book includes general guidance of tests that could be clinically helpful where available *(3)*.
- In countries with an NRL and/or NIH, or similar function, such institutions can play a key role in supporting the introduction of antibiotics to countries. The WHO *GLASS guidance for national reference laboratories (48)* focuses specifically on the functions and activities of NRLs for national surveillance of AMR.
- The microbiology laboratory is a key component to support and provide routine diagnostics, including culture, identification, characterization of microorganisms, and AST. This capacity is variable, but countries should consider opportunities to introduce or expand this capacity when introducing antibiotics. The microbiology laboratory is also key to supporting surveillance activities and to report local AMR patterns and trends in health care facilities. The NRL/NIH provide support to laboratories in health care facilities to maintain quality assurance processes, perform quality and timely tests, proficiency testing and provide information on the local prevalence of bacteria/diseases and AMR patterns.

Relevant resources and tools

- Refer to Annex 14 for detailed considerations for strengthening laboratory and diagnostic capacity.
- WHO GLASS guidance for national reference laboratories *(48)*.
- Antimicrobial Resistance Diagnostic Initiative *(14)*.
- WHO country guidance to develop and update nEDLs *(49)*.
- WHO Model List of Essential In-Vitro Diagnostics *(47)*.
- Clinical and Laboratory Standards Institute *(50)*.
- WHO AMR Surveillance and Quality Assessment Collaborating Centres Network *(51)*.
- European Committee on Antimicrobial Susceptibility Testing *(52)*.
- AWaRe classification of antibiotics for evaluation and monitoring of use, 2023 *(3)*.

4.6 Procurement planning

Purpose

To ensure consistent supply without interruptions or shortages, efficient procurement processes and robust distribution networks through optimizing demand forecasting, quantification, and procurement practices to maintain a healthy market and sustainable

access to the antibiotic being introduced, while preserving its efficacy. Further, to ensure that procurement strategies – such as pooled procurement and addressing supply challenges that can help balance limited budgets with supplier order requirements – are explored.

Actions

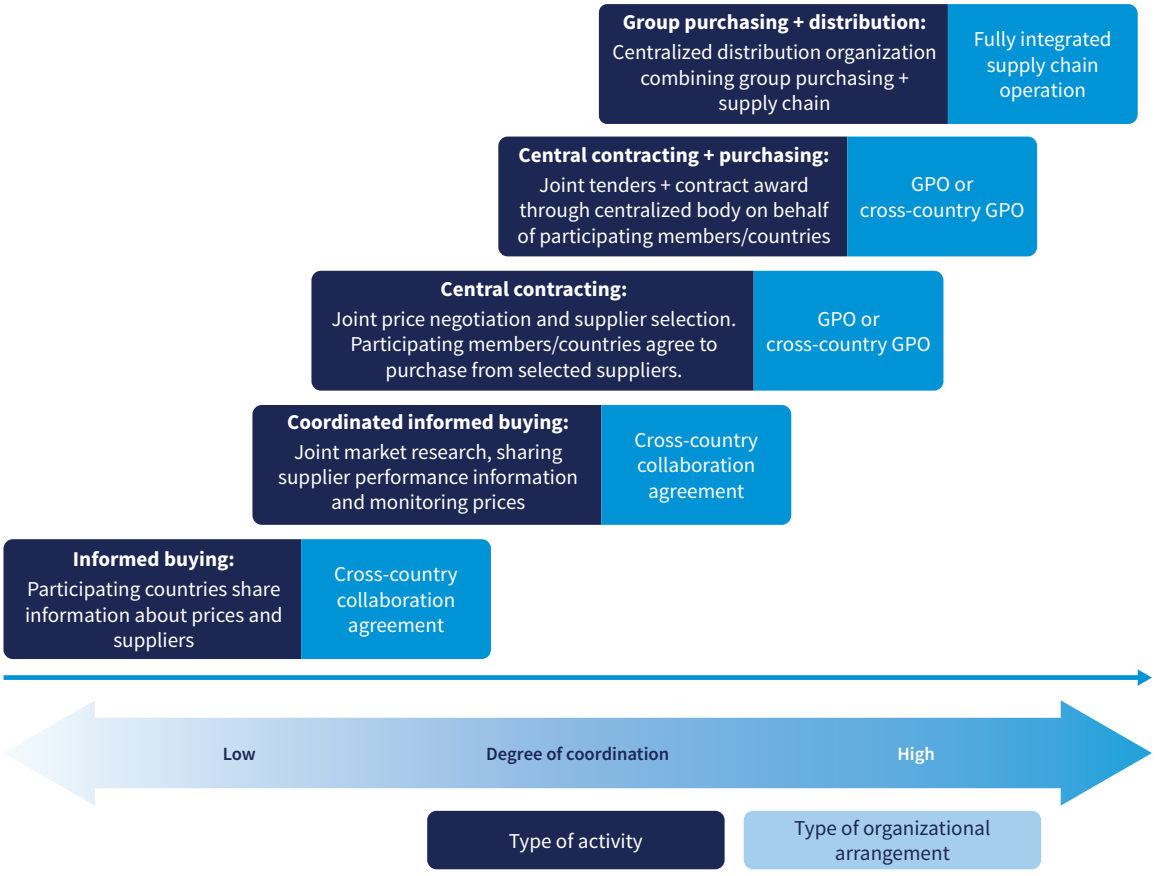
1. Centralize demand planning and procurement processes where possible, and include newer classes of antibiotics into existing in-country forecasting and demand planning exercises.
2. Consider skill-sharing or job-shadowing across other disease programmes to guide demand forecasting and quantification exercises.
3. Consider participating in global or regional pooled procurement initiatives, or through bodies that can support coordinated forecasting, order alignment across multiple procurers or other coordinated procurement activities.
4. Develop a procurement plan for the selected antibiotic based on need and demand forecasting:
    a. Conduct source and supplier mapping (e.g. through an expression of interest).
    b. Know the procurement channel (e.g. donor-based procurement, regional procurement, national procurement).
    c. Refer to pricing policies (Section 4.2 and Annex 12.1), select the optimal procurement approach(es) (e.g. tenders, negotiations, combining purchasing power with regional neighbours i.e. pooled procurement etc.).
    d. Consolidate demand within countries and align procurement plans at the national level. This can include collaboration with the private sector and other channels to aggregate overall national demand.

Key considerations

- Establishing efficient procurement planning and management, as well as better demand visibility (that includes robust long-term demand planning) can address some access obstacles like low volumes, high prices, supply insecurity/stock outs, and can address over-marketing and promotion, or perverse incentives for suppliers and prescribers.
- Procurement planning should include a wide range of activities that consider many different components of the supply chain. A key activity is linking surveillance to forecasting to better inform antibiotic demand.
- Antibiotic suppliers have indicated that low and unpredictable demand, as well as poor demand forecasting, especially for **Reserve** antibiotics, are reasons for not entering a market and also for high, unstable prices *(37,53)*. Procurement planning, supported by long-term demand forecasting and accurate demand quantification, can help alleviate this tension with the antibiotic supplier to secure supply.
- Procurement offices and/or agencies are generally responsible for issuing tenders, purchasing drugs and managing stocks to prevent stock-outs. In some countries, the roles also include integrated services, such as storage and delivery. The structure of procurement systems may differ by country and health system. Public procurement agencies may also be responsible for public facilities, with private procurers for private, faith-based or not-for-profit health facilities and international donor-funded organizations.

- While demand is comparatively large for **Access** antibiotics, there have been global stockouts and shortages due to demand peaks caused by global increases in certain infections and cessation of manufacturing of some products due to lack of return on investment. It is therefore equally important to apply robust procurement planning for all antibiotics:
  - Ministries of health, procurement officers and/or NRAs can work together to ensure that appropriate policies are in place, that there are the required buffer stocks, to collaborate with manufacturers to increase the supply of products, or to create incentives for manufacturers to register antibiotics.
  - Other procurement policies could include tendering policies for off-patent antibiotics that may allow for multiple suppliers in the procurement process.
- Regional and global coordinated procurement/pooling activities that pool demand may support access, especially in LMICs. These activities can be applied in many ways, with each approach requiring a different level of effort (Fig. 8). The different approaches should be considered based on the context, participating countries, and be appropriate for the antibiotic being introduced (see Annex 15).
- Fully integrated supply chain operations (Fig. 8) can include negotiating prices, contracting with suppliers, managing distribution and logistics, repackaging products, and balancing members' supplies.

Fig. 8. Different pooling activities and types of organizational arrangements



Source: (54).

Note: GPO: Group purchasing organization.

Relevant resources and tools

- Refer to Annex 15 for detailed considerations for procurement planning. This annex also includes a list of factors and risks to consider for effective regional pooled procurement.
- WHO Procurement principles and processes *(55)*.
- Other organization's procurement guidance tools (e.g. the *Managing procurement* chapter as part of Management Science for Health *MDS-3: Managing access to medicines and health technologies (56)*.

4.7 Preparing logistics and supply chain management

Purpose

To outline activities across the supply chain for managing the distribution of antibiotics, and other essential health care commodities (including diagnostics and laboratory equipment) for appropriate treatment, so they are delivered to facilities and patients. To ensure that effective storage, logistics and medicine management systems have robust inventory processes to prevent stockouts or overstocking, and systems to manage waste. This requires engagement with stakeholders involved in managing and distributing stock of antibiotics and other health care commodities (i.e. warehousing and distributors, logistics including storage and transportation, etc.).

Actions

1. Engage logistics and supply chain stakeholders and identify those that have capacity to deliver the antibiotic to facilities:
    a. Work with stakeholders to optimize the supply chain for the antibiotic being introduced, as well as for all other health commodities required for appropriate use (e.g. diagnostics and laboratory supplies, including supplies for basic bacterial isolation and for AST etc.).
    b. Ensure appropriate stock management processes are in place (e.g. stock rotation management, buffer stock and/or stockpiling as appropriate for each individual antibiotic).
    c. Ensure appropriate warehousing and storage.
    d. Ensure appropriate due diligence procedures are in place for checking product quality throughout the supply chain, as well as processes to monitor the integrity of the supply chain. This is important to safeguard that the antibiotic is delivered in a way that does not compromise product quality.
    e. Engage distributors; ensure a clear distribution and transport network (i.e. develop clear processes to manage stock levels, especially for low volume antibiotics). Consider distribution models such as hub-and-spoke, and ensure standardized transportation procedures.
2. Plan product quality checks and monitoring along the supply chain. This is recommended to manage leakage from the public to private sector or unregulated market, and to control substandard and falsified products.

3. Update, enhance or establish national logistics management information systems (LMISs) to support the supply chain for antibiotics. This will help with managing stock, but also with improving data quality to inform forecasting and procurement quantification. If national LMISs are not fit-for-purpose, consider more localized LMISs or approaches to leveraging systems used by distributors and suppliers to manage stock across the supply chain.
4. Check if the LMISs are connected to other national databases and information systems used to track and monitor antibiotic use. Where possible, explore the potential for connecting systems to avoid duplication of data collection/input, and for more timely action on outputs from data.

Key considerations

- The private sector may have a key role in logistics and supply chain management of medicines, especially through distributors and warehouses, so it is important that these stakeholders are engaged.
- Logistics and supply chain for other commodities should also be considered, such as reagents, diagnostic equipment, intravenous (IV) administration equipment such as catheters, infusion pumps, needles and syringes, and IV bags, etc. so all necessary equipment is available to appropriately administer the antibiotic.
- Centralized and/or regional warehousing/distribution hubs may be useful in managing stock levels for low volume, infrequently used antibiotics (see Annex 16).
- Some **Watch** and **Reserve** antibiotic products require cold storage before and/or after reconstitution. For example, Cefiderocol IV, Ceftolozane–tazobactam IV, and Plazomicin IV all require refrigerated storage at 2°C to 8°C before reconstitution *(57–59)*.
- Supply chain models and incentive programmes that have been successfully implemented in LMICs and may be applicable for efficient last mile delivery of antibiotics include (Annex 16):
  - Claw-back systems to eliminate wastage and loss.
  - Hub-and-spoke models for delivering antibiotics in LMICs.
  - The vendor-managed inventory model.

Relevant resources and tools

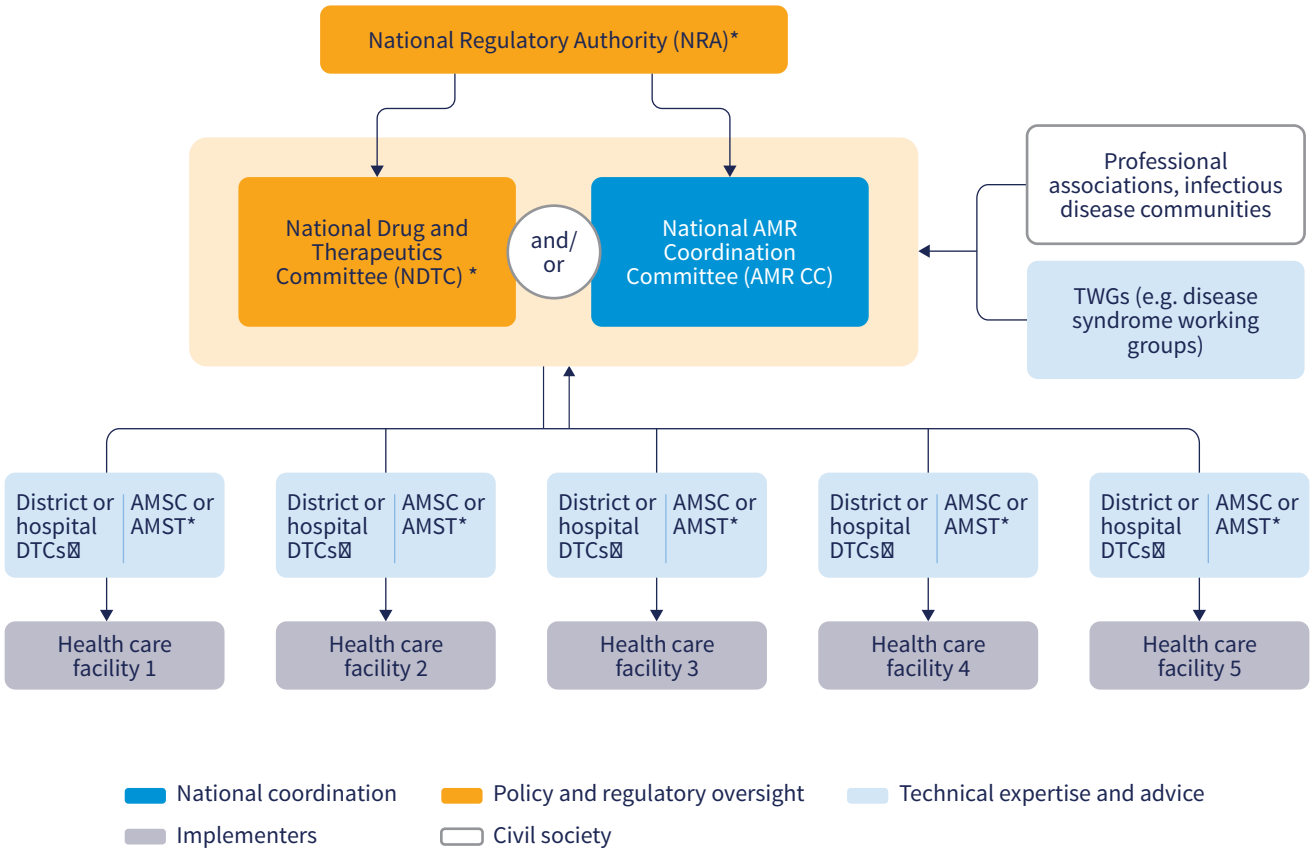
- Refer to Annex 16 for detailed considerations for logistics and supply chain management.

4.8 Preparing facilities – health care worker readiness and promoting antimicrobial stewardship

Purpose

To ensure there are locally-tailored processes for translating policy into practice (i.e. facility adoption of the newly introduced antibiotic) (Fig. 9), and that facilities that will be using the selected antibiotic are prepared (i.e. that they have AMS programmes and the appropriate processes, skills and resources to use the antibiotic appropriately).

Fig. 9. Illustrative example of structural flows from the national level through to facilities, by function

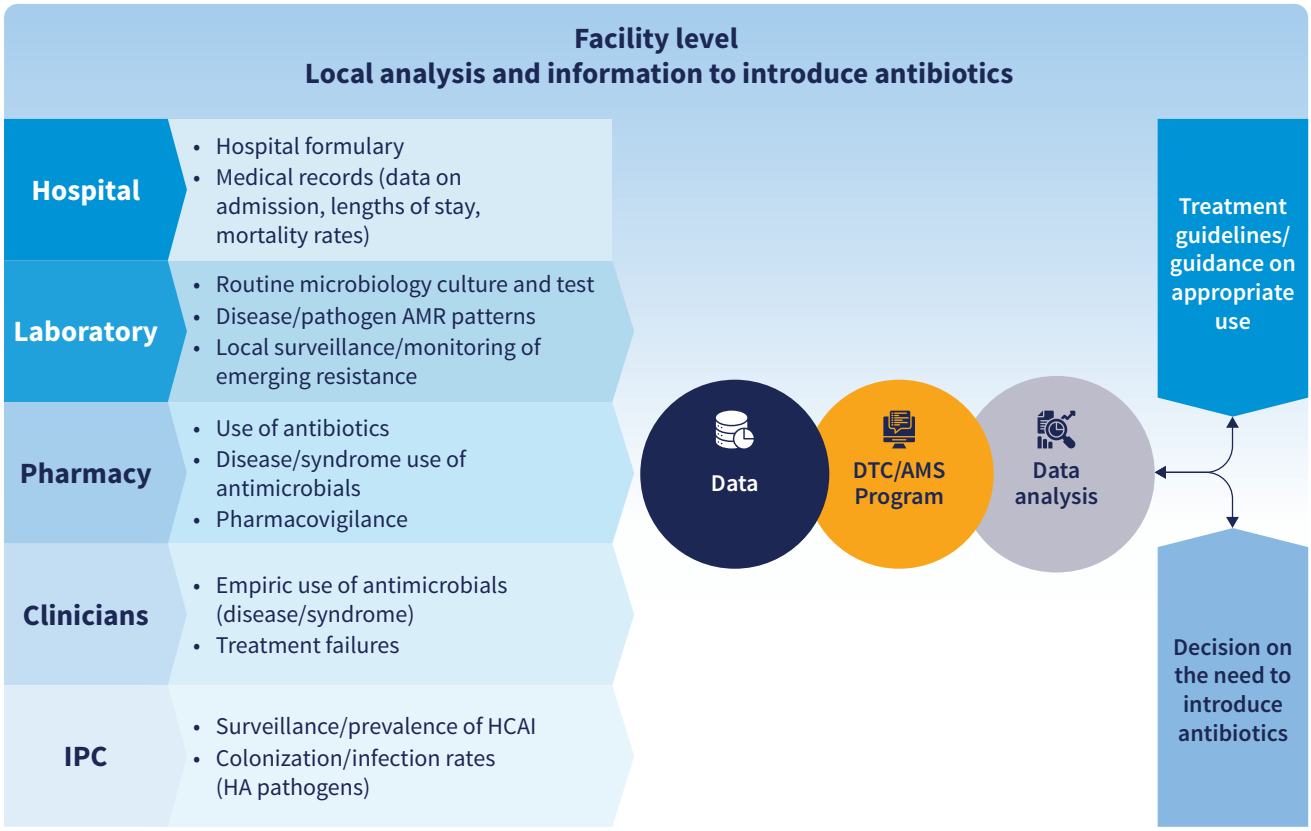


Notes: *: Policy-makers and NRA representatives are usually part of the AMR CC. In some countries AMR CC TWGs may play the role of the NDTC for antimicrobials (as part of AMR NAPs), or both the NDTC and AMR CC may work together; +: DTCs can operate at a national, district or hospital level. The AMSCs operate at the facility level. In countries where the DTCs are established and functioning, the AMSC work in tandem with, or form part of, the DTC. Where DTCs are less established, the AMSC could operate in place of the DTC for antibiotics, or more independently from the DTC.

Actions

1. Engage stakeholders and/or conduct a capacity assessment to understand how facilities that will be using the selected antibiotic operate, the current capacity and resource situation (refer to checklists and assessment tools in the WHO AMS practical toolkit *(23)*).
2. Prepare facilities for implementation (refer to the WHO AMS practical toolkit *(23)* for a detailed overview of the steps to ensure facilities are prepared to implement AMS):
    a. Utilize or adopt a structured approach for facility adoption, use and monitoring of antibiotics (Fig. 10).
    b. Integrate the antibiotic into existing AMS programmes and measures, IPC (including the surveillance of hospital acquired infections) and WASH provisions at facilities. If they don't exist, set up AMS programmes, as well as IPC and WASH provisions at facilities.
    c. Facilitate updates to facility treatment protocols/guidelines so they include the selected antibiotic and stewardship measures.
    d. Ensure procedures are in place at the facility to implement appropriate waste management.
    e. Plan to enhance, or make improvements to diagnostic capacity, links to microbiology laboratories, referral networks and integrated services.
    f. Develop tools for health care workers (e.g. infectious disease specialists, clinicians, prescribers, pharmacists, dispensers, nurses, laboratory managers/workers etc.) to implement AMS programmes. These tools could include training materials, product memos, job aids, and patient information guides, for example.
    g. Incorporate supervision of appropriate prescribing and use of the antibiotic into ongoing training and mentorship activities at facilities.
    h. Train health care workers to correctly use any reporting and recording tools for the antibiotic introduction, including for M&E of the antibiotic introduction plan, how to appropriately dispose of any expired antibiotics and appropriately manage waste. Educate health care workers about the benefits and characteristics of the antibiotic so that they can better understand the treatment.
    i. Update facility-level stock monitoring tools and ordering forms, and patient management systems to include the selected antibiotic.

Fig. 10. A general illustrative guide of a structured approach for facility adoption, use and monitoring of antibiotics



Notes: HCAI: health care-associated infection; HA pathogens: microorganisms responsible for health care-associated infections.

Key considerations

- Countries will likely have existing processes for translating policies into practice. The actions described are non-exhaustive approaches and countries should plan and implement facility-level adoption based on local health systems, needs, capacities and existing infrastructure. A flexible clinical model for introducing an antibiotic into facilities should be tailored to the local context.
- In some settings, there may be no effective national or regional process for the selection of medicines, including antibiotics. Additionally in some contexts a facility may rely on its own financing to select and procure medicines (see Annex 14). In these cases, facilities can utilize global or regional recommendations and implement a facility-tailored process for monitoring and assessing the appropriate use of all antimicrobials.
- At a minimum, health facilities should adopt a flexible structural and multistakeholder approach to introducing antibiotics and strengthening AMS efforts. The approach should go beyond a small range of health care professionals working in a facility and consider the multi-layered medicines selection and guideline development processes applicable for each unique health system.

- The WHO Antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries: a WHO practical toolkit *(23)* provides a useful outline of the core elements of an AMS programme at facilities, and what to do if the facility does not have all the core elements in place.
- AMS programmes in low-capacity settings will vary compared to approaches in higher-capacity settings, but should include a form of audit and feedback, and clinician engagement.
- Some strategies to consider implementing AMS programmes in low-resource settings include:
  - task-shifting;
  - hub-and-spoke models where a larger facility supports smaller facilities;
  - telemedicine-based AMS programmes;
  - developing straightforward processes;
  - introducing processes for managing prescribing practices, such as pre-authorization, prospective audits, retrospective audits and feedback.
- In facilities where there is capacity for an AMS committee and AMS team, the AMS committee should be responsible for oversight, and the AMS team should be responsible for the day-to-day activities of implementing the AMS programme.
- Trainings for clinicians using any antibiotic may include instructions on the following (non-exhaustive):
  - When and how to use the antibiotic and any related processes to follow (e.g. pre-approval or national regulations etc.).
  - Diagnostic stewardship (i.e. when to order a microbiology test for patients, such as blood culture, etc.) to guide the treatment choices.
  - How to implement appropriate waste management.
- Training should be followed by supportive supervision to monitor that health care workers implement what they have learned and apply the training correctly.
- Where feasible, strengthen facility-level diagnostic capacity and links to microbiology laboratories.
- As antibiotics and their metabolites are excreted with urine and faeces, and consequently end up in the wastewater stream, ensure that appropriate waste management is in place for antibiotics as well as human waste *(60)*.

Relevant resources and tools

- Refer to Annex 17 for detailed considerations for preparing facilities.
- WHO Antimicrobial stewardship programmes in health care facilities in low- and middle-income countries: a WHO practical toolkit *(23)* includes a checklist of essential health care facility core elements for AMS programmes in LMICs, as well as checklist of essential national core elements for AMS programmes in LMICs. It also includes guidance on assessing AMS programmes.
- WHO *Drug and therapeutics committees: a practical guide (61)*.
- WHO *Safe management of wastes from health-care activities (60)*.

4.9 Developing a communication plan to raise awareness for the appropriate use of all antibiotics

Purpose

To develop and implement communication messages and materials that aim to raise awareness about AMR and the appropriate use of all antibiotics, across all parts of society.

Actions

1. Conduct a baseline assessment of public (for **Access** antibiotics) and health care workers' (for all antibiotics, but especially for **Watch** and **Reserve**) knowledge, attitudes and practice on antimicrobial use and AMR.
2. Leverage awareness-raising activities and processes already in the NAP (if applicable).
3. Engage stakeholders including communities and civil society organizations, including professional associations, in both the design and implementation of awareness-raising strategies and activities.
4. Develop the dissemination plan and communication materials with clear objectives and using simplified messages. These should be tailored to the local setting and audience, use real-life examples and leverage multi-channel approaches (e.g. videos, infographics, social media content, local radio, television, and community newsletters etc., selecting materials appropriate for the target audience as well as the message being communicated).

Key considerations

- Awareness campaigns should target health care workers or the general public, depending on the context and which antibiotic is being introduced. For example, there may be limited awareness among health care workers on the importance of preserving **Reserve** antibiotics, and the challenges associated with developing new antibiotics to address AMR. Within the general public, common misconceptions about antibiotics include their ability to treat all infections, including viral infections, and underestimating the threat of antimicrobial resistance.
- Communication messages and materials specifically aimed at raising health care workers' awareness about introduction of **Watch** and **Reserve** antibiotics could include information on the following:
  - Regulations and enforcements for the use of the antibiotic(s).
  - Implementation of AMS programmes, IPC and WASH initiatives (e.g. through targeted messaging on the risks of health care-associated infections and the importance of AMS, IPC and WASH to control and prevent infections).
  - Available training for clinicians using the newly introduced antibiotic(s), how to access training, the training frequency/requirements for health care workers to use **Watch** and **Reserve** antibiotics, and whether trainings are recognized as part of local, ongoing accreditation programmes.

  - Importance of patient adherence when using **Watch** and **Reserve** antibiotics (e.g. through sharing stories of doctors working to tackle drug resistance or stories of patients struggling with the impacts of drug resistance).

- The WHO TAP toolbox *(62)* and TAP quick guide *(63)* are useful resources to guide countries with understanding awareness and perceptions on AMR.
- Community and civil society engagement/consultation on developing awareness campaigns, and how to implement them, can include working with local leaders such as religious leaders, teachers, professional associations and community influencers to understand behaviour and spread awareness. Facilitated sessions or workshops with different community and civil society groups may be useful to hear from people living in high-risk areas or their experiences with antibiotic access and use. Other strategies could include developing education programmes, such as peer-to-peer exchanges, to spread the importance of AMR prevention and control.

Relevant resources and tools

- Refer to Annex 18 for detailed considerations for preparing and developing a communication plan to raise awareness about the appropriate use of all antibiotics.
- WHO *TAP toolbox: exercises, tools and templates to support your tailoring antimicrobial resistance programmes plan (62)*.
- WHO *TAP quick guide: a practical handbook for implementing tailoring antimicrobial resistance programmes (63)*.
- Illustrative key objectives of an AMR awareness programme or campaign (non-exhaustive):
  - Educate communities (including health care workers)/civil society organizations.
  - Encourage responsible antibiotic use.
  - Foster community/civil society engagement (including health care workers).
  - Encourage dialogue between patients and health care workers.
- Illustrative focus areas of key messages in an AMR awareness programme or campaign (non-exhaustive):
  - Overuse and misuse of antibiotics.
  - Importance of compliance and adherence.
  - Manging non-bacterial infections without antibiotics.
  - Individual and community led prevention measures (e.g. WASH, vaccination, safe food handling etc).

5 Planning for monitoring, evaluation and quality improvements

Purpose

To ensure a plan for monitoring, evaluation and making quality improvements for introducing antibiotics is in place. Additionally, to scope potential operational research opportunities, focusing on closing data gaps and generating evidence to inform decision-making.

Steps involved

1. Developing a monitoring and evaluation (M&E) framework.
2. Exploring operational research needs and opportunities.

5.1 Developing a monitoring and evaluation (M&E) framework

Purpose

To develop a monitoring and evaluation (M&E) framework that measures the impact of introducing the antibiotic on patient outcomes and the health system more broadly, that tracks appropriate use that allows for course correction and can inform future antibiotic introduction.

Actions

1. Collect baseline evidence to support clinical best practice for introducing the antibiotic(s):
    a. Collect the best quality data available on AMR and AMU at the local and national levels, including leveraging global or regional data if needed.
    b. In settings with more mature data collection and reporting systems, utilize data collected through diagnostic, laboratory and surveillance systems on AMR and AMU, and basic health information systems, that can track both AMU and AMR.
    c. Collect baseline data from facilities:
        i. Explore what antibiotic use data facilities are already collecting and how they are collected.
        ii. Ideally, conduct surveys such as point prevalence surveys on AMR and on antibiotic use.

   iii. Perform audits to assess antibiotic usage patterns and compliance with guidelines focusing on the newly introduced antibiotic(s).
   iv. Collect and analyse data from pharmacy records to monitor antibiotic dispensing to wards and antibiotic use trends focusing on the new antibiotic(s).
2. Develop recording and reporting tools or templates to efficiently collect evidence.
3. Integrate the antibiotic(s) into AMR surveillance, pharmacovigilance and sample transport/referral systems.
4. Ensure pharmacovigilance programmes capture product quality failure as a reason for treatment failure, if possible. This could be done through including a specific question in reporting systems that asks, for example, is there is any reason to suspect that the antibiotic is substandard of falsified?
5. Ensure laboratory capacity is sufficient for AST and to collect as many routine sources of data as possible.
6. Develop a thorough risk management strategy at baseline to track risks. Have risk mitigation plan ready to respond to any concerns as they may arise.
7. Update information systems and ensure their readiness.
8. Develop a national M&E framework to measure impact:
   a. Set the evaluation frequency (i.e. time intervals at which data will be collected and analysed).
   b. Develop indicators as part of the M&E framework (consider using a log frame).
   c. If applicable and possible, include aspects of socioeconomic evaluation (e.g. through health technology assessment) into the M&E framework (including data collection and assessment).
9. Leverage introducing the antibiotic to make quality improvements and to inform future antibiotic introduction.

Key considerations

- The introduction and use of antibiotics can be strengthened by implementing robust monitoring systems that track prescription patterns and usage. This can be achieved through electronic health records, regular audits, and feedback mechanisms to ensure adherence to guidelines and identify areas for improvement.
- WHO is developing a composite index for access to health products that will combine existing indicators already reported by countries that measure antibiotic use patterns *(64)*. If a country is already reporting these data to the Global Health Observatory, then these data could be used as impact indicators and to gauge baselines for AMU.
- Adapt the data collection approach to the local setting and consider capacity and resources.
- If baseline data are limited, explore using global data repositories such as the GRAM study *(25)* and the Global Point Prevalence Survey of Antimicrobial Consumption and Resistance (Global-PPS) *(65)*. The Global-PPS can be used as a measurement benchmark as it includes data on hospital-acquired infection rates, as well as AMS and AMU.
- Another approach when baseline data is limited is to work with facilities to access existing data sets and use current data collection channels. Utilize WHO published methodologies to inform the approach, e.g.:
  – GLASS methodology for surveillance of national antimicrobial consumption *(66)*.

  - GLASS guide for national surveillance systems for monitoring antimicrobial consumption in hospitals *(67)*.
  - WHO methodology for point prevalence survey on antibiotic use in hospitals *(68)*.
- Consider the workload involved in data collection, reporting and analyses, who is responsible for collecting data and how they will collect it, how it will be stored and how it will be utilized.
- Explore utilizing smart technology used by health care workers that have free communication applications (e.g. such as WhatsApp), to collect and share data.
- To detect warning signs that need urgent attention, ensure that a strong pharmacovigilance system to monitor adverse drug reactions, drug resistance, toxicities and treatment failure, in line with WHO guidance, is in place.
- To develop the M&E framework, consider the type of data collection methods that are needed (e.g. data collection can be qualitative or quantitative in nature).
- Tailor indicators to the local health system, accounting for the local infrastructure, existing health information systems, data availability and local disease trends. Consider the type of infrastructure available to allow for real-time or regular monitoring (e.g. surveillance – including pharmacovigilance – and/or digital infrastructure).
- Factor the number of patients, the number and type of facilities prescribing and dispensing the product, and stock availability in the M&E framework.
- Consider using a tool to track use trends of the newly introduced antibiotic(s) on a more frequent basis than regular reporting in the early stages of roll out to monitor uptake against planned usage and available supply. Adjust the procurement plan accordingly (i.e. closely monitor high-volume facilities as these greatly impact stock availability). If uptake is slower than planned, consider strategies to utilize existing stock and avoid expiries and waste (e.g. stock-sharing across facilities).
- Monitor supplier performance to ensure suppliers are delivering according to their contractual obligations. Consider joint communications/collaborative meetings with suppliers to identify and address shortages and share best practices such as digitalizing supply chains and building procurement systems *(39)*.

Relevant resources and tools

- Refer to Annex 19 for detailed considerations on planning for monitoring, evaluation and quality improvements.
- Refer to Annex 19.3.2 for example indicators that have been aligned to a theory of change model.
- Refer to Annex 19.4 for considerations on implementing operational research.
- WHO *Monitoring and evaluation of the global action plan on antimicrobial resistance: framework and recommended indicators (69)*.
- WHO *Guidance to facilitate monitoring and evaluation for antimicrobial resistance national action plans (70)*.
- GLASS guide for national surveillance systems for monitoring antimicrobial consumption in hospitals *(67)*.
- WHO methodology for point prevalence survey on antibiotic use in hospitals *(68)*.
- GRAM study *(25)*.

- Global-PPS *(65)*.
- Global antimicrobial resistance and use surveillance system (GLASS)*(26)*.
- *Barriers to use of health data in low- and middle-income countries. A review of the literature (71)*.
- Log frame template (for documenting indicators – see tabs 1 – 3 in accompanying web annex)

5.2 Exploring operational research needs and opportunities

Purpose

To expand the M&E plan beyond routine data collection and assessment. Additionally, to scope operational research activities that aim to assess the impact and effectiveness of the antibiotic introduction plan, or that generate evidence to close data gaps and inform decision-making.

Actions

1. Define research questions to measure the impact and effectiveness of the introduction plan, as well as adherence to it and areas for improvement.
2. Design operational research activities aligned to the research question.
3. Leverage the antibiotic introduction plan to inform future research.

Key considerations

- If operational research is not initially feasible (e.g. due to resource limitations, or there is an urgent need for an antibiotic and so operational research cannot be planned, or the introduction plan does not lend itself to research), as part of evaluating the antibiotic introduction plan it is important to ask the following questions:
  - What lessons can be drawn from the antibiotic introduction that can inform future product introduction programmes?
  - Are there emerging gaps in evidence that should be addressed through further research?
- While the primary focus should be on assessing the success of the introduction plan including outcomes and impact, research questions and additional data collection activities can be opportunistically incorporated into the M&E framework with the purpose of identifying evidence gaps, as well as areas for future academic and operational research on AMU and AMR.

Relevant resources and tools

- Refer to Annex 19.4 for further details on planning operational research. The annex includes a table with illustrative examples of the different types of operational research questions countries may consider when planning any research around the introduction of an antibiotic.

6 Costing activities in the antibiotic introduction plan

Purpose

To ensure that there is a documented costed antibiotic introduction plan, summarizing all introduction activities and their costs worked through in steps 1 – 9 of Developing the antibiotic introduction plan (Section 4), as well as M&E activities. To map out activities along a timeline and to cost activities by contextually applicable financial periods.

