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

World Health Organization

HEALTH EMERGENCIES programme

Agenda (Part 1)

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)

Part 2: Drug specific recommendations			
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 Coracao, 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, WHE Program, WHO, Switzerland*

Panelists

Panel Members

Francois Lamontagne
Critical Care Specialist and Clinical Scientist, University de Sherbrooke, Canada

Erlina Burhan
Pulmonologist, Head of Infection Division Department of Pulmonology and Respiratory Medicine, University of Indonesia

Vu Quoc Dat
Vice Head, Intensivist at the National Hospital for Tropical Diseases & Harm Reduction, Lecturer Department of Infectious Diseases, Hanoi Medical University, Viet Nam

Yae Jee Kim
Paediatric Infectious Diseases Specialist and Professor of Department of Paediatrics, Sungkyunkwan University School of Medicine, Samsung Medical Centre, Republic of Korea

Saniya Sabzwari
Associate Professor in the Department of Family Medicine, Aga Khan University, Pakistan

Rohit Sarin
Principal Consultant National Institute of TB and Respiratory Diseases, Technical Advisor for the National TB Elimination Program Government of India

Yingzong Shen
Chief Physician, Associate Professor of Shangqi Public Health Clinical Centre, Fudan University, China

Joao Paulo Souza
Professor of Public Health, Ribeirao Preto Medical School, University of Sao Paulo, Brazil

Shalini Sri Ranganathan
Specialist in Pharmacology and Paediatrics, University of Colombo, Sri Lanka

Sridhar Ram Venkatapu
Global Health Ethicist, Associate Professor and Director of Global Health Education and Training, Kings College London, United Kingdom

Per Olav Vandvik
Professor at the Institute of Health and Society, University of Oslo, Senior researcher at the Norwegian Institute of Public Health, Oslo, Norway

Gordan Guyatt
Professor in the Department of Clinical Epidemiology and Biostatistics, McMaster University, Canada

Akthem Fourati
Chief, Medicines and Nutrition Centre, Supply Division, UNICEF

Lorenzo Moja
Scientist, WHO, Switzerland

Review of the Development of WHO Living Guidelines for Therapeutics & COVID-19

Janet Diaz
Case Management Lead, Health Care Readiness, WHE Program, WHO, Switzerland

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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.

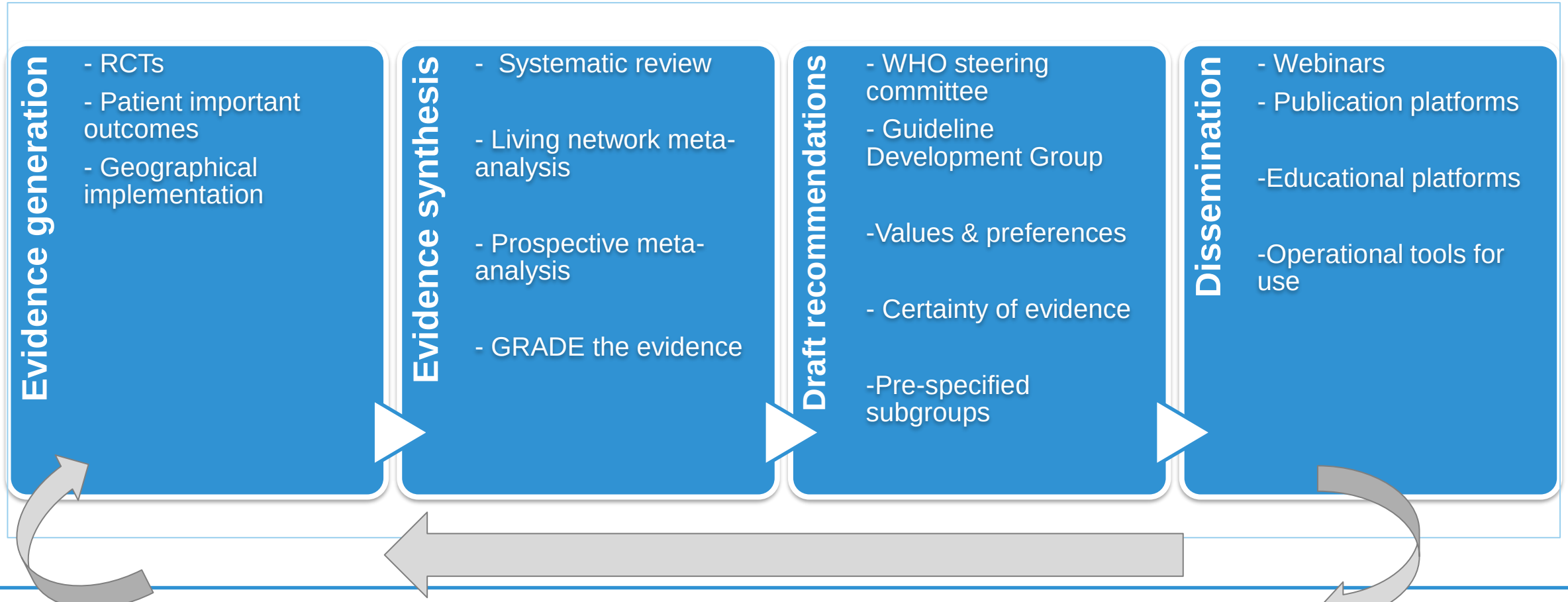
Numerous randomized clinical trials are ongoing, some are robust, large platform trials, and others smaller randomized clinical trials; all of them generating evidence at rapid speed.

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

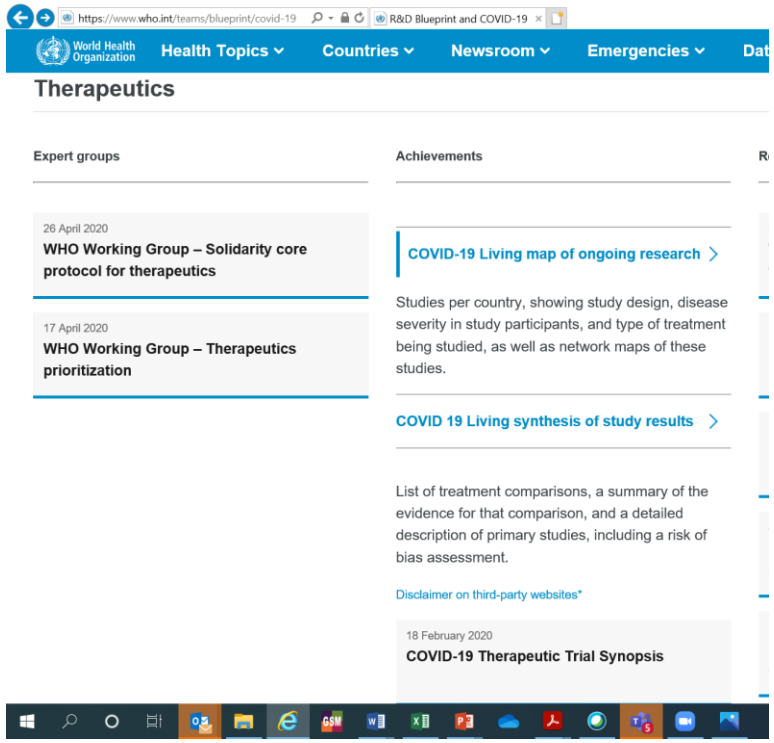
Rapid transformation of evidence to recommendation

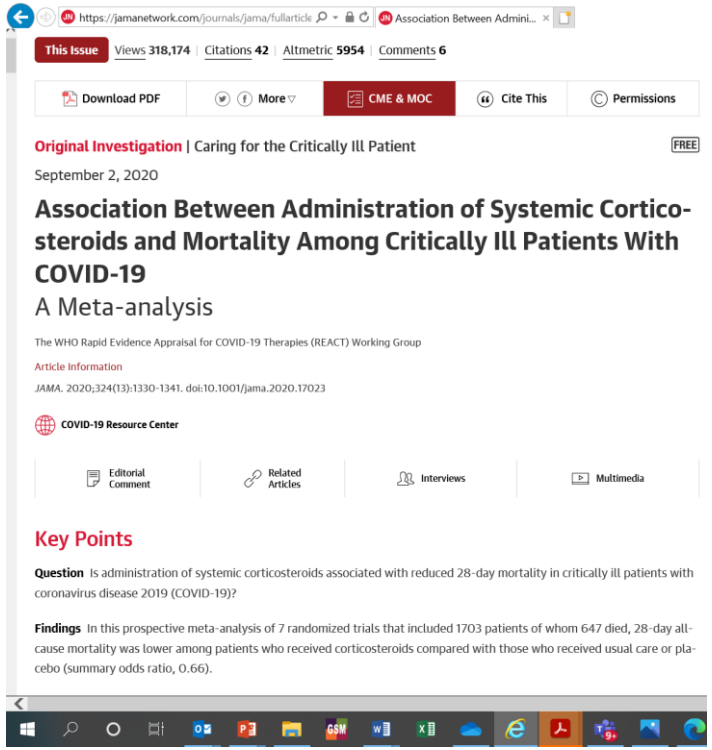
Trigger: likelihood to change practice, sufficient RCT data to inform high quality evidence synthesis (> 2000 patients, > 50 events), relevant to global audience

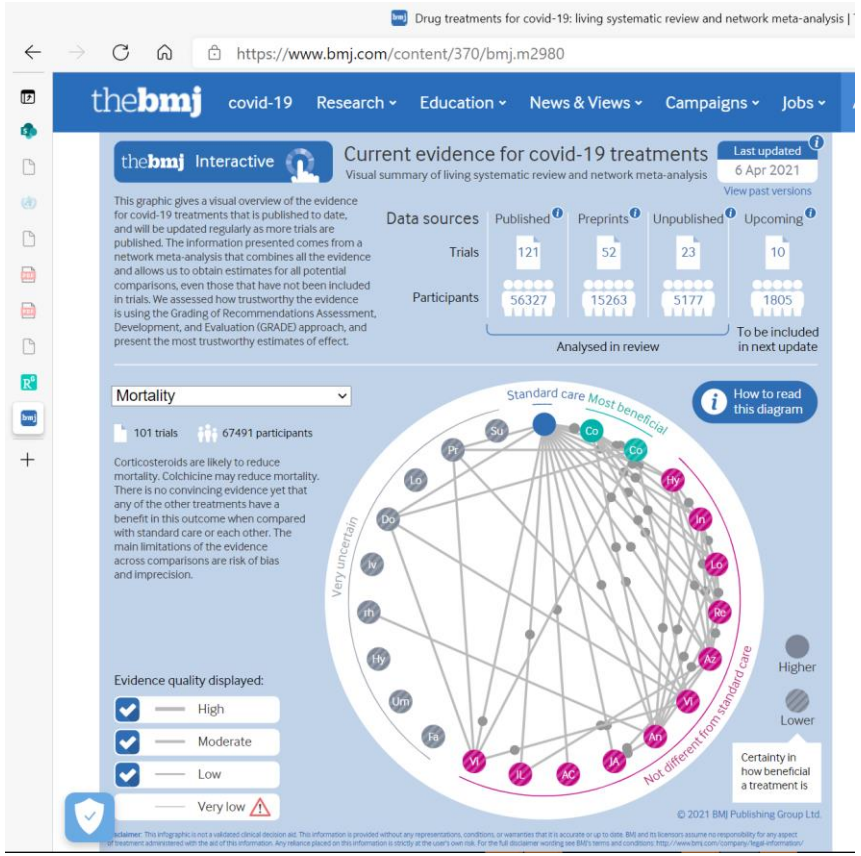


Innovation in evidence monitoring and synthesis

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







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https://covid-nma.com/living_data/index.php

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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 , independant panel draft the recommendations

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

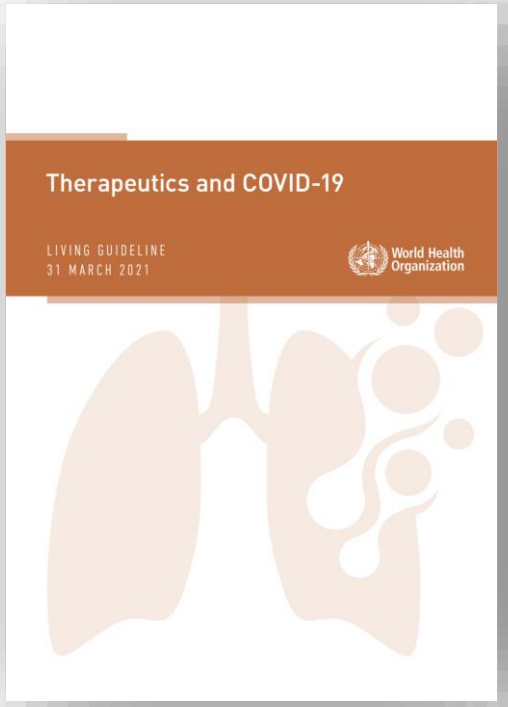
Clinical and Methods Chairs

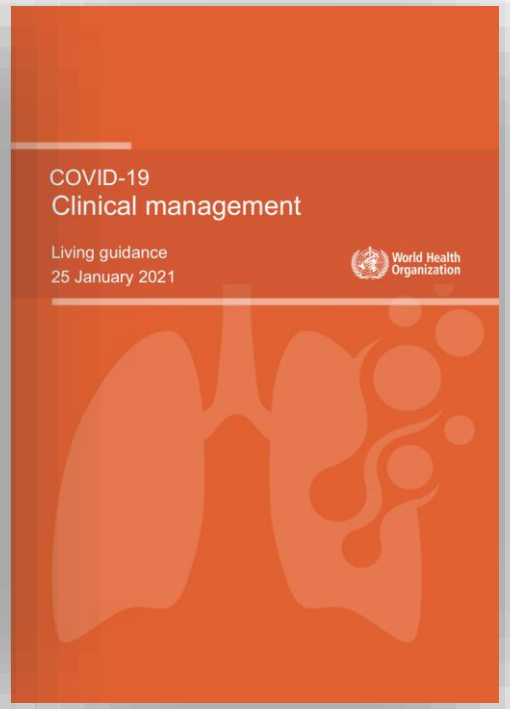
Methods support: experts in methodology, experience in interpretation of evidence, development of recommendations

