

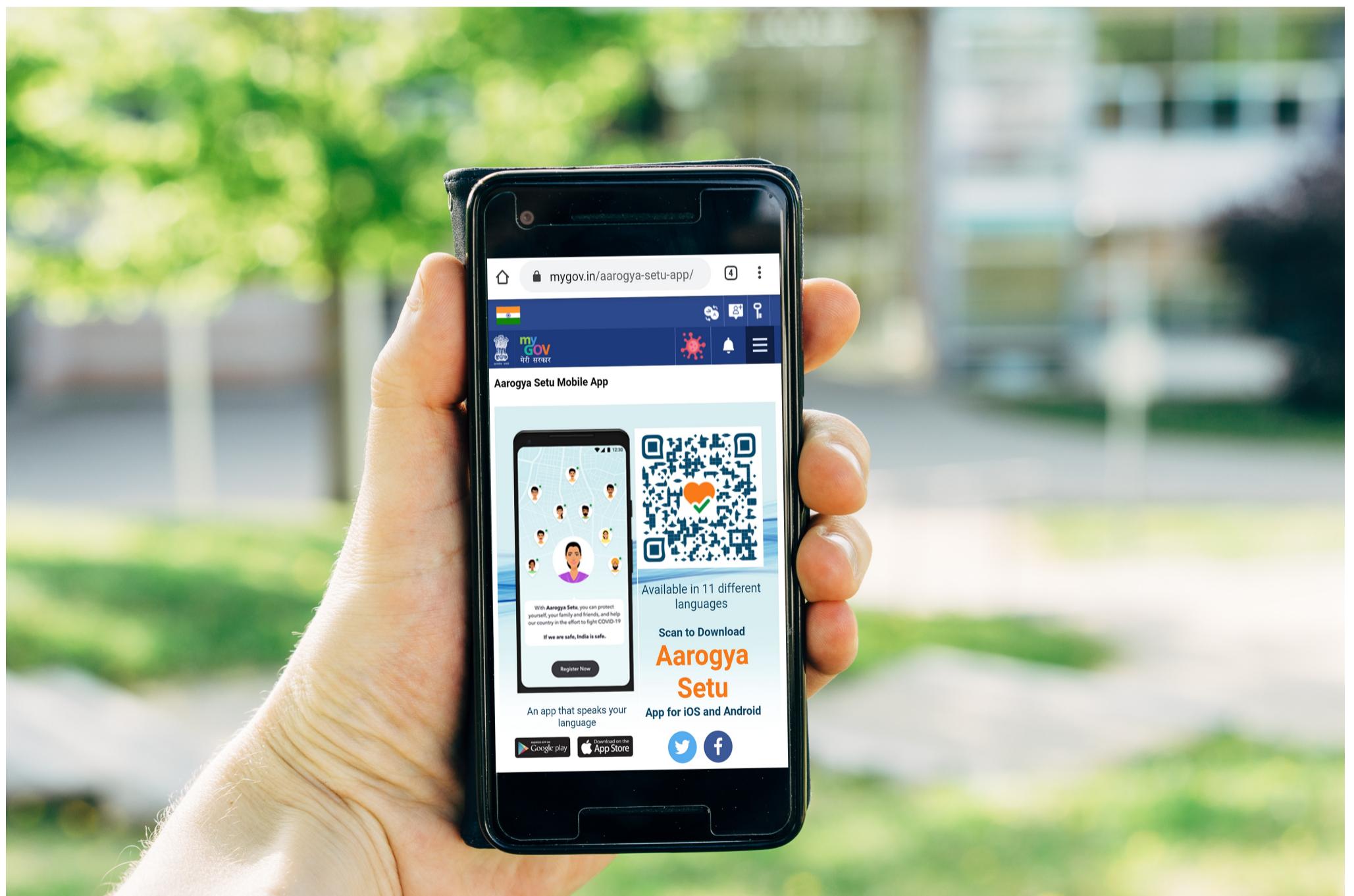
Educational Content on COVID 19

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COVID-19 CORNER

BHABHA ATOMIC RESEARCH CENTRE



COVID-19 Helpline Centre at DAE Convention Centre

Covid-19 Helpline Centre has been functioning at the DAE Convention Centre since 6th June 2020. Since the number of Covid-19 cases among DAE employees and their dependents has now significantly reduced and the public awareness about Covid-19 has taken the edge off ignorance and panic, it is proposed to discontinue the activities of the Helpline Centre and to close the Centre with effect from 13th December 2020. Until then, the Centre shall function from 9 am to 6 pm. However, for any demanding situation at odd hours, our

volunteers may be contacted on their personal contact numbers listed herewith. For the benefit of CHSS beneficiaries, Covid-19 related contact numbers and FAQ have been provided for quick reference. We record our sincere thanks to all the officials who have supported this noble endeavour.

- [**BARCH Doctors to be contacted in emergency \(for patients shifted to outside hospitals\)**](#)
- [**Contact Number of Dispensaries**](#)
- [**Procedure for Test Reports**](#)
- [**BARC Panel Hospitals for Covid-19**](#)
- [**COVID-19 Testing Labs**](#)
- [**BMC Control Room Numbers for Bed Availability**](#)
- [**Ambulance Services**](#)
- [**Volunteers to be contacted in case of urgent situations \(Revised\)**](#)
- [**Other Important Numbers**](#)

(Rev.) Standard Operating Procedure (SOP) for Covid-19

GUIDELINES FOR THE RESIDENTS REGARDING COVID-19 PANDEMIC

1. A helpline is functional in BARC hospital for answering the queries. This helpline is available at 25598402 on all working days from Monday to Friday during 10:00 am to 1:00 pm and 2:00 pm to 3:00 pm.
2. In case of any symptoms of COVID-19, kindly report to your dispensary and follow the guidance given by doctor. If the dispensary is not functioning, visit causality facility of the BARC hospital and follow the instructions given by doctors.
3. If any patient is tested positive, the concerned administrative head will be informed for facilitating the contact tracing.
4. Residents are requested to visit the 'COVID Corner' of BARC website periodically and to follow the latest instructions. The Medical Division would be sharing important information including audio and video instructions about COVID-19 at this website.
5. If a non-CHSS beneficiary family member is tested positive, Medical Division and Anushaktinagar Security should be intimated immediately.
6. If any resident in a particular building is identified as COVID-19 positive, that portion of the building will be sealed by the local authorities. If single entrance is used for more than one wing in a building, all such wings will be sealed. Movement of residents in and out from this containment will be highly restricted.
7. If any resident is Home Quarantined suspecting Covid-19 case, the residents' association or the other residents in the building are requested to help the quarantined family to meet essential needs from outside. Besides, Control Monitoring System (CMS) of Anushaktinagar security can also be contacted regarding this. The phone numbers are 25562666, 25486701 and 25486706.
8. On receipt of the information about the COVID-19 positive case, DCS&EM will carry out sanitisation of common areas in contained area.
9. Sealed condition will continue until clearance obtained from local authorities.
10. The residents of Anushaktinagar are requested to follow the COVID-19 related guidelines issued by the Ministry of Health & Family Welfare, from time to time.
11. Residents are requested to remain indoors and minimise their movement only for the essential needs.
12. The norms of social distancing should strictly be followed. Wearing of face mask is mandatory while moving outside the residence.
13. Going out of the Anushaktinagar colony should be avoided as far as possible.
14. Periodically, announcement by Anushaktinagar Security is being done in the colony and all residents are requested to adhere to the instructions.

Read PDF 

ANUSHAKTINAGAR

ANUSHAKTINAGAR, CLOSE TO NATURAL GREEN, IS A RESIDENTIAL TOWNSHIP FOR THE EMPLOYEES OF DEPARTMENT OF ATOMIC ENERGY IN MUMBAI, MAHARASHTRA, INDIA.

NOTICES & CIRCULARS REGARDING COVID-19 PANDEMIC during March-April, 2021

Sr. No.	Title	Date	View / Download
1  1	Preventive measures to contain the spread of COVID-19	16/04/2021	More..
2	Preventive measures to contain the spread of COVID-19 & Attendance	06/04/2021	More..
3	Preventive measures to contain the spread of Covid 19	01/04/2021	More..
4	Preventive measures to contain the spread of Covid 19	17/03/2021	More..
5	Regarding High risk contacts and Positive asymptomatic patient	09/03/2021	More..
6	Curbing spread of Covid-19 Infection	05/03/2021	More..

NOTICES & CIRCULARS REGARDING COVID-19 PANDEMIC during July-October, 2020

NOTICES & CIRCULARS REGARDING COVID-19 PANDEMIC during June, 2020 

NOTICES & CIRCULARS REGARDING COVID-19 PANDEMIC during May, 2020 

NOTICES & CIRCULARS REGARDING COVID-19 PANDEMIC during April, 2020 

NOTICES & CIRCULARS REGARDING COVID-19 PANDEMIC during March, 2020 

Also Visit [BARC Notices](#)

General Advisory from BARC Hospital

0:00 / 2:06

2.06 Minutes (Hindi)

Published by: Medical Division, Bhabha Atomic Research Centre, Mumbai

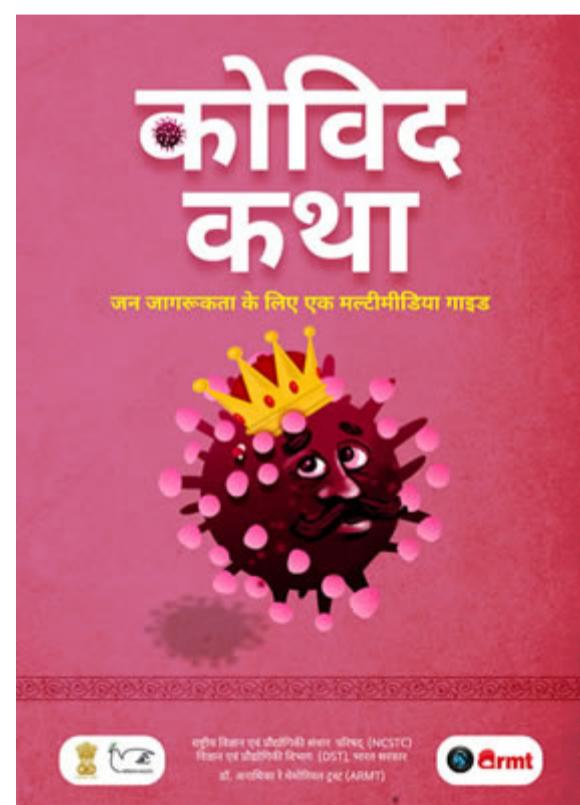
Blood Donation during COVID-19 Pandemic

0:00 / 4:31

4.31 Minutes (Animated Hindi)

Published by: Medical Division, Bhabha Atomic Research Centre, Mumbai

A Multimedia Guide for Mass Awareness



BARC HOSPITAL

BARC Hospital is multispecialty centre at Anushaktinagar, Mumbai. The hospital is accredited by the National Board of Examination (NBE), New Delhi for DNB (Diplomate of National Board) program. At a time 22 post graduate DNB student undergo through this course.

Medical Division is providing healthcare facility to the Employees of DAE and their dependant family members inside Mumbai. This facility is provided under Contributory Health Services Scheme (CHSS). For this purpose a 390 bedded Multispeciality Hospital along with 13 zonal residential dispensaries inside Mumbai and 3 occupational health centers are functioning under the Medical Division.

SOCIAL DISTANCING



USE FACE MASKS





REGULAR HAND WASH



USE AAROGYA SETU



Aarogya Setu

मैं सुरक्षित | हम सुरक्षित | भारत सुरक्षित

Last Updated on: September 25, 2020

Quick Information

BARC Hospital helpline

Monday to Friday during 10:00 am to 1:00 pm and 2:00 pm to 3:00 pm

+91-22-25598402

Contact Us

Bhabha Atomic Research Centre,
Central Complex, Trombay,
Mumbai, 400 085

Quick Information

Control Monitoring System

Anushaktinagar Security

+91-22-25562666, 25486701 and 25486706

[BARC Website](#) | [BARC Webmail](#)
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Design & Developed by Information Resources Management Section, SIRD



BRIHANMUMBAI MUNICIPAL CORPORATION

HOME ISOLATION GUIDELINES

PATIENTS & CAREGIVERS

BMC HOME ISOLATION PROGRAM IMPORTANT NUMBERS



1 COVID WARD WAR-ROOM NUMBERS

In case patient develops fresh symptoms or there is worsening of symptoms, please contact your WARD CONTROL ROOM during emergency for booking an ambulance or a hospital bed.

WARD	NUMBER
A	022 22700007 / 23
B	022 23759023 / 25
C	022 22197331
D	022 23835004 8879713135
E	022 23797901 9321296335
F South	022 24177507 / 8657792809
F North	022 24011380 / 8879148203
G South	022 24219515 / 7208764360
G North	022 24210441 / 8291163739
H East	022 26635400
H West	022 26440121
K East	022 26847000 / 8657933681
K West	022 26208388 / 8928443687 8592388243

WARD	NUMBER
P South	022 28780008 / 8828476098 / 7304776098
P North	022 28440001 / 9321598131
R South	022 28054788 / 8828495740
R North	022 28947350 / 8369324810
R Central	022 28947360 / 9920089097
L	7678061274 / 7710870510 / 7304883359
M East	022 25526301
M West	022 25284000
N	022 21010201 7208543717
S	022 25954000 / 022 25947570 / 72 9004869830 / 9004869668
T	022 25694000 / 9004744480

Updated as of 5th April 2021

HOME ISOLATION REMOTE MONITORING PROGRAM IS A BMC INITIATIVE IN PARTNERSHIP WITH PROJECT STEPONE.

StepOne

INSTRUCTIONS FOR THE PATIENT



1 DOWNLOAD AAROGYA SETU APP AND SHOULD BE ACTIVE AT ALL TIMES



2 ENSURE HOME ISOLATION RULES FOR YOURSELF



Separate well ventilated room with attached / dedicated toilets. Do not share space with other family members.



Don't share personal items (utensils, towels, linen, clothes, etc) with other people.



Strictly follow the physician's instructions and take your routine medications as prescribed by your doctor.

3 EARLY WARNING SIGNS



Difficulty in breathing.



Oxygen saturation less than 95% (measured on fingertip pulse oxymeter)



Persistent fever more than 100°F



Persistent pain / pressure in the chest or cough.



Mental confusion or inability to arouse or drowsiness

Any other symptom as advised by treating medical officer / physician.

4 SELF-MONITORING



Self-monitor your health and inform your physician / BMC ward war room if you develop any deterioration of symptoms.

Update your health status on the daily automated IVR call received from BMC

HOW TO SELF-MONITOR?

Do health checks thrice a day or every 8 hourly:



Temperature checks (a normal range is 97°F-99°F or 36.1°C-37.2°C)

Measure your oxygen saturation by placing your middle finger in the pulse oximeter (Normal range is more than 95%).

6 minute walk test: Measure your oxygen after mild exertion activity like a 6 minute walk in your room and measure if there is any drop in the oxygen level.



Continue monitoring blood pressure / blood sugar if required.

Keep a record of your temperature, oxygen saturation level and other symptoms in a register.

5 OTHER SYMPTOMS CHECK

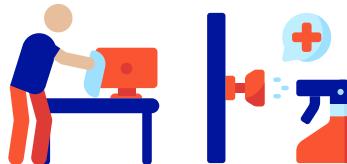
Sore throat, Fatigue, Body aches, Running nose/cold, Loss of smell and taste, Headache, Vomiting, Loose motions, Any other new symptoms or worsening of symptoms

Please consult your family physician / treating medical officer regularly for treatment.

INSTRUCTIONS FOR THE PATIENT



6 MAINTAIN HAND HYGIENE AND OTHER HYGIENE ETIQUETTES



Clean surfaces in the room that are touched often (tabletops, doorknobs, handles, etc.) once or twice a day with 1% hypochlorite solution.

7 USE MASK



Wear a triple layer medical mask appropriately (covering both mouth and nose and well fitted to the face) all the time.



Discard mask after use or when they become wet or visibly soiled, only after disinfecting it with 1% Sodium Hypo-chlorite for 15 mins.

8 REGULAR HAND WASHING / SANITIZATION



Wash your hands with soap and water at least for 40 seconds using seven steps of hand washing. Ideally, wash hands every 2 hours / before and after eating / after using the toilet / and whenever hands look dirty. Use dedicated clean hand towels for drying your hands.



Alcohol-based hand rub (having >60% alcohol) can be used, if hands are not visibly soiled.

9 REST, DIET, NUTRITION, AND EXERCISE



Take adequate rest 7-8 hrs a day.



Diet – Eat a healthy high protein diet, with three meals per day, containing adequate vegetables and fruits.

Protein rich food: Pulses if vegetarian / Egg if non-vegetarian.



Drink lots of fluids to maintain adequate hydration. Water intake: 8-10 cups.



Alcohol intake / smoking if the patient has any such habits.



Steam inhalation and warm water gargles.



Do meditation or yoga to de-stress yourself.

INSTRUCTIONS FOR THE PATIENT



10 TREATMENT PROTOCOL FOR HOME ISOLATION



Those patients who do not have family physicians are advised the following medications.

For asymptomatic patients

Tab. Vitamin C 500 twice a day (daily)

Tab. Zinc 50 mg once per day (daily)

Tab. Vit. D 60000 IU stat (only once during the treatment)

For mild symptomatic patients

Tab. Vitamin C 500 twice a day (daily)

Tab. Zinc 50 mg once per day (daily)

Tab. Vit. D 60000 IU stat (only once during the treatment)

Tab. Paracetamol SOS if fever

Tab. Levocetirizine if cold

Steam inhalation, salt warm water gargles [3 times a day]

Senior citizens and patients having co-morbidities like Diabetes, High Blood Pressure, Asthma, Cancer, Kidney / Lung / Heart diseases have to take special care and consult their doctor regularly.



Patients who are under home isolation are advised to carry out the following investigations at their own expense from pathology testing labs: CBC, Fasting Sugar, LFT, RFT, HbA1C.

(Investigations specially advised for co-morbid patients).

Please consult your physician / medical officer / doctor for any other medications or any other investigations.



The patients under home isolation or discharged from a hospital (post COVID) must keep a close check on their symptoms. In case of worsening of any symptoms, immediately contact the nearby post COVID OPD at a BMC or private hospital or contact your physician for a check-up.

11 UNDERSTAND THAT THE PROCESS IS 'PHYSICAL' ISOLATION AND NOT 'EMOTIONAL' ISOLATION.



Keep contact with family members or relatives and friends over a phone and video call.



Watch Television & Play games on Laptops.



Read books.

EMOTIONAL WELLNESS HELPLINE NUMBER

Due to Covid-19 are you feeling: STRESSED / DEPRESSED / LONELY / ANXIOUS / WORRIED?
For your emotional wellness speak to our trained counsellors **1800-102-4040**.

INSTRUCTIONS FOR THE CAREGIVER



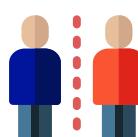
1 DOWNLOAD AAROGYA SETU APP AND SHOULD BE ACTIVE AT ALL TIMES



2 ENSURE HOME ISOLATION RULES FOR COVID POSITIVE PATIENTS



Assign one person who is in good health and no co-morbidities as a caregiver.



- Limit movement of patient to the assigned room
- No shared space with the patient



No visitors in the house until complete patient recovery.

3 USE MASK



Wear a triple layer medical mask / N95 mask appropriately (covering both mouth, nose and well fitted to the face).

Ideally all the time but especially when in the same room as the patient.



- Do not touch the front, but instead, untie it from behind.
- Don't touch the mask during use.
- Change masks daily
- Do not reuse masks



Change immediately if the mask gets wet or dirty with secretion.



Discard mask after 8 hr use or when they become wet or visibly soiled, only after disinfecting it with 1% Sodium Hypo-chlorite for 15 mins.

4 REGULAR HAND WASHING / SANITIZATION



Wash your hands with soap and water at least for 40 seconds using seven steps of hand washing. Ideally, wash hands thoroughly before and after interacting with the patient. Use dedicated clean hand towels for drying your hands.



Alcohol-based hand rub (having >60% alcohol) can be used, if hands are not visibly soiled.



Follow respiratory etiquettes like coughing and sneezing in mask/tissues.



Avoid touching your face, nose, or mouth as far as possible without washing hands.



WHEN TO WASH HANDS? *Ideally, every 2 hours*

ESSENTIAL:

- Immediately after contact with patient or patient's immediate environment
- Before & after preparing food

- Before & after eating
- After using the toilet
- And whenever hands look dirty.

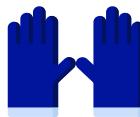
INSTRUCTIONS FOR THE CAREGIVER



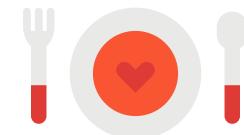
5 FOLLOW THESE RULES WHILE BEING WITH THE PATIENT



Use of PPEs (triple-layered medical mask, gloves, plastic apron) while handling the patient



Clean hands before & after taking off gloves or handling any items used by patient



Provide food to patient in their room



Avoid direct contact with the body fluids of the patient and contaminated items in patient's immediate environment (e.g. masks, utensils, dishes, gloves, drinks, used towels, bed linen).



Wash patient's utensils & dishes with soap/detergent & water while wearing gloves (Note: Utensils and dishes may be re-used)



Disinfect the patient's room and surfaces that are frequently touched (e.g. bedside table, bathroom, and toilet surfaces) at least once daily with regular household soap or detergent followed by 1% hypochlorite solution.



Use PPEs (triple-layered medical mask, gloves, plastic apron) while cleaning or handling surfaces, clothing, or linen used by the patient



Patient's laundry to be washed separately using regular laundry soap and water or machine wash at 60-90 °C (140-194 °F) with common household detergent and dry thoroughly (preferably sun dry).



BIOMEDICAL WASTE MANAGEMENT

Segregate all masks, tissues, or other disposable items used by the patient in a closed dustbin and pack separately in a bag for disposal only after disinfecting it with 1% Sodium Hypo-chlorite for 15 mins.

INSTRUCTIONS FOR THE CAREGIVER



6 MONITORING HEALTH STATUS OF OTHER FAMILY MEMBERS

Do health checks thrice a day or every 8 hourly:

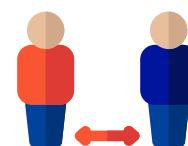


- In case of onset of any COVID symptoms, please get the Covid test done immediately.
- Special care to be taken for family members with Diabetes, Hypertension, COPD, Asthma, Heart / Kidney / Lung diseases / Liver disease and elderly / pregnant women since they are at high risk of contracting the disease.
- Ensure that all close contacts shall remain in home quarantine and not leave the house.

7 IF TRAVELING TO SEEK EMERGENCY CARE FOR PATIENT



Wear a medical mask.



Maintain social distancing.



Avoid public transport / autos / cabs (call an ambulance from the ward war-room or use a private vehicle).



Carry an alcohol-based hand sanitizer.



Inform medical centre beforehand about your visit and share the COVID report.

Therapeutics and COVID-19

LIVING GUIDELINE
31 MARCH 2021



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1. Summary: what is this living guideline?

Clinical question: What is the role of drugs in the treatment of patients with COVID-19?

Target audience: The target audiences are clinicians and health care decision-makers.

Current practice: The evidence base for therapeutics for COVID-19 is increasing rapidly, and some treatments of proven benefit have emerged. Numerous randomized trials of many drugs are underway to further inform practice. This version of the WHO living guideline contains new information and a recommendation on ivermectin (1). Increased international attention on ivermectin as a potential treatment for COVID-19 triggered this recommendation.

Recommendations: In this update, the panel makes a recommendation not to use ivermectin in patients with COVID-19 except in the context of a clinical trial. Previous recommendations include:

- a strong recommendation for systemic corticosteroids in patients with severe and critical COVID-19;
- a conditional recommendation against systemic corticosteroids in patients with non-severe COVID-19;
- a conditional recommendation against remdesivir in hospitalized patients with COVID-19;
- a strong recommendation against hydroxychloroquine in patients with COVID-19 of any severity;
- a strong recommendation against lopinavir/ritonavir in patients with COVID-19 of any severity.

How this guideline was created: This living guideline represents an innovation from the World Health Organization (WHO), driven by the urgent need for global collaboration to provide trustworthy and evolving COVID-19 guidance informing policy and practice worldwide. WHO has partnered with the non-profit Magic Evidence Ecosystem Foundation (MAGIC) for methodologic support and development and dissemination of living guidance for COVID-19 drugs to prevent and treat COVID-19. These guidelines are also published in the BMJ (2), supported by two living systematic reviews with network analysis that inform the recommendations (3, 4). An international Guideline Development Group (GDG) of content experts, clinicians, patients, ethicists and methodologists produced recommendations following standards for trustworthy guideline development using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. No conflict of interest was identified for any panel member or other contributors to the guideline development process.

The latest evidence: Results from a living systematic review and network meta-analysis (NMA) that pooled data from 16 randomized controlled trials (RCTs) with 2407 participants, including both inpatients and outpatients with COVID-19, informed the recommendation on ivermectin (3). The effects of ivermectin on mortality, need for invasive mechanical ventilation, hospital admission, duration of hospitalization and time to viral clearance all remain very uncertain (all very low certainty evidence). The uncertainty results from important concerns related to risk of bias in the included studies, and imprecision from a very low number of events and, in some cases, wide confidence intervals (CIs) in pooled estimates.

Ivermectin may increase the risk of serious adverse events (SAEs) leading to drug discontinuation (odds ratio [OR] 3.07; 95% CI: 0.77–12.09; low certainty evidence) and may have little or no impact on time to clinical improvement (mean difference [MD] 0.5 fewer days; 95% CI: 1.7 fewer days to 1.1 more days; low certainty evidence). There was no credible subgroup effect based on dose. Subgroup analyses were not performed examining between-study differences in age or illness severity as per our pre-defined decision to limit subgroup analysis to within-study comparisons.

Understanding the recommendations: When moving from evidence to the recommendation not to use ivermectin except in the context of a clinical trial, the panel emphasized the large degree of uncertainty in the evidence on mortality, need for mechanical ventilation, need for hospital admission, time to clinical improvement, and other patient-important outcomes. There remains potential for harms with an increased risk of adverse events leading to study drug discontinuation. The panel believed that most well-informed patients would be reluctant to use a medication for which the evidence left high uncertainty regarding effects. The panel considered contextual factors such as resources, feasibility, acceptability, and equity for countries and health care systems were unlikely to alter the recommendation.