Actions

1. Summarize all planned implementation activities for rolling out the antibiotic (i.e. steps 1 – 9 of Developing the antibiotic introduction plan (Section 4)) along a timeline (e.g. by using a Gantt chart).
2. Develop a budget by costing activities based on realistic assumptions, and using estimates, benchmarks or quoted work. Most countries will have their own budget and costing tools to work with. Alternatively, the WHO costing and budgeting tool for national action plans on antimicrobial resistance *(19)* is a flexible costing tool that can be used to create a budget for the antibiotic introduction. See Fig. 11 for an example of how the NAP tool can be adapted and used to cost an antibiotic introduction plan. An online course is also available here to learn how to use the tool *(72)*.
3. Refine activities to align with available funding. Either scale back or expand activities, ensuring that the plan can be implemented within the available funding envelope as secured earlier in the planning process (see Section 3.3).
4. If required, obtain ministerial and budget approval to start introducing the antibiotic(s).
5. During implementation, track expenditure/spending and monitor that budget spending rates are in line with planning.

Key considerations

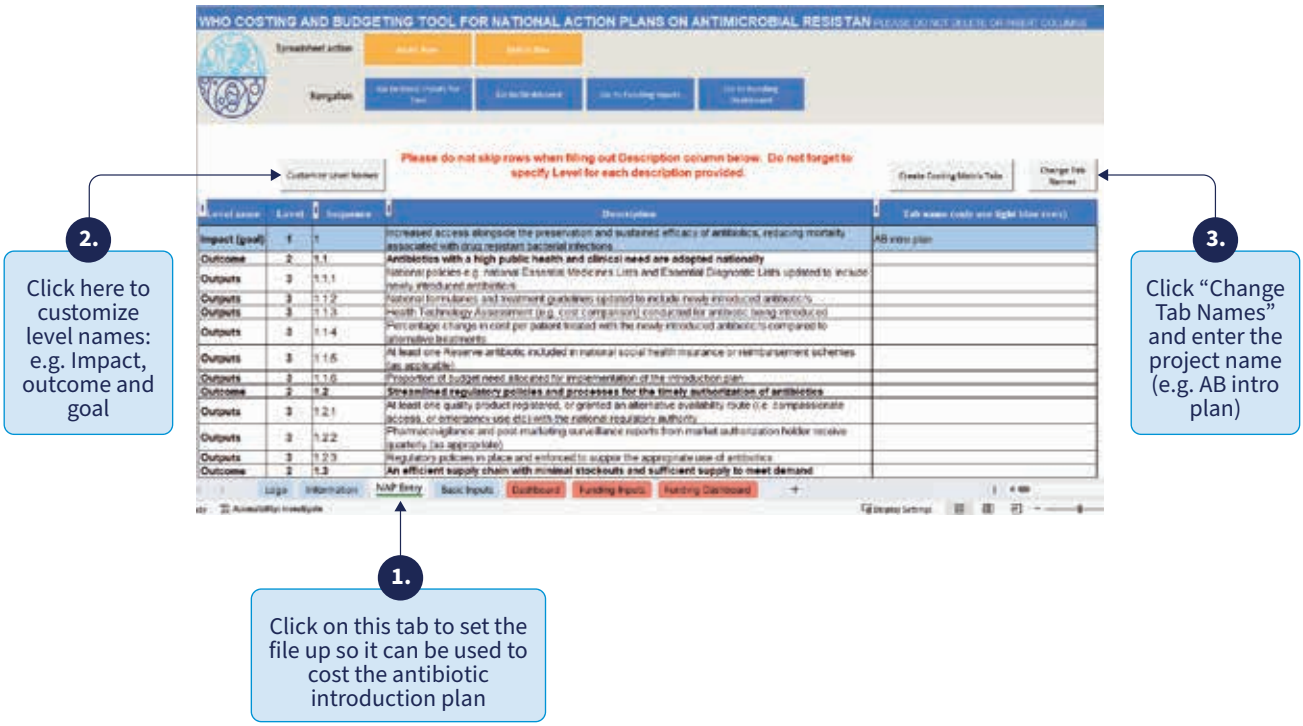
- The aim of the costing exercise is to develop a more granular budget for implementing all activities in the plan. When developing budgets, plan for operational costs related to short- and long-term activities (i.e. the initial antibiotic roll-out, as well as ongoing costs to sustain implementation).
- While developing the budget, it might become clear that there is insufficient funding available to complete all activities. In this case, activities and budgets would need to be scaled back to achieve the maximum impact within available resources. If there are gaps in funding to implement the entire plan, the plan can be used to advocate for additional funding with the relevant government departments.

- The costing exercise may show that additional funding is available, in which case activities such as operational research, could be included in the plan.
- Costs to consider including in the budget (non-exhaustive):
  - Human resources (e.g. project implementation, oversight, monitoring and evaluation).
  - Drug (antibiotic) unit price and total budget requirement (i.e. budget impact analysis).
  - Auxiliary commodity costs.
  - Costs for specific AMS/appropriate use programmes including training and supervision.
  - Diagnostic commodity costs (e.g. tests, equipment and reagents). Where possible, costing for introducing antibiotics should incorporate funding required to improve laboratory infrastructure and information systems for better overall surveillance and monitoring.
  - AST disks or other relevant reagents.
  - Information technology costs.
  - Logistics costs including storage and transportation.
  - Waste management costs.
  - Meetings, technical/advisory (consultants) services and trainings.
  - Communication costs (including materials).
  - Monitoring and evaluation costs.
  - Additional costs to implement operational research.

Relevant resources and tools

- WHO costing and budgeting tool for national action plans on antimicrobial resistance *(19)*.
- WHO costing and budgeting tool for national action plans on antimicrobial resistance online course *(72)*.
- Gantt chart template (see tab 4 in accompanying web annex)

Fig. 11. An illustrative example of how the WHO costing and budgeting tool for NAPs on AMR *(20)* can be adapted and used to budget an antibiotic introduction plan



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Annexes

Annex 1. WHO guidance and other existing guidance relevant to introducing antibiotics

The *People-centred approach for addressing AMR in human health (8)* describes 13 core interventions and accompanying priority actions to address AMR that puts people at the centre of the AMR response. The people-centred approach addresses the importance of access to essential medicines and health services as one of the four pillars critical to overcoming people and systems challenges in addressing AMR. The four pillars cover: i) prevention; ii) access to essential health services; iii) timely and accurate diagnosis; and iv) appropriate, quality assured treatment.

To guide countries on surveillance approaches, the World Health Organization (WHO) Global antimicrobial resistance and use surveillance system (GLASS) *(26)* aims to better understand and monitor the global epidemiology of AMR and AMU patterns. GLASS provides a standardized approach to the collection, analysis, interpretation and sharing of data by countries and seeks to actively support capacity building and monitor the status of existing and new national surveillance systems. Furthermore, GLASS promotes a shift from AMR surveillance approaches based solely on laboratory data to a system that includes epidemiological, clinical and population-level data. Additionally, GLASS also provides national estimates for AMU to support the development and monitoring of policies, targets and antimicrobial stewardship interventions.

WHO has also developed the **Access**, **Watch**, and **Reserve** (AWaRe) system (including the AWaRe classification *(3)*, antibiotic book *(4)*, and indicators and targets) to support countries in monitoring antibiotic use and implementing antimicrobial stewardship (AMS) programmes. The AWaRe classification categorizes antibiotics according to their spectrum of activity and their potential to develop resistance:

- **Access** antibiotics are narrow spectrum with a lower resistance potential than antibiotics in other groups and recommended as empiric first- and second-line treatment options for common infections.
- **Watch** antibiotics are broader spectrum and have a higher potential of developing resistance. They are recommended as first-choice options only for patients with severe clinical presentations or for infections where the causative pathogens are likely to be resistant to **Access** antibiotics.
- **Reserve** antibiotics are last resort agents used for infections due to multidrug-resistant infections.

To further promote the appropriate use of antibiotics, WHO has developed the AWaRe antibiotic book, which provides evidence-based guidance on management of more than 30 of the most common clinical infections in children and adults in both primary

health care and hospital settings *(4)*. The information included in the book supports the recommendations for antibiotics listed on the *WHO Model List of Essential Medicines* (EML; 23rd list, 2023)*(16, 73)*, the *WHO Model List of Essential Medicines for Children* (9th list, 2023) *(74)*, and the WHO *AWaRe classification of antibiotics for evaluation and monitoring of use* (2023) *(3)*. Additionally, the *WHO Model List of Essential in vitro Diagnostics (EDL) (75)* serves as an evidence-based reference point for countries to develop their own national list to include diagnostics that may be needed to introduce new antibiotics. Alongside the EDL, WHO has developed specific country guidance to support countries to develop and update a national list of essential diagnostics *(47 – 49, 75)*.

As preserving antibiotics is a public health priority, WHO has also developed policy guidance on integrated AMS activities *(76)* that provides a coherent set of integrated actions that promote responsible and appropriate antibiotic use with a focus on systems and processes that should be in place at the national level. The guidance outlines actions for appropriate use alongside access to affordable and quality antimicrobials and infection prevention interventions, including the implementation of infection prevention and control (IPC) programmes, enhancing water, sanitation, and hygiene (WASH), and optimizing vaccination coverage. The WHO document *Antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries: a WHO practical toolkit (23)* provides guidance on how to implement antimicrobial stewardship in facilities, with a focus on hospitals providing higher levels of patient care.

Annex 2. Global and regional initiatives relevant for antibiotic introduction

2.1 Global access initiatives (non-exhaustive)

There are several global and regional level initiatives ongoing and under development that aim to accelerate access to antibiotics. The initiatives described below have been included for increased awareness and to highlight potential participation opportunities for countries to consider when developing introduction plans. It should be noted that these may not represent an exhaustive list, other initiatives and efforts are likely to be underway.

SECURE *(1)* is a global initiative focused on improving access to new and existing antibiotics, led by WHO and the Global Antibiotic Research & Development Partnership (GARDP). SECURE works directly, as well as through partnerships, with organizations and countries and plays a key role in ensuring that global, regional and country AMR activities are coordinated and mutually reinforcing. SECURE is entering a test phase where it will apply market-based strategies to improve access to antibiotics. Given the issue of low demand and high prices for most **Reserve** and some **Watch** antibiotics, SECURE is looking at ways to work with existing procurement entities to pool or coordinate procurement across multiple countries and stockpile supply, with the goal of stabilizing global demand for these antibiotics and reduce prices. SECURE is also exploring other market-based strategies, such as volume or revenue guarantees and commodity co-payments/subsidies to test what could work in tandem to pooling procurement to achieve optimal market conditions for antibiotics.

Aranda *(78)* is a hybrid non- and for-profit global access initiative working on the fast, safe delivery of all antibiotics. Aranda also uses market-based strategies to create and build markets for diagnostics and antimicrobials. Some strategies include deriving sustainable revenue from fixed-price royalties and performance fees, investing cash flow into areas that drive patient impact, and using traditional financial instruments to leverage initial grants and seed capital. Aranda aims to be self-sustaining after 3 – 5 years of deployment.

GARDP also has an access-focused initiative for the products in the GARDP portfolio *(79)* that includes access-oriented licensing, support for lower cost and distributed manufacture including through technology transfers, piloting pooled procurement and working with local partners to support introduction planning.

2.2 Global and/or regional initiatives that can support overcoming affordability or pricing barriers for antibiotics

In recent years, high prices of pharmaceutical products have posed challenges to accessing medicines of many types. In many instances, high prices of pharmaceutical products have led to significant financial hardship for individuals and negatively impacted health care systems' ability to provide population-wide access to essential medicines. In 2020 WHO updated the *WHO guideline on country pharmaceutical pricing policies (35)*. The guideline includes recommendations on the different types of pricing approaches and policies countries can consider improving national pricing (for a snapshot of different medicines pricing policies see Annex 12.1 Pricing and access policies to lower antibiotic prices).

2.2.1 Intellectual property management

Intellectual property (IP) laws play a critical role in shaping the pricing and procurement of antibiotics in LMICs by delaying the entry of generics, keeping prices high until the market becomes competitive. Hence, balancing the need to incentivize pharmaceutical innovation with the necessity of ensuring access to life-saving medications remains a crucial issue for policy-makers in LMICs. In 2008, WHO adopted the *Global strategy and plan of action on public health, innovation and intellectual property* (GSPA-PHI) *(80)* with the aim of promoting new thinking on innovation and access to medicines and to secure an enhanced and sustainable basis for needs-driven essential health research and development (R&D) relevant to diseases that disproportionately affect developing countries, the plan of action of the GSPA-PHI was recently extended by Member States until 2030 to be co-terminus with the SDGs *(81)*.

Patents on novel antibiotics grant pharmaceutical companies exclusive rights to manufacture and sell these medicines for a period, typically 20 years or longer according to national patent laws, allowing them to set higher prices to recover R&D costs and maximize profits without competition. This can limit the affordability and accessibility of antibiotics in LMICs, where high prices often pose a significant barrier to access and development of local manufacturing. Conversely, IP flexibilities, such as compulsory licensing and parallel importation, can help mitigate these challenges by allowing the production or importation of more affordable generic versions.

Well-functioning IP systems should consider the interests of a wide range of stakeholders, such as start-ups, R&D institutions, both public and private, universities and corporations, as well as the interests of funders, whether public or private, and of the public at large, including patients, who ultimately benefit from innovation that meets their needs. To achieve this delicate balance, each country can tailor its domestic IP system to its particular needs and circumstances, including through TRIPS flexibilities.

2.2.2 TRIPS flexibilities for public health

The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) provides several flexibilities that countries can use to improve access to medicines and health technologies. There are several provisions that support and facilitate R&D and access, including certain exclusions from patentable subject matter and exceptions to patent rights. Those options are available to support countries' access to medical technology and innovation policies *(82)*.

The GSPA-PHI (see section A.4(c) and Box 2.2) includes explicit actions relating to the flexibilities reaffirmed by the *Doha Declaration*. It urges Member States to consider implementing TRIPS flexibilities, including those recognized in the Doha Declaration, by incorporating them into their national laws (Element 5.2a). Regarding more extensive IP protection than that required under the TRIPS Agreement, Member States are urged to take the impact on public health into account when considering the adoption or implementation of such obligations (Element 5.2b). Member States should also take flexibilities into account when negotiating other (bilateral or regional) trade agreements (Element 5.2c). In addition, the GSPA-PHI highlights a number of flexibilities and public policy options available to Member States, which are designed to facilitate research and access to medical technologies: Research exception (Element 2.4e): For countries with manufacturing capacities, consideration can be given to taking measures to implement the World Trade Organization (WTO) Paragraph 6 System (Element 5.2d); Develop effective and sustainable mechanisms in LDCs [least developed countries] in order to improve access to existing needs, acknowledging the transitional period until 2016 that was expanded by WTO Members (Element 6.1b); Regulatory review exception, also known as "Bolar"-type exception (Element 6.3a) *(81,83)*.

2.2.3 Technology transfer and licensing

Global and regional initiatives are ongoing to support voluntary out-licensing and technology transfers for local and/or regional production. Technology transfers enable countries, particularly LMICs, to build capacity in local production of medical products in the short term. Technology transfer is a logical procedure that controls the transfer of products, processes, skills, technology and knowledge together with its documentation and professional expertise, allowing the diffusion of innovation to new institutions and markets *(84)*. The WHO Local Production and Assistance (LPA) unit supports Member States in strengthening sustainable local production and technology transfer to improve access to safe, effective, quality, and affordable medicines and other health technologies, by applying a holistic and strategic approach in collaboration with governments, partners and other stakeholders. Linked to the WHO-LPA is the World Local Production Forum (WLPF) *(85)*. The WLPF is a WHO initiative that provides Member States and the global community with a regular platform to shape strategies, galvanize collective action, and foster partnerships on sustainable local production to improve timely and equitable access to quality-assured health products.

An important IP intervention for novel antibiotics was in 2022, when the cefiderocol (a **Reserve** antibiotic to treat certain gram-negative infections) manufacturer Shionogi announced that it would out-license the manufacturing for use in 135 countries, including LMICs, to GARDP. Since that announcement, in 2023, GARDP and Orchid Pharma Ltd. have signed a sub-license agreement to manufacture cefiderocol. Based on these agreements, CHAI is facilitating the technology transfer process between Shionogi and Orchid, and Shionogi will convey essential information for the manufacture of cefiderocol to Orchid, thus accelerating Orchid's ability to manufacture the product and reducing costs that might otherwise be passed on to patients *(86)*.

Technology transfer modalities may vary depending on the legal provisions and manufacturing capabilities available in-country but this important work allows for countries with local manufacturing capacity to explore opportunities to produce quality antibiotics locally and build supply chain resilience.

Moreover, licensing agreements can fast track the production of medicines in-country as compared to full generic development. Countries can explore the use of either compulsory or voluntary licensing frameworks to facilitate technology transfer. The Medicines Patent Pool (MPP) *(87)* collaborates with patent holders on pooled voluntary licensing so countries can access essential medicines, especially where access has been limited. However, patent holders exclude many countries with potential capacities to manufacture from MPP licenses, in particular middle-income countries. As part of the 2019 report *Exploring the expansion of the Medicines Patent Pool's mandate to patented essential medicines (88)* – namely New antibiotics to combat antimicrobial resistance (chapter 7) – the MPP outlines their potential role in contributing to access and antimicrobial stewardship, and how countries can leverage their work to expand antibiotic access. Countries should explore ways to leverage the MPPs negotiations to be included in the scope of their licenses and support introducing policies to expand antibiotic access.

Compulsory licensing allows the exploitation of a patented technology during the patent term without the consent of the patent holder, but with the authorization of competent national authorities.

Government use licenses: A number of national laws explicitly entitle the government, or a third-party authorized by the government, to use a patented invention without authorization of the patent holder.

Additional information can be found in a WHO–World Intellectual Property Organization (WIPO)–WTO trilateral study *(89)*.

2.2.4 Considerations for local manufacturing and/or regional production of antibiotics

Countries with manufacturing capacity may choose to explore opportunities to manufacture products locally for supply chain resilience, timely access and greater self-sufficiency. These activities could be explored in the very early stages of planning, research and product development but not necessarily so. Technology transfer can introduce local production capacity in a given country relatively quickly, but also introduce innovative antibiotics and antibiotics to treat infectious diseases specific to the country or region. Technology transfer modalities may vary depending on, for instance, the legal provisions and manufacturing capabilities available in-country. Additionally, technology transfer procedures can take several years to complete, depending on factors such as the capabilities of the technology receiver to absorb technology, the need for facility re-designs and regulatory approvals. Alternatively, licensing agreements can fast track the production of medicines in-country as compared to full generic development, and countries should consider ways to leverage licensing agreements to enforce better access conditions, such as early access to treatment. Countries can also explore the use of either compulsory or voluntary licensing frameworks to facilitate technology transfer.

The WHO-LPA unit supports countries and regions with a holistic, ecosystem-wide, strategic approach in strengthening sustainable local production and technology transfer along the entire value chain and throughout the product life cycle. The LPA Unit fosters global coordination and synergies in local production and technology transfer as the secretariat of the World Local Production Forum. The unit conducts holistic ecosystem assessments to help countries and regions identify gaps and prioritize actions to build conducive ecosystems, and to develop business cases for sustainable quality local

production and technology transfer of health products. Informed by the ecosystem assessments, the LPA unit supports countries and regions to set and implement holistic national strategies/roadmaps in a coordinated, collaborative, multisectoral manner. Data on markets, production capacities and scalability, etc. are collected and analysed by the LPA unit. Technical assistance and capacity building by the LPA unit is both comprehensive and tailored to train the public and private sectors to achieve conducive ecosystems, sustainability and quality in local production, and facilitate technology transfer (such as from R&D to production) and absorption of health products. The LPA unit also provides specialized prequalification (PQ)/emergency use listing (EUL)-related technical assistance to manufacturers to attain WHO PQ/EUL faster for health products eligible for WHO PQ/EUL and the expert review panels for medicines and diagnostics, using a tailored, needs-based approach.

The LPA unit also plays a pivotal role in early product development and technology transfer, guiding companies from formulation through to stability data generation. It helps in compiling product data in the Common Technical Document (CTD) format necessary for regulatory prequalification and authorization. This involvement is crucial for manufacturers, especially in LMICs, enabling them to fast-track regulatory approvals by developing high-quality dossiers that meet safety, quality, efficacy and performance standards. LPA's early intervention also mitigates development costs by preventing unnecessary activities and identifying gaps sooner, which could be more costly to address later and might risk application rejection. Additionally, the LPA unit offers 'mock' good manufacturing practices (GMP) inspections and assists in developing corrective and preventive actions (CAPA) plans post-inspection, accelerating GMP certification. Besides technical support, the LPA unit provides training on GMP, CTD preparation, and product specifications. The focus on building local manufacturing capacities in LMICs aims to reduce dependency on imports and enhance local availability of health products. By ensuring compliance with WHO prequalification standards, it also positions companies to compete in international tenders, promoting their financial sustainability and supporting local health care needs more effectively.

2.2.5 WHO Fair Pricing Forum

The WHO Fair Pricing Forum *(34)* convenes biennially with Member States and all relevant stakeholders to discuss the affordability and transparency of prices and costs relating to health products. The forum's goal is to ensure that WHO Member States and stakeholders better understand existing approaches and emerging policies to address issues pertaining to market transparency and affordability of essential medicines and health products. WHO has also published the *WHO guideline on country pharmaceutical pricing policies (35)* to support countries with planning and developing pharmaceutical pricing policies.

2.2.6 Pooled procurement

Pooled procurement is a formal arrangement where financial and other resources are combined across different purchasing authorities, to create a single entity for procuring health products on behalf of individual purchasing authorities *(90)*. It is a process where demand is forecasted and aggregated across multiple countries or buyers. Procurement volumes are combined to get better commercial terms, including lower prices, from manufacturers than countries, or purchasers could get on their own. It gives suppliers a longer-term visibility and greater reliability of demand, which allows better production planning and means suppliers and manufacturers can competitively price products.

Several global organizations use pooled procurement to obtain optimal prices of health care products, including the United Nations Children's Fund (UNICEF) Supply Division, the STOP TB Global Drug Facility *(91)* and the Global Fund Pooled Procurement Mechanism (PPM) *(92)*.

Regionally, the Pan American Health Organization (PAHO) Strategic Fund *(93)* is a well-established pooled procurement entity for Latin America and Caribbean countries. In February 2024, the African Centre for Disease Control and Prevention (Africa CDC) announced the creation of African pooled procurement mechanism *(94)* and has the aim of achieving a Pan-African Medicines Regulatory Family. Additionally, the Southern African Development Community has developed and is implementing a *Strategy for pooled procurement of essential medicines and health commodities (95)* that promotes a harmonized approach to securing medicines for the region.

Other established procurement mechanisms include the Gulf Cooperation Council's group purchasing programme that has been pooling procurement for over 30 years for the Gulf Cooperation Council group-purchasing programme (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia and United Arab Emirates) *(96 – 97)*; pooled financing through the United Nations Economic and Social Council and the Organisation for Eastern Caribbean States which has a longstanding pooled procurement mechanism (*98*); and the Small Island Developing States (SIDS) pooled procurement initiative in the WHO African Region (*99*).

2.3 WHO prequalification and regulatory initiatives

2.3.1 WHO Prequalification

The WHO prequalification (WHO PQ) programme is a service provided by WHO to assess the quality, safety and efficacy of eligible health care products. While the original focus of WHO PQ was on medicines for treating HIV, tuberculosis (TB) and malaria, it has expanded over time to cover 316 medicines for priority diseases as well as other health care products including vaccines, diagnostic and vector control products.

Many international procurement agencies that source and distribute health care commodities to LMICs leverage WHO's PQ work to expand their catalogues of quality products to purchase. In March 2023, WHO PQ issued its first invitation to manufacturers of medicinal products for the treatment of multidrug-resistant bacterial infections (beyond those for tuberculosis) *(100)*. Since this invitation, WHO PQ prequalified Cefidericol *(40)*, a **Reserve** antibiotic for multidrug-resistant infections, in February 2024. Discussions are now underway to expand the product eligibility of the programme to include additional antibiotics that can treat and manage drug-resistant infections.

Regulatory initiatives

The registration or regulatory approval of medical products can be lengthy in some countries, in particular due to a combination of factors including, scarcity of human and financial resources, technical capacity, developing regulatory systems, complexity of global supply chains and clinical trial programmes and external factors (such as health emergencies). As a result, patients' timely access to much-needed safe, effective and quality-assured medicines may be delayed. It is therefore important to consider facilitating the registration step, through reliance and collaboration between regulators both regionally and globally.

While not specific to antibiotics, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) *(101)* is a global initiative for harmonizing regulatory requirements. It involves regulatory authorities and pharmaceutical industry representatives from the United States, European Union, Japan, and many other countries (21 members and 37 observers). This initiative works to develop and implement harmonized guidelines for pharmaceutical product standards that are applicable to the development and approval of antibiotics.

Additionally, WHO has developed collaborative regulatory strategies for facilitated national registration of medical products. In 2013, WHO launched the WHO Collaborative procedure for accelerated registration (CRP) of prequalified finished pharmaceutical products (FPPs) for products already prequalified, and later for products approved by a stringent regulatory authority (SRA) *(42)*. The CRP accelerates registration through improved information sharing between WHO PQ and NRAs. By leveraging product assessment and manufacturing site GMP inspection outputs already produced by WHO PQ, or SRAs/WLAs, it speeds up in-country registration of quality-assured products and contributes to their wider availability.

Several other regulatory strategies and mechanisms, using the concept of reliance and collaboration, co-exist with the shared aim of increasing regulatory efficiency globally and supporting countries in accelerating the registration of quality-assured medicines. Some other mechanisms available to facilitate regulatory decisions in countries, include: regional joint assessments (such as ASEAN Joint Assessment Procedure, the African Regional Economic Community Joint Assessments, the Caribbean Public Health Agency (CARPHA)); and global health procedures (such as EU-Medicines for All from the European Union and the Swissmedic Marketing Authorization for Global Health Products procedure). Utilizing these mechanisms, countries can optimize their available resources and time, reducing duplication of regulatory efforts and workload for the registration of antibiotics. More information on facilitated regulatory pathways can be found in the WHO Facilitated Product Introduction website *(43)*.

Specific to antibiotic regulatory challenges, in 2023, the Regulatory Agencies Global Network Against AMR (RAGNA) *(102)* was established following a regulatory summit. RAGNA is hosted by the Swedish Medical Products Agency and the aims of the network are to: Strengthen the international collaboration between regulatory agencies against AMR; identify concrete actions that regulatory agencies can contribute with against AMR; and exchange experiences and good practices between regulatory agencies, human- and veterinary medicines, against AMR.

Due to recent antibiotic shortages caused by a rise in respiratory infections, the European Medicines Agency (EMA) is actively implementing response measures. The EMA has: created the EMA Medicines Shortages Steering Group (MSSG) Toolkit *(103)*, which encompasses a series of measures for critical antibiotic shortages; developed a solidarity mechanism *(104)* to allow Member States to assist one another to source products during critical shortages; and published the first version of the *Union list of critical medicines (105)*. Additionally, to mitigate the scarcity of medicines, the EMA is also supporting the Coordination and Harmonization of Existing Systems against the shortages of Medicines – European Network (CHESSMEN) *(106)*. In response to the risk of antibiotic shortages globally, WHO has recently published a report on *Policy and regulatory interventions to address antibiotic shortages in low and middle-income countries (39)*. The report provides a review of measures initiated by NRAs globally to address antibiotic shortages.

In 2021, following pandemic-related disruptions in global pharmaceutical supply chains that led to stock-outs and delayed procurement of essential medicine, including antibiotics, PAHO responded to countries and territories across Latin America and the Caribbean requesting urgent support through loans and donations. Fostering strong regional collaboration, the Strategic Fund and PAHO country offices, facilitated more than 18 multi-country collaborations. This included supporting over 100 requests for loans and donations across the Americas to mitigate stock-outs for tuberculosis, mental health, HIV and COVID-19 critical care.

Annex 3. Compendium of relevant WHO guidance (in development; non-exhaustive)

Resource materials for in-country development and implementation of national action plans to address antimicrobial resistance:

- 2023 antibacterial agents in clinical and preclinical development: an overview and analysis *(5)*.
- WHO bacterial priority pathogens list, 2024: Bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance *(107)*.
- The selection and use of essential in vitro diagnostics: report of the fourth meeting of the WHO Strategic Advisory Group of Experts on In Vitro Diagnostics, 2022 (including the fourth WHO model list of essential in vitro diagnostics) *(108)*.
- Antimicrobial stewardship interventions: a practical guide *(109)*.
- Paediatric drug optimization for antibiotics: meeting report, 30 November, 5–7 December 2022 *(110)*.
- WHO implementation handbook for national action plans on antimicrobial resistance: guidance for the human health sector *(21,22)*.
- Sample terms of reference for a national multisectoral coordinating group, for a national focal point and for a technical working group *(22, 111)*.
- Antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries: a WHO practical toolkit *(23)*.
- WHO Model List of Essential Medicines (EML**)** – 23rd list, 2023 *(73)*.
- WHO AWaRe classification of antibiotics for evaluation and monitoring of use, 2023 *(3)*.
- WHO AWaRE (Access, Watch, Reserve) antibiotic book *(4)*.
- People-centred approach to addressing antimicrobial resistance in human health: WHO core package of interventions to support national action plans *(8)*.
- Global Antimicrobial Resistance and Use Surveillance System (GLASS) *(26)*.
- Global Database for Tracking AMR Country Self-Assessment Survey (TrACSS) *(27)*.
- Antimicrobial resistance diagnostic initiative: strengthening bacteriology and mycology diagnostic capacity, laboratory systems and service delivery *(14)*.
- Providing guidance to countries on institutionalizing health technology assessment *(28)*.
- Medicine prices and other market information sources *(32)*.
- WHO guideline on country pharmaceutical pricing policies *(35)*.
- Collaborative Procedure for Accelerated Registration (CRP) *(42)*.
- Facilitated Product Introduction Website *(43)*.

- WHO-Listed Authority (WLA) *(44)*.
- Product assessment and manufacturing site GMP inspection outputs already produced by WHO PQ *(45)* or SRAs *(46).*
- WHO Model List of Essential In-Vitro Diagnostics (EDL) *(47)*.
- A national list of essential diagnostics (*48*).
- WHO Selection of essential in vitro diagnostics at country level: using the WHO model list of essential in vitro diagnostics to develop and update a national list of essential in vitro diagnostics *(49)*.
- WHO AMR Surveillance and Quality Assessment Collaborating Centres Network *(51)*.
- Principles and processes for managing procurement *(112)*.
- Drug and therapeutics committees: a practical guide *(61)*.
- TAP toolbox: exercises, tools and templates to support your tailoring antimicrobial resistance programmes plan *(62)*.
- TAP quick guide: a practical handbook for implementing tailoring antimicrobial resistance programs *(63)*.
- Monitoring and evaluation of the Global action plan on antimicrobial resistance: framework and recommended indicators *(69)*.
- Guidance to facilitate monitoring and evaluation for antimicrobial resistance national action plans *(70)*.
- WHO costing and budgeting tool for national action plans on antimicrobial resistance: user guide *(19)*.
- Safe management of wastes from health-care activities: a summary *(60)*.

Annex 4. Antibiotic introduction checklist

Pre-planning

Identifying leadership, governance and other partners for the entire process

- [ ] Identify the governance structure for the antibiotic introduction process including:
  - [ ] Leadership (leader/s to manage the antibiotic introduction)
  - [ ] National coordination
  - [ ] Policy/regulatory oversight
  - [ ] Technical experts/advisors
- [ ] Identify other partners to engage
  - [ ] Implementers (facilities, private sector including market authorization holder)
  - [ ] Civil society

Mapping stakeholders and planning engagement

- [ ] Map stakeholders focusing on who, why and how to engage by:
  - [ ] Decision makers
  - [ ] Informers (i.e. stakeholders that will inform actions/activities but may not have a direct decision making or implementing role e.g. technical advisors
  - [ ] Implementers

Deciding to introduce an antibiotic

Reminder!
Refer to stakeholder map to identify key stakeholders for this part of the process.

Developing and implementing a decision-making process to prioritize and select antibiotics

- [ ] Identify the public health and clinical need
  - [ ] Consult and engage stakeholders
  - [ ] Review and assess policies including global recommendations
  - [ ] Gather, review and analyse data
- [ ] Select antibiotic matched to the public health and clinical need
  - [ ] Assess the product characteristics of antibiotics
  - [ ] If feasible, conduct health technology assessment
  - [ ] Make a preliminary selection on antibiotics matched to the need

Linking decision-making to demand from healthcare facilities and providers

- [ ] Reengage with stakeholders (across the supply chain to facilities) to validate and communicate selected antibiotic
- [ ] Check if facilities have current capacity to appropriately use antibiotics
- [ ] Decide whether to move forward and develop a policy brief to secure political alignment and financing to introduce the selected antibiotic

High-level cost estimates, political alignment and securing financing

- [ ] Estimate high-level costs using available benchmarks
- [ ] Develop policy brief
  - [ ] Obtain ministerial support and secure funding
- [ ] Political support and funding secured to start developing a costed implementation plan

Developing the antibiotic introduction plan

Reminder!
Refer to stakeholder map to identify key stakeholders for this part of the process.

Defining goals, objectives and expected impact

- [ ] Draft high-level measurable goals, outcomes, outputs linked to assumed activities (with consideration to using a theory of change)
- [ ] Articulate feedback mechanism/process to assess progress and course correct as needed

Deciding the antibiotic introduction approach

- [ ] Assess the capacity of facilities and other elements of the health system to inform the optimal introduction approach
- [ ] Consult stakeholders and decide on the introduction approach based on resources and infrastructure
- [ ] If required, design an entirely new introduction approach that has been co-designed through a multi-stakeholder approach.

Updating and adopt policies to support introducing antibiotics

- [ ] Engage relevant stakeholders (NDTC, NRA, or nEML committee etc) to update necessary policies
    - [ ] nEML
    - [ ] National/Standard Treatment guidelines
    - [ ] National formulary lists (if applicable)
    - [ ] Pricing policies
    - [ ] Regulatory policies (see section 4.4)
    - [ ] Surveillance systems and policies to monitor the emergence of resistance
- [ ] Develop a plan to communicate policy changes, including new treatment guidelines to facilities and other stakeholders

Developing the antibiotic introduction plan (cont.)

Preparing for antibiotic registration/market authorization

- [ ] Work with NRAs and ensure clear pathways for collaboration/coordination
  - [ ] Explore and implement regulatory strategies that facilitate access e.g., registration incentives; fee waivers, participation in regional and global regulatory harmonization efforts
  - [ ] Facilitate a strong regulatory environment for the appropriate use of all antibiotics
  - [ ] Ensure policy and regulatory decisions relevant to the selected antibiotic are accessible

Preparing laboratory and surveillance systems

- [ ] Assess national and facility-level diagnostic and microbiology capacity and ensure that capacity is sufficient to introduce the selected antibiotic (e.g. through stakeholder engagements or capacity assessment surveys.)
- [ ] Ensure capacity meets the minimum requirements
  - [ ] Diagnostic stewardship policies are at the HCF
  - [ ] Well trained staff
  - [ ] Adequate equipment and diagnostic supplies
  - [ ] Standard Operation Procedures
  - [ ] Standards on Antimicrobial Susceptibility Testing (AST) e.g. refer to established guidelines like Clinical and Laboratory Standards Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST)
  - [ ] An established laboratory information system.
  - [ ] Quality Assurance System (such as participation in Proficiency Testing)
- [ ] Select a diagnostic approach for the antibiotic being introduced that best reflects to local scenario:
  - [ ] **Scenario 1:** No laboratory capacities in place
  - [ ] **Scenario 2:** Weak Laboratory capacities
  - [ ] **Scenario 3:** Laboratory capacity in place

Developing the antibiotic introduction plan (cont.)