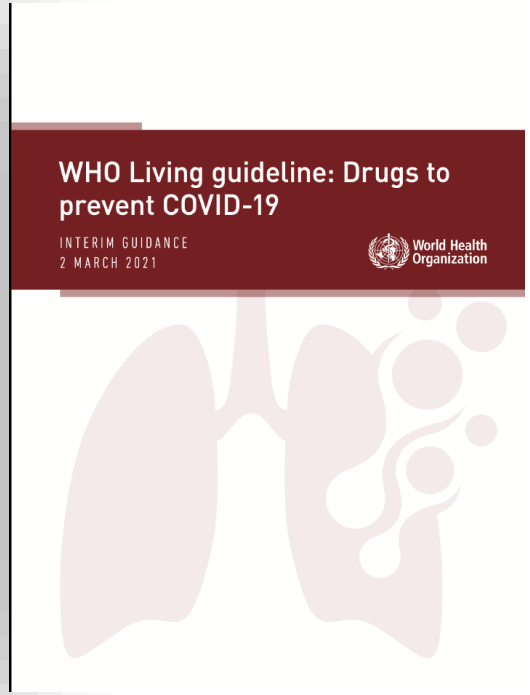
Panel members: > 40 experts, regional representation, gender balance, different areas of specialty, ethics/equity expert, patient partners.

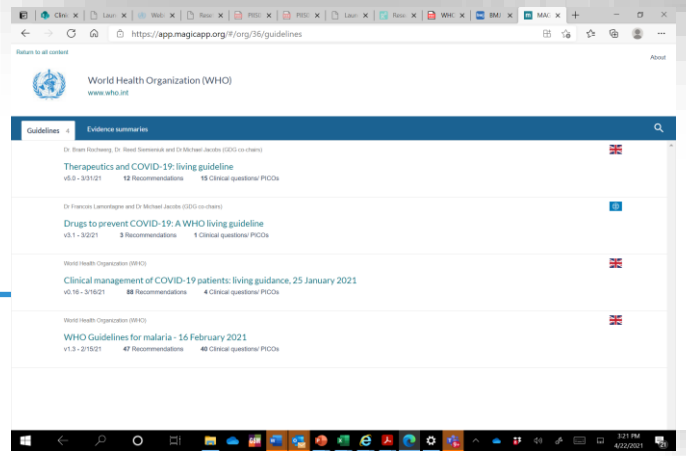
Expert advisors: pharmacologists, as needed.

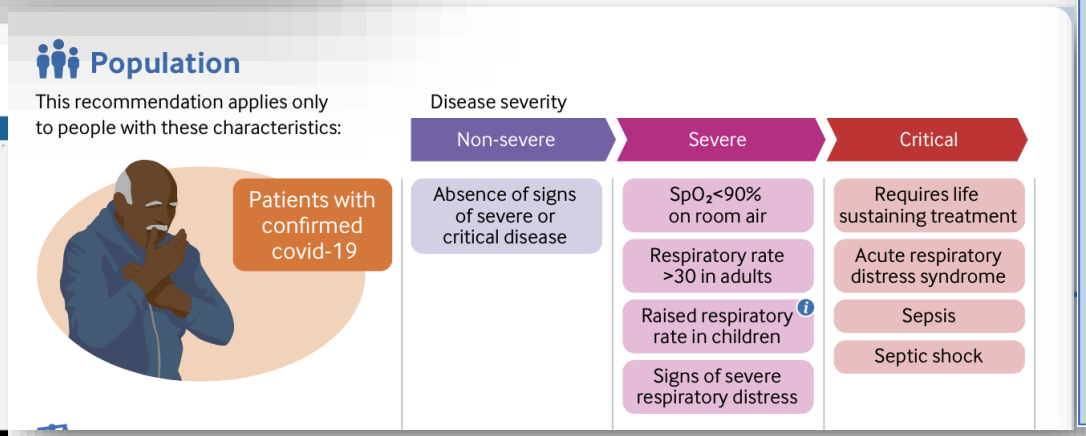
Innovative publication platforms: WHO, MAGICapp, BMJ

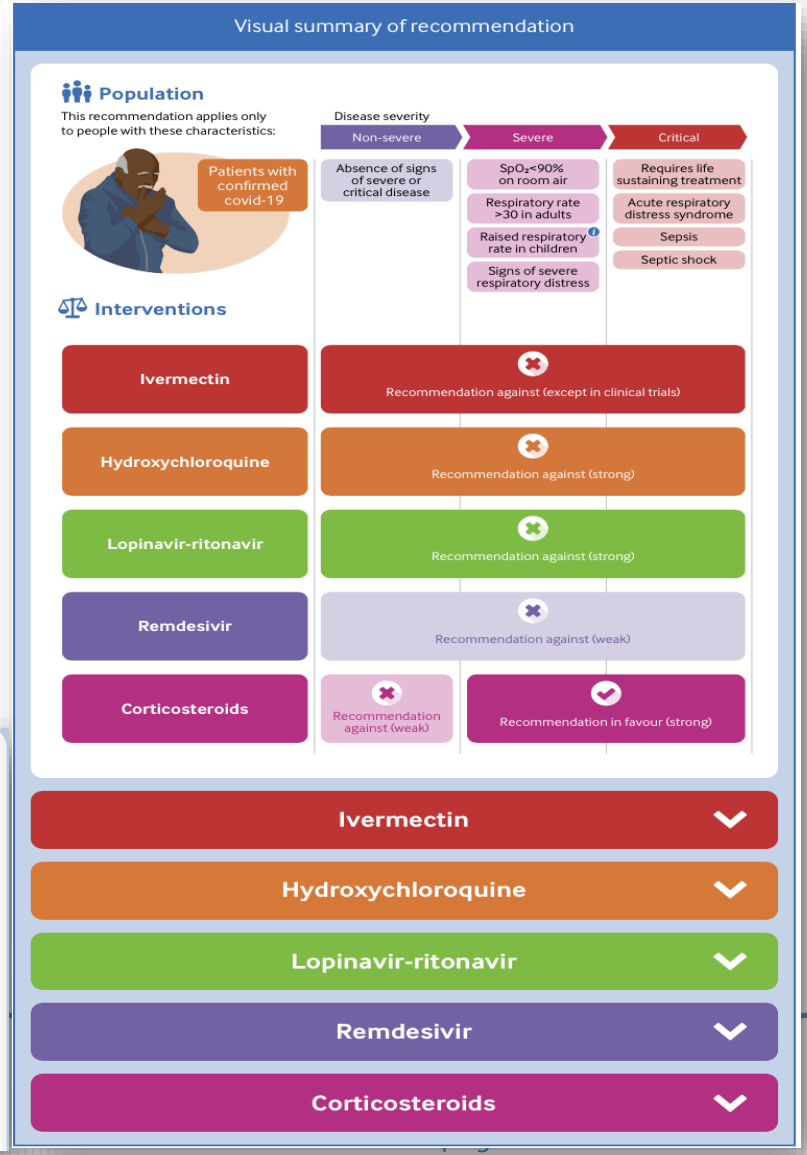












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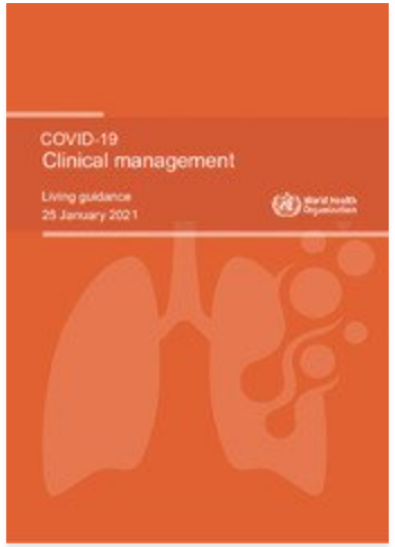

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Overview

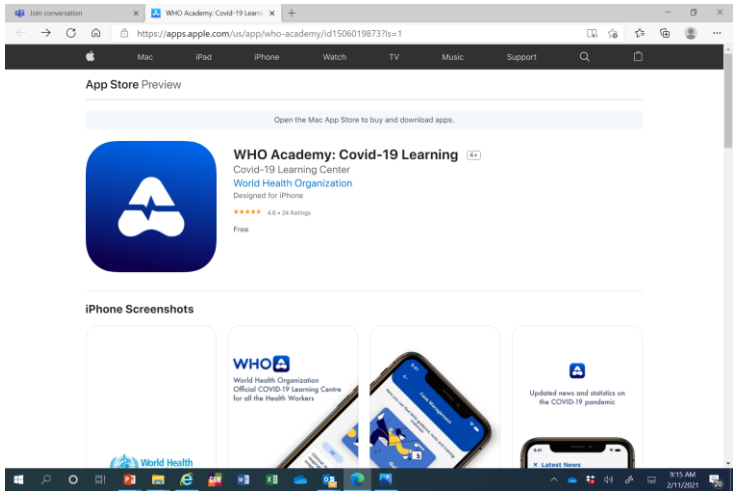
This document is the update of an interim guidance originally published under the title " Clinical management of COVID-19: interim guidance, 27 May 2020".

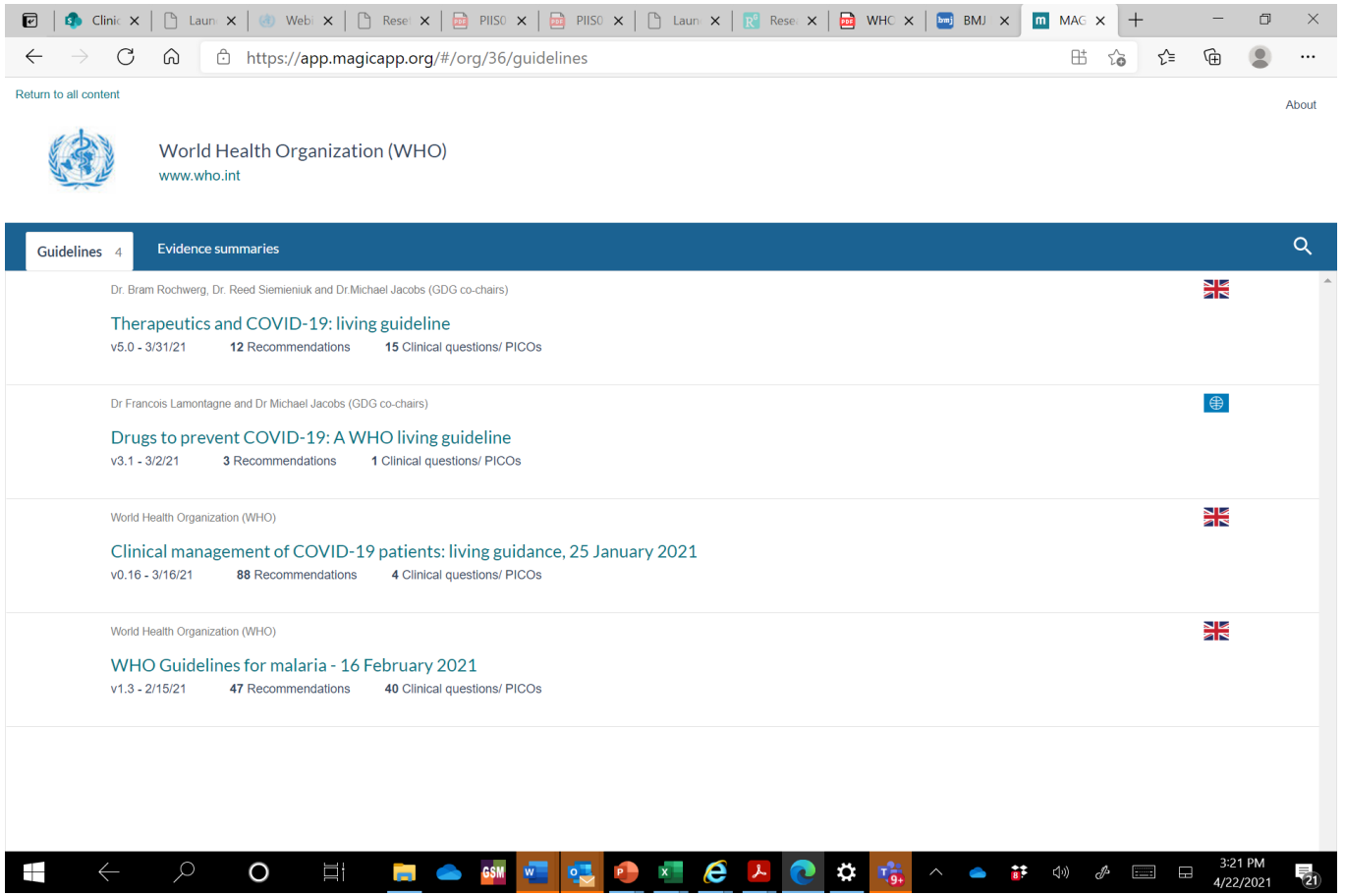
Providing trustworthy guidance that is comprehensive and holistic for the optimal care of COVID-19 patients, throughout their entire illness is necessary. The previous version of the Clinical management of COVID-19 provided recommendations that can be applied when caring for patients during the COVID-19 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).