Info Box

This WHO *Therapeutics and COVID-19: living guideline* now includes a recommendation not to use ivermectin except in the context of a clinical trial. The guideline was initiated in response to international attention on ivermectin as a potential treatment for COVID-19. The section text provides an executive summary of the guidance. The [first version](#) of the living WHO guideline, published 2 September 2020, provides recommendations for corticosteroids (5); the [second version](#) published 20 November 2020 provides recommendations for remdesivir (6); the [third version](#) published 12 December 2020 provides recommendations for hydroxychloroquine and lopinavir/ritonavir (7). This update does not include changes for any of these drugs.

This living guideline will incorporate new recommendations on other therapies for COVID-19 and updates on existing recommendations. The guideline is therefore written, disseminated, and updated here in MAGICapp, with a user-friendly format and easy to navigate structure that accommodates dynamically updated evidence and recommendations, focusing on what is new while keeping existing recommendations within the guideline.

Please visit the [WHO website](#) for the latest version of the guidance (1), also available in the BMJ as [Rapid Recommendations](#) (2), together with the [living network meta-analysis](#) (LNMA) (3), a major evidence source for the guidelines. The updated LNMA informing the recommendation on ivermectin has been published in the BMJ, with the updated guideline in the BMJ pending (3).

2. Abbreviations

ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
CAP	community-acquired pneumonia
CI	confidence interval
COVID-19	coronavirus disease 2019
eGFR	estimated glomerular filtration rate
GDG	guideline development group
GI	gastrointestinal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRC	guideline review committee
LNMA	living network meta-analysis
MAGIC	Magic Evidence Ecosystem Foundation
MD	mean difference
NMA	network meta-analysis
OIS	optimal information size
PICO	population, intervention, comparator, outcome
PMA	prospective meta-analysis
RCT	randomized controlled trial
RR	relative risk/risk ratio
SAE	serious adverse event
WHO	World Health Organization

3. Background

As of 20 March 2021, over 121 million people worldwide have been diagnosed with COVID-19, according to the WHO dashboard (8). The pandemic has thus far claimed more than 2.6 million lives, and although some areas of the world are seeing a drop in case counts, other areas are experiencing a resurgence in cases. Vaccination is beginning to have a substantial impact on case numbers and hospitalizations in a few countries, but limitations in global access to vaccines mean that many populations remain vulnerable (9). Even in vaccinated individuals, uncertainties remain about duration of protection and efficacy of current vaccines against emerging SARS-CoV-2 variants. Taken together, there remains a need for more effective treatments for COVID-19. The COVID-19 pandemic – and the explosion of both research and misinformation – has highlighted the need for trustworthy, accessible and regularly updated living guidance to place emerging findings into context and provide clear recommendations for clinical practice (10).

This living guideline responds to emerging evidence from randomized controlled trials (RCTs) on existing and new drug treatments for COVID-19. More than 3800 trials investigating interventions for COVID-19 have been registered or are ongoing (see Section 8 – emerging evidence) (11). Among these are national and international platform trials (e.g. RECOVERY, WHO SOLIDARITY, DISCOVERY, REMAP-CAP and ACTIV) that recruit large numbers of patients in many countries, with a pragmatic and adaptive design (12, 13). These platform trials are currently investigating and reporting on interventions, including antiviral monoclonal antibodies and immunomodulators. This rapidly evolving evidence landscape requires trustworthy interpretation and expeditious clinical practice guidelines to inform clinicians and health care decision-makers.

3.1 What triggered this version of the guideline?

This fourth version of the WHO living guideline addresses the use of ivermectin in patients with COVID-19. It follows the increased international attention on ivermectin as a potential therapeutic option. While ivermectin is also being investigated for prophylaxis, this guideline only addresses its role in the treatment of COVID-19. Ivermectin is relatively inexpensive and accessible, and some countries have already witnessed its widespread use in the treatment of COVID-19; in other countries, there is increasing pressure to do so (14).

In response to this international attention, the WHO GDG now provides recommendations on ivermectin for treatment of COVID-19. Ivermectin is an antiparasitic agent that interferes with nerve and muscle function of helminths through binding glutamate-gated chloride channels (15). We currently lack persuasive evidence of a mechanism of action for ivermectin in COVID-19, and any observed clinical benefit would be unexplained (see Section 5).

3.2 Who made this guideline

WHO selected GDG members that represent all WHO regions, has equal gender balance and includes specialists in infectious diseases, pulmonary medicine, intensive care, emergency care, primary care, ethics and four patient panel members, headed by a clinical chair (Dr Michael Jacobs) and a methods chair (Dr Bram Rochwerg). Declaration of interest forms were collected, assessed and managed by the WHO secretariat according to WHO standard procedures. No panel members were assessed to have a conflict of interest. GDG member bios can be found on the [WHO website](#). Evidence summaries were prepared by the systematic review team (see Section 9). Methodologic support, with high-level expertise in GRADE, was provided by the MAGIC Evidence Ecosystem Foundation ([MAGIC](#)) (see Section 9). The methodological experts were not involved in the formulation of recommendations.

3.3 How to use this guideline

This is a living guideline from WHO. The guideline is written, disseminated and updated in MAGICapp, with a format and structure that ensures user-friendliness and ease of navigation (16). It accommodates dynamic updating of evidence and recommendations that can focus on what is new while keeping existing recommendations, as appropriate, within the guideline. Section 4 outlines key methodological aspects of the living guideline process. In addition, the methodologic support team (MAGIC), under the coordination of the Guideline Collaboration Committee (see Section 9), worked with the BMJ to coordinate the simultaneous scientific publication of the living WHO guidelines (2).

The guideline is available here in MAGICapp in online, multilayered formats and via:

- [WHO website in PDF format](#)
- [WHO Academy app](#)

- [BMJ Rapid Recommendations \(2\)](#)

The purpose of the MAGICapp online formats and additional tools, such as the infographics, is to make it easier to navigate and make use of the guideline in busy clinical practice. The online multilayered formats are designed to allow end-users to find recommendations first and then drill down to find supporting evidence and other information pertinent to applying the recommendations in practice, including tools for shared decision-making ([clinical encounter decision aids](#)) (16).

4. Methods: how this guideline was created

The team developed this living WHO guideline according to standards and methods for trustworthy guidelines, making use of an innovative process to achieve efficiency in dynamic updating of recommendations (1). The methods are aligned with the [WHO Handbook for guideline development](#) and according to a pre-approved protocol (planning proposal) by the Guideline Review Committee (18).

Related guidelines

This living WHO guidance for COVID-19 treatments will be related to the larger, more comprehensive guidance for [Clinical management of COVID-19: interim guidance](#), which has a wider scope of content and has been updated and is available on MAGICapp (17). The first three WHO living guidelines, addressing corticosteroids (5), remdesivir (6), hydroxychloroquine and lopinavir/ritonavir (7), were disseminated via the WHO website, BMJ and MAGICapp.

Timing

This guidance will be living: dynamically updated and globally disseminated once new evidence warrants a change in recommendations (19). The aim is for a timeframe from trials that trigger guideline development process to WHO publication within one month, while maintaining standards for trustworthy guidelines (WHO Handbook of guideline development) (18, 19).

Stepwise approach

Here we outline the approach, involving simultaneous processes, taken to improve efficiency and timeliness of development and dissemination of living, trustworthy guidance.

Step 1: Evidence monitoring and mapping and triggering of evidence synthesis

Comprehensive daily monitoring of all emerging RCTs occurs on a continuous basis, within the context of the living systematic review and NMA, using experienced information specialists, who review all relevant information sources for new RCTs addressing interventions for COVID-19. Once practice-changing evidence, or increasing international interest, are identified, the WHO Therapeutics Steering Committee triggers the guideline development process. The trigger for producing or updating specific recommendations is based on the following (any of the three may initiate a recommendation):

- likelihood to change practice;
- sufficient RCT data on therapeutics to inform the high-quality evidence synthesis living systematic review;
- relevance to a global audience.

Step 2: Convening the GDG

The pre-selected expert panel (see Section 9) convened on two occasions to address this drug. The first meeting, held 4 February 2021, reviewed the basics of GRADE methodology including formulating population, intervention, comparator, outcome (PICO) questions and subgroups of interests, and prioritization of patient-important outcomes. At this meeting the panel finalized the PICOs and pre-specified subgroups of interest. Subsequent to the meeting, the panel participated, through email correspondence, in an outcome prioritization exercise. At the second meeting, held on 4 March 2021, the GDG panel reviewed evidence summaries, including pre-specified subgroup analysis, and a recommendation was drafted.

Step 3: Evidence synthesis

The living systematic review/NMA team, as requested by the WHO Therapeutics Steering Committee, performed an independent systematic review to examine the benefits and harms of the intervention. The systematic review team includes systematic review experts, clinical experts, clinical epidemiologists and biostatisticians. Team members have expertise in GRADE methodology and rating certainty of evidence specifically in NMAs. The NMA team considered deliberations from the initial GDG meeting, specifically focusing on the outcomes and subgroups prioritized by the panel. To conduct the subgroup analysis of high versus low dose of ivermectin, Professor Andrew Owen (see Section 9), provided direction on analysis of different dosing regimens. Based on pharmacokinetic data, Professor Owen and the methods support team recommended analysing cumulative dose as a continuous variable, further adding a covariate for single vs multiple dosing regimens. This subgroup analysis informed the direct comparison of ivermectin compared with standard of care only, and not the network analysis.

Step 4: Final recommendations

The GRADE approach provided the framework for establishing evidence certainty and generating both the direction and strength of recommendations (20, 21). While a priori voting rules informed procedures if the panel failed to reach consensus, these procedures proved unnecessary for this recommendation.

The following key factors informed transparent and trustworthy recommendations.

- absolute benefits and harms for all patient-important outcomes through structured evidence summaries (e.g. GRADE summary of findings tables) (22);
- quality/certainty of the evidence (20, 23);
- values and preferences of patients (24);
- resources and other considerations (including considerations of feasibility, applicability, equity) (24);
- effect estimates and confidence intervals for each outcome, with an associated rating of certainty in the evidence, as presented in summary of findings tables. If such data are not available, the panel reviews narrative summaries;
- recommendations are rated as either conditional or strong, as defined by GRADE. If the panel members disagree regarding the evidence assessment or strength of recommendations, WHO will apply voting according to established rules.

Step 5: External and internal review

The WHO guideline was reviewed by pre-specified external reviewers (see Section 9) and approved by the WHO Guideline Review Committee (GRC).

5. The latest evidence

This section outlines what information the GDG panel requested and used in making their recommendation for ivermectin.

Mechanism of action

Based on in vitro experiments, some have postulated that ivermectin may have a direct antiviral effect against SARS-CoV-2. However, in humans the concentrations needed for in vitro inhibition are unlikely to be achieved by the doses proposed for COVID-19 (25-27). Ivermectin had no impact on SARS-CoV-2 viral RNA in the Syrian golden hamster model of SARS-CoV-2 infection (28). The proposed mechanism remains unclear: multiple targets have been proposed based upon either analogy to other viruses with very different life cycles, or, like several hundred other candidates, simulations indicating molecular docking with multiple viral targets including spike, RdRp and 3CLpro (29-33). No direct evidence for any mechanism of antiviral action against SARS-CoV-2 currently exists.

Some have proposed, based predominantly upon research in other indications, that ivermectin has an immunomodulatory effect, but again the mechanism remains unclear. Historical data showed that ivermectin improved survival in mice given a lethal dose of lipopolysaccharide (34), and has benefits in murine models of atopic dermatitis and allergic asthma (35, 36). For SARS-CoV-2, one hypothesis suggests immunomodulation mediated by allosteric modulation of the alpha-7 nicotinic acetylcholine receptor (indirectly by modulating the activity of ligands of the receptor). Although investigators have demonstrated this action in vitro, concentrations used in these experiments have been even higher than those required for an antiviral effect (37), and therefore very unlikely to be achieved in humans. In the Syrian golden hamster model of SARS-CoV-2 infection, ivermectin resulted in some changes in pulmonary immune phenotype consistent with allosteric modulation of the alpha-7 nicotinic acetylcholine receptor (28). However, ivermectin did not appear to rescue body weight loss which is a hallmark of disease in this model, and drug concentrations were not measured to extrapolate to those achieved in humans. Taken together, there remains great uncertainty regarding the relevance of any immunomodulatory or anti-inflammatory action of ivermectin.

Benefits and harms

The GDG members prioritized outcomes (rating from 1 [not important] to 9 [critical]) taking a patient's perspective. The panel prioritized outcomes from both an inpatient (Table 1) and outpatient (Table 2) perspective. The panel's questions were structured using the PICO format (see evidence profile under the recommendations). These prioritized outcomes were used to update the LNMA.

Table 1. Panel outcome rating from an inpatient perspective

Outcome	Mean	SD	Range
Death	9.0	0.0	9
Need for invasive mechanical ventilation	8.2	0.9	6-9
Duration of invasive mechanical ventilation	7.6	0.9	6-9
Quality of life	6.9	1.3	5-9
Duration of hospitalization	6.7	1.2	4-9
Serious adverse effects (e.g. adverse events leading to drug discontinuation)	6.7	1.8	3-9
Time to symptom resolution	6.5	1.6	4-9
New non-SARS-CoV2 infection	6.4	1.8	3-9
Duration of oxygen support	6.3	1.3	4-9
Time to viral clearance	4.7	2.3	1-9

SD: standard deviation.

Note: 1: not important, 9: critically important.

Table 2. Panel outcome rating from an outpatient perspective

Outcome	Mean	SD	Range
Admission to hospital	8.5	0.7	7-9
Death	8.1	1.9	3-9
Quality of life	7.5	1.3	5-9
Serious adverse effects (e.g. adverse events leading to drug discontinuation)	7.4	1.8	3-9
Time to symptom resolution	7.3	1.7	4-9
Duration of hospitalization	6.6	0.9	5-8
Duration of oxygen support	6.6	1.2	5-9
Need for invasive mechanical ventilation	5.9	2.3	1-8
New non-SARS-CoV2 infection	5.6	2.1	3-9
Time to viral clearance	5.5	2.4	1-9
Duration of invasive mechanical ventilation	5.4	2.1	1-8

SD: standard deviation.

Note: 1: not important, 9: critically important.

Evidence summary

The evidence summary was based on 16 trials and 2407 participants for which the NMA provided relative estimates of effect for patient-important outcomes. Of the included trials, 75% examined patients with non-severe disease and 25% included both severe and non-severe patients. A number of the included trials did not report on our outcomes of interest. Of the trials, 25% were published in peer-reviewed journals, 44% were available as preprints and 31% were completed but unpublished (See [Table on trial characteristics](#)). We excluded a number of quasi-RCTs (38-41).

Subgroup analysis

The NMA team performed subgroup analyses which could result in distinct recommendations by subgroups. From the available data, subgroup analyses were only possible by dose of ivermectin and considering the outcomes of mortality, mechanical ventilation, admission to hospital, and adverse events leading to drug discontinuation. The ivermectin dose subgroup analyses were performed from the direct comparison of ivermectin versus usual care. For these analyses, meta-regression was used to evaluate the effect of cumulative dose as a continuous variable, and further adding a co-variate for single vs multiple dosing regimens. This approach was based on input from the pharmacology experts (led by Professor Andrew Owen) who performed pharmacokinetic simulations across trial doses, and found that cumulative ivermectin dose was expected to correlate with key pharmacokinetic parameters when single- and multiple-dose studies were segregated. It should be noted that the included trials did not directly assess the pharmacokinetics of ivermectin, and our approach was based upon simulations validated where possible against published pharmacokinetics in humans. The panel used a pre-specified framework incorporating the ICEMAN tool to assess the credibility of subgroup findings (42).

The GDG panel requested subgroup analyses based on: age (considering children vs younger adults vs older adults [70 years or older]); illness severity (non-severe vs severe vs critical COVID-19); time from onset of symptoms; and use of concomitant medications. However, there was insufficient within-trial data to perform any of these subgroup analyses, based on our pre-specified protocol. The panel recognized that usual care is likely variable between centres and regions, and has evolved over time. However, given all of the data come from RCTs, use of these co-interventions that comprise usual care should be balanced between study patients randomized to either the intervention or usual care arms.

Baseline risk estimates (prognosis of patients with COVID-19): informing absolute estimates of effect

The evidence summaries that informed the guideline recommendation reported the anticipated absolute effects of ivermectin compared with usual care across all patient-important outcomes. The absolute effects of treatment are informed by the prognosis (i.e. baseline risk estimates) combined with the relative estimates of effects (e.g. risk ratios [RR], OR) obtained from the NMA.

The control arm of the WHO SOLIDARITY trial (13), performed across a wide variety of countries and geographical regions, was identified by the GDG panel as generally representing the most relevant source of evidence for baseline risk estimates for mortality and mechanical ventilation. The rationale for selecting the WHO SOLIDARITY trial was to reflect the overall prognosis of the global population for which the WHO guideline recommendations are made. However, the SOLIDARITY trial only enrolls patients who are hospitalized with COVID-19. Since ivermectin has been proposed for use and often studied in outpatients, on this occasion the panel used the median of risk in the standard care arms of the included trials for baseline risk estimates for these outcomes. When applying the evidence to a particular patient or setting, for any medication with a convincing effect, clinicians should consider the individual's risk of mortality and need for mechanical ventilation. In view of the study designs, the GDG judged that for other outcomes using the median or mean of all patients randomized to usual care across the included studies would provide the most reliable estimate of baseline risk.

Values and preferences

We had insufficient information to provide the GDG with a trustworthy description of patients' experiences or values and preferences regarding treatment decisions for COVID-19 drug treatments. The GDG therefore relied on their own judgments of what well-informed patients would value after carefully balancing the benefits, harms and burdens of treatment. The GDG included four patient-partners who had lived experience with COVID-19.

The GDG agreed that the following values and preferences would be typical of well-informed patients:

- Most patients would be reluctant to use a medication for which the evidence left high uncertainty regarding effects on outcomes they consider important. This was particularly so when evidence suggested treatment effects, if they do exist, are small, and the possibility of important harm remains.
- In an alternative situation with larger benefits and less uncertainty regarding both benefits and harms, more patients would be inclined to choose the intervention.

Although the GDG focused on an individual patient perspective, they also considered a population perspective in which feasibility, acceptability, equity and cost are important considerations.

6. Who do the recommendations apply to?

Info Box

The guideline for COVID-19 therapeutics applies to all patients with COVID-19. For some drugs (such as corticosteroids), recommendations may differ based on the severity of COVID-19 disease. The GDG used the WHO severity definitions based on clinical indicators, adapted from WHO COVID-19 disease severity categorization (see below) (17). These definitions avoid reliance on access to health care to define patient subgroups.

WHO Severity definitions

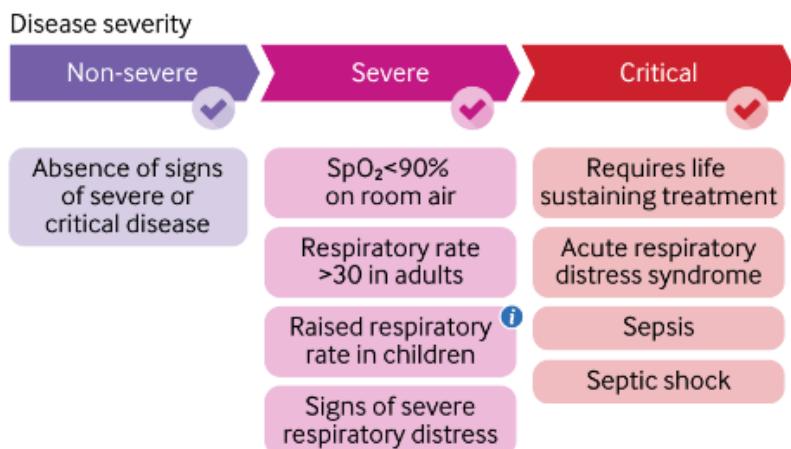
- **Critical COVID-19** – Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.
- **Severe COVID-19** – Defined by any of:
 - Oxygen saturation <90% on room air;
 - Respiratory rate > 30 breaths/min in adults and children > 5 years old; ≥ 60 breaths/min in children < 2 months old; ≥ 50 in children 2–11 months old; and ≥ 40 in children 1–5 years old;
 - Signs of severe respiratory distress (accessory muscle use, inability to complete full sentences, and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs).
- **Non-severe COVID-19** – Defined as absence of any criteria for severe or critical COVID-19.

Caution: The panel noted that the oxygen saturation threshold of 90% to define severe COVID-19 was arbitrary and should be interpreted cautiously when used to define disease severity. For example, clinicians must use their judgment to determine whether a low oxygen saturation is a sign of severity or is normal for a given patient with chronic lung disease. Similarly, a saturation > 90–94% on room air is abnormal (in patient with normal lungs) and can be an early sign of severe disease, if patient is on a downward trend. Generally, if there is any doubt, the panel suggested erring on the side of considering the illness as severe.

The infographic illustrates these three disease severity groups and key characteristics to apply in practice.

Population

This recommendation applies only to people with these characteristics:



Infographic co-produced by BMJ and MAGIC; designer Will Stahl-Timmins (see [BMJ Rapid Recommendations](#)).

7. Recommendations for therapeutics

7.1 Ivermectin

Only in research settings

New

We recommend not to use ivermectin in patients with COVID-19 except in the context of a clinical trial.

Remark: This recommendation applies to patients with any disease severity and any duration of symptoms.

A recommendation to only use a drug in the setting of a clinical trials is appropriate when there is very low certainty evidence and future research has a large potential for reducing uncertainty about the effects of the intervention and for doing so at reasonable cost.

Practical info

The GDG made a recommendation against using ivermectin for treatment of patients with COVID-19 outside the setting of a clinical trial and therefore practical considerations are less relevant for this drug.

Evidence to decision

Benefits and harms

The effects of ivermectin on mortality, mechanical ventilation, hospital admission, duration of hospitalization and viral clearance remain uncertain because of very low certainty of evidence addressing each of these outcomes. Ivermectin may have little or no effect on time to clinical improvement (low certainty evidence). Ivermectin may increase the risk of SAEs leading to drug discontinuation (low certainty evidence).

Subgroup analyses indicated no effect modification based on dose. We were unable to examine subgroups based on patient age or severity of illness due to insufficient trial data (see Section 5). Therefore, we assumed similar effects in all subgroups. This recommendation applies to patients with any disease severity and any duration of symptoms.

Certainty of the evidence

For most key outcomes, including mortality, mechanical ventilation, hospital admission, duration of hospitalization and viral clearance, the panel considered the evidence of very low certainty. Evidence was rated as very low certainty primarily because of very serious imprecision for most outcomes: the aggregate data had wide confidence intervals and/or very few events. There were also serious concerns related to risk of bias for some outcomes, specifically lack of blinding, lack of trial pre-registration, and lack of outcome reporting for one trial that did not report mechanical ventilation despite pre-specifying it in their protocol (publication bias).

For more details, see the Justification section for this recommendation. For other outcomes, including SAEs and time to clinical improvement, the certainty of the evidence was low.

Preference and values

Applying the agreed values and preferences (see Section 5), the GDG inferred that almost all well-informed patients would want to receive ivermectin only in the context of a randomized trial, given that the evidence left a very high degree of uncertainty in effect on mortality, need for mechanical ventilation, need for hospitalization and other critical outcomes of interest and there was a possibility of harms, such as treatment-associated SAEs. The panel anticipated little variation in values and preferences between patients when it came to this intervention.

Resources and other considerations

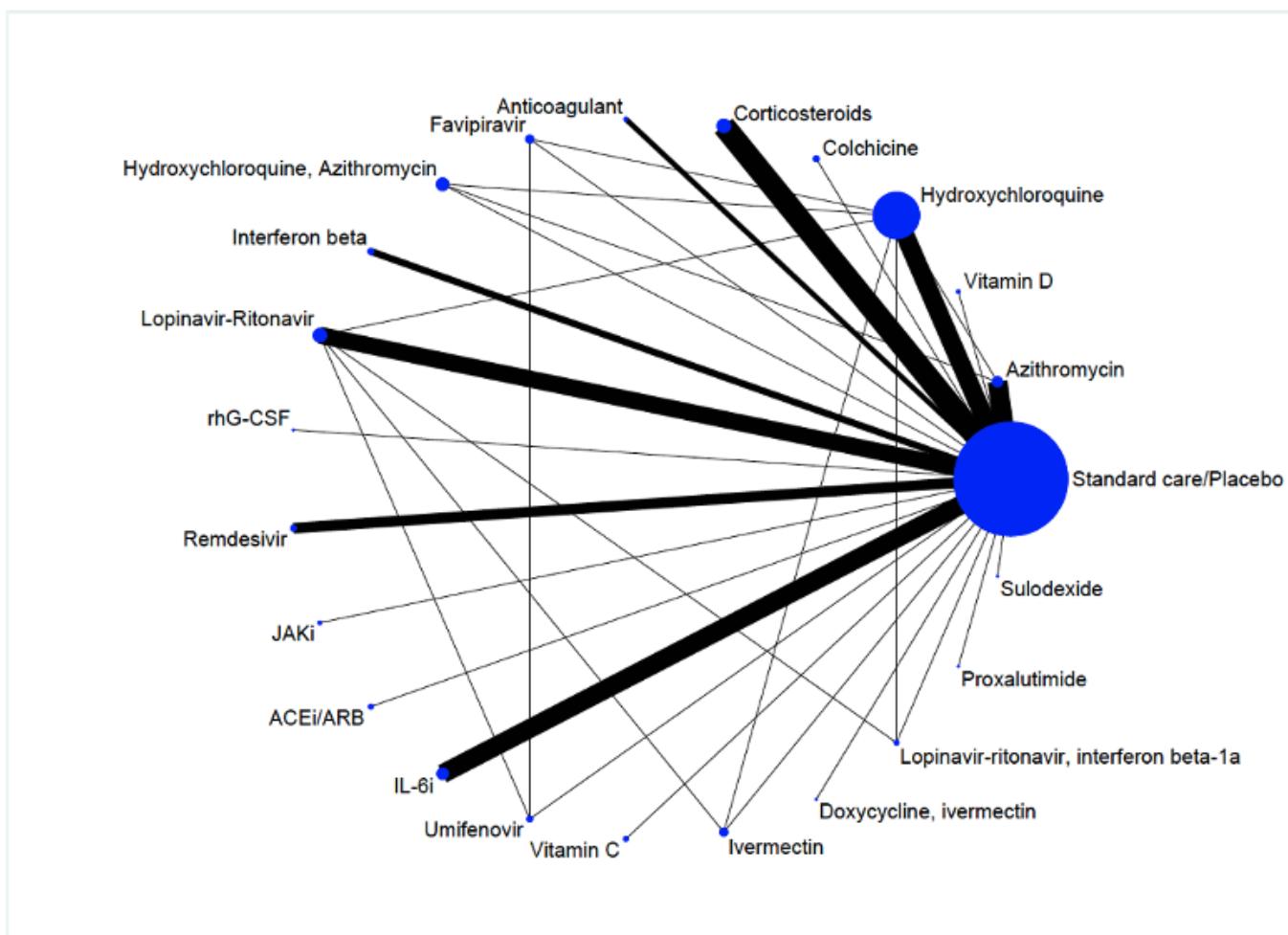
Ivermectin is a relatively inexpensive drug and is widely available, including in low-income settings. The low cost and wide availability do not, in the panel's view, mandate the use of a drug in which any benefit remains very uncertain and ongoing concerns regarding harms remain. Although the cost may be low per patient, the GDG panel raised concerns about diverting attention and resources away from care likely to provide a benefit such as corticosteroids in patients with severe COVID-19 and other supportive care interventions. Also, use of ivermectin for COVID-19 would divert drug supply away from pathologies for which it is clearly indicated, potentially contributing to drug shortages, especially for helminth control and elimination programmes. Other endemic infections that may worsen with corticosteroids should be considered. If steroids are used in the treatment of COVID-19, empiric treatment with ivermectin may still be considered in Strongyloidiasis endemic areas, at the discretion of clinicians overseeing treatment, albeit not for treatment of COVID-19 itself.