Procurement

- [ ] Streamline and centralize demand planning and procurement processes where possible
- [ ] Develop procurement plans based on need/demand forecasting
  - [ ] Conduct supplier mapping e.g. through an expression of interest
  - [ ] Know the procurement channel e.g. donor-based procurement, regional procurement, national procurement
  - [ ] Select the optimal procurement approach(es) e.g. tenders, negotiations, combining purchasing power with regional neighbours etc
  - [ ] Complete a need/demand assessment of the antibiotic, reagents, diagnostics etc and quantify demand in the procurement plan

Logistics and supply chain management

- [ ] Optimise the supply chain for the antibiotic being introduced
  - [ ] Ensure appropriate warehousing, storage and waste management
  - [ ] Engage distributors; ensure a clear distribution and transport network
  - [ ] Develop clear processes to manage stock levels especially for low volume antibiotics (e.g. hub-and-spoke networks)
- [ ] Plan product quality checks and monitoring along the supply chain
- [ ] Update, enhance or establish logistics management information systems (LMIS)
- [ ] Explore opportunities to connect information systems

Developing the antibiotic introduction plan (cont.)

Preparing facilities - healthcare worker readiness and promoting antimicrobial stewardship

- [ ] Ensure that there is a locally tailored process for translating policy into practice i.e., facility adoption of the selected antibiotic
- [ ] Prepare facilities for implementation
  - [ ] Utilize or adopt a structured approach for facility adoption, use and monitoring of antibiotics
  - [ ] Integrate the selected antibiotic into existing antimicrobial stewardship (AMS) programmes and measures at facilities, or set up new ones
  - [ ] Facilitate the process to update treatment guidelines, formularies and managing the facility formulary process
  - [ ] Plan to enhance, or make improvements to diagnostic capacity, links to microbiology laboratories, referral networks and integrated services
  - [ ] Develop HCW tools to implement AMS programmes
  - [ ] Develop and implement trainings/ training modules for HCWs
  - [ ] Make plans to enhancing diagnostic capacity, links to microbiology laboratories, referral networks and integrated services
  - [ ] Update facility-level stock monitoring tools and ordering forms, and patient management systems to include the selected antibiotic
  - [ ] Improving awareness for the appropriate use of all antibiotics

Improving awareness for the appropriate use of all antibiotics

- [ ] Develop AMR awareness campaigns and materials engaging key stakeholders and audiences (as relevant for the antibiotic)
  - [ ] HCWs
  - [ ] Professional associations
  - [ ] Education institutions (medical teaching schools etc)
  - [ ] Communities
- [ ] Develop the dissemination plan and communication materials

Developing the antibiotic introduction plan

Reminder!
Refer to stakeholder map to identify key stakeholders for this part of the process.

Collect baseline evidence to support clinical best practice

- [ ] Collect the best quality data available at the national level, including leveraging global or regional data if needed
- [ ] Collect baseline data from facilities
- [ ] Develop recording and reporting tools/templates or approaches to efficiently collect data for baseline collection and routine monitoring
- [ ] Integrate the antibiotic into AMR surveillance, pharmacovigilance and sample transport/referral systems
- [ ] Ensure laboratory capacity is sufficient for AST testing and to collect as many routine sources of data as possible
- [ ] Develop a risk management strategy

Update information systems

- [ ] Update information systems (e.g. DHIS2 and LMIS)

Develop national level M&E framework to measure impact

- [ ] Set frequency of data collection and analysis
- [ ] Develop key indicators as part of the M&E framework to track impact, outcomes and objectives.
- [ ] Ensure M&E framework for antibiotic introduction is linked to the NAP M&E plan
- [ ] Ensure targeted surveillance is in place to monitor emerging resistance to the newly introduced antibiotic
    - [ ] Identify surveillance sites
    - [ ] Determine frequency and timing of data collection points
    - [ ] Develop materials to collect data, for reporting and synthesizing (e.g. surveys and reporting templates

Developing the antibiotic introduction plan (cont.)

Operational research and antibiotic introduction

- ☐ Develop operational research questions to assess key elements of the antibiotic introduction plan
- ☐ Design operational research studies to answer questions and fill data gaps

Leverage introducing an antibiotic to inform future research

- ☐ Use M&E results to inform persisting data gaps and needs for future research

Costing the antibiotic introduction plan

- [ ] Summarize all planned implementation activities for rolling-out the antibiotic along a timeline (e.g. Gantt chart)
- [ ] Develop a budget – i.e. cost activities based on realistic assumptions using the WHO Costing and Budgeting Tool for NAPs on AMR
- [ ] Refine activities to align with available funding
- [ ] If required, obtain Ministerial and budget approval to start introducing the antibiotic

All steps in the action plan completed. Start implementing activities and introducing the antibiotic/s

Annex 5. Identifying leadership, governance and other partners for the entire process

Antibiotic introduction requires strong governance that is inclusive and considers the roles and responsibilities of stakeholders at the national level through to the sub-national level (i.e. from policy-makers through the supply chain to facilities where patients receive treatment). It should consider the impact of change on different stakeholders, interact with stakeholders across both the public and private sectors, and engage civil society to have a meaningful role through the entire process. Additionally, while the focus is on antibiotics for human health, governance should integrate with One Health platforms, so there is a unified approach to addressing AMR across different sectors.

Even if strong governance structures are already in place, for successful planning and to avoid unexpected implementation challenges, consideration should be given to the different functions involved in or impacted by the antibiotic introduction process. Overall, it is important that the governance is fit-for-purpose, and any gaps are addressed before planning starts.

Countries will have governance and processes already in place to introduce all medicines, and what is in place will vary from country to country. For example, some countries may have robust, multi-sectoral governance processes for policy-making such as managing national essential medicines lists (nEMLs) and formularies, developing national treatment guidelines, and supporting facility implementation. These may exist alongside a strong regulatory authority that manages the market authorization of medicines and other regulatory policies. In other countries, policy-making may be the responsibility of a single person within the ministry of health (MoH), and the regulatory agency is less mature and so relies more on regional or global cooperation.

In some instances, the NAP may already include leadership and governance frameworks that countries can adapt and/or follow to support antibiotic introduction (see the six steps for sustainable implementation of NAPs on AMR – Step 1: Strengthen coordination, collaboration and governance for NAP on AMR implementation) *(21)*. In countries where governance may be less formalized or structured, it is recommended that countries develop a strong, inclusive governance structure with all the required functions that reflects country-specific capacity and resources, and that can govern successful implementation. The following section outlines considerations for leadership of the antibiotic introduction process and what is required in terms of leadership, the different governance functions, and other stakeholders needed for successful planning and implementation.

5.1 Leadership

Strong leadership with clear accountability is needed to steer the antibiotic introduction process and develop and implement an antibiotic introduction plan. Specific project leads (i.e. an individual or multiple individuals), usually within the MoH, and should have managerial and project management experience with designing and implementing national health programmes.

5.1.1 Roles and responsibilities of leaders in the antibiotic introduction process

Leaders should be assigned and responsible for final decision-making, overseeing the daily implementation of the plan, and ensuring a collaborative and coordinated approach with key stakeholders. Project leads should coordinate advice from those empowered to inform decisions and steer the process. This may include national coordination groups, technical experts and advisors, policy-makers, national regulatory authorities and other relevant committees.

Project leads can be empowered to lead the design and implementation of activities, approve activities, and have accountability for the end-to-end plan. Leaders should ensure all stakeholders, including civil society, are engaged and included in the entire process. In some settings, a project lead may have both a leadership and national coordination role as resources may be limited, existing national coordination efforts may be nascent or not fit-for-purpose or have additional capacity.

5.2 Key governance functions

5.2.1 National coordination

The antibiotic introduction process, including decision-making, implementation and M&E activities, should be coordinated nationally, and if possible, tied into existing national AMR coordination efforts. National coordination is important for aligning the introduction plan to AMR NAPs and for effective communication between different government departments and stakeholders. It should be multisectoral and multidisciplinary bringing together civil society organizations, communities, experts, government officials, policy-makers, regulators, and other stakeholders, and make links to existing sub-national AMR efforts, committees or teams if they exist.

In resource-limited settings, project leaders may need to have a more active role in national coordination and take on the role and responsibilities of this function. If a country has an existing, more formal national coordination function – either as part of the NAP or another relevant coordination mechanism such as an AMR coordination committees (AMR CC) *(113)* – they should be leveraged where possible and tailored so they are fit-for-purpose and relevant for local settings. Some countries may have additional resources and capacity and so decide to opportunistically create a national AMR coordination group as part of the NAP and to facilitate the antibiotic introduction process.

WHO has developed sample terms of reference for creating national coordinating groups for AMR NAPs that can be used to guide setting up such functions *(111)*. In countries with both a separate project leader and national coordination group, they should work side-by-side through the antibiotic introduction process and to develop and implement the plan.

Roles and responsibilities of national coordinators in the antibiotic introduction process

This function can have the mandate to inform, coordinate or make national-level decisions throughout the antibiotic introduction process. National coordinators can be empowered to decide which antibiotics have a high public health need and those that are prioritized for introduction.

National coordinators can have the role of coordinating technical experts and advisors, linking national efforts to sub-national implementation, and coordinating implementation of the introduction plan. They can be tasked to act on recommendations from technical advisors, translate recommendations into actionable activities (i.e. design activities, programmes or policies that are part of the introduction plan), and make recommendations to governments. Their role can include developing or advising on interventions to improve patient treatment outcomes and evidence-based strategies to address AMR.

National coordinators can also work with relevant policy-makers, and regulators to introduce change and guide project leads or those responsible for final decision-making. This includes working with existing governance mechanisms such as NRAs and national drug and therapeutics committees (NDTCs) etc. In some countries NRAs have established NDTCs, or similar groups, that: support the selection of priority medicines including antibiotics; update national formulary lists and treatment protocols; and support translating national policy into practice at facilities. If NDTCs are not fit-for-purpose or absent, it may be beneficial that national coordinators establish a separate national level group, or technical advisory group, responsible for making recommendations on priority antibiotics. In some cases where resources are limited, national coordinators may take on similar functions.

At a minimum, there should be a national coordination process in place to receive input from technical experts and advisors (e.g. government agencies, infectious disease specialists, specialists in relevant medical fields, clinical microbiologists, pharmacists, and public health experts), to document and regularly revise the national list of priority pathogens or infections that could result in an unmet clinical need, and to identify and antibiotics to meet those needs.

National coordinators should be responsible for ensuring alignment between national policy and facility-level implementation. They should ensure a clear line of engagement with civil society and the private sector at the country level and have a process to proactively capture and identify critical or emerging public health needs related to AMR.

National coordinators can also be responsible for designing solutions around how to manage and control the dispensing of antibiotics in both the public and private sectors in ways that align with global standards while remaining practical and feasible for implementation in LMICs.

If a country has an AMR CC or equivalent to coordinate the NAP or govern medicine introduction generally *(113)*, depending on their capacity and resources, they can be empowered to have a main role in the process and have a key role in ensuring appropriate use. Technical experts and advisors for AMR policy, regulation and implementation may already be coordinated through an AMR CC. Depending on their maturity and terms of reference, these bodies, including their technical experts, can play an overarching decision-making and coordination role to support the introduction process. Often, regulators and policy-makers are represented on AMR CCs, and they may already include

appropriate technical working groups (TWGs) such as a TWG on optimizing antibiotic use/antimicrobial stewardship (AMU/AMS). Alternatively, they may have an established way of working with the NDTC to select and adopt priority antibiotics and make national formulary changes, or there may be a process in place where a TWG works with a NDTC to select priority antibiotics. Depending on their remit, AMR CCs can establish mechanisms to fill gaps in technical expertise and implementation (e.g. in the absence of a TWG that can recommend priority antibiotics or a fit-for-purpose NDTC, an AMR CC may decide to set up a committee/TWG to make recommendations on priority antibiotics).

AMR CCs can also coordinate and support facilities by linking to and supporting existing facility-level governing groups such as district or hospital drug and therapeutics committees (DTCs) and/or antimicrobial stewardship committees (AMS committees), or an AMS team. They can also guide the activities of implementers and operators and provide a channel to capture real-world clinical and community experiences, ensuring that decisions and activities reflect local needs and the current situation.

5.2.2 Policy and regulatory oversight

Policy-makers and regulators have an important role in decision-making and shaping the policy and regulatory environment for introducing antibiotics. In most countries, policy-makers and regulators sit within specific government departments or agencies, so it is important that the right individuals are identified and engaged to support the introduction of antibiotics (see Annex 12 and Annex 13 for the different policy and regulatory activities that may be part of the introduction plan).

Roles and responsibilities of policy-makers and regulators in the antibiotic introduction process

Policy-makers: Policy-makers and government officials, across different government departments, will have a role in supporting the adoption of new policies or revising existing ones. This includes policy-makers within the MoH, such as those responsible for updating national formulary lists (e.g. NDTC), developing national treatment guidelines, or policy-makers in the treasury or finance ministry responsible for allocating health budgets etc. In some countries, NDTCs may have the role of managing a national formulary list (or antibiotic list) as well as for the planning and coordination of the antibiotic introduction, as well as managing supplies.

Regulators: NRAs need to be a part of the process and have visibility on the introduction plan so they can provide the necessary regulatory oversight and apply/develop regulatory policies that can facilitate antibiotic introduction. In some countries, NRAs may already have a specific team working on antibiotic regulation as part of the NAP or have teams that work on the regulation of medicines that fall within a special category (e.g. life-saving or emergency use), which may apply to the antibiotic being introduced.

5.2.3 Technical expertise and advice

Technical experts and advisory functions are needed to guide the technical components of the antibiotic introduction process. They are essential for ensuring that decisions are guided by the most recently available evidence, reflect the current local AMR situation and experience of patients, clinicians and care providers, and address priority public health needs. Beyond technical expertise, advisory functions can also include channels to seek advice from civil society.

Roles and responsibilities of technical experts and advisors in the antibiotic introduction process

Technical experts and advisors can provide technical guidance, assess data, inform decisions, and make recommendations on which antibiotics to introduce, when and where to introduce them, and how to ensure they are appropriately used. They can also make recommendations on different policy or regulatory changes and provide technical guidance on different implementation strategies. Technical expertise should be multidisciplinary with representation from different fields (e.g. infectious disease experts, clinicians and other leaders from the health care sector such as pharmacists and nurses, microbiologists and laboratory experts), and representatives from relevant departments within the MoH responsible for the selection, procurement, supply, distribution, prescribing and use of antibiotics at the national level. Technical experts and advisors can also form groups, teams or committees to provide guidance on clinical management questions from facilities and health care workers. They may also have a role to play in designing and implementing stewardship policies and programmes.

In some countries, some facilities have local governing groups such as district/hospital DTCs, AMS committees and AMS teams, that include technical experts from facilities. These groups have experience with managing AMR and can share real-world experiences and facility data, and information from experience at the point of care.

5.3 Other key partners

5.3.1 Implementers

On the ground implementers and operators execute activities in the introduction plan. Implementers' functions include implementing supply chain activities such as procurement planning, procuring, distribution, and quality control. They also include laboratory managers, facility-level decision-makers, hospital managers, clinicians and other health care workers who play a critical role in ensuring patients receive care. Implementers can be from both the public and private sectors, and can include those who will be responsible for monitoring and evaluating the antibiotic introduction plan, and they may also conduct operational research, as included in plans.

The role of private sector implementers in the governance structure needs to be carefully considered and engagement should depend on each country's individual setting and health system. In some countries, the private sector may have a large role in delivering medicines. It may be well regulated and assessed as an appropriate channel that can deliver last resort antibiotics safely and appropriately. In other countries, the private sector may be less regulated or controlled, limiting the ability to ensure and enforce the appropriate use of antibiotics, especially for **Reserve** and **Watch** antibiotics. For **Reserve** and **Watch** antibiotics in particular, it is important that private sector engagement considers its capacity to appropriately use these antibiotics and the level of visibility the government has to monitor use and resistance in this sector.

Roles and responsibilities of implementers in the antibiotic introduction process

Facility-level implementation: Many countries have existing mechanisms to introduce medicines, including antibiotics into public health care facilities. Private facilities may have different pathways, depending on the country and health care system. Some facilities may have sub-national DTCs and/or AMS committees that have a lead role in managing, monitoring and introducing antibiotics at facilities. For example, South Africa's AMR One Health and Governance Guidelines require that all health facilities establish a hospital AMS committee to provide oversight and coordination for antibiotic activities in individual institutions *(114)*. Both facility DTCs and/or AMS committees can be linked to NDTCs if they are operating. Existing DTCs and/or AMS committees should be engaged and leveraged for the introduction of antibiotics into facilities or created in the absence of a similar type of mechanism. Further guidance on facility level implementation can be found in the WHO *Antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries: A WHO practical toolkit (23)*. This includes sample terms of reference for facility AMS committees and AMS teams (see Annex II and Anex III in the document). The role of these committees in setting up and designing AMS teams and infection prevention and control (IPC) committees in facilities is detailed further in Annex 17.

Supply chain implementers including the private sector: The role of supply chain implementers is to deliver the antibiotic across the pharmaceutical supply chain, so it is available at the point of care. These implementers can be from the public or private sector and include pharmacies, central medical stores, distributors and wholesalers. Distributors are critical supply chain stakeholders in LMICs but are often overlooked by AMS programmes. Distributors play an important role in delivering last-mile access to patients who need treatment. While private sector partners have an important role to play, for impartiality, engagement with some private sector implementers should be limited to consultations only and they should not be involved in decision-making (e.g. as private sector partners such as distributors and/or suppliers, they may stand to profit financially from certain decisions).

5.3.2 Civil society

Civil society are an important part of governance as they can hold governments to account and ensure that commitments are delivered. Civil society broadly includes nongovernmental organizations (NGOs), faith-based organizations (FBOs), professional associations and local community groups, and patient groups. Including civil society in the decision-making process and governance structure can foster transparency, accountability, and inclusivity.

Roles and responsibilities of civil society the antibiotic introduction process

Civil society can advocate for the equitable distribution of antibiotics and ensure that vulnerable populations are not overlooked. Civil society organizations have technical expertise and can support implementers, technical working groups and AMR CC activities at all levels. Their participation should focus on ensuring that policies reflect the needs of diverse communities, promote public trust, support appropriate use, and support long-term, sustainable availability of antibiotics. Additionally, by giving patients and those most impacted by the introduction of an antibiotic a voice, they have a role in ensuring health care interventions are both patient-centred and responsive to real-world needs.

Annex 6. Developing and implementing a decision-making process to prioritize and select antibiotics

This section provides guidance for those tasked with making recommendations and decisions on identifying and selecting priority antibiotics. The first decision needed is to identify antibiotics that have a clear public health and clinical need. It is important to apply a systematic, transparent evidence-based process. Using the stakeholder map, it should be clear who is responsible for making decisions and developing recommendations on which antibiotics to introduce. The map can also be used to indicate who to engage and when in the decision-making process.

The decision-making process for prioritizing and selecting antibiotics can be split into two key steps:

1. Prioritize antibiotics based on the public health and clinical need; and
2. Select antibiotics matched to the public health and clinical need.

6.1.1 Prioritize antibiotics based on the public health and clinical need

The decision to introduce an antibiotic requires a thorough understanding of the public health and clinical need. This can be identified by assessing the current situation (e.g. considering local, regional and global trends and threats) and the underlying need (i.e. the burden of infectious diseases, the burden of multidrug-resistant organisms (MDROs) and resistance rates).

It is also important to assess/consider current antibiotic use patterns (i.e. the use of antibiotics already in use for the indication being targeted), delivery channels (i.e. public, private or unregulated sectors), and treatment gaps (e.g. for recommended and currently available products, for recommended but unavailable products and why, for not recommended but available products and why). Consideration should also be given to the costs and benefits of introducing an antibiotic and the impact it might have on the overall health system.

6.1.2 Consult and engage stakeholders

Using the stakeholder map (see Table 1), identify key stakeholders – both within and outside the health system – that can inform antibiotic prioritization and selection. Then conduct stakeholder consultations. This step is essential for buy-in, ownership and overall

implementation success, and to ensure that real world antibiotic access challenges, issues and priority needs are at the forefront of the antibiotic prioritization and selection process. Consultations should capture the views and opinions of policy-makers, regulators, technical experts, health care professionals and civil society, including communities and patient associations, and private sector stakeholders such as distributors. Depending on resourcing, capacity and urgency, consultations might be conducted through face-to-face meetings with relevant individuals or groups, or countries may choose to have a more systematic approach by developing paper-based or digital surveys to capture views from different stakeholders. Consultation can also happen at several stages of the decision-making process – but ideally at least twice, once at the beginning of the decision-making process and again at the end to validate and communicate decisions.

Plan ahead to ensure consultations capture the right information (e.g. develop questions tailored for each consultation and share them before meeting). Planning ahead will help steer the discussion and ensure the most relevant information is captured.

6.1.3 Reviewing and assessing existing AMR and antibiotic relevant policies

Countries are likely to have existing medicines, AMR and antibiotic policies that include information on priority products, treatment protocols/guidelines, and specific regulations for antibiotics including AMU/AMS measures or requirements.

Policies should be reviewed to ensure that current frameworks, policies and guidelines are up to date, contextually relevant to the local setting, and reflect structural, financial and geographical factors. Reviewing policies will also inform relevant, achievable targets and designing feasible interventions.

In countries with an NAP, a good place to start is by reviewing the NAP so that antibiotic priorities align with the national AMR strategy. The NAP may include information on the burden of infectious diseases and country or regional priority pathogens. They may also include intervention opportunities or priority geographical areas or population groups within a country.

When reviewing the NAP and other policies, consider if they will require updating during planning and implementation. Also consider if there are policy gaps and if any new policies might be needed during planning and implementation (see Annex 12).

Below is a list of relevant policies to review:

- National action plan on AMR (NAP).
- National essential medicines lists (nEML).
- National formularies.
- Current national antibiotic treatment guidelines.
- Medicines regulatory policies (e.g. those for life-saving or urgent treatments such as import waivers for high-priority products, or those that can be leveraged to facilitate expedited or temporary marketing authorization).
- National insurance and reimbursement policies for medicines that could include antibiotics.
- Pharmaceutical pricing policies (e.g. import waivers might already be in place for high-priority antibiotics).

For efficiency, and in resource-limited settings, regional and global policies should also be reviewed. For example, if a country's nEML cycle does not align with recent global treatment recommendations, reviewing the WHO EML and the WHO AWaRE antibiotic book for the most recent treatment recommendations can guide identification of antibiotics for optimal clinical practice and treatment outcomes. Similarly, a region might have adopted and started to implement a regional procurement policy for a high-cost antibiotic or have included an antibiotic in their procurement catalogue. For example, the PAHO Strategic Fund has made ceftazidime-avibactam available for procurement via the strategic fund for participating countries *(93)*.

6.1.4 Gather, review and analyse available data

Antibiotic prioritization should be based on locally available data and evidence where possible. However, availability of data varies from country to country. As a starting point, to understand both the public health and clinical need, data that can inform the burden of infectious diseases, resistance patterns and current antibiotic use patterns should be gathered, reviewed and analysed (Table A1). This step will help provide an understanding of local infection trends and current treatment gaps in treating and managing bacterial infections, including MDRO. It will also provide insights on what type of data are already available and what is being collected to inform AMR strategies and planning. It will also help set a baseline for measuring impact.

Table A1 summarizes data and corresponding sources that can be used to assess the public health and clinical need.

Gather data points from national policy documents, alongside published literature and surveillance systems/data collection tools for baseline information on current infection rates and resistance patterns. For example, national health management information systems may have relevant burden of disease data, and surveillance data can be obtained via cumulative national antibiograms to establish AMR patterns at the local level and to determine pathogen susceptibility to treatments, giving insights on the efficacy of current treatments and the prevalence of AMR. In countries where routine testing and testing capacity is low, or baseline resistance data are unavailable, an estimate of disease prevalence can be used to guide decisions alongside situation insights from clinicians and health care professionals based on current clinical practice. Likewise, if local or national-level data are unavailable, external global and regional sources can be used to guide decision-making, including data from neighbouring countries.

Additionally, gather data on current antibiotic use and prescribing patterns to inform how antibiotics are currently used in practice and if there are treatment gaps. This will give a picture of current clinical practice and trends and can inform current capacity to manage MDRO infections at facilities and health services. It can also indicate patient admission and hospital throughput rates, indicating the size, capacity and treatment outcomes at different health services. This will also be useful to guide other planning steps such as selecting the optimal implementation and roll-out approach (see Annex 11).

Point prevalence surveys can be useful in informing use and prescribing patterns (refer to *WHO methodology for point prevalence survey on antibiotic use in hospitals*) *(68)*. Relevant AMR data that can inform decision-making may also be available via the Global-PPS *(65)*. Data and insights from prescription audits and clinician, pharmacist or professional association reports can also be useful in identifying the need especially in areas where laboratory capacity is limited. These reports give a perspective on clinical experiences and could include data and trends on resistance patterns in local facilities.

Table A1. Data types and sources to support prioritizing antibiotics

Data types	Data source
Current treatment recommendations • National policies • Global guidelines and recommendations • National treatment guidelines	• National action plans • National EML • National treatment protocols/guidelines • WHO EML • AWaRe classification and antibiotic book
Burden of disease data • Incidence and mortality rates • Disability-adjusted life years (DALYs) associated with multidrug-resistant infections (if available)	• National health management information systems (e.g. DHIS2 to illustrate burden of disease districts for diseases such as pneumonia that require an antibiotic for treatment) • Routine surveillance (for demographic data such as age, gender, community vs hospital-acquired infections and clinical presentation etc.) • Data from the Global Research on Antimicrobial Resistance (GRAM) project *(25)* • Data from research on local epidemiology
Resistance patterns • Pathogen susceptibility to different antimicrobials • Treatment failure rates	• National antibiograms and/or facility-level cumulative antibiograms • Routine surveillance • National AMR surveys (if available) • Global antimicrobial resistance and use surveillance system (GLASS) *(26)* • Global database for tracking AMR country self-assessment survey (TrACSS) *(27)* • Scientific literature (from other published studies)[4]
Current antibiotic use • Antibiotic use data • Prescribing data • Supply data	Data from national reporting channels: • GLASS data on antimicrobial use • Available data on country antibiotic sales Data from facility-level reporting channels: • Point prevalence surveys • Prescription audits • Professional association reports (e.g. clinician and pharmacist reports) • Facility-level treatment protocols

Gathering data can also be an opportunity to identify data gaps, and corresponding infrastructure/capacity limitations with data collection and routine AMR surveillance. This can also inform decisions on the optimal implementation and roll-out approach (see Annex 11). For instance, if a country currently does not have capacity to collect cumulative antibiograms, then this may be an indication of the working diagnostic capacity of facilities and clinical laboratory services, and the current limitations in collecting and sharing data.

[4] If local data on resistance patters are not available, publications that provide regional trends can be a useful source to inform decision making. For *exampl*e, Tadesse et al (*115*).

Once data sources are gathered, analyse data to determine the public health and clinical need. Technical advisors and experts can be engaged to support this exercise. Assessing data can identify if there are treatment gaps, for example, data from reviewing treatment guidelines and the nEML may indicate that there are currently no or limited treatment options for treating carbapenem-resistant *Acinetobacter baumannii* (CRAB) in a country, but there is a clear clinical need (i.e. from burden of disease data, or surveillance data if available). Or data may indicate that even though policies and treatment guidelines are up to date and the public health need is clear, a product has never been registered to allow for the implementation of the policy. The assessment should consider the burden of different pathogens, the diseases they cause, and their susceptibility to existing and available antibiotics. Efforts should be made to rationalize the epidemiological and clinical 'real need' for an antibiotic relative to country-specific contexts, including the urgency of accessing an antibiotic to respond to emerging threats and trends. The assessment should also include broader, additional considerations such as determining whether introducing an antibiotic is aligned with national, regional and/or global priorities, if it will improve equity, if it is considered a priority antibiotic by the medical and broader community, and if introducing a given antibiotic will impact other areas of the health system.

6.1.5 Select antibiotics matched to the public health and clinical need

Once the need has been established, it should be matched to an antibiotic that best addresses the treatment gap. For example, following the example used above where there are no or limited treatment options for CRAB infections, select an antibiotic(s) that best suit(s) the local context (including working capacity and infrastructure), and can close the treatment gap for an identified need regarding CRAB infections. This is important for priority setting within the context of the country's health system and for inclusion in national treatment protocols/guidelines.

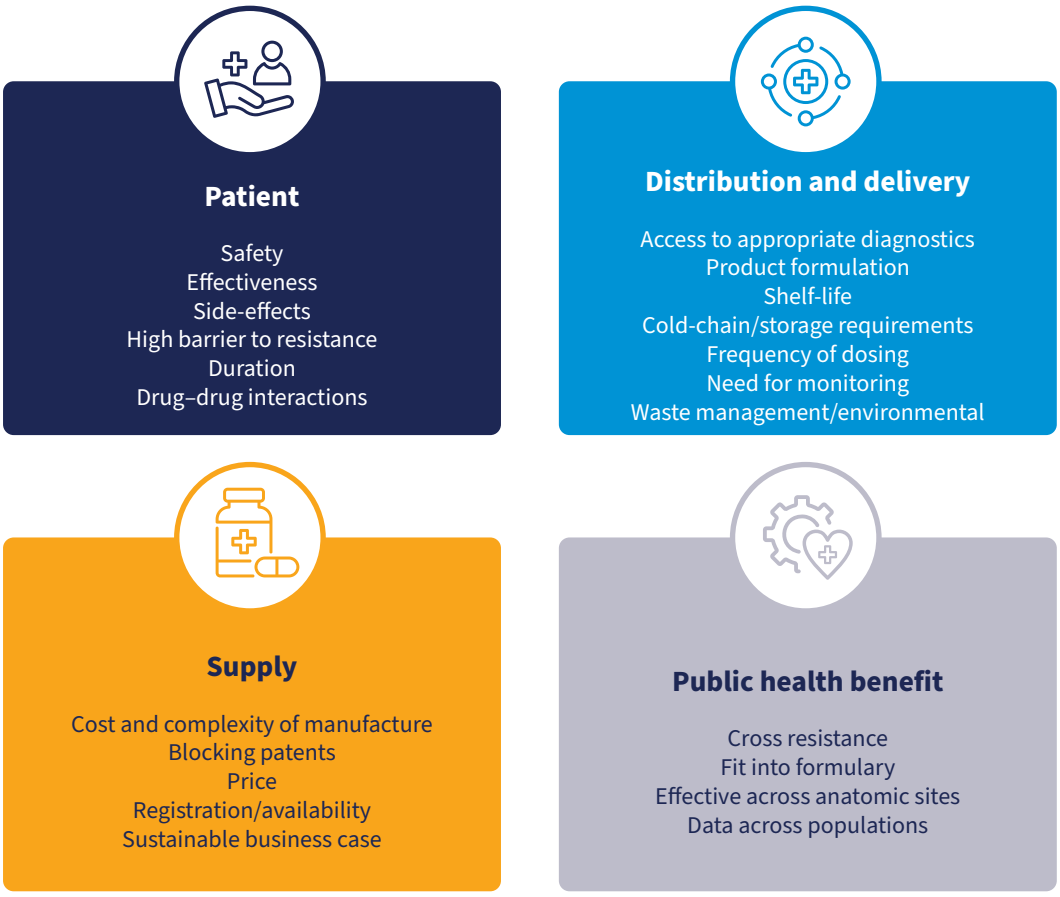
To match an antibiotic that responds to the need and to close the treatment gap, apply a clear, evidence-based selection process. For example, assessing products by pre-defined characteristic criteria can guide the selection (Fig. A1). Criteria may already exist, or a relevant product selection process may be active through NDTCs, so it is recommended to leverage existing processes and technical groups where possible. In the absence of an existing process, leverage other health care advisory bodies that support the selection of products for nEMLs. In the absence of an existing mechanism, a new process can be set up, starting with organizing a selection committee. In countries where an AMR CC is working, it could be an opportunity to set up a TWG specifically charged with making recommendations on priority antibiotics that meet a public health and clinical need. Whether using existing channels or setting up new ones, it is important to ensure that facility-level clinicians, pharmacy representatives, civil society and communities are included in the selection process.

The selection process for product inclusion on national treatment guidelines should be based on a country's AMR/AMU situation, products recommended in the WHO EML, the WHO AWaRE antibiotic book, or other recent guidance. nEML's are also relevant depending on their focus (e.g. some nEMLs primarily focus on products for primary health care and may not be fit-for-purpose for **Reserve** and **Watch** antibiotics that are used in hospital settings). The process should also safeguard that first- and second-line options

are available and are being used, and that **Reserve** classified products are introduced only as a last resort option. It should also ensure that selected antibiotics can and will be introduced with antimicrobial stewardship activities to ensure appropriate use. This includes ensuring that there is access to the tests needed to inform appropriate treatment.

Reviewing and comparing product characteristics with criteria can help assess the benefits and risks of an individual product, the potential impact of introducing an antibiotic and support setting clear targets and indicators. It can also facilitate optimizing and streamlining national formularies. Considering product characteristics could indicate that multiple antibiotics should be introduced. Product characteristics can have implementation and financial implications, as well as different patient outcomes. Criteria for selecting antibiotics against their characteristics and linking to a related treatment gap can be organized into four groups: patients; supply; distribution and delivery; and the public health benefit.

Fig. A1. Product characteristics to consider when selecting antibiotics



Source: Adapted from GARDP (unpublished presentation), 2024.

These product characteristics are all key considerations for selecting the best treatment option for the identified need and can support streamlining antibiotics included in treatment protocols/guidelines, nEMLs and/or national formularies. Selected antibiotics should fit within a country's existing treatment guidelines for bacterial infections (i.e. the antibiotics that are currently available and used as per national treatment protocols/guidelines and the nEML, if relevant). Likewise, a selected antibiotic should align with the

NAP and complement or improve current infection treatment and management. Patient safety and treatment outcomes are core to the selection.

Consideration is needed on how to integrate the selected antibiotic into national guidelines and how it will be made available, e.g.:

- Will it replace or be added as an additional antibiotic?
- Are multiple antibiotics needed to manage infections and are they all currently available?
- How does it fit with a comprehensive, people-centred approach to addressing AMR in human health *(8)* and in tandem with other complementary interventions such as WASH and IPC programmes.

Supply availability is also a key consideration for all antibiotics. If there is insufficient supply, and there are no ongoing global or regional access projects, a country may consider using alternative products and delaying product introduction until the supply situation has improved. Moreover, to mitigate supply risks, a country may be positioned to explore aspects related to intellectual property that could create a pathway for local manufacturing, such as TRIPS flexibilities and voluntary licenses for patents and other exclusivity rights, which could accelerate availability and lower the cost of the antibiotic in the local market (see Annex 2.2.2). However, the urgency to meet a treatment gap should be considered against the time to unblock patents and develop a locally manufactured antibiotic.

Attention also needs to be given to the capacity of the health system to appropriately use the antibiotic and whether additional guidance, guidelines or capacity strengthening is needed for testing/diagnosing, treating, dispensing, auditing prescriptions, and physically accessing medications, especially for **Reserve** antibiotics.

Recognizing that data may be limited, Table A2 outlines the types of data that support assessing a product's characteristics.

Table A2. Data types and sources for assessing a product's characteristics

Data types	Data source
Product-specific data: • Patient populations (including exclusions) • Efficacy • Toxicity • Side-effects • Contraindications • Drug durability • Drug–drug interactions	• WHO EML *(73,74)* • WHO AWaRe Antibiotic Book *(4)* • Clinical trial data including clinical utility data • Scientific literature • Product information (i.e. the product information sheet available on company websites, or product labels published on SRA websites e.g. FDA (https://labels.fda.gov/ *(116)*) and EMA (https://www.ema.europa.eu/en/medicines) *(117)*

The WHO EML and the WHO AWaRE antibiotic book can be used to guide selection of products that have been assessed for safety and efficacy. Clinical trial data as well as product information and product labels can also be referenced. For **Reserve** antibiotics, there are currently limited product choices, but the selection may expand over time. Decision-makers and technical experts making recommendations should be familiar with the characteristics of all available antibiotics and assess how introducing them will

impact implementation (e.g. will there be additional costs to improve testing capacity to support the appropriate use of the antibiotic being introduced).

Once an antibiotic has been selected, technical groups and decision-makers may also then need to decide if there is preference for a specific presentation or product, based on these considerations (e.g. stating a preference for an antibiotic that does not require a cold chain).

