WHO COVID-19 Case Management Webinar Series

*Insights to therapeutic guidance development and review of current recommendations*

Clinical management COVID-19 response
WHO Health Emergencies Programme
11 May 2021, 1330-1530 hours CET
<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Duration</th>
<th>Speaker/Details</th>
</tr>
</thead>
</table>
| 1355 | Pharmacology: understanding mechanistic plausibility                  | 5 min    | Andrew Owens  
  *Professor in the Department of Pharmacology and Therapeutics, University of Liverpool, United Kingdom* |
| 1400 | Clinical chair – ensuring balanced consensus reflecting global perspective | 5 min    | Srinivas Murthy  
  *Paediatric Infectious Diseases and Critical Care Physician, Associate Professor University of British Columbia, Canada* |
| 1405 | Introduction to Prospective Meta-Analysis                             | 5 min    | Jonathan Sterne  
  *Professor of Medical Statistics and Epidemiology, Bristol Medical School (PHS), United Kingdom* |
| 1410 | Publication, dissemination and implementation of WHO recommendations   | 5 min    | Lisa Askie  
  *Methods Scientist, WHO, Switzerland* |
# Agenda (Part 2)

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Duration</th>
<th>Presenter</th>
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</thead>
</table>
| 1420 | Systemic Corticosteroids | 5 min | Sebastian Ugarte  
*Intensivist, Specialist in Critical care, ICU Director, INDISA Clinic Universidad Andres Bello, Chile*
| 1425 | Remdesivir | 5 min | Manu Shankar Hari  
*Professor in Critical Care Medicine and NIHR Clinician Scientist, Kings College London, United Kingdom*
| 1430 | Lopinavir | 5 min | Duncan Chanda  
*Director of Adult Infectious Diseases Centre, University Teaching Hospital, Zambia*
| 1435 | Hydroxychloroquine treatment and prophylaxis | 10 min | Heike Geduld  
*Associate Professor and Head of the Division of Emergency Medicine at Stellenbosch University, South Africa*
| 1445 | Ivermectin | 5 min | Leticia Kawano-Dourado  
*Respiratory Medicine Physician and Clinical Researcher at the Research Institute Hospital do Caracca, Brazil*
| 1450 | Future drugs being considered | 5 min | Nerina Harley  
*Associate Professor, Director of Epworth’s Intensive Care Council, Freemasons Intensive Care Unit, Geelong Intensive Care Unit, Australia*
| 1455 | Q&A | 30 min | Presenters and Panel |
| 1525 | Wrap Up | 5 min | Janet Diaz  
*Case Management Lead, Health Care Readiness, WHR, Program, WHO, Switzerland*
## Panel Members

<table>
<thead>
<tr>
<th>Name</th>
<th>Position and Affiliation</th>
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<tbody>
<tr>
<td>Francois Lamontagne</td>
<td>Critical Care Specialist and Clinical Scientist, University de Sherbrooke, Canada</td>
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<tr>
<td>Erlna Burhan</td>
<td>Pulmonologist, Head of Infection Division Department of Pulmonology and Respiratory Medicine, University of Indonesia</td>
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<tr>
<td>Vu Quoc Dat</td>
<td>Vice Head, Intensivist at the National Hospital for Tropical Diseases &amp; Harm Reduction, Lecturer Department of Infectious Diseases, Hanal Medical University, Viet Nam</td>
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<tr>
<td>Yee Iee Kim</td>
<td>Paediatric Infectious Diseases Specialist and Professor of Department of Paediatrics, Sungkyunkwan University School of Medicine, Samsung Medical Centre, Republic of Korea</td>
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<tr>
<td>Saniya Sabzvari</td>
<td>Associate Professor in the Department of Family Medicine, Aga Khan University, Pakistan</td>
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<tr>
<td>Rohit Sarin</td>
<td>Principal Consultant National Institute of TB and Respiratory Diseases, Technical Advisor for the National TB Elimination Program Government of India</td>
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<tr>
<td>Yingzong Shen</td>
<td>Chief Physician, Associate Professor of Shanghai Public Health Clinical Centre, Fudan University, China</td>
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<tr>
<td>Joao Paulo Souza</td>
<td>Professor of Public Health, Ribeirao Preto Medical School, University of Sao Paulo, Brazil</td>
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<tr>
<td>Shalini Sri Ranganathan</td>
<td>Specialist in Pharmacology and Paediatrics, University of Colombo, Sri Lanka</td>
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<tr>
<td>Sridhar Ram Venkatapu</td>
<td>Global Health Ethicist, Associate Professor and Director of Global Health Education and Training, Kings College London, United Kingdom</td>
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<tr>
<td>Per Olav Vardal</td>
<td>Professor at the Institute of Health and Society, University of Oslo, Senior researcher at the Norwegian Institute of Public Health, Oslo, Norway</td>
</tr>
<tr>
<td>Gordon Guyatt</td>
<td>Professor in the Department of Clinical Epidemiology and Biostatistics, McMaster University, Canada</td>
</tr>
<tr>
<td>Akthem Freyati</td>
<td>Chief, Medicines and Nutrition Centre, Supply Division, UNICEF</td>
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<tr>
<td>Lorenzo Moja</td>
<td>Scientist, WHO, Switzerland</td>
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Janet Diaz
Case Management Lead, Health Care Readiness, WHE Program, WHO, Switzerland
Why making guidelines during a pandemic is so challenging?

Current practices to treat COVID-19 continue to be variable, reflecting continued uncertainty; despite growing levels of evidence.

Numerous randomized clinical trials are ongoing, some are robust, large platform trials, and others smaller randomized clinical trials; all of them generating evidence at rapid speed.

Communication of this evidence varies, with read-outs on a daily basis through various mechanisms such as press-releases, pre-prints, and of course, peer-review publication.

WHO has put into place mechanisms to capture data live and then write guidelines...
Rapid transformation of evidence to recommendation

Trigger: likelihood to change practice, sufficient RCT data to inform high quality evidence synthesis (> 2000 patients, > 50 events), relevant to global audience

Evidence generation
- RCTs
- Patient important outcomes
- Geographical implementation

Evidence synthesis
- Systematic review
- Living network meta-analysis
- Prospective meta-analysis
- GRADE the evidence

Draft recommendations
- WHO steering committee
- Guideline Development Group
- Values & preferences
- Certainty of evidence
- Pre-specified subgroups

Dissemination
- Webinars
- Publication platforms
- Educational platforms
- Operational tools for use

World Health Organization
Innovation in evidence monitoring and synthesis

Living systematic reviews: COVID-NMA (WHO, Cochrane), LNMA (BMJ-McMaster), WHO REACT PMA (WHO-trialists)

https://covid-nma.com/living_data/index.php
Pre-specified Values and Preferences

- Mortality would be the outcome most important to patients, followed by need and duration of mechanical ventilation, time to clinical improvement, and serious intervention-related adverse events.

- Most patients would be reluctant to use a medication for which the evidence left high uncertainty regarding effects on the outcomes listed above. 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.

The GDG acknowledged, however, that values and preferences are likely to vary. There will be patients inclined to use a treatment in which evidence has not excluded important benefit, particularly when the underlying condition is potentially fatal.

On the other hand, there will be those who have a high threshold of likely benefit before they will choose the intervention.
GDG, independent panel draft the recommendations

**WHO steering committee:** members from various departments within WHO, and all WHO regions

**Clinical and Methods Chairs**

**Methods support:** experts in methodology, experience in interpretation of evidence, development of recommendations

**Panel members:** > 40 experts, regional representation, gender balance, different areas of specialty, ethics/equity expert, patient partners.

**Expert advisors:** pharmacologists, as needed.
Innovative publication platforms: WHO, MAGICapp, BMJ
Overview

This document is the update of an interim guidance originally published under the title "Clinical management of COVID-19: interim guidance, 27 May 2020".