Do the basics well!

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

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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 Rochwerg
Associate Professor, McMaster University,
Hamilton, ON, Canada

World Health Organization

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CLINICAL PRACTICE GUIDELINES WE CAN TRUST

INSTITUTE OF MEDICINE

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

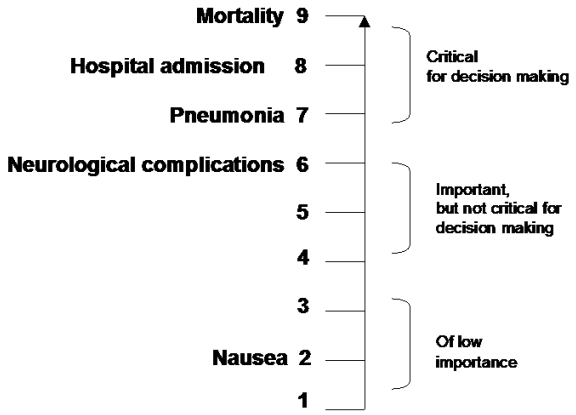
Patients

Intervention

Comparison

Outcomes

PICO



Rating Outcome

Inpatient

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

Outpatient

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

Certainty of evidence

(quality of the evidence, confidence in estimates)

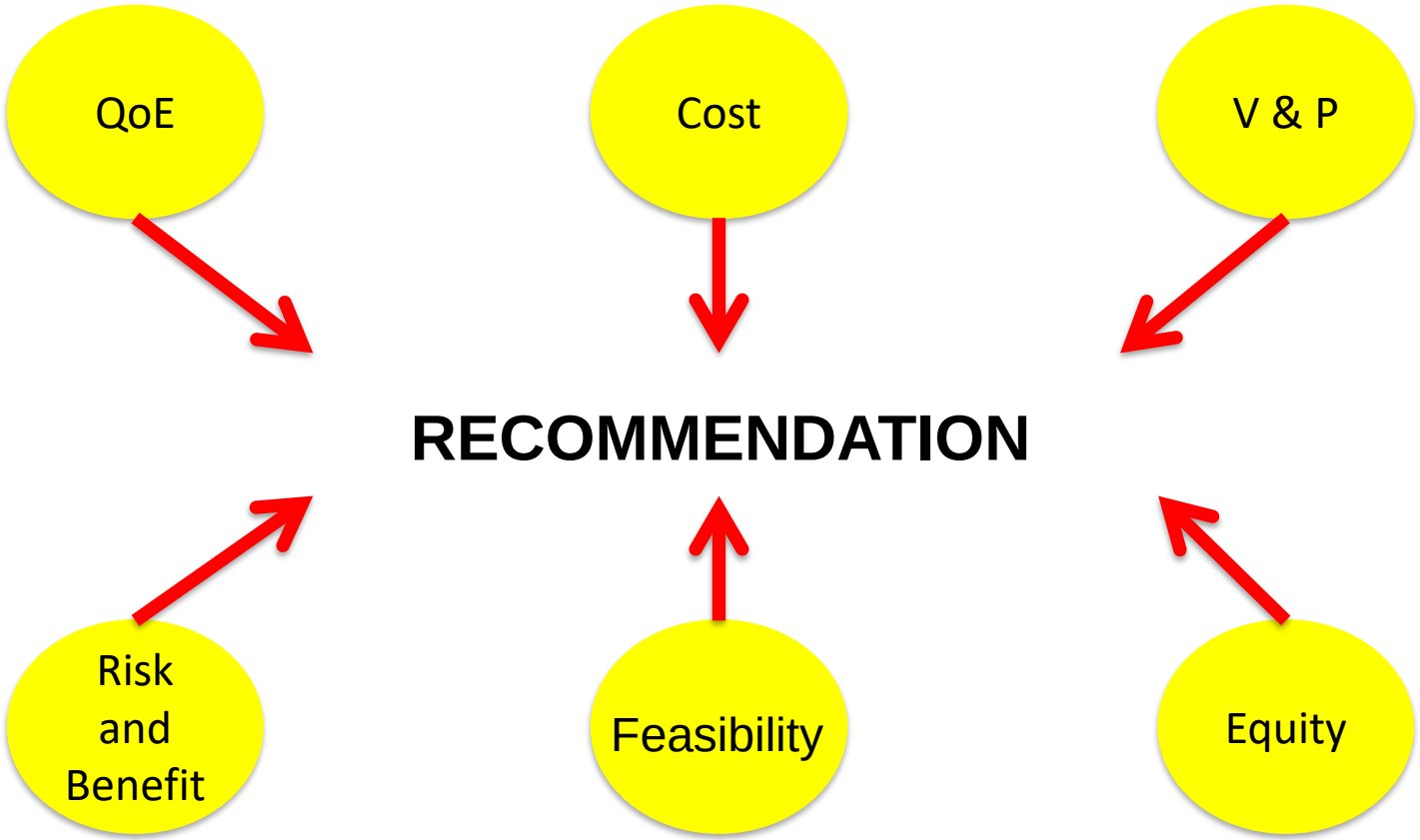
Table: GRADE's approach to rating quality of evidence (aka confidence in effect estimates)

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

1. Establish initial level of confidence		**2. Consider lowering or raising level of confidence**		**3. Final level of confidence rating**
Study design	***Initial confidence in an estimate of effect***	***Reasons for considering lowering or raising confidence***		***Confidence in an estimate of effect across those considerations***
		↓ Lower if	**↑ Higher if***	
Randomized trials →	**High confidence**	**Risk of Bias** **Inconsistency** **Indirectness** **Imprecision** **Publication bias**	**Large effect** **Dose response** **All plausible confounding & bias** • would reduce a demonstrated effect **or** • would suggest a spurious effect if no effect was observed	**High** ⊕⊕⊕⊕
				Moderate ⊕⊕⊕◯
Observational studies →	**Low confidence**			**Low** ⊕⊕◯◯
				Very low ⊕◯◯◯

*upgrading criteria are usually applicable to observational studies only.

Moving from Evidence to 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 Siemienuik
Physician, Methodologist
Mc Master University, Hamilton, Ontario, Canada

www.covid19lnma.com

11 May 2021

World Health Organization

thebmj

McMaster University

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COVID-19 Living Systematic Review & Network Meta-Analysis (NMA)

Drug therapies → 284 RCTs

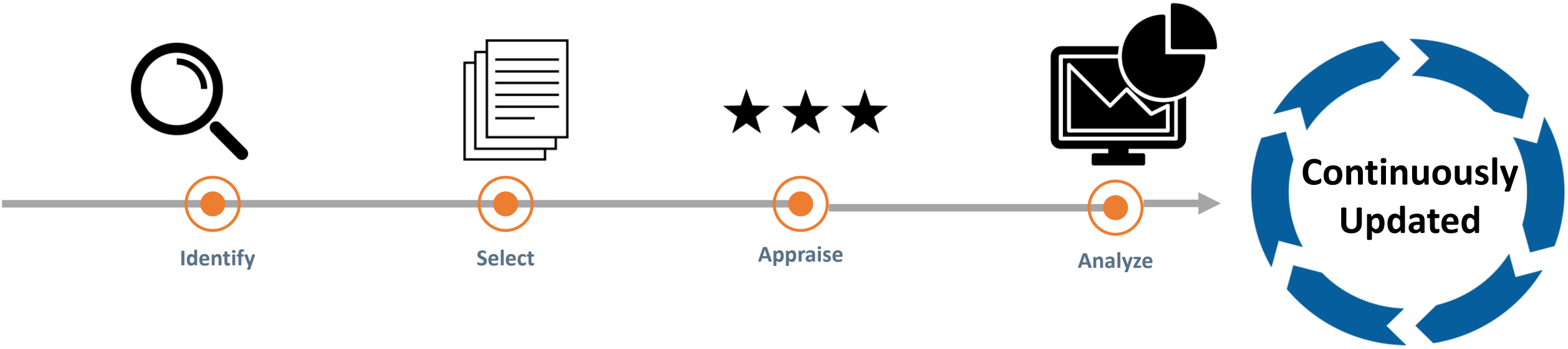
Antiviral antibodies and cellular therapies → 33 RCTs

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.

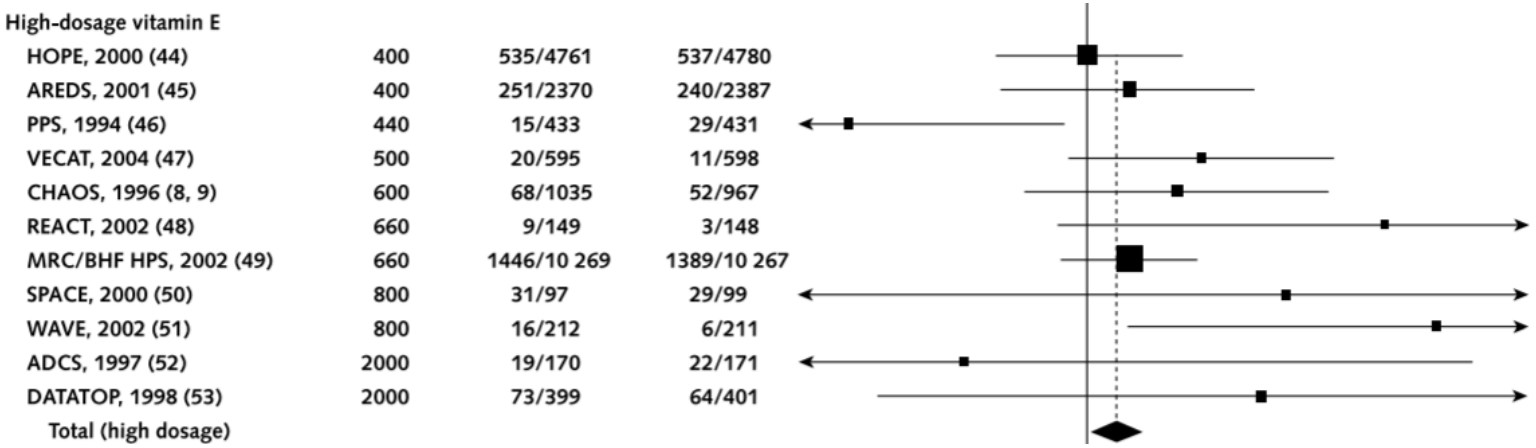
A living systematic review is updated based on a predefined schedule or when new evidence emerges.

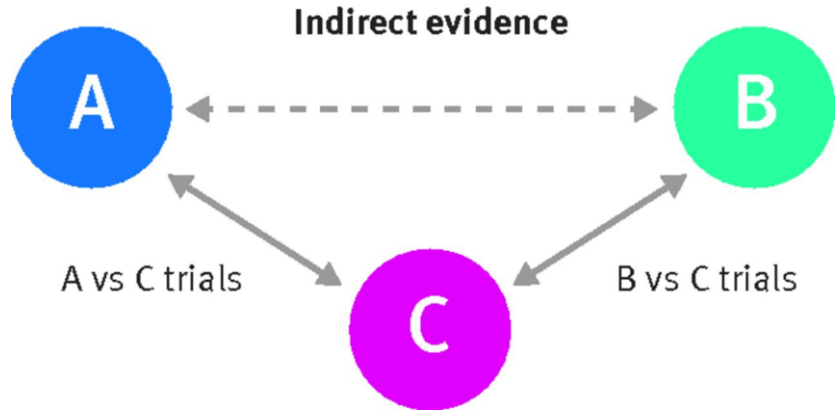


Living network meta-analysis (NMA)

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





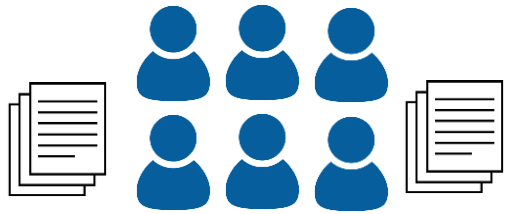
Search and Screening

World Health Organization
COVID-19 database

Machine Learning Model

6 Chinese databases

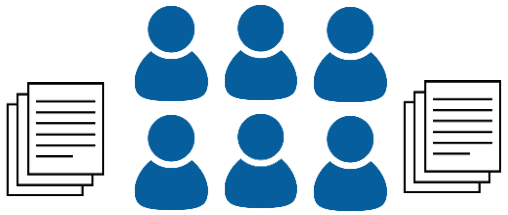
Epistemonikos



Screening team

- **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



Data collection and study appraisal team

Trial characteristics

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

Participant characteristics

- Age
- Sex
- Smoking
- Respiratory/cardiometabolic 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