Spotlight

The recent global antibiotic supply situation and the potential impact on country level access

Recently, several antibiotics including **Access**, **Watch** and **Reserve** antibiotics have been subject to global supply shortages, which have been documented in both high-income countries (HICs) and LMICs. Notably, the European Union experienced amoxicillin shortages over the 2022–2023 winter due to a surge in respiratory illnesses, and have since made concerted efforts to address antibiotic supply shortages going forward *(118)*. It is important to be aware of the current and future supply situation, particularly for **Reserve** antibiotics as most of these products are initially patented and produced by one manufacturer. At the same time, while there may be multiple suppliers of **Access** and **Watch** antibiotics that are off-patent, in many cases, there are only a few manufacturers of the raw materials or the active pharmaceutical ingredient , which can impact supply availability. The very low price of these antibiotics, and resulting small profit margins, has sometimes been a disincentive for some manufacturers to continue making the more commonly used antibiotics, which has also put pressure on supply and prices when demand has spiked. Global shortages and stock-outs can occur if there are production problems, or if demand outpaces supply. Supply shortages can also result in higher prices, even for **Access** antibiotics. Where possible, it is important to gather information on the supply situation when planning to introduce a new antibiotic.

Annex 7. Health technology assessment to support decision-making

The main purpose of health technology assessment (HTA) is to inform policy decision-making on improving the uptake of new, cost-effective health technologies and interventions, and preventing the uptake of technologies with unclear value *(119)*.

HTA has been defined as follows: "The systematic evaluation of properties, effects and/or impacts of a health care technology and interventions. It should include medical, social, ethical and economic dimensions and consider benefits and efficacy, clinical and technical safety, and cost-effectiveness. HTA should be within the goal of moving towards universal health coverage (UHC) and is useful to inform decision-making on issues surrounding coverage and reimbursement, pricing decisions, clinical guidelines and treatment protocols, and lastly, medical device regulation"*(120).*

While HTA can be a useful decision-making tool, it is just one option countries can use to support decisions. HTA should be linked to other policy tools for decision-making and managing resources efficiently. For example, HTA should link with decision-making processes around budgeting, social health insurance (SHI) benefit packages, or reimbursement lists (if applicable). In some countries, pricing of pharmaceuticals or technologies is explicitly linked to HTA (most often narrowed down to economic evaluations), but in combination with other policies such as reference pricing, generic substitution, and control of supply chain mark-ups *(121)*.

HTA capacity varies across LMICs. Some countries have a dedicated HTA agency, but in other countries it is more nascent. For example, at least six countries in the WHO Region of the Americas have institutionalized HTA, and 21 countries are members of the Health Technology Assessment Network of the Americas (RedETSA) *(122)*. HTA adoption is less prominent in the WHO African Region, although many countries have made progress with developing nEMLs and providing social health insurance *(121)*.

Spotlight

RedETSA and knowledge exchange to support HTA regionally

RedETSA (Health Technology Assessment Network of the Americas) is an example of how countries can leverage regional initiatives when national capacities and resources are limited, or to find efficiencies *(122)*. RedETSA is a collaborative network that connects health ministries, technology assessment agencies, regulatory authorities, and educational institutions across 21 member countries. Its primary goal is to evaluate and promote effective health technologies. Since its inception, RedETSA has launched BRISA, a comprehensive regional database offering over 3500 health technology evaluation reports, accessible for free. BRISA centralizes the reports developed by the member institutions of RedETSA in a single platform, and gives visibility to information that would otherwise remain dispersed or without public access. By fostering the exchange of knowledge and creating a unified approach, RedETSA has significantly contributed to improving HTA and decision-making in the Americas *(123)*.

Even with limited HTA capacity, countries can still apply HTA to inform decision-making. At the same time, through ongoing data collection and implementation research, countries with less mature HTA agencies and/or limited capacities can start building relevant data sets that can contribute to future decision-making.

A country with less developed HTA capacities and/or processes can consider the following to inform the best HTA approach for the local setting:

- The capacity of staff or personnel to critically appraise clinical and economic evidence.
- The availability of local or localized data in relation to costs, utilization and expenditures, including access to national health insurance data if applicable, for the purpose of undertaking assessments and monitoring.
- In the absence of local data, an ability to access data estimates from neighbouring countries with similar epidemiological and health system profiles.
- The availability and generalizability of trial data for a given health technology (i.e. local data can be supplemented with international data).
- The availability of economic models relevant for use in the local setting.
- Other policies such as regulatory policies that HTA needs to be linked with.
- The type of analyses needed (as complex analyses are not always necessary).

HTA can be implemented both before and/or after a product is registered. For many LMICs, the market for **Reserve** and **Watch** antibiotics is small (i.e. low demand/small volumes), which equates with low potential profit margins for suppliers. This may partly explain why suppliers may be less willing to pursue registration of products in LMICs, and they may need assurances, or guarantees, to start the process. For suppliers of newer antibiotics, and in countries with SHI (or those that use tax-based public procurement mechanisms or reimbursement schemes), HTA can play a role in signalling that if the antibiotic is made available, they may be reimbursed at a level that reflects its underlying value *(124)*.

Before a product is registered, national coordinators, regulators, policy-makers, nEML committees and SHI bodies (if applicable) can work together to conduct HTA and use that assessment to inform whether an antibiotic should be made available. For novel

antibiotics to treat MDROs, HTA assessments may be limited due to antimicrobial clinical trial design *(125)*. This is a challenge for both HICs and LMICs when conducting HTA.

Potential HTA approaches for antibiotics in resource-limited settings

A simple budget impact analysis (BIA) may be sufficient for some antibiotics and countries. A BIA assesses whether the antibiotic is affordable relative to the treatment population, and considering the resource constraints of the country (i.e. to assess the likely financial impact of the antibiotic before it is implemented), and to work out whether it will be affordable within the budget constraints if it is recommended for use *(126)*. This type of assessment only evaluates affordability and not value for money. If doing a BIA for antibiotics to treat MDROs (i.e. **Reserve** and some **Watch** antibiotics), consider that the introduction costs are likely to be high, but the treatment population will be small. So, if the total treatment cost is high per patient, a country still may decide that it is affordable and decide to introduce it. See Table A3 for example data requirements to complete a BIA.

For many antibiotics, especially **Reserve** and **Watch** antibiotics, comparative trials demonstrating superior efficacy are limited. For **Reserve** antibiotics particularly, trials have mostly been designed to demonstrate non-inferiority, and therefore there are limited reports showing significant differences in their efficacy compared to comparator products. In these situations, a HTA analysis could take the form of a **comparative cost assessment or a cost minimisation analysis**. In these types of analyses only costs are analysed, and the least costly treatment approach is chosen because outcomes are known to be equal between approaches. There are several ways a country can conduct a comparative cost assessment. For example, if available, cost data from observing patient resource use can be used, or if data are unavailable, a Delphi panel of experts can be used to provide information on treatment costs *(127)*. See Table A3 for example data requirements to complete a typical BIA.

Other HTA approaches for antibiotics with greater data availability and HTA capacity

If data and capacity are available, a cost-benefit analysis can be used to consider cost factors relating to the characteristics and the use of antibiotics (i.e. diagnosis, comparative costs and comparative effectiveness, resistance, patient compliance with treatment, and treatment failure) and related to external factors (i.e. funding source, clinical pharmacy interventions, and guideline implementation interventions) *(128)*. A more complex cost-effectiveness analysis might also consider both direct costs (such as the purchase and distribution of the antibiotic) and indirect costs (such as avoided costs due to the reduction of resistant infections) *(124)*. A recent paper explores ways to adapt incremental cost-effectiveness ratio (ICER) calculations to the limitations of antimicrobial clinical trial design *(125)*. This paper may provide strategies for countries where data are limited, but that are nevertheless planning to use HTA to support assessing cost-effectiveness through determining ICERs.

Countries that have sufficient capacity and data available to apply economic models from published literature can model the value of introducing antibiotics for MDROs. For example, a validated dynamic disease transmission and cost-effectiveness model published in 2020 *(129)* was used to estimate the clinical and economic outcomes of introducing ceftazidime + avibactam for treating resistant infections in Zhejiang province, China with the purpose of informing reimbursement decision-making. This example utilized the published model to assess outcomes over a 10-year infectious period and an annual discount rate of 5%. Costs were extracted from the hospital's health information system (HIS) and obtained after data cleaning, aggregation and discounting *(130)*.

Estimating the economic burden of AMR has been a key part of modelling the value of introducing novel antibiotics in high-income settings. However, there are many different models, and each have a different utility. In 2019, a systematic review was published on *Using the best available data to estimate the cost of antimicrobial resistance: a systematic review (131).* The paper describes the diverse approaches of studies quantifying the economic burden of AMR and provides a narrative review of the costs related to the economic burden of clinically important hospital- and community-acquired infections. This paper can provide a useful guide on the strengths and weaknesses of different published models. While broad assumptions can be made regarding some predictable factors contributing to future AMR rates – which is generally needed to assess cost-effectiveness – cost-effectiveness modelling for antibiotics should be used with caution given that the unexpected emergence, establishment and spread of new resistance genes is likely to introduce uncertainty into estimates of future economic burden and in models evaluating the effectiveness of interventions or policies to address AMR *(132)*.

Linking HTA to other policies and regulations

If a country decides to use HTA to inform decision-making – and the given antibiotic is assessed as having potential value and the decision is to move forward with introduction – then they can leverage different instruments to accelerate or support product registration, while also ensuring there is ongoing data collection to address evidence gaps for robust HTA. This should be factored into the implementation and planning stages of the antibiotic introduction process. For example, if the antibiotic has WHO prequalification, then registration waivers, fast-track procedures or working through the WHO CRP could be considered. Additionally, compassionate access programmes as interim options to bridge data gaps, or policies that allow special exemptions for unregistered medicines for life saving treatments, could also be explored for antibiotics that are urgently needed. HTA agencies in some countries have adapted their processes to include time-limited recommendations (TLRs) to facilitate timely access to innovative therapies for patients with rare or life-threatening diseases and with high unmet medical needs. Due to the limited availability of clinical utility data for novel antibiotics in low-resource settings, TLRs might be an option to consider if a country needs to introduce and register a novel antibiotic rapidly. A typical component of TLR approvals are additional data-generation requirements by the supplier to address important uncertainties in the existing evidence base at the time of regulatory approval *(133)*. TLR data collection requirements can be linked to product registration conditions/requirements that are designated by the NRA. Beyond leveraging regulatory mechanisms to build evidence, countries can also explore conducting implementation studies or operational research that is designed to assess the cost-benefit or cost-efficacy of antibiotics as they are being introduced (see Annex 19.4).

In countries that have more established, or larger markets (i.e. both LMICs and HICs), suppliers may be more willing to register products because there is a clear financial benefit. In those countries, HTA is still recommended but it will likely happen in parallel to, or following marketing authorization, and HTA is usually submitted by the marketing authorization holder. The same approach should still be applied where national coordinators work with policy-makers and regulators, nEML and SHI bodies to conduct HTA and use data to inform if and how the new antibiotic should be made available in the public sector.

For more specific guidance on conducting HTA, WHO provides guidance to countries to institutionalize HTA mechanisms *(28)*.

Table A3. Example data requirements for two different types of HTA assessments

HTA assessment type	Objective of the assessment	Data needed	Additional data if available
Budget impact analysis *(126), (134),*	To assess whether the antibiotic is affordable, relative to the treatment population, and considering the resource constraints of the country, i.e.: • to assess the likely financial impact of the antibiotic before it is implemented; and • to work out whether the antibiotics will be affordable within the budget constraints if it is recommended for use	• Population size (i.e. the prevalence and the incidence). The cases that require treatment and are likely to benefit from the antibiotic, including potential untreated individuals • Disease progression information – population and use by severity or stage • Budget period that will be impacted by health expenditure and cost savings • Projected uptake (e.g. 50% of those needing treatment are expected to receive it) • If the product replaces or supplements current antibiotic options • Costs to implement the antibiotic • Cost savings associated with introducing the antibiotic (e.g. expected reduction in hospital stays etc.)	• Avoided costs of treating other conditions
Comparative cost or cost minimization analysis	To compare the costs of two or more antibiotics that have equal clinical outcomes, i.e. safety and efficacy are the same	**Direct costs** • Antibiotic costs (e.g. purchase price and administration) • Health care services costs (e.g. hospital stays, physician visits, laboratory tests) **Clinical equivalence** • Clinical data that confirms the outcomes of the antibiotics being compared are the same	**Resource utilization** • Data on resource use per intervention (e.g. frequency of visits, duration of hospital stays) **Indirect costs** • Costs relating to patient outcomes, such as time lost from work or unpaid caregiving

Annex 8. High-level cost estimates, political alignment and securing financing

Securing political buy-in and ensuring financing is available to introduce an antibiotic is a necessary step before starting the planning and implementation stage of the introduction process. The cost of adding an antibiotic into the health system and how it will be financed are important considerations when deciding whether to move forward or not. **Reserve** antibiotics and some **Watch** antibiotics cost much more than most **Access** antibiotics. Even if the population using **Watch** and **Reserve** products is much smaller, the high unit costs can mean a greater cost to the budget. Alternatively, the smaller population size may mean the high unit costs are acceptable within the overall budget (refer to budget impact analysis in Annex 7).

Before developing a full costed implementation plan, it is prudent to estimate a high-level budget using what is already known about the public health and clinical need aspects, the product characteristics, and outputs from a HTA if feasible. This estimated figure uses benchmark estimates for assumed activities (e.g. infrastructure improvements, procurement, distribution, facility health care worker (HCW) training, operational research etc.). A high-level budget estimate can then be used to engage government officials responsible for allocating national budgets and health budgets to understand funding availability at a portfolio level, that could then be allocated to the antibiotic introduction.

It is also an important step to identify any major funding gaps and to consider if introducing an antibiotic is financially sustainable over the long term. This can be done in the form of developing a high-level policy or project brief, that can be used as a tool to advocate for resources to introduce an antibiotic. Countries can follow their own policy/project brief templates and processes for requesting to implement a policy or project with budget implications (if a local template is not available, refer to the antibiotic introduction policy/project brief template provided in Annex 9). This step will ensure political buy-in, support identification of available funding, and prioritize domestic resources (i.e. the contribution from the government), and help to secure resources for the work. Once there is a clear picture of available financing, and the antibiotic introduction plan has been designed, a full costed budget can be developed (see guide section 1.3 on Planning and implementation).

It is also useful to check that all steps involved in deciding to introduce an antibiotic have been considered and action taken where possible. The checklist in Annex 4 can be used to check all steps before moving to the next stage of the process.

Annex 9. Example policy/project brief template to introduce a Reserve antibiotic

Country X Ministry of Health and Ministry of Finance **Ref:** xx/xx **File:** xx/xx	**APPROVAL REQUIRED BY** **xx/xx/xx**

TITLE

Introducing a RESERVE antibiotic to treat multidrug-resistant organisms national-wide

PURPOSE

To seek approval from the Minister of Health to:

- Implement quality-assured antibiotic Y in high-risk areas through a phased approach.

RECOMMENDATIONS

That the Minister of Health:

- Note the potential impact of multidrug-resistant organisms on patients and the health system (as per available disease burden information).
- Endorse the proposal to introduce antibiotic Y as a priority for both the Minister of Health and the Minister of Finance.
- Approve funding of USD $x.x million over X years from the health budget to carry out planned activities.

IMPACT OF RECOMMENDATIONS

- **On patients:** Reduction of treatment failure caused by ineffective antibiotics.
- **On health care workers:** Better outcomes for patients and increased skills to identify and treat using the new antibiotic X.
- **On finances:** A budget of USD $x.x million over X years (20xx-20xx) is requested from the health budget to fund the introduction plan.

KEY ISSUES

•

BACKGROUND

•

CONSULTATION

•

Author: Policy Officer – Antibiotic Introduction Project Lead **Date:** xx.xx.xx

Approved by:

1. **Deputy Director, Food and Drug Department** [xx] **Date:**
2. **Minister of Health** [xx] **Date:**
2. **Minister of Finance** [xx] **Date:**
3. **Return to Author** [Policy Officer – Antibiotic introduction project lead]

TWO PAGE BRIEF/ EXECUTIVE SUMMARY

Policy proposal

Background

Target population

Stakeholders

Implementation

Monitoring and evaluation

Estimates of cost (see table below)

Budget impact analysis

Category	Y1	Y2	Y3	Total
Personnel				
Infrastructure and other equipment				
Commodities (antibiotics and other health care commodities)				
Supply chain warehousing and distribution				
Training, awareness and communication				
M&E				
Operational research				
Total				

Annex 10. Theory of change template

Goal/ objective: to address the public health and clinical need	**Access** antibiotics for empiric first- and second-line treatment options for common infections. **Watch** antibiotics for broader spectrum and have a higher potential of developing resistance. They are recommended as first-choice options only for patients with severe clinical presentations or for infections where the causative pathogens are likely to be resistant to **Access** antibiotics. **Reserve** antibiotics as last-resort agents used for multidrug-resistant infections.

Inputs	Activities	Outputs	Outcomes	Impact

Annex 11. Deciding on the antibiotic introduction approach

Once an antibiotic has been selected for introduction, it is important to decide on the introduction approach that suits the local infrastructure (e.g. facilities, logistics and supply chain), health care worker capacity, and the product characteristics of the antibiotic. Tailoring the approach to country context and health system factors will optimize the introduction success. The selected approach should align with and integrate into routine practices for all antibiotics, foster antimicrobial stewardship and promote continuous and equitable access to products.

There are many ways a country can choose to introduce an antibiotic. For example, a country may consider a phased-and-monitored, or pilot approach, or choose to simultaneously roll-out an antibiotic nationally. A phased-and-monitored approach allows for testing and refining antibiotic distribution and deployment before broader dissemination, while a national simultaneous roll-out may be suitable to respond to an urgent or widespread need (Fig. A2). A mix of these approaches sub-nationally might also be optimal, or a country may choose to design an entirely new introduction approach that has been co-designed through a multi-stakeholder approach. While antibiotics for bacterial infections generally do not fit within vertical programmes in LMICs (i.e. such as malaria, HIV or TB programmes), depending on the setting and resources, a country could consider an approach where a structured programme is designed specifically for last-line antibiotic treatments.

It is also important that deciding the approach considers stakeholders and partners in both the public and private sectors, and that existing or potential public–private partnerships (PPPs) are explored as an approach to introducing antibiotics, especially where access and availability are high in the private sector. The following case study presents an example of PPPs being used to steward the introduction and distribution of new antimalarial medicines into the private sector to facilitate last mile delivery and access.

Case study

Affordable Medicines Facility–Malaria (AMFm) to facilitate the introduction of higher priced antimalaria medicines into the private sector in LMICs

AMFm was a global initiative launched by the Global Fund to Fight AIDS, Tuberculosis and Malaria in 2009 *(135)*. The AMFm aimed to increase access to effective antimalarial treatments, particularly artemisinin-based combination therapies (ACTs), by reducing their prices and promoting their availability in both public and private sector outlets. The initiative aimed to curb the use of less effective antimalarials and to delay the development of drug resistance by making quality-assured ACTs more affordable and widely accessible, especially in the private sector. The AMFm worked by negotiating price reductions with ACT manufacturers and providing subsidies to both public and private sector distributors while at the same time supporting countries to introduce measures to enhance awareness, improve supply chain management, and monitor the programme's impact.

Governments worked to integrate AMFm-supported ACTs into public health facilities and ensure that they were available in both rural and urban areas. At the same time, national governments and health ministries, administered the subsidies provided by the AMFm that were intended to lower the cost of ACTs at the point of sale, making them affordable for the general population. The public sector was also responsible for regulating the distribution of ACTs, ensuring that only high-quality, WHO-approved treatments were provided under the AMFm programme.

The private sector, including pharmacies and private clinics, was critical in distributing subsidized ACTs to the population. The AMFm aimed to reach as many people as possible by leveraging the extensive networks of private sector distributors and retailers especially in rural areas where public health facilities were limited. At the same time, the packaging of quality-assured AMFm-funded ACTs was branded with a green AMFm logo as a strategy to monitor the product through distribution network and to communicate to purchasers that the product had been quality assured. By involving the private sector, the AMFm fostered competition among suppliers and retailers, which helped drive down prices and improve the availability of ACTs. The programme encouraged private distributors to source ACTs at the subsidized price and pass on the cost savings to consumers.

Overall, the PPP model adopted as part of AMFm contributed to its success in making ACTs more affordable and widely available in countries such as Nigeria, Ghana, Kenya and Uganda.

It is recommended that countries conduct a preliminary capacity assessment to identify the facilities that need the antibiotic and can appropriately use it. The capacity assessment should focus on identifying the number of facilities that will need to receive the antibiotic and facility readiness (i.e. those with current and/or potential capacity). Likewise, national and sub-national testing and diagnostic capacity should also be assessed (i.e. do facilities have existing diagnostic capacity? Is that capacity being used? If not, why? What is the current pharmacovigilance capacity of the clinical and laboratory network of a facility?) This assessment can inform what is realistic based on a country's capacity, the optimal roll-out strategies including where antibiotics are needed and how to deploy them, the urgency, and if old products need phasing out etc. Other capacities to assess include the facilities ability to manage the introduction of an antibiotic (such as staffing and beds to account for any anticipated changes in patient volume), facility infrastructure such as good availability of first- and second-line antibiotics, adequate refrigeration, energy supplies, water, sanitation and hygiene and IPC capacity. The capacity assessment should also help indicate if there is a need to strengthen infrastructure to safely introduce the antibiotic.

The main points of consideration when deciding on which introduction approach include:

1. **The number of antibiotics being introduced** (i.e. one or more than one, at the same time or staggered). If more than one antibiotic is being introduced at the same time, or around similar timelines, this might impact how and where to introduce each antibiotic.
2. **The urgency based on the volume of patients with MDROs needing treatment.** Consider if an antibiotic being introduced is needed to respond to growing number of patients being treated for drug-resistant infections. Also consider if it is an emergency, and if the emergency is national or limited to a specific area within a country. If the need is less urgent, introduction may lend itself to a more stepwise approach.
3. **The level of care where the treatment should be made available.** Consider where patients will be receiving the antibiotic (i.e. the antibiotic may be prescribed by doctors at primary health care facilities, it may be a hospital-only medication to treat severely ill inpatients, or its use is linked to testing capacity that may only be available at hospitals. This information should be available in updated nEMLs or in the WHO AWaRe antibiotic book. Most **Reserve** products are currently for tertiary hospital use only, but other antibiotics can be delivered through primary care or other facilities that have capacity to treat with **Watch** and **Access** antibiotics. With that in mind, the health care facility level (i.e. primary, secondary or tertiary care) where the antibiotic will be used will shape the approach. It is also important to consider where patients seek care and treatment with antibiotics (i.e. through the private sector or the public sector, at pharmacies or in clinics or hospitals etc.). Understanding treatment-seeking behaviour is important to understanding where there is the greatest need, but also to inform any new or enhanced stewardship measures as part of the selected introduction approach to safeguard the introduction of antibiotics.
4. **The location of facilities and links to other services.** Consider where facilities are located (i.e. are they in areas with high disease burden clusters or in large catchment areas). Also consider if the facility is linked to a referral centre. Likewise, consider if facilities are linked to the national referral laboratory (NRL), the national institute of health (NIH), or microbiology laboratories, can be linked to one, or have in-house services.

5. **The implementation of AMS programmes, processes, policies and sufficient capacity so the antibiotic is used appropriately.** Consider whether a facility is currently implementing an AMS programme, if there is an AMS committee, AMS team or individuals appointed to manage AMS within the facility. This should also include other relevant strategies including IPC and WASH activities. If facilities do not have these in place, then the approach should be adapted to ensure that there is time and resourcing to put this capacity in place before the antibiotic is rolled out.
6. **The current and potential infrastructure and capacity.** Consider facility capacity (including facility testing capacity) and catchment area, health care worker skills and capacities, microbiology laboratory capacity and links with facilities. Laboratory and skill capacity should also link to an assessment of current pharmacovigilance capacity and mapping. Consider the complexity of patient cases in terms of MDROs and the available resources. Priority might be given to facilities with an active DTC and/or AMS committee, or to those with the capacity to initiate one, have skilled health care workers, adequate testing services and clinical microbiology laboratory services to support accurate diagnosis, appropriate treatment and use. Some **Reserve** antibiotics and some of the antibiotics listed on the WHO EML may require specialized diagnostic or monitoring alongside specialist medical care, and/or specialist training.[5] Last-resort antibiotics will require capacity to conduct specialized in-house training or be well connected to laboratory services that can manage and absorb testing requirements. See Annexes 14 and 17 for additional capacity considerations when selecting sites and the introduction approach.
7. **The cost of different approaches**: Different introduction approaches will likely have different financial implications so the selected approach should also take into account potential costs.

[5] Antibiotics on the complementary list in the WHO EML are 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.

Fig. A2. An illustrative example of two selected introduction approaches that a country might consider

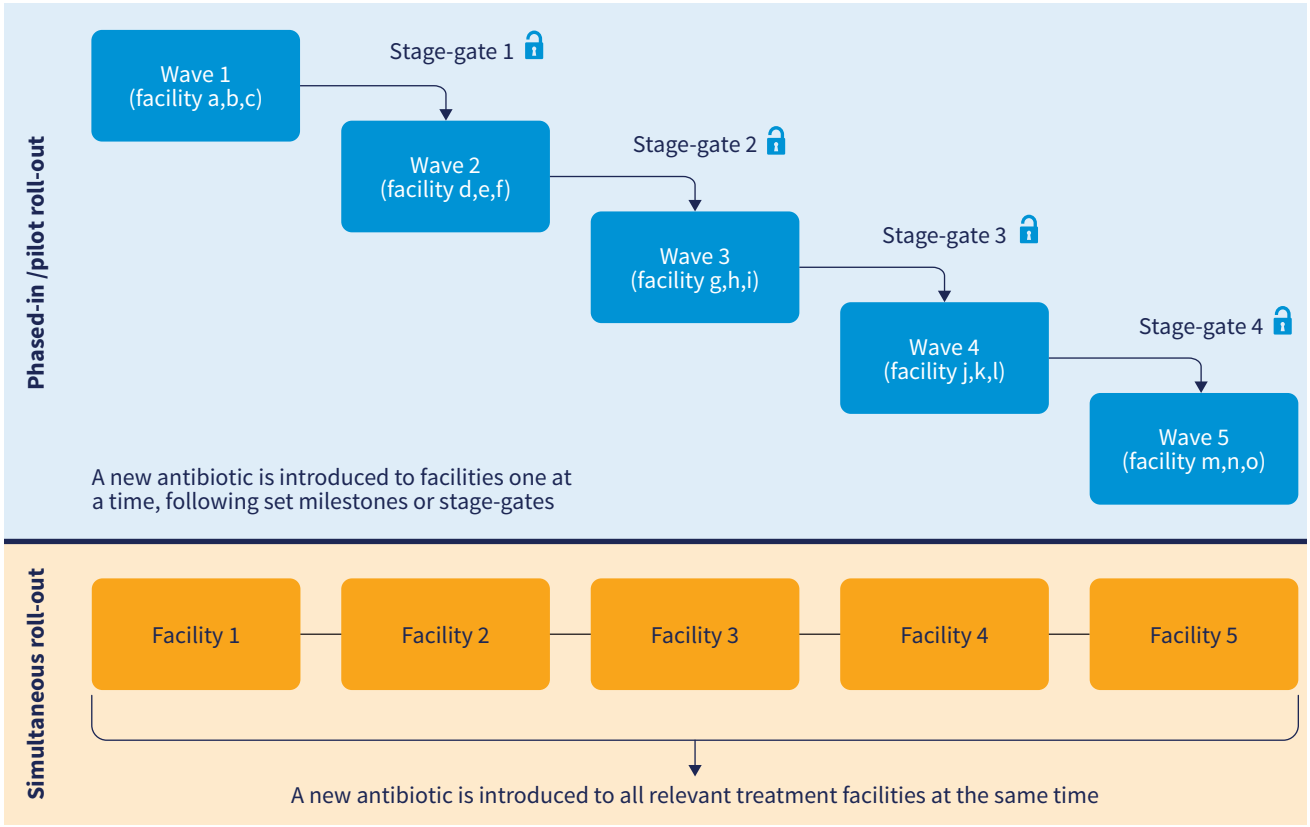


Table A4 outlines some considerations that can be worked through when selecting the approach to introducing antibiotics.

Table A4. Considerations for two selected approaches for introducing antibiotics

Introduction approach examples	Key considerations
Phased-and-monitored introduction	• A single antibiotic is being introduced with complex use measures. • Multiple antibiotics being introduced at the same time. • Pilot implementation is needed to identify and address programmatic or logistical challenges. • Only some target facilities have capacity, including infrastructure, to accommodate any increases in patient flows. • Only some target facilities can conduct the required specialized diagnostic and monitoring requirements, or are linked to a laboratory service that does. • Human resource capacity and the capacity to train and supervise staff restricts introduction to a select few districts or regions at a time. • The antibiotic is replacing an old one and time is needed to switch out an older product. • Total expenditure needs are not immediately available.
Simultaneous roll-out/national introduction	• In addition to the above considerations for a phased-and-monitored introduction, also consider if: • there is an urgent need calling for national roll-out; • existing infrastructure withstands national introduction; • the health workforce is prepared and ready to use the antibiotic and to implement within antimicrobial stewardship programmes.

Annex 12. Updating and adopting policies to support antibiotic introduction

If policy reviews when reviewing and assessing existing AMR and antibiotic relevant policies (Annex 6.1.3) indicate a need to update or adopt new policies, in this step take action to implement policy change.

If the selected antibiotic is not on the nEML, then the first action in this step is to start the process for its inclusion. In most countries, nEMLs can help prioritize medicines available in the public health sector. They can be referenced for streamlining procurement or reimbursement decisions among the thousands of medicines on the market. In most health care settings, especially in LMICs, the nEML serves as the basis for procurement priorities, as well as the development of national/standard treatment guidelines (STGs) and formularies. nEMLs in many LMICs have not been updated to include **Reserve** and **Watch** antibiotics that are listed on the most recent WHO EML *(73)*. For example, a 2021 study that compared antibiotics included in nEML across 138 countries found that of the 44 unique essential antibiotics (24 were **Access**, 15 were **Watch**, and five were **Reserve**), the median number of **Access** antibiotics was 18, 16 for **Watch** antibiotics, and one for **Reserve** antibiotics *(136)*.

Leaders, national coordinators, technical experts/advisors, in collaboration with policy-makers, regulators and NDTCs can work together to support nEML updates, which could then be considered by nEML committees for inclusion of the selected antibiotic on the national list. These stakeholders can work together to prepare the technical information and other materials required by nEML committees. National coordination functions and technical experts can play a lead role in compiling dossiers for nEML submissions.

nEML requirements may include:

- the most recent evidence demonstrating safety and efficacy;
- the antibiotic use case,[6] specifically stating special circumstances for use, any use limitations aimed at preserving the antibiotic's efficacy (e.g. prescribing restrictions, pre-authorization requirements etc.), and as required, emphasising that some second- and third-line treatments should only be used as a last resort;
- recommended level of care including treatment providers such as who can prescribe the antibiotic;
- evidence regarding comparative costs or cost-effectiveness (see Annex 7), overall budget impact assessment and broader health system benefits;
- letters from community groups, patients and clinicians emphasising the importance for inclusion.

[6] Note that Reserve antibiotics, except for linezolid, are currently for hospital use only, but other antibiotics can be delivered through primary health care and secondary facilities so the appropriate level of care should be articulated in the nEML dossier to ensure that it is reflected in the nEML.

While it might not be possible to add an antibiotic to an nEML immediately, plans should be developed around national schedules for updating nEMLs and timing activities so that the focus antibiotic(s) are included in the next update round.

In some countries, nEMLs may only target medicines used in primary health care. In this instance, some countries have developed specific lists or sub-lists to complement nEMLs that include medicines only for use in specialized health settings or higher-level health facilities. For example, South Africa has a tertiary and quaternary level EML *(137)*. These types of lists may be ideal for **Reserve** antibiotics as they can target use and reimbursements to facilities, and support stewarding use. Where these lists do not exist and current nEMLs target primary care, countries can consider developing specific nEML lists or sub-lists.

Other policy updates or new policies that might be needed include: adding or adopting the antibiotic into the NAP; developing or updating treatment protocols/guidelines in line with diagnostic capacity and stewardship and AWaRe principles; applying appropriate pricing policies, integrating the antibiotic into social health insurance (SHI) or reimbursement schemes; and incorporating the antibiotic into surveillance systems and policies to monitor patterns of use and the emergence of resistance.

Once policies are updated, consideration needs to be given to how these policies will be translated into practice. For facilities that develop their own treatment protocols based on national STGs, integrating antibiotics into facility-level STGs and treatment protocols will be needed, so it is important to ensure that any policy change is coupled with clear communication and supported by any necessary trainings to ensure fluid adoption from the national- to the sub-national level.

Some LMICs have active and mature NDTCs that make national-level decisions on nEMLs, drug policies, develop treatment recommendations on the appropriate use of all medicines, and they are then responsible for disseminating these to facilities. In other countries, this role might sit with another group within the ministry of health, or national coordinators like an AMS CC might work directly with facilities to support change and implementation.

This link between the national-level and facilities is explored in further detail in Annex 17. As an illustrative example of how the NDTCs can work to support disseminating new policies or STGs, their role may be to:

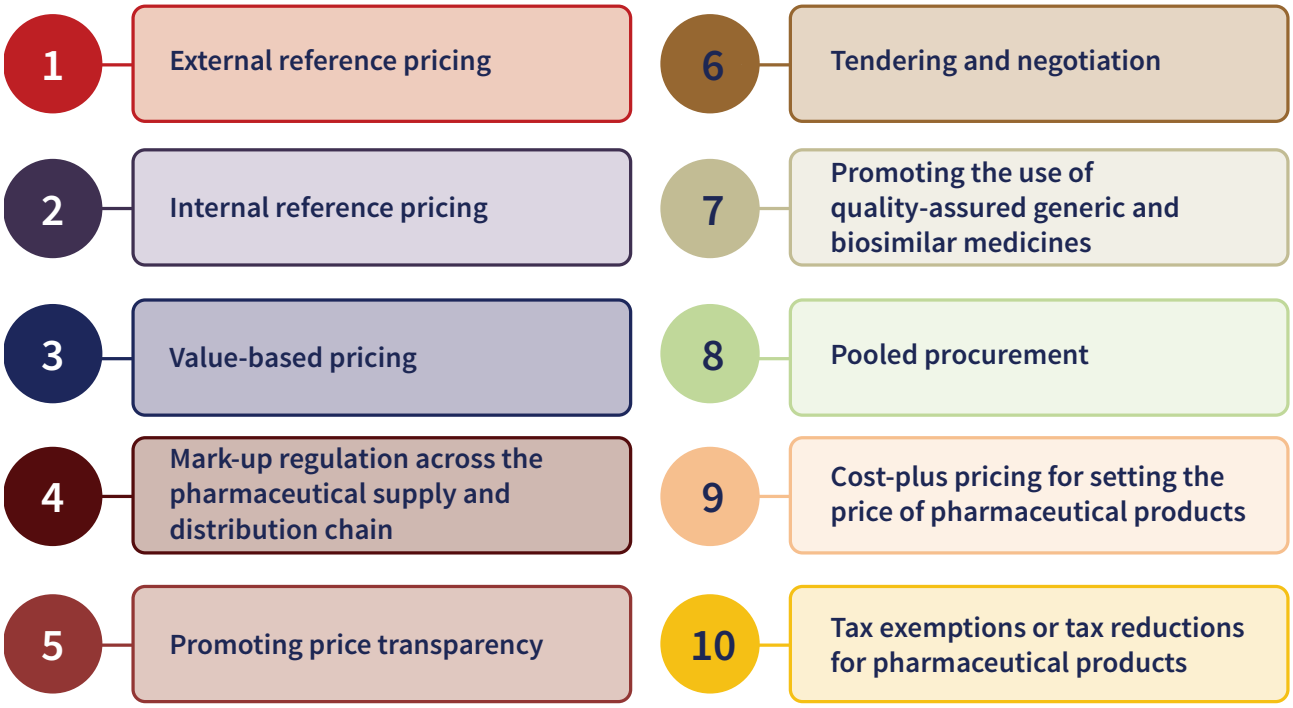
- evaluate and select drugs, based on nEMLs, for inclusion on the facility formulary list;
- craft and disseminate national STGs (including antimicrobial treatment guidelines), and treatment protocols, tailored to specific patient needs;
- develop antibiotic policies for facilities to adopt;
- support forming facility-level DTCs and/or AMS committees if appropriate to support the integration of the national policy.