Providing trustworthy guidance that is comprehensive and holistic for the optimal care of COVID-19 patients, throughout their entire illness is necessary. The previous version of the Clinical management of COVID-19 provided recommendations that can be applied when caring for patients during the COVID-19 care pathway. This guideline now also includes Best Practice Statement on caring for COVID-19 patients after their acute illness and 5 new recommendations:

- A conditional recommendation to use clinical judgment, including consideration of patients’ values and preferences and local and national policy if available, to guide management decisions including admission to hospital and to the intensive care unit (ICU), rather than currently available prediction models for prognosis (very low certainty).
- A conditional recommendation for use of pulse oximetry monitoring at home as part of a package of care, including patient and provider education and appropriate follow-up in symptomatic patients with COVID-19 and risk factors for progression to severe disease who are not hospitalized (very low certainty).
- A conditional recommendation for the use of awake prone positioning in patients with severe COVID-19 that are hospitalized requiring supplemental oxygen or non-invasive ventilation (low certainty).
- A conditional recommendation to use thromboprophylaxis dosing of anticoagulation rather than intermediate or therapeutic dosing in patients hospitalized with COVID-19, without an established indication for higher dose of anticoagulation (very low certainty).
- A conditional recommendation for the use of existing care bundles (defined as three or more evidence-informed practices delivered together and consistently to improve care) chosen locally by hospital or ICU and adapted as necessary for local circumstances in patients with critical COVID-19 (very low certainty).
Innovative publication platform: WHO Academy App and MAGICapp

WHO Academy: Covid-19 Learning on the App Store (apple.com)
World Health Organization (WHO) Academy – Apps on Google Play
https://openwho.org/channels/clinical-management
Final comments

• Evidence to recommendations requires massive collaboration at all phases of the process to be efficient, fast, and trustworthy (4-6 weeks).

• Implementation of guidelines into clinical practice is an area to improve and monitor over time.

• COVID-19 Clinical Care Package needs to be holistic and multidisciplinary and needs Trained Staff, Safe Structures, Sufficient Supplies and Systems to do the basics well!
Introduction to GRADE Framework

Bram Rochwerger
Associate Professor, McMaster University,
Hamilton, ON, Canada
CLINICAL PRACTICE GUIDELINES WE CAN TRUST
Tenets of Trustworthy Guidelines

- COI management policy
- Representative panel composition
- A priori question/outcome prioritization
- Systematic review of the literature
- Explicit rating of the quality/certainty of the literature
- Consideration of all relevant factors in generating recommendations
- Clear articulation of recommendations with clinical implications
- Transparent process
Patients

Intervention

Comparison

Outcomes
# Rating Outcome

## Inpatient

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

## Outpatient

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>Admission to hospital</td>
<td>8.5</td>
<td>0.7</td>
<td>7-9</td>
</tr>
<tr>
<td>Death</td>
<td>8.1</td>
<td>1.9</td>
<td>3-9</td>
</tr>
<tr>
<td>Quality of life</td>
<td>7.5</td>
<td>1.3</td>
<td>5-9</td>
</tr>
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<td>Serious adverse effects (e.g. adverse events leading to drug discontinuation)</td>
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<td>1.7</td>
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<tr>
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<td>6.6</td>
<td>0.9</td>
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<td>1-9</td>
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<tr>
<td>Duration of invasive mechanical ventilation</td>
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<td>2.1</td>
<td>1-8</td>
</tr>
</tbody>
</table>
**Certainty of evidence**

*(quality of the evidence, confidence in estimates)*

**Table: GRADE’s approach to rating quality of evidence (aka confidence in effect estimates)**

For each outcome based on a systematic review and across outcomes (lowest quality across the outcomes critical for decision making)

<table>
<thead>
<tr>
<th>Study design</th>
<th>Initial confidence in an estimate of effect</th>
<th>Reasons for considering lowering or raising confidence</th>
<th>Confidence in an estimate of effect across those considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized trials ➔</td>
<td>High confidence</td>
<td>↓ Lower if</td>
<td>High</td>
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<tr>
<td></td>
<td></td>
<td>↑ Higher if*</td>
<td>Moderate</td>
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<tr>
<td>Observational studies ➔</td>
<td>Low confidence</td>
<td></td>
<td>Low</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Very low</td>
</tr>
</tbody>
</table>

*upgrading criteria are usually applicable to observational studies only.*
Moving from Evidence to Recommendation

- QoE
- Cost
- V & P
- Risk and Benefit
- Feasibility
- Equity

RECOMMENDATION
Strength of recommendations - Benefits clearly outweigh risks/hassle/cost, OR - Risk/hassle/cost clearly outweighs benefit

What makes a strong recommendation?
- Close balance between up and downsides (benefits/harms)
- Values and preferences
- Costs, practical limitations
- Low certainty evidence

What can downgrade strength to a weak recommendation?

Four options for recommendations

Strong in favour → Almost all informed patients would choose to have the intervention

Weak in favour → A majority of informed patients would choose to have the intervention but many would not

Weak against → A majority of informed patients would choose not to have the intervention but many would

Strong against → Almost all informed patients would choose not to have the intervention
COVID-19 living network meta-analysis

Reed Siemieniuk
Physician, Methodologist
Mc Master University, Hamilton, Ontario, Canada

www.covid19lnma.com
11 May 2021
COVID-19 Living Systematic Review & Network Meta-Analysis (NMA)

Drug therapies: 284 RCTs
Antiviral antibodies and cellular therapies: 33 RCTs
Prophylaxis: 13 RCTs
Living systematic review & network meta-analysis (NMA)

**Systematic reviews** identify, select, critically appraise, and analyze primary research addressing a particular research question.

A living systematic review is updated based on a predefined schedule or when new evidence emerges.
Living network meta-analysis (NMA)

**Meta-analysis** is a statistical analysis that combines the results of multiple studies to provide more precise estimates and quantify inconsistency across studies.

**Network meta-analysis** accounts for data from both direct and indirect comparisons.
Search and Screening

- Preprint, in press, and published reports of RCTs
- Randomize patients with suspected, probable, or confirmed COVID-19 to drug treatments, antiviral antibodies and cellular therapies, placebo, or standard care; OR
- Randomize healthy participants exposed or unexposed to COVID-19 to prophylactic drugs, standard care, or placebo.
Data Collection and Risk of Bias Assessments

**Trial characteristics**
- Country
- Trial status
- Design
- Funding
- Country
- Interventions investigated
  - Dose
  - Duration

**Participant characteristics**
- Age
- Sex
- Smoking
- Respiratory/cardiovascular conditions
- Baseline medications
- Confirmed or suspected COVID-19
- COVID-19 severity
- Care intensity (i.e., outpatient, inpatient, ICU)
- Lab findings (i.e., inflammatory markers)

**Outcomes**

**Therapy trials**
- Mortality
- Mechanical ventilation
- Admission to hospital
- Hospital length of stay
- ICU length of stay
- Time to symptom resolution/clinical improvement
- Adverse events

**Prophylaxis trials**
- Mortality
- COVID-19 infection
- Admission to hospital
- Time to symptom resolution
Data Collection and Risk of Bias Assessments

Data collection and study appraisal team

Modified RoB 2.0 tool

Randomization/confounding

Performance bias

Bias due to missing data

Detection bias

Reporting bias
Drug treatments

Prophylaxis

Antiviral antibodies

Coming soon!

bmj.com/content/370/bmj.m2980
bmj.com/content/373/bmj.n949

www.covid19lnma.com
reed.siemiieniuk@medportal.ca
Prioritizing interventions for guidelines

Reed Siemieniuk
Physician, Methodologist
Mc Master University, Hamilton, Ontario, Canada
Drug treatments

- 330 unique randomized trials
- Up to 20 new RCTs published each
- >100 unique interventions
"The latest research shows that we really should do something with all this research."
Evidence to Decision Framework

- A process for making complex decisions
- Ensures that decision makers consider all relevant considerations
- Transparent

GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction

Pablo Alonso-Coello,1,2 Holger J Schünemann,2,3 Jenny Moberg,4 Romina Brignardello-Petersen,2,5 Elie A Akl,2,6 Marina Davoli,7 Shaun Treweek,8 Reem A Mustafa,9 Gabriel Rada,10,11,12 Sarah Rosenbaum,4 Angela Morelli,4 Gordon H Guyatt,2,3 Andrew D Oxman4 the GRADE Working Group
<table>
<thead>
<tr>
<th></th>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Drug 3</th>
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<tbody>
<tr>
<td><strong>Signal on Benefit</strong></td>
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<tr>
<td><strong>Certainty regarding Benefit</strong></td>
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<tr>
<td><strong>Signal on Harm</strong></td>
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<td><strong>Certainty regarding Harm</strong></td>
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<td><strong>Values &amp; Preferences</strong></td>
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<tr>
<td><strong>Resource consideration</strong></td>
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<td><strong>Feasability, practical considerations</strong></td>
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<td><strong>Acceptability</strong></td>
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<td><strong>Equity</strong></td>
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<tr>
<td><strong>Current practice &amp; variability (Implement vs De-implement?)</strong></td>
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<td><strong>Special considerations</strong></td>
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<tr>
<td>e.g. subgroup hypotheses, co-management, timing of administration, etc.</td>
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<tr>
<td><strong>N trials / N pre-prints</strong></td>
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<td><strong>Upcoming large trials</strong></td>
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<tr>
<td><strong>Date of assessment</strong></td>
<td>Date...</td>
<td>Date...</td>
<td>Date...</td>
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</table>
Pharmacology: Approach to assessing Mechanistic Plausibility

Andrew Owens
Professor Pharmacology & Therapeutics
University of Liverpool, UK
Approach to assessing mechanistic plausibility

- Are there empirical data to directly support the mechanism of action?
- Have the data been generated in model systems for SARS-CoV-2 / COVID-19 or does interpretation require extrapolation from another indication?
- If data are generated specifically for SARS-CoV-2 / COVID-19, what is the quality / strength of the data?
  - In silico molecular docking.
  - In vitro antiviral activity in a cell line or in vitro data supporting an immunological / anti-inflammatory mechanism in response to virus or viral proteins.
  - In vivo data demonstrating antiviral activity and/or reversal of disease pathology / symptomology in SARS-CoV-2 infected animals.
- If only in vitro evidence exit, is there reasonable confidence that the proposed mechanism plays a meaningful role during SARS-CoV-2 infection.
- Are the in vitro or in vivo target concentrations expected to be achieved at doses being investigated for SARS-CoV-2 infection / COVID-19.

While robust data in support of the mechanism of action improves confidence in an intervention, neither preclinical data nor the absence of it can in its own right be used to rule in or rule out candidates. However, interventions should only be clinically evaluated where a robust and plausible preclinical case can be made.
New comedication: Alendronic acid, Alfuzosin, Cabotegravir (oral), Cabotegravir/Rilpivirine (long acting), Cefepime, Fostemsavir, Potassium, Pramipexole, Pyridostigmine.
Role of Clinical Chair—ensuring balanced consensus reflecting global perspective

Srinivas Murthy
Paediatric Infectious Diseases and Critical Care Physician, Associate Professor University of British Columbia, Canada
“WHO’s legitimacy and technical authority lie in its rigorous adherence to the systematic use of evidence as the basis for all policies”
Introduction to Prospective Meta Analysis

Jonathan Sterne
Professor of Medical Statistics and Epidemiology, Bristol Medical School (PHS), United Kingdom
Some problems with most meta-analyses

• Come too late
• Compromised by missing information
• Affected by reporting biases

• A prospective approach to meta-analysis aims to overcome these problems
Some problems with most meta-analyses

- Come too late
- Compromised by missing information
- Affected by reporting biases

RCT

Start

Publish

End/Result
Some problems with most meta-analyses

- Come too late
- Compromised by missing information
- Affected by reporting biases
Some problems with most meta-analyses

- Come too late
- Compromised by missing information
- Affected by reporting biases
Selecting registered trials helps
Selecting registered trials helps

Meta-analysis

Communicating with trialists helps
Prospective, collaborative meta-analysis

Identify trials before results

- Unbiased
- Rapid
- Complete

Collaborate with trialists
A guide to prospective meta-analysis

Anna Lene Seidler,1 Kylie E Hunter,1 Saskia Cheyne,1 Davina Gherzi,1,2 Jesse A Berlin,3 Lisa Askie1

In a prospective meta-analysis (PMA), study selection criteria, hypotheses, and analyses are specified before the results of the studies related to the PMA research question are known, thus reducing many of the problems associated with a traditional (retrospective) meta-analysis. PMAs have many advantages: they can help reduce research waste and bias, and they are adaptive, efficient, and collaborative. Despite an increase in

Chapter 22: Prospective approaches to accumulating evidence

James Thomas, Lisa M Askie, Jesse A Berlin, Julian H Elliott, Davina Gherzi, Mark Simmonds, Yemisi Takwoingi, Jayne F Tierney, Julian PT Higgins

Key Points:

- Cochrane Reviews should reflect the state of current knowledge, but maintaining their currency is a challenge due to resource limitations. It is difficult to know when a given review might become out of date, but tools are available to assist in identifying when a review might need updating.
- Living systematic reviews are systematic reviews that are continually updated, with new evidence being incorporated as soon as it becomes available. They are useful in rapidly evolving fields where research is published frequently. New technologies and better processes for data storage and reuse are being developed to facilitate the rapid identification and synthesis of new evidence.
- A prospective meta-analysis is a meta-analysis of studies (usually randomized trials) that were identified or even collectively planned to be eligible for the meta-analysis before the results of the
Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19
A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

**IMPORTANCE**  Effective therapies for patients with coronavirus disease 2019 (COVID-19) are needed, and clinical trial data have demonstrated that low-dose dexamethasone reduced mortality in hospitalized patients with COVID-19 who required respiratory support.

**OBJECTIVE**  To estimate the association between administration of corticosteroids compared with usual care or placebo and 28-day all-cause mortality.
Corticosteroids for COVID-19

Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19
A Randomized Clinical Trial

Pierre-François D, Julio Badía, MD, I
Vourenn Josan, M
Céline Lengelle, F
Djilali Annane, M

Effect of Dexamethasone on Days Alive a Moderate or Severe Acute Respiratory Disease
The CoDEX Randomized Clinical Trial

Bruno M. Tomassini, MD; Israel S. Maia, MD, MSc; Alexandre B. Cavalcanti, MD, PhD; Viviane C. Veiga, MD, PhD; Alvaro Avezedo, MD, PhD; Renato D. Lopes, MD, PhD; Fábio Eduardo L. V. Costa, MD, PhD; Ricardo A. B. Moura, MD; Michele O. Honorato, MD; Thiago Lisboa, MD, PhD; Leticia Kawano-Dourado, MD, PhD; Fernando G. Zampieri Cristina P. Amendola, MD; Roberta M. L. Roepke, MD; Daniela H. M. Freitas, MD; Di Caio C. F. Fernandes, MD; Livia M. G. Melo, MD; Gedealves F. S. Junior, MD; Domingos Luciano C. P. Azevedo, MD, PhD, for the COALITION COVID-19 Brazil Investigators

Corticosteroids in COVID-19 ARDS
Evidence and Hope During the Pandemic

Hallie C. Prescott, MD, MSc; Todd W. Rice, MD, MSc

Corticosteroids, such as hydrocortisone and dexamethasone, have anti-inflammatory, anti-fibrotic, and vasoconstrictive effects, which intensivists have been trying to leverage for decades to improve outcomes in patients with acute respiratory distress syndrome (ARDS) and COVID-19. The Surviving Sepsis Campaign guidelines for COVID-19 published in March 2020 issued a weak recommendation to use corticosteroids in patients with COVID-19 and ARDS who required mechanical ventilation, but also indicated...
**Figure 2. Association Between Corticosteroids and 28-Day All-Cause Mortality in Each Trial, Overall, and According to Corticosteroid Drug**