Justification

When moving from evidence to a recommendation on the use of ivermectin in patients with COVID-19 only in the context of a clinical trial, the panel emphasized the high degree of uncertainty in the most critical outcomes such as mortality and need for mechanical ventilation. It also noted the evidence suggesting possible harm associated with treatment, with increased adverse events. The GDG did not anticipate important variability in patient values and preferences. Other contextual factors, such as resource considerations, accessibility, feasibility and impact on health equity did not alter the recommendation.

Compared with previous drugs evaluated as part of the WHO Living Guidelines for Therapeutics in COVID-19 (see below), currently there are far fewer RCT data available for ivermectin. The existing data on ivermectin also have a substantially higher degree of uncertainty, with included trials having enrolled substantially fewer patients with far fewer events. Fig. 1 is the network map for mortality from the accompanying LNMA informing this guideline. Within the map, the size of the nodes (blue circles) correlates with the number of patients randomized to that intervention across all included trials; it is clear that the size of the ivermectin node is much smaller than other interventions which have been subjected to WHO guidelines, such as corticosteroids, hydroxychloroquine and lopinavir/ritonavir. The width of the line connecting two specific interventions correlates with the number of patients and number of events in this comparison across all trials; again, the lines connecting ivermectin to standard of care, as well as to the comparators lopinavir/ritonavir and hydroxychloroquine, are much thinner compared with drugs that have been assessed previously in this guideline.

Fig. 1. Network map from the living network meta-analysis informing this guideline

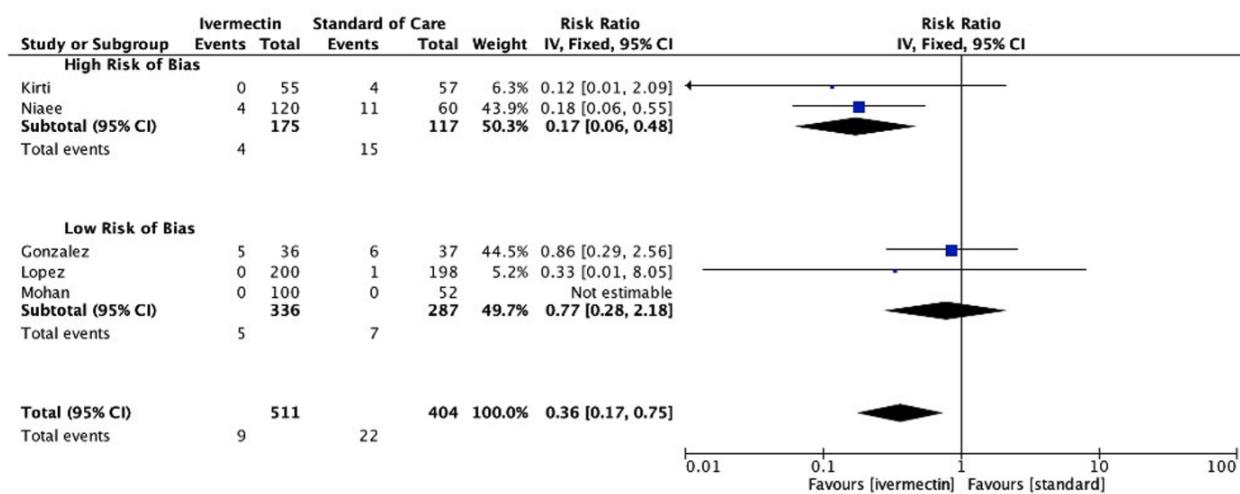


Drugs for which this guideline has already addressed with recommendations include corticosteroids, remdesivir, hydroxychloroquine and lopinavir/ritonavir.

High degree of uncertainty

The certainty in effect estimates for ivermectin on the main outcomes of interest, including mortality, is very low and therefore the effect of ivermectin on these outcomes remains uncertain. There are two domains that contribute to this uncertainty: serious risk of bias; and serious imprecision. Although 16 RCTs contributed to the evidence summary informing this drug, only five directly compared ivermectin with standard of care and reported mortality (43-47). Of note, and in keeping with our methodology, the LNMA team excluded quasi-randomized trials, or any RCT that did not use explicit randomization techniques. Of these five RCTs, two (43, 44) were at high risk of bias, due to inadequate blinding. One of these two trials (43) also started enrolling and randomizing patients prior to the protocol being publicly posted, another factor that contributes to an increased risk of bias. The potential impact of risk of bias is exemplified by subgroup analyses for mortality based on trial risk of bias. As demonstrated in the forest plot (Fig. 2), the pooled estimate across all five RCTs that directly compare ivermectin with standard care suggests a reduction in mortality with ivermectin, but this effect is not apparent if we only consider the trials at low risk of bias (which together contribute nearly two-thirds of the evidence). This finding increases the degree of uncertainty regarding the true effect of ivermectin on mortality. Consistent with the direct evidence, a similar phenomenon is observed with the indirect evidence comparing ivermectin to standard of care (via comparisons against hydroxychloroquine and lopinavir/ritonavir). The indirect evidence suggesting a reduction in mortality with ivermectin is driven almost entirely by one study which is at high risk of bias (48) due to a lack of detailed description of blinding or randomization and the lack of a publicly available study protocol (figure not shown).

Fig. 2. Forest plot demonstrating direct comparison of ivermectin versus standard of care for mortality with subgroup analysis by risk of bias



IV: inverse variance.

In addition to concerns related to risk of bias, for the outcome of mortality, there are very serious concerns related to imprecision. According to GRADE, imprecision is evaluated based on both a confidence interval approach and an evaluation of information size (event number), ensuring there is adequate information on which to make informed judgments (49). In this case, despite confidence intervals that suggest benefit with ivermectin, the information size is very low. For mortality (and ignoring the concerns related to risk of bias discussed above), there were nine deaths across all 511 patients randomized to ivermectin (1.76%) and 22 deaths across all 404 patients randomized to standard of care (5.45%). This is an extremely small number of events on which to base conclusions, and far below the optimal information size. In fact, performing a theoretical exercise in which a change of three events (deaths) is made from those randomized to standard of care to those randomized to ivermectin eliminates any statistical significance, a finding that suggests that results could reasonably be due to chance alone. Furthermore, the evidence informing this comparison is from multiple small trials, adding to the risk of unrecognized imbalances in study arms. Given the strong likelihood that chance may be playing a role in the observed findings, the panel believed there was very serious imprecision further lowering the overall certainty in findings.

This combination of serious risk of bias and very serious imprecision contributed to very low certainty of evidence for mortality despite a point estimate and confidence interval that appear to suggest benefit with ivermectin. As a result, the panel concluded that the effect of ivermectin on mortality is uncertain. Similar considerations were applied to the other critical outcomes including mechanical ventilation, hospital admission, and duration of hospitalization and resulted in very low certainty for these outcomes as well.

Subgroup analyses

We conducted subgroup analysis only for effect by ivermectin dose and the panel did not find any evidence of a subgroup effect (see Section 5). A lack of within-trial comparisons prevented subgroup analyses by age or disease severity. Therefore, the panel did not make any subgroup recommendation for this drug. In other words, the recommendation against ivermectin except in the context of clinical trials is applicable across disease severity, age groups, and all dose regimens of ivermectin.

Applicability

None of the included RCTs enrolled children under 15, and therefore the applicability of this recommendation to children is currently uncertain. However, the panel had no reason to think that children with COVID-19 would respond any differently to treatment with ivermectin. There were similar considerations for pregnant women, with no data directly examining this population, but no rationale to suggest they would respond differently to other adults.

Uncertainties

Please see end of document for residual uncertainties (Section 8).

Clinical question/ PICO

Population: Patients with COVID-19 infection (all disease severities)
Intervention: Ivermectin
Comparator: Usual care

Summary

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care Ivermectin	Certainty of the evidence (Quality of evidence)	Plain text summary
Mortality	Odds ratio 0.19 (CI 95% 0.09 - 0.36) Based on data from 1,419 patients in 7 studies. ¹ (Randomized controlled)	70 per 1000 14 per 1000 Difference: 56 fewer per 1000 (CI 95% 63 fewer - 44 fewer)	Very Low Due to serious risk of bias and very serious imprecision ²	The effect of ivermectin on mortality is uncertain.
Mechanical ventilation	Odds ratio 0.51 (CI 95% 0.12 - 1.77) Based on data from 687 patients in 5 studies. (Randomized controlled)	20 per 1000 10 per 1000 Difference: 10 fewer per 1000 (CI 95% 18 fewer - 15 more)	Very Low Due to very serious imprecision and publication bias ³	The effect of ivermectin on mechanical ventilation is uncertain.
Viral clearance 7 days	Odds ratio 1.62 (CI 95% 0.95 - 2.86) Based on data from 625 patients in 6 studies. (Randomized controlled)	500 per 1000 618 per 1000 Difference: 118 more per 1000 (CI 95% 13 fewer - 241 more)	Low Due to serious inconsistency and imprecision ⁴	Ivermectin may increase or have no effect on viral clearance.
Hospital admission (outpatients only)	Odds ratio 0.36 (CI 95% 0.08 - 1.48) Based on data from 398 patients in 1 studies. (Randomized controlled)	50 per 1000 18 per 1000 Difference: 32 fewer per 1000 (CI 95% 47 fewer - 23 more)	Very Low Due to extreme imprecision ⁵	The effect of ivermectin on hospital admission is uncertain.
Serious adverse events	Odds ratio 3.07 (CI 95% 0.77 - 12.09) Based on data from 584 patients in 3 studies. (Randomized controlled)	9 per 1000 27 per 1000 Difference: 18 more per 1000 (CI 95% 2 fewer - 89 more)	Low Due to very serious imprecision ⁶	Ivermectin may increase the risk of serious adverse events leading to drug discontinuation.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care Ivermectin	Certainty of the evidence (Quality of evidence)	Plain text summary
Time to clinical improvement	Measured by: days Lower better Based on data from: 633 patients in 2 studies. (Randomized controlled)	11 days (Mean) 10.5 days (Mean) Difference: MD 0.5 fewer (CI 95% 1.7 fewer - 1.1 more)	Low Due to very serious imprecision ⁷	Ivermectin may have little or no difference on time to clinical improvement
Duration of hospitalization	Measured by: days Lower better Based on data from: 252 patients in 3 studies. (Randomized controlled)	12.8 days (Mean) 11.7 days (Mean) Difference: MD 1.1 fewer (CI 95% 2.3 fewer - 0.1 more)	Very Low Due to serious imprecision, inconsistency and serious risk of bias ⁸	The effect of ivermectin on hospital length of stay is uncertain.
Time to viral clearance	Measured by: days Lower better Based on data from: 559 patients in 4 studies. (Randomized controlled)	7.3 days (Mean) 5.7 days (Mean) Difference: MD 1.6 fewer (CI 95% 4.1 fewer - 3 more)	Very Low Due to very serious imprecision and serious risk of bias. ⁹	We are uncertain whether ivermectin improves or worsens time to viral clearance

1. Systematic review (3). **Baseline/comparator:** Control arm of reference used for intervention. We elected to use the control arm of the WHO solidarity trial, reflecting usual care across countries participating in the trial.
2. **Risk of bias:** Serious. The large trial contributing most of the effect estimate was driven by studies that were not blinded.. **Inconsistency:** No serious. **Indirectness:** No serious. **Imprecision:** Very Serious. The number of total events was very small.. **Publication bias:** No serious.
3. **Inconsistency:** No serious. **Indirectness:** No serious. **Imprecision:** Very Serious. Very few events and credible intervals that include both important benefit and harm.. **Publication bias:** Serious.
4. **Inconsistency:** Serious. The point estimates varied widely and credible intervals do not substantially overlap.. **Indirectness:** No serious. **Imprecision:** Serious. Credible interval includes no effect.. **Publication bias:** No serious.
5. **Inconsistency:** No serious. **Indirectness:** No serious. **Imprecision:** Very Serious. Credible interval includes important benefit and harm.. **Publication bias:** No serious.
6. **Inconsistency:** No serious. **Indirectness:** No serious. **Imprecision:** Serious. Credible interval includes little to no difference.. **Publication bias:** No serious.
7. **Inconsistency:** No serious. **Indirectness:** No serious. **Imprecision:** Very Serious. **Publication bias:** No serious.
8. **Risk of bias:** Serious. Result driven by one study that was not blinded.. **Inconsistency:** Serious. Despite overlapping confidence intervals, point estimates discrepant.. **Indirectness:** No serious. **Imprecision:** Serious. Credible intervals include no difference.. **Publication bias:** No serious.
9. **Risk of bias:** Serious. Concerns around risk of bias.. **Inconsistency:** No serious. **Indirectness:** No serious. **Imprecision:** Very Serious. Credible interval includes important benefit and important harm.. **Publication bias:** No serious.

7.2 Hydroxychloroquine (published December 17 2020)

The third version of the WHO living guideline addressed the use of hydroxychloroquine (and lopinavir/ritonavir, see below) in patients with COVID-19. It followed the pre-print publication of the WHO SOLIDARITY trial on 15 October, 2020, reporting results on treatment with remdesivir, hydroxychloroquine and lopinavir-ritonavir in hospitalized patients with COVID-19 (50). The role of

these drugs in clinical practice has remained uncertain, with limited prior trial evidence. The WHO SOLIDARITY trial adds 11,266 randomized patients (2570 to remdesivir, 954 to hydroxychloroquine, and 1411 to lopinavir-ritonavir, 6,331 to usual care) and had the potential to change practice (13, 50).

The evidence

The evidence summary for hydroxychloroquine was based on 30 trials and 10 921 participants for which the NM provided relative estimates of effect for patient-important outcomes (Table 3). Five of the trials (414 total participants) randomized some patients to chloroquine.

**Table 3. Summary of trials and trial characteristics informing the hydroxychloroquine recommendation
(trials = 30, total patients = 10 921)**

Geographic region	Region of the Americas South-East Asia Region Western Pacific Region European Region Eastern Mediterranean Region	Region of the Americas (12 trials, 2358 patients) South-East Asia and Western Pacific Regions (7 trials, 731 patients) European Region (10 trials, 7638 patients) Eastern Mediterranean Region (1 trial, 194 patients)
Severity of illness ^a	Non-severe Severe Critically ill	Mild/Moderate (10 trials, 2436 patients) Severe (1 trials, 479 patients) Critically ill (0 trials, 0 patients)
Mechanically ventilated at baseline ^b	Mean (range), %	3.23 (0–16.8)
Age ^c	Mean (range of means), years	50.8 (32.9–77.0)
Sex ^d	Mean (range of means), % women	46.9 (30.0–71.0)
Loading doses Day 1 ^e	Mean (range of means), mg	1010 (800–1600)
Total cumulative doses ^f	Median (range), mg	4000 (2000–11200)
Duration of therapy ^g	Median (range), days	7 (4–16)
Type of care	n (%) inpatient n (%) outpatient	Inpatient: 9549 (87.4) Outpatient: 1372 (12.6)
Trial participants	Median (range)	364 (2–4716)
Concomitant use of corticosteroids ^h	Mean (range across trials that report this), %	12.61 (8.0–19.5)

Notes:

- ^a 19 trials did not report the disease severity of patients.
- ^b 19 trials did not report the proportion of mechanical ventilation at baseline.
- ^c Based on 15 trials and 8006 patients. For the other 15 trials: 1 trial did not report the age of patients; and the other 14 trials reported that the age of patients were ≥ 12, 18 or 40.
- ^d 14 trials did not report the sex of patients.
- ^e 10 trials did not use a loading dose.
- ^f 1 trial reported range of treatment duration.
- ^g 1 trial reported range of treatment duration.
- ^h 23 trials did not report the concomitant use of corticosteroids.

Baseline risk

The absolute effects of treatment are informed by the prognosis (i.e. baseline risk estimates) combined with the relative estimates of effects (e.g. risk ratio, odds ratio) obtained from the NMA.

The control arm of the WHO SOLIDARITY Trial (13), performed across a wide variety of countries and geographical regions, was identified by the GDG panel as representing the most relevant source of evidence to make the baseline risk estimates for the outcomes of mortality and mechanical ventilation. The rationale for selecting the WHO SOLIDARITY Trial was to reflect the overall prognosis of the global population for which the WHO guideline recommendations are made. When applying the evidence to a particular patient or setting, the individual or setting's risk of mortality and mechanical ventilation should be considered. In view of the study designs, the GDG determined that for other outcomes using the median or mean of all patients randomized to usual care

across the included studies would provide the most reliable estimate of baseline risk.

Subgroup analysis

For hydroxychloroquine, the GDG panel requested subgroup analyses based on age (considering children vs younger adults [e.g. under 70 years] vs older adults [e.g. 70 years or older]), illness severity (non-severe vs severe vs critical COVID) and based on whether or not it was co-administered with azithromycin.

The panel also requested a subgroup analysis based on high dose vs low dose hydroxychloroquine. A categorical approach to hydroxychloroquine dosing proved impossible because the trials used varying loading doses, continuation doses and durations. Therefore, in collaboration with a pharmacology expert (Professor Andrew Owen), we modelled the expected serum concentrations over time. We hypothesized that higher trough concentrations early in the treatment course (e.g. trough concentration on Day 3) might be more effective than lower early trough concentrations. We also hypothesized that higher maximum serum concentrations (e.g. peak concentration on the last day) might result in higher risk of adverse effects than lower maximum serum concentrations. In our pharmacokinetic model, the cumulative dose was highly correlated with all measures of serum concentrations on Day 3 and the final day of treatment, and therefore we decided to use cumulative dose as the primary analysis. Day 3 trough concentration was least strongly correlated with total cumulative dose ($R^2 = 0.376$) and therefore we performed a sensitivity subgroup analysis with predicted Day 3 trough concentrations for efficacy outcomes.

Info Box

The recommendation concerning hydroxychloroquine was published December 17 2020 as the [third version](#) of the WHO living guideline and in the BMJ as [Rapid Recommendations](#). No changes were made for the hydroxychloroquine recommendation in this fourth version of the guideline. Please view the section text for a summary of the evidence requested to inform the recommendation, triggered by the WHO Solidarity trial.

Recommendation against

We recommend against administering hydroxychloroquine or chloroquine for treatment of COVID-19.

Remark: This recommendation applies to patients with any disease severity and any duration of symptoms.

Practical info

The GDG made a strong recommendation against using hydroxychloroquine or chloroquine for treatment of patients with COVID-19. The use of hydroxychloroquine may preclude the use of other important drugs that also prolong the QT interval, such as azithromycin and fluoroquinolones. Concomitant use of drugs that prolong the QT interval should be done with extreme caution.

Evidence to decision

Benefits and harms

Hydroxychloroquine and chloroquine probably do not reduce mortality or mechanical ventilation and may not reduce duration of hospitalization. The evidence does not exclude the potential for a small increased risk of death and mechanical ventilation with hydroxychloroquine. The effect on other less important outcomes, including time to symptom resolution, admission to hospital, and duration of mechanical ventilation, remains uncertain.

Hydroxychloroquine may increase the risk of diarrhoea and nausea/vomiting; a finding consistent with evidence from its use in other conditions. Diarrhoea and vomiting may increase the risk of hypovolaemia, hypotension and acute kidney injury, especially in settings where health care resources are limited. Whether or not and to what degree hydroxychloroquine

increases the risk of cardiac toxicity, including life-threatening arrhythmias, is uncertain.

Subgroup analyses indicated no effect modification based on severity of illness (comparing either critical vs severe/non-severe or non-severe vs critical/severe) or age (comparing those aged < 70 years versus those > 70 years old). Further, the cumulative dose and predicted Day 3 serum trough concentrations did not modify the effect for any outcome. Therefore, we assumed similar effects in all subgroups.

We also reviewed evidence comparing the use of hydroxychloroquine plus azithromycin vs hydroxychloroquine alone. There was no evidence that the addition of azithromycin modified the effect of hydroxychloroquine for any outcome (very low certainty).

Certainty of the evidence

For the key outcomes of mortality and mechanical ventilation, the panel considered the evidence to be of moderate certainty. There were residual concerns about lack of blinding in the largest trials and the imprecision. For example, the credible interval around the pooled effect leaves open the possibility of a very small reduction in mortality. The quality of evidence was low for diarrhoea and nausea/vomiting because of lack of blinding in many of the trials and because the total number of patients enrolled in trials reporting these outcomes was smaller than the optimal information size (although the credible interval laid entirely on the side of harm for both outcomes).

For all other outcomes, the certainty of the evidence was low or very low. The primary concerns with the data were imprecision (credible intervals included both important benefit and important harm) as well as risk of bias (lack of blinding).

Preference and values

Applying the agreed values and preferences (see Evidence section above), the GDG inferred that almost all well-informed patients would not want to receive hydroxychloroquine given the evidence suggesting there was probably no effect on mortality or need for mechanical ventilation and there was a risk of adverse events including diarrhoea and nausea and vomiting. The panel did not expect there would be much variation in values and preferences between patients when it came to this intervention.

Resources and other considerations

Hydroxychloroquine and chloroquine are relatively inexpensive compared with other drugs used for COVID-19 and are already widely available, including in low-income settings. Despite this, the panel felt that almost all patients would choose not to use hydroxychloroquine or chloroquine because the harms outweigh the benefits. Although the cost may be low per patient, the GDG panel raised concerns about diverting attention and resources away from care likely to provide a benefit such as corticosteroids in patients with severe COVID-19 and other supportive care interventions.

Justification

When moving from evidence to the strong recommendation against the use of hydroxychloroquine or chloroquine for patients with COVID-19, the panel emphasized the moderate certainty evidence of probably no reduction in mortality or need for mechanical ventilation. It also noted the evidence suggesting possible harm associated with treatment, with increased nausea and diarrhoea. The GDG did not anticipate important variability in patient values and preferences, and other contextual factors, such as resource considerations, accessibility, feasibility and impact on health equity (see summary of these factors under Evidence to decision).

Subgroup analyses

The panel did not find any evidence of a subgroup effect across patients with different levels of disease severity, between adults and older adults, and by different doses, and therefore did not make any subgroup recommendation for this drug. In other

words, the strong recommendation is applicable across disease severity, age groups, and all doses and dose schedules of hydroxychloroquine.

The trials included patients from around the world, with all disease severities, and treated in different settings (outpatient and inpatient). Although the trials did not report subgroup effects by time from symptom onset, many of the trials enrolled patients early in the disease course. The GDG panel therefore felt that the evidence applies to all patients with COVID-19.

Applicability

Special populations

None of the included RCTs enrolled children, and therefore the applicability of this recommendation to children is currently uncertain. However, the panel had no reason to think that children with COVID-19 would respond any differently to treatment with hydroxychloroquine. There were similar considerations in regards to pregnant women, with no data directly examining this population, but no rationale to suggest they would respond differently than other adults. Hydroxychloroquine crosses the placental barrier and there are concerns that it may lead to retinal damage in neonates. Although hydroxychloroquine has been used in pregnant women with systemic autoimmune diseases, such as systemic lupus erythematosus, pregnant women may have even more reasons than other patients to be reluctant to use hydroxychloroquine for COVID-19.

In combination with azithromycin

There was no evidence from the NMA that the addition of azithromycin modified the effect of hydroxychloroquine for any outcome. As there were no trial data suggesting that azithromycin favourably modifies the effect of hydroxychloroquine, the recommendation against hydroxychloroquine and chloroquine applies to patients whether or not they are concomitantly receiving azithromycin.

Uncertainties

Please see end of document for residual uncertainties (Section 8). The GDG panel felt that it was unlikely future studies would identify a subgroup of patients that are likely to benefit from hydroxychloroquine or chloroquine.