12.1 Pricing and access policies to lower antibiotic prices

Given that most **Reserve** and some **Watch** antibiotics are high-cost, it may be necessary to plan and introduce strategic policies that aim to control costs and maximize coverage while preserving antibiotics. Note that pricing and access policies should be linked to regulatory activities (Annex 13) and procurement activities (Annex 15).

WHO has developed guidelines to support countries with implementing pricing policies and strategies, namely the WHO guideline on country pharmaceutical pricing policies *(35)*. The guideline includes recommendations on formulating and implementing policies relating to price management of, and access to, pharmaceutical products. The guideline covers 10 pricing policies (Fig. A3) that could be applied for setting, managing or influencing prices of products. Some of these policies may be relevant when developing pricing policies for antibiotics, so it is recommended that countries refer to these guidelines when considering pricing approaches. Pricing policies should be applied based on the antibiotic, setting and health system. It is also important that countries consider the relationship and link between different pricing policies, as more than one pricing policy might be needed, and the source and reliability of sources when using external information on pricing.

Fig. A3. Ten pricing policies that can be applied for setting, managing or influencing prices of pharmaceutical products



Source: Adapted from WHO guideline on country pharmaceutical pricing policies, second edition *(35)*.

The expensive nature of **Reserve** and some **Watch** antibiotics generally limits their availability in LMICs. For instance, in the public sector they are often stocked-out and even when available, they are not typically included in the benefits packages of health insurance providers (both public and private sector). Countries should also consider pricing strategies to manage the difference in price between the private and public sector, where public sector prices are generally much lower, and patients in the private sector frequently experience large out-of-pocket costs. For instance, WHO has previously reported that in about half of the countries in Africa, at least 40% of the total health expenditure is constituted of household out-of-pocket payments *(138)*. As purchasing antibiotics for multidrug-resistant infections in LMICs is unaffordable for many, and with their potential to save-lives, countries should consider including both testing for antibiotic sensitivity/resistance and second- and last-line antibiotic treatment in social health insurance (SHI) schemes or advocating for their inclusion the benefits package of private insurance providers.

Case study

The importance of including antibiotics for drug-resistant organisms in national insurance or reimbursement schemes: a clinical case study of managing a patient with a carbapenem-resistant infection in Nigeria

In Nigeria, there is a multi-step process in place to steward the use of second- and third-line antibiotics. When a patient with a carbapenem-resistant infection presents for treatment, the process includes: microbiological testing to identify the pathogen; a diagnostic and antimicrobial stewardship meeting on available management options; identifying the required clinical treatment (ceftazidime-avibactam); submitting a letter to the Director General of the National Agency for Food and Drug Administration and Control (NAFDAC) requesting to use the required clinical treatment (ceftazidime-avibactam); and receiving a positive feedback letter from the drug regulator as well as the market authorization holder, in this case Pfizer.

In a patient case in Nigeria, from initial presentation to treatment approval, 14 days had lapsed and even though treatment approval was granted, as ceftazidime-avibactam is not currently included in Nigeria's national health insurance scheme, the high out-of-pocket costs to the patient prevented access. Currently, in many countries including HICs and LMICs, there is limited coverage of antibiotics to treat drug-resistant infections on national health insurance and/or reimbursement schemes. This low coverage in many settings means access ultimately lies with the patient's ability to make out-of-pocket payments.

In low-resource settings, **Reserve** antibiotics are often not included in social health insurance schemes. This case highlights the challenges clinicians face with delivering urgent, life-saving treatments to patients, and emphasizes that even when there are sound stewardship steps in place, to ensure equitable access for all, countries should consider covering these life-saving treatments in national insurance schemes.

SHI can be closely linked to reimbursement schemes. Reimbursement schemes are when governments or third parties, like private insurers, pay for all or part of the costs of health care technologies. These types of schemes are not widely available in LMICs, but some countries have started to introduce them. As part of efforts to achieve universal health care, countries with active reimbursement schemes should consider the inclusion of antibiotics in these schemes. WHO defines the different approaches to reimbursement *(139)* as:

- Product-specific reimbursement: Eligibility for reimbursement depends on the medicine in question (i.e. either a medicine is considered as reimbursable or as non-reimbursable).
- Disease-specific reimbursement: Eligibility for reimbursement is linked to the underlying disease that shall be treated. The disease-specific reimbursement targets the reimbursement status and the reimbursement rate. A medicine may be reimbursed at different reimbursement rates for the treatment of different diseases. Specific programmes for some indications also fall under disease-specific reimbursement.
- Population group-specific reimbursement: Specific population groups (e.g. children, older people) are eligible for free medicines, or medicines at higher reimbursement rates, while others are not.
- Consumption-based reimbursement: The level of reimbursement depends on the expenses for medicines of a patient within a certain period of time (e.g. typically increasing reimbursement with rising consumption).

Countries should consider the benefits and risks of different pricing strategies for antibiotics. For example, external reference pricing may be considered if there are limited data available to conduct value-based pricing and HTA, but price accuracy can be difficult to obtain and requires a high-level of skill (e.g. prices collected from publicly available sources in comparison countries may not be accurate and may not reflect the final net price accounting for discounts, rebates and taxes etc *(36)*.

12.1.1 Pooled procurement as a pricing strategy for Reserve and some Watch antibiotics

For smaller markets introducing **Reserve** and some **Watch** antibiotics, coordinating pricing policies and pooling procurement across multiple countries, or a region, can create greater purchasing power and obtain favourable pricing.

Pooled procurement works through economies of scale and scope, as well as greater efficiency through sharing of human resources (i.e. expertise and workload), and the streamlining of procurement processes. Combining financial and non-financial resources and forming a single entity to purchase high-price low-volume antibiotics can help smaller countries/markets in accessing such products by leveraging additional volumes and creating better demand visibility for suppliers.

For smaller markets, regional or international pooled procurement examples include the Pharmaceutical Procurement Services of the Organization of Eastern Caribbean States, the pooled procurement services for member states of the Southern African Development Community, the Small Island Developing States pooled procurement initiative in the WHO African Region, and the group purchasing programme of the Gulf Cooperation Council. Some countries could explore pooling or coordinating procurement with neighbouring countries, but it is important to be aware of the legal and regulatory issues that may be encountered depending on the existing legal frameworks of each individual country.

Countries can also secure lower prices of medicines when purchasing products that are available through third-parties that implement pooled procurement such as: the United Nations Children's Fund (UNICEF) Supply Division; the Global Fund to Fight AIDS, Tuberculosis and Malaria; the Stop TB Partnership Global Drug Facility; and the Pan American Health Organization (PAHO) Regional Revolving Fund for Strategic Public Health Supplies. In larger markets, pooled procurement may be effective in bringing down prices nationally or sub-nationally where centralized procurement systems work to aggregate procurement across different sectors and purchasing streams. For example India, through the Central Medical Services Society (CMSS), has implemented a Centralized Procurement Agency (CPA). The CPA has played a key role in procuring medicines for diseases such as tuberculosis, HIV, malaria, and for various other public health initiatives *(140).*

12.1.2 Medicine access strategies and pricing

In terms of access strategies, and their link to insurance and reimbursement, some HICs have developed antibiotic payment models, such as reimbursement and subscription-based models, as well as revenue guarantees, to incentivize suppliers to operate in a country, but also to manage high costs and the overuse of novel antibiotics. Subscription style payments have been used in the United Kingdom, and revenue guarantees have been used in Sweden, for reimbursement of antibiotics at the national level where countries make fixed up-front payments each year for access to a predetermined quantity of antibiotics that is aligned with epidemiology and clinical/public health need, regardless of how much product is utilized *(141).*

Subscription style payments are not only relevant for HICs and can be considered for adoption in LMICs *(142).* Access strategies can have varied benefits or consequences, so they should be considered based on the antibiotic, the country context/health system, and the problem that the policy is trying to solve. For example, some marketing authorization holders may withdraw applications if a country pushes for pricing that is below a companies' profit-to-loss ratio limits. This can be a particular problem for countries with smaller markets, and so exploring alternative price-lowering solutions such as regional or pooled procurement may achieve better outcomes.

12.1.3 IP laws and pricing

IP laws also play a critical role in shaping the pricing and procurement of antibiotics in LMICs (see Annex 2.2.1 Intellectual property management), especially through their potential to influence and increase in the supplier base, creating competition.

Competition law and policies have an important role to play in enhancing access to health technologies and fostering innovation. Unwarranted restrictions on competition, whether resulting from the abuse of a dominant position resulting from intellectual property rights or other factors, or anti-competitive agreements, can be addressed through competition law enforcement.

12.1.4 Currency fluctuations and pricing

With most **Reserve** and some **Watch** antibiotics requiring importation, it is also important to plan for the impact of currency fluctuations in LMICs and the impact on affordability and pricing. When the local currency weakens against foreign currencies, the expenses incurred in procuring medicines rise, driving up the overall prices of medicines in the country. A December 2023 Premium Times news article detailed how the local retail price of Ampliclox 500mg packs in Nigeria increased by over 1000% between 2019 and 2023 due to the devaluation of the local currency against the dollar *(143).*

Annex 13. Preparing for antibiotic registration/market authorization

Regulatory planning is an important step in introducing an antibiotic. Carefully planning regulatory activities can avoid unnecessary market authorization delays and enable access. Additionally, assuring the quality of products is of paramount importance and national regulatory authorities (NRA) play an important role in safeguarding the availability of safe, efficacious and quality-assured products. Introduction plans include collaboration and partnership with NRAs and should be centred on a collaborative approach to prevent any regulatory delays.

For **Reserve** and **Watch** antibiotics, suppliers may be reluctant to apply for marketing authorization in LMICs because demand is too low or the market is too opaque for the supplier to have confidence that registering a product will yield a positive return *(37,38).* In some cases, specific data requirements for antibiotics may also lead to slowing the registration process or increasing costs to register a product, which a company may find cost-prohibitive and consequently decide to not submit a registration application or rescind an existing application *(38).* This emphasizes the importance of engaging with NRAs closely when planning to introduce an antibiotic.

Collaborating with NRAs is important for implementing and streamlining facilitated regulatory pathways that can support the quality assurance of antibiotics, as well as for developing and implementing policies that can apply to antibiotics, such as granting accelerated approval for use. Pathways to reviewing and updating regulatory policies, treatment guidelines and legislation to facilitate regulatory expedited approaches need to be accessible to both policy-makers and registration applicants to avoid delays.

Some examples of facilitated registration pathways available to countries and respective NRAs that aim to accelerate antibiotic registration are identified in Annex 2.3. These include the collaborative registration procedure (CRP) for products prequalified by WHO or approved by SRAs/WHO-listed authorities (WLA), and regional joint assessments. NRAs may have already set up expedited regulatory approvals for other products critical to public health (e.g. for orphan drugs or for urgent life-saving treatments). It is therefore important to verify in advance whether an antibiotic needed for a clear or urgent unmet medical need would fit within existing fast-track pathways. A collaborative approach with the NRA, project leadership, national coordination and technical experts responsible for the antibiotic selection can guide an understanding if this would be the case. If not, changes may need to be explored with the NRA to ensure preparedness. Such expedited regulatory approval, emergency use waivers, or orphan drug pathways may also allow fee waivers/reductions or have built in pre-submission meetings and allow for rolling submissions. It is generally recommended that NRAs make adequate use of reliance to accelerate and simplify the approval of medical products already authorized by trusted reference regulatory authorities, such as WLAs. Exploring these options is especially relevant for **Reserve** antibiotics that are very low volume.

Some countries that conduct HTA (see Annex 7) to understand the cost-effectiveness of products may require data that can demonstrate superiority to already available products (i.e. data demonstrating additional clinical outcomes). However, most trials for antibiotics are based on non-inferiority clinical trial designs, which does not account for any additional benefits of new products *(144).* These are all common challenges for suppliers of **Reserve** and **Watch** antibiotics, especially the former, where the volumes are very low, use is often restricted and obtaining required clinical trial data can be complex and expensive.

There should be close collaboration between the leadership, national coordination, nEML committees, the NDTC and the NRA in defining, informing and enforcing the prescription and delivery status of antibiotics. Adequate recommendations should be provided in the product information to support the good use of antibiotics. NRAs can play a role in enforcing marketing restrictions (i.e. prohibiting marketing authorization holders from marketing **Reserve** antibiotics at lower levels of care and/or restricting who they can market to). NRAs can also support active pharmacovigilance activities through collaboration with public health programmes to strengthen the monitoring of the safety of these antibiotics in the general population.

Various strategies and approaches can be considered by an NRA to address access challenges for **Reserve** and **Watch** antibiotics:

- Incentivize antibiotic registration through adequate implementation and use of facilitated registration pathways (FRPs). This can accelerate the approval of antibiotics, and if appropriate reduce the resources, time and workload required for the registration of an antibiotic for all relevant parties (see Annex 2.3).
- Implement reliance mechanisms to leverage outputs of other regulators and organizations (e.g. WHO CRPs and WLAs) whenever possible. This will allow for greater focus on national level value-added regulatory activities.
- Incentivize registration by explicitly recognizing new antibiotic chemical entities targeting serious or life-threatening infections as a critical unmet medical need, and formalize their inclusion in regulatory frameworks for accelerated drug approvals.
- Consider allowing fee waivers/reductions and build in pre-submission meetings in the early stages of dossier preparation and rolling submissions, allowing applicants to submit dossier sections in a staged process, rather than all at once.
- Participate in regulatory harmonization and convergence initiatives for accelerated approval of antibiotics as part of the global and regional coordination in the fight against AMR:
  - Advocate that regional harmonization initiatives should add **Reserve** and **Watch** antibiotics to their priority list of products considered for regional review.
  - Establish memoranda of understanding to facilitate collaboration, trust building and exchange of information between NRAs.
- Support appropriate use by incorporating data monitoring and reporting requirements into dossier submissions, and/or including labelling requirements that manage or restrict prescribing new antibiotics.
- Foster the implementation of pharmacovigilance measures by facilitating integration between the pharmacovigilance and public health programmes, and consider the needs for active pharmacovigilance activities

- Ensure regulatory systems are based on well-defined and strengthened market surveillance regulatory processes capable of identifying and rejecting sub-standard or non-recommended antibiotics.

For all medicines including antibiotics, a strong regulatory environment is required to ensure access and appropriate use. Some strategies for a strong regulatory environment overall include:

- Define and enforce clear rules and regulations for antibiotic prescribing and sales through close collaboration across relevant stakeholders, including inspection of pharmacies and adequate recommendations in the approved product information.
- Regulate safe and proper disposal of unused or expired antibiotics, reducing environmental contamination and the risk of AMR spread through wastewater and agricultural run-off.
- Establish a regulatory framework for the quality control of all antibiotics to comply with pharmacopoeia standards across both public and private channels. Enforce national guidelines and international best practices on substandard and falsified or non-recommended antibiotics. This could include the expanded use of smart technology for monitoring entry of unregulated products into the market.

Annex 14. Preparing testing and surveillance systems

A cornerstone for introducing antibiotics and ensuring antimicrobial stewardship is the availability of a robust national laboratory and diagnostic network. Strong laboratory and diagnostic capacity are needed both nationally, connected to facilities, and within facilities, for timely diagnosis and for running optimal surveillance programmes.

All antibiotics should be prescribed based on local treatment protocols that support good antibiotic stewardship practices. This involves prescribing antibiotics empirically or following test results, depending on the antibiotic, scenario and health system. A general exception to empiric treatment is for the use of **Reserve** antibiotics, where use should ideally follow test results. However, it is important to highlight that in cases of severe, life-threatening infections with an MDRO, **Reserve** antibiotics may be used based on empirical knowledge or in combination with other treatments prior to, or in the absence of, antibiotic susceptibility testing (AST) results. This is because early treatment of MDROs with a **Reserve** antibiotic has the greatest benefit and delaying use until after AST results are available may decrease health benefits. After treatment initiation, laboratory and diagnostic capacity is also important to support treatment modification if needed, for example, culture testing and results may indicate a need to either step-up or step-down use. For these reasons, it is paramount to ensure that treatment protocols are updated to reflect different scenarios and settings, and that they are based on the local laboratory and diagnostic capacity for the antibiotic being introduced (see Annex 12)

Moreover, some **Reserve** antibiotics and other antibiotics listed on the WHO EML require specialized testing for the confirmation of antimicrobial susceptibility of resistant isolates. Despite this important need, and that this capacity is needed for introducing many antibiotics, many LMICs lack the necessary infrastructure or have not established the protocols needed to conduct specialized testing, deliver time-appropriate results and track antibiotic resistance and susceptibility (although laboratory capacity can vary widely from country to country, or even within a country).

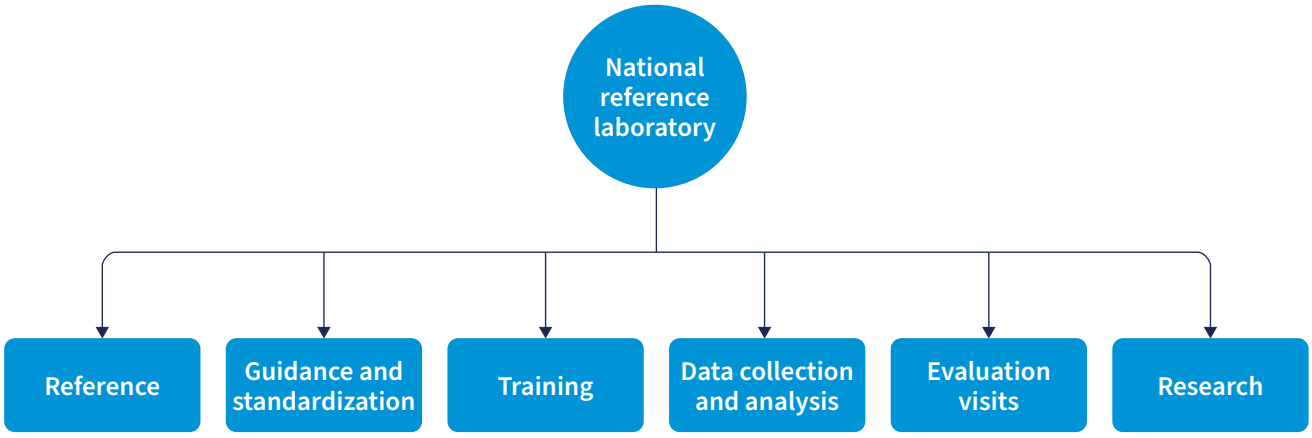
14.1 The role of national-level bacteriology laboratories and diagnostics

At the national level, some countries have established laboratory and diagnostic capacity entities to coordinate and develop technical standards and provide certification for laboratories (e.g. Clinical Laboratory Improvement Amendments (CLIA) *(145)* in the United States, and the United Kingdom Accreditation Service (UKAS) *(146)*). In some LMICs this role is coordinated by the national reference laboratory (NRL) or national institute of health (NIH) that coordinates related activities including quality assurance programmes for the laboratory network, mainly in the public sector. In countries with an NRL or NIH, or similar function, these can play a key role in supporting the introduction of antibiotics to

countries. For example, they can support the development of national guidelines for the laboratory network, coordinate and assess quality assurance programmes, coordinate surveillance activities in conjunction with the national body, and support the performance of specialized tests and methods for the confirmation and characterization of pathogens and antimicrobial resistance. Due to the specialized role and capacities, an NRL or NIH can provide support to hospitals and health care facilities where laboratory capacity is scarce.

The WHO GLASS guidance for national reference laboratories *(48)* focuses specifically on the functions and activities of NRLs for national surveillance of AMR. Details of the various functions are provided, including reference functions such as confirmation and characterization of resistance mechanisms, quality control for surveillance sites, external quality assessment, outbreak support, guidance and standardization, test validation and verification, providing training, data collection and analysis for national surveillance of AMR and laboratory assessments. Fig. A4 shows the type of support an NRL can provide to microbiology laboratories.

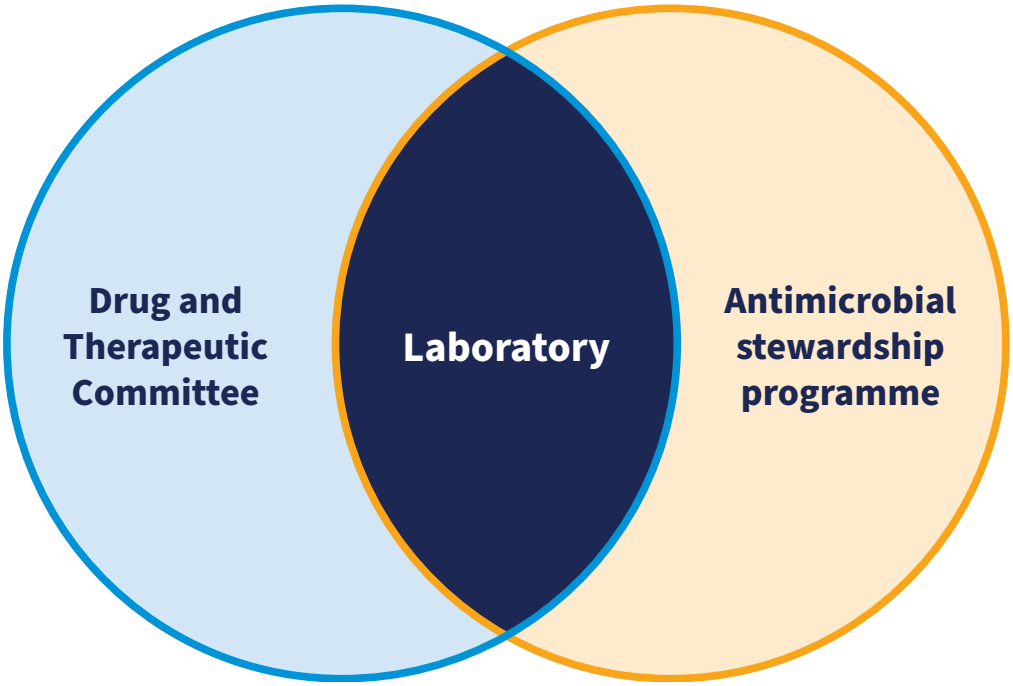
Fig. A4 Overview of the type of support NRL or NIH functions can provide to microbiology laboratories



14.2 The role of health care facility level bacteriology laboratories and diagnostics

In many health care facilities, the microbiology laboratory is a key component to support and provide routine diagnostics, including culture, identification, characterization of microorganisms, and AST. Its role goes beyond routine diagnosis, and it is a critical component for local AMR surveillance, and for informing facility functions working to support the antibiotic introduction such as the facility drug and therapeutics committee (DTC), AMS and IPC programmes (see Annex 17.1.2). Such laboratories provide the information needed for AMR monitoring, and for facility functions and programmes like a DTC, IPC and AMS programme to monitor antimicrobial use, changes to antibiotic effectiveness, the prevalence of MDRO and to evaluate AMS interventions. The microbiology laboratory has a central role in supporting facility-level antimicrobial introduction and stewardship (Fig. A5).

Fig. A5 The central role of the microbiology laboratory between two example facility-level programmes to support antibiotic introduction



In many LMICs, microbiology laboratory capacity is still a critical challenge at the facility-level. Lack of access to diagnostics, sub-optimal testing, and weak performance is common in many low-resource settings. There are many potential reasons for sub-optimal testing and weak laboratory and diagnostic capacity, including: a limited skilled workforce (i.e. microbiologists); weak supply chains and procurement systems; poorly connected sample transport and referral systems, and complexities in specimen referral for bacterial diagnosis due to specimen viability and turnaround time requirements; the limited availability of inexpensive reliable diagnostic tests; inadequate financing; a lack of political will to expand testing capacity; a lack of standardized protocols for data collection; poor collaboration and information sharing between laboratories, facilities and government agencies; and challenges with integrating surveillance activities into routine health care practices. Once capacity weaknesses have been identified (see Annex 11), activities to improve capacity are needed to safeguard the introduction of antibiotics.

WHO has developed, and continues to improve, tools and guidance for countries to improve laboratory capacities and performance. The Antimicrobial Resistance Diagnostic Initiative *(14)* supports countries in strengthening microbiology laboratory capacity and providing equitable access to quality testing for bacterial, fungal and resistant pathogens at all levels of the health system and in the community. These efforts aim to ensure the appropriate utilization of diagnostics to support patient management, AMS initiatives, IPC measures, outbreak investigations, and routine AMR surveillance.

14.3 Microbiology laboratory and diagnostic capacities in support of the introduction of antimicrobials

Diagnostic capacities are crucial for health care facilities in the introduction of antibiotics. The AMR local situation depends on the continued monitoring of the most common infectious diseases, syndromes, and pathogens in hospitals. A major problem in many LMICs is that laboratories often do not have the necessary procedures, equipment and reagents for AST *(147).* Additionally, many laboratories do not have the right tools available or standard operating procedures (SOPs) in place to conduct regular molecular testing and whole genome sequencing that can identify genetic mechanisms underlying resistance.

With limited laboratory capacity, and without inexpensive reliable diagnostic testing or standard operating procedures (SOPs) to support clinical decisions based on susceptibility, clinicians are more likely to treat with broad spectrum antibiotics. For example, it has been estimated that up to 50% of all prescribed antibiotics are either unnecessary or are not properly 'matched' to the susceptibility pattern of bacteria causing the infection (i.e. treatment is not changed following laboratory testing) *(148).*

The following list outlines the minimum capacity requirements for microbiology laboratories so they can provide key information of the local situation to facility functions overseeing and managing the antibiotic introduction (i.e. such as a DTC, AMS or IPC programme) , as well as antimicrobials more broadly.

- Well trained staff.
- Adequate equipment and diagnostic supplies.
- Standard operation procedures.
- Standards on AST (e.g. refer to established guidelines such as Clinical and Laboratory Standards Institute (CLSI) *(50)* or the European Committee on Antimicrobial Susceptibility Testing (EUCAST) *(52)).*
- Laboratory information system.
- Quality assurance system (such as participation in proficiency testing).

14.4 Scenario considerations to support the introduction of antibiotics

Countries should consider the capacities needed to perform AST based on the availability of clinical breakpoints of new antimicrobials.

- For antibiotics with standardized AST breakpoints countries should implement the methodology based on their capacities and the availability of resources. In case of no available resources, countries can be supported by regional or supranational centres (e.g. WHO Collaborating Centres (WHO CC)).
- For antibiotics without standardized breakpoints countries should consider the revision of existing scientific evidence or contact Regional or Supranational Centres (e.g. WHO CC) for support.

As laboratory and diagnostic capacity is a challenge in many countries, especially in LMICs, the following scenarios and suggested approaches can be considered by countries to support the introduction of antibiotics:

Scenario 1. No laboratory capacities in place

Countries with a weak or without laboratory and without NRL/NIH can be supported by regional or supranational reference centres (e.g. WHO CC).

Scenario 2. Weak Laboratory capacities

Countries with weak laboratory capacities can be supported by the NRL/NIH, which can implement AST for all health care facilities and provide the information to monitor the newly introduced antibiotic, while capacity to perform targeted AST is being strengthened in stepwise manner.

Scenario 3. Laboratory capacity in place

Countries with capacities in place should implement standard AST and include the newly introduced antibiotic as part of the routine surveillance system.

Case study

Overcoming uptake barriers to introduce tafenoquine alongside a new G6PD diagnostic test

Malaria remains one of the most persistent public health challenges globally, and *Plasmodium vivax* malaria remains a major challenge for Asia and the Americas where it is mostly prevalent. Tafenoquine, a new antimalarial drug to prevent relapses by targeting the liver stage infection of *P. vivax*, received SRA approval in 2018, offering an advantage over the older 7-to-14-day primaquine regimen by providing a single-dose treatment. The correct use of tafenoquine requires first establishing a patient's G6PD (glucose-6-phosphate dehydrogenase) status; this is determined with a quantitative G6PD test, to avoid treating patients with insufficient G6PD activity who are at risk of haemolysis when treated with any 8-aminoquinoline (i.e. tafenoquine or primaquine). Additionally, as tafenoquine is intended to complement and enhance existing malaria treatment protocols, rather than replace them entirely, its introduction needs to be integrated into existing treatment protocols.

Despite its potential benefits and approval by SRAs and NRAs, tafenoquine's introduction faces numerous challenges before it can be globally adopted. Challenges include: the higher cost of tafenoquine compared to older options, plus the need for a new G6PD diagnostic; a single supplier market coupled with low-volume sales following SRA approval; global policy delays; implementation challenges with the need for system-wide training to use the medicine and diagnostic; and product label use restrictions limiting tafenoquines use in a large portion of vivax malaria patients globally.

Case study (cont.)

The Partnership for Vivax Elimination (PAVE), a global collaborative response led by Medicines for Malaria Venture (MMV) and PATH, has been at the forefront of efforts to overcome these challenges. PAVE brings together national malaria programmes, researchers, funders, and other organizations with the shared goal of eliminating *P. vivax* malaria. Key strategies adopted by global partners include:

- Real-*w*orld feasibility *s*tudies.
- National adoption support (policy and practice) with early engagement with national malaria control programmes.
- Effectiveness data collection through the TRuST study in Brazil *(149).*
- Convening for cross-country experience exchange.
- Evidence generation for global guidance.

While significant challenges remain, the collaborative efforts of global and national stakeholders are supporting the successful introduction of a new product where there is a public health need. Overcoming barriers related to affordability, diagnostics capacity, regulatory approval and operational feasibility are key to ensuring optimal treatments are available to patients at the point of care. Additional clinical work will be required to determine how tafenoquine may be used in countries that have adopted artemisinin-based combination therapies (ACTs) for the blood stage treatment of vivax patients.

Lessons from PAVE for countries introducing antibiotics:

- Engage early with national policy-makers and update national policies based on emerging evidence.
- Explore regional regulatory cooperation and harmonization pathways.
- Address affordability and cost-effectiveness.
- Strengthen supply chain security.
- Ensure diagnostic availability and integration.
- Enhance operational feasibility and training.

A full extended overview of this case study, plus detailed lessons for antibiotic introduction can be found in Annex 20.1.3.

Annex 15. Procurement

Procurement planning for antibiotics, especially for **Reserve** and **Watch** antibiotics is crucial to ensuring sustainable access and is also a way to manage antibiotic use rates and antibiotic preservation. As **Reserve** products should only be used as a last resort, by nature, actual procurement volumes will be low. Low volumes, alongside inadequate demand planning and demand visibility, and inconsistent procurement practices, contributes to a cycle of low volumes and high prices for these high-priority products. At the same time, many of these products are relatively new to market and there may only be one supplier if the product is on-patent, which can also keep prices relatively high. On the other hand, while demand is comparatively large for **Access** antibiotics, there have been global stock-outs and shortages due to demand peaks caused by global increases in certain infections, as well as cessation of manufacturing of some products due to lack of return on investment. For example, shortages of amoxicillin in combination with clavulanic acid for paediatrics have been documented in Europe with manufacturing delays and production issues unable to meet increased demand *(150).* Many LMICs have also experienced frequent stock-outs and shortages of amoxicillin and gentamicin due to changing or inconsistent demand *(151).*

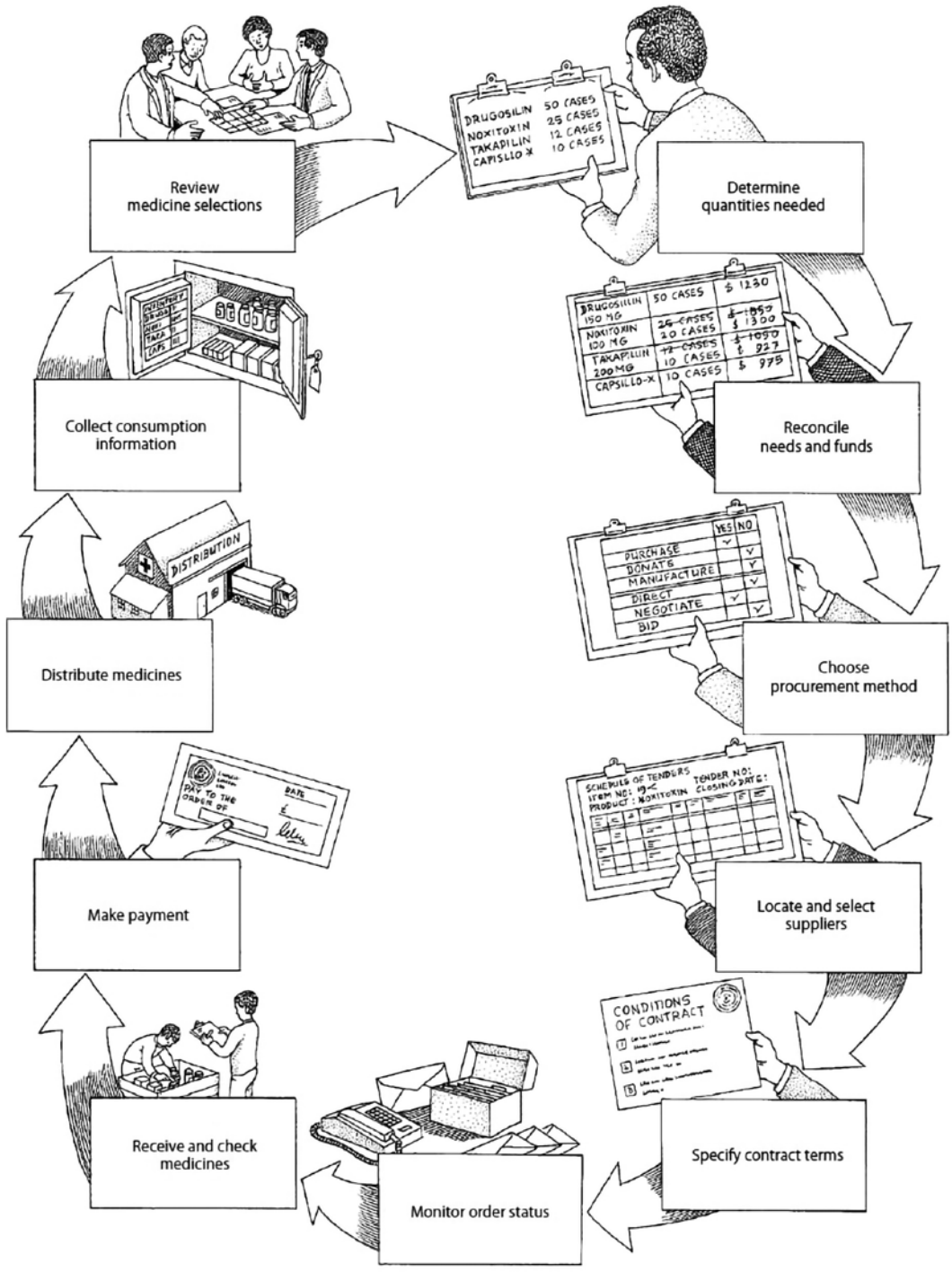
Many companies have indicated that low and unpredictable demand, as well as poor demand forecasting are reasons for not entering a market and a reason for high, unstable prices *(37,53).* Sound procurement planning, supported by accurate demand quantification, can help alleviate this tension with the antibiotic supplier, helping to secure supply.

At the country level, LMICs often face challenges meeting minimum order quantities due to limited country procurement budgets but also due to the overall need being low, especially for many **Reserve** antibiotics where the use is restricted to last resort treatment. For **Reserve** and some **Watch** antibiotics, procurement strategies such as pooled or coordinated procurement (see Annex 2.2.6 and Annex 12.1.1) can be explored to overcome low volume access barriers, obtain optimal prices and secure supplies. In some countries there may also be over-marketing and promotion, creating perverse incentives for suppliers and prescribers that can sometimes result in an overuse of antibiotics, or the widespread availability of unregulated products. Establishing efficient procurement planning and management can help address some of these challenges.

Procurement management should include a wide range of activities that consider many different components of the supply chain. Specific guidance on managing overall procurement and supply chain issues have been developed by WHO, such as *Principles and processes for managing procurement (55)*. Additionally, other organizations, such as Management Science for Health (MSH), have also developed useful procurement guidance tools *(56)*.