<table>
<thead>
<tr>
<th>Drug and trial</th>
<th>ClinicalTrials.gov identifier</th>
<th>Initial dose and administration</th>
<th>No. of deaths/total No. of patients</th>
<th>Odds ratio (95% CI)</th>
<th>Favors steroids</th>
<th>Favors no steroids</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEXA-COVID 19</td>
<td>NCT04325061</td>
<td>High: 20 mg/d intravenously</td>
<td>2/7 2/12</td>
<td>2.00 (0.21-18.69)</td>
<td></td>
<td></td>
<td>0.92</td>
</tr>
<tr>
<td>CoDEX</td>
<td>NCT04327401</td>
<td>High: 20 mg/d intravenously</td>
<td>69/128 76/128</td>
<td>0.80 (0.49-1.31)</td>
<td></td>
<td></td>
<td>18.69</td>
</tr>
<tr>
<td>RECOVERY</td>
<td>NCT04381936</td>
<td>Low: 6 mg/d orally or intravenously</td>
<td>95/324 283/683</td>
<td>0.59 (0.44-0.78)</td>
<td></td>
<td></td>
<td>57.00</td>
</tr>
<tr>
<td>Subgroup fixed effect</td>
<td></td>
<td></td>
<td></td>
<td>0.64 (0.50-0.82)</td>
<td></td>
<td></td>
<td>76.60</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPE COVID</td>
<td>NCT02517489</td>
<td>Low: 200 mg/d intravenously</td>
<td>11/75 20/73</td>
<td>0.46 (0.20-1.04)</td>
<td></td>
<td></td>
<td>6.80</td>
</tr>
<tr>
<td>COVID STEROID</td>
<td>NCT04348305</td>
<td>Low: 200 mg/d intravenously</td>
<td>6/15 2/14</td>
<td>4.00 (0.65-24.66)</td>
<td></td>
<td></td>
<td>1.39</td>
</tr>
<tr>
<td>REMAP-CAP</td>
<td>NCT02735707</td>
<td>Low: 50 mg every 6 h intravenously</td>
<td>26/105 29/92</td>
<td>0.71 (0.38-1.33)</td>
<td></td>
<td></td>
<td>11.75</td>
</tr>
<tr>
<td>Subgroup fixed effect</td>
<td></td>
<td></td>
<td></td>
<td>0.69 (0.43-1.12)</td>
<td></td>
<td></td>
<td>19.94</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Steroids-SARI</td>
<td>NCT04244591</td>
<td>High: 40 mg every 12 h intravenously</td>
<td>13/24 13/23</td>
<td>0.91 (0.29-2.87)</td>
<td></td>
<td></td>
<td>3.46</td>
</tr>
<tr>
<td>Overall (fixed effect)</td>
<td></td>
<td></td>
<td></td>
<td>0.66 (0.53-0.82)</td>
<td></td>
<td></td>
<td>100.0</td>
</tr>
<tr>
<td>$P = .31$ for heterogeneity; $I^2 = 15.6%$</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Overall (random effects)</td>
<td></td>
<td></td>
<td></td>
<td>0.70 (0.48-1.01)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Overall, IMV ($I^2 = 44\%$)

<table>
<thead>
<tr>
<th>Trial and IMV subgroup</th>
<th>Steroids n/N</th>
<th>No Steroids n/N</th>
<th>Odds ratio (95% CI)</th>
<th>% Weight</th>
<th>Ratio of odds ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPE_COVID (NCT02517489)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No IMV</td>
<td>1/14</td>
<td>3/14</td>
<td>0.28 (0.03, 3.11)</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>IMV</td>
<td>10/61</td>
<td>17/59</td>
<td>0.48 (0.20, 1.17)</td>
<td>6.01</td>
<td>1.72 (0.06, 51.26)</td>
</tr>
<tr>
<td>COVID STEROID (NCT04348305)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No IMV</td>
<td>2/8</td>
<td>2/8</td>
<td>1.00 (0.10, 9.61)</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>IMV</td>
<td>4/7</td>
<td>0/6</td>
<td>16.71 (0.68, 409.09)</td>
<td>0.46</td>
<td>16.71 (0.68, 410.29)</td>
</tr>
<tr>
<td>REMAP-CAP (NCT02735707)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No IMV</td>
<td>8/37</td>
<td>19/43</td>
<td>0.35 (0.13, 0.94)</td>
<td>4.79</td>
<td></td>
</tr>
<tr>
<td>IMV</td>
<td>18/68</td>
<td>10/49</td>
<td>1.40 (0.58, 3.38)</td>
<td>6.04</td>
<td>4.03 (1.00, 16.28)</td>
</tr>
<tr>
<td>Steroids-SARI (NCT04244591)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No IMV</td>
<td>3/11</td>
<td>4/9</td>
<td>0.47 (0.07, 3.04)</td>
<td>1.34</td>
<td></td>
</tr>
<tr>
<td>IMV</td>
<td>10/13</td>
<td>9/14</td>
<td>1.85 (0.34, 10.05)</td>
<td>1.63</td>
<td>3.95 (0.28, 55.46)</td>
</tr>
</tbody>
</table>

Favours greater benefit of steroids with IMV

Favours greater benefit of steroids with no IMV

p = 0.0084

4.34 (1.46, 12.91)

3.95 (0.28, 55.46)

4.03 (1.00, 16.28)

16.71 (0.68, 410.29)

1.72 (0.06, 51.26)

1.40 (0.58, 3.38)

0.46

3.95 (0.28, 55.46)

0.80 (0.49, 1.31)
<table>
<thead>
<tr>
<th>Trial and vasoactive medication subgroup</th>
<th>Treatment ( n/N )</th>
<th>Control ( n/N )</th>
<th>Odds ratio (95% CI)</th>
<th>% Weight</th>
<th>Ratio of odds ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEXA-COVID19 (NCT04325061)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not on vasoactive medication</td>
<td>1/4</td>
<td>1/5</td>
<td>1.33 (0.06, 31.12)</td>
<td>1.14</td>
<td></td>
</tr>
<tr>
<td>On vasoactive medication</td>
<td>1/3</td>
<td>1/7</td>
<td>3.00 (0.12, 73.64)</td>
<td>1.11</td>
<td></td>
</tr>
<tr>
<td>CoDEX (NCT04327401)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not on vasoactive medication</td>
<td>16/44</td>
<td>22/40</td>
<td>0.47 (0.19, 1.12)</td>
<td>14.84</td>
<td></td>
</tr>
<tr>
<td>On vasoactive medication</td>
<td>53/83</td>
<td>54/88</td>
<td>1.11 (0.60, 2.07)</td>
<td>29.53</td>
<td></td>
</tr>
<tr>
<td>CAPE_COVID (NCT02517489)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not on vasoactive medication</td>
<td>9/57</td>
<td>18/60</td>
<td>0.44 (0.18, 1.08)</td>
<td>13.99</td>
<td></td>
</tr>
<tr>
<td>On vasoactive medication</td>
<td>2/18</td>
<td>2/13</td>
<td>0.69 (0.08, 5.64)</td>
<td>2.56</td>
<td></td>
</tr>
<tr>
<td>COVID STEROID (NCT04348305)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not on vasoactive medication</td>
<td>4/10</td>
<td>1/9</td>
<td>5.33 (0.47, 60.80)</td>
<td>1.92</td>
<td></td>
</tr>
<tr>
<td>On vasoactive medication</td>
<td>2/5</td>
<td>1/5</td>
<td>2.67 (0.16, 45.14)</td>
<td>1.42</td>
<td></td>
</tr>
<tr>
<td>REMAP-CAP (NCT02735707)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not on vasoactive medication</td>
<td>12/59</td>
<td>22/65</td>
<td>0.50 (0.22, 1.13)</td>
<td>17.06</td>
<td></td>
</tr>
<tr>
<td>On vasoactive medication</td>
<td>14/46</td>
<td>7/27</td>
<td>1.25 (0.43, 3.63)</td>
<td>10.00</td>
<td></td>
</tr>
<tr>
<td>Steroids-SARI (NCT04244591)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not on vasoactive medication</td>
<td>9/10</td>
<td>4/5</td>
<td>2.25 (0.11, 45.72)</td>
<td>1.25</td>
<td></td>
</tr>
<tr>
<td>On vasoactive medication</td>
<td>4/14</td>
<td>9/18</td>
<td>0.40 (0.09, 1.76)</td>
<td>5.17</td>
<td></td>
</tr>
<tr>
<td>Overall (not on vasoactive medication ) ( (I^2 = 0.0%) )</td>
<td>184</td>
<td>184</td>
<td>0.55 (0.34, 0.88)</td>
<td>50.21</td>
<td></td>
</tr>
<tr>
<td>Overall (on vasoactive medication)</td>
<td>169</td>
<td>158</td>
<td>1.05 (0.65, 1.69)</td>
<td>49.79</td>
<td></td>
</tr>
</tbody>
</table>