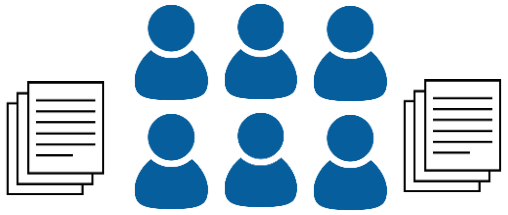
Therapy trials

- 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

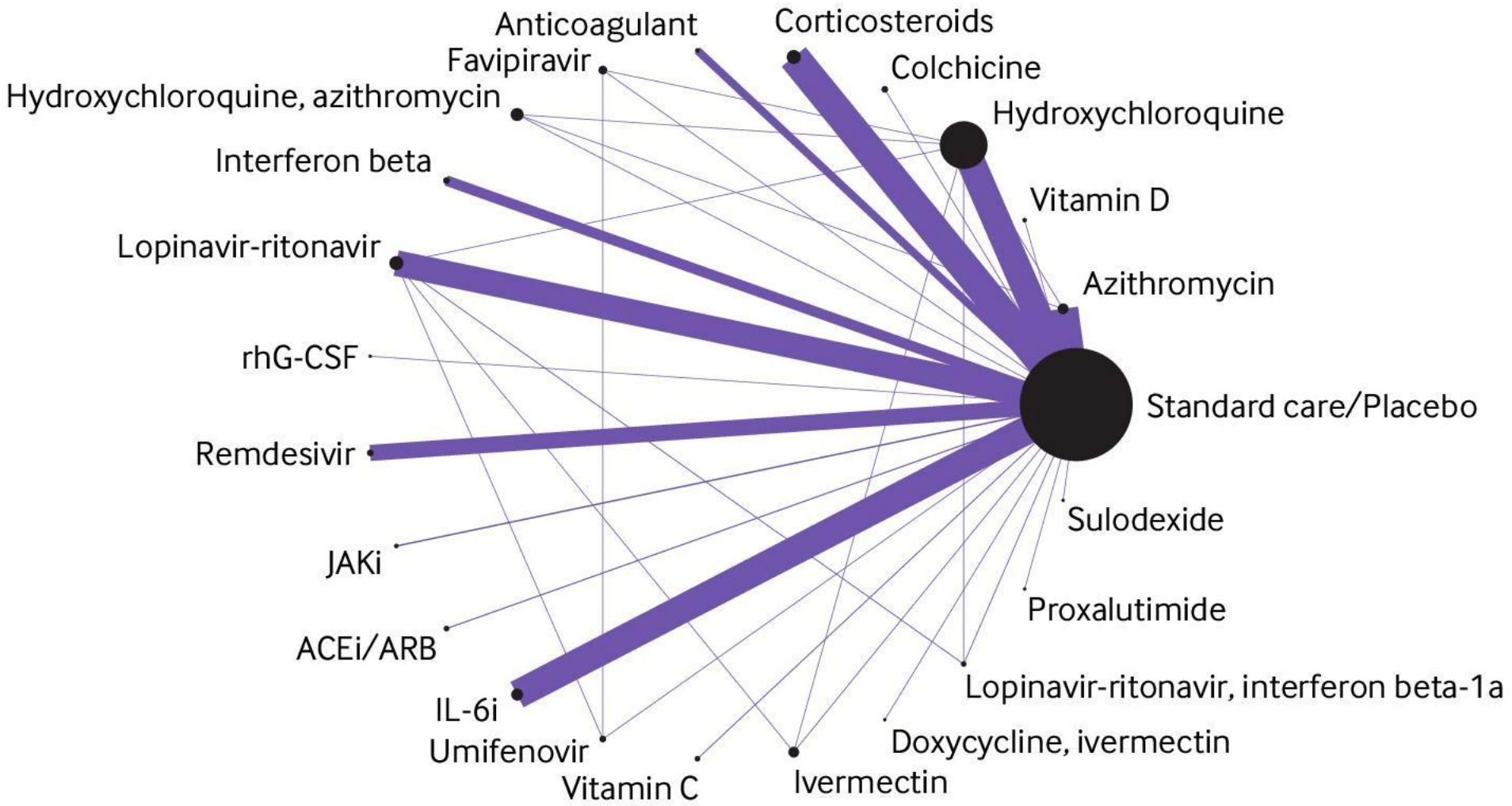
Performance bias

Bias due to missing data

Detection bias

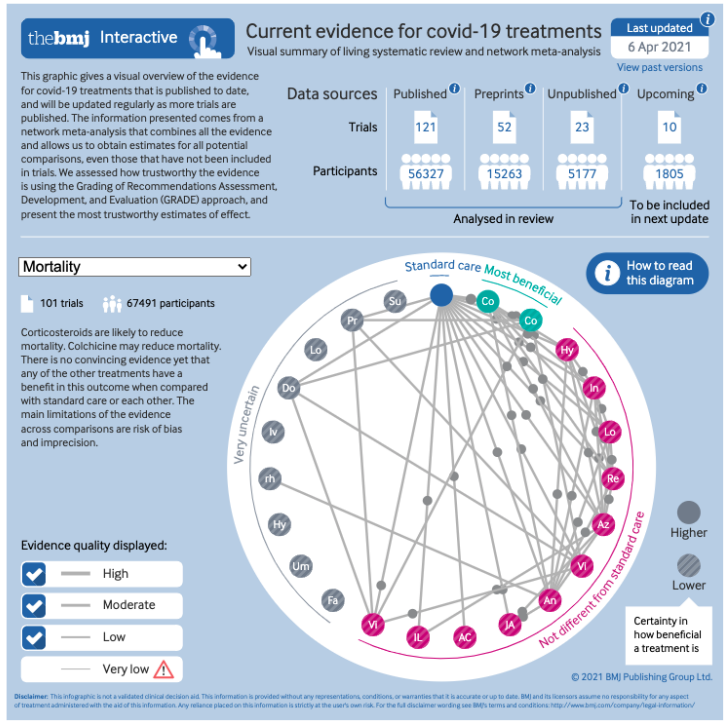
Reporting bias

Network plot



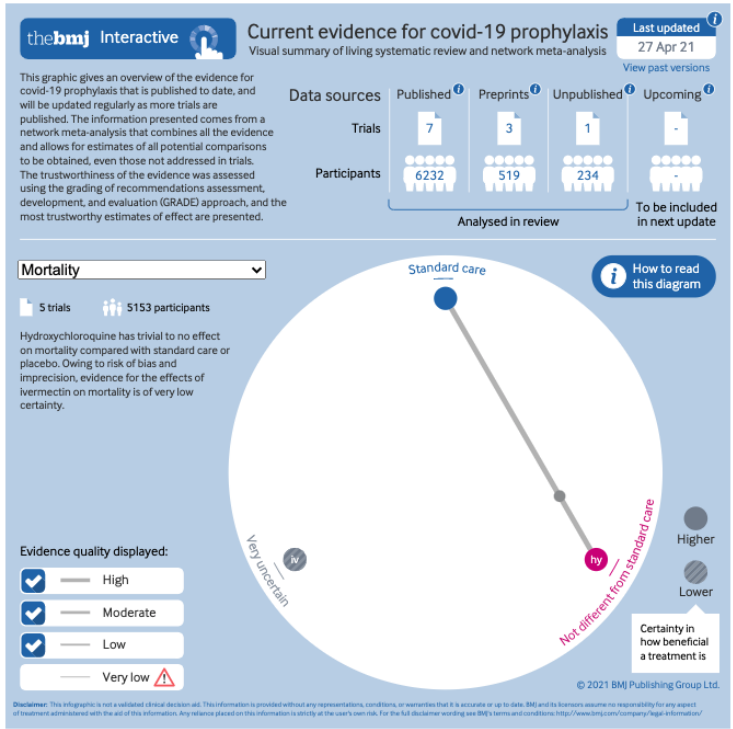
Access

Drug treatments



bmj.com/content/370/bmj.m2980

Prophylaxis



bmj.com/content/373/bmj.n949

Antiviral antibodies

Coming soon!

www.covid19lnma.com

reed.siemieniuk@medportal.ca

Prioritizing interventions for guidelines

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

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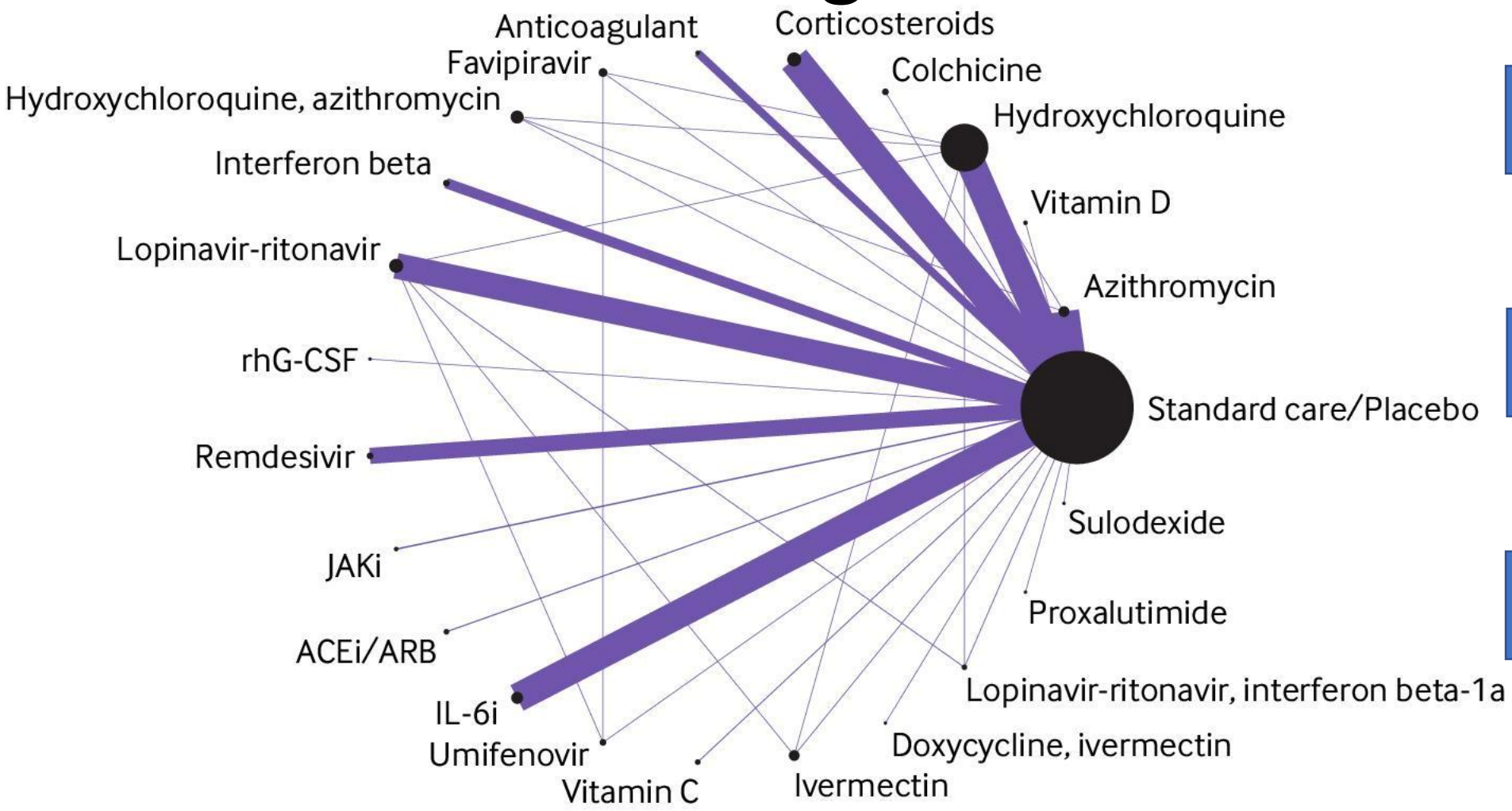
Drug treatments



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

RESEARCH METHODS AND REPORTING

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,[2,9] Gabriel Rada,[10,11,12] Sarah Rosenbaum,[4] Angela Morelli,[4] Gordon H Guyatt,[2,3] Andrew D Oxman[4] the GRADE Working Group

GRADE

	Drug 1	Drug 2	Drug 3
Signal on Benefit			
Certainty regarding Benefit			
Signal on Harm			
Certainty regarding Harm			
Values & Preferences			
Resource consideration			
Feasability, practical considerations			
Acceptability			
Equity			
Current practice & variability (Implement vs De-implement?)			
Special considerations e.g. subgroup hypotheses, co-management, timing of administration, etc.			
N trials / N pre-prints			
Upcoming large trials …			
	Date of assessement	Date...	Date...

Pharmacology :Approach to assessing Mechanistic Plausibility

Andrew Owens
Professor Pharmacology & Therapeutics
University of Liverpool, UK

World Health Organization

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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.

COVID-19 Drug Interactions

UNIVERSITY OF LIVERPOOL

About Us | Interaction Checkers | Prescribing Resources | Contact Us

New comedications: Alendronic acid, Alfuzosin, Cabotegravir (oral), Cabotegravir/Rilpivirine (long acting), Cefepime, Fostemsavir, Potassium, Pramipexole, Pyridostigmine.