Fig. A6 illustrates the different steps of the procurement cycle that need to be implemented to ensure efficient and consistent supply and supports timely treatment access.

Fig. A6 The procurement cycle



Source: Figure adapted from *(56)*.

Frequent stock-outs of antibiotics in LMICs calls for improved demand forecasting, quantification and procurement practices. Data on demand and consumption of antibiotics is not routinely collected and tracked at national and sub-national levels, which in turn leads to inaccurate demand forecast and stock-outs. In many countries, antibiotics in the health systems are procured through various sources, including central procurement (via national and state/provincial level tenders), direct sourcing by hospitals in the public and private sector, and direct sourcing by patients via pharmacies. Procurement and data management systems across these three channels are not harmonized, making demand consolidation across the channels very difficult. National demand planning exercises for antibiotics, unlike what exists for HIV, malaria and other donor-supported products, is currently not commonplace in LMICs.

The absence of clear demand forecasts makes supply planning difficult and can discourage manufacturers from seeking marketing authorization. It also makes it difficult for any one buyer to achieve manufacturer minimum order quantities, particularly if the local distributor is not keeping sufficient stock on the ground, which is often the case for low-volume high-value products. For these reasons, in planning for the introduction of antibiotics, it is important that efforts are made to include antibiotics, especially newer classes of antibiotics, into existing in-country demand planning exercises.

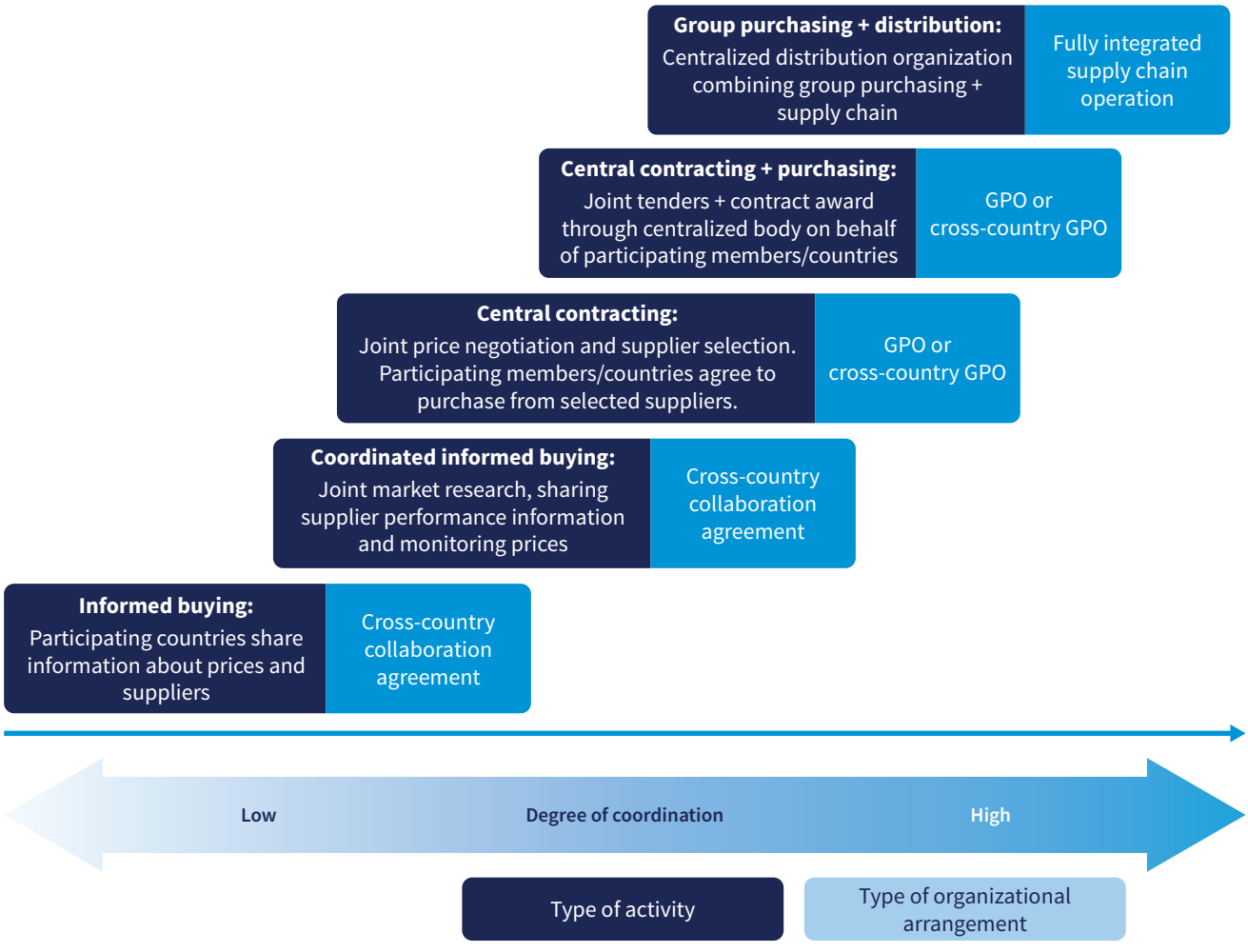
Demand planning is a supply chain management system of forecasting or predicting the future demand for products to ensure that plans can be made to meet the demand. Demand planning is seen as an essential exercise that reduces the risk of stockout and increases predictability for suppliers.

Alongside demand planning, countries can also consider a range of procurement strategies to facilitate the adequate and timely procurement of antibiotics. While there are many strategies that a country can adopt, it is important that countries consider the advantages and disadvantages of each solution, and assess which ones work best for each individual antibiotic, as the same approach might not be suitable for all products. Some procurement strategies that countries can consider are listed below.

- **Centralize demand planning and procurement processes** to optimize resource allocation and ensure a steady supply. This centralized approach facilitates bulk purchasing, which can lead to significant cost savings and more predictable demand for manufacturers.
- **Include newer classes of antibiotics into existing in-country forecasting and demand planning exercises.** Demand planning should utilize data available from surveillance systems as a basis for needs estimates. This information is central to appropriate forecasting. It is important to note that data might be limited for effective demand planning and so initial estimates likely need to be based on the disease burden and the expected use rate. This approach may overestimate the need and so a careful quantification process is needed to rationalize need, demand and 'realistic' demand. Demand planning should also include the necessary diagnostics and laboratory infrastructure that introducing an antibiotic requires.
- **Consolidate demand within countries and align procurement plans at the national level.** This can include collaboration with the private sector and other channels to aggregate overall national demand. Procurement planning should take a total market approach that leverages private sector volumes, or volumes from other channels (e.g. the military) and the higher willingness-to-pay threshold. Including the private sector in demand planning could achieve the minimum volume requirements for some antibiotics. It could also opportunistically allow for better data surveillance and use monitoring in the sector, which can be opaque.

- **Consider skill-sharing or job-shadowing across other disease programmes to guide demand forecasting and quantification exercises.** Significant sourcing and distribution infrastructure has been built around vertical disease programmes (e.g. HIV, TB and Malaria) that can be leveraged in the short to medium term as in-country AMR programmes mature and volumes gradually become substantial. For example, to address low demand for antimalarial medicines for countries progressing towards malaria elimination, the PAHO Strategic Fund, in collaboration with the Regional Malaria Program, has developed an innovative tool for planning antimalarial medicine needs – Quantmet Malaria *(152).* The tool focuses on local stratification to maintain minimum a volume inventory, which is then distributed based on risk level, protocols, and parasitic resistance profile. The tool is currently being piloted, but the methodology applied to improve procurement planning could provide useful insights to procurement planning for low-volume antibiotics.
- **Participate in global or regional pooled procurement initiatives.** Despite thorough forecasting and quantification, country procurement volumes may not meet the minimum volumes for a company to fill orders. In these instances, consider participating in global or regional procurement efforts, or see if pooling or coordinating demand across a small number of countries within a region is sufficient to satisfy minimum volume thresholds.

Fig. A7 Different pooling activities and types of organizational arrangements



Source: (54).
Note: GPO: Group purchasing organization.

- **Understand and know available procurement channels, and the antibiotics available for procurement via different channels.** For products being procured through regional or global pooled procurement mechanisms, ensure procurement plans align with the associated requirements and timelines (e.g. SRA or NRA approvals), and that procurement plans are communicated to procurement entities, donors and/or suppliers to support visibility of global demand.
- **Conduct source and supplier mapping.** Launch expressions of interest to support supplier mapping, gauge possible suppliers' willingness and ability to supply, and obtain pricing information.
- **Know national pricing policies** and ensure that procurement is aligned with pricing policies:
  - For antibiotics with more than one supplier, consider tender processes when procuring antibiotics to ensure a fair, transparent, and competitive process.
  - For single source antibiotics, engage with the company to know if tiered pricing is offered by the originator company or if the company would do voluntary licensing for countries considering local manufacturing or importing generic versions.

Spotlight

A snapshot of regional pooled procurement initiatives

In LMICs, orders for many **Reserve** and **Watch** antibiotics usually come directly from prescribing physicians and facilities. Orders are generally small quantities and there is often limited order consolidation at the health system level to increase economies of scale and market attractiveness for suppliers. Regional procurement entities are currently considering how to make more antibiotics eligible for procurement through their existing mechanisms with a particular focus on antibiotics for MDROs. However, these mechanisms are at varying degrees of functionality and not every country is eligible to procure through these mechanisms.

The PAHO Strategic Fund is a mature, successful regional pooled procurement mechanism, procuring hundreds of products annually for Member States in the Region of the Americas. Through a regional approach, better purchasing power has contributed to lower prices for vaccines, medicines and other health care products. PAHO both centralizes procurement orders for multiple countries, but it also concentrates procurement if there is a specific health area that requires a special focus. It is fully dependent on Member State requests, so even when access gaps, regional product needs or supply issues are identified, PAHO cannot expand the product offering or advocate for procurement until there is a request from a Member State. For example, ceftazidime-avibactam is eligible for procurement via the PAHO Strategic Fund, but no Member States have requested to procure this product via the fund (as of June 2024).

The Organization of Eastern Caribbean States (OECS) has been operating since August 1986 with nine participating countries: Anguilla, Antigua and Barbuda, British Virgin Islands, Dominica, Grenada, Montserrat, Saint Kitts and Nevis, Saint Lucia, and Saint Vincent and the Grenadines *(98).*

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The Gulf Joint Procurement Programme run by the Gulf Health Council started in 1976 with six countries: Bahrain, Kuwait, Oman, Qatar, Saudi Arabia and United Arab Emirates, later joined by Yemen in 2003. Today, the programme meets 80% of their collective procurement needs. Its success has been attributed to readily available funding, use of a common language among the participating countries, similar culture and socioeconomic policies, and a well-structured and functional secretariat *(97)*.

In sub-Saharan Africa, pooled procurement mechanisms are at varying levels of maturity. There are five different regional pooled procurement initiatives across the African continent, but currently these mechanisms do not include antibiotics. All African regional pooled procurement mechanisms have operational frameworks in place. The Southern African Development Community (SADC) is at an advanced stage of implementing pooled procurement, while three other African economic groups are at the preparation phase: the Central African Economic and Monetary Community (CEMAC); the Economic Community of West African States (ECOWAS); and the East African Community *(95)*.

The Small Island Developing States (SIDS) pooled procurement initiative in the WHO African Region is operational (99). It was set up specifically to address small quantity orders due to the small individual population sizes of SIDS. As a result, SIDS have had little bargaining power with international suppliers, including manufacturers. As a result of the first pooled procurement tender in 2022, SIDS received an average 56% cost reduction across 47 medicine formulations, irrespective of the small individual volumes forecasted by each state *(99)*.

Factors for effective regional pooled procurement

Effective regional pooled procurement relies on a combination of political commitment, clear goals, strong governance, and harmonized processes. The following factors are critical to ensuring the success and sustainability of such initiatives (*99*).

- Political will at the highest level of government through the signing of a formal agreement.
- Clearly defined goals and objectives for the initiative.
- Setting up of a permanent, autonomous and competent secretariat responsible for the day-to-day technical management of the initiative.
- Goods procurement and quality assurance practices agreed upon by the participating entities.
- Adequate and sustainable financing generally from participating countries and subsequently sustained through a revolving fund with the financial gains from the initiative.
- Sustainable financing to fund the procurement and operational costs.
- Standardization and harmonization of requirements, specifications, processes and procedures among participating entities. Including governance, policy and regulatory affairs activities within regional pooled procurement operations to reduce barriers to access.

- Creating efficiencies by including market shaping activities that address both the supply and demand.
- Pushing for single pricing regardless of destination markets (i.e. if some countries in a region are upper middle-income and others are LMICs, the goal should still focus on a single price for all countries in the region). Despite country income status, patients in greatest need for subsidized medicines care are seeking care in all countries.

Risks and challenges for effective regional pooled procurement

While regional pooled procurement offers many benefits, its effectiveness can be hindered by a range of legal, financial and political challenges. The following risks highlight potential barriers that must be addressed to ensure successful implementation and sustained participation (*99*).

- Different legal provisions and regulations for procurement activities, which can restrict information sharing and financing procurement managed by a third-party/regional procurement entity.
- Laws and attitudes that may place the sovereignty of the individual state above the collective good.
- Limited financing for procurement activities. In some countries, national health allocations may already be very constrained and unable to unable to fully fund ongoing health programmes. This can leave very little funding available for procuring medicines, which can limit participation in regional pooled procurement efforts that may require clear funding availability, or pathways to address delayed payments.
- Individual countries' taxes and duties policies on imported medicines may negate some of the gains from pooled procurement. Likewise, limited regulation on price mark-ups may also lead to higher national prices despite lower prices being achieved through pooling.

There are ongoing global efforts to make antibiotics, particularly those with identified access issues, available through regional and global pooled procurement initiatives. While this promises to become a solution to increasing antibiotic access in the future, in the meantime countries can consider advocating and working with third-party procurement agencies such as the Global Fund and Stop TB Partnership Global Drug Facility to explore solutions that leverage the procurement infrastructure built around vertical programmes.

Annex 16. Logistics and supply chain management

Planning logistics and managing the supply chain to deliver the antibiotic to health care facilities – so that patients can receive treatment – is closely linked to forecasting and procurement. Key to delivering an antibiotic to a facility is a good storage, distribution and transport network, and a clear process to manage stock – both at storage facilities (e.g. warehouses) and at health care facilities. This is important so that the antibiotic is available when it is needed, but to also manage unnecessary waste and control overuse or misuse. In most countries, the private sector has a key role in logistics and the supply chain management of medicines, especially through distributors and warehouses, so it is important to engage private sector stakeholders in planning and implementing the antibiotic introduction.

When planning logistics and the supply chain, other auxiliary commodities should also be considered such as diagnostic equipment, intravenous (IV) administration equipment such as catheters, infusion pumps, needles and syringes, and IV bags etc., so all necessary equipment is available to appropriately administer the antibiotic. While most **Reserve** and **Watch** antibiotics do not require cold chain storage prior to reconstitution, some products do require cold storage before and/or after reconstitution such as Cefiderocol IV, Ceftolozane-tazobactam IV, and Plazomicin IV (these all require storage at 2°C to 8°C) (*57–59*). The availability of cold chain infrastructure (i.e. refrigeration and a consistent energy supply with back-up generators) will ultimately determine deployment strategies for these products, especially at lower levels of the health system where cold chain capabilities are often insufficient in LMICs. Some products that do not require cold chain may still require validated, temperature-controlled shipping containers. If stock is not managed properly, and there is a need for expedited shipping, cold-chain shipping requirements eliminates cheaper transportation options of sea and road freight.

Another key consideration for logistics and supply chain management is manging stock levels. To ensure that patients who need antibiotic treatment have timely access, they need to be readily available locally so they can be used to quickly to treat life-threatening infections. But given that some antibiotics have low demand and national volumes are low, aligning stock availability with real use can be difficult. For **Reserve** and **Watch** antibiotics that are generally ‘slow moving’, many distributors hold minimal stock to minimize the risk of losses from expiry. Some distributors will place orders on immediate demand, which can extend lead times and can take up to a minimum of four weeks from order placement to product clearance by local customs, assuming timely fulfilment by manufacturers. Lead times are likely to be at least double this estimate for products coming by sea or where there is restricted manufacturing capacity.

For antibiotics, collaboration with the private sector can support efficient last mile delivery. Private sector pharmacies, distributors and wholesalers are critical stakeholders in the product introduction supply chain in LMICs but are often not targeted by AMS programmes. In some circumstances, countries can consider developing specific training programmes for pharmacy retailers and/or designing activities or programmes to facilitate antibiotic introduction by minimizing the risks associated with stocking or distributing some antibiotics. For example, countries can explore claw-back mechanisms, volume guarantees in national tenders, tax and duty exemptions for commodities, as well as the use of long-term agreements to ease the tendering process over an extended period. Any activity that is aimed at minimizing risk for private sector stakeholders should take into account the unique market dynamics of the country context and the public and private sector side-by-side, in order not to create further market distortions.

Supply chain distribution models and incentives programmes have been implemented in LMICs for other health care technologies as a way to manage restricted-use or low volume products. Some illustrative examples are presented to demonstrate the different types of supply chain solutions countries can consider when planning for the introduction of antibiotics.

Spotlight

Claw-back systems to eliminate wastage and loss

In many LMICs, distributors import directly from manufacturers. For slow moving products, distributors or importers often resist stock refreshment or holding large stock levels due to the economic risks of wastage and loss. One successful solution has been a claw-back system implemented in Francophone Africa. The claw-back system allows pharmacies to return unsold drugs nearing expiry to importers and distributors, who then return these stocks to European pre-wholesalers. This works in this setting because of the unique nature of the pharmaceutical sector in the region which mandates that supplies be channelled through approved European pre-wholesalers, irrespective of the product's manufacturing origin. These pre-wholesalers then manage short-dated or expired stocks due to their large trade volumes and their ability to redistribute short-dated stock to alternative markets at discounted prices *(147).*

Spotlight

Hub-and-spoke models for delivering antibiotics in LMICs

Given antibiotic access and antimicrobial stewardship is often constrained in LMICs, countries could consider adopting hub-and-spoke models that have been effectively used in other disease areas. Context-adapting the hub-and-spoke model to support antimicrobial stewardship, can enable optimal access and maximize efficiencies within scarce resources *(20).*

There are several documented successes for hub-and-spoke models for drug-resistant TB programmes and HIV advanced disease management. For example, in a Zimbabwean HIV programme, diagnostics and drugs are typically procured from national procurement budgets, stocked by the central medical stores and dispatched to central hub facilities. The dispatch of drugs is informed by historical consumption data, as well as diagnostic testing data. Drug stock is also kept at the hub facility, which can be used to address order requests from spoke sites for commodities. This programme has resulted in an increase in the number of patients tested and receiving appropriate treatment *(153).*

In a hub-and-spoke model for antibiotics, antibiotics are distributed to selected referral hospitals from central medical stores, which serve as the hubs. Surrounding health facilities act as the spokes. Local strategic stockpiles of **Reserve** and **Watch** antibiotics can be maintained at the hub sites. These products can then be distributed to downstream facilities for administration when appropriate cases are identified. This centralizes supply, reducing the likelihood of wastage and expiry when the number and location of cases are uncertain. Alternatively, spoke facilities can refer patients to the central hub if they lack the necessary infrastructure, such as diagnostics, inventory management, or drug administration capabilities. GARDP has been working with countries to develop antibiotic introduction plans and in doing so has also examined the merits of the hub-and-spoke model for antibiotics *(20)*.

Case study

Life Bank Nigeria: A hub-and-spoke model for last mile delivery of life saving health products

Life Bank is a health technology company that focuses on delivering essential medical supplies, such as blood, oxygen and vaccines, to hospitals including those in the public sector. Hub-and-spoke models work by hospitals placing orders for blood products, oxygen and vaccines, which are then dispatched by Life Bank typically through motorcycle riders. They also use drones and boats to reach hard to access, often rural areas. Life Bank works closely with the Ministry of Health to align its services to national health priorities and the work they do complements the existing public health system infrastructure. Notably, Life Bank played a critical role in ensuring the supply of oxygen to hospitals during the COVID-19 pandemic. They also partnered with MSD for Mothers in 2020 and 2022 to address last mile delivery challenges for blood and uterotonics (used to manage post-partum bleeding), and succeeded in supplying 30 000 units of blood to hospitals in Nigeria and Kenya, as well as 4000 units of heat stable Carbetocin to four states in Nigeria. Additionally, Life Bank was recently awarded the contract to facilitate the distribution of pharmaceutical products to the last mile within Yobe State, Nigeria. Life Bank handles the logistics involved in the distribution of products from the State's Central Medical Store to the three zonal stores within the state. Yobe State pays Life Bank a monthly fee each month for its services.

Spotlight

The vendor-managed inventory (VMI) model

VMI can help ensure optimal stock levels by placing the responsibility for inventory management with the supplier. The supplier monitors stock levels and automatically replenishes supplies when they reach a predefined threshold. This not only reduces the risk of overstocking or stock-outs but also allows for more accurate forecasting and planning. By shifting the inventory management responsibility to the vendor, health care facilities can focus on patient care, while vendors can optimize the supply chain for cost and efficiency.

Supply chain management activities should also include product quality checks and monitoring along the supply chain. This is recommended to manage leakage from the public to private sector or unregulated market, and to control substandard and falsified products. Countries can consider using smart technology for monitoring the quality of products as they move through the supply chain and capture the prevalence of unregulated products in the market. For instance, activities could include working closely with the NRA and the private sector to deploy technologies such as serialization, track-and-trace systems, and tamper evident packaging to further protect end-users from substandard medications, and to also monitor diversion and use of antibiotics.

Technology and information technology (IT) infrastructure has an important role in supply chain efficiency. Gaps in IT infrastructure can impact logistics and distribution. It is recommended that countries consider updating, enhancing or establishing logistics management information systems (LMIS) to support the supply chain for antibiotics. This will help with managing stock, but also with improving data quality to inform forecasting and procurement quantification. This may involve coordinating with the departments responsible for creating, revising, hosting and/or rolling out updates or technologies. Following is a case study demonstrating the positive impact of utilizing a web-based logistics management system to support the delivery of a low-volume, urgent need product.

Case study

Thai National Antidote Programme: Overcoming shortages and resource challenges through a new nationwide, web-based distribution system

The Thailand National Antidote Programme (TNAP) was established in 2010 to improve access to antidotes and antivenoms across the country *(154,155).* Antidotes and antivenoms are critical medicines used to treat poisoning and envenomation, and quick access to these products can significantly reduce mortality and morbidity. Despite the high public health need, persistent supply shortages in Thailand have resulted in limited access to these life-saving treatments. The root causes of nationwide stock-outs included an unattractive market for industry investment in research, development and supply, as well as the very low, infrequent, and unpredictable demand for some antidotes. Additionally, there were high wastage rates, and for snake antivenoms specifically, only one supply source existed. Furthermore, the distribution of antivenoms across Thailand lacked a systematic approach, leading to a mismatch between stock availability and demand in different geographical areas. For example, certain types of antivenoms were understocked in some regions but overstocked in others.

In response to these challenges, the Ramathibodi Poison Centre, the National Health Security Office (NHSO), the Government Pharmaceutical Organization (GPO), Queen Saovabha Memorial Institute (QSMI) and the Thai Food and Drug Administration collaborated to develop and implement a new nationwide distribution system through the TNAP. This system was initially designed to ensure the rapid availability of antidotes and save lives. This collaboration meant that the TNAP was built on strong and sustained policy support, allowing for its successful implementation.

Case study (cont.)

The TNAP introduced a new nationwide distribution system, initially focused on antidotes, with the goal of establishing sustainable national and sub-national antidote stocks, managing distribution, and training health care providers on clinical management and antidote use.

The TNAP national web-based system centralizes antidote procurement and distribution. Public and university hospitals are invited to serve as stocking sites, but they are not required to purchase the products. Instead, the NHSO purchases the products and retains ownership of the stock. The web-based system includes geographical information on stocking sites and stock levels, allowing for direct requests from treating sites to source antidotes. To ensure consistent supply and meet national and sub-national stock requirements, products are stocked based on local epidemiology, urgency of need, stockpiling capacity, and product availability. The system, developed using the GPO vendor-managed inventory and global positioning system (GPS) technology, provides real-time stock updates (by type and volume) at stocking sites. The NHSO not only finances the stock but also manages the centralized procurement of all antidotes, ensuring that all Thai patients have access to these medicines, regardless of their health insurance status. In addition to the distribution system, the Ramathibodi Poison Centre provides training to clinicians on poison testing and antidote use, as well as 24-hour consultation services and outcome monitoring. The QSMI invests in research and development of new antivenoms, and production of essential antivenoms, and the Thai Food and Drug Administration ensures quality, safety and efficacy of antidotes and antivenoms including pre-market to post-market product regulation.

Following an initial two-year trial period, the success of the TNAP supported its expansion beyond antidotes. Since 2012, all types of snake antivenoms have been included in the programme. Through the TNAP, antidotes and antivenoms in Thailand are now readily available. The appropriate use of these products, clinical management and patient outcomes have all improved. Additionally, the estimated cost of antivenoms in Thailand has decreased from US$ 2.23 million to US$ 1.2 million annually due to improved stock and distribution management and reductions in product wastage.

Annex 17. Preparing facilities – health care worker readiness and promoting antimicrobial stewardship

WHO has developed the Antimicrobial stewardship programmes in health-care facilities in LMICs: A WHO practical toolkit *(23)*, which is a useful guide that details the different types of facility-level considerations when introducing an antibiotic within AMS programmes and includes health care worker readiness and stewarding antimicrobial use.

Successful deployment of an antibiotic depends on the readiness of health facilities, referral networks and HCWs. Facilities have a key role in introducing antibiotics by adopting antibiotics included in nEMLs, national treatment protocols/guidelines and implementing AMS practices. Facility managers, HCWs and health care networks linked to facilities are integral to ensuring national level policies or projects are integrated into individual facilities. They also play an important role in identifying critical needs and emerging threats and can provide actionable solutions to many of the problems related to AMR that need to be solved. For these reasons, it is important that facilities and HCWs have an active role in antibiotic introduction, and there is a clear pathway for facilities to share experiences with project leadership and national coordination. In the process of introducing antibiotics, countries should consider minimal facility capacity and other requirements (see capacity assessment guidance in Annex 11), such as:

- infrastructure and resources for AMU/AMR monitoring;
- a willingness to enhance and develop as many routine sources of data as possible;
- capacity to appropriately analyse data and identify patients who need antibiotics in the first place;
- to rationalize the process to detect and identify emerging resistance and treatment failures;
- capacity to notify the national authorities on evolving AMR situation and be willing to work with authorities.

The following sections include some recommended approaches to support the introduction of an antibiotic into facilities (i.e. integrating national policies into practice). These are non-exhaustive approaches, and countries should plan and implement facility-level adoption based on local health systems, needs, capacities and existing infrastructure. A flexible clinical model for introducing an antibiotic into facilities should be tailored to the local context (i.e. from more sophisticated settings with a greater capacity for data generation, collection and analysis as well as greater financial and human resources, to more resource-constrained settings with various degrees of

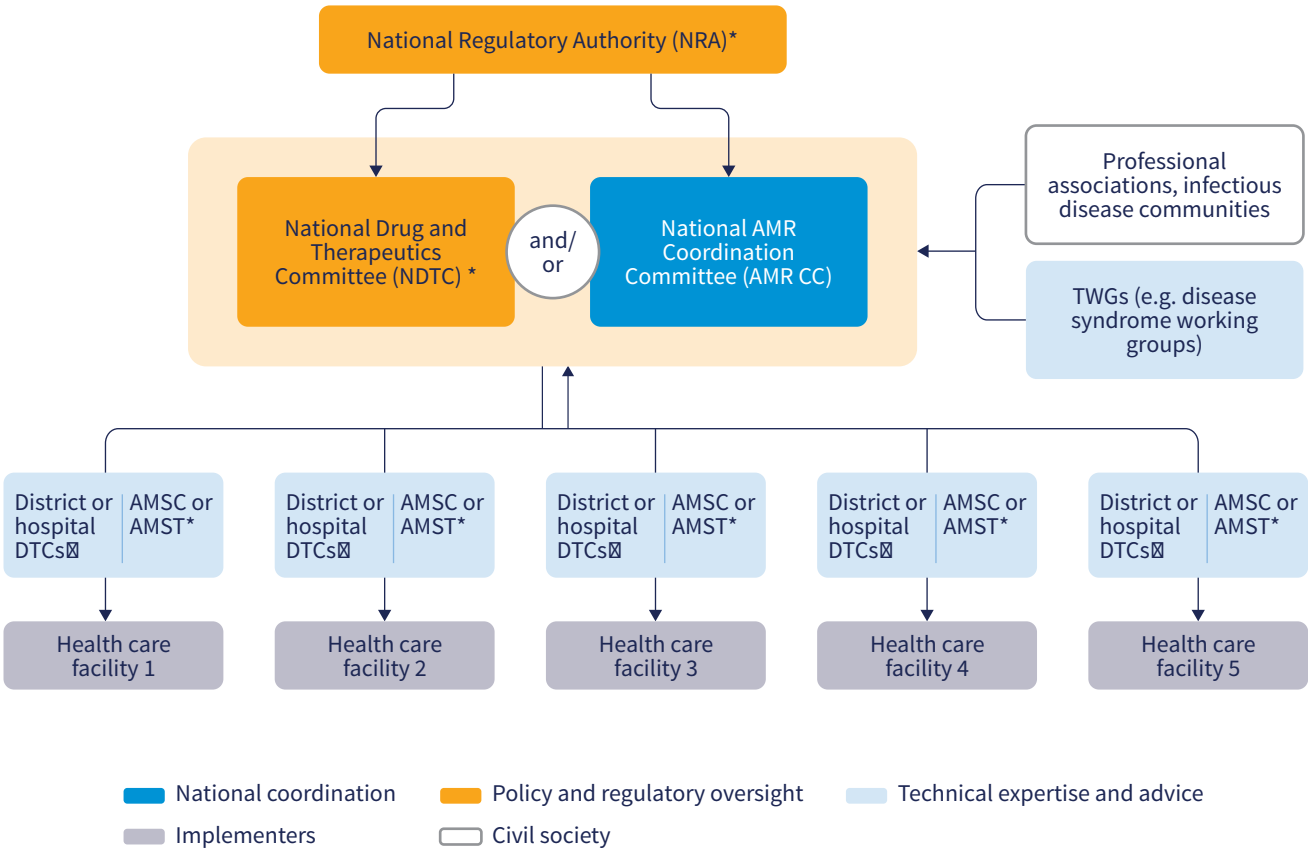
existing facility level structures and capacities). At a minimum, health facilities should adopt a flexible structural and multistakeholder approach to introducing antibiotics and strengthening AMS efforts. The approach should go beyond a small range of health professionals working in a facility and consider the multi-layered medicines selection and guideline development processes applicable for each unique health system.

17.1 Establish a process for translating policy into practice

Many countries have an existing process to centralize national policies and treatment guidelines/protocols for facilities. Depending on the country context, these processes should be leveraged to support the translation of policy from the national level through to facilities, ultimately ensuring that patients needing treatment, receive it in a timely and safe way. To streamline practices and ensure efficiencies, facilities should utilize centrally developed policies, formulary lists and standard treatment guidelines (STGs) for antibiotics whenever possible.

In some countries, NRAs have established a national drugs or medicines and therapeutics committee (NDTCs) or body for antimicrobial policy (including for antibiotics) that supports the introduction of medicines including antimicrobials. Some LMICs have active and mature NDTCs that have a mandate to make national-level decisions on treatment recommendations and the appropriate use of medicines. NTDCs in some countries are also responsible for disseminating policies and guidelines to facilities. In other countries, this role might sit with another group within the ministry of health, or national coordinators – such as an AMR CC – might work directly with treating facilities to support change and implementation. These types of national level groups can also play a key role in guiding the formation of facility-level DTCs and/or AMS committees, if appropriate, and coordinating the implementation of antibiotics in facilities to ensure that they are used appropriately. In some cases, this body can also establish agreements with professional associations to guide the analysis of the local situation of AMR, the use of antimicrobials including antibiotics, and the evidence on antimicrobials to be introduced/included as new options in the national or local treatment protocols/guidelines (**Fig. A7**).

Fig. A7 Illustrative example of structural flows from the national level through to facilities, by function



As described in **Annex 12**, NDTCs, AMR CCs, or other similar structures may take on the following roles to support antibiotic introduction at facilities. This following list is exemplary only and the roles will vary across different health systems:

- Identification of antibiotics with a high public health and clinical need for adoption at facilities (see Annex 6).
- Assess and update the antibiotics included in the nEML.
- Develop and update national/standard treatment guidelines and support facilities to adopt them.
- Update national formulary lists for procurement and reimbursement (where applicable).
- Monitor the use of antibiotics nationwide (including in facilities) to ensure appropriate and safe use.
- Ensure that appropriate AMR surveillance and use is conducted to inform medicine selection for the formulary list and individual patients.
- Analyse the information and evidence to facilitate the introduction of antibiotics.
- Participate and liaise with the NRA and other public and private entities to conduct the process for the introduction of antibiotics.
- Coordinate activities with facility DTCs, AMS and IPC programmes in facilities.

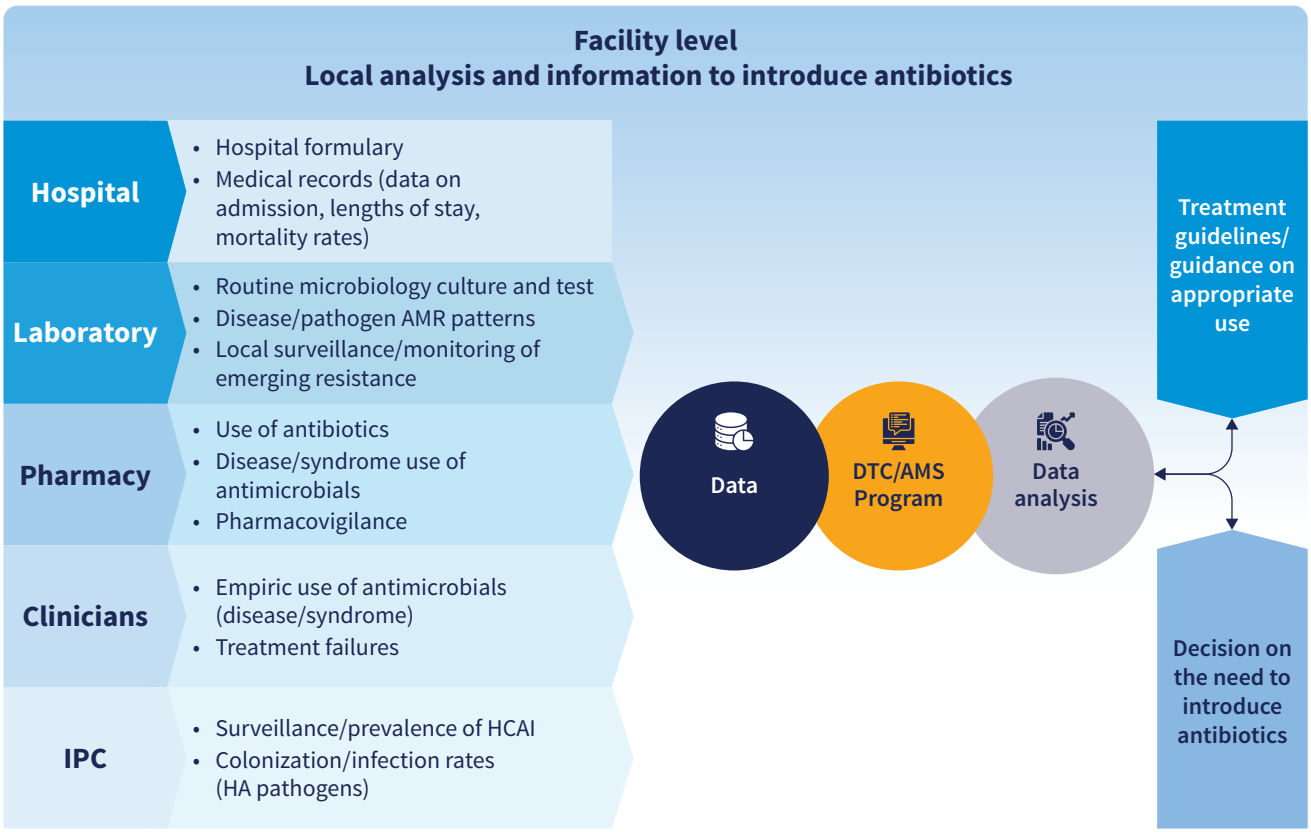
In some settings, there may be no effective national or regional process for the selection of medicines, including antibiotics, or where a facility relies on its own financing to select and procure medicines. In these settings, facilities may have to take on some of the described roles above and could also make a case for the facility-led selection of antibiotics, based on the best available local epidemiological data and backed by systems designed to carefully and effectively document antimicrobial use (see Annex 14). On the other hand, if a facility is well established and resourced, facility managers may have processes to develop facility-led treatment protocols and antibiotic use policies. It may also have processes to update facility formularies that guide procurement. Therefore, it is important to understand how the facilities that will be using the newly introduced antibiotic operate, and what the current capacity and resource situation is at each facility. Understanding how facilities run can be learned through stakeholder engagement activities as well as taking the proposed steps, like a capacity assessment, that are part of selecting the antibiotic introduction approach (see Annex 11).