Favours steroids | Favours no steroids | Favours greater benefit of steroids with vasoactive medication | Favours greater benefit of steroids with no vasoactive medication

\( p=0.001 \)
Publication, Dissemination and Implementation of WHO recommendations

Lisa Askie
Scientist,
Methods Lead,
Quality Norms & Standards, WHO
Living guidelines: trustworthy and up-to-date

Conventional guidelines are **updated every 3-5 years**

- 'Living' guidelines are **updated every week / month / ?** and/or **triggered by rules or algorithms** that determine when emerging evidence would **change a recommendation**

**REMDENVIR GUIDELINE**

<table>
<thead>
<tr>
<th>Date of publication</th>
<th>Development of chronic pain in children</th>
<th>Planning Closure</th>
<th>Submission: 15-JAN-20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of publication</td>
<td>Planning Closure</td>
<td>Submission: 15-JAN-20</td>
<td>1st Submission of Guideline Text: 4-NOV-20</td>
</tr>
<tr>
<td>Date of publication</td>
<td>Planning Closure</td>
<td>Submission: 15-JAN-20</td>
<td>GRC Decision: 18-NOV-20</td>
</tr>
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<td>1st Submission of Guideline Text: 4-NOV-20</td>
</tr>
</tbody>
</table>

- **404 days** (13.5 mo)

- **Living Evidence**: Continuously updated guidelines
- **Current Model**: Intermittently updated guidelines

- **Change in policy**?
- **New product in market**?
- **Currency / reliability**

- **Implements agility and responsiveness** of WHO guidance by **shortening time from availability of relevant evidence to use at country level**
Platforms with digitally structured data
for production of living evidence and guidance + publication, dissemination, adaptation, in-country utilization

Using MAGICapp

to create, publish, update, share and re-use evidence and guidance from WHO

Individual recommendations, for individual intv updated as data become available
1. WHO website pdf + links
   https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.1

2. MAGICapp online platform
   https://app.magicapp.org/#/guideline/nBkO1E

3. BMJ journal publication
   https://www.bmj.com/content/370/bmj.m3379
Bringing evidence to the bedside: Transforming WHO COVID-19 Living guidelines to training modules for health workers

Training modules available for the following therapeutics on WHO Academy mobile app

- Corticosteroids
- Remdesivir
- Lopinavir
- Hydroxychloroquine
- Ivermectin

(Case management → Learning Centre → W) Therapeutics for COVID-19)

Full course development underway with additional modules on WHO guideline process, to be posted on OpenWHO.org Clinical Channel in coming weeks

Additional courses for frontline clinicians already available: https://openwho.org/channels/clinical-management
Drug Specific Recommendations (Part 2)
Systemic corticosteroids
(published 2 September 2020)

Sebastián Ugarte MD
Intensivist, Specialist in Critical care, ICU Director,
Andrés Bello University - INDISA
Santiago, Chile
Corticosteroids in COVID-19: summary of recommendations

In September 2020, the following recommendations regarding systemic corticosteroids for patients with COVID-19 were released by WHO:

- **Strong recommendation:** We recommend systemic corticosteroids rather than no corticosteroids for the treatment of patients with severe and critical COVID-19.

- **Conditional recommendation:** We suggest not to use corticosteroids in the treatment of patients with non-severe COVID-19.
Corticosteroids in COVID-19: guideline development process

- In July 2020, WHO partnered with principal investigators of 7 corticosteroid trials and formed the Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group to conduct a prospective meta-analysis (PMA) of randomized trials for corticosteroid therapy for COVID-19.³

- WHO also partnered with the MAGIC Evidence Ecosystem Foundation for methodologic support with the goal to develop and disseminate living guidance for COVID-19 drug treatments, including corticosteroid therapy.

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19
A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group
The RECOVERY trial

- The RECOVERY trial demonstrated a lower 28-day mortality in patients who received corticosteroids and were either receiving oxygen alone or receiving invasive mechanical ventilation, compared to usual care.
  - Largest of the 7 trials: enrolled 6425 hospitalized patients
  - At time of randomization, 60% receiving oxygen only (with or without non-invasive ventilation), 16% receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 24% receiving neither
  - Approximately ⅓ randomized to dexamethasone and ⅔ randomized to usual care
    - Dexamethasone 6mg was given daily for up to ten days
## Corticosteroids for severe/critical disease

11 randomized trials
5950 participants

<table>
<thead>
<tr>
<th>Condition</th>
<th>Events per 1000 people</th>
<th>Evidence quality</th>
</tr>
</thead>
</table>
| Mortality with critical illness| 415  
87 fewer  
328 | ★★★★ Moderate  More ✔ |
| Mortality with severe illness  | 334  
67 fewer  
267 | ★★★★ Moderate  More ✔ |
| Gastrointestinal bleeding      | 48  
No important difference  
51 | ★★★ Low  More ✔ |
| Superinfections                | 186  
No important difference  
188 | ★★★ Low  More ✔ |
| Hyperglycaemia                 | 286  
46 fewer  
332 | ★★★★ Moderate  More ✔ |
| Neuromuscular weakness         | 69  
No important difference  
75 | ★★★ Low  More ✔ |
| Neuropsychiatric effects       | 35  
No important difference  
28 | ★★★ Low  More ✔ |
Special Considerations

- In contrast to other candidate treatments for COVID-19 that, systemic corticosteroids are low cost, easy to administer, and readily available globally.

- Dexamethasone and prednisolone are among the most commonly listed medicines in national essential medicines lists; listed by 95% of countries.

- 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.

- 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.
Resource implications, feasibility, equity and human rights from Latin American perspective

- Individual patient perspective, but also placed a high value on resource allocation.

- Attention is paid to the opportunity cost associated with the widespread provision of therapies for COVID-19
Corticosteroids in COVID-19: clinical use

- Various formulations exist. There are no clear differences in efficacy or adverse effects among different preparations.
- May be given intravenously or orally.
- A duration of 7-10 days may be used.
- Glucose should be monitored in all patients receiving steroids, regardless of prior history of diabetes.

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>6 mg every 24 hours</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>160 mg every 24 hours (as 50 mg every 8 hours or as 100 mg every 12 hours)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>40 mg every 24 hours</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>32 mg every 24 hours (as 8 mg every 6 hours or 16 mg every 12 hours)</td>
</tr>
</tbody>
</table>
Subgroup analysis

Visual summary of recommendation

Population
This recommendation applies only to people with these characteristics:

- Patients with confirmed covid-19

Disease severity
- Non-severe: Absence of signs of severe or critical disease
- Severe: SpO₂<90% on room air, Respiratory rate >30 in adults, Raised respiratory rate in children, Signs of severe respiratory distress
- Critical: Requires life sustaining treatment, Acute respiratory distress syndrome, Sepsis, Septic shock

Corticosteroids
- Recommendation against (weak)
- Recommendation in favour (strong)

A living WHO guideline on drugs for covid-19. BMJ 2020;370:m3379. https://doi.org/10.1136/bmj.m3379
**Recommendation 2**

**Usual supportive care**
- **Strong**

**Corticosteroids**
- **Weak**
  - **Strong**

Patients with non-severe covid-19

"We suggest no corticosteroids"

**Evidence profile**

- Favourites usual supportive care
- No important difference
- Favourites corticosteroids

**Events per 1000 people**
- Mortality with non-severe illness:
  - Usual supportive care: 17/6
  - Corticosteroids: 39 fewer

**Evidence quality**
- Low

**Individual considerations**

**Key practical issues**

**Usual supportive care**
- No additional practical issues

**Corticosteroids**
- In order to help guarantee access to therapy for severe and critical covid-19 patients, it is reasonable to avoid administering corticosteroids to patients who are less likely to derive benefit.