Interaction Checker

Access our free, comprehensive and user-friendly drug interaction charts

Prescribing Resources

Printable interaction tables, interaction summary charts and clinical prescribing resources

Twitter

@covidDDIs

Follow us on Twitter for interaction news and for the latest additions and changes to the website

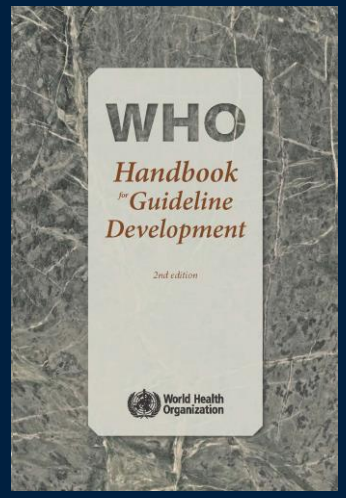
www.covid19-druginteractions.org/checker

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

World Health Organization

HEALTH EMERGENCIES programme



"WHO's legitimacy and technical authority lie in its rigorous adherence to the systematic use of evidence as the basis for all policies"

Role of the clinical chair

Consensus
Perspective
Representativeness
Inclusivity

Srinivas Murthy, MD CM, MHSc
Infectious Diseases and Critical Care
University of British Columbia
Health Research Foundation and Innovative Medicines Chair in Pandemic Preparedness Research
Co-Chair, COVID19 Clinical Characterization and Management, World Health Organization
Srinivas.murthy@cw.bc.ca

Introduction to Prospective Meta Analysis

Jonathan Sterne
Professor of Medical Statistics and Epidemiology, Bristol Medical School (PHS), United Kingdom

World Health Organization

HEALTH EMERGENCIES programme

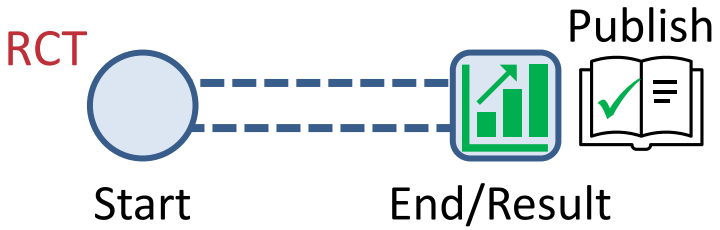
Some problems with most meta-analyses

- 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



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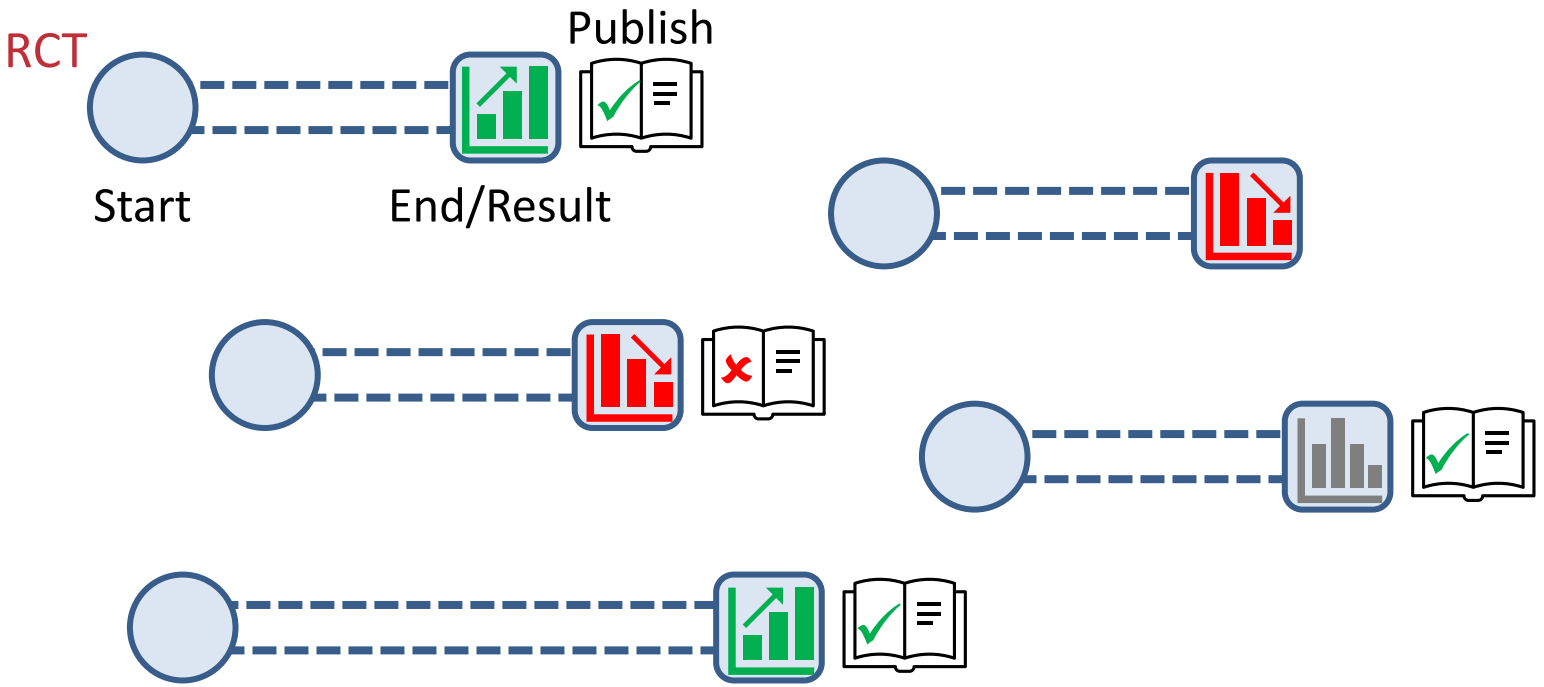

Some problems with most meta-analyses

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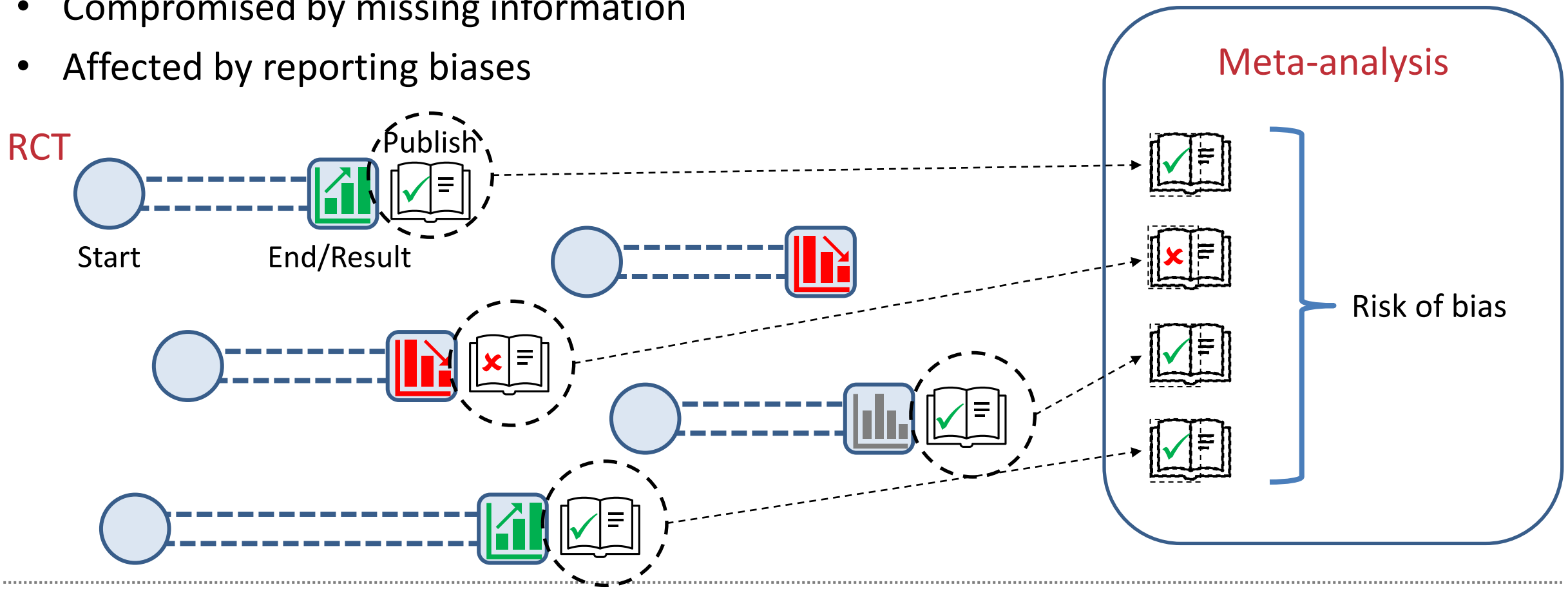
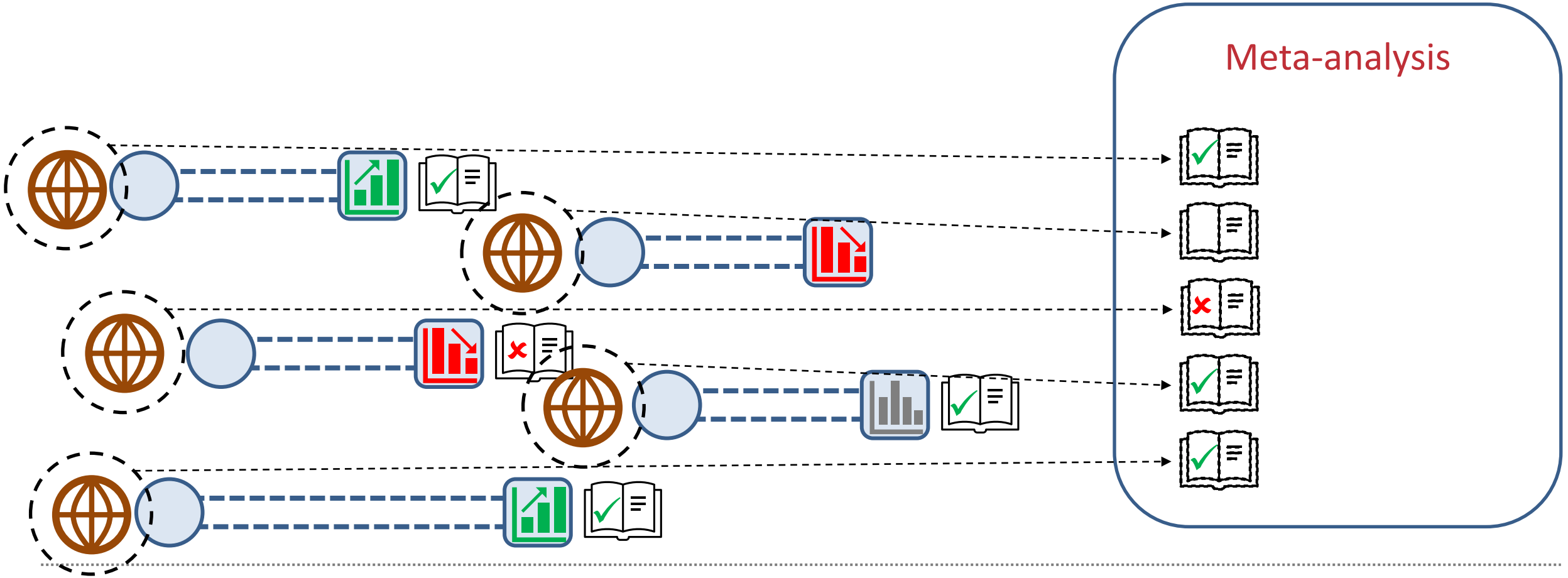
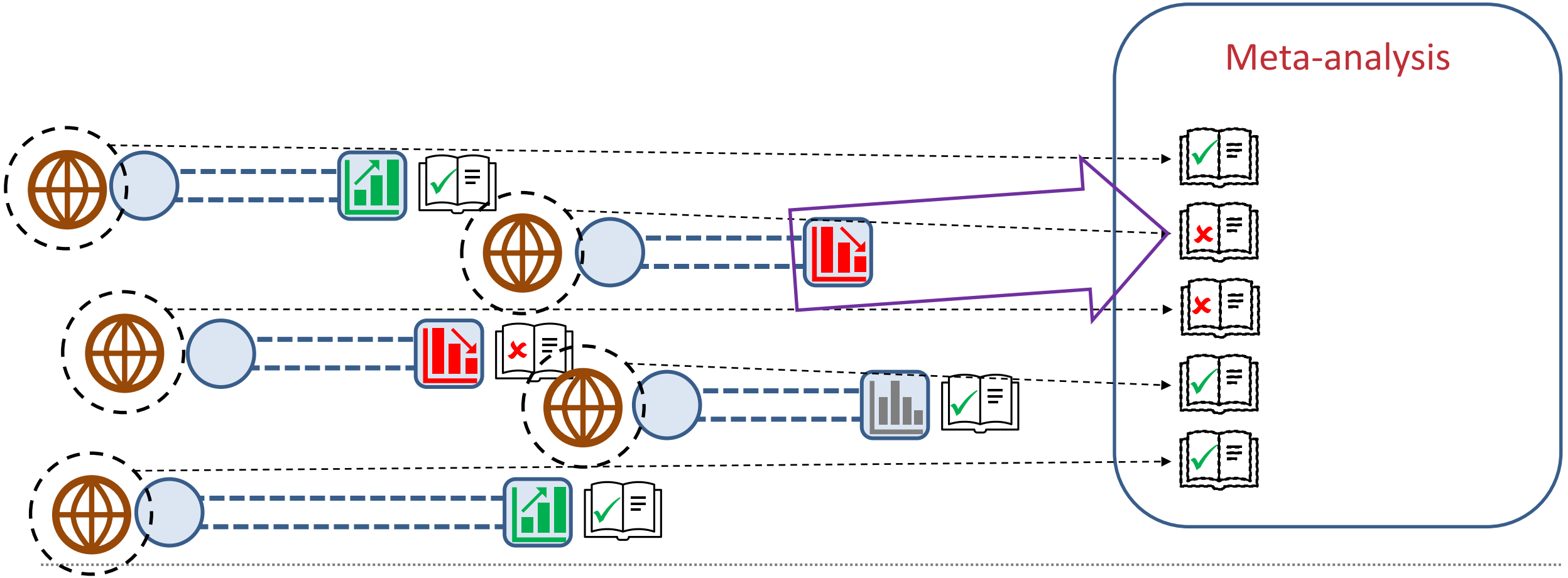