Clinical question/ PICO

Population:	Patients with COVID-19 infection (all disease severities)
Intervention:	Hydroxychloroquine + usual care
Comparator:	Usual care

Summary

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care Hydroxychloroquine	Certainty of the evidence (Quality of evidence)	Plain text summary
Mortality	Odds ratio 1.11 (CI 95% 0.95 - 1.31) Based on data from 10,859 patients in 29 studies. ¹ (Randomized controlled)	106 per 1000 116 per 1000 Difference: 10 more per 1000 (CI 95% 5 fewer - 28 more)	Moderate Due to borderline risk of bias and imprecision ²	Hydroxychloroquine probably does not reduce mortality.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care Hydroxychloroquine	Certainty of the evidence (Quality of evidence)	Plain text summary
Mechanical ventilation	Odds ratio 1.2 (CI 95% 0.83 - 1.81) Based on data from 6,379 patients in 5 studies. (Randomized controlled)	105 per 1000 123 per 1000 Difference: 18 more per 1000 (CI 95% 16 fewer - 70 more)	Moderate Due to borderline risk of bias and serious imprecision ³	Hydroxychloroquine probably does not reduce mechanical ventilation.
Viral clearance 7 days	Odds ratio 1.08 (CI 95% 0.25 - 4.78) Based on data from 280 patients in 4 studies. (Randomized controlled)	483 per 1000 502 per 1000 Difference: 19 more per 1000 (CI 95% 294 fewer - 334 more)	Very Low Due to very serious imprecision ⁴	The effect of hydroxychloroquine on viral clearance is very uncertain.
Admission to hospital	Odds ratio 0.39 (CI 95% 0.12 - 1.28) Based on data from 465 patients in 1 studies. (Randomized controlled)	47 per 1000 19 per 1000 Difference: 28 fewer per 1000 (CI 95% 41 fewer - 12 more)	Very Low Due to very serious imprecision and serious indirectness ⁵	The effect of hydroxychloroquine on admission to hospital is uncertain.
Cardiac toxicity	Based on data from 3,287 patients in 7 studies. (Randomized controlled)	46 per 1000 56 per 1000 Difference: 10 more per 1000 (CI 95% 0 more - 30 more)	Very Low Due to serious imprecision, risk of bias, and indirectness ⁶	The effect of hydroxychloroquine on cardiac toxicity is uncertain.
Diarrhoea	Odds ratio 1.95 (CI 95% 1.4 - 2.73) Based on data from 979 patients in 6 studies. (Randomized controlled)	149 per 1000 255 per 1000 Difference: 106 more per 1000 (CI 95% 48 more - 174 more)	Low Due to serious imprecision and risk of bias ⁷	Hydroxychloroquine may increase the risk of diarrhoea.
Nausea/ vomiting	Odds ratio 1.74 (CI 95% 1.26 - 2.41) Based on data from 1,429 patients in 7 studies. (Randomized controlled)	99 per 1000 161 per 1000 Difference: 62 more per 1000 (CI 95% 23 more - 110 more)	Low Due to serious imprecision and risk of bias ⁸	Hydroxychloroquine may increase the risk of nausea and vomiting.
Delirium	Odds ratio 1.59 (CI 95% 0.77 - 3.28) Based on data from 423 patients in 1 studies. (Randomized controlled)	62 per 1000 95 per 1000 Difference: 33 more per 1000 (CI 95% 14 fewer - 116 more)	Very Low Due to very serious imprecision and serious indirectness ⁹	The effect of hydroxychloroquine on delirium is uncertain.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care Hydroxychloroquine	Certainty of the evidence (Quality of evidence)	Plain text summary
Time to clinical improvement	Lower better Based on data from: 479 patients in 5 studies. (Randomized controlled)	11 days (Mean) 9 days (Mean) Difference: MD 2 fewer (CI 95% 4 fewer - 0.1 more)	Very Low Due to serious risk of bias, imprecision, and indirectness ¹⁰	The effect of hydroxychloroquine on time to clinical improvement is uncertain.
Duration of hospitalization	Lower better Based on data from: 5,534 patients in 5 studies. (Randomized controlled)	12.8 days (Mean) 12.9 days (Mean) Difference: MD 0.1 more (CI 95% 1.9 fewer - 2 more)	Low Due to serious imprecision and serious risk of bias ¹¹	Hydroxychloroquine may have no effect on duration of hospitalization.
Time to viral clearance	Lower better Based on data from: 440 patients in 5 studies. (Randomized controlled)	9.7 days (Mean) 10.6 days (Mean) Difference: MD 0.7 fewer (CI 95% 4.3 fewer - 4.8 more)	Very Low Due to serious risk of bias and very serious imprecision ¹²	The effect of hydroxychloroquine on time to viral clearance is uncertain.
Adverse events leading to drug discontinuation	Based on data from: 210 patients in 3 studies. (Randomized controlled)	Two of 108 patients randomized to hydroxychloroquine discontinued treatment because of adverse effects. None of 102 patients did so in the placebo/standard care group.	Very Low Due to extremely serious imprecision ¹³	The effect of hydroxychloroquine on adverse events leading to drug discontinuation is uncertain.

1. Systematic review (3). **Baseline/comparator:** Control arm of reference used for intervention. We elected to use the control arm of the WHO solidarity trial, reflecting usual care across countries participating in the trial.
2. **Risk of bias: Serious.** We rated two trials as high risk of bias due to high or probably high risk of bias in deviations from the intended intervention. . **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: Serious.** The 95% CI crosses the minimally important difference (2% reduction in mortality). . **Publication bias: No serious.**
3. **Risk of bias: Serious.** **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
4. **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: Very Serious.** Wide confidence intervals. **Publication bias: No serious.**
5. **Inconsistency: No serious.** **Indirectness: Serious.** **Imprecision: Very Serious.** **Publication bias: No serious.**
6. **Risk of bias: Serious.** unblinded studies -> cardiac toxicity differential detection. **Inconsistency: No serious.** **Indirectness: Serious.** Studies measured serious cardiac toxicity differently.. **Imprecision: Serious.**
7. **Risk of bias: Serious.** Concerns mitigated because of large effect and indirect evidence showing consistent results. **Imprecision: Serious.** OIS not met. **Upgrade: Large magnitude of effect.**
8. **Risk of bias: Serious.** Concerns mitigated because of large effect and indirect evidence showing consistent results. **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: Serious.** OIS not met.. **Publication bias: No serious.** **Upgrade: Large magnitude of effect.**
9. **Indirectness: Serious.** This outcome was not collected systematically and the definition of delirium was not specified.. **Imprecision: Very Serious.**
10. **Risk of bias: Serious.** **Inconsistency: No serious.** **Indirectness: Serious.** Studies measured clinical improvement

differently.. **Imprecision: Serious.** **Publication bias: No serious.**

11. **Risk of bias: Serious.** **Indirectness: No serious.** **Imprecision: Serious.** Wide confidence intervals.
12. **Risk of bias: Serious.** **Imprecision: Very Serious.**
13. **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: Very Serious.** **Publication bias: No serious.**

7.3 Lopinavir/ritonavir (published December 17 2020)

The third version of the WHO living guideline addressed the use of lopinavir/ritonavir (and hydroxychloroquine, see above) in patients with COVID-19. It followed the pre-print publication of the WHO SOLIDARITY Trial on 15 October 2020, reporting results on treatment with remdesivir, hydroxychloroquine and lopinavir-ritonavir in hospitalized patients with COVID-19 (50). The role of these drugs in clinical practice has remained uncertain, with limited prior trial evidence. The WHO SOLIDARITY Trial adds 11,266 randomized patients (2570 to remdesivir, 954 to hydroxychloroquine, and 1411 to lopinavir-ritonavir, 6,331 to usual care) and had the potential to change practice (13, 50).

The evidence

For lopinavir/ritonavir, the evidence summary was based on 7 trials with 7429 participants. Of note, none of the included studies enrolled children or adolescents under the age of 19 years old (Table 4).

**Table 4. Summary of trials and trial characteristics informing the lopinavir/ritonavir recommendation
(trials = 7, total patients = 7429)**

Geographic region	Region of the Americas South-East Asia Region Western Pacific Region European Region Eastern Mediterranean Region	Region of the Americas (0 trials, 0 patients) South-East Asia and Western Pacific Regions (5 trials, 535 patients) European Region (2 trials, 6894 patients) Middle East (0 trials, 0 patients)
Severity of illness ^a	Non-severe Severe Critically ill	Mild/Moderate (4 trials, 336 patients) Severe (1 trials, 199 patients) Critically ill (0 trials, 0 patients)
Mechanically ventilated at baseline ^b	Mean (range), %	7.3 (0–16.1)
Age ^c	Mean (range of means), years	52.6 (42.5–66.2)
Sex	Mean (range of means), % women	48.7 (38.9–61.7)
Loading doses Day 1 ^d	Mean (range of means), mg	
Total cumulative doses (lopinavir/ ritonavir) ^e	Median (range), mg	11200/2800(8000–11 200/2000–2800)
Duration of therapy ^f	Median (range), days	14 (10–14)
Type of care	n (%) inpatient n (%) outpatient	Inpatient: 7429 (100) Outpatient: 0 (0)
Trial participants	Median (range)	101 (60–5040)
Concomitant use of corticosteroids ^g	Mean (range across trials that report this), %	17.1 (0–32.3)

Notes:

^a 2 trials did not report the disease severity of patients.

^b 3 trials did not report proportion of mechanical ventilation at baseline.

^c 2 trials did not report the age of patients.

^d No trial reported loading dose.

^e 1 trial did not report cumulative doses; 2 trials only reported range of treatment duration.

^f 1 trial did not report the duration of therapy, 2 trials used a range of treatment duration.

^g 2 trials did not report the concomitant use of corticosteroids.

Baseline risk

The absolute effects of treatment are informed by the prognosis (i.e. baseline risk estimates) combined with the relative estimates of effects (e.g. risk ratio, odds ratio) obtained from the NMA.

The control arm of the WHO SOLIDARITY Trial (13), performed across a wide variety of countries and geographical regions, was identified by the GDG panel as representing the most relevant source of evidence to make the baseline risk estimates for the outcomes of mortality and mechanical ventilation. The rationale for selecting the WHO SOLIDARITY Trial was to reflect the overall prognosis of the global population for which the WHO guideline recommendations are made. When applying the evidence to a particular patient or setting, the individual or setting's risk of mortality and mechanical ventilation should be considered. In view of the study designs, the GDG determined that for other outcomes using the median or mean of all patients randomized to usual care across the included studies would provide the most reliable estimate of baseline risk.

Subgroup analysis

For lopinavir/ritonavir, the GDG panel requested subgroup analyses based on age (considering children vs younger adults [e.g. under 70 years] vs older adults [e.g. 70 years or older]), and illness severity (non-severe vs severe vs critical COVID). The GDG discussed other potential subgroups of interest including time from onset of symptoms until initiation of therapy and concomitant medications, but recognized that these analyses would not be possible without access to individual participant data and/or more detailed reporting from the individual trials.

Info Box

The recommendation concerning lopinavir-ritonavir was published December 17 2020 as the [third version](#) of the WHO living guideline and in the BMJ as [Rapid Recommendations](#). No changes were made for the lopinavir/ritonavir recommendation in this fourth version of the guideline. Please view the section text for a summary of the evidence requested to inform the recommendation, triggered by the WHO Solidarity trial.

Recommendation against

We recommend against administering lopinavir/ritonavir for treatment of COVID-19.

Remark: This recommendation applies to patients with any disease severity and any duration of symptoms.

Evidence to decision

Benefits and harms

The GDG panel found a lack of evidence that lopinavir/ritonavir improved outcomes that matter to patients such as reduced mortality, need for mechanical ventilation, time to clinical improvement and others. For mortality and need for mechanical ventilation this was based on moderate certainty evidence, for the other outcomes low or very low certainty evidence.

There was low certainty evidence that lopinavir/ritonavir may increase the risk of diarrhoea and nausea and vomiting, a finding consistent with the indirect evidence evaluating its use in patients with HIV. Diarrhoea and vomiting may increase the risk of hypovolaemia, hypotension and acute kidney injury, especially in settings where health care resources are limited. There was an uncertain effect on viral clearance and acute kidney injury.

Subgroup analysis indicated no effect modification based on severity of illness (comparing either critical vs severe/non-severe or non-severe vs critical/severe) or age (comparing those aged < 70 years versus those 70 years and older). As there was no evidence of a statistical subgroup effect, we did not formally evaluate using the ICEMAN tool.

Certainty of the evidence

The evidence is based on a linked systematic review and NMA of seven randomized controlled trials; pooling data from 7429 patients hospitalized with various severities of COVID-19 and variably reporting the outcomes of interest to the guideline panel (3). The panel agreed that there was moderate certainty for mortality and need for mechanical ventilation, low certainty for diarrhoea, nausea and duration of hospitalization and very low certainty in the estimates of effect for viral clearance, acute kidney injury and time to clinical improvement. Most outcomes were lowered for risk of bias and imprecision (wide confidence intervals which do not exclude important benefit or harm).

Preference and values

Applying the agreed values and preferences (see Evidence section above), the GDG inferred that almost all well-informed patients would not want to receive lopinavir/ritonavir given the evidence suggested there was probably no effect on mortality or need for mechanical ventilation and there was a risk of adverse events including diarrhoea and nausea and vomiting. The panel did not expect there would be much variation in values and preferences between patients when it came to this intervention.

Resources and other considerations

Although the cost of lopinavir/ritonavir is not as high as some other investigational drugs for COVID-19, and the drug is generally available in most health care settings, the GDG raised concerns about opportunity costs and the importance of not drawing attention and resources away from best supportive care or the use of corticosteroids in severe COVID-19.

Justification

When moving from evidence to the strong recommendation against the use of lopinavir/ritonavir for patients with COVID-19, the panel emphasized the moderate certainty evidence of probably no reduction in mortality or need for mechanical ventilation. It also noted the evidence suggesting possible harm associated with treatment, with increased nausea and diarrhoea. The GDG did not anticipate important variability in patient values and preferences, and other contextual factors, such as resource considerations, accessibility, feasibility and impact on health equity would not alter the recommendation (see summary of these factors under Evidence to decision).

Subgroup analysis

The panel did not find any evidence of a subgroup effect across patients with different levels of disease severity, or between adults and older adults and therefore did not make any subgroup recommendation for this drug. Although the trials did not report subgroup effects by time from symptom onset, many of the trials enrolled patients with patients early in the disease course. The strong recommendation is applicable across disease severity and age groups.

Applicability

None of the included RCTs enrolled children, and therefore the applicability of this recommendation to children is currently uncertain. However, the panel had no reason to think that children with COVID-19 would respond any differently to treatment with lopinavir/ritonavir. There were similar considerations in regards to pregnant women, with no data directly examining this population, but no rationale to suggest they would respond differently than other adults. In patients using lopinavir/ritonavir for HIV infection, it should generally be continued while receiving care for COVID-19.

Uncertainties

Please see end of document for residual uncertainties (Section 8). The GDG panel felt that it was unlikely future studies would identify a subgroup of patients that are likely to benefit from lopinavir/ritonavir.

Additional considerations

In patients who have undiagnosed or untreated HIV, use of lopinavir/ritonavir alone may promote HIV resistance to important antiretrovirals. Widespread use of lopinavir/ritonavir for COVID-19 may cause drug shortages for people living with HIV.

Clinical question/ PICO

Population: Patients with COVID-19 (all disease severities)
Intervention: Lopinavir-ritonavir
Comparator: Standard care

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care Lopinavir- ritonavir	Certainty of the evidence (Quality of evidence)	Plain text summary
Mortality	Odds ratio 1 (CI 95% 0.82 - 1.2) Based on data from 8,061 patients in 4 studies. ¹ (Randomized controlled)	106 per 1000 106 per 1000 Difference: 0 fewer per 1000 (CI 95% 17 fewer - 19 more)	Moderate Due to borderline risk of bias and imprecision ²	Lopinavir-ritonavir probably has no effect on mortality
Mechanical ventilation	Relative risk 1.16 (CI 95% 0.98 - 1.36) Based on data from 7,579 patients in 3 studies. ³ (Randomized controlled)	105 per 1000 122 per 1000 Difference: 17 more per 1000 (CI 95% 2 fewer - 38 more)	Moderate Due to borderline risk of bias and imprecision ⁴	Lopinavir-ritonavir probably does not reduce mechanical ventilation
Viral clearance	Odds ratio 0.35 (CI 95% 0.04 - 1.97) Based on data from 171 patients in 2 studies. (Randomized controlled)	483 per 1000 246 per 1000 Difference: 237 fewer per 1000 (CI 95% 447 fewer - 165 more)	Low Due to serious risk of bias, Due to very serious imprecision ⁵	the effects of lopinavir-ritonavir on viral clearance is very uncertain
Acute kidney injury	Relative risk Based on data from 259 patients in 2 studies. (Randomized controlled)	45 per 1000 25 per 1000 Difference: 20 fewer per 1000 (CI 95% 70 fewer - 20 more)	Very Low Due to serious risk of bias and very serious imprecision, Due to very serious imprecision ⁶	The effect of lopinavir-ritonavir on acute kidney injury is uncertain
Diarrhoea	Odds ratio 4.28 (CI 95% 1.99 - 9.18) Based on data from 370 patients in 4 studies. (Randomized controlled)	67 per 1000 235 per 1000 Difference: 168 more per 1000 (CI 95% 58 more - 330 more)	Moderate Due to serious risk of bias and imprecision, Upgraded due to Large magnitude of effect ⁷	Lopinavir-ritonavir may increase the risk of diarrhoea.
Nausea/ vomiting	Relative risk Based on data from 370 patients in 4 studies. ⁸ (Randomized controlled)	17 per 1000 177 per 1000 Difference: 160 more per 1000	Moderate Due to serious risk of bias and imprecision ⁹	Lopinavir-ritonavir may increase the risk of nausea/vomiting

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care Lopinavir- ritonavir	Certainty of the evidence (Quality of evidence)	Plain text summary
Time to clinical improvement	Lower better Based on data from: 199 patients in 1 studies. (Randomized controlled)	11 days (Mean) Difference: MD 1 fewer (CI 95% 4.1 fewer - 3.2 more)	10 days (Mean) Due to serious risk of bias, Due to very serious imprecision ¹⁰	Very Low The effect of lopinavir-ritonavir improves on time to clinical improvement is very uncertain
Duration of hospitalization	Lower better Based on data from: 5,239 patients in 2 studies. (Randomized controlled)	12.8 days (Mean) Difference: MD 0.3 lower (CI 95% 3 lower - 2.5 higher)	12.5 days (Mean) Due to serious risk of bias and imprecision ¹¹	Low Lopinavir-ritonavir may have no effect on duration of hospitalization

1. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** (3),
2. **Risk of bias: No serious.** We rated two trials as high risk of bias due to high or probably high risk of bias in deviations from the intended intervention.. **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: Serious.** The 95% CI crosses the minimally important difference (2% reduction in mortality).. **Publication bias: No serious.**
3. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** (3),
4. **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
5. **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: Very Serious.** Wide confidence intervals. **Publication bias: No serious.**
6. **Risk of bias: Serious.** **Inconsistency: No serious.** **Imprecision: Very Serious.** Wide confidence intervals. **Publication bias: No serious.**
7. **Risk of bias: Serious.** Concerns mitigated because of large effect and indirect evidence showing consistent results. **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: Serious.** Few patients and events. **Publication bias: No serious.** **Upgrade: Large magnitude of effect.**
8. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** (3),
9. **Risk of bias: Serious.** Concerns mitigated because of large effect and indirect evidence showing consistent results. **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: Serious.** Few patients and events. **Publication bias: No serious.** **Upgrade: Large magnitude of effect.**
10. **Risk of bias: Serious.** **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: Very Serious.** Wide confidence intervals, low number of patients. **Publication bias: No serious.**
11. **Risk of bias: Serious.** **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**

7.4 Remdesivir (published Nov 20 2020)

The second version of the WHO living guideline addressed the use of remdesivir in patients with COVID-19. It followed the pre-print publication of the WHO SOLIDARITY trial on 15 October, 2020, reporting results on treatment with remdesivir, hydroxychloroquine and lopinavir-ritonavir in hospitalized patients with COVID-19 (13). The role of these drugs in clinical practice has remained uncertain, with limited prior trial evidence. The WHO SOLIDARITY trial adds 11,266 randomized patients (2570 to remdesivir, 954 to hydroxychloroquine, and 1411 to lopinavir-ritonavir, 6,331 to usual care) and had the potential to change

practice (13).

The WHO GDG started with developing trustworthy recommendations on remdesivir, followed by the now published recommendations on hydroxychloroquine and lopinavir-ritonavir in the third update. Remdesivir is a novel monophosphoramide adenosine analogue prodrug which is metabolized to an active tri-phosphate form that inhibits viral RNA synthesis. Remdesivir has *in vitro* and *in vivo* antiviral activity against several viruses, including SARS-CoV2. Remdesivir is widely used in many countries, with several guidelines recommending its use in patients with severe or critical COVID-19 (51, 52).

The evidence

The GDG panel requested an update of the living NMA of RCTs of drug treatments for COVID-19, based around important clinical questions to be addressed in the recommendations. The rating of importance of outcomes, selection of estimates for baseline risk and considerations about values and preferences were similar to what is presented in Section 5.

Based on 4 trials with 7333 participants (13, 53-55), the NMA provided relative estimates of effect for patient-important outcomes (Table 4). Of note, none of the included studies enrolled children or adolescents under the age of 19 years old.

Table 5. Summary of trials and trial characteristics informing the remdesivir recommendation

Study	N	Country	Mean age (years)	Severity (as per WHO criteria)	% IMV (at baseline)	Treatments (dose and duration)	Outcomes
Biegel (ACTT-1)	1063	United States, Europe, Asia	58.9	Non-severe (11.3%) Severe ^a (88.7%)	44.1%	Remdesivir IV (100 mg/day for 10 days)	-Mortality -Adverse events -Time to clinical improvement
Spinner (SIMPLE MODERATE)*	596	United States, Europe, Asia	56-58	Non-severe (100%)	0%	Remdesivir IV (200 mg at day 1, then 100 mg for 4 days or 9 days)	-Mortality -Time to clinical improvement -Duration of hospitalization -Mechanical ventilation -Adverse events
Pan (SOLIDARITY)	5451	Worldwide	< 50 35% 50-70 47% > 70 18%	Non-severe (24%) Severe ^b (67%) Critical (9%)	8.9%	Remdesivir IV (200 mg at day 1, then 100 mg day 2-10)	-Mortality -Mechanical ventilation
Wang	237	China	65	Severe ^c (100%)	16.1%	Remdesivir IV (100 mg/day for 10 days)	-Mortality -Mechanical ventilation -Adverse events -Viral clearance -Duration of hospitalization -Duration of ventilation -Time to clinical improvement

IMV: invasive mechanical ventilation; IV: intravenous; N: number; NR: not reported; Sx: symptom.

Severity criteria based on WHO definitions unless otherwise stated. a – defined severe as SpO₂ < 94% on room air OR respiratory rate > 24 breaths per minute; b – defined severe as requiring oxygen support; c – defined severe as SpO₂ < 94% on room air. Notes:

*Only SIMPLE MODERATE was included in the analysis, as SIMPLE SEVERE did not have a placebo/usual care arm.

Subgroup analysis

The GDG panel requested subgroup analyses based on age (considering children vs adults vs older people), illness severity (non-severe vs severe vs critical COVID – see subgroup under Section 7 - Recommendations for therapeutics section for details), and duration of remdesivir therapy (5 days vs longer than 5 days). The GDG discussed other potential subgroups of interest including time from onset of symptoms until initiation of therapy, concomitant medications (especially corticosteroids) however recognized these analyses would not be possible without access to individual participant data. To this last point, the panel recognized that usual care is likely variable between centres, regions and evolved over time. However, given all of the data comes from RCTs, use of these co-interventions that comprise usual care should be balanced between study patients randomized to either the intervention or usual care arms.

Following the panel's request, the NMA team performed subgroup analyses in order to assess for effect modification which, if present, could mandate distinct recommendations by subgroups. From the data available from the included trials, subgroup analysis was only possible for severity of illness and the outcome of mortality. This subgroup analysis was performed using a random effects frequentist analysis based on the three WHO severity definitions. A post-hoc Bayesian analysis was also performed, which incorporated meta-regression using study as a random effect. This latter approach has the advantage of more accurately accounting for within-study differences but can only compare two subgroups at a time. The panel used a pre-specified framework incorporating the ICEMAN tool to assess the credibility of subgroup findings (13).

Info Box

The recommendation concerning remdesivir was published November 20 2020 as the [second version of the WHO living guideline](#) and in the BMJ as [Rapid Recommendations](#). No changes were made for the remdesivir recommendation in this third version of the guideline. Please view the section text for a summary of the evidence requested to inform the recommendation, triggered by the WHO SOLIDARITY trial.

Hospitalized patients with COVID-19 infection, regardless of disease severity

Conditional recommendation against

We suggest against administering remdesivir in addition to usual care

Practical info

The GDG made a conditional recommendation against using remdesivir for treatment of hospitalized patients with COVID-19. If administration of remdesivir is considered, it should be noted that its use is contraindicated in those with liver (ALT >5 times normal at baseline) or renal (eGFR <30 mL/minute) dysfunction. To date, it can only be administered intravenously, and it has relatively limited availability.

Evidence to decision

Benefits and harms

The GDG panel found a lack of evidence that remdesivir improved outcomes that matter to patients such as reduced mortality, need for mechanical ventilation, time to clinical improvement and others. However, the low certainty evidence for these outcomes, especially mortality, does not prove that remdesivir is ineffective; rather, there is insufficient evidence to confirm that it does improve patient-important outcomes.

There was no evidence of increased risk of severe adverse events (SAEs) from the trials.. However, further pharmacovigilance is needed because SAEs are commonly underreported and rare events could be missed, even in large RCTs.

A subgroup analysis indicated that remdesivir treatment possibly increased mortality in the critically ill and possibly reduced mortality in the non-severely and severely ill. The panel judged the overall credibility of this subgroup effect (evaluated using the ICEMAN tool) to be insufficient to make subgroup recommendations. The overall low certainty evidence on the benefits and harms of remdesivir, driven by risk of bias and imprecision limitations in the included studies, also contributed to the judgement.

Certainty of the evidence

Low

The evidence is based on a linked systematic review and NMA of four RCTs; pooling data from 7333 patients hospitalized with various severities of COVID-19 and variably reporting the outcomes of interest to the guideline panel (3). The panel agreed that there was low certainty in the estimates of effect for all patient-important outcomes across benefits and harms, mostly driven by risk of bias and imprecision (wide confidence intervals which do not exclude important benefit or harm). There was very low certainty evidence for viral clearance and delirium.

Preference and values

Substantial variability is expected or uncertain

Applying the agreed values and preferences (see Evidence section above), the GDG inferred that most patients would be reluctant to use remdesivir given the evidence left high uncertainty regarding effects on mortality and the other prioritized outcomes. This was particularly so as any beneficial effects of remdesivir, if they do exist, are likely to be small and the possibility of important harm remains. The panel acknowledged, however, that values and preferences are likely to vary, and there will be patients and clinicians who choose to use remdesivir given the evidence has not excluded the possibility of benefit.

Resources and other considerations

Important issues, or potential issues not investigated

A novel therapy typically requires higher certainty evidence of important benefits than currently available for remdesivir, preferably supported wherever possible by cost-effectiveness analysis. In the absence of this information, the GDG raised concerns about opportunity costs and the importance of not drawing attention and resources away from best supportive care or the use of corticosteroids in severe COVID-19. It was noted that remdesivir is administered only by the intravenous route currently, and that global availability is currently limited.

Justification

When moving from evidence to the conditional recommendation against the use of remdesivir for patients with COVID-19, the panel emphasized the evidence of possibly no effect on mortality, need for mechanical ventilation, recovery from symptoms and other patient-important outcomes, albeit of low certainty; it also noted the anticipated variability in patient values and preferences, and other contextual factors, such as resource considerations, accessibility, feasibility and impact on health equity (see summary of these factors under Evidence to decision).

Importantly, given the low certainty evidence for these outcomes, the panel concluded that the evidence did not prove that remdesivir has no benefit; rather, there is no evidence based on currently available data that it does improve patient-important outcomes. Especially given the costs and resource implications associated with remdesivir, but consistent with the approach that should be taken with any new drug, the panel felt the responsibility should be on demonstrating evidence of efficacy, which is not established by the currently available data. The panel noted that there was no evidence of increased risk of SAEs in patients receiving remdesivir, at least from the included trials. Further pharmacovigilance is required to confirm this, as SAEs are commonly underreported and rare events would be missed, even in large RCTs.