**Values and preferences**

The panel inferred that most fully informed individuals with non-severe illness would not want to receive corticosteroids, but many could want to consider this intervention through shared decision-making with their treating physician. When treating patients with non-severe disease, even after 7 days of symptoms, the panel concluded that it was preferable to err on the side of no corticosteroids.

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A living WHO guideline on drugs for covid-19.
BMJ 2020;370:m3379.
https://doi.org/10.1136/bmj.m3379
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Remdesivir
(published 20 November 2020)

Manu Shankar-Hari
NIHR Clinician Scientist

Department of Health disclaimer (NIHR-CS-2016-16-011). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.
In December 2020, the following recommendations regarding remdesivir for patients with COVID-19 were released by WHO:

- **Conditional recommendation:** We suggest against the use of remdesivir in the treatment of hospitalized patients with COVID-19.
### Table 2. Summary of trials and trial characteristics informing the remdesivir recommendation

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Country</th>
<th>Mean age (years)</th>
<th>Severity (as per WHO criteria)</th>
<th>% IMV (at baseline)</th>
<th>Treatments (dose and duration)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biegel (ACTT-1)</td>
<td>1063</td>
<td>United States, Europe, Asia</td>
<td>58.9</td>
<td>Non-severe (11.3%) Severe (88.7%)</td>
<td>44.1%</td>
<td>Remdesivir IV (100 mg/day for 10 days)</td>
<td>-Mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Adverse events</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Time to clinical improvement</td>
</tr>
<tr>
<td>Spinnler</td>
<td>596</td>
<td>United States, Europe, Asia</td>
<td>56-58</td>
<td>Non-severe (100%)</td>
<td>0%</td>
<td>Remdesivir IV (200 mg at day 1, then 100 mg for 4 days or 9 days)</td>
<td>-Mortality</td>
</tr>
<tr>
<td>(SIMPLE MODERATE)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Time to clinical improvement</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>-Duration of hospitalization</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>-Mechanical ventilation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Adverse events</td>
</tr>
<tr>
<td>Pan (SOLIDARITY)</td>
<td>5451</td>
<td>Worldwide</td>
<td>&lt; 50 53% 50-70 47% &gt; 70 18%</td>
<td>Non-severe (2.4%) Severe (6.7%) Critical (9%)</td>
<td>8.9%</td>
<td>Remdesivir IV (200 mg at day 1, then 100 mg day 2-10)</td>
<td>-Mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Mechanical ventilation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang</td>
<td>237</td>
<td>China</td>
<td>65</td>
<td>Severe (100%)</td>
<td>16.1%</td>
<td>Remdesivir IV (100 mg/day for 10 days)</td>
<td>-Mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Adverse events</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>-Viral clearance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Duration of hospitalization</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Duration of ventilation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Time to clinical improvement</td>
</tr>
</tbody>
</table>

**WHO SOLIDARITY Trial on 15 October 2020**
- 11,266 randomized patients
  - 2570 to Remdesivir
  - 954 to Hydroxychloroquine and
  - 1411 to Lopinavir-Ritonavir,
  - 6,331 to usual care)

**Notes:** IMV – invasive mechanical ventilation; IV – intravenous; N – number; NR (not reported); Sx – symptom.
Severity criteria based on WHO definitions unless otherwise stated: * defined severe as SpO2 < 94% on room air OR respiratory rate > 24 breaths /min; † defined severe as requiring oxygen support; ‡ defined severe as SpO2 < 94% on room air
*Only SIMPLE MODERATE was included in the analysis, as SIMPLE SEVERE (14) did not have a placebo/usual care arm.
LNMA Diagram for Remdesivir
Remdesivir

4 randomized trials
7333 participants

<table>
<thead>
<tr>
<th>Event</th>
<th>Events per 1000 people</th>
<th>Evidence quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>106</td>
<td>No important difference</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>105</td>
<td>No important difference</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>15</td>
<td>No important difference</td>
</tr>
<tr>
<td>Viral clearance at 7 days</td>
<td>483</td>
<td>No important difference</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>56</td>
<td>No important difference</td>
</tr>
<tr>
<td>Delirium</td>
<td>16</td>
<td>No important difference</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>Mean days</th>
<th>Evidence quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to clinical improvement</td>
<td>11.0</td>
<td>No important difference</td>
</tr>
<tr>
<td>Hospitalisation duration</td>
<td>12.8</td>
<td>No important difference</td>
</tr>
<tr>
<td>Mechanical ventilation duration</td>
<td>14.7</td>
<td>No important difference</td>
</tr>
</tbody>
</table>
## Special Considerations

### Individual considerations

<table>
<thead>
<tr>
<th>Key practical issues</th>
<th>Remdesivir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Usual supportive care</strong></td>
<td>Administration via intravenous infusion</td>
</tr>
<tr>
<td>No additional practical issues</td>
<td>Optimal timing, duration and dosing remain unclear</td>
</tr>
<tr>
<td></td>
<td>Not a significant inducer or inhibitor of CYP enzymes but should be monitored when co-administered with strong inducers or inhibitors</td>
</tr>
<tr>
<td></td>
<td>May be relatively costly, and there may be limited availability</td>
</tr>
</tbody>
</table>

### Values and preferences

The panel concluded that *most patients would not prefer intravenous treatment with remdesivir given the low certainty evidence.* Any beneficial effects of remdesivir, if they do exist, are likely to be small and the possibility of important harm remains. They 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.
### What is a conditional recommendation

#### Four options for recommendations

<table>
<thead>
<tr>
<th>Option</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong in favour</td>
<td>Almost all informed patients would choose to have the intervention</td>
</tr>
<tr>
<td>Weak in favour</td>
<td>A majority of informed patients would choose to have the intervention but many would not</td>
</tr>
<tr>
<td>Weak against</td>
<td>A majority of informed patients would choose not to have the intervention but many would</td>
</tr>
<tr>
<td>Strong against</td>
<td>Almost all informed patients would choose not to have the intervention</td>
</tr>
</tbody>
</table>
Recommendation as published in Guideline

**RAPID RECOMMENDATIONS**

A living WHO guideline on drugs for covid-19

Bram Rispens, 1,2,3,4 Nanny de Vos, 1,5 Bethany Thammangrungkiet, 1,5 Thomas Armstrong, 1,5,6 Christina Stotz, 1,5,6,7 Yee Lee Tan, 1,5,6,7 Herbert Walther, 1,5,6,7 Natassia Levendag, 1,5,6,7

**ABSTRACT**

**CLINICAL QUESTION**

There are numerous high-quality trials in the treatment of patients with severe COVID-19. These trials have led to several recommendations.

**NEW RECOMMENDATION**

If used, contraindicated in those with liver or renal dysfunction.