Selecting registered trials helps

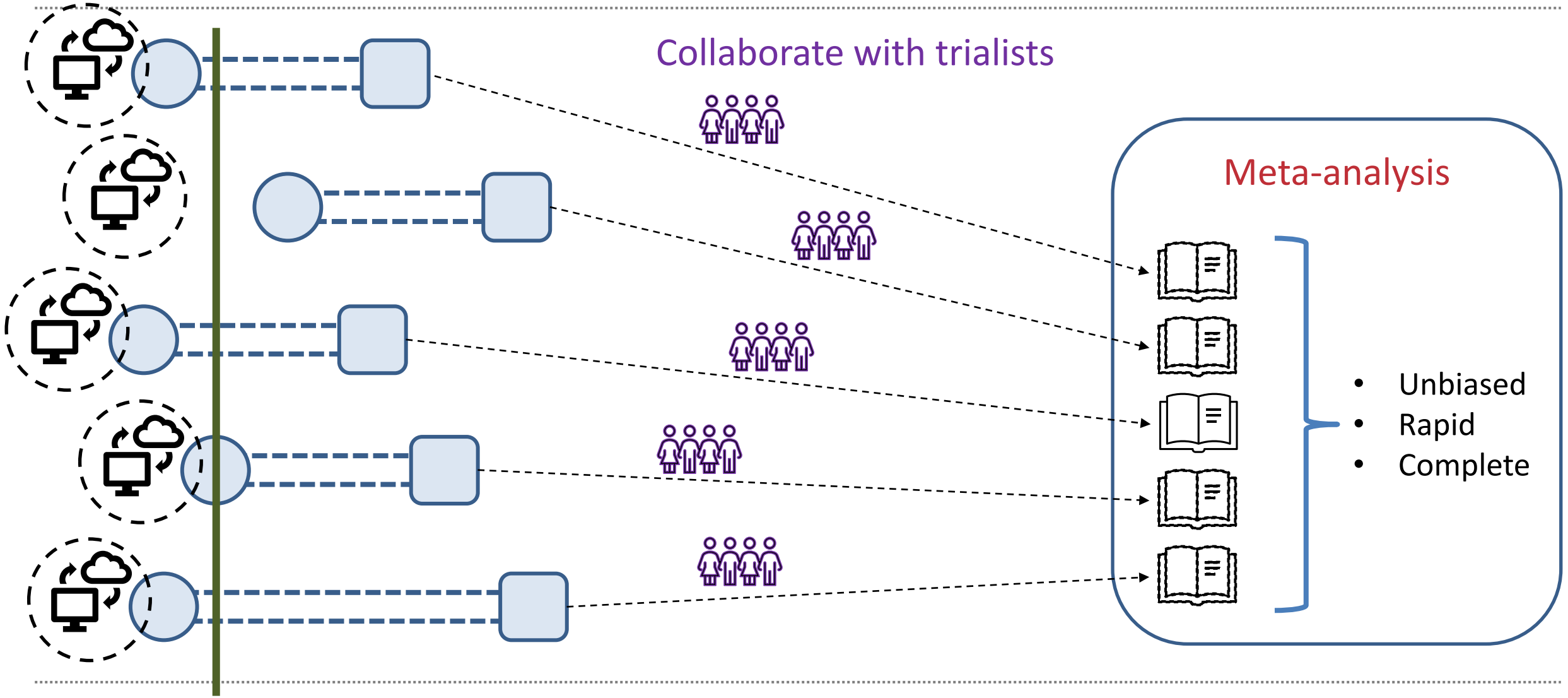


Selecting registered trials helps

Communicating with trialists helps



Prospective, collaborative meta-analysis



RESEARCH METHODS AND REPORTING

A guide to prospective meta-analysis

Anna Lene Seidler,[1] Kylie E Hunter,[1] Saskia Cheyne,[1] Davina Ghersi,[1,2] Jesse A Berlin,[3] Lisa Askie[1]

[1]NHMRC Clinical Trials Centre, University of Sydney, Locked bag 77, Camperdown NSW 1450, Australia
[2]National Health and Medical Research Council, Canberra, Australia
[3]Johnson & Johnson, Titusville, NJ, USA

Correspondence to: A L Seidler lene.seidler@ctc.usyd.edu.au (ORCID 0000-0002-0027-1623)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2019;367:l5342
http://dx.doi.org/10.1136/bmj.l5342

Accepted: 8 August 2019

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

BMJ 2019; ;367:l5342

Cochrane Training

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Informed decisions.
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Chapter 22: Prospective approaches to accumulating evidence

Search Handbook

James Thomas, Lisa M Askie, Jesse A Berlin, Julian H Elliott, Davina Ghersi, 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

Cochrane Handbook for Systematic Reviews of Interventions, 2019

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

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.

+ Editorial
+ Related articles
+ Supplemental content

Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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 Badié, MD; I
Youenn Jouan, M
Céline Lengellé, F
Djillali Annane, M

IMPORTANC
Corticoster
OBJECTIVE
critically ill p
infection an
DESIGN, SET
conducted i
the intensiv
March 7 to
290 patient
monitoring

Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY IL

Effect of Dexamethasone on Days Alive a Moderate or Severe Acute Respiratory Di

The CoDEX Randomized Clinical Trial

Bruno M. Tomazini, MD; Israel S. Maia, MD, MSc; Alexandre B. Cavalcanti, MD, PhD
Viviane C. Veiga, MD, PhD; Alvaro Avezum, MD, PhD; Renato D. Lopes, MD, PhD; Fl
Eduardo L. V. Costa, MD, PhD; Ricardo A. B. Moura, MD; Michele O. Honorato, MD;
Thiago Lisboa, MD, PhD; Letícia Kawano-Dourado, MD, PhD; Fernando G. Zampieri
Cristina P. Amendola, MD; Roberta M. L. Roepke, MD; Daniela H. M. Freitas, MD; Da
Caio C. F. Fernandes, MD; Livia M. G. Melro, MD; Gedealvares F. S. Junior, MD; Doug
Luciano C. P. Azevedo, MD, PhD; for the COALITION COVID-19 Brazil III Investigator

IMPORTANCE Acute respiratory distress
(COVID-19) is associated with substantia
Dexamethasone use might attenuate lu
OBJECTIVE To determine whether intrav
ventilator-free days among patients wit
DESIGN, SETTING, AND PARTICIPANTS Mu
conducted in 41 intensive care units (ICU
severe ARDS, according to the Berlin de
Final follow-up was completed on July 2
publication of a related study before rea

Research

JAMA | Original Investigation | CARING FOR THE CRIT

Effect of Hydrocortisone on Morta With Severe COVID-19

The REMAP-CAP COVID-19 Corticos

The Writing Committee for the REMAP-CAP Investigators

IMPORTANCE Evidence regarding corticosteroid use for sev
(COVID-19) is limited.
OBJECTIVE To determine whether hydrocortisone improve
with severe COVID-19.

EDITORIAL

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, antifibrotic, and vasoconstrictive effects, which intensivists have been trying to leverage for decades to improve outcomes in patients with acute respiratory