Subgroup analysis

The panel carefully considered a potential subgroup effect across patients with different levels of disease severity, suggesting a possible increase in mortality in the critically ill and a possible reduction in mortality in the non-severely and severely ill. For this analysis, critical illness was defined as those requiring invasive or non-invasive ventilation, severe illness as those requiring oxygen therapy (but not meeting critical illness criteria), and non-severe as all others. Patients requiring high-flow nasal cannula represented a small proportion and were characterized as either severe (SOLIDARITY) (13) or critical (ACTT-1) (55). The analysis focused on within-study subgroup comparisons across the different severities, and therefore the SIMPLE-MODERATE trial could not be included in the subgroup analysis as it only enrolled patients with non-severe COVID-19. The panel reviewed the results of both the random effects frequentist analysis and the post-hoc Bayesian analysis which incorporated meta-regression using study as a random effect.

The GDG panel judged the credibility in the subgroup analysis assessing differences in mortality by severity of illness to be

insufficient to make subgroup recommendations. Important factors influencing this decision included a lack of a priori hypothesized direction of subgroup effect by trial investigators, little or no previously existing supportive evidence for the subgroup finding, and relatively arbitrary cut points used to examine the subgroups of interest. The overall low certainty evidence for the benefits and harms of remdesivir, driven by risk of bias and imprecision limitations, also contributed to the judgement. The panel highlighted that despite the conditional recommendation against remdesivir, they support further enrolment into RCTs evaluating remdesivir, especially to provide higher certainty of evidence for specific subgroups of patients.

The panel had *a priori* requested analyses of other important subgroups of patients including children and older persons, but there were no data to address these groups specifically. None of the included RCTs enrolled children, and although older people were included in the trials, their outcomes were not reported separately. Also, there is no pharmacokinetic or safety data on remdesivir for children. Given this, the applicability of this recommendation to children is currently uncertain.

Clinical question/ PICO

Population:	Patients with COVID-19 infection (all disease severities)
Intervention:	Remdesivir + usual care
Comparator:	Usual care

Summary

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care Remdesivir	Certainty of the evidence (Quality of evidence)	Plain text summary
Mortality 28 days	Odds ratio 0.9 (CI 95% 0.7 - 1.12) Based on data from 7,333 patients in 4 studies. ¹ (Randomized controlled)	106 per 1000 96 per 1000 Difference: 10 fewer per 1000 (CI 95% 29 fewer - 11 more)	Low Due to serious risk of bias and serious imprecision ²	Remdesivir possibly has little or no effect on mortality.
Mechanical ventilation	Odds ratio 0.89 (CI 95% 0.76 - 1.03) Based on data from 6,549 patients in 4 studies. ³ (Randomized controlled)	105 per 1000 95 per 1000 Difference: 10 fewer per 1000 (CI 95% 23 fewer - 3 more)	Low Due to serious risk of bias and serious imprecision ⁴	Remdesivir possibly has little or no effect on mechanical ventilation.
Serious adverse events leading to discontinuation	Odds ratio 1 (CI 95% 0.37 - 3.83) Based on data from 1,894 patients in 3 studies. ⁵ (Randomized controlled)	15 per 1000 15 per 1000 Difference: 0 fewer per 1000 (CI 95% 9 fewer - 40 more)	Low Due to very serious imprecision ⁶	Remdesivir possibly has little or no effect on serious adverse events leading to discontinuation.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care Remdesivir	Certainty of the evidence (Quality of evidence)	Plain text summary
Viral clearance 7 days	Odds ratio 1.06 (CI 95% 0.06 - 17.56) Based on data from 196 patients in 1 studies. ⁷ (Randomized controlled)	483 per 1000 498 per 1000 Difference: 15 more per 1000 (CI 95% 430 fewer - 460 more)	Very Low Due to very serious imprecision ⁸	The effect of remdesivir on viral clearance is uncertain.
Acute kidney injury	Odds ratio 0.85 (CI 95% 0.51 - 1.41) Based on data from 1,281 patients in 2 studies. ⁹ (Randomized controlled)	56 per 1000 48 per 1000 Difference: 8 fewer per 1000 (CI 95% 27 fewer - 21 more)	Low Due to serious imprecision and serious indirectness ¹⁰	Remdesivir possibly has little or no effect on acute kidney injury.
Delirium	Odds ratio 1.22 (CI 95% 0.48 - 3.11) Based on data from 1,048 patients in 1 studies. ¹¹ (Randomized controlled)	16 per 1000 19 per 1000 Difference: 3 more per 1000 (CI 95% 8 fewer - 32 more)	Very Low Due to very serious imprecision and serious indirectness ¹²	We are uncertain whether remdesivir increases or decreases delirium
Time to clinical improvement	Measured by: days Lower better Based on data from: 1,882 patients in 3 studies. ¹³ (Randomized controlled)	11 days 9 days Difference: MD 2 lower (CI 95% 4.2 lower - 0.9 higher)	Low Due to serious imprecision and serious indirectness ¹⁴	Remdesivir possibly has little or no effect on time to clinical improvement.
Duration of hospitalization	Measured by: days Lower better Based on data from: 1,882 patients in 3 studies. ¹⁵ (Randomized controlled)	12.8 days 12.3 days Difference: MD 0.5 lower (CI 95% 3.3 lower - 2.3 higher)	Low Due to serious imprecision and serious indirectness ¹⁶	Remdesivir possibly has little or no effect on duration of hospitalization.
Duration of ventilation	Measured by: days Lower better Based on data from: 440 patients in 2 studies. ¹⁷ (Randomized controlled)	14.7 days 13.4 days Difference: MD 1.3 lower (CI 95% 4.1 lower - 1.5 higher)	Low Due to very serious imprecision ¹⁸	Remdesivir possibly has little or no effect on duration of ventilation.

1. Systematic review (3). **Baseline/comparator:** Control arm of reference used for intervention (50).
2. **Risk of bias: Serious.** We rated two trials as high risk of bias due to high or probably high risk of bias in deviations from the intended intervention. . **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: Serious.** The 95% CI crosses the minimally important difference (2% reduction in mortality). . **Publication bias: No serious.**
3. Systematic review (3) . **Baseline/comparator:** Control arm of reference used for intervention (50).
4. **Risk of bias: Serious.** **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: Serious.** Wide confidence

intervals. **Publication bias: No serious.**

5. Systematic review (3). **Baseline/comparator:** Systematic review (3). Used the median or mean of all patients randomized to usual care across the included studies..

6. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Wide confidence intervals. **Publication bias: No serious.**

7. Systematic review (3). **Baseline/comparator:** Systematic review (3). Used the median or mean of all patients randomized to usual care across the included studies..

8. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Wide confidence intervals. **Publication bias: No serious.**

9. Systematic review (3). **Baseline/comparator:** Systematic review (3). Used the median or mean of all patients randomized to usual care across the included studies..

10. **Inconsistency: No serious. Indirectness: Serious.** Studies used change in serum creatinine rather than patient-important measures of acute kidney injury.. **Imprecision: Serious.** Wide 95% credible intervals.. **Publication bias: No serious.**

11. Systematic review (3). **Baseline/comparator:** Systematic review (3). Used the median or mean of all patients randomized to usual care across the included studies..

12. **Indirectness: Serious.** Differences between the outcomes of interest and those reported (e.g short-term/surrogate,not patient-important). **Imprecision: Very Serious.**

13. Systematic review (3). Used the median or mean of all patients randomized to usual care across the included studies.. **Baseline/comparator:** Control arm of reference used for intervention.

14. **Inconsistency: No serious. Indirectness: Serious. Imprecision: Serious. Publication bias: No serious.**

15. Systematic review (3). Used the median or mean of all patients randomized to usual care across the included studies.. **Baseline/comparator:** Control arm of reference used for intervention.

16. **Indirectness: Serious. Imprecision: Serious.** Wide confidence intervals.

17. Systematic review (3). Used the median or mean of all patients randomized to usual care across the included studies.. **Baseline/comparator:** Control arm of reference used for intervention.

18. **Imprecision: Very Serious.** Wide confidence intervals.

7.5 Systemic corticosteroids (published 2 September 2020)

This guideline was triggered on 22 June 2020 by the publication of the preliminary report of the RECOVERY trial, which has now been published as a peer-reviewed paper (12). Corticosteroids are listed in the WHO Model List of Essential Medicines, readily available globally at a low cost, and of considerable interest to all stakeholder groups. The guideline panel was informed by combining two meta-analyses which pooled data from eight randomized trials (7184 participants) of systemic corticosteroids for COVID-19 (3, 58). The panel discussions were also informed by two other meta-analyses, which were already published and pooled data about the safety of systemic corticosteroids in distinct but relevant patient populations.

On 17 July 2020, the panel reviewed evidence from eight RCTs (7184 patients) evaluating systemic corticosteroids versus usual care in COVID-19. RECOVERY, the largest of the seven trials, from which mortality data were available by subgroup (severe and non-severe), evaluated the effects of dexamethasone 6 mg given once daily (oral or intravenous) for up to 10 days in 6425 hospitalized patients in the United Kingdom (2104 were randomized to dexamethasone and 4321 were randomized to usual care) (12). At the time of randomization, 16% were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation; 60% were receiving oxygen only (with or without non-invasive ventilation); and 24% were receiving neither.

The data from seven other smaller trials included 63 non-critically ill patients and approximately 700 critically ill patients (definitions of critical illness varied across studies). For the latter, patients were enrolled up to 9 June 2020, and approximately four-fifths were invasively mechanically ventilated; approximately half were randomized to receive corticosteroid therapy, and half randomized to no corticosteroid therapy. Corticosteroid regimens included: methylprednisolone 40 mg every 12 hours for 3 days and then 20 mg every 12 hours for 3 days (GLUCOCOVID) (68); dexamethasone 20 mg daily for 5 days followed by 10 mg daily for 5 days (two trials, DEXA-COVID19, CoDEX) (60, 64); hydrocortisone 200 mg daily for 4 to 7 days followed by 100 mg daily for 2 to 4 days and then 50 mg daily for 2 to 3 days (one trial, CAPE-COVID) (59); hydrocortisone 200 mg daily for 7 days (one trial, REMAP-CAP) (63);

methylprednisolone 40 mg every 12 hours for 5 days (one trial, Steroids-SARI) (61).

Seven of the trials were conducted in individual countries (Brazil, China, Denmark, France, Spain) whilst REMAP-CAP was an international study (recruiting in 14 European countries, Australia, Canada, New Zealand, Saudi Arabia and the United Kingdom). All trials reported mortality 28 days after randomization, except for one trial at 21 days and another at 30 days. Because the mortality data from one trial (GLUCOCOVID, n=63) were not reported by subgroup, the panel reviewed only the data pertaining to the outcome of mechanical ventilation from this trial (68). An additional trial, which randomized hospitalized patients with suspected SARS-CoV-2 infection, published on 12 August 2020 (MetCOVID) (62), was included as a supplement in the prospective meta-analysis (PMA) publication, as it was registered after the searches of trial registries were performed. The supplement showed that inclusion would not change results other than reduce inconsistency.

Subgroup effect for mortality

While all other trials evaluated systemic corticosteroids exclusively in critically ill patients, the RECOVERY Trial enrolled hospitalized patients with COVID-19. The panel considered the results of a subgroup analysis of the RECOVERY Trial suggesting that the relative effects of systemic corticosteroids varied as a function of the level of respiratory support received at randomization. On the basis of the peer-reviewed criteria for credible subgroup effects (42), the panel determined that the subgroup effect was sufficiently credible to warrant separate recommendations for severe and non-severe COVID-19.

However, acknowledging that during a pandemic, access to health care may vary considerably over time as well as between different countries, the panel decided against defining patient populations concerned by the recommendations on the basis of access to health interventions (i.e. hospitalization and respiratory support). Thus, the panel attributed the effect modification in the RECOVERY Trial to illness severity.

The panel also acknowledged the existence of variable definitions for severity and use of respiratory support interventions. The WHO clinical guidance for COVID-19 published on 27 May 2020 (version 3) defined severity of COVID-19 by clinical indicators, but modified the oxygen saturation threshold from 94% to 90% (16), in order to align with previous WHO guidance (17). See Section 6 for the WHO severity criteria and Infographic below for three disease severity groups for which the recommendations apply in practice.

Info Box

The recommendations for corticosteroids below were first published as [WHO living guidelines](#) 2 September 2020, and as [BMJ Rapid Recommendations](#) 5 September 2020, including links to MAGICapp. Please visit the [WHO website](#) guidelines for details (e.g. composition of the guideline panel) and view section text to understand what evidence the panel applied in creating these recommendations. By 15 November 2020 there was no new evidence to suggest any change in the recommendations, as identified in the living systematic review and NMA informing this living guideline.

For patients with severe or critical COVID-19-infection (see disease severity criteria above)

Recommended

We recommend systemic corticosteroids rather than no corticosteroids

Practical info

Route—Systemic corticosteroids may be administered both orally and intravenously. Of note, while the bioavailability of dexamethasone is very high (that is, similar concentrations are achieved in plasma after oral and intravenous intake), critically ill patients may be unable to absorb any nutrients or medications due to intestinal dysfunction. Clinicians therefore may consider administering systemic corticosteroids intravenously rather than orally if intestinal dysfunction is suspected.

Duration—While more patients received corticosteroids in the form of dexamethasone 6 mg daily for up to 10 days, the total

duration of regimens evaluated in the seven trials varied between five and 14 days, and treatment was generally discontinued at hospital discharge (that is, the duration of treatment could be less than the duration stipulated in the protocols).

Dose—The once daily dexamethasone formulation may increase adherence. A dose of 6 mg of dexamethasone is equivalent (in terms of glucocorticoid effect) to 150 mg of hydrocortisone (that is, 50 mg every 8 hours), 40 mg of prednisone, or 32 mg of methylprednisolone (8 mg every 6 hours or 16 mg every 12 hours).

Monitoring—It would be prudent to monitor glucose levels in patients with severe and critical covid-19, regardless of whether the patient is known to have diabetes.

Timing—The timing of therapy from onset of symptoms was discussed by the panel. The RECOVERY investigators reported a subgroup analysis suggesting that the initiation of therapy seven days or more after symptom onset may be more beneficial than treatment initiated within seven days of symptom onset. A post hoc subgroup analysis within the prospective meta-analysis did not support this hypothesis. While some panel members believed that postponing systemic corticosteroids until after viral replication is contained by the immune system may be reasonable, many noted that, in practice, it is often impossible to ascertain symptom onset and that signs of severity often appear late (that is, denote a co-linearity between severity and timing). The panel concluded that, given the evidence, it was preferable to err on the side of administering corticosteroids when treating patients with severe or critical covid-19 (even if within 7 days of symptoms onset) and to err on the side of not giving corticosteroids when treating patients with non-severe disease (even if after 7 days of symptoms onset).

Evidence to decision

Benefits and harms	Substantial net benefits of the recommended alternative
<p>Panel members who voted for a conditional recommendation argued that the trials evaluating systemic corticosteroids for COVID-19 reported limited information regarding potential harm. Between the two panel meetings, indirect evidence regarding the potential harmful effects of systemic corticosteroids from studies in sepsis, ARDS and community-acquired pneumonia (CAP) was added to the summary of findings table (66, 67). While generally of low certainty, these data were reassuring and suggested that corticosteroids are not associated with an increased risk of adverse events, beyond likely increasing the incidence of hyperglycaemia (moderate certainty evidence; absolute effect estimate 46 more per 1000 patients, 95% CI: 23 more to 72 more) and hypernatraemia (moderate certainty evidence; 26 more per 1000 patients, 95% CI: 13 more to 41 more). Panel members also noted that, given the expected effect of systemic corticosteroids on mortality, most patients would not refuse this intervention to avoid adverse events believed to be markedly less important to most patients than death.</p> <p>In contrast with new agents proposed for COVID-19, clinicians have a vast experience of systemic corticosteroids and the panel was reassured by their overall safety profile. Moreover, the panel was confident that clinicians using these guidelines would be aware of additional potential side-effects and contraindications to systemic corticosteroid therapy, which may vary geographically in function of endemic microbiological flora. Notwithstanding, clinicians should exercise caution in use of corticosteroids in patients with diabetes or underlying immunocompromise.</p> <p>Ultimately, the panel made its recommendation on the basis of the moderate certainty evidence of a 28-day mortality reduction of 8.7% in the critically ill and 6.7% in patients with severe COVID-19 who were not critically ill, respectively.</p>	
<p>Preference and values</p> <p>The panel took an individual patient perspective to values and preferences but, given the burden of the pandemic for healthcare systems globally, also placed a high value on resource allocation and equity. The benefits of corticosteroids on mortality was deemed of critical importance to patients, with little or no anticipated variability in their preference to be offered treatment if severely ill from COVID-19.</p>	No substantial variability expected

Resources and other considerations	No important issues with the recommended alternative
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Resource implications, feasibility, equity and human rights

In this guideline, the panel took an individual patient perspective, but also placed a high value on resource allocation. In such a perspective, attention is paid to the opportunity cost associated with the widespread provision of therapies for COVID-19. In contrast to other candidate treatments for COVID-19 that, generally, are expensive, often unlicensed, difficult to obtain and require advanced medical infrastructure, systemic corticosteroids are low cost, easy to administer, and readily available globally (57). Dexamethasone and prednisolone are among the most commonly listed medicines in national essential medicines lists; listed by 95% of countries. Dexamethasone was first listed by WHO as an essential medicine in 1977, while prednisolone was listed 2 years later (56).

Accordingly, systemic corticosteroids are among a relatively small number of interventions for COVID-19 that have the potential to reduce inequities and improve equity in health. Those considerations influenced the strength of this recommendation.

Acceptability

The ease of administration, the relatively short duration of a course of systemic corticosteroid therapy, and the generally benign safety profile of systemic corticosteroids for up to 7–10 days led the panel to conclude that the acceptability of this intervention was high.

Justification

This recommendation was achieved after a vote, which concerned the strength of the recommendation in favour of systemic corticosteroids. Of the 23 voting panel members, 19 (83%) voted in favour of a strong recommendation, and 4 (17%) voted in favour of a conditional recommendation. The reasons for the four cautionary votes, which were shared by some panel members who voted in favour of a strong recommendation, are summarized below.

Applicability

Panel members who voted for a conditional recommendation argued that many patients who were potentially eligible for the RECOVERY trial were excluded from participating in the evaluation of corticosteroids by their treating clinicians and that without detailed information on the characteristics of excluded patients, this precluded, in their opinion, a strong recommendation. Other panel members felt that such a proportion of excluded patients was the norm rather than the exception in pragmatic trials and that, while detailed information on the reasons for excluding patients were not collected, the main reasons for refusing to offer participation in the trial were likely related to safety concerns of stopping corticosteroids in patients with a clear indication for corticosteroids (confirmed as per personal communication from the RECOVERY Principal Investigator). Panel members noted that there are few absolute contraindications to a 7–10 day course of corticosteroid therapy, that recommendations are intended for the average patient population, and that it is understood that even strong recommendations should not be applied to patients in whom the intervention is contraindicated as determined by the treating clinician.

Eventually, the panel concluded that this recommendation applies to patients with severe and critical COVID-19 regardless of hospitalization status. The underlying assumption is that these patients would be treated in hospitals and receive respiratory support in the form of oxygen; non-invasive or invasive ventilation if these options were available. Following GRADE guidance, in making a strong recommendation, the panel has inferred that all or almost all fully informed patients with severe COVID-19 would choose to take systemic corticosteroids. It is understood that even in the context of a strong recommendation, the intervention may be contraindicated for certain patients. Absolute contraindications for 7–10 day courses of systemic corticosteroid therapy are rare. In considering potential contraindications, clinicians must determine if they warrant depriving a patient of a potentially life-saving therapy.

The applicability of the recommendation is less clear for populations that were under-represented in the considered trials, such as children, patients with tuberculosis, and those who are immunocompromised. Notwithstanding, clinicians will also consider the risk of depriving these patients of potentially life-saving therapy. In contrast, the panel concluded that the recommendation should definitely be applied to certain patients who were not included in the trials, such as patients with severe and critical COVID-19 who could not be hospitalized or receive oxygen because of resource limitations.

The recommendation does not apply to the following uses of corticosteroids: transdermal or inhaled administration, high-dose or long-term regimens, or prophylaxis.

Clinical question/ PICO

Population: Patients with critical COVID-19
Intervention: Steroids
Comparator: Standard Care

Summary

Outline of the evidence on systemic corticosteroids

While six trials evaluated systemic corticosteroids exclusively in critically ill patients, the RECOVERY trial enrolled hospitalized patients with covid-19 and reported mortality data by subgroup, whereas the smaller GLUCOCOVID trial, which also enrolled hospitalized patients did not. The panel considered the results of a subgroup analysis of the RECOVERY trial suggesting that the relative effects of systemic corticosteroids varied as a function of the level of respiratory support received at randomization. On the basis of the peer-reviewed criteria for credible subgroup effects (42), the panel determined that the subgroup effect was sufficiently credible to warrant separate recommendations for severe and non-severe covid-19.

Population - There were data from 1703 critically ill patients in seven trials. RECOVERY, the largest of the seven trials randomized 6425 hospitalized patients in the United Kingdom (2104 were randomized to dexamethasone and 4321 were randomized to usual care). At the time of randomization, 16% were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 60% were receiving oxygen only (with or without non-invasive ventilation), and 24% were receiving neither (12). The mortality data from six other smaller trials included approximately 700 critically ill patients (definitions of critical illness varied across studies) enrolled up to 9 June 2020, approximately four-fifths were invasively mechanically ventilated; approximately one-half were randomized to receive corticosteroid therapy, and one-half randomized to no corticosteroid therapy. For patients with severe and non-severe covid-19, data was only available by relevant subgroup in RECOVERY (3883 patients with severe and 1535 patients with non-severe covid-19). Because the mortality data from one trial (GLUCOCOVID, n=63) was not reported separately for severe and non-severe covid-19 [68], the panel reviewed only the data pertaining to the outcome of mechanical ventilation from this trial.

Interventions – RECOVERY evaluated the effects of dexamethasone 6 mg given once daily (oral or intravenous) for up to 10 days. Other corticosteroid regimens included: dexamethasone 20 mg daily for 5 days followed by 10 mg daily for 5 days (two trials, DEXA-COVID, CoDEX); hydrocortisone 200 mg daily for 4 to 7 days followed by 100 mg daily for 2 to 4 days and then 50 mg daily for 2 to 3 days (one trial, CAPE-COVID); hydrocortisone 200 mg daily for 7 days (one trial, REMAP-CAP); methylprednisolone 40 mg every 12 hours for 5 days (one trial, Steroids-SARI); and methylprednisolone 40 mg every 12 hours for 3 days and then 20 mg every 12 hours for 3 days (one trial, GLUCOCOVID) (3). Seven of the trials were conducted in individual countries (Brazil, China, Denmark, France, Spain) whilst REMAP-CAP was an international study (recruiting in 14 European countries, Australia, Canada, New Zealand, Saudi Arabia and United Kingdom).

Outcomes - All trials reported mortality 28 days after randomization, except for one trial at 21 days and the another at 30 days.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard Care Steroids	Certainty of the evidence (Quality of evidence)	Plain text summary
Mortality 28 days	Relative risk 0.79 (CI 95% 0.7 - 0.9) Based on data from 1,703 patients in 7 studies. Follow up: 28 days.	415 per 1000 328 per 1000 Difference: 87 fewer per 1000 (CI 95% 124 fewer - 41 fewer)	Moderate Due to serious risk of bias ¹	Systemic corticosteroids probably reduce the risk of 28-day mortality in patients with critical illness due to COVID-19.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard Care Steroids	Certainty of the evidence (Quality of evidence)	Plain text summary
Need for invasive mechanical ventilation 28 days	Relative risk 0.74 (CI 95% 0.59 - 0.93) Based on data from 5,481 patients in 2 studies. Follow up: 28 days.	116 per 1000 86 per 1000 Difference: 30 fewer per 1000 (CI 95% 48 fewer - 8 fewer)	Moderate Due to serious risk of bias ²	Systemic corticosteroids probably reduce the need of mechanical ventilation
Gastrointestinal bleeding	Relative risk 1.06 (CI 95% 0.85 - 1.33) Based on data from 5,403 patients in 30 studies.	48 per 1000 51 per 1000 Difference: 3 more per 1000 (CI 95% 7 fewer - 16 more)	Low Due to serious indirectness, Due to serious imprecision ³	Corticosteroids may not increase the risk of gastrointestinal bleeding.
Super-infections	Relative risk 1.01 (CI 95% 0.9 - 1.13) Based on data from 6,027 patients in 32 studies.	186 per 1000 188 per 1000 Difference: 2 more per 1000 (CI 95% 19 fewer - 24 more)	Low Due to serious indirectness, Due to serious imprecision ⁴	Corticosteroids may not increase the risk of super-infections.
Hyperglycaemia	Relative risk 1.16 (CI 95% 1.08 - 1.25) Based on data from 8,938 patients in 24 studies.	286 per 1000 332 per 1000 Difference: 46 more per 1000 (CI 95% 23 more - 72 more)	Moderate Due to serious indirectness ⁵	Corticosteroids probably increase the risk of hyperglycaemia.
Hypernatremia	Relative risk 1.64 (CI 95% 1.32 - 2.03) Based on data from 5,015 patients in 6 studies.	40 per 1000 66 per 1000 Difference: 26 more per 1000 (CI 95% 13 more - 41 more)	Moderate Due to serious indirectness ⁶	Corticosteroids probably increase the risk of hypernatremia.
Neuromuscular weakness	Relative risk 1.09 (CI 95% 0.86 - 1.39) Based on data from 6,358 patients in 8 studies.	69 per 1000 75 per 1000 Difference: 6 more per 1000 (CI 95% 10 fewer - 27 more)	Low Due to serious indirectness, Due to serious imprecision ⁷	Corticosteroids may not increase the risk of neuromuscular weakness.
Neuropsychiatric effects	Relative risk 0.81 (CI 95% 0.41 - 1.63) Based on data from 1,813 patients in 7 studies.	35 per 1000 28 per 1000 Difference: 7 fewer per 1000 (CI 95% 21 fewer - 22 more)	Low Due to serious indirectness, Due to serious imprecision ⁸	Corticosteroids may not increase the risk of neuropsychiatric effects.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Plain text summary
		Standard Care	Steroids		
Duration of hospitalization	Measured by: days Lower better Based on data from: 6,425 patients in 1 studies. (Randomized controlled)	13 days	12 days CI 95%	Low Due to serious risk of bias, Due to serious imprecision ⁹	Steroids may result in an important reduction in the duration of hospitalizations

1. Risk of bias: Serious. lack of blinding. Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.
2. Risk of bias: Serious. lack of blinding. Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.
3. Inconsistency: No serious. Indirectness: Serious. Imprecision: Serious. Publication bias: No serious.
4. Inconsistency: No serious. Indirectness: Serious. Imprecision: Serious. Publication bias: No serious.
5. Indirectness: Serious.
6. Indirectness: Serious.
7. Indirectness: Serious. Imprecision: Serious.
8. Indirectness: Serious. Imprecision: Serious.
9. Risk of bias: Serious. lack of blinding. Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious. confidence interval includes no benefit. Publication bias: No serious.