**PRACTICAL RECOMMENDATIONS**

1. A strong recommendation against the use of remdesivir in patients with severe COVID-19.

**FOR THIS GUIDELINE WAS CHARGED**

This living guideline is from the WHO Drugs for COVID-19 Initiative. It is available on the WHO Drugs for COVID-19 Initiative website: https://www.who.int/drugs/en/
In December 2020, the following recommendations regarding remdesivir for patients with COVID-19 were released by WHO:

- **Conditional recommendation:** We suggest against the use remdesivir in the treatment of hospitalized patients with COVID-19.
Lopinavir
(published 17 December 2020)

Duncan Chanda
Director of Adult Infectious Diseases Centre,
University Teaching Hospital, Zambia
In December 2020, the following WHO recommendation released:⁴

**Strong 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.
Research trials that included lopinavir/ritonavir

- The WHO SOLIDARITY trial published preprint results 15 October 2020.\(^2\)
  - Results reported for hydroxychloroquine, lopinavir/ritonavir, and remdesivir.
- Release of SOLIDARITY results triggered systematic review and network meta-analysis for hydroxychloroquine, lopinavir/ritonavir, and remdesivir.\(^3\)
  - Lopinavir data from 7 trials with 7,429 participants
### Lopinavir/ritonavir

**7 randomized trials**

**8061 participants**

### Events per 1000 people

<table>
<thead>
<tr>
<th>Condition</th>
<th>Favours usual supportive care</th>
<th>No important difference</th>
<th>Favours lopinavir-ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>106</td>
<td>No important difference</td>
<td>106</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>105</td>
<td>No important difference</td>
<td>120</td>
</tr>
<tr>
<td>Viral clearance at 7 days</td>
<td>483</td>
<td>No important difference</td>
<td>246</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>45</td>
<td>No important difference</td>
<td>25</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td><strong>67</strong></td>
<td>168 fewer</td>
<td>235</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td><strong>17</strong></td>
<td>160 fewer</td>
<td>177</td>
</tr>
</tbody>
</table>

### Mean days

<table>
<thead>
<tr>
<th>Condition</th>
<th>Favours usual supportive care</th>
<th>No important difference</th>
<th>Favours lopinavir-ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to clinical improvement</td>
<td>11.0</td>
<td>No important difference</td>
<td>10.0</td>
</tr>
<tr>
<td>Duration of hospitalisation</td>
<td>12.8</td>
<td>No important difference</td>
<td>12.5</td>
</tr>
</tbody>
</table>
**Recommendation 1**

**Usual supportive care**

- Strong
- Weak

**Lopinavir-ritonavir**

- Weak
- Strong

Patients with covid-19 at any severity

We recommend against administering lopinavir/ritonavir

---

**Evidence profile**

<table>
<thead>
<tr>
<th>Event</th>
<th>Usual Supportive Care</th>
<th>Lopinavir-Ritonavir</th>
<th>Evidence Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>100</td>
<td>109</td>
<td>Moderate</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>No important difference</td>
<td>No important difference</td>
<td>More</td>
</tr>
<tr>
<td>Vital clearance at 7 days</td>
<td>482</td>
<td>249</td>
<td>Very low</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>45</td>
<td>23</td>
<td>Very low</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>67</td>
<td>235</td>
<td>Low</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>17</td>
<td>177</td>
<td>Low</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Usual Supportive Care</th>
<th>Lopinavir-Ritonavir</th>
<th>Evidence Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean days</td>
<td>11.0</td>
<td>10.0</td>
<td>Very low</td>
</tr>
<tr>
<td>Duration of hospitalization</td>
<td>12.0</td>
<td>12.5</td>
<td>Low</td>
</tr>
</tbody>
</table>

See all outcomes MAGIC 56
See patient decision aide MAGIC 56

---

**Individual considerations**

**Key practical issues**

**Usual supportive care**

- No additional practical issues

**Lopinavir-ritonavir**

- Should be used with caution in those with severe hepatic impairment
- Contraindicated in breastfeeding mothers
- Risk of drug-drug interactions with potent CYP3A inhibitors

---

**Values and preferences**

The panel inferred that almost all well informed patients would not want to receive lopinavir/ritonavir given there are probably no positive effects and there was a risk of adverse events. The panel did not expect there would be much variation in values and preferences between patients for this intervention.

---

A living WHO guideline on drugs for covid-19. BMJ 2020;370:m3379. [https://doi.org/10.1136/bmj.m3379](https://doi.org/10.1136/bmj.m3379)
Additional considerations

- In patients who have undiagnosed or untreated HIV, use of lopinavir/ritonavir alone may promote HIV resistance.

- Widespread use of lopinavir/ritonavir for COVID-19 may cause drug shortages for people living with HIV.
Lopinavir/ritonavir in COVID-19: Summary of recommendations

In December 2020, the following WHO recommendation released:⁴

**Strong 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.
Hydroxychloroquine Prophylaxis
(published on 17 December 2020)

Heike Geduld
Associate Professor and Head of the Division of Emergency Medicine at Stellenbosch University, South Africa
In February 2021, the following WHO recommendation was released:

**Strong recommendation against**

We recommend against administering hydroxychloroquine prophylaxis to individuals who do not have COVID-19.

**Remark:** This recommendation applies to individuals with any baseline risk of developing COVID-19 and any hydroxychloroquine dosing regimen.
Research trials that included hydroxychloroquine as potential prophylactic agent

- The resulting systematic review\(^2\) pooled data from six trials, with a total of 6059 participants who did not have COVID-19 and received hydroxychloroquine.\(^3,4,5,6,7,8\)
  - Three of those trials enrolled participants with known exposure to COVID-19.

[Image: Prophylaxis for covid-19: living systematic review and network meta-analysis](https://doi.org/10.1101/2021.02.24.21250469)
Summary of Findings Table (Hydroxychloroquine Prophylaxis)

Clinical question/PICO

Population: Individuals who do not have COVID-19
Intervention: Hydroxychloroquine
Comparator: Standard care

Outcome Timeframe | Study results and measurements | Absolute effect estimates | Certainty of the evidence | Plain text summary
--- | --- | --- | --- | ---
Mortality | Odds Ratio 0.7 (CI 95% 0.24 - 1.99) Based on data from 4649 patients in 4 studies. (Randomized controlled) | 3/1000 | 2/1000 | High | Hydroxychloroquine has a small or no effect on mortality.
Admission to hospital | Odds Ratio 0.87 (CI 95% 0.42 - 1.77) Based on data from 5659 patients in 5 studies. (Randomized controlled) | 5/1000 | 4/1000 | High | Hydroxychloroquine has a small or no effect on hospital admission.

Lab-confirmed COVID-19 diagnosis

Outcomes | Study results and measurements | Absolute effect estimates | Certainty of the evidence | Plain text summary
--- | --- | --- | --- | ---
 | Odds Ratio 2.34 (CI 95% 0.93 - 6.08) Based on data from 3616 patients in 4 studies. | 15/1000 | 34/1000 | Moderate | Hydroxychloroquine probably increases adverse events leading to discontinuation.

Adverse events leading to discontinuation

Outcomes | Study results and measurements | Absolute effect estimates | Certainty of the evidence | Plain text summary
--- | --- | --- | --- | ---
 | Odds Ratio 1.03 (CI 95% 0.71 - 1.47) Based on data from 5294 patients in 6 studies. | 65 per 1000 | 67 per 1000 | Moderate | Hydroxychloroquine probably has a small or no effect on lab-confirmed COVID-19 diagnosis.

World Health Organization
Resources and other considerations

• The GDG raised important negative issues:
  – Although hydroxychloroquine is relatively inexpensive and widely available, including in low income settings, the overall cost of delivering a prophylactic intervention on a large scale may be significant.
  – Additionally, diverting hydroxychloroquine stocks away from patients with other conditions for whom this medication is indicated is concerning.
In February 2021, the following WHO recommendation was released:⁹

**Strong recommendation against**

We recommend against administering hydroxychloroquine prophylaxis to individuals who do not have COVID-19.

**Remark:** This recommendation applies to individuals with any baseline risk of developing COVID-19 and any hydroxychloroquine dosing regimen.
Hydroxychloroquine Treatment
(published on 17 December 2020)

Heike Geduld
Associate Professor and Head of the
Division of Emergency Medicine at Stellenbosch University,
South Africa
Background

Fear, misinformation and disinformation

Politicians espousing medical beliefs “taking HCQ just in case”

Application of unsupervised machine learning to identify and characterise hydroxychloroquine misinformation on Twitter

www.thelancet.com/digital-health Vol 3 February 2021
In December 2020, the following WHO recommendation was released:\textsuperscript{13}

\textbf{Strong recommendation against}

\textit{We recommend against administering hydroxychloroquine or chloroquine for treatment of COVID-19.}

\textbf{Remark:} This recommendation applies to patients with any disease severity and any duration of symptoms.
Research trials that included hydroxychloroquine as potential therapeutic agent

- The WHO SOLIDARITY trial published pre-print results 15 October 2020.¹¹
  - Results reported for hydroxychloroquine, lopinavir-ritonavir, and remdesivir.
- Release of SOLIDARITY results triggered a systematic review and network meta-analysis for hydroxychloroquine, lopinavir-ritonavir, and remdesivir.¹

BMJ 2020; 370 doi: https://doi.org/10.1136/bmj.m2980
Special Considerations (Hydroxychloroquine Treatment)

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.