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

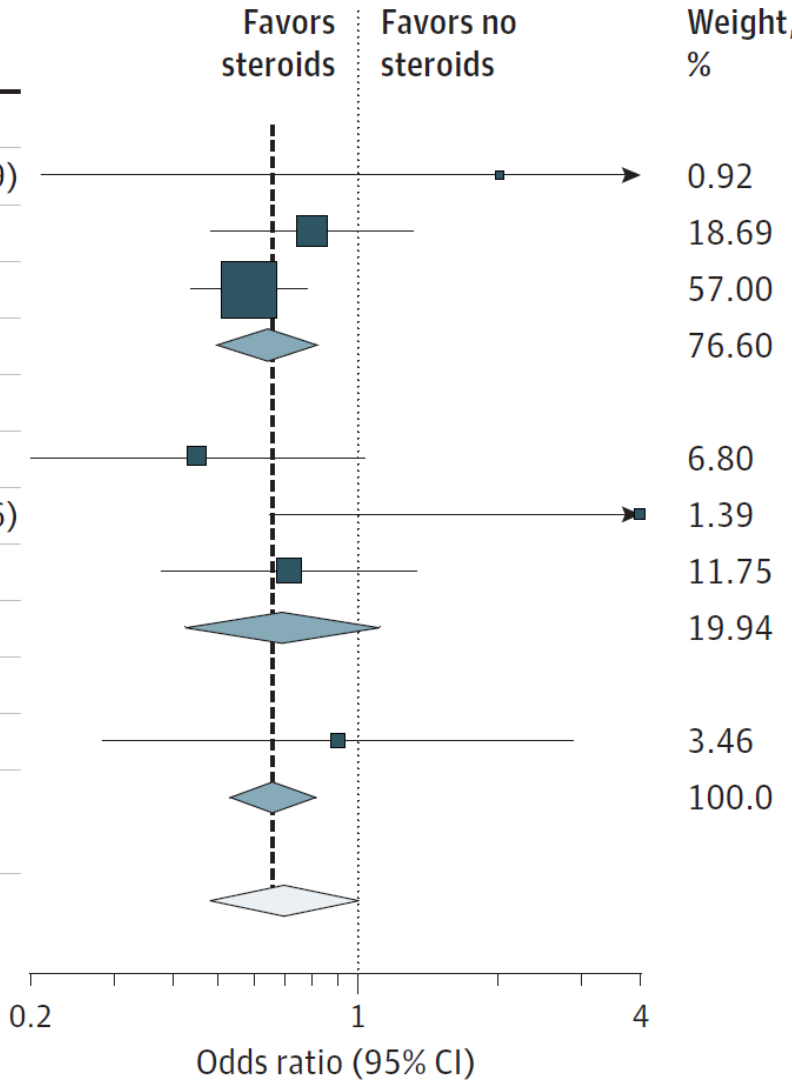
Corticosteroids for COVID-19

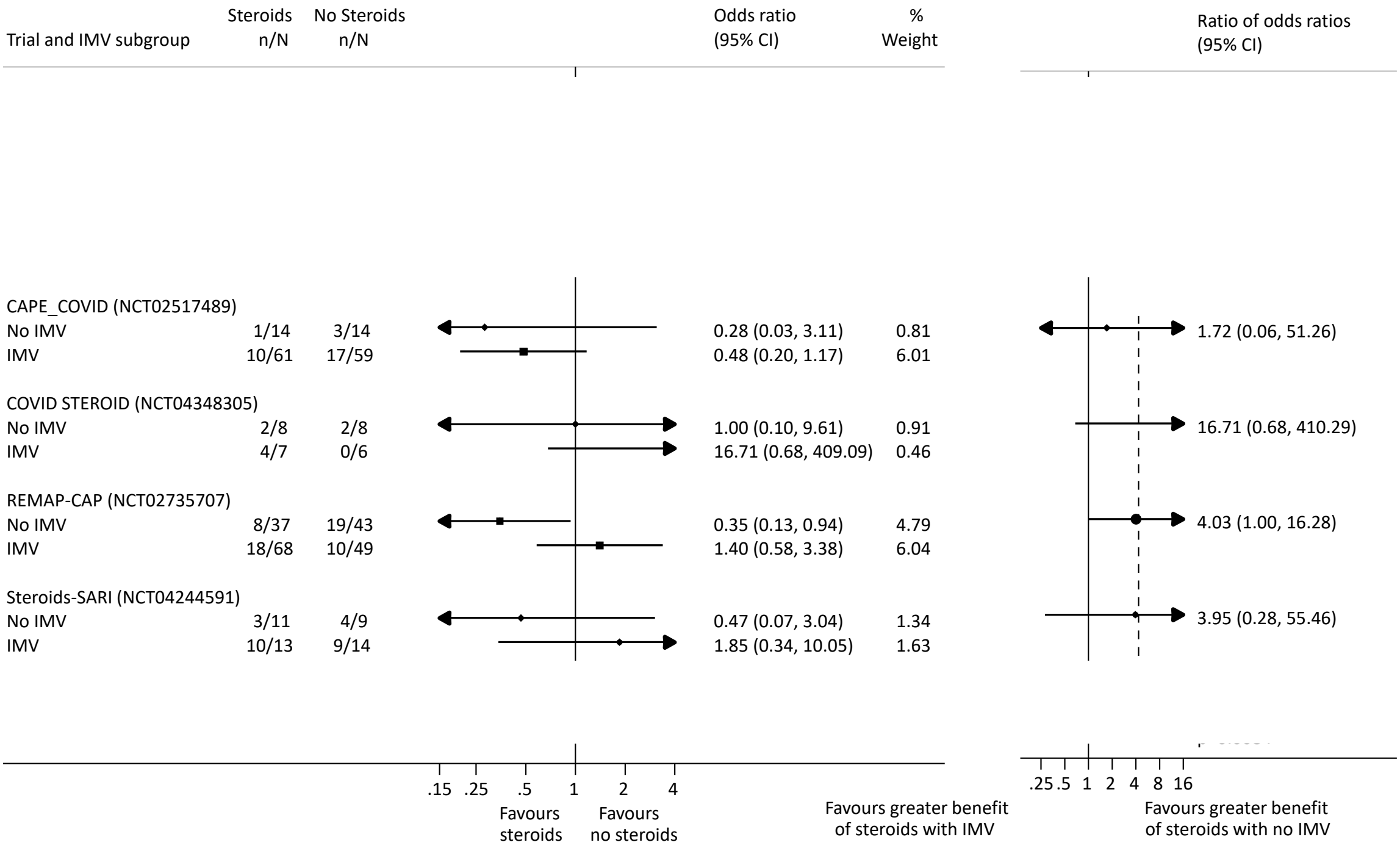
LIVING GUIDANCE
2 SEPTEMBER 2020

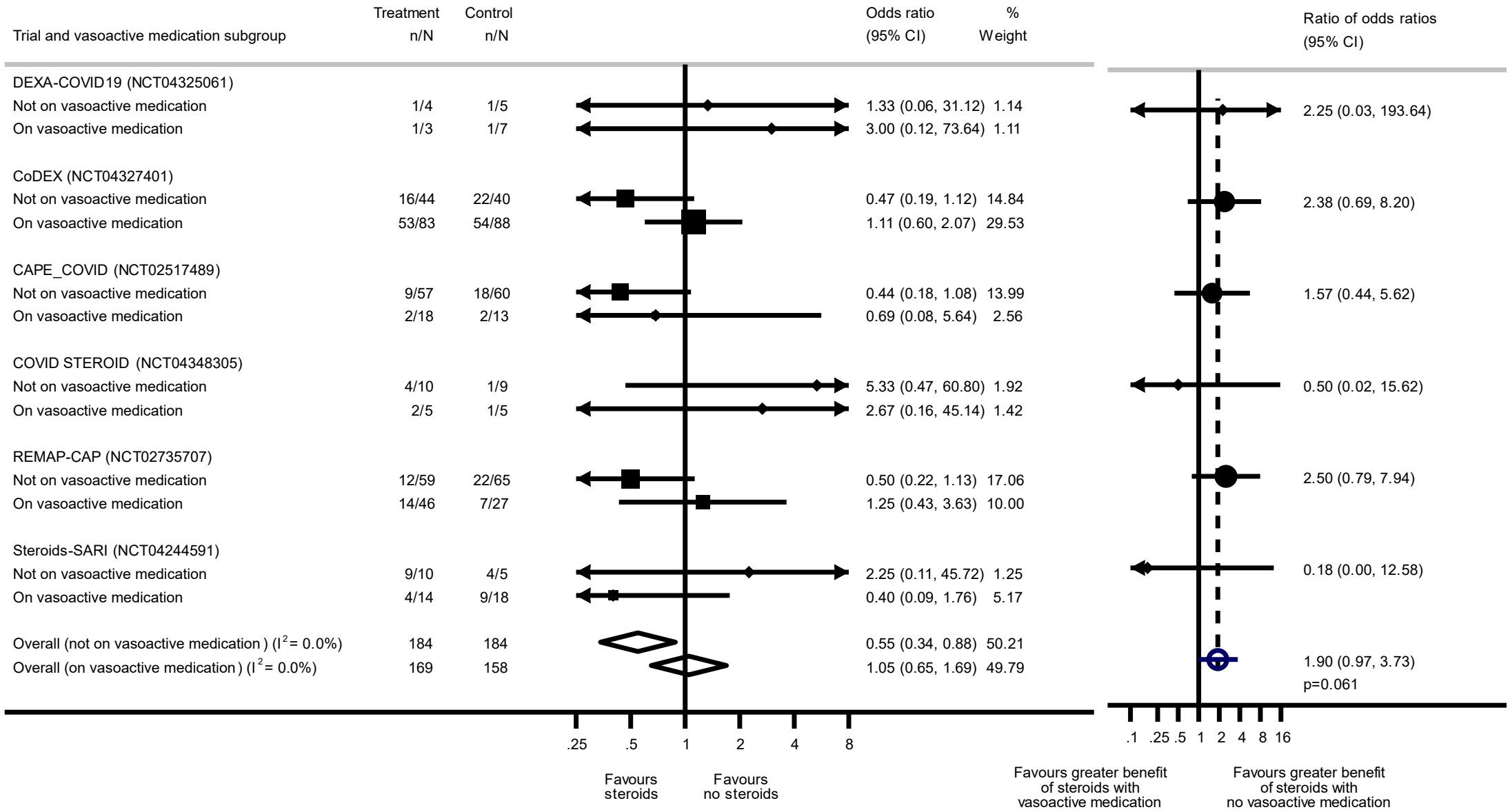
World Health Organization

Figure 2. Association Between Corticosteroids and 28-Day All-Cause Mortality in Each Trial, Overall, and According to Corticosteroid Drug

Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients		Odds ratio (95% CI)	Weight, %
			Steroids	No steroids		
Dexamethasone						
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)	0.92
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)	18.69
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)	57.00
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)	76.60
Hydrocortisone						
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	11/75	20/73	0.46 (0.20-1.04)	6.80
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	6/15	2/14	4.00 (0.65-24.66)	1.39
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	26/105	29/92	0.71 (0.38-1.33)	11.75
Subgroup fixed effect			43/195	51/179	0.69 (0.43-1.12)	19.94
Methylprednisolone						
Steroids-SARI	NCT04244591	High: 40 mg every 12 h intravenously	13/24	13/23	0.91 (0.29-2.87)	3.46
Overall (fixed effect) $P = .31$ for heterogeneity; $I^2 = 15.6\%$			222/678	425/1025	0.66 (0.53-0.82)	100.0
Overall (random effects[a])			222/678	425/1025	0.70 (0.48-1.01)	




Trial and IMV subgroup
Steroids n/N
No Steroids n/N
Odds ratio (95% CI)
% Weight
Ratio of odds ratios (95% CI)
CAPE_COVID (NCT02517489)
No IMV 1/14 3/14 0.28 (0.03, 3.11) 0.81 1.72 (0.06, 51.26)
IMV 10/61 17/59 0.48 (0.20, 1.17) 6.01
COVID STEROID (NCT04348305)
No IMV 2/8 2/8 1.00 (0.10, 9.61) 0.91 16.71 (0.68, 410.29)
IMV 4/7 0/6 16.71 (0.68, 409.09) 0.46
REMAP-CAP (NCT02735707)
No IMV 8/37 19/43 0.35 (0.13, 0.94) 4.79 4.03 (1.00, 16.28)
IMV 18/68 10/49 1.40 (0.58, 3.38) 6.04
Steroids-SARI (NCT04244591)
No IMV 3/11 4/9 0.47 (0.07, 3.04) 1.34 3.95 (0.28, 55.46)
IMV 10/13 9/14 1.85 (0.34, 10.05) 1.63
.15 .25 .5 1 2 4
Favours steroids
Favours no steroids
Favours greater benefit of steroids with IMV
.25 .5 1 2 4 8 16
Favours greater benefit of steroids with no IMV


Trial and vasoactive medication subgroup
Treatment n/N
Control n/N
Odds ratio (95% CI)
% Weight
Ratio of odds ratios (95% CI)
DEXA-COVID19 (NCT04325061)
Not on vasoactive medication 1/4 1/5 1.33 (0.06, 31.12) 1.14 2.25 (0.03, 193.64)
On vasoactive medication 1/3 1/7 3.00 (0.12, 73.64) 1.11
CoDEX (NCT04327401)
Not on vasoactive medication 16/44 22/40 0.47 (0.19, 1.12) 14.84 2.38 (0.69, 8.20)
On vasoactive medication 53/83 54/88 1.11 (0.60, 2.07) 29.53
CAPE_COVID (NCT02517489)
Not on vasoactive medication 9/57 18/60 0.44 (0.18, 1.08) 13.99 1.57 (0.44, 5.62)
On vasoactive medication 2/18 2/13 0.69 (0.08, 5.64) 2.56
COVID STEROID (NCT04348305)
Not on vasoactive medication 4/10 1/9 5.33 (0.47, 60.80) 1.92 0.50 (0.02, 15.62)
On vasoactive medication 2/5 1/5 2.67 (0.16, 45.14) 1.42
REMAP-CAP (NCT02735707)
Not on vasoactive medication 12/59 22/65 0.50 (0.22, 1.13) 17.06 2.50 (0.79, 7.94)
On vasoactive medication 14/46 7/27 1.25 (0.43, 3.63) 10.00
Steroids-SARI (NCT04244591)
Not on vasoactive medication 9/10 4/5 2.25 (0.11, 45.72) 1.25 0.18 (0.00, 12.58)
On vasoactive medication 4/14 9/18 0.40 (0.09, 1.76) 5.17
Overall (not on vasoactive medication) (I^2= 0.0%) 184 184 0.55 (0.34, 0.88) 50.21
Overall (on vasoactive medication) (I^2= 0.0%) 169 158 1.05 (0.65, 1.69) 49.79 1.90 (0.97, 3.73) p=0.061
.25 .5 1 2 4 8
.1 .25 .5 1 2 4 8 16
Favours steroids
Favours no steroids
Favours greater benefit of steroids with vasoactive medication
Favours greater benefit of steroids with no vasoactive medication

Publication, Dissemination and Implementation of WHO recommendations

Lisa Askie
Scientist,
Methods Lead,
Quality Norms & Standards, WHO

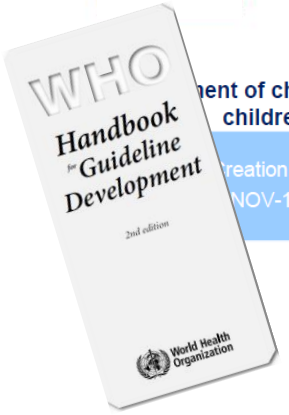
World Health Organization

HEALTH EMERGENCIES programme

Living guidelines: trustworthy *and* up-to-date

World Health Organization

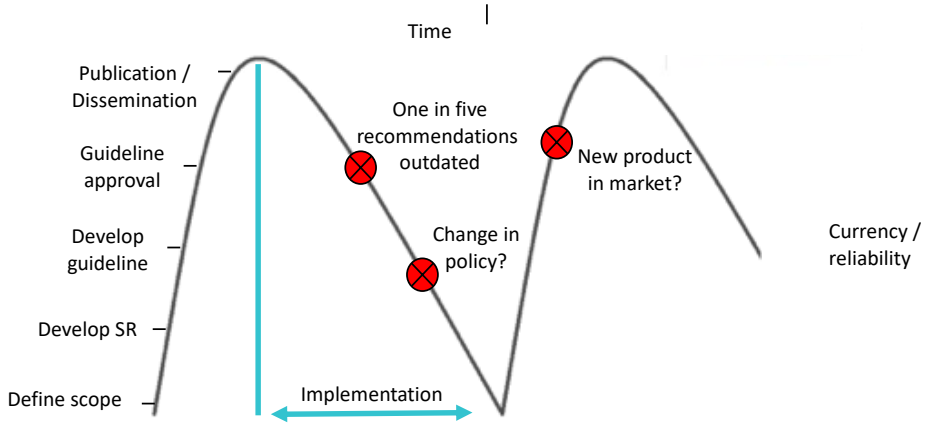
Conventional guidelines are **updated every 3-5 years**



…ent of chronic pain in children

…reation: …NOV-19 | Planning Clearance Submission: 15-JAN-20 | 1x | GRC Decision: 15-JUL-20 | 112 days 3.7 mo | 1st Submission of Guideline Text: 4-NOV-20 | 2x | GRC Decision: 18-NOV-20 | Date of Publication: 22-DEC-2020 | 404 days (13.5 mo)

Current Model: Intermittently updated guidelines



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

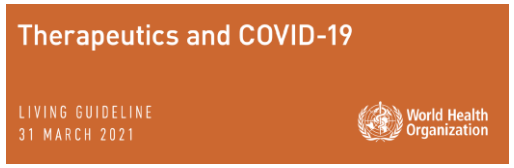
Living Evidence: Continuously updated guidelines