For example, facilities may already have a facility-level Drug and Therapeutics Committee (DTC) and/or AMS committees to oversee manage, monitor and introduce medicines and/or antimicrobials into health care facilities. Generally, facility-level DTCs work with NDTCs, and AMS committees generally work with national coordinators such as the AMR CC, as they have been set up as part of the NAP. The strength and capacity of these existing committees can vary from country to country, and from facility to facility, so it is important to know how they are currently operating and what capacity they have to take on extra work to support activities around a newly introduced antibiotic. If facilities have other processes and governance in place that can be leveraged for the antibiotic introduction, it is not necessary to set up a facility level DTC or similar committee. However, for facilities that have been identified as having capacity or resources to implement a DTC, guidance has been included below on the considerations when supporting facilities to set up and run DTCs as part of the antibiotic introduction.

17.1.1 Prepare facilities for implementation

In the process of introducing antibiotics facilities play a fundamental role in treating bacterial infections, monitoring antibiotic use, monitoring the effectiveness of antibiotics, and detecting resistance to antibiotics. Facilities have a lead role in adopting national treatment protocols/guidelines, monitoring adherence to treatment protocols/guidelines, and sharing information on the effectiveness of the antibiotics. There are many ways facilities can introduce antibiotics, and the process will vary depending on the health care system. As a general illustrative guide, **Fig. A8** shows how different facility components and committees can be structured and work together to support antibiotic introduction, with a focus on stewardship, as well as monitoring and evaluating the local situation of AMR/AMU, including initiating the introduction process based on the needs of the local situation.

Fig. A8 A general illustrative guide of a structured approach for facility adoption, use and monitoring of antibiotics



The facility DTC

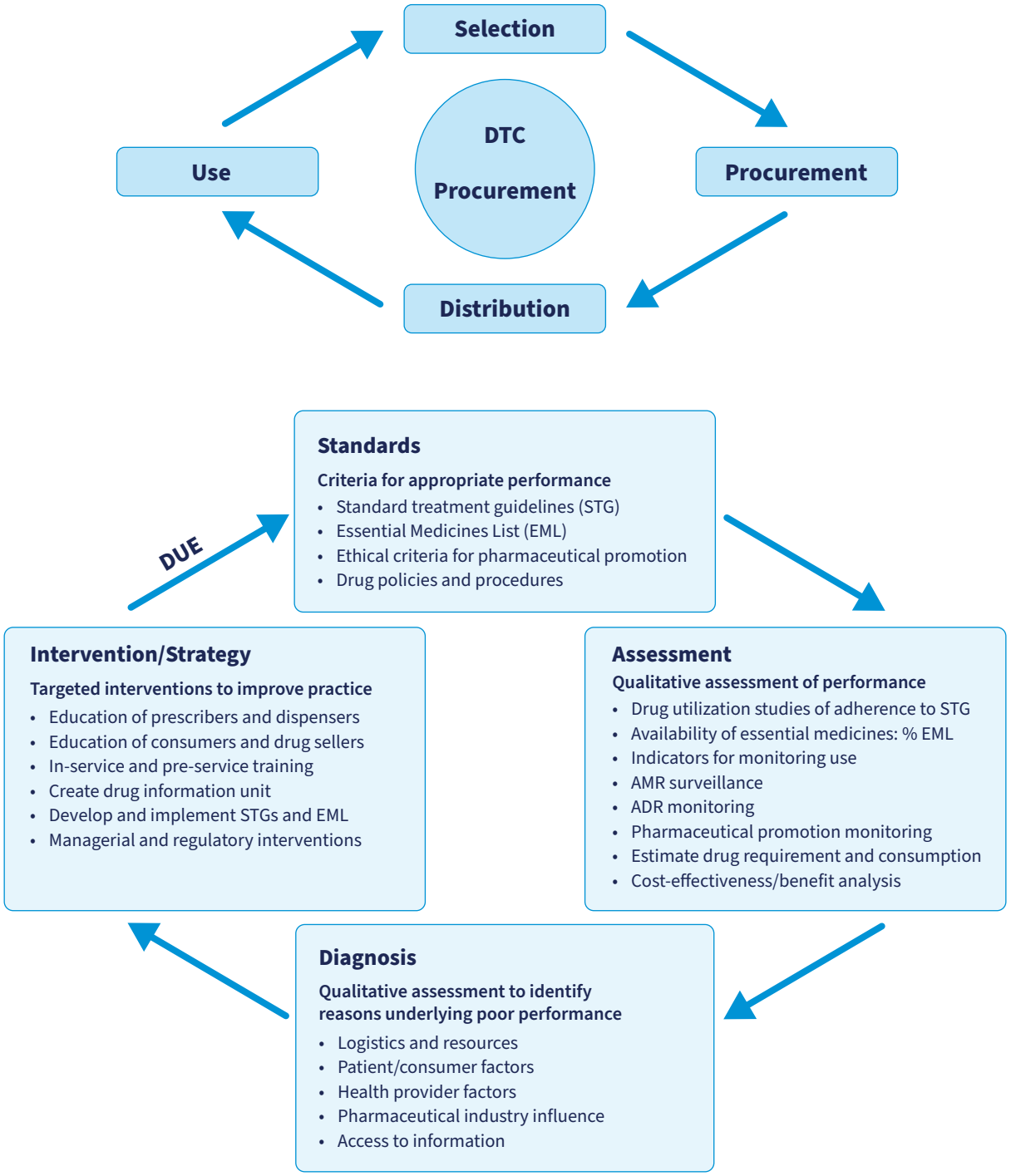
WHO has developed a practical guide to support countries in establishing DTCs in facilities to improve the quality and cost-efficiency of therapeutic care *(61)*. This guide provides tools to investigate drug use and strategies to promote appropriate use of all medicines including antibiotics. In many HICs, a well-functioning DTC is very effective in supporting medicine introduction into facilities and addressing related medicine use problems. However, in many LMICs, DTCs do not exist and in others, they do not function optimally often due to a lack of local expertise or a lack of incentives, frequent changes in the DTC mandate and an absence of clear roles and responsibilities for actors at all levels *(156).*

The goal of a facility DTC is to have governance and oversight that ensures that patients are provided with the best possible, cost-effective, quality care at the facility by determining what medicines will be available in the facility, at what cost and how they will be used. A DTC generally covers all medicines used at the facility, and its role is not specific to antimicrobials. For effective management, DTCs usually have targeted roles and responsibilities (**Fig. A9**), with clear priority functions. They have a multidisciplinary and transparent approach; they also have technical competence and an official mandate.

For antibiotics specifically, facility DTCs can play an instrumental role in documenting and implementing rules and policies for all aspects of antimicrobial management *(61).* For example, DTCs can monitor antibiotic use to ensure they are used appropriately. They can also ensure suitable IPC policies and practices are in place. DTCs can also conduct

resistance surveillance to inform which antibiotics are included in formularies (both national and facility level formularies) and guide individual patient treatment. They may also have a role in AMS programmes/teams, or a more formal AMS committee, or as facility focal point to specifically implement antimicrobial-related policies and guide clinicians, pharmacists and facility administration of antimicrobials.

Fig. A9 Illustrative example of the roles and functions of a DTC in managing and coordinating antibiotic introduction into a facility

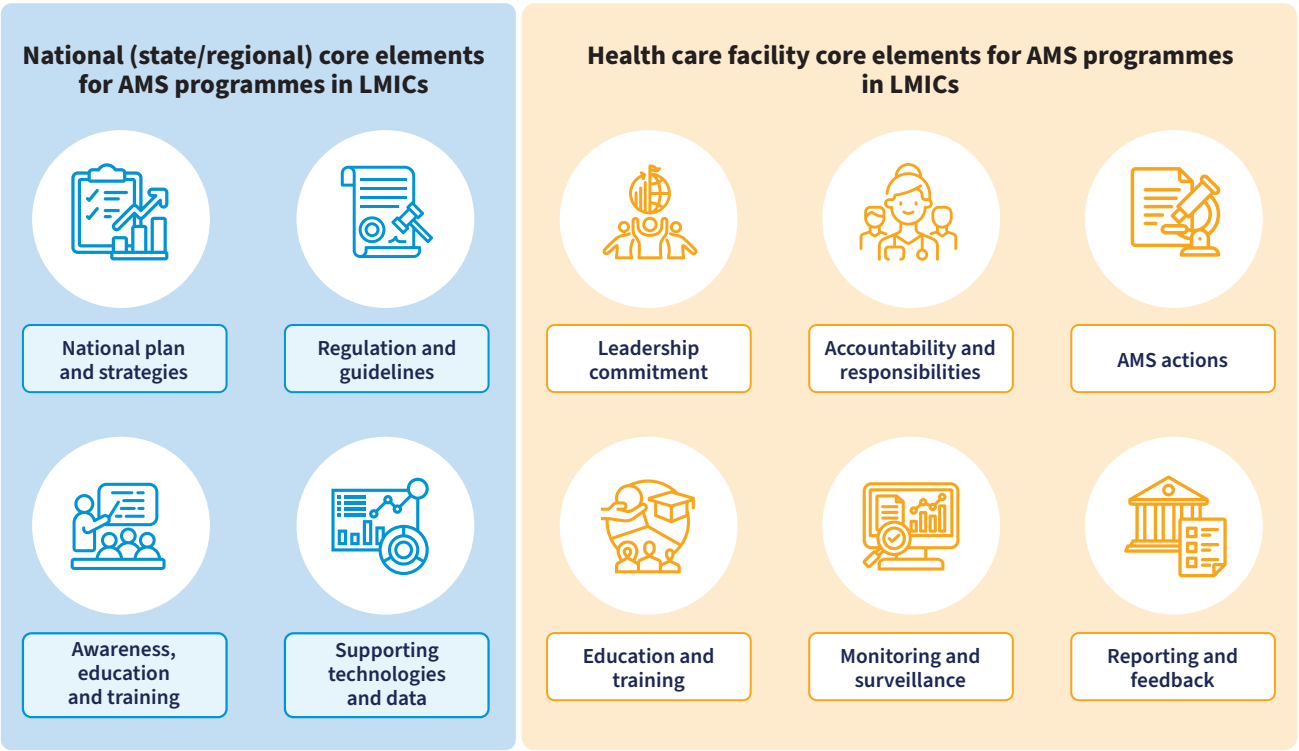


Source: (61).

Another important component of translating national policy to antibiotic introduction at the facility level is to ensure that facilities have a dedicated function that leads/supports AMS efforts, and/or programmes, and specific AMS activities related to the antibiotic being introduced. AMS programmes are critical within a facility, including for monitoring infection and resistance trends. AMS programmes or activities are also important and preventing and controlling resistance. Details on recommended AMS programmatic activities at facilities is provided in Annex 17.1.4.

The WHO Antimicrobial stewardship programmes in health-care facilities in LMICs: A WHO practical toolkit provides a useful outline of the core elements of an AMS programme at facilities, and what to do if the facility does not have all the core elements in place *(23).* It is recommended that countries reference the toolkit to ensure that appropriate AMS measures are in place both nationally and at facilities for the antibiotic being introduced. Importantly, countries need to ensure that facility level AMS programmes or plans reflect national policies and guidelines. As a snapshot of the toolkit, **Fig. A10** outlines the core elements needed for effective AMS programmes.

Fig. A10 National (state/regional) and health care facility core elements for AMS programmes in LMICs



Source: (23).

However facilities operate (i.e. using formal structures such as a DTS or AMS committee to support antibiotic implementation, or less formalized solutions that work for the capacity and resources of the facility), sufficient planning, appropriate use and monitoring in facilities is critical for the introduction and management of all antimicrobials. In settings where there is only capacity for a less formal facility committee, or no committee at all, it is important that however AMS efforts are approached, at a minimum, facilities should adopt and adhere to national guidelines, and ensure there is a rational process for monitoring and assessing the appropriate use of all antimicrobials.

To foster appropriate antimicrobial use at facilities, the following list outlines minimum requirements, capacities and activities that facilities can implement to introduce antibiotics regardless of the working group/team or committee responsible for implementing the activities:

- Identifying/establishing facility governance and leadership to support stewardship activities and that can share information on the clinical need for antibiotics, and how they will be used. If funding is available, this could be through establishing local committees and programmes (DTC or AMS committees) with dedicated human resources to monitor the use of antimicrobials and management of AMR.
- Updating and implementing antibiotic use policies (reflecting any national level AMS policies):
  - Adopting national treatment guidelines/protocols in facilities, tailoring them to specific patient needs within the local population.
  - Updating the facility formulary list (this is only applicable if the facility uses a separate list to the national list. In this case it should be based on guidance from the NDTC, nEMLs and national treatment guidelines).
- Promoting appropriate use by communicating and implementing targeted interventions to enhance antibiotic use practices and disseminating pertinent information regarding antibiotic use policies/decisions across all facets of the facility such as:
  - education and training to inform prescribers and treating health care workers;
  - managerial references to guide prescriber and treating clinicians' actions;
  - facility policies that can control or restrict prescribing.
- Managing and coordinating antibiotic procurement, storage, distribution and use at the facility.
- Implementing monitoring and surveillance of AMR/AMU at the facility, such as:
  - ensuring laboratory capacity, or links to external capacity, to perform microbiology analysis and antimicrobial susceptibility testing and surveillance of AMR;
  - pharmacovigilance, including identifying adverse drug reactions and treatment errors;
  - Conducting systematic assessments of antibiotic use to ensure alignment/adherence to treatment protocols and to identify targets for quality improvements and implement change if needed (i.e. audits and feedback).

17.1.2 Set up antimicrobial stewardship (AMS) programmes and measures at facilities

AMS is a critical pillar in antibiotic management, resistance containment, and the promotion of appropriate AMU. Given the challenges associated with developing new antibiotics, AMS serves as an essential tool for preserving existing antibiotics. The WHO practical toolkit *(23)* provides checklists to guide what is needed for successful AMS programmes in health care facilities in LMICs.

Substantial efforts have been made across the globe to preserve antibiotics through AMS programmes. Since WHO launched the Global action plan on antimicrobial resistance (GAP), most countries have developed NAPs to address AMR, which include stewardship measures. However, few LMICs have been able to fully implement AMS programmes due to limited resourcing (including limited technical capacity and human resources) and

competing priorities *(157).* Other challenges with implementing AMS programmes include resistance to change amongst health care professions, a lack of sufficient data to guide prescribing practices, and limited access to evidence-based resources such as reliable testing *(158).*

Antibiotic introduction should be integrated within a comprehensive, well thought out AMS programme that fosters stewardship at facilities. It is recommended that AMS programmes are led and managed at facilities by either an AMS committee, AMS team or an AMS focal point. The type of structure or individual/s given this role will need to be determined based on local capacities and resources. However, ideally an AMS committee provides governance/oversight of appropriate antimicrobial use in the facility, while an AMS team works with the AMS committee and implements day-to-day activities such as audit and feedback.

The following sections provide guidance on the different approaches to implementing AMS programmes depending on available resources and capacity in different contexts.

17.1.2.1 Approaches to AMS programmes in low-capacity and low-resourced health care settings

Regardless of the local situation, it is important that facilities that will be receiving the newly introduced antibiotic have functions that can provide oversight and coordination for all antimicrobials and AMS activities. In smaller facilities, if there is insufficient capacity or where resources are limited, the role of implementing AMS programmes can potentially sit with an AMS team, the health care facility administrator/manager, or an individual person (i.e. an AMS focal point, assigned to manage antimicrobial use at the facility).

A strategy to overcome human resource capacity limitations in facilities is to adopt task-shifting. Where the number of doctors is low, task-shifting to nurses and pharmacists, supported by appropriate guidance and training, has been shown to be effective in expanding AMS resources. If task-shifting is used, a review and revision of policies must be undertaken to support task-shifting plans. For this approach, involving relevant professional groups in policy updates, and having a good communication strategy for disseminating the AMS programme across the facility, will help to ensure its success.

Other approaches to consider include using a hub-and-spoke model, where a larger facility supports smaller facilities in an area with activities such as updating cumulative antibiograms, local antibiotic use guidance, and helping to train staff to lead prospective audit or pre-authorization programmes for **Reserve** antibiotics *(20).* Additionally, telemedicine-based AMS programmes have been shown to be beneficial in managing antimicrobial use at facilities *(159).*

To support facility-level monitoring and evaluation of newly introduced antibiotics, resource-limited facilities can consider developing straightforward processes. These processes might include steps such as following national treatment protocols, defining eligible patient groups likely to benefit from antibiotics, and managing prescribing practices to ensure compliance with AMS standards and stewardship. Additionally, these processes can provide guidance on treating patients with suspected multidrug-resistant infections while awaiting test results, including AST results *(20).* They can also offer information on consulting national committees, technical experts or other hospitals for clinical management support when needed. These are practical, simple methods for introducing structured antibiotic use in facilities with limited resources.

Another strategy is to manage prescribing practices by requiring pre-authorization by a health care worker with infectious diseases expertise who can make a clinical decision on using antibiotics or not, especially for **Reserve** broader spectrum antibiotics. This strategy has demonstrated effectiveness across multiple settings *(160),* and can be integrated into treatment protocols and guidelines. However, pre-authorization requires technical capacity and resources such as access to expert advice in resource-limited settings, so other strategies like prospective audit may be a more suitable approach.

Prospective audits, retrospective audits and feedback are other ways to capture feedback and identify inappropriate use *(161).* These approaches still require input from technically skilled health care workers, but can be useful to avoid delaying access for patients who need life-saving antibiotics when specialists may not be immediately available at the facility (e.g. due to limited resources to manage the volume or requests, after-hours requests, or limited on-site resources with reliance on off-site expertise).

Once algorithms have been developed, training health care workers and communicating the content across the facility is paramount to ensuring it is adopted. Supportive supervision in the weeks following training courses should also be used to make sure workers are adhering to the new guidance.

In resource-limited settings, it may be appropriate to support facilities to develop workplans that outline specific AMS activities. Having a similar workplan across multiple facilities will allow facilities to track key performance indicators that can then be reported nationally. Some key areas to include in an AMS workplan could include:

- Building leadership commitment.
- Establishing accountability and responsibility for delivering the AMS programme.
- Key activities such as implementation of guidelines, conducting audits and establishing surveillance systems for hospital-acquired infections.
- Education and training activities.
- Monitoring and evaluation of activities.
- Reporting and feedback within health facilities.
- Reporting and feedback nationally.

17.1.2.2 Approaches to AMS programmes in health care settings with greater capacity and resources

If the health care setting has available capacity and resources, and the antibiotic being introduced has been classified as a **Reserve** and **Watch** antibiotic by WHO, it is highly recommended that treating facilities have a specific internal approach to managing AMS within the facility, which is assigned to implementing and monitoring the use of the antibiotic, as well as other antimicrobials. This can take form as an AMS committee or an AMS team, or both where an AMS team reports into the AMS committee. Whichever approach is used, the key is to ensure that this function is in place and it is clear within facilities who is responsible for overseeing and implementing AMS.

17.2.2.2.1 The AMS committee and the AMS team

One approach to operationalizing AMS programmes in facilities is by setting up an AMS committee and an AMS team. If a facility has capacity to set up an AMS committee to govern and provide oversight of AMS programmes, then an accompanying AMS team should be instated to manage the day-to-day implementation of the AMS programme. This section assumes that facilities have or plan to have both an AMS committee and

AMS team. However, the main principles in this section can apply to less formal facility governances, or where only an AMS team is possible and is responsible for governance, oversight and implementation.

AMS committees' and AMS teams already exist in some countries and have been introduced as part of the NAP and AMS programmes that enable antibiotic introduction and stewardship in health care facilities. If facilities have DTCs, then they may use a governance model where the AMS committee and AMS team sits within the DTC. But AMS committees and AMS teams can sit outside of a facility DTC or can be established without a DTC depending on the local setting.

If having both a DTC and an AMS committee and team are part of the antibiotic introduction plan, generally these functions operate separately to each other but can be linked for efficiencies depending on what is set up and already in operation. If an AMS committee and AMS team do not exist, and resources are available, countries may consider supporting their set up. If having an AMS committee and AMS team is the decided approach to managing AMS in a facility, but they do not yet exist, DTCs can facilitate their formation, or facility managers can independently do so.

In facilities where a DTC and an AMS committee and AMS team are in place, ideally, the introduction and adoption of antibiotics into facilities should be led by an AMS committee, integrated with the DTC to enable the availability and use of the antibiotic so treatment access is not delayed. AMS committees can deal with the management of all antimicrobials, including antibacterials. For antibiotics, the AMS committee should ensure that safe, effective and cost-effective antibiotics are made available, that they are only used when clinically indicated, at the correct dose and for the appropriate duration of time, and that correct information is given to patients to ensure adherence and compliance. AMS committees should include all the various hospital functions required to implement an AMS. Most importantly, when setting up these functions in facilities, it is critical that there is a clear responsibility and accountability framework in place that includes senior staff and hospital management.

The WHO Practical Toolkit *(23)* provides a sample terms of reference for an AMS committee and an AMS team, so it is recommended these are referenced when planning to set up these facility level functions. Like AMS programmes in resource-limited settings, AMS approaches adopted by the AMS committee and AMS team could include developing facility treatment protocols and algorithms for antibiotic use, designing and implementing strategies to manage prescribing practices such as requiring prospective audits or pre-authorization to use **Reserve** antibiotics, and training health care workers and communicating AMS programmes and policies throughout the facility. Supportive supervision in the weeks following training courses could also be applied to ensure that health care workers are implementing learnings from training.

17.1.2.2.2 The infection and prevention control committee (IPCC)

Countries may decide that IPC in facilities is managed by an infection and prevention control committee (IPCC) or team. IPCC's usually work independently to the DTC or AMS committee and AMS team, but they rely on them as an advisory function. If IPCC's do not exist, and there is a DTC, the AMS committee can support creating one to specifically deal with all issues relating to infection prevention and control (see *(162,163)* for what to include in infection prevention and control at the facility level).

The link between the NDTC, the facility DTC, AMS committee, AMS team and an IPCC is outlined in Fig. A8. This is an illustrative example of how policy set at the national level flows through to facilities, and the interaction between the different groups. This is a comprehensive model and may not be appropriate for all settings, so the example is an illustration that countries can adapt to the local setting.

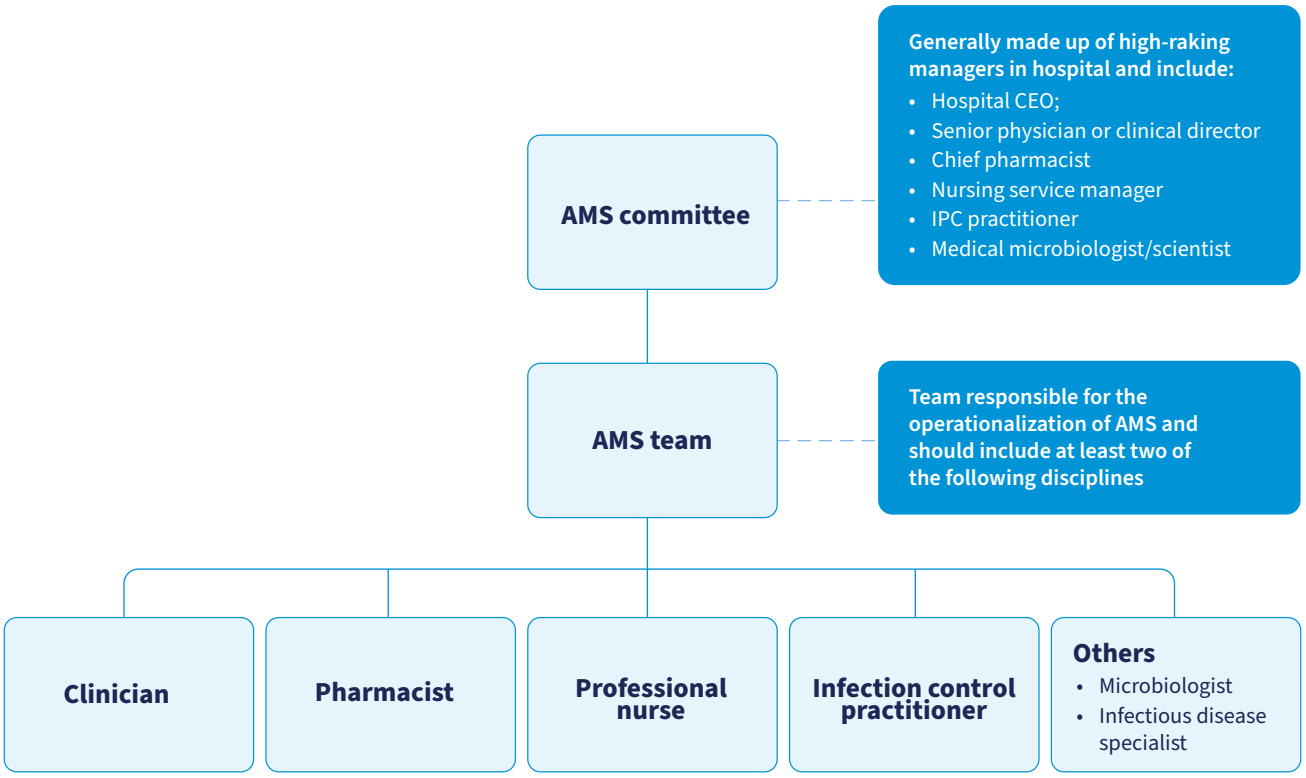
In AMS programmes, it is ideal to include representation from across the facility to have a multidisciplinary team. This is important for buy-in and can create a sense of ownership of the AMS programme throughout the facility. Key facility functions to engage are listed in **Table A*5*** below. *(23)*

Table A5. Overview of the key functions in an AMS committee and their roles

Function	Role in the AMS committee
Administrators and management	Provides insights into the running of the hospital and can provide guidance on how to implement and AMS programme. Engaging management also assigns responsibility and accountability in senior staff.
Prescribing clinician	Provides expertise in treatment management and patient care.
Clinician with infectious disease or antibiotic expertise	Expertise in infection management and can support prescribers with diagnoses and treatments.
Pharmacist and a clinical pharmacologist	Expertise in antimicrobials and antibiotics. They oversee antibiotic procurement and review prescriptions. They also have a fundamental role in monitoring antibiotic consumption, point prevalence surveys and prescription audits. Optimizing antimicrobial dosing and promoting best practices in prescribing, dispensing and administering antimicrobials are also essential functions.
Nurse	Expertise in patient care. Manage the effective delivery of antibiotics to patients and they can conduct drug monitoring as well as obtaining high-quality samples for laboratory testing.
Clinical microbiologist or laboratory technician	Expertise in microbiology especially in the absence of an in-house laboratory. They conduct antibiotic susceptibility testing, provide feedback to prescribers, and develop and update the aggregate antibiogram.
IPCC	Responsible for infection prevention and control across the entire facility.

The *Guidelines for the prevention and containment of antimicrobial resistance in South African Hospitals (164)* includes a useful example of an AMS committee and AMS team structure within the facility (**Fig. A11**). In this example, the AMS committee includes senior representation from across the facility and plays more of advisory/overseeing role. The AMS team is responsible for the day-to-day operation of an AMS programme. Having both an AMS committee and an AMS team might be a suitable approach for facilities introducing new antibiotics. However, it is important that the capacity of the facility is assessed, and a context-driven approach is employed.

Fig. A11 Illustrative example of guidance for an AMS committee/AMS team governance structure for facility AMS programmes in South Africa



Source: (164).

17.1.3 Update treatment protocols/guidelines, formularies and manage the facility formulary process

For a newly introduced antibiotic to be used at facilities, it needs to be included in national protocols/treatment guidelines. These contain instructive information on how to prescribe, treat and manage diseases and infections, including MDROs. In many LMICs, these are developed centrally at the national level and are updated or developed to contain information on clinical features, diagnostic criteria, antibiotic treatments (including first-, second- and third-line), non-medicinal treatments, and referral criteria. They should be updated based on nEMLs and the WHO AWaRE antibiotic book, using evidence and reflect local antibiotic susceptibility patterns (see Annex 12). Facility formulary lists and manuals should reflect national treatment guidelines/protocols and

policies. These should then be adopted by facilities, and integrated into clinical practice, which should involve engagement with key and senior staff for buy-in and ownership. Their involvement in updating processes, the quality of the content, a user-friendly format, adequate information dissemination and follow-up supervision, is critical to acceptance and use of new antibiotics by health care workers.

17.1.4 Training health care workers

National treatment guidelines/protocols are a proven, effective strategy to promote appropriate prescribing, monitoring compliance, and better patient treatment outcomes when used in conjunction with training and education programmes or modules to promote their use *(165).*

National training modules should be developed based on the type of implementation model being deployed. These can then be adapted by facilities to either integrate into existing programmes, or new ones developed specifically for using the antibiotic. Training and education should be continuously provided to all health care workers involved in treating patients including clinicians (all relevant specialists), nurses, pharmacists and laboratory technicians. Training modules should be followed by supportive supervision to monitor that health care workers implement what they have learned and apply the training correctly. Whether leveraging existing or creating new training programmes, antibiotic appropriate use should be at the centre of the training course and all training materials developed (e.g. training materials should emphasize appropriate antibiotic prescribing practices for all antibiotics. Education modules on appropriate use of antibiotics should include advocacy on the appropriate implementation of treatment protocols/guidelines and include up-to-date information on current antibiotic susceptibility patterns. They should also be closely involved in the design and implementation of training courses.

17.1.5 Enhancing diagnostic capacity and links to microbiology laboratories

Alongside the AMS programme measures, facilities need access to diagnostics, microbiology laboratories, and IPC resources. Strong in-country laboratory capacity and laboratory networks are a cornerstone of AMS programmes. This is because laboratories can identify the root cause of an infection, as well as discover and track resistance through laboratory culture and sensitivity testing. While laboratories rarely collate resistance data, they can share data with those managing AMS programmes, who can then use that information to make decisions such as formulary changes or notify authorities about emerging resistance trends. Despite this important role, many countries lack the necessary capacity to deliver time-appropriate results and track antibiotic resistance/activity (although laboratory capacity can vary widely from country to country, or even within a country). Diagnostic stewardship is equally as important as AMS. In the absence of diagnostic and laboratory capacity, good empirical prescribing is just as important. When developing AMS programmes, laboratory capacity as well as the laboratory locations across a country need to be considered. For further guidance on ways to strengthen laboratory capacity see Annex 14.

17.1.6 Enhancing referral networks and integrated services

While **Reserve** and some **Watch** antibiotics will mostly be administered in hospitals, enhancing referral networks is an opportunity to promote appropriate use and to increase awareness of the AMR situation in a country. For example, strong referral networks can improve treatment by assuring primary health care workers that any concerns about treatment failures will be addressed – ensuring that patients are switched from empiric to definitive treatment sooner – and allow for senior clinicians in referral hospitals to play a larger role in promoting and implementing local appropriate use guidelines. It also allows for a double-check of treatment use and prescribing patterns.

Enhancing referral networks presents an opportunity to promote appropriate use and raise awareness of AMR across the country. When planning the introduction of an antibiotic, mapping referral networks can guide facility selection and support forecasting exercises. Referral networks encompass the patient pathway from community health care to primary, secondary and tertiary facilities, including inter-facility transfers. Understanding how different antibiotics are utilized at various levels of care, across both the public and private sector, and the referral patterns of a patient with a serious infection is crucial.

Awareness of AMR varies among health care professionals and across levels of care. Stewardship programmes should be tailored to the level of engagement and awareness, as well as the current prescribing practices of health care professionals. To monitor antibiotic usage within referral networks, it is important to enhance pharmacovigilance surveillance for both existing and newly introduced antibiotics if possible. Implementing monitoring systems and establishing warning mechanisms to detect inappropriate use promptly is also a strategy that can be included in the plan. Some examples of warning systems include: the National Alert System for Critical Antimicrobial Resistances (CARAlert), Australia *(166)*; the National Antimicrobial Resistance Sentinel Surveillance System (AR-ISS), Italy *(167)*; and the National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS) in the United States of America *(168)*.

Case study

Connecting supply interventions with an antimicrobial stewardship programme in Japan

Japan has implemented a successful AMS programme as part of its national action plan to address AMR, providing valuable insights for other countries considering ways to enhance their own AMS programmes. Japan's AMS programme integrates stewardship into national policy, while also connecting the efforts of various ministries and organizations through multisectoral collaboration and a One Health approach.

Through a comprehensive people-centred approach, the programme coordinates public awareness, surveillance, infection prevention, supply and price management, research and development incentives, and international cooperation. With this approach, Japan has made strides in managing AMR, ensuring the responsible use of both existing and new antibiotics and creating market certainty for suppliers.

Key elements of Japan's successful AMS programme:

- Financial incentives for stewardship, robust surveillance systems, and policies ensuring the sustainable introduction of novel antibiotics.
- Promoting AMS in clinical settings through financial incentives: Japan provides financial incentive premiums to medical institutions that establish and implement stewardship practices. These incentives encourage facilities to adopt AMS policies that improve antibiotic use and patient outcomes.
- Standardizing AMS clinical practice: Japan has developed a standardized AMS manual that guides clinical practices, ensuring consistency across health care settings. This manual serves as a reference for medical professionals to implement effective AMS strategies.
- Monitoring AMS adherence through surveillance: The Japanese Surveillance System for Infection Prevention and Healthcare Epidemiology (J-SIPHE) monitors adherence to AMS policies. The system facilitates data connectivity, visualization, and feedback loops, which are essential for tracking AMR trends and ensuring compliance with stewardship practices.
- The antimicrobial securement support programme (ASSP) for novel antibiotics: Japan's AMS policy also includes the introduction of novel antimicrobials. The ASSP promotes stewardship by ensuring that novel antibiotics are introduced responsibly, and sustainable supply is secured and managed. Japan's ASSP includes an annual revenue guarantee to suppliers of novel antibiotics, which helps maintain the availability of new antimicrobials on the market. The revenue guarantee also provides an indirect incentive for ongoing research and development as it signals to suppliers that there is sustainable market for low-volume novel antibiotics. The ASSP achieves this by assessing sales volumes, guaranteeing revenue for suppliers and ensuring supply does not exceed the national need and thus ensuring the stewardship of antibiotics.

Annex 18. Improving awareness for the appropriate use of all antibiotics

Despite AMR being a global threat, public and health care worker awareness of the dangers of antibiotic resistance, and ways to prevent and manage AMR, are limited. There is also limited awareness of the importance of preserving **Reserve** antibiotics and the challenges with developing new antibiotics to address AMR. Among the general public, misconceptions about antibiotics include their ability to treat all infections, including viral infections, and underestimating the threat of antimicrobial resistance. For health care workers, targeted awareness campaigns may be needed to reinforce the importance of appropriate use and change perceptions and practices.