Clinical question/ PICO

Population: Patients with severe COVID-19
Intervention: Steroids
Comparator: Standard Care

Summary

Outline of the evidence on systemic corticosteroids

While six trials evaluated systemic corticosteroids exclusively in critically ill patients, the RECOVERY trial enrolled hospitalized patients with covid-19 and reported mortality data by subgroup, whereas the smaller GLUCOCOVID trial, which also enrolled hospitalized patients did not. The panel considered the results of a subgroup analysis of the RECOVERY trial suggesting that the relative effects of systemic corticosteroids varied as a function of the level of respiratory support received at randomization. On the basis of the peer-reviewed criteria for credible subgroup effects (42), the panel determined that the subgroup effect was sufficiently credible to warrant separate recommendations for severe and non-severe covid-19.

Population - There were data from 1703 critically ill patients in seven trials. RECOVERY, the largest of the seven trials randomized 6425 hospitalized patients in the United Kingdom (2104 were randomized to dexamethasone and 4321 were randomized to usual care). At the time of randomization, 16% were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 60% were receiving oxygen only (with or without non-invasive ventilation), and 24% were receiving neither (12). The mortality data from six other smaller trials included approximately 700 critically ill patients (definitions of critical illness varied across studies) enrolled up to 9 June 2020, approximately four-fifths were invasively mechanically ventilated; approximately one-half were randomized to receive corticosteroid therapy, and one-half randomized to no corticosteroid therapy. For patients with severe and non-severe covid-19, data was only available by relevant subgroup in RECOVERY (3883 patients with severe and 1535 patients with non-severe covid-19). Because the mortality data from one trial (GLUCOCOVID, n=63) was not reported separately for severe and non-severe covid-19

(68), the panel reviewed only the data pertaining to the outcome of mechanical ventilation from this trial. *Interventions* – RECOVERY evaluated the effects of dexamethasone 6 mg given once daily (oral or intravenous) for up to 10 days. Other corticosteroid regimens included: dexamethasone 20 mg daily for 5 days followed by 10 mg daily for 5 days (two trials, DEXA-COVID, CoDEX); hydrocortisone 200 mg daily for 4 to 7 days followed by 100 mg daily for 2 to 4 days and then 50 mg daily for 2 to 3 days (one trial, CAPE-COVID); hydrocortisone 200 mg daily for 7 days (one trial, REMAP-CAP); methylprednisolone 40 mg every 12 hours for 5 days (one trial, Steroids-SARI); and methylprednisolone 40 mg every 12 hours for 3 days and then 20 mg every 12 hours for 3 days (one trial, GLUCOCOVID) (3). Seven of the trials were conducted in individual countries (Brazil, China, Denmark, France, Spain) whilst REMAP-CAP was an international study (recruiting in 14 European countries, Australia, Canada, New Zealand, Saudi Arabia and United Kingdom).

Outcomes - All trials reported mortality 28 days after randomization, except for one trial at 21 days and the another at 30 days.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard Care Steroids	Certainty of the evidence (Quality of evidence)	Plain text summary
Mortality 28 days	Relative risk 0.8 (CI 95% 0.7 - 0.92) Based on data from 3,883 patients in 1 studies. Follow up: 28 days.	334 per 1000 267 per 1000 Difference: 67 fewer per 1000 (CI 95% 100 fewer - 27 fewer)	Moderate Due to serious risk of bias ¹	Systemic corticosteroids probably reduce the risk of 28-day mortality in patients with severe COVID-19.
Need for invasive mechanical ventilation 28 days	Relative risk 0.74 (CI 95% 0.59 - 0.93) Based on data from 5,481 patients in 2 studies. Follow up: 28 days.	116 per 1000 86 per 1000 Difference: 30 fewer per 1000 (CI 95% 48 fewer - 8 fewer)	Moderate Due to serious risk of bias ²	Systemic corticosteroids probably reduce the need for mechanical ventilation
Gastrointestinal bleeding	Relative risk 1.06 (CI 95% 0.85 - 1.33) Based on data from 5,403 patients in 30 studies.	48 per 1000 51 per 1000 Difference: 3 more per 1000 (CI 95% 7 fewer - 16 more)	Low Due to serious indirectness, Due to serious imprecision ³	Corticosteroids may not increase the risk of gastrointestinal bleeding.
Super-infections	Relative risk 1.01 (CI 95% 0.9 - 1.13) Based on data from 6,027 patients in 32 studies.	186 per 1000 188 per 1000 Difference: 2 more per 1000 (CI 95% 19 fewer - 24 more)	Low Due to serious indirectness, Due to serious imprecision ⁴	Corticosteroids may not increase the risk of super-infections.
Hyperglycaemia	Relative risk 1.16 (CI 95% 1.08 - 1.25) Based on data from 8,938 patients in 24 studies.	286 per 1000 332 per 1000 Difference: 46 more per 1000	Moderate Due to serious indirectness ⁵	Corticosteroids probably increase the risk of hyperglycaemia.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard Care Steroids	Certainty of the evidence (Quality of evidence)	Plain text summary
		(CI 95% 23 more - 72 more)		
Hypernatremia	Relative risk 1.64 (CI 95% 1.32 - 2.03) Based on data from 5,015 patients in 6 studies.	40 per 1000 66 per 1000 Difference: 26 more per 1000 (CI 95% 13 more - 41 more)	Moderate Due to serious indirectness ⁶	Corticosteroids probably increase the risk of hypernatremia.
Neuromuscular weakness	Relative risk 1.09 (CI 95% 0.86 - 1.39) Based on data from 6,358 patients in 8 studies.	69 per 1000 75 per 1000 Difference: 6 more per 1000 (CI 95% 10 fewer - 27 more)	Low Due to serious indirectness, Due to serious imprecision ⁷	Corticosteroids may not increase the risk of neuromuscular weakness.
Neuropsychiatric effects	Relative risk 0.81 (CI 95% 0.41 - 1.63) Based on data from 1,813 patients in 7 studies.	35 per 1000 28 per 1000 Difference: 7 fewer per 1000 (CI 95% 21 fewer - 22 more)	Low Due to serious indirectness, Due to serious imprecision ⁸	Corticosteroids may not increase the risk of neuropsychiatric effects.
Duration of hospitalization	Measured by: days Lower better Based on data from: 6,425 patients in 1 studies. (Randomized controlled)	13 days 12 days CI 95%	Low Due to serious risk of bias, Due to serious imprecision ⁹	Steroids may result in an important reduction in the duration of hospitalizations

1. Risk of bias: Serious. lack of blinding. Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.
2. Risk of bias: Serious. lack of blinding. Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.
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5. Indirectness: Serious.
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7. Indirectness: Serious. Imprecision: Serious.
8. Indirectness: Serious. Imprecision: Serious.
9. Risk of bias: Serious. lack of blinding. Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious. confidence interval includes no benefit. Publication bias: No serious.

For patients with non-severe COVID-19 infection (absence of criteria for severe or critical infection)

Conditional recommendation against

We suggest not to use corticosteroids.

Practical info

With the conditional recommendation against the use of corticosteroids in patients with non-severe COVID-19 the following practical information apply in situations where such treatment is to be considered:

Route Systemic corticosteroids may be administered both orally and intravenously. Of note, while the bioavailability of dexamethasone is very high (i.e. similar concentrations are achieved in plasma after oral and intravenous intake), critically ill patients may be unable to absorb any nutrients or medications due to intestinal dysfunction. Clinicians therefore may consider administering systemic corticosteroids intravenously rather than orally if intestinal dysfunction is suspected.

Duration While more patients received corticosteroids in the form of dexamethasone 6 mg daily for up to 10 days, the total duration of regimens evaluated in the seven trials varied between 5 and 14 days, and treatment was generally discontinued at hospital discharge (i.e. the duration of treatment could be less than the duration stipulated in the protocols).

Dose The once daily dexamethasone formulation may increase adherence. A dose of 6 mg of dexamethasone is equivalent (in terms of glucocorticoid effect) to 150 mg of hydrocortisone (e.g. 50 mg every 8 hours), or 40 mg of prednisone, or 32 mg of methylprednisolone (e.g. 8 mg every 6 hours or 16 mg every 12 hours). It would be prudent to monitor glucose levels in patients with severe and critical COVID-19, regardless of whether the patient is known to have diabetes.

Timing The timing of therapy from onset of symptoms was discussed by the panel. The RECOVERY investigators reported a subgroup analysis suggesting that the initiation of therapy 7 days or more after symptom onset may be more beneficial than treatment initiated within 7 days of treatment onset. A post hoc subgroup analysis within the PMA did not support this hypothesis. While some panel members believed that postponing systemic corticosteroids until after viral replication is contained by the immune system may be reasonable, many noted that, in practice, it is often impossible to ascertain symptom onset and that signs of severity frequently appear late (i.e. denote a co-linearity between severity and timing). The panel concluded that, given the evidence, it was preferable to err on the side of administering corticosteroids when treating patients with severe or critical COVID-19 (even if within 7 days of symptoms onset) and to err on the side of not giving corticosteroids when treating patients with non-severe disease (even if after 7 days of symptoms onset).

Other endemic infections that may worsen with corticosteroids should be considered. For example, for Strongyloides stercoralis hyperinfection associated with corticosteroid therapy, diagnosis or empiric treatment may be considered in endemic areas if steroids are used.

Evidence to decision

Benefits and harms

The panel made its recommendation on the basis of low certainty evidence suggesting a potential increase of 3.9% in 28-day mortality among patients with COVID-19 who are not severely ill. The certainty of the evidence for this specific subgroup was downgraded due to serious imprecision (i.e. the evidence does not allow to rule out a mortality reduction) and risk of bias due to lack of blinding. In making a conditional recommendation against the indiscriminate use of systemic corticosteroids, the panel inferred that most fully informed individuals with non-severe illness would not want to receive systemic corticosteroids, but many could want to consider this intervention through shared decision-making with their treating physician (6).

Note: WHO recommends antenatal corticosteroid therapy for pregnant women at risk of preterm birth from 24 to 34 weeks' gestation when there is no clinical evidence of maternal infection, and adequate childbirth and newborn care is available. However, in cases where the woman presents with mild or moderate COVID-19, the clinical benefits of antenatal

corticosteroid might outweigh the risks of potential harm to the mother. In this situation, the balance of benefits and harms for the woman and the preterm newborn should be discussed with the woman to ensure an informed decision, as this assessment may vary depending on the woman's clinical condition, her wishes and that of her family, and available health care resources.

Preference and values

The weak or conditional recommendation was driven by likely variation in patient values and preferences. The panel judged that most individuals with non-severe illness would decline systemic corticosteroids. However, many may want them after shared decision making with their treating physician.

Resources and other considerations

Resource implications, feasibility, equity and human rights

The panel also considered that in order to help guarantee access to systemic corticosteroids for patients with severe and critical COVID-19, it is reasonable to avoid administering this intervention to patients who, given the current evidence, would not appear to derive any benefit from this intervention.

Justification

This recommendation was achieved by consensus.

Applicability

This recommendation applies to patients with non-severe disease regardless of their hospitalization status. The panel noted that patients with non-severe COVID-19 would not normally require acute care in hospital or respiratory support, but that in some jurisdictions, these patients may be hospitalized for isolation purposes only, in which case they should not be treated with systemic corticosteroids. The panel concluded that systemic corticosteroids should not be stopped for patients with non-severe COVID-19 who are already treated with systemic corticosteroids for other reasons (e.g. patients with chronic obstructive pulmonary disease need not discontinue a course of systemic oral corticosteroids; or other chronic autoimmune diseases). If the clinical condition of patients with non-severe COVID-19 worsens (i.e. increase in respiratory rate, signs of respiratory distress or hypoxaemia) they should receive systemic corticosteroids (see recommendation 1).

Clinical question/ PICO

Population:	Patients with non-severe COVID-19
Intervention:	Steroids
Comparator:	Standard Care

Summary

Outline of the evidence on systemic corticosteroids

While six trials evaluated systemic corticosteroids exclusively in critically ill patients, the RECOVERY trial enrolled hospitalized patients with covid-19 and reported mortality data by subgroup, whereas the smaller GLUCOCOVID trial, which also enrolled hospitalized patients did not. The panel considered the results of a subgroup analysis of the RECOVERY trial suggesting that the relative effects of systemic corticosteroids varied as a function of the level of respiratory support received at randomization. On the basis of the peer-reviewed criteria for credible subgroup effects (42), the panel determined that the subgroup effect was sufficiently credible to warrant separate recommendations for severe and non-severe covid-19.

Population - There were data from 1703 critically ill patients in seven trials. RECOVERY, the largest of the seven trials randomized 6425 hospitalized patients in the United Kingdom (2104 were randomized to dexamethasone and 4321

were randomized to usual care). At the time of randomization, 16% were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 60% were receiving oxygen only (with or without non-invasive ventilation), and 24% were receiving neither (12). The mortality data from six other smaller trials included approximately 700 critically ill patients (definitions of critical illness varied across studies) enrolled up to 9 June 2020, approximately four-fifths were invasively mechanically ventilated; approximately one-half were randomized to receive corticosteroid therapy, and one-half randomized to no corticosteroid therapy. For patients with severe and non-severe covid-19, data was only available by relevant subgroup in RECOVERY (3883 patients with severe and 1535 patients with non-severe covid-19). Because the mortality data from one trial (GLUCOCOVID, n=63) was not reported separately for severe and non-severe covid-19 (68), the panel reviewed only the data pertaining to the outcome of mechanical ventilation from this trial.

Interventions – RECOVERY evaluated the effects of dexamethasone 6 mg given once daily (oral or intravenous) for up to 10 days. Other corticosteroid regimens included: dexamethasone 20 mg daily for 5 days followed by 10 mg daily for 5 days (two trials, DEXA-COVID, CoDEX); hydrocortisone 200 mg daily for 4 to 7 days followed by 100 mg daily for 2 to 4 days and then 50 mg daily for 2 to 3 days (one trial, CAPE-COVID); hydrocortisone 200 mg daily for 7 days (one trial, REMAP-CAP); methylprednisolone 40 mg every 12 hours for 5 days (one trial, Steroids-SARI); and methylprednisolone 40 mg every 12 hours for 3 days and then 20 mg every 12 hours for 3 days (one trial, GLUCOCOVID) (3) Seven of the trials were conducted in individual countries (Brazil, China, Denmark, France, Spain) whilst REMAP-CAP was an international study (recruiting in 14 European countries, Australia, Canada, New Zealand, Saudi Arabia and United Kingdom).

Outcomes - All trials reported mortality 28 days after randomization, except for one trial at 21 days and the another at 30 days.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard Care Steroids	Certainty of the evidence (Quality of evidence)	Plain text summary
Mortality 28 days	Relative risk 1.22 (CI 95% 0.93 - 1.61) Based on data from 1,535 patients in 1 studies. Follow up: 28 days.	176 per 1000 215 per 1000 Difference: 39 more per 1000 (CI 95% 12 fewer - 107 more)	Low Due to serious risk of bias, Due to serious imprecision ¹	Systemic corticosteroids may increase the risk of 28-day mortality in patients with non-severe COVID-19
Need for invasive mechanical ventilation 28 days	Relative risk 0.74 (CI 95% 0.59 - 0.93) Based on data from 5,481 patients in 2 studies. Follow up: 28 days.	116 per 1000 86 per 1000 Difference: 30 fewer per 1000 (CI 95% 48 fewer - 8 fewer)	Moderate Due to serious risk of bias ²	Systemic corticosteroids probably reduce the need for mechanical ventilation
Duration of hospitalization	Based on data from 6,425 patients in 1 studies. Follow up: NR.	13 12 Difference: 1 fewer	Low Due to serious risk of bias, Due to serious imprecision ³	Steroids may result in an important reduction in the duration of hospitalizations
Gastrointestinal bleeding	Relative risk 1.06 (CI 95% 0.85 - 1.33) Based on data from 5,403 patients in 30	48 per 1000 51 per 1000	Low Due to serious indirectness, Due to serious	Corticosteroids may not increase the risk of gastrointestinal bleeding.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard Care Steroids	Certainty of the evidence (Quality of evidence)	Plain text summary
	studies.	Difference: 3 more per 1000 (CI 95% 7 fewer - 16 more)	imprecision ⁴	
Super-infections	Relative risk 1.01 (CI 95% 0.9 - 1.13) Based on data from 6,027 patients in 32 studies.	186 per 1000 188 per 1000 Difference: 2 more per 1000 (CI 95% 19 fewer - 24 more)	Low Due to serious indirectness, Due to serious imprecision ⁵	Corticosteroids may not increase the risk of super-infections.
Hyperglycaemia	Relative risk 1.16 (CI 95% 1.08 - 1.25) Based on data from 8,938 patients in 24 studies.	286 per 1000 332 per 1000 Difference: 46 more per 1000 (CI 95% 23 more - 72 more)	Moderate Due to serious indirectness ⁶	Corticosteroids probably increase the risk of hyperglycaemia.
Hypernatremia	Relative risk 1.64 (CI 95% 1.32 - 2.03) Based on data from 5,015 patients in 6 studies.	40 per 1000 66 per 1000 Difference: 26 more per 1000 (CI 95% 13 more - 41 more)	Moderate Due to serious indirectness ⁷	Corticosteroids probably increase the risk of hypernatremia.
Neuromuscular weakness	Relative risk 1.09 (CI 95% 0.86 - 1.39) Based on data from 6,358 patients in 8 studies.	69 per 1000 75 per 1000 Difference: 6 more per 1000 (CI 95% 10 fewer - 27 more)	Low Due to serious indirectness, Due to serious imprecision ⁸	Corticosteroids may not increase the risk of neuromuscular weakness.
Neuropsychiatric effects	Relative risk 0.81 (CI 95% 0.41 - 1.63) Based on data from 1,813 patients in 7 studies.	35 per 1000 28 per 1000 Difference: 7 fewer per 1000 (CI 95% 21 fewer - 22 more)	Low Due to serious indirectness, Due to serious imprecision ⁹	Corticosteroids may not increase the risk of neuropsychiatric effects.
Duration of hospitalization	Measured by: days Lower better Based on data from: 6,425 patients in 1 studies. (Randomized controlled)	13 days 12 days CI 95%	Low Due to serious risk of bias, Due to serious imprecision ¹⁰	Steroids may result in an important reduction in the duration of hospitalizations

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Publication bias: No serious.

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10. **Risk of bias: Serious.** lack of blinding. **Inconsistency: No serious.** Indirectness: No serious. **Imprecision: Serious.** confidence interval includes no benefit. **Publication bias: No serious.**

8. Uncertainties, emerging evidence and future research

The guideline recommendations for COVID-19 therapeutics demonstrate remaining uncertainties concerning treatment effects for all outcomes of importance to patients. There is also a need for better evidence on prognosis and values and preferences of patients with COVID-19 infection. Here we outline key uncertainties for ivermectin identified by the GDG, adding to those for corticosteroids, remdesivir and hydroxychloroquine and lopinavir/ritonavir in previous versions of the living guideline. These uncertainties may inform future research, i.e. the production of more relevant and reliable evidence to inform policy and practice. We also outline emerging evidence in the rapidly changing landscape of trials for COVID-19.

Ongoing uncertainties and opportunities for future research

Ivermectin

Given the very low certainty in estimates for most critical outcomes of interest, the GDG felt that further high-quality clinical trials examining this drug would be essential before any recommendation for use as part of clinical care. This includes further RCTs examining both inpatients and outpatients and those with varying disease severities and using different ivermectin dosing regimens. The focus of these studies should be on outcomes important to patients such as mortality, quality of life, need for hospitalization, need for invasive mechanical ventilation and time to clinical or symptom improvement. Also, a better characterization of potential harms with ivermectin in patients with COVID-19 would be important.

Hydroxychloroquine

Although some uncertainty remains, the GDG panel felt that further research was unlikely to uncover a subgroup of patients that benefit from hydroxychloroquine on the most important outcomes (mortality, mechanical ventilation) given the consistent results in trials across disease severity and location.

Lopinavir/ritonavir

Although some uncertainty remains, the GDG panel felt that further research was unlikely to uncover a subgroup of patients that benefit from hydroxychloroquine on the most important outcomes (mortality, mechanical ventilation) given the consistent results in trials across disease severity and location.

Remdesivir and effects on

- critical outcomes of interest, particularly those that impact resource allocation, such as the need for mechanical ventilation, duration of mechanical ventilation and duration of hospitalization;
- specific subgroups, such as different severities of illness, different time (days) since onset of illness, children and older adults, pregnant women, and duration of therapy;
- long-term outcomes such as mortality at extended endpoints or long-term quality of life;
- long-term safety and rare but important side-effects;
- patient-reported outcomes such as symptom burden;
- outcomes, when used in combination with other agents, such as, but not limited to, corticosteroids;
- impact on viral shedding, viral clearance, patient infectivity.

Corticosteroids and effects on

- long-term mortality and functional outcomes in COVID-19 survivors;
- patients with non-severe COVID-19 (i.e. pneumonia without hypoxaemia);
- outcomes, when used in combination with additional therapies for COVID-19, such as novel immunomodulators. It will become increasingly important to ascertain how these interact with systemic corticosteroids. All investigational therapies for severe and critical COVID-19 (including remdesivir) should be compared with systemic corticosteroids or evaluated in combination with systemic corticosteroids vs systemic corticosteroids alone;
- immunity and the risk of a subsequent infection, which may impact the risk of death after 28 days;
- outcomes, by different steroid preparation, dosing and optimal timing of drug initiation.

Emerging evidence

The unprecedented volume of planned and ongoing studies for COVID-19 interventions – over 3000 RCTs as of 1 March 2021 – implies that more reliable and relevant evidence will emerge to inform policy and practice (11). An overview of registered and ongoing trials for COVID-19 therapeutics and prophylaxis is available from the [Infectious Diseases Data Observatory](#), through their living

systematic review of COVID-19 clinical trial registrations (11), the WHO website and other repositories, such as the [COVID-NMA initiative](#).

Whereas most of these studies are small and of variable methodological quality, a number of large, international platform trials (e.g. RECOVERY, SOLIDARITY and DISCOVERY) are better equipped to provide robust evidence for a number of potential treatment options (10). Such trials can also adapt their design, recruitment strategies and selection of interventions based on new insights, exemplified by the uncertainties outlined above.

Concerning ivermectin used to treat COVID-19, more than 66 RCTs planning to enrol more than 12 000 participants (range 24 - 2724) are registered or ongoing (11).

9. Authorship, contributions, acknowledgements

WHO would like to thank the collaborative efforts of all those involved to make this process rapid, efficient, trustworthy and transparent, including in-kind support from the Magic Evidence Ecosystem Foundation (MAGIC) and their partner, the BMJ, to develop and disseminate this living guidance for COVID-19 drug treatments, based on a living systematic review and network meta-analysis from investigators at McMaster University, Canada.

WHO Therapeutics Steering Committee

The committee includes representatives from various WHO departments at headquarters and the regions and has been approved by the WHO Director of the Country Readiness Department, and the WHO Chief Scientist. The WHO Secretariat meets on a regular basis to discuss when to trigger guideline updates based on evidence updates from the WHO rapid review team, and other sources of evidence and selects the members of the **Guideline Development Group (GDG)** for living guidance.

Janet V Diaz (Lead, Clinical Team for COVID-19 Response, Health Emergencies Programme, Geneva); John Appiah (Lead, Case Management, WHO Regional Office for Africa); Lisa Askie (Quality Assurance of Norms and Standards Department); Silvia Bertagnolio (Communicable and Noncommunicable Diseases Division/Clinical Team for COVID-19 Response); Sophie Harriet Dennis (Infection Prevention and Control and Clinical Management); Nedret Emiroglu (Country Readiness Strengthening, Health Emergencies Department); Nathan Ford (Department of HIV/AIDS and Global Hepatitis Programme); John Grove (Quality Assurance of Norms and Standards Department); Maria Van Kerkhove (Health Emergencies Programme); Rok Ho Kim (Quality Assurance of Norms and Standards Department); Chiori Kodama (WHO Regional Office for the Eastern Mediterranean); Marta Lado Castro-Rial (Country Readiness Strengthening, Health Emergencies Department); Lorenzo Moja (Health Products Policy and Standards Department); Olufemi Oladapo (Sexual and Reproductive Health and Research Department); Alonso Pedro (Global Malaria Programme); Dina Pfeifer (WHO Regional Office for Europe/Health Emergencies Programme); Jacobus Preller (Clinical Team for COVID-19 Response); Pryanka Relan (Integrated Health Services Department/Clinical Team for COVID-19 Response); Ludovic Reveiz (Evidence and Intelligence for Action in Health Department, Incident Management Systems for COVID-19, Pan American Health Organization); Vaseeharan Sathiyamoorthy (Research for Health, Science Division); Archana Seahwag (Country Readiness Strengthening, Health Emergencies Department); Anthony Solomon (Neglected Tropical Diseases); Juan Soriano Ortiz (Country Readiness Strengthening, Health Emergencies Department); Soumya Swaminathan (Office of Chief Scientist); Wilson Were (Maternal, Newborn, Child and Adolescent Health and Ageing Department); Pushpa Wijesinghe (Lead, Case Management, Regional Office for South-East Asia). Supporting project officer: Jacqueline Lee Endt (Health Care Readiness Unit, Health Emergencies Department).

The WHO Therapeutics Steering Committee is fully responsible for decisions about guidance production and convening the GDG.