As there were no trial data suggesting that azithromycin favorably modifies the effect of hydroxychloroquine, the recommendation against hydroxychloroquine and chloroquine applies to patients irrespective of whether they are concomitantly receiving azithromycin.
In December 2020, the following WHO recommendation was released:\textsuperscript{13}

**Strong 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.
Ivermectin
(published 31 March 2021)

Leticia Kawano-Dourado, MD
Pulmonology & Critical Care Medicine
HCor Research Institute – Hospital do Coracao
Sao Paulo Brazil
In March 2021, the following WHO recommendation released:

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.
Recommendation: Use ivermectin only in research settings

- The WHO Guideline Development Group made a recommendation not to use ivermectin in patients with COVID-19 except in the context of a clinical trial, based on the following:
  - **Little or no effect on time to clinical improvement** (low certainty evidence).
  - Effects on mortality, mechanical ventilation, hospital admission, duration of hospitalization and viral clearance remain uncertain due to very low certainty of evidence.
  - May increase the risk of serious adverse events leading to drug discontinuation (low certainty evidence)
- This was based on a living systematic review and network meta-analysis regarding use of Ivermectin for COVID-19 was conducted in early 2021, which pooled data from **16 randomized trials and 2407 participants** with COVID-19
List of Trials that informed the Guidance (Ivermectin)

- 16 RCTs contributed to the evidence summary informing this drug
  - Only five directly compared ivermectin with standard of care and reported mortality
  - Quasi-randomized trials, or any RCT that did not use explicit randomization techniques were excluded
  - Of these five RCTs, two were at high risk of bias, due to inadequate blinding
Living Network Meta Analysis (Ivermectin)
### Ivermectin

7 randomized trials
1419 participants

#### Events per 1000 people

<table>
<thead>
<tr>
<th>Event</th>
<th>Favours usual supportive care</th>
<th>No important difference</th>
<th>Favours ivermectin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>70</td>
<td>No important difference</td>
<td>14</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>20</td>
<td>No important difference</td>
<td>10</td>
</tr>
<tr>
<td>Viral clearance at 7 days</td>
<td>500</td>
<td>118 more</td>
<td>618</td>
</tr>
<tr>
<td>Admission to hospital</td>
<td>50</td>
<td>No important difference</td>
<td>18</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>9</td>
<td>18 fewer</td>
<td>27</td>
</tr>
</tbody>
</table>

#### Mean days

<table>
<thead>
<tr>
<th>Event</th>
<th>Favours usual supportive care</th>
<th>No important difference</th>
<th>Favours ivermectin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to clinical improvement</td>
<td>11.0</td>
<td>No important difference</td>
<td>10.5</td>
</tr>
<tr>
<td>Duration of hospitalisation</td>
<td>12.8</td>
<td>No important difference</td>
<td>11.7</td>
</tr>
<tr>
<td>Time to viral clearance</td>
<td>7.3</td>
<td>No important difference</td>
<td>5.7</td>
</tr>
</tbody>
</table>

#### Evidence quality

- ★★★★☆ Very low
- ★★★☆☆ Low
- ★★☆☆☆ More
Special Considerations

- GDG panel raised concerns that unproven use of this drug, may divert attention and resources away from evidence-based patient care.

- Negative impact on helminth control/elimination programs.

- If steroids are used for COVID-19, empiric treatment with ivermectin may still be considered in Strongyloidiasis endemic areas, at the discretion of clinicians, albeit not for treatment of COVID-19 itself.
Resources and other considerations

- Ivermectin is a relatively inexpensive drug and is widely available, including in low-income settings.
- In the GDG’s view, the low cost and wide availability do not mandate the use of a drug in which any benefit remains very uncertain and ongoing concerns regarding harms remain.
- The GDG raised concerns regarding opportunity costs and the importance of not drawing attention and resources away from best supportive care or from the use of corticosteroids in severe COVID-19.
- Use of ivermectin for COVID-19 would divert drug supply away from pathologies for which it is clearly indicated, potentially contributing to drug shortages for helminth control and elimination programmes.
Summary

• Increased international attention on ivermectin as a potential therapeutic option triggered an evidence review through network meta-analysis, followed by the convening of the WHO Guideline Development Group panel and an update to the WHO Living Guideline: Therapeutics and COVID-19 regarding the use of ivermectin.

• There currently is no persuasive evidence of a mechanism of action for ivermectin against COVID-19. Any observed clinical benefit would be unexplained.

• **Ivermectin should not be used in patients with COVID-19 except in the context of a clinical trial.** This recommendation applies to patients with any disease severity and any duration of symptoms.
Ivermectin in COVID-19: Summary of recommendations

In March 2021, the following WHO recommendation released:

**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.
Future Drugs

Dr Nerina Harley
Assoc Professor Nerina Harley AM MBBS MD  FRACP FCICM AFRACMA
Intensive Care Specialist
Affiliations:
Royal Melbourne Hospital and Epworth Healthcare ,
Melbourne, Australia
WHO Living Guideline on Therapeutics and COVID-19

- IL-6 receptor blockers in COVID-19
IL-6 Receptor Blockers: PICO

**Patients:** Severe or critical illness related to COVID-19
**Intervention:** IL6 RB (tociluzimab, sarilumab)
**Comparator:** usual care
**Outcomes:** mortality, need for invasive ventilation

WHO Guideline Development Group
Meeting 29th April 2021
Trigger: IL6-RB

A significant number of major trials of IL6-RB have been undertaken.

- 30 RCTs
- 10,618 patients
- Trigger - RECOVERY trial 4116 patients

Sufficient trial data to inform meta-analysis.
Prospective meta-analyses

Prospective meta-analysis aim to estimate the effect of anti IL-6 therapy vs usual care in hospitalised patients with COVID-19

- Pooling data from published and unpublished sources
- Prof Manu Shankar Hari, Professor of Critical Care Medicine at Guy’s and St Thomas’ London, Clinical lead of the PMA
- https://www.who.int/publications/i/item/WHO-2019-nCoV-PMA_protocols-anti-IL-6-2021.1
Tocilizumab, sarilumab and siltuximab

(30 RCTs with 10,618 participants)

Data sources
- Journal: 37%
- Preprint: 3%
- Unpublished data: 60%

Trial registration
- Registered: 100%

Drug
- Tocilizumab: 70%
- Sarilumab: 30%
- Siltuximab: 7%

Outcomes reported
- Mortality: 90%
- Mechanical ventilation: 33%
- Duration of mechanical ventilation: 33%
- Adverse effects: 7%

Sources – Journals, 1 preprint, unpublished data from PMA
All trials registered and no publication bias
Majority of trials Tocilizumab or Sarilumab, some both

30 RCTs- Two large trials RECOVERY and REMAP-CAP contributed the majority of power
Biologic plausibility

IL-6 pleiotropic effects
- Immune cell differentiation
- Cytokine storm
- Inflammatory changes
- Structural remodelling

IL-6 receptor antagonists
- Monoclonal antibody that blocks the membrane bond and soluble form of IL-6 receptor
- Approved for Rheumatoid arthritis; the doses investigated for COVID-19 are the same. Expect high level of receptor occupancy at the doses used. Long half life.
- Repurposed in terms of indication rather than primary pharmacological mechanism of action.
- Plausibility therefore hinges on the importance of IL-6 signalling in COVID-19

Corticosteroids – now considered standard care
- Downregulate IL-6
- Different mechanism of action
- IL-6 antagonists different mechanism
Future Research (Therapeutic Agents of Interest)

- Heparin / Anticoagulation
- Colchicine
- Inhaled corticosteroids
- Interferons
- JAK inhibitors
- Monoclonal antibodies
- Convalescent plasma
Q&A
Thank You