The WHO *TAP toolbox: exercises, tools and templates to support your tailoring antimicrobial resistance programmes plan (62)* and the *WHO TAP quick guide: a practical handbook for implementing tailoring antimicrobial resistance programmes (63)* are useful resources to guide countries with understanding AMR awareness and perceptions on AMR. It is recommended that countries reference these documents and consider following the exercises included in these tools as part of designing AMR awareness campaigns. Additionally, some countries have ongoing AMR awareness programmes or campaigns that have been developed as part of AMR national action plans. In countries that have mature AMR CCs, there may be technical working groups on awareness and education. If there are ongoing awareness efforts, and such technical working groups exist, it is recommended to leverage the expertise and skills already operating to support enhancing AMR awareness as part of the antibiotic introduction plan.

When developing activities to increase awareness, it is also important to engage communities and civil society organizations, including professional associations, in both the design and implementation of awareness activities. Community and civil society engagement and consultation is recommended throughout the entire antibiotic introduction process, and it is especially important when developing approaches to improving local AMR awareness. Engagement includes working with local leaders such as religious leaders, teachers, professional associations and community influencers to understand behaviour and spread awareness. Facilitated sessions or workshops can be held with different community and civil society groups to hear from health care workers, people living in high-risk areas or their experiences with antibiotic access and use. Other strategies could include developing education programmes such as peer-to-peer education programmes to spread the importance of AMR prevention and control.

To inform awareness campaigns (i.e. the strategy and messaging), countries can consider budgeting activities to conduct a baseline survey with the aim of assessing public or health care worker knowledge, attitudes and practice on antimicrobial use and AMR.

Awareness programmes and campaigns should have clear objectives with simplified messages that are tailored to the local setting and audiences, using real-life examples and that leverage multichannel approaches (e.g. using videos, infographics, social media content, local radio, television, and community newsletters etc.). Implementing targeted public health campaigns using multiple channels can raise awareness on the appropriate use of antibiotics, including the importance of seeking advice from a health care professional before using an antibiotic, the importance of newly introduced antibiotics and the increasing risk of the AMR. Individuals can play a major role in preserving antibiotics, so campaign messaging should focus on empowering individuals through education, language and cultural connections to improve awareness. Other awareness-raising approaches include integrating AMR themes into school curricula to empower future generations with knowledge about responsible antibiotic use and the impact of AMR on public health. Individuals, groups, schools, associations or community/civil society-led organizations should also be recognized for their contributions in AMR awareness, so profiling appropriate antibiotic use and efforts to promote AMR awareness is also another strategy to consider.

Below are some illustrative examples of the key objectives and areas of focus for key messages in an AMR awareness campaign. In the antibiotic introduction plan, both the objectives and key messages of an awareness campaign need to adapt to the local context and for the intended audiences. Key messages particularly should be culture-, and context-specific (i.e. educational materials should be tailored to fit local languages, cultural practices, and health care systems).

Illustrative key objectives of an AMR awareness programme or campaign (non-exhaustive):

- Educate communities/civil society organizations.
- Encourage responsible use.
- Foster community/civil society engagement
- Encourage dialogue between patients and health care workers.

Illustrative focus areas of key messages in an AMR awareness programme or campaign (non-exhaustive):

- Overuse and misuse.
- Importance of compliance and adherence.
- Manging non-bacterial infections without antibiotics.
- Individual and community-led prevention measures (e.g. WASH, vaccination, safe food handling etc.).

Annex 19. Planning monitoring, evaluation and quality improvements

Monitoring antibiotic use is a critical component of preserving efficacy. It is also important for evaluating the impact of introducing an antibiotic on patients and other parts of the health system. For these reasons, the introduction of an antibiotic requires a comprehensive approach to rigorous monitoring and evaluation (M&E) of its use. The antibiotic introduction plan should include planning M&E and quality improvements that involves key stakeholders, measurable targets and indicators, the use of available technologies and surveillance systems to continuously collect data, and a process to analyse collected data. These factors are all important for ensuring that the antibiotic is used efficiently and responsibly, and to ensure that the introduction is on track, or to identify when it may require course correction.

To monitor and evaluate AMR prevention and control progress of AMR NAPs, WHO has developed the tool: *Monitoring and evaluation (M&E) of the Global action plan on antimicrobial resistance (69)*. This document includes an M&E framework as well as recommended indicators for NAPs. More specifically, WHO has made available a Guidance to facilitate M&E for AMR NAPs *(70)*. This provides assistance on how to develop an M&E plan for NAPs, building on existing national reporting systems and recommended indicators from the action plan.

In addition to managing NAP M&E, the antibiotic introduction programme needs to be monitored and assessed for both success and impact. The NAP M&E guidance can be tailored to make an M&E framework, that includes indicators relevant for the antibiotic(s) being introduced.

19.1 Collect baseline evidence to support clinical best practice

When developing an M&E plan for the introduction of an antibiotic, there are different types of data that need to be gathered, and different infrastructure requirements to consider.

Collecting baseline evidence before rolling out an antibiotic is important for understanding the public health and clinical need, but to also set targets for planned indicators. Baseline data collection is also useful for improving data quality and understanding the current need, the problem, and setting M&E indicators, including both their numerators and denominators.

Obtaining high quality data on antibiotic coverage can be challenging in many countries, so identifying accurate denominators – that is, the total number of people in the target population – can be especially difficult due to inaccurate census estimates or projections, or multiple sources of population data, all with different estimates. As **Reserve** and **Watch** products will be used in hospitals, patient days or admissions could be used as alternative denominator if population data is weak.

Other points of consideration for collecting baseline data are the workload involved in data collection, reporting and analyses, who is responsible to collect data, how it will be stored and how it will be utilized.

As part of a robust surveillance system, and to detect warning signs that need urgent attention, countries should also ensure that a strong pharmacovigilance system to monitor adverse drug reactions, drug resistance, toxicities and treatment failure, in line with WHO guidance, is in place.

The following includes suggested sources and approaches to collecting baseline data, noting that the approach taken to collecting baseline data should be adapted to the local setting, and considers local capacities and resources.

19.1.1 Collect baseline data at the national level

In settings with more mature data collection and reporting systems, it might be possible to collect and utilize data collected through diagnostic, laboratory and surveillance systems, and basic health information systems, that can track both AMU and AMR. In these settings, surveillance systems should ideally monitor AMU at a national aggregate level, and should also capture data at local and sub-national levels.

However, if these data are not available, national aggregates can also be collected through global data repository and AMR surveillance projects, and other national sources. For example:

- WHO GLASS includes aggregated AMU data at the national level *(26).* GLASS-AMU data provides information on the types and quantities of antimicrobials used annually by reporting countries. Key GLASS-AMU indicators include total use and relative use of antimicrobials (by AWaRe classification, pharmacological classes, route of administration) and most used antimicrobials.
- The Global Point Prevalence Survey (GPSS) *(65)* can be used as a measurement benchmark as it includes data on hospital-acquired infection rates, as well as AMS and AMU. It compares facilities to each other within a country, and also globally.
- The GRAM study *(25)* can be useful in collecting baseline data to develop specific indicators. It can also be used to assess the cost-comparison or cost-benefit of different delivery interventions of the antibiotic (e.g. if implemented, data could be used to evaluate the cost-effectiveness of a hub-and-spoke distribution model).
- National antibiotic use patterns (such as relative use by AWaRe classification) could be used as access and appropriate use indicators, but further work is likely needed to appropriately utilise AMU data to develop national estimates and determine an adequate level of use for different antibiotics and AWaRe categories.

- Academic groups have also outlined approaches *(169)* using national disease burden information and demographic characteristics to model ranges for appropriate levels of use, which can help countries set baseline indicators and targets.
- National data on pharmaceutical expenditure/spending on antibiotics should be collected at baseline if available.

19.1.2 Collect baseline data from facilities

A good place to start is to work with facilities to find out what data sets exist at the facility and the data collection channels in use. This approach can be a practical way to overcome national data limitations and resource challenges. For example, hospital pharmacies might have substantial or useful data on antibiotic prescription or stock rotation, which can be obtained from routine prescription and/or reimbursement audit systems.

Other ways to collect baseline data at facilities can be through AMU point prevalence surveys (PPSs) that survey antibiotic prescribing practices and can be used to identify the number of people with a disease or condition at a specific point in time. If there is limited capacity to develop a PPS, there may be surveys published in the literature or surveys from other countries that can be followed and implemented. WHO has supported 10 African countries to undertake PPS on antibiotic use and collect patient-level data on antibiotic treatments at hospitals. Indicators built around PPS may facilitate more nuanced analyses on the quality of prescribing and also patient equity in terms of the use of and access to antibiotics, affordability, or access to **Reserve** antibiotics.

How and when data will be collected at facilities also needs to be considered. If there is limited capacity, a phased approach might be more suitable where basic information is collected in the first stages of rolling out the antibiotic, and then progressing to more detailed data as milestones are achieved. Additionally, there can be simple, efficient approaches to collecting baseline and routine data. For instance, many individuals working in facilities have access to smartphones that have free communication applications. These applications, such as WhatsApp for example, could be used to create specific AMU or AMR communication channels where data are both collected and shared.

Case study

Implementing a national point prevalence survey to establish baseline data through regional collaboration

Bhutan, a small Himalayan kingdom with a population of 0.7 million people, has made significant strides in improving health care access and AMR. The country has demonstrated a strong commitment to AMR-related policies and activities. In 2017, Bhutan endorsed the National Action Plan on Antimicrobial Resistance with a One Health focus *(170)* and in 2018 national antimicrobial prescribing guidelines were developed, endorsed and implemented across all hospitals *(170)*. While Bhutan's AMR national action plan promotes the appropriate use of antibiotics, baseline data on appropriate use and clinician prescribing practices across four sentinel sites across the country had never been collected *(171)*. To overcome limited data availability, individuals from facility AMS units worked with the Fleming Fund and the National Antimicrobial Stewardship Centre (NCAS) in Australia to adapt and utilize the Australian National Antibiotic Prescribing Survey (NAPS) to collect baseline data. Subsequently, in June 2022, a point prevalence survey on antibiotic use among inpatients was conducted in Bhutan using the NAPS. Conducting the survey uncovered key areas for targeted AMS programmes in Bhutan including improving facility policies and algorithms on the duration of use, improving antibiotic use to align with national guideline recommendations including improving antibiotic use for surgical prophylaxis *(172).*

Since conducting the first point prevalence survey, Bhutan's health care system continues to collect and analyse data on antibiotic prescriptions, resistance rates, and patient outcomes. This data-driven approach allows for timely interventions and adjustments to antibiotic policies and practices, ensuring that they remain effective and relevant. Additionally, efforts are underway for sharing AMR data generated from laboratories around the country at the global level, and progress is being made towards establishing an AMR surveillance network for both human and animal sectors under the coordination of the National Referral Laboratory *(172,173).*

19.1.3 Develop recording and reporting tools or templates to efficiently collect evidence

For data collection and monitoring of the roll-out and use of the antibiotic, it is recommended that recording and reporting tools or templates to efficiently collect evidence are developed. It may be essential to work with national statistics departments to develop reporting forms and templates. Other government departments may be able to support linking forms to electronic data information systems and find ways to harmonize data collection to minimize the burden on the health workforce. Recording and reporting tools should include measuring the appropriateness of treatments prescribed as part of routine antimicrobial use activities. Before using the tools widely, they should be tested for ease of use and functionality. Adequate training is then needed to ensure that the reporting and recording tools are correctly used (see 17.1.4).

19.1.4 Develop a thorough risk management strategy

Introducing an antibiotic comes with some risks, and for **Reserve** and **Watch** antibiotics the risk that they will be overused is a serious concern. It is therefore essential to develop a thorough risk management strategy at baseline to track risks and have risk mitigation plans ready to respond to any concerns as they may arise.

19.2 Update information systems

Information systems should be updated to capture information relevant to the antibiotic being introduced. Introducing an antibiotic may also present opportunities to revise or update health information systems including national health databases (e.g. DHIS2) and logistics management information systems, to improve data quality and ensure existing systems have the capacity to collect data relevant to introducing a given antibiotic. This may involve coordinating with the departments responsible for creating, revising, printing and/or distributing health information system forms, or planning to integrate new data points into the system so they are ready for use once the product is rolled out.

19.3 Develop a national level M&E framework to measure impact

Once baseline evidence has been collected, a national level M&E framework to measure the impacts of the antibiotic introduction can be developed. To develop the framework, consider the data collection methods (e.g. data collection can be qualitative or quantitative in nature). Qualitative data collection methods include surveys, interviews, focus groups and observation. Quantitative data collection methods include surveys, questionnaires and secondary data analysis. To avoid duplication of effort, existing M&E frameworks for other similar health-related programmes should be reviewed and adapted where possible.

There is also available guidance on collecting, synthesizing, analysing and presenting data that can be used in developing the framework. As mentioned, WHO has developed Guidance to facilitate M&E for AMR NAPs *(70),* which can be tailored to a new antibiotic introduction programme. Other useful guidance includes MEASURE Evaluation's publicly available guidance on how to collect data and use data for M&E *(71)*. The M&E framework should include useful, relevant, measurable indicators that aim to monitor and evaluate the impact the antibiotic introduction. Some illustrative examples of indicators that may be relevant for an antibiotic introduction plan are detailed in section 19.3.2

19.3.1 Set the evaluation frequency

Evaluation frequency should also be set out as part of the M&E framework. For example, it is useful to evaluate progress at six and/or twelve months after the product has been introduced. Data collection and analysis should be ongoing and used to inform decision-makers about progress, ways to improve the use of the newly introduced antibiotic, or new issues that might need addressing. For example, data could indicate that there is a strong rationale to focus efforts or to expand access of the antibiotic to vulnerable populations such as neonates and children.

Throughout the course of antibiotic introduction, the framework can be used to track and monitor the impact of the antibiotic introduction on AMU, AMR and patient outcomes e.g. tracking impact on morbidity and mortality.

19.3.2 Develop indicators as part of the M&E framework

There are three key drivers for developing indicators for introducing an antibiotic:

1. Tailoring indicators to the local context, considering the local infrastructure, data availability and local disease trends.
2. The type of infrastructure to allow for real-time or regular monitoring. Consider what surveillance (including pharmacovigilance) and/or digital infrastructure is in place that can support elements of the introduction plan, such as monitoring prescription practices, adverse events, and/or for tracking stock levels. Where possible, leverage existing national health information systems such as DHIS2 and LMIS for data collection and reporting
3. Identify feedback loops so that findings from implementing the M&E plan are fed back into operational processes and implementation/strategies are adjusted as needed.

The following provides some illustrative, non-exhaustive indicators that could be used to evaluate the progress and impact of the antibiotic introduction plan. These example indicators are aligned to the theory of change example in Annex 10, but indicators can be grouped and categorized in many ways. It is also recommended that local M&E tools are utilized, if available, and the illustrative indicators below are tailored for the antibiotic being introduced and to the local setting, including baseline data available to inform relevant indicators and infrastructure available to collect data to track progress.

Impact (goal): Increased access alongside the preservation and sustained efficacy of antibiotics, reducing mortality associated with drug resistant bacterial infections

Global Health Observatory *(64)* indicators: WHO is currently developing a composite index for access to health products that will combine existing indicators already reported by countries, which measure antibiotic use patterns. If a country is already reporting these data to the Global Health Observatory, then they could be used as impact indicators and to gauge baselines for AMU:

- Pattern of antibiotic use at national level expressed as relative use of antibiotics by AWaRe classification *(174)*.
- ≥60% of total antibiotic use are **Access** group antibiotics (GPW13 Target 4b) *(175)*.
- Total use of antibiotics expressed as defined daily doses (DDD) per 1000 inhabitants per day *(176)*.

Other impact indicators

- Reduction in mortality rate of patients with drug-resistant bacterial infections in target facilities (e.g. proportion of patients treated with the newly introduced antibiotic who fully recover).

Outcome 1: Antibiotics with a high public health and clinical need are adopted nationally

1.1 National policies (e.g. nEMLs and essential diagnostic lists updated to include newly introduced antibiotic(s) and related tests.

1.2 National formularies and treatment guidelines updated to include newly introduced antibiotic(s).

1.3 Health technology assessment (e.g. budget impact analysis or cost comparison) conducted for antibiotic being introduced.

1.4 Percentage change in cost per patient treated with the newly introduced antibiotic(s) compared to alternative treatments.

1.5 At least one **Reserve** antibiotic included in national social health insurance or reimbursement schemes (as applicable).

1.6 Proportion of budget need allocated for implementation of the introduction plan.

Outcome 2: Streamlined regulatory policies and processes for the timely authorization of antibiotics

2.1 At least one quality product registered, or granted an alternative availability route (i.e. compassionate access, or emergency use etc) with the national regulatory authority.

2.2 Pharmacovigilance and post-marketing surveillance reports from market authorization holder received quarterly (as appropriate).

2.3 Regulatory policies in place and enforced to support the appropriate use of antibiotics.

Outcome 3: An efficient supply chain with minimal stock-outs and sufficient supply to meet demand

3.1 Improved forecasting and quantification for the antibiotic/s where procurement volumes match forecasted demand (+/- 5%).

3.2 Percentage of facilities with stock-outs or overstock of the antibiotic.

3.3 Proportion of facilities with stock that has expired or been discarded.

3.4 Proportion of target health care facilities (i.e. hospitals, clinics) on plan where the antibiotic is available.

3.5 Proportion of eligible patients who received the antibiotic(s) within a specific time period (e.g. ≤ 2-day turnaround time between request to use antibiotic (for **Reserve** antibiotics) and patient initiation).

Outcome 4: Antibiotics are used appropriately and patient outcomes improved

4.1 Number of target facilities trained to administer and use the antibiotic(s) appropriately, including pharmacovigilance.

4.2 Number of target facilities using the antibiotic(s) in line with national policy and programmes for appropriate use (i.e. antimicrobial stewardship programmes):

- Proportion of prescriptions for the antibiotic(s) that adhere to national guidelines for antimicrobial use.
- Percentage of health care workers adhering to updated clinical guidelines post-training.
- Proportion of patients where antibiotic treatment is initiated following a confirmatory test.
- Change in overall use of antibiotics before and after the antibiotic introduction.
- Percentage of patients receiving the correct dosage, duration and route of administration.

4.3 Proportion of patients receiving **Watch** or **Reserve** antibiotics appropriately, as defined by WHO AWaRe (**Access**, **Watch**, **Reserve**) classification.

4.4 Average reduction in hospital length of stay for patients treated with the newly introduced antibiotic.

4.5 Proportion of patients who experience adverse drug reactions (through pharmacovigilance systems).

4.6 Communication plans implemented according to plan.

Outcome 5: Strengthened laboratory/diagnostic capacity and local data available for better decision making

5.1 Number of laboratories trained and with capacity to test for related infectious pathogen(s), including MDRO.

5.2 Emerging resistance linked to the newly introduced antibiotic reported within 48 hours – 1 week of identification (measured through AMR surveillance).

5.3 Proportion of patients who experience treatment failures (through pharmacovigilance systems).

19.4 Operational research and antibiotic introduction

If resources permit to expand M&E frameworks beyond routine data collection and assessment, it is recommended that countries design and set up operational research as a framework for assessing the impact and effectiveness of the antibiotic introduction plan. Operational research can be used to put structure around the way the challenges and issues are identified through antibiotic introduction activities and find solutions that can then be fed through feedback loops to course correct or continue as planned. It can also help with making improved future decisions so that efforts are more efficient and effective in achieving a goal.

Operational research can take many forms. At a minimum, it should specifically aim to measure the effectiveness of the introduction plan, as well as adherence to it and areas for improvement. For example, it can include assessing the impact and/or cost-effectiveness of an antibiotic delivery model (e.g. hub-and-spoke), or it may assess the cost-effectiveness of a newly introduced antibiotic; or it can also evaluate the effectiveness of surveillance systems. It can also provide insights on and test project assumptions including the intended impact of certain interventions (e.g. did the hub-and-spoke model improve treatment availability for patients? Or how accurate was the original costing estimates for the introduction plan?).

To develop optimal operational research questions, it is important to consider if there is a current research agenda for antibiotics? What needs to be tested in the antibiotic introduction plan to assess its impact? What data are needed to inform and/or improve decision-making on introducing an antibiotic? What data gaps need addressing? **Table A6** provides some illustrative examples of the different types of operational research questions countries may consider when planning any research around the introduction of an antibiotic.

Table A6. Illustrative examples of some operational research questions for introducing an antibiotic(s)

Thematic research area	Example questions
Impact on access and availability	• What impact has the introduction plan had on the availability of antibiotics? • How widely available is the newly introduced antibiotic nationally, sub-nationally and at facilities? • What are the persistent barriers to access and equitable distribution of the antibiotic? • Have regulatory efforts increased the number of quality products available over x years? • Have pricing strategies for the antibiotic been effective in lowering national purchasing prices and patient out-of-pocket costs? • How does the cost-effectiveness of the new antibiotic compare to alternatives?
Impact on appropriate use	• Are prescribing patterns consistent with national and/or global guidelines? • How frequently is the newly introduced antibiotic being used incorrectly (i.e. rate of appropriate vs inappropriate use)? • Are there clear disparities in prescribing between different health care settings (e.g. urban vs rural, public vs private)?
Impact on AMU and AMR	• How effective are existing surveillance systems in tracking AMU and AMR associated with the newly introduced antibiotic? • What are the persisting gaps in pharmacovigilance and adverse event reporting for the newly introduced antibiotic? • Are data on use patterns effectively used to adjust supply and improve treatment availability? • Have the planned appropriate use (stewardship) activities and efforts led to a reduction in the use of antibiotics? • What is the impact of the newly introduced antibiotic on antimicrobial resistance patterns over time? • How has the introduction affected the overall antibiotic consumption (nationally or at treating facilities)?
Impact on patient outcomes	• What are the clinical outcomes (e.g. recovery rates, reduced hospital stays) for patients treated with the new antibiotic compared to previous treatments? • Are there specific patient populations (e.g. children, women, immunocompromized patients) who benefit more from the newly introduced antibiotic? • What proportion of patients experience adverse events and/or treatment failures? • How are treatment failures and adverse events being managed in real-world settings?
Impact on antibiotic delivery	• Are distribution models (e.g. hub-and-spoke) effective in the timely and efficient delivery of antibiotics? • How effective is the supply chain/the implemented distribution model in ensuring timely delivery and avoiding stock-outs or expiries? • What are the key challenges for distributing **Reserve** and **Watch** antibiotics?

If operational research is not initially feasible due to resource limitations, or there is an urgent need for an antibiotic and so operational research cannot be planned in advance – or the introduction plan does not lend itself to research as part of evaluating the antibiotic introduction plan – it is important to ask the following questions:

- What lessons can be drawn from the antibiotic introduction that can inform future product introduction programmes?
- Are there emerging gaps in evidence that should be addressed through further research?
- What operational research opportunities have emerged to improve appropriate use practices or the broader AMR strategy?

19.5 Leverage introducing an antibiotic to inform future research

While the primary focus of the M&E framework should be on assessing the success of the introduction plan including outcomes and impact, research questions and additional data collection activities could be opportunistically incorporated into the M&E framework with the purpose of identifying evidence gaps, as well as areas for future academic and operational research on AMU and AMR.

This information can be used to inform new strategies and models that support appropriate use and could contribute to the development of a broader implementation science agenda for introducing antibiotics. Additionally, data collected through M&E could also inform operational research needs that could improve existing or future product introduction strategies:

- Consider using a tool to track uptake trends on a more frequent basis than regular reporting in the early stages of roll-out to monitor uptake against planned usage and available supply.
- Monitor antibiotic use patterns and support adjustment of the supply plan accordingly (closely monitor high-volume facilities as these greatly impact stock availability).
- If uptake is slower than planned, consider strategies to utilize existing stock and avoid expiries and waste (e.g. stock-sharing across facilities).
- Monitor supplier performance to ensure suppliers are delivering according to their contractual obligations.

Case study

An end-to-end solution to drive rapid uptake and expansion of a new multidrug-resistant tuberculosis treatment regimen

Approval of the new drug pretomanid (Pa) as part of the BPaL regimen (i.e. bedaquiline, pretomanid and linezolid) by stringent regulatory authority (in 2019) for the treatment of pre-extensively drug-resistant TB (pre-XDR TB), offered a simplified treatment regimen and improved success rates up to 90%. However, there were several access challenges that prevented large scale use of this treatment. This included a lack of global policy and country awareness and a very small market segment, which made it difficult to create a viable market for manufacturers to service.

To address these challenges and to create a sustainable market for pretomanid, the drug's non-profit developer, the TB Alliance, worked in collaboration with countries, WHO and other key partners to design and implement a range of strategic interventions that have helped catalyse the widest and most rapid roll-out and uptake of a new TB treatment.

Engagement with WHO on policy and regulatory alignment: The TB Alliance worked with WHO proactively to provide data and to enable BPaL's inclusion in WHO initial guidelines resulting in a rapid communication from WHO within four months of the first SRA approval. The initial guideline for the narrow segment of pre-XDR-TB opened the market for pretomanid and enabled initial use. Subsequently, the TB Alliance and Médecins Sans Frontières (MSF) worked with WHO to provide evidence from further clinical trials to help expand the scope of guidelines to almost all of MDR-TB, multiplying the addressable segment of pretomanid 10–20 fold, establishing BPaL as the regimen of choice within 2.5 years. The TB Alliance also worked to engage and inform other stakeholders such as the Global Fund, resulting in endorsements for the regimen that helped country-level adoption of WHO guidelines. Working with the manufacturer, the TB Alliance facilitated rapid regulatory submission and registration of pretomanid by national regulators, starting with high-burden countries (e.g. India became the first country after the United States Food and Drug Administration to approve pretomanid – in less than one year).

Early engagement with national TB programmes: The TB Alliance's early engagement with national TB programmes, even while clinical trials were ongoing, proved very helpful for eventual integration of BPaL into national treatment protocols, resulting in swift adoption of the new treatment regimen in several countries. During early engagement with countries, the TB Alliance conducted research to understand the types of evidence gaps that typically existed at the time of introducing a new treatment, and the data countries needed to make decisions about protocol changes for introducing new treatments such as BPaL. This was accomplished through a variety of appropriate market studies conducted in a set of representative countries. It identified common evidence gaps and requirements including limited local evidence, limited cost effectiveness data, need for country level gap-analysis for laboratory and clinical infrastructure, guidance on how to transition from older regimens, and integrating BPaL into existing TB treatment protocols, strengthening drug safety monitoring, as well as capacity building of health care workers, etc.

Case study (cont.)

Generating evidence to support national decision-making: Guided by results of market studies, the TB Alliance work identified and engaged early adopter countries to conduct multi-country implementation projects in 9–10 high-burden countries. The projects, implemented as operational research (or pilots) generated field evidence and local experience and paved the way for programmatic use of BPaL in these high-burden countries.

Additionally, the TB Alliance worked with countries to conduct cost-effectiveness and budget impact studies to generate further local evidence to help examine and establish value proposition for BPaL. These studies provided insights into how the new treatment could benefit patients and health care systems, including the cost-saving potential of the new regimen for both TB programmes and people with TB in countries.

Findings from implementation projects and costing studies supported country-level guideline change. In most cases, implementation plans were also developed to facilitate rapid and smooth transition of guidelines into scale-up and routine clinical practice. The projects created real-world examples for other countries to follow and resulted in global momentum for BPaL.

These interventions executed in a large number of representative countries helped in the creation of a sustainable market.

The TB Alliance was able to work in a relatively large number of countries by engaging local partners as often as possible. This approach offered deeper insights into country-specific processes, facilitated more efficient decision-making and communication, and ultimately enhanced cost-effectiveness.

Knowledge hub for capacity building: To further support the global scale-up of BPaL, the TB Alliance established PeerLinc, a knowledge hub for capacity building. Relying on a peer-to-peer learning approach, PeerLinc brings together findings and best practices from operations research, pilot programmes and implementation experience of early adopter countries, and provides training and capacity building in clinical, laboratory and programmatic management aspects of MDR-TB, helping countries adopt and scale up BPaL. Led by the TB Alliance and hosted by the Tropical Disease Foundation, the PeerLINC programmes are delivered by experts who gained early and deep experience with BPaL. The programme closely collaborates with the Department of Health of the Philippines, where PeerLINC is based and has successfully facilitated free, efficient and rapid information exchange and capacity-building projects in countries in Asia, Africa, and South America within six months of its formation, aiding regional and international collaboration.

Community engagement: Community engagement was a key component to the successful introduction of BPaL. It began early on in the implementation process, focused on co-creation and partnership with local communities, and aimed to empower them to raise awareness and educate their peers about new treatments. This played a vital supporting role in demand generation and scale up. Community partners continue to orchestrate community-led activities that increase grassroots demand for new treatments and support rapid scale up. These efforts have been conducted most prominently through a multi-country project called ‘Fast-track-the-cure’.

Case study (cont.)

Market shaping strategies to reduce price: While pretomanid was introduced at an access-friendly price – which was 60–80% lower than lowest comparable prices of new TB medicines introduced in LMICs in the past decade – the TB Alliance brokered a volume guarantee with another non-profit MedAccess and the pretomanid manufacturer helping reduce the price by another 34% within two and half years of the initial WHO guideline in mid-2020. The resulting price reduction in late-2022 was timed to coincide with a major guideline update by WHO that multiplied the addressable market for BPaL several times, by expanding the use of pretomanid and BPaL to almost all of MDR-TB. The alignment of a significant price reduction and WHO guideline publication provided a major global boost to the uptake of BPaL. At the lower price, countries were able to purchase more treatments for the same cost, enabling access for almost all MDR-TB patients who became eligible for the treatment. This helped increase pretomanid volume to the range of viability and ensured the supplier would be able to sustainably supply the drug. In addition to a volume guarantee, the TB Alliance has supported expanding the manufacturer base to increase market competition. These suppliers are expected to gain WHO pre-qualification soon, which will further reduce prices, further increasing availability of pretomanid.

The TB Alliance's comprehensive approach in which high-, moderate- and lower-burden countries have all progressively been engaged over a relatively short period of three to five years, has successfully transformed a small, unstable market for pretomanid into a sustainable and viable one. As of mid-2024, more than 85 countries had procured the drug. By orchestrating collaboration among global and national stakeholders, implementing innovative market strategies, and providing sustained leadership to access efforts, the TB Alliance ensured that a critical new treatment reached the patients who needed it most. Key strategies such as early policy, stakeholder, regulatory and programmatic engagement, capacity building, and market shaping provide learnings when planning to introduce antibiotics.

Annex 20. Additional case studies

20.1 Case study. India's success with introducing new antibiotics

India has faced significant challenges with AMR and has made notable strides in introducing and managing the use of new antibiotics.

In 2011, the Indian Government introduced the 'H1 rule' to prohibit over-the-counter (OTC) sales of antibiotics without a prescription, responding to the growing concern over AMR. However, due to the health care system's heterogeneity across the country, implementation of this rule has faced significant challenges, and no state government has adopted it, with the exception of Kerala.

In 2013, the Indian Government modified the rule to limit the OTC restriction to second- and third-line antibiotics, allowing the sale of first-line antibiotics without a prescription. This modification was aimed to ensure that life-saving antibiotics remained accessible to the public, especially in remote areas of the country *(177).* However, Kerala's Operation AMRITH (Antimicrobial Resistance Intervention for Total Health) abides by the H1 rule prohibiting sale of any class of antibiotics without a prescription.

Kerala Antimicrobial Resistance Strategic Action Plan (KARSAP)

KARSAP is a standout example within India. Launched in response to rising AMR, KARSAP integrates a One Health approach, involving multiple stakeholders from health care, veterinary and environmental sectors. Key components of KARSAP include:

- Surveillance and monitoring: Establishing robust systems to track antibiotic use and resistance patterns.
- Antibiotic stewardship programmes: Promoting the appropriate use of antibiotics through guidelines and training for health care providers.
- Public awareness campaigns: Educating the public about the dangers of antibiotic misuse and the importance of adhering to prescribed treatments

In line with KARSAP, in January 2024, Operation AMRITH was launched by Kerala's Drug Control Department to combat the sale of antibiotics without prescriptions. Under the initiative, pharmacies must keep accurate records of antibiotic sales and posters stating: "Antibiotics not sold without doctor's prescription" should be displayed in establishments. The public can also participate in this initiative by reporting any pharmacies selling antibiotics without a prescription to the Drug Control Department. Unannounced raids are conducted under this initiative, as well as availability of a toll-free number provided to the public for lodging complaints. Strict action is taken against pharmacies and medical stores that supply antibiotics without doctor's prescription *(178).*

Strengthening regulatory frameworks

India has reinforced its regulatory frameworks to control the sale and distribution of antibiotics. The Central Drugs Standard Control Organization (CDSCO) plays a crucial role in regulating the approval and post-market surveillance of new antibiotics. Stricter regulations have been implemented to curb over-the-counter sales of antibiotics, ensuring that they are dispensed only with a valid prescription.

Collaboration with international organizations

India's success in introducing new antibiotics is also attributed to its collaboration with international organizations such as WHO and GARDP. These collaborations provide technical support, funding and access to global best practices, enhancing India's capacity to manage antibiotic use effectively.

Research and development initiatives

India has been proactive in fostering R&D in the field of antibiotics. Initiatives such as the India Council of Medical Research AMR research programme support the development of new antibiotics and alternative therapies. Public–private partnerships have been instrumental in advancing R&D efforts, leading to the introduction of innovative treatments to combat resistant infections.

Impact and outcomes

The combined efforts of policy implementation, regulatory strengthening, public awareness and international collaboration have led to significant improvements in the management of antibiotic use in India. Notable outcomes include:

- Reduced misuse and overuse of antibiotics in health care settings.
- Enhanced capacity for AMR surveillance and monitoring.
- Increased public awareness about the risks associated with antibiotic misuse.

Conclusion

India's multifaceted approach to introducing and managing new antibiotics offers valuable lessons for other LMICs. The successful deployment of initiatives such as KARSAP underscore the importance of comprehensive policies, strong regulatory frameworks, international collaboration, and public engagement in combating AMR.

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Annex 22. List of participants of the Technical Consultation on Country Preparedness for the Introduction and Preservation of Essential Antibiotics: Operational Guidance, 25 – 26 June, WHO headquarters, Geneva, Switzerland

Participants (in person)		
Name	**Affiliation**	**Country**
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Dr Paul Bouanchaud	Senior Research Adviser, Population Services International	United Kingdom
Dr Sujith J Chandy	Executive Director, International Centre for Antimicrobial resistance solutions (ICARS)	Denmark
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Dr Jennifer Cohn	Director Global Access, GARDP	Switzerland
Dr Kim Faure	SECURE Lead, GARDP	Switzerland
Ms Cecilia Ferreyra	Director of Antimicrobial Resistance Programme	Switzerland
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Participants (in person)		
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Ms Tracie Muraya	Head Policy & Strategy, ReAct Africa	Kenya
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Mr Angus O'Shea	CEO, ARANDA	United States
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Mr Michiel Peters	Secretariat Representative, AMR Industry Alliance	United States
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Dr Robert Skov	Science Director, International Centre for Antimicrobial resistance solutions (ICARS)	Denmark
Prof Mike Sharland	Professor and consultant in paediatric infectious diseases, St Georges University	United Kingdom
Mr Luka Srot	International Federation of Pharmaceutical Manufacturers and Associations/AMR Industry Alliance	United Kingdom
Dr Nur Sufiza Ahmad	Deputy Director, Pharmacy Service and Development Division, Malaysian Ministry of Health	Malaysia
Dr Jun Sugihara	Principal Deputy Director, Division of Infectious Disease Prevention and Control, Public Health Bureau, Ministry of Health, Labor and Welfare of Japan	Japan
Mr Martijn van Gerven	Research Coordinator, Access to Medicine Foundation	Netherlands
Dr Linda Venczel	Director, Epidemic Preparedness and Response Program, PATH	United States
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Dr Philippe Doo-Kingue	Technical Officer, AFRO	Republic of the Congo
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Mr Walter Fuller	Coordinator (Stewardship), AMR, AFRO	Republic of the Congo
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WHO headquarters		
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Ms Erika Duena Loayza	Technical Officer, MHP	Switzerland
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Dr Valeria Gigante	Team Lead, IRC	Switzerland
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Dr Jorge Matheu	Team Lead, IRC	Switzerland
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Mr Arno Muller	Team Lead, CSR	Switzerland
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Mr Jean-Pierre Nyemazi	Acting Director of GCP, AMR	Switzerland
Dr Sarah Paulin-Deschenaux	Technical Officer, AMR	Switzerland
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