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Guideline Development Group (GDG)

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Citizen Registration and Appointment for Vaccination

User Manual

Date: 27-Feb-2021

Version: 1.1

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Citizen Registration and Appointment for Vaccination

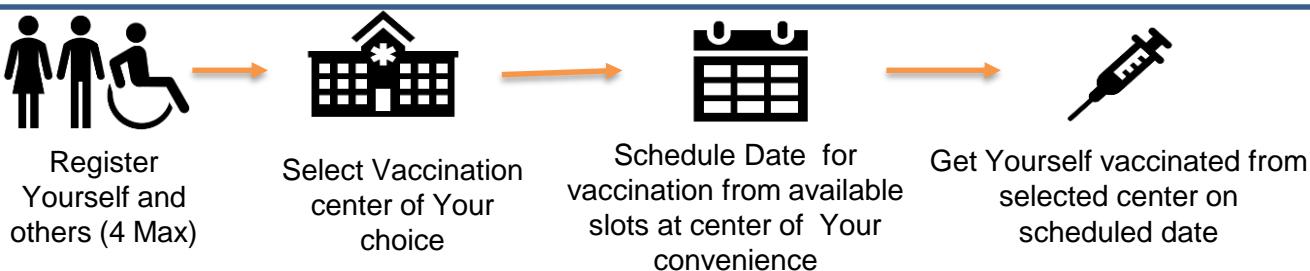
Overview

Government of India is taking all necessary steps to ensure that the nation is prepared to face the challenge and threat posed by the growing contagion of COVID-19. The exemplary groundwork and precaution advisory by the Government has helped in containing the spread of the virus in our country. At present, the priority is to make COVID -19 vaccine available to all, ensuring vaccine traceability and beneficiary tracking from production to last mile administration. COVID-19 vaccination drive has been initiated to cover healthcare and frontline workers and is to be scaled up to cover citizens above 60 years of age and and/or citizen above 45 years of age suffering from comorbidities.

Co-WIN application is the digital back bone for the vaccination drive in India. With scaling up of vaccination; the number of vaccination facilities and sessions has to be increased and managed effectively. The CO-WIN application will facilitate the citizen with an option to register and schedule the vaccination session online in Centers of their choice. The Citizen self-registration module will ensure fool-proof identification of deserving candidates for receiving the vaccines. The Co-WIN application facilitates multiple role creations for orchestrating vaccination drive at various levels.

The objective of the document is to handhold the citizens to register and schedule an appointment for vaccination. Currently the application is open for Citizens above 60yrs of age and for People above 45 yrs of age with comorbidities

Features of Citizen Self registration Module



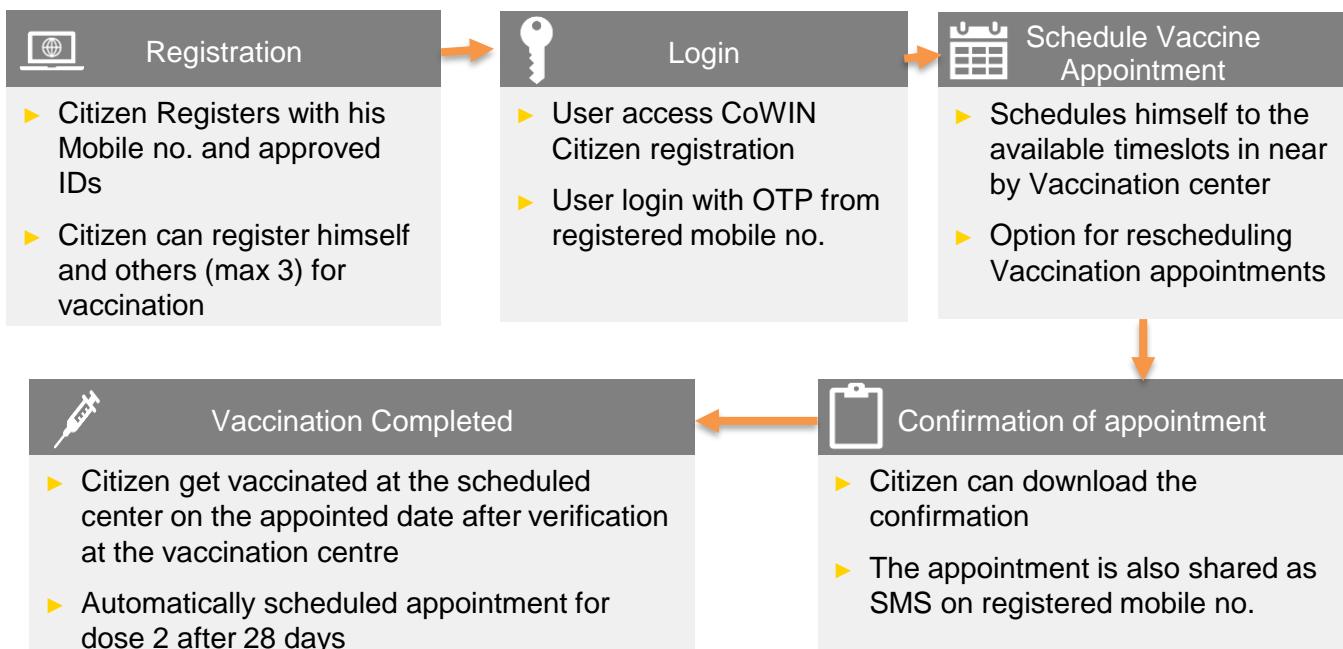
The following features will be available for the Citizen in Self Registration module

- Register for a vaccination session (with a choice of registering additional 3 members)
- Selection of Vaccination center of convenience
- Schedule vaccination Date as per slot availability at a Center
- Reschedule Vaccination date

User Manual

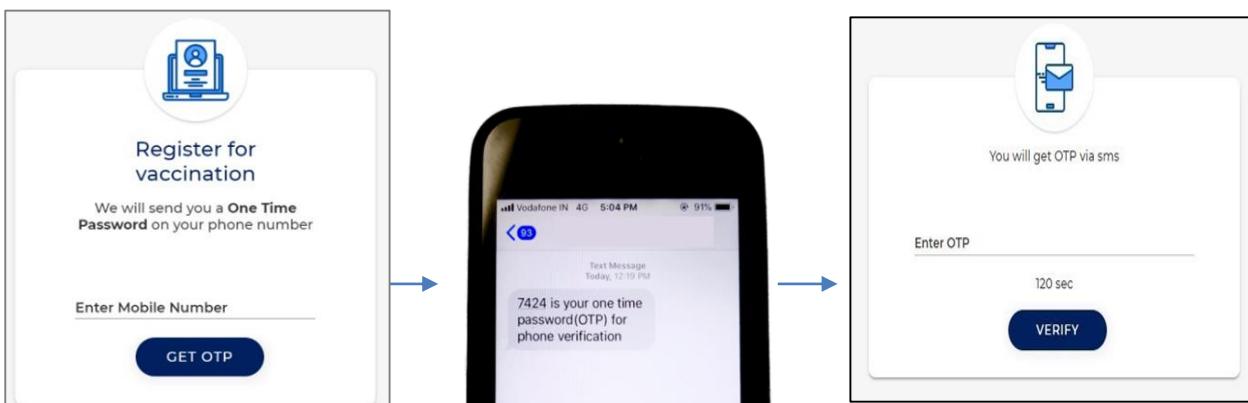
Citizen Registration and Appointment for Vaccination

Work Flow



1 Register

- Citizens can register by logging in “www.cowin.gov.in”



- Enter valid mobile number. Clicks on “Get OTP” button.
- OTP is sent at the phone number via SMS.
- Enter the OTP and click “Verify” button.

User Manual

Citizen Registration and Appointment for Vaccination

- Once the OTP is validated, the “Registration of Vaccination” page appears
- Enter details required in the “Registration of Vaccination” page

Register for Vaccination

Your Photo Id will be verified at the time of your vaccination appointment. Please provide the details of the Photo Id you will carry for vaccination.

Photo ID Proof
Driving License

Driving License Number
MH01 327821

Name (as in Driving License)
Damini Sharma

Gender
 Male Female Others

Year of Birth (as in Driving License in YYYY format)
1972

Do you have any comorbidities (pre-existing medical conditions)?
If you have any comorbidities, please carry a medical certificate with you for the vaccination appointment.

Yes No

REGISTER

* All fields are mandatory

Mandatory Field to be Filled by
the Citizen for Registration

Click “Register”
Button

- The below table shows the details to be entered in the “Registration of Vaccination” page.
Please note that all fields in this Form are **Mandatory**

#	Field Name	Details
1.	Photo ID Proof	<ul style="list-style-type: none">Select appropriate ID Card from the Dropdown list . <p>Citizen must carry selected ID at the time of taking the vaccination.</p>
2	Photo ID Number	Citizen to enter ID number
2.	Name	Enter the name as per the selected ID proof
3.	Year of Birth	Enter the year of birth as per the ID Proof in the format YYYY
4.	Gender	Select Gender (Male/ Female/ Others)
5.	Comorbidities	Citizens 45+ years of age to select the relevant option as per the case. Citizen should carry a medical certificate at the time of vaccination

Once the details are entered for registration, Click “Register” Button at the bottom right.

Receives Confirmation message on successful registration

Beneficiary Registered Successfully

User Manual

Citizen Registration and Appointment for Vaccination

2 Add More Individuals

- Once registration is completed; the system will show the “Account Details”
- Citizen can further add 3 more people linked with this mobile number by clicking on “Add More” button at the bottom right side of the Page

Account Details

Individuals linked to mobile number 7021565500

#	Name	Gender	Year Of Birth	Photo Id	Id Number	Status	Action
1	Sunita Devi	Female	1972	Aadhaar Card	XXXX-8458	Not Scheduled	
2	Deva Nandy	Male	1961	Driving License	XXXX-3344	Scheduled	

+ Add More

Click on “Add More” for adding 3 more individuals linked to this mobile number

Enter all the details of the individual to be included and then click on the **Add** button

Register for Vaccination (Open for age 60 and above)

Your Photo Id will be verified at the time of your vaccination appointment. Please provide the details of the Photo Id you will carry for vaccination.

Photo ID Proof

Photo ID Number

Name

Year of Birth

Gender

Male Female Others

Mobile

*** All fields are mandatory**

Back **ADD**

You can add 3 more members

Click on “Add” for adding additional members linked to this account

Receives Confirmation message on successful addition of member

Beneficiary Registered Successfully

All Fields are Mandatory to be filled

User Manual

Citizen Registration and Appointment for Vaccination

3 Delete Individuals

- Citizen can Delete individuals linked with his mobile number

Account Details

Individuals linked to mobile number 7021565500

#	Name	Gender	Year Of Birth	Photo Id	Id Number	Status	Action
1	Sunita Devi	Female	1972	Aadhaar Card	XXXX-8458	Not Scheduled	
2	Deva Nandy	Male	1961	Driving License	XXXX-3344	Scheduled	
3	Damini Sharma	Female	1972	Driving License	XXXX-821	Not Scheduled	

+ Add More

“Delete” button – to Delete existing member

1. Login with username and password, and Navigate to the dashboard.

1. Click action button to Delete a member

Account Details

Individuals linked to mobile number 7021565500

#	Name	Gender	Year Of Birth	Photo Id	Id Number	Status	Action
1	Sunita Devi	Female	1972	Aadhaar Card	XXXX-8458	Not Scheduled	Delete Individual
2	Deva Nandy	Male	1961	Driving License	XXXX-3344	Scheduled	
3	Damini Sharma	Female	1972	Driving License	XXXX-821	Not Scheduled	

+ Add More

- Confirmation message will appear on Deletion

Beneficiary Deleted Successfully

Citizen Registration and Appointment for Vaccination

4 Booking Appointment for Vaccination

- Citizen can schedule Appointment from the “Account Details” page.

Account Details

Individuals linked to mobile number 7021565500

#	Name	Gender	Year Of Birth	Photo Id	Id Number	Status	Action
1	Deva Nandy	Male	1961	Driving License	XXXX-3344	Scheduled	Schedule Appointment
<input checked="" type="checkbox"/>	Damini Sharma	Female	1972	Driving License	XXXX-821	Not Scheduled	 

“Schedule” Button – to book vaccination appointment 

SCHEDULE APPOINTMENT

- Clicks on  button for Booking Vaccination Appointment or Click “SCHEDULE APPOINTMENT”
- System navigates to “ Book Appointment for Vaccination” page
- Searches the Vaccination Centre of choice by State, District, Block and Pin Code from the dropdowns

Book Appointment for Vaccination

Search Vaccination Center

State/UT District Block Pincode

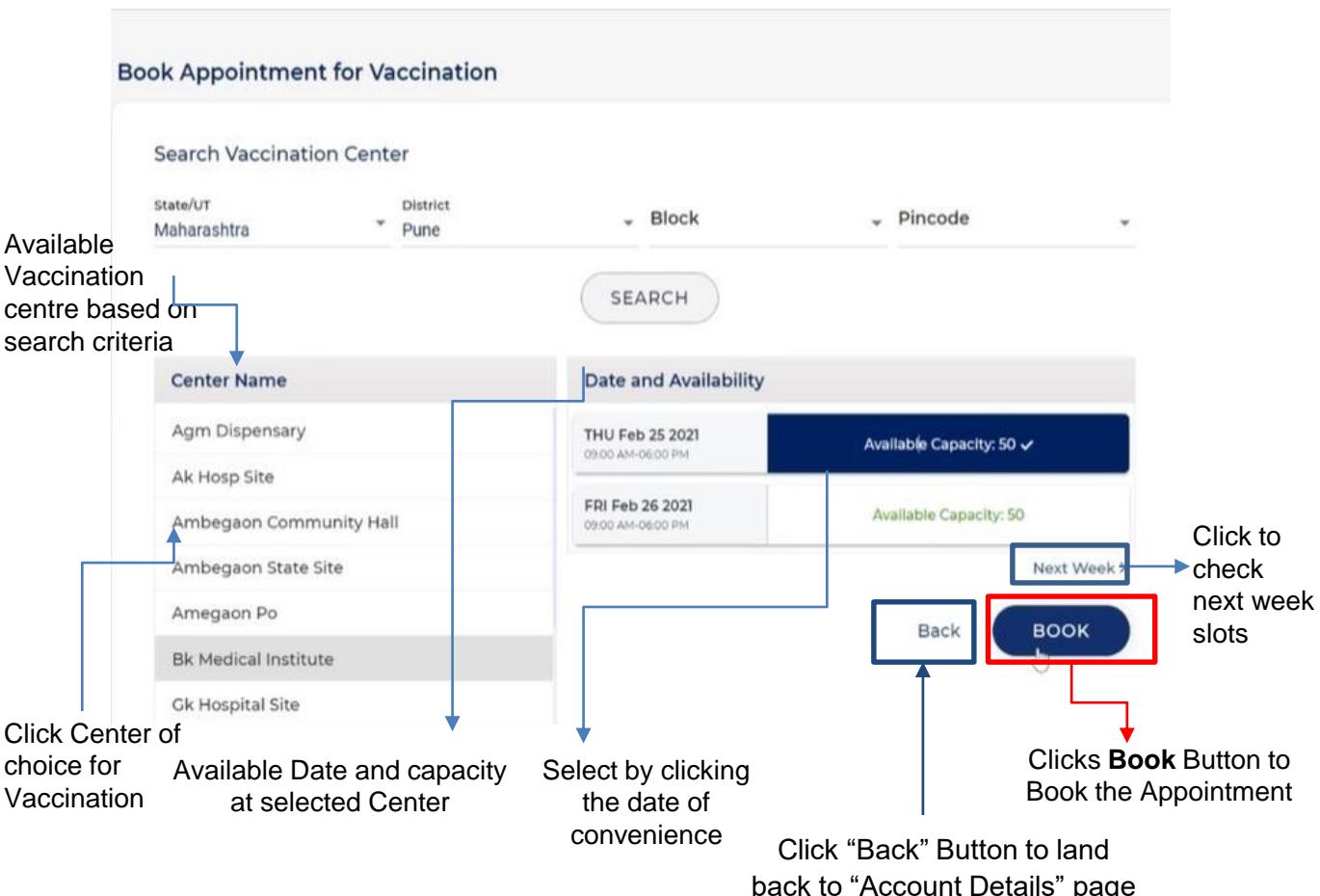
Select the State/UT from the drop down Select the District coming under the selected State from the drop down Select the Block coming under the selected District from the drop down Select the PINCODE coming under selected Block from the drop down

Click “Back” Button to land back to “Account Details” page Click “Search” Button to find the Vaccination Center in selected location

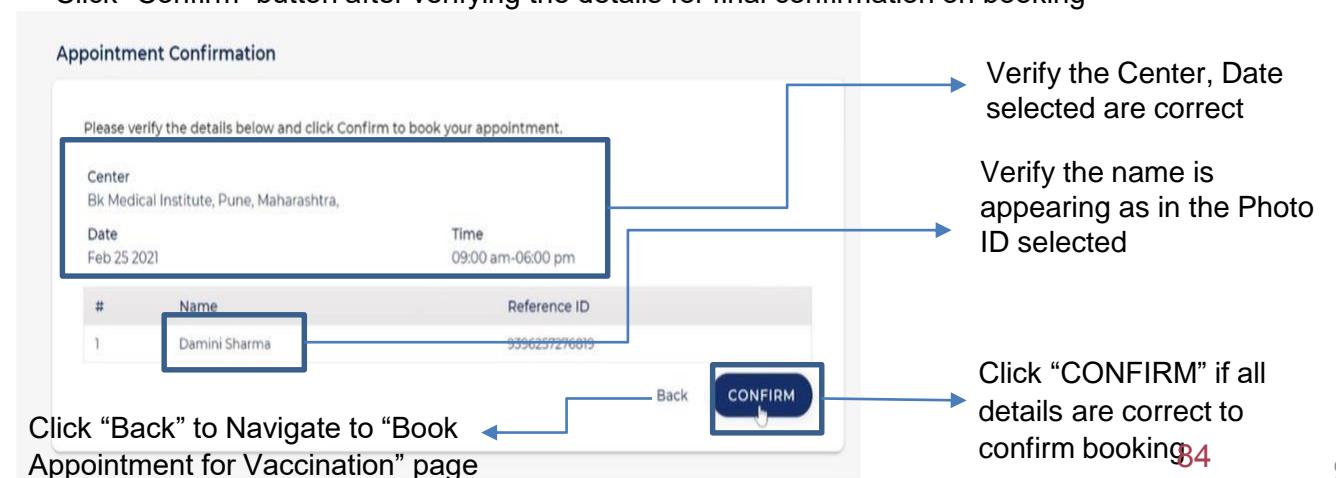
User Manual

Citizen Registration and Appointment for Vaccination

- On clicking “Search” button, system will display below the list of Vaccination centre as per Search Criteria
- Center Name will be displayed at right panel of the page
- On clicking any centre at the panel, the available slots (date and capacity) will be displayed



- Once “Book” button is clicked, the “Appointment Confirmation” page is displayed
- Click “Confirm” button after verifying the details for final confirmation on booking



User Manual

Citizen Registration and Appointment for Vaccination

- Once confirmed, the confirmation page with “Appointment Successful” message will be displayed

Appointment Successful

Your vaccination appointment is confirmed.

Download

Your appointment details have also been sent on your registered mobile number through an SMS.

Center
Bhabha Hospital Kbbh, Bandra, Mumbai, Maharashtra,

Date	Time	Time Prefrence
Feb 22 2021	03:30 am - 12:30 pm	FORENOON

#	Name	Reference Id	Photo Id to Carry
1	Pravin Mathur	3218379647657	Driving License

Instructions

- Please carry the Photo Id card mentioned in your appointment

Click “Download” to download and save the confirmation

APPOINTMENT DETAILS			
Center	BK Medical Institute, Bawdhan, Pune, Maharashtra,		
Date	Feb 25 2021	Time	09:00 am-06:00 pm
DETAILS OF INDIVIDUALS			
#	Name	Reference Id	Photo Id to Carry
1	Damini Sharma	9396257276819	Driving License
INSTRUCTIONS			
1. Please carry the Photo Id card mentioned in your appointment details for vaccination. 2. If you have any comorbidities, please carry a medical certificate with you for the vaccination appointment. 3. For any additional information, please visit our website - https://cowin.gov.in or call CoWIN helpline number 1075.			

Citizen should keep the confirmation details to show at the Vaccination Center on scheduled date

Get your COVID Vaccination Certificate on



5 Rescheduling an Appointment

- Once the Appointment is fixed, it can be rescheduled at any later stage but before the vaccination appointment day.
- For this, Re-login to “Citizen Registration” module; with your already registered mobile no.

How to Re-Login to “Citizen Registration Module”?

Register for vaccination
(Open for age 60 and above)

We will send you a One Time Password on your phone number

Enter Mobile Number

GET OTP



Enter his/her already registered mobile number. Clicks on “Get OTP” button.

OTP is sent at the phone number via SMS.

Enter the OTP and click “Verify” button.

Navigate to “Account Details” Page

User Manual

Citizen Registration and Appointment for Vaccination

Account Details

Individuals linked to mobile number 7021565500

#	Name	Gender	Year Of Birth	Photo Id	Id Number	Status	Action
1	Deva Nandy	Male	1961	Driving License	XXXX-3344	Scheduled	Reschedule Appointment
2	Damini Sharma	Female	1972	Driving License	XXXX-821	Scheduled	

+ Add More

Click on to re-schedule an already booked appointment.

- 1 Citizen is Directed to Book Appointment for Vaccination" page; wherein he can Search the revised date and Center
- 2 Once the new Date is selected; Click "Book" to reschedule;
- 3 Confirm by clicking "Confirm" of the revised Schedule
- 4 Once confirmed, the confirmation page with "Appointment Successful" message will be displayed

Book Appointment for Vaccination

Search Vaccination Center

State/UT District Block Pincode

Back **SEARCH**

1

Search new Center

Appointment Confirmation

Please verify the details below and click Confirm to book your appointment.

Center: Bik Medical Institute, Pune, Maharashtra,
Date: Feb 25 2021 Time: 09:00 am-06:00 pm
Name Reference ID
1 Damini Sharma 9396257276819

Back **CONFIRM**

3

Verify and confirm new Slot and Book

Book Appointment for Vaccination

Search Vaccination Center

State/UT: Manipur District: Imphal West Block: Imphal West Pincode: 795001

SEARCH

Center Name	Date and Availability
Manipur High School	TUE Feb 23 2021 03:30 AM-02:30 PM Available Capacity: 50 Forenoon Afternoon
Test Site Dh	
Today Site	
Test Site Dhania	
Megha Private Hospital	

Back **BOOK**

2

Search new Slot and

Instructions

Your vaccination appointment is confirmed.
Your appointment details have also been sent on your registered mobile number through an SMS.

Center: Bhabha Hospital Kbbh, Bandra, Mumbai, Maharashtra,
Date: Feb 22 2021 Time: 03:30 am - 12:30 pm Time Preference: FORENOON
Name Reference ID Photo Id to Carry
1 Pravin Mathur 3218379647657 Driving License

4 1. Please carry the Photo Id card mentioned in your appointment

Confirmation

- Once Vaccinated for the 1st Dose, the Citizen will be automatically scheduled appointment for dose 2 for the same centre of receiving the first dose of vaccination.
- In case the user has moved to another city, appointment can be rescheduled for the nearest vaccination centre in that city.

“ दवाई भी और कड़ाई भी।

Together, India will defeat COVID-19 ”

- *Prime Minister Narendra Modi*



Annexure 1(B): Certificate to identify individuals with co-morbidities that enhance the risk of mortality in COVID-19 disease for priority vaccination
(To be filled by a Registered Medical Practitioner)

Name of beneficiary:

Age: _____ Gender: _____

Address: _____

Mobile phone number: _____

Identification document: _____

I, Dr. _____, working as _____ have reviewed the above named individual and certify that he/she has the below mentioned conditions based on the records presented to me. A copy of the records on which this certificate is based is attached.

Presence of ANY ONE of the following criteria will prioritize the individual for vaccination

SN	Criterion	Yes/No
1.	Heart Failure with hospital admission in past one year	
2.	Post Cardiac Transplant/Left Ventricular Assist Device (LVAD)	
3.	Significant Left ventricular systolic dysfunction (LVEF <40%)	
4.	Moderate or Severe Valvular Heart Disease	
5.	Congenital heart disease with severe PAH or Idiopathic PAH	
6.	Coronary Artery Disease with past CABG/PTCA/MI AND Hypertension/Diabetes on treatment	
7.	Angina AND Hypertension/Diabetes on treatment	
8.	CT/MRI documented stroke AND Hypertension/Diabetes on treatment	
9.	Pulmonary artery hypertension AND Hypertension/Diabetes on treatment	
10.	Diabetes (> 10 years OR with complications) AND Hypertension on treatment	
11.	Kidney/ Liver/ Hematopoietic stem cell transplant: Recipient/On wait-list	
12.	End Stage Kidney Disease on haemodialysis/ CAPD	
13.	Current prolonged use of oral corticosteroids/ immunosuppressant medications	
14.	Decompensated cirrhosis	
15.	Severe respiratory disease with hospitalizations in last two years/FEV1 <50%	
16.	Lymphoma/ Leukaemia/ Myeloma	
17.	Diagnosis of any solid cancer on or after 1st July 2020 OR currently on any cancer therapy	
18.	Sickle Cell Disease/ Bone marrow failure/ Aplastic Anemia/ Thalassemia Major	
19.	Primary Immunodeficiency Diseases/ HIV infection	
20.	Persons with disabilities due to Intellectual disabilities/ Muscular Dystrophy/ Acid attack with involvement of respiratory system/ Persons with disabilities having high support needs/ Multiple disabilities including deaf-blindness	

I am aware that providing false information is an offence.

Name of RMP: _____

Medical Council registration number of RMP: _____

Date of issuing the certificate: _____

Place of issue: _____

(Signature of RMP)



How does Covaxin compare with Covishield? Which is better?



Indian Government started the vaccination rollout on 16th January 2021 and so far around 1.8 crore people (as of 4th March) have been vaccinated with priority to healthcare and other frontline workers. From 1st March, the drive at the private vaccination centers has begun with the Prime Minister also taking the vaccine. As we are all aware by now, 2 vaccines produced in India i.e. "Covishield" and "Covaxin" have been authorized for emergency use in India. In near future when choices may be given to the recipients, the most important question will haunt people; "which vaccine to prefer?" On 3rd March, Covaxin phase-3 interim results were also declared and therefore head-to-head comparison is now possible. Firstly, it is important to understand basic differences between Covishield and Covaxin in a comprehensive manner and then make interpretations.

Covishield vs Covaxin comparison:

1. Biological Components:

Covishield is a viral vector vaccine. It uses a weakened, non-replicating strain of Chimpanzee cold virus (adenovirus) to carry genetic material of the spike protein of SARS-CoV-2 into human cells.

Covaxin contains an inactivated SARS-CoV-2 (Strain: NIV-2020-770) which is disabled for replication. However, the proteins are intact which are able to provoke immunity of the host. There are other chemical ingredients in the form of excipients which are detailed out in the table below.

If you want to understand these vaccine types further, read another article on Covipedia by clicking the link below:

[Overview of types of vaccine](#)

2. Chemical Ingredients:

Covishield	Covaxin
L-Histidine Ethanol	Aluminum Hydroxide gel
L-Histidine Hydrochloride Monohydrate	Imidazoquinolinone # (TLR 7/8 agonist)
Magnesium Chloride Hexahydrate	2-Phenoxyethanol
Polysorbate 80*	Phosphate buffer saline
Sucrose	
Sodium Chloride	
Disodium Eddate Dihydrate (EDTA)	
Water for injection	
<i>*Polysorbate 80 which is an ingredient of Covishield is known to cause anaphylactic reactions in patients as can be read here whereas Covaxin has no such component.</i>	<i>#Also known as Algel-IMDG which is an adjuvant required for Covaxin but not for Covishield.</i>



How does Covaxin compare with Covishield? Which is better?



Storage Conditions:

Both vaccines can be stored at 2 to 8 degrees Celsius making them convenient to store and transport.

3. Mechanism of Immunization:

Covishield – This vaccine produces antibodies against only a specific region of the virus. It contains a portion of the DNA that codes for the spike protein (S-protein). Once inside the cells, the DNA part first needs to enter the nucleus to create its mirror image (complementary RNA). Then this RNA comes out in the cytoplasm as a messenger and starts making S-protein through a machine available for this purpose called ribosome. Since it is S-protein that provokes immunity it may not be as close to natural immunity as created by Covaxin. If there are any long-term side effects of the DNA material remaining inside the nucleus (e.g. integration in human DNA) is not yet known. So far, DNA vaccines were only being tried out for treating cancer patients and never used for preventing infections in normal subjects.

Covaxin – This vaccine can produce antibodies against many regions of the complete virus. Since this vaccine contains a full inactivated virus with all its 29 proteins intact, the immunity provoked by it will be more comprehensive and closer to natural immunity arising out of an infection. This does not contain any genetic material that can either replicate or go inside the nucleus but provokes the immunity against virulent proteins other than S-protein as well. This uses a tried and tested technology platform used by other vaccines like polio vaccine. However, these vaccines require an adjuvant to provoke immunity. For this purpose, alum is commonly used which mainly provokes Th-2 type immunity which also leads to more side effects. Hence, Bharat Biotech has used an alternative adjuvant “Algel-IMDG (Imidazoquinolinone)” which stimulates Th-1 type immunity that is also generated by mRNA/DNA vaccines.

4. Clinical Development:

Covishield has been developed by AstraZeneca with Oxford university in the UK and is being manufactured by the Serum Institute India (SII) in Pune. Covishield has completed phase 3 trials in S. Africa, Brazil and UK. 90% of the subjects in these studies were under the age of 55 making the efficacy and safety data applicable to this age group. The company has presented bridging study results in Indian population to the regulatory authorities based on which the approval was granted by DCGI. This data is not yet available in the public domain.

Covaxin has been developed by Hyderabad based Bharat Biotech along with the Indian Council of Medical Research (ICMR) and National Institute of Virology (NIV) in Pune. The phase 1 and phase 2 studies enrolled 375 people and phase 3 study enrolled 25,800 participants between 18-98 years of age, including 2,433 over the age of 60 and 4,500 with comorbidities making it the largest clinical trial in India.

5. Dosage Regimen:

Covishield has been recommended to be taken in 2 doses. Observation of data from the UK shows improved protection with a gap of 12 weeks between 2 doses; though currently the



How does Covaxin compare with Covishield? Which is better?



expert committee set up by the Drug Controller General of India (DCGI) has recommended a gap of 4 weeks.

Covaxin has been recommended to be taken in 2 doses 4 weeks apart.

6. Efficacy:

Covishield has an average efficacy of 70% when 2 doses are administered 4 weeks apart. This data is from a meta-analysis (pooled analysis of multiple studies) of 4 Covishield trials in 11,636 patients out of which 3 trials were single blind and one double blind in 3 different countries. The efficacy of Covishield was published in The Lancet ([link to the article](#)). Observation of data has shown that the efficacy improves as the gap between the 2 doses is increased reaching a reported efficacy of 82.4% with a 12-week gap. Since, the phase-3 trials were conducted with a 4-week interval, it has become the standard.

Covaxin phase-3 interim results show an efficacy of 81%. This data is from one double blind study of 28,500 patients in India. Thus, from efficacy angle, Covaxin scores higher than Covishield with more robust and coherent data in Indian subjects.

7. Protection against Mutations:

Preliminary research shows both vaccines are effective against the variant of the novel coronavirus first detected in the UK but there is no data on their efficacy against the mutants found in South Africa and Brazil. Data against these 2 variants is yet to be generated for both these vaccines.

8. Side Effects:

Based on the fact-sheets released by both manufacturers:

Side Effects	Covishield	Covaxin
Anaphylaxis	✓	✗
Tenderness, pain, warmth, redness, itching, swelling or bruising at the injection site, generally feeling unwell	✓	✓
Stiffness in upper arm	✗	✓
Fever	✓	✓
Fatigue / Malaise / Weakness	✓	✓
Headache	✓	✓
Nausea / Vomiting	✓	✓
Joint pain / Muscle ache	✓	✗
Bodyache	✗	✓
Feeling dizzy, decreased appetite, abdominal pain	✓	✗
Enlarged lymph nodes	✓	✗
Excessive sweating, itchy skin	✓	✗
Rashes	✓	✓



How does Covaxin compare with Covishield? Which is better?



9. Precaution and Contraindications:

Based on the fact-sheets released by both manufacturers:

Covishield		Covaxin	
What should you mention to your healthcare provider before vaccination? <i>(HCP to decide on whether to vaccinate or not in such conditions)</i>	Who should not get the vaccine?	What should you mention to your healthcare provider before vaccination? <i>(It is advisable not to take the vaccine in any of these conditions)</i>	Who should not get the vaccine?
Any history of allergies	Has a severe allergic reaction after a previous dose of this vaccine	Any history of allergies	Any history of allergies
Fever	Has a severe allergic reaction to an ingredient of this vaccine	Fever	Has fever
A bleeding disorder or if you are on a blood thinner		Bleeding disorder or if you are on a blood thinner	Has a bleeding disorder or is on a blood thinner
Immunocompromised or on a medicine that affects the immune system		Immunocompromised or on a medicine that affects the immune system	Is immunocompromised or is on a medicine that affects the immune system
Pregnant / Breastfeeding		Pregnant / Breastfeeding	Pregnant / Breastfeeding
Received another Covid-19 vaccine		Received another Covid-19 vaccine	Has received another COVID-19 vaccine
Any other serious health related issues, as determined by the vaccinator/officer			Has any other serious health related issues, as determined by the vaccinator/officer

10. Consent:

Covishield does not require any consent form as it has completed the phase-3 clinical trials.



How does Covaxin compare with Covishield? Which is better?



Covaxin – Since it was approved by the Indian regulatory authorities before phase 3 results were available, it is being administered to people in a large clinical trial setting. This is being termed as “clinical trial mode”. Such use is similar to some of the anti-cancer drugs which have been used on compassionate basis before its formal approval. This requires pre-informed consent of the patient who is explained that it is not yet approved and he provides his consent for the same. This form states that the beneficiaries will be provided care in government authorized hospitals if they faced side-effects from the vaccine. They will also reportedly get compensated if they face adverse effects from the vaccine. Now that the phase 3 efficacy data is available, once it is presented to the authorities and restricted emergency use is granted the need for informed consent will be removed.

11. Price

While the vaccine is being given for free at the government institutions, the price at private institutions has been capped at ₹250 per dose.

Currently, the person does not get to choose which vaccine he/she would receive. It is likely that once the vaccines are available for private market sale, choice of brand will be given to the people.

Recommendation:

At the face value, the stellar reputation of Oxford University, AstraZeneca and Serum Institute of India is daunting enough to prefer Covishield if a choice is given to you. However, an objective comparison of properties, attributes and available information indicates that Covaxin is better placed to receive our recommendation for the following reasons: Higher efficacy of Covaxin comes out of robust data from one double blind controlled clinical trial as compared to lower efficacy of Covishield with results pooled from multiple studies that were not blinded and were dissimilar. Covaxin also seems to have distinct safety advantage with the lack of anaphylaxis and potential for neurological adverse events with Covishield. Two cases of transverse myelitis in the UK had stalled the clinical trial for some time but resumed once the safety was reconfirmed.

On the regulatory front, Covishield (its original codename of AZD1222) seems to have an advantage over Covaxin being approved in European countries and Australia whereas Covaxin has been approved in India and Zimbabwe so far. Also, by now millions of doses have been used in India and Europe without any major concern. Covishield may therefore be a natural choice for those who value external endorsement (in this case UK, EU, Australia). However, without extraneous considerations on the strength of head-to-head comparison shown above Covaxin is a compelling choice.

-Authored by Dr. Pranit Desai, Dr. Kshipra M. Gharpure, reviewed by Dr. Chitra Bargaje and edited by Dr. Dhananjay Bakhle (Medical Research)

Sources:

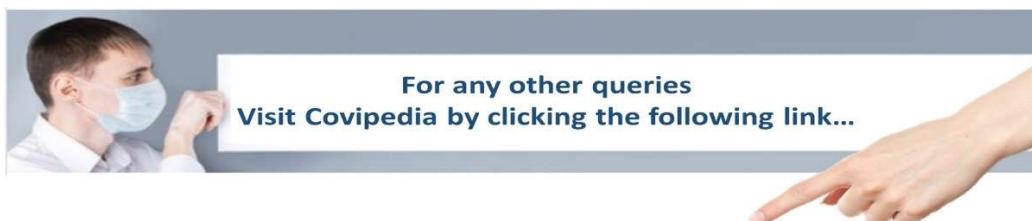
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How does Covaxin compare with Covishield? Which is better?



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- How to deal with the after-effects of Covid vaccine shot (msn.com)
- <https://science.thewire.in/health/lack-of-efficacy-data-for-indias-covid-vaccines-against-sars-cov-2-variants/>
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- [Efficacy of ChAdOx1 nCoV-19 \(AZD1222\) Vaccine Against SARS-CoV-2 VOC 202012/01 \(B.1.1.7\)](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8030203/)
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- https://www.seruminstitute.com/pdf/covishield_fact_sheet.pdf



<https://lupinworld.sharepoint.com/sites/Intranet/Liberate#/!>

RT PCR report CT (Cycle Threshold): In value, RT PCR report Ct (cycle threshold) is evaluated to understand the viral load and infectiousness.
Lower the value higher is the viral load

Score	Viral load
17-24	High viral load
24-35	Moderate viral load
>35	Mild viral load

HRCT Chest

CT Severity Score

Score	CT severity
< 8	Mild
9-15	Moderate
> 15	Severe

CO-RADS score:

Level of suspicion for COVID-19

CO-RADS 1	No
CO-RADS 2	Low
CO-RADS 3	Intermediate
CO-RADS 4	High
CO-RADS 5	Very high
CO-RADS 6	Very high with PCR+

CRP (mg/dl)	Severity of inflammation
0-6	Normal
<26	Mild
26-100	Moderate
>100	Severe

D dimer (Micro gram/ml)	Severity of inflammation
<0.5	Normal
<1	Mild
>1	Moderate-severe

IF D dimer measured in ng/ml then multiply above reading by 1000

Neutrophil to Lymphocyte ration (NLR)
<3.5 -Mild >3.5- Moderate-severe

IL6 (pg/ml)	Severity of inflammation
0-7	Normal
<15	Mild
15-100	Moderate
100-500	Severe
>500	Critical

	Normal range
Ferritin	13-150 ng/ml
LDH	0-250 U/L
ESR	0-22 mm/ hour

Antibody Tests

- 1) **Specific:** SARS COV2 Anti Spike Protein Antibody Test- 15 required for protection
- 2) General: SARS COV2 IgG Antibody Test



संघमेव जयते

प्रोफेसर (डा.) बलराम भार्गव, पदम श्री
एम्डी. डॉल, एफआरसीपी (टी), एफआरसीपी (ई), एफसीसीपी,
एफएचएस, एफएचएस, एफएससी, एफएचएस, डीएस सी.
सचिव, भारत सरकार
स्वास्थ्य अनुसंधान विभाग
स्वास्थ्य एवं परिवार कल्याण मंत्रालय एवं
महानिदेशक, आई सी एम आर

Prof. (Dr.) Balram Bhargava, Padma Shri

MD, DM, FRCR (Glasg.), FRCP (Edin.),
FACC, FAHA, FAMS, FNASC, FASc, FNA, DSc

Secretary to the Government of India
Department of Health Research
Ministry of Health & Family Welfare &
Director-General, ICMR



भारतीय आयुर्विज्ञान अनुसंधान परिषद
स्वास्थ्य अनुसंधान विभाग
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
भारत सरकार
श्री. रामालिंगस्वामी भवन, अंसारी नगर
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Indian Council of Medical Research

Department of Health Research
Ministry of Health & Family Welfare
Government of India
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New Delhi - 110 029

D.O.No. VIR/4/2021/ECD-I
Dated: 5th April 2021

Dear Dr Vyas

This is with reference to your letter dated 1st April 2021 regarding CT (cycle threshold) value for RTPCR test for COVID-19.

2. Globally, the accepted cut-off for Ct value for COVID-19 ranges from 35-40 depending upon the instructions laid down by individual manufacturers.
3. However, ICMR has taken inputs from different virology laboratories across the country to arrive at a single Ct value cut-off based on individual laboratory experiences. As per uniform consensus, a Ct value cut-off of 35 with a good sigmoidal real-time RTPCR curve is acceptable. All patients with a Ct value ≤ 35 may be considered as positive while those with Ct value > 35 may be considered as negative. All samples with Ct value ≤ 35 with poor sigmoidal curves should be essentially re-tested.
4. Implementing a Ct value cut-off of 24 is not at all advisable as this will lead to missing of several infectious patients and increased disease transmission.

With best regards

Yours sincerely

(Balram Bhargava)

Dr. Pradeep Vyas

Principal Secretary
Department of Health & Family Welfare,
Government of Maharashtra,
10th Floor, B Wing GT Hospital Complex Building
Mumbai – 400001, Maharashtra

Copy to:- Shri Rajesh Bhushan, Secretary (H&FW), MoH&FW, Nirman Bhavan ,New Delhi – 110011

Ms. Arti Ahuja, Additional Secretary, Ministry of Health & Family Welfare, Nirman Bhawan, New Delhi



POST DISCHARGE COVID PATIENTS: INFORMATION BOOK

DO'S AND DON'TS

**GOVERNMENT MEDICAL COLLEGE AND
HOSPITAL SECTOR 32, CHANDIGARH**

Congratulations !!

You've won against COVID 19

- You have shown great courage and patience
- Now you are being discharged
- You've **another responsibility of keeping yourself healthy**

REMEMBER

Follow the suggested plan and do not miss or forget to take medications

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PREFACE

This book is dedicated to all the COVID 19 warriors who defeated the deadly disease courageously.

The book was needed because inspite of the verbal instructions, given to the patients at the time of the discharge from COVID Hospital, many patients were not able to implement the instructions completely but in a piecemeal manner.

The present book starts from the footstep of the patient just out of the hospital as they board a vehicle for transportation to their home. Then the way, the room is to be prepared where the patient should stay in at home, has been explained and the precautions regarding sanitization of the articles in room, handling of linen, food etc. have been discussed. The importance of continuing all general precautions for prevention and control of the COVID 19 disease and the use and disposal of masks has also been discussed.

Finally, some life style measures to keep the patient healthy and happy have been discussed.

We present this book to our esteemed patients with a hope that they will now act as ambassadors for the control and prevention of COVID 19 disease.

Prof. Ravi Gupta
Medical Superintendent
GMCH-32, Chandigarh

Table of Contents

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PREPARATIONS AT HOME



Do Not Use Public Transport For Going Home



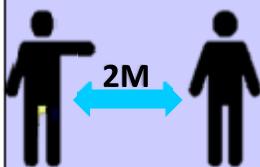
**Make sure you have a separate room in your home
Home isolation is necessary for at least 07 days**



**Monitor temperature and signs of breathlessness
In case of emergency contact hospital**

**FOLLOW ALL THE INSTRUCTIONS GIVEN AT
TIME OF DISCHARGE**

SAFETY PRACTICES AT HOME



Maintain Social
Distancing



STAY HOME STAY SAFE (at least 07 days)

Make sure
your room is
well
ventilated



Do not go out of the house

Do not share till 14 days



Bed, belongings like utensils, glasses, mobile phones, towel, bedding etc.



Do not violate SOCIAL DISTANCING



No Party

No Family time, without precautions.



Do not go for weddings/ functions

USE SEPARATE WASH ROOM IF AVAILABLE



**Sanitize with alcohol based
sanitizer or 1% sodium
hypochlorite**

- bathroom fixtures
- light switches
- toilet seat
- sink
- floor
- table tops
- kitchen surfaces
- door knobs
- toys
- remote controls
- any other article



**WASH YOUR HANDS AFTER CLEANING
AND SANITIZING**

HANDLING OF LINEN /CLOTHING



While handling the used clothes - wear gloves



Wash used clothes and beddings at hot temperature in washing machine

If hot water facility (in washing machine) not available then soak the clothes in the Hot Water & Detergent for 30 minutes



Dry Clothes In Direct Sunlight

Preferably Iron (press) clothes after wash.



Hand Washing Technique

Wash hands frequently for 20 seconds



Wet your hands & apply soap

Rub fingers and palms and spaces between fingers



Scrub the finger nails well



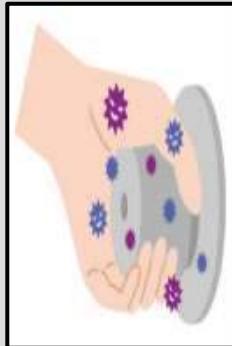
Scrub knuckles well in palms.



Work on thumbs in palms



**But how
frequently
I have to wash
hands?**



**Whenever you touch any
surfaces**



Before eating and after eating

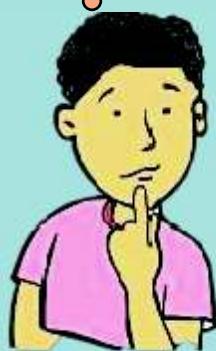


After coughing and sneezing

Do I have to wash hands when I am home?

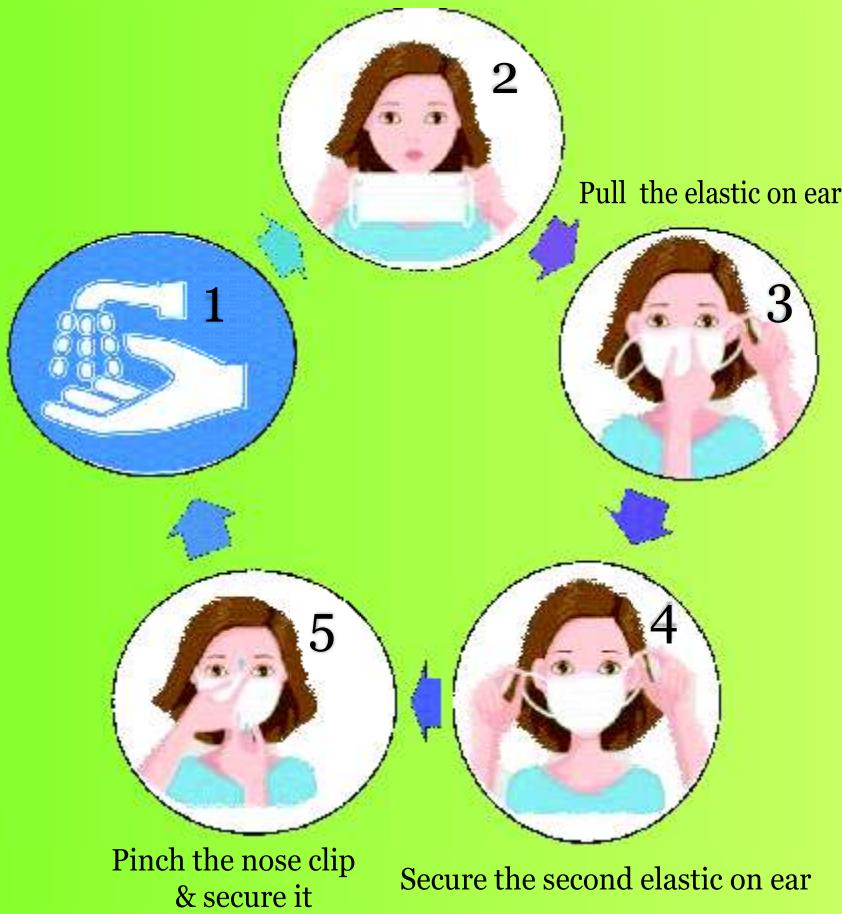
YES

It will keep you safe and protect your family also



HOW TO WEAR MASK

Hold the mask in front of face from strings



- Wash hands before wearing and after removing the mask
- Do not reuse a disposable mask
- Change if its wet

DO'S AND DON'TS RELATED TO MASK

Do's	Don'ts
  <i>Fully covered face and nose</i>	  <i>Nose uncovered</i>
  <i>Nose clip Secured to prevent leakage</i>	  <i>Air leakage from nose and not snuggly fitted</i>
  <i>Snuggly fitted mask</i>	  <i>Air sucked in from all sides of mask</i>



MASK RELATED PRECAUTIONS



Wear mask all the time, even at home



Do not touch your mask / eyes / nose or face



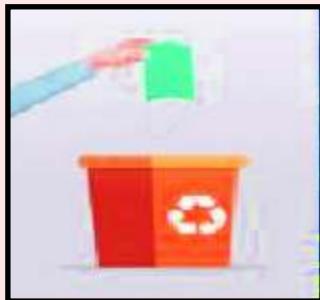
Do not remove mask and do not cough / sneeze without mask or mouth uncovered



While coughing or sneezing cover mouth and nose with tissue



Throw used MASK/TISSUE in covered dustbin and wash your hands



Throw used masks / tissue papers in closed dustbin



Keep dustbin in sunlight for 72hours
then treat the waste like general waste

THEN

WASH YOUR HANDS



WASTE MANAGEMENT



Burn the waste generated
OR



Put it in double yellow bag and hand it over to the nearest biomedical waste management facility

After handling waste/ used articles

WASH YOUR HANDS





LIFESTYLE CHANGES



Always wash raw fruits and vegetables with baking powder and water



- Eat balanced diet -home cooked food
- Eat fresh fruits after washing or peeling



Drink 3-4 liters
(8-10 glasses)
of water

- Drinking kadha may be beneficial for boosting immunity
- Drinking golden milk – 150ml milk with 1 teaspoon of turmeric added in it



Drink fluids - for example coconut water, lemon juice, tea and coffee



Do not drink alcohol



Do not smoke



Sleep for 6-8 hours

Remaining home doesn't mean isolation



Keep yourself busy by doing some online courses or interaction with relatives via video call or phone calls

BREATHING EXERCISES

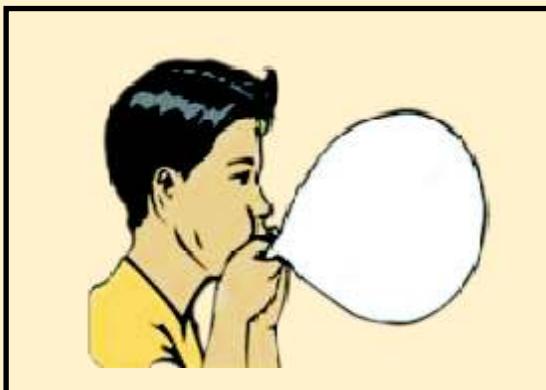


1



2

1. Simply think of smelling a flower
2. Then blow out your breath as if you are blowing the pinwheel or birthday candles.



BLOW BALLOON

BE ACTIVE

You have to stay home for at least another 7 days.
Keep yourself busy and fit



PRACTICE PRANAYAM



Regular practice of Yoga (Minimum 20 minutes)

- Loosening /Breathing exercises
- Gentle Yoga
- Stretching exercises
- Pranayama

For more information visit :
<http://www.ayush.gov.in//>

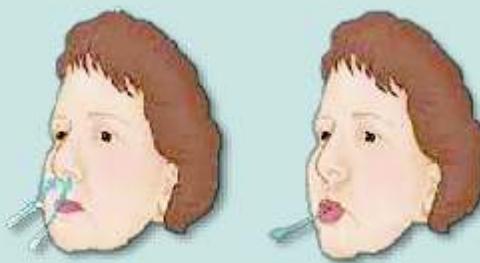
OTHER BREATHING EXERCISES



**SPIROMETER
EXERCISE**



DIAPHRAGM BREATHING



PURSED LIP BREATHING

Practice these exercises 5-10 minutes about 3-4 times/ day,
with mask on till 07 days then in an open area



You are a warrior
But the battle is half won yet
Follow all precautions to PREVENT SPREAD

YOU ARE A SAVIOUR IF.....YOU

HOSTED A
VIRTUAL PARTY
INSTEAD OF
REAL ONE



DIDN'T GO OUT FOR PARTY WITH
FRIENDS



STAYED HOME &
FOLLOWED SOCIAL
DISTANCING



WORKED FROM
HOME





COVID-19 Crisis



Ministry of AYUSH recommendations, based on Ayurvedic literature and scientific publications, for preventive health measures and boosting immunity with special reference to respiratory health.

Measures for Enhancing Immunity

- ④ Drink warm water throughout the day.
- ④ Daily practice of Yogasana, Pranayama and Meditation for at least 30 minutes.
- ④ Spices like Haldi (Turmeric), Jeera (Cumin), Dhaniya (Coriander) and Lahsun (Garlic) recommended in cooking.

Simple Ayurvedic Procedures

- ④ **Nasal Application**— Apply Sesame Oil/Coconut oil or Ghee in both the nostrils (Pratimash Nasya) in morning and evening.
- ④ **Oil Pulling Therapy**— Take 1 table spoon Sesame or Coconut Oil in mouth. Do not drink, swish in the mouth for 2 to 3 minutes and spit it off followed by warm water rinse. This can be done once or twice a day.

Immunity Boosting Measures for Self-Care

Ayurvedic Immunity Enhancing Tips

- ④ Take Chyavanprash 10gm (1tsf) in the morning. Diabetics should take sugar free Chyavanprash.
- ④ Drink Herbal Tea/Decoction (Kadha) made from Tulsi (Basil), Dalchini (Cinnamon), Kalimirch (Black Pepper), Shunthi (Dry Ginger) and Munakka (Raisin) - once or twice a day. Add jaggery (Natural Sugar) and/or fresh Lemon Juice to your taste, if needed.
- ④ Golden Milk- half tea spoon Haldi (Turmeric) powder in 150 ml Hot Milk - once or twice a day.

Actions During Dry Cough/Sore Throat

- ④ Steam inhalation with fresh Pudina (Mint) leaves or Ajwain (Caraway Seeds) can be practiced once in a day.
- ④ Lavang (Clove) powder mixed with Natural Sugar/Honey can be taken 2-3 times a day in case of cough or throat irritation.
- ④ These measures generally treat normal dry cough and sore throat. However, it is best to consult doctors if these symptoms persist.