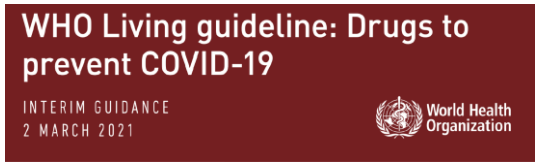
REMDESIVIR GUIDELINE

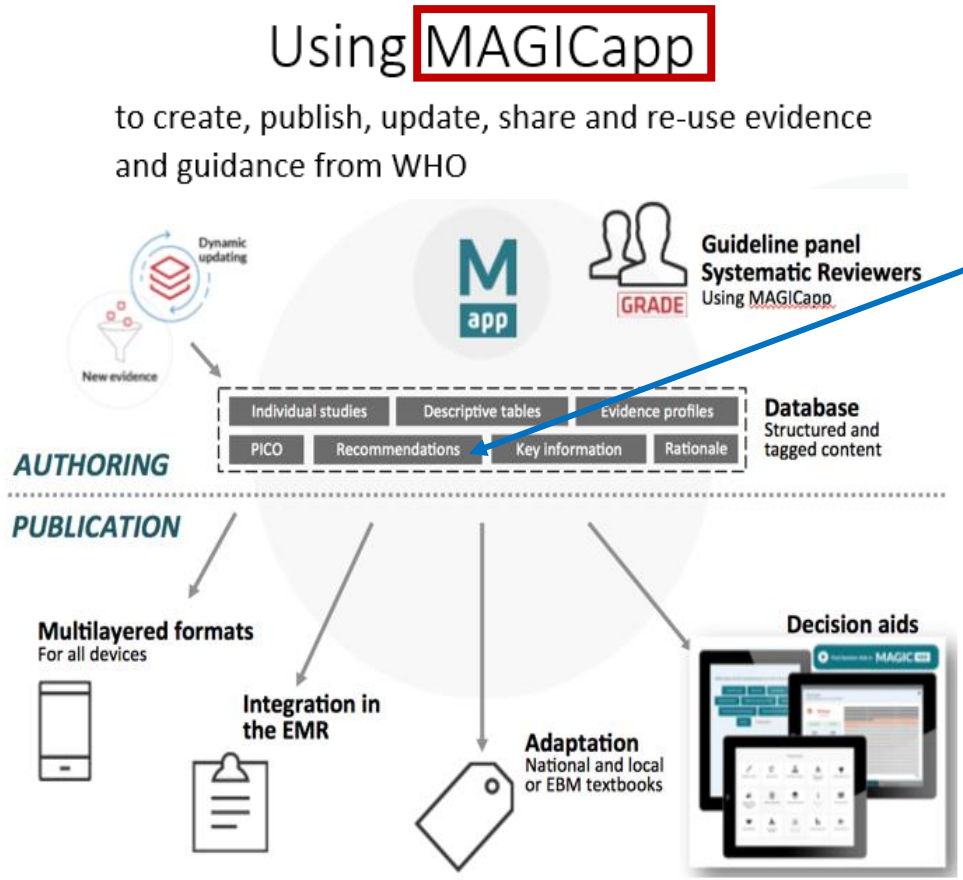
- **Improves agility and responsiveness** of WHO guidance by **shortening time from availability of relevant evidence to use <u>at country level</u>**

Platforms with digitally structured data

for production of living evidence and guidance + publication, dissemination, adaptation, in-country utilization







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

Overview

The WHO *Therapeutics and COVID-19: living guideline* contains the Organization's most up-to-date recommendations for the use of therapeutics in the treatment of COVID-19. The **latest version** of this living guideline is available in pdf format (via the 'Download' button) and via an online platform, and is updated regularly as new evidence emerges.

This fourth version of the WHO guideline now contains six recommendations, including a new recommendation regarding ivermectin. This latest update was initiated in response to international attention on ivermectin as a potential treatment for COVID-19. No further updates to the previous existing recommendations were made in this latest version.

The WHO *Therapeutics and COVID-19: living guideline* currently includes a:

- ** **NEW** ** recommendation not to use ivermectin in patients with COVID-19 except in the context of a clinical trial (published 31 March 2021);
- strong recommendation against hydroxychloroquine in patients with COVID-19 of any severity (published 17 December 2020);
- strong recommendation against lopinavir/ritonavir in patients with COVID-19 of any severity (published 17 December 2020);
- conditional recommendation against remdesivir in hospitalized patients with COVID-19 (published 20 November 2020);
- strong recommendation for systemic corticosteroids in patients with severe and critical COVID-19 (published 2 September 2020); and
- conditional recommendation against systemic corticosteroids in patients with non-severe COVID-19 (published 2 September 2020).

2. MAGICapp online platform

https://app.magicapp.org/#/guideline/nBkO1E

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.

Research evidence (1) | Evidence to Decision | Justification | Practical info | Decision Aids | References

Hydroxychloroquine + usual care vs Usual care
Patients with COVID-19 infection (all disease severities)
12 Outcomes | Graphical view | Summary

Outcome / Timeframe	Study results and measurements	Absolute effect estimates: Standard care	Absolute effect estimates: 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 10859 patients in 29 studies	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	Hydroxychloroquine probably does not reduce mortality.

World Health Organization

Health Topics | Countries | Newsr

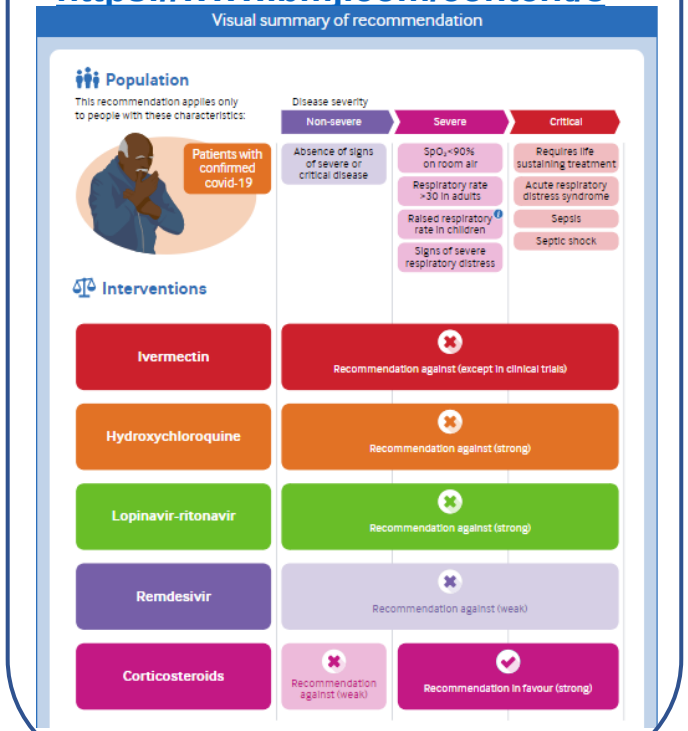
Home / Publications / Overview / Therapeutics and COVID-19: living guideline

Therapeutics and COVID-19: living guideline

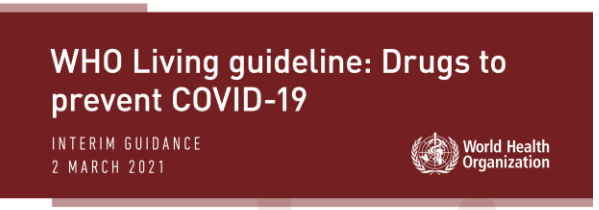
31 March 2021 | COVID-19: Clinical care

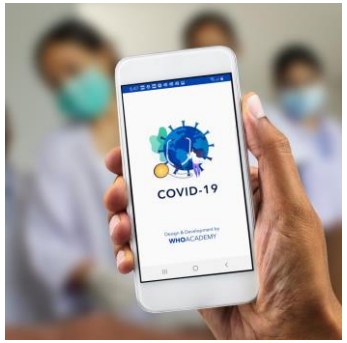
3. *BMJ* journal publication

https://www.bmj.com/content/3



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**

Apple Store: https://apps.apple.com/us/app/who-academy/id1506019873?ls=1
Google Play: https://play.google.com/store/apps/details?id=org.who.WHOA
(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

World Health Organization

HEALTH EMERGENCIES programme

Drug Specific Recommendations (Part 2)

World Health Organization

HEALTH EMERGENCIES programme

Systemic corticosteroids

(published 2 September 2020)

Sebastián Ugarte MD
Intensivist, Specialist in Critical care, ICU Director,
Andrés Bello University - INDISA
Santiago, Chile

World Health Organization

HEALTH EMERGENCIES programme

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.

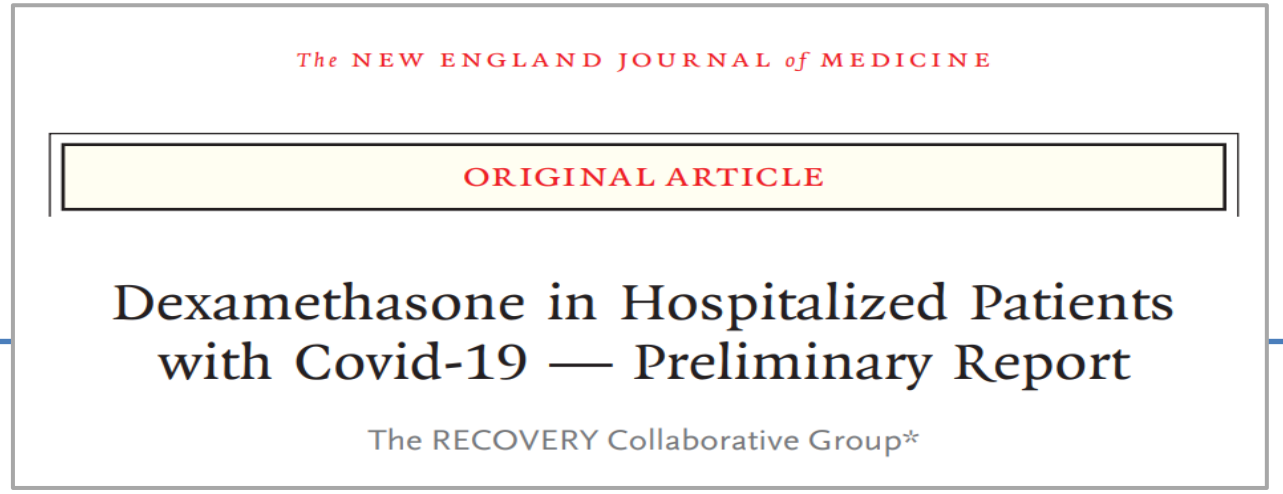

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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

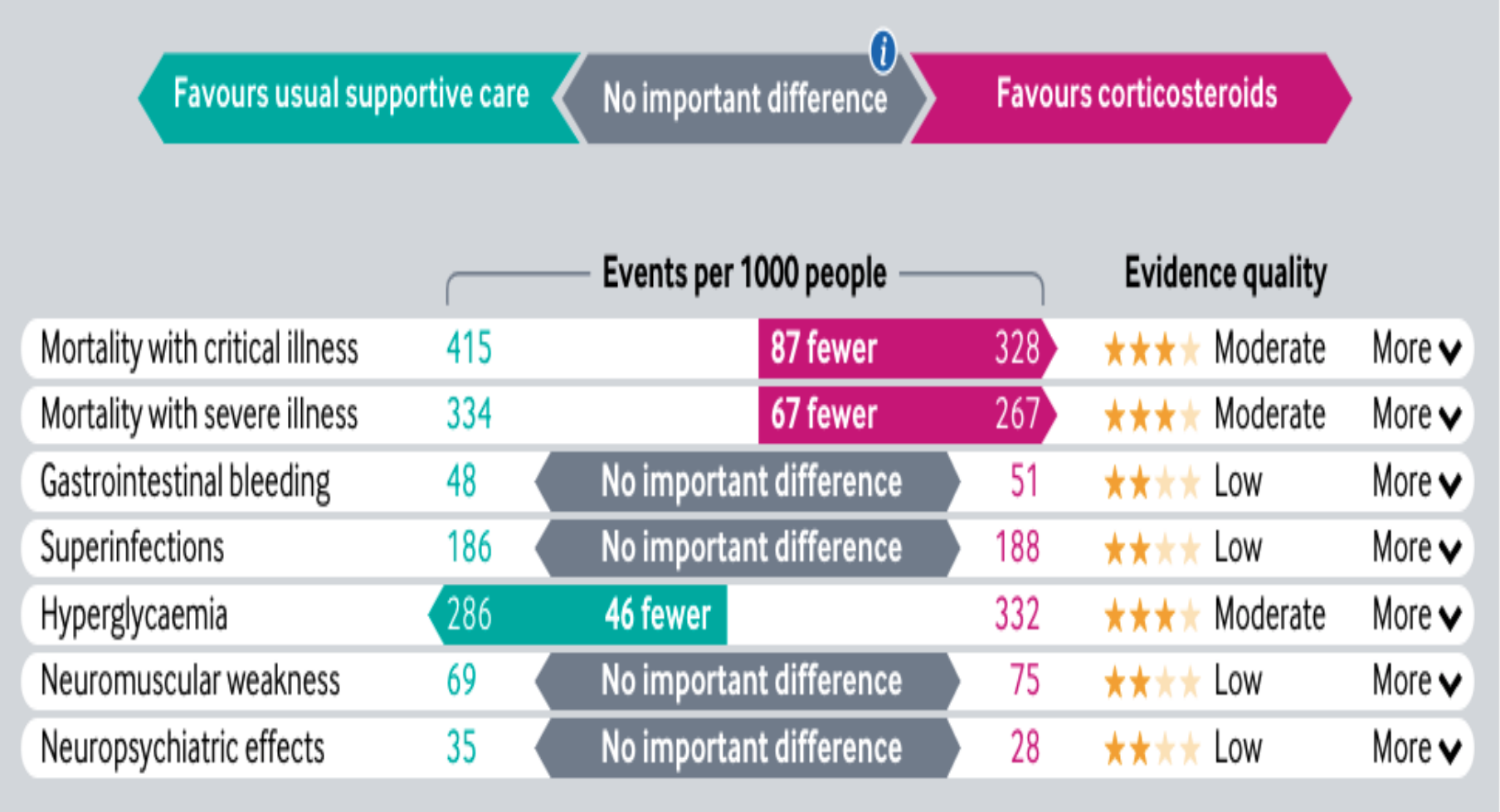
The RECOVERY trial

- **The RECOVERY trial[6] 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



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.

Corticosteroid	**Dosage**
Dexamethasone	6 mg every 24 hours
Hydrocortisone	160 mg every 24 hours (as 50 mg every 8 hours or as 100 mg every 12 hours)
Prednisone	40 mg every 24 hours
Methylprednisolone	32 mg every 24 hours (as 8 mg every 6 hours or 16 mg every 12 hours)

Subgroup analysis

Visual summary of recommendation

Population

This recommendation applies only to people with these characteristics:

Patients with confirmed covid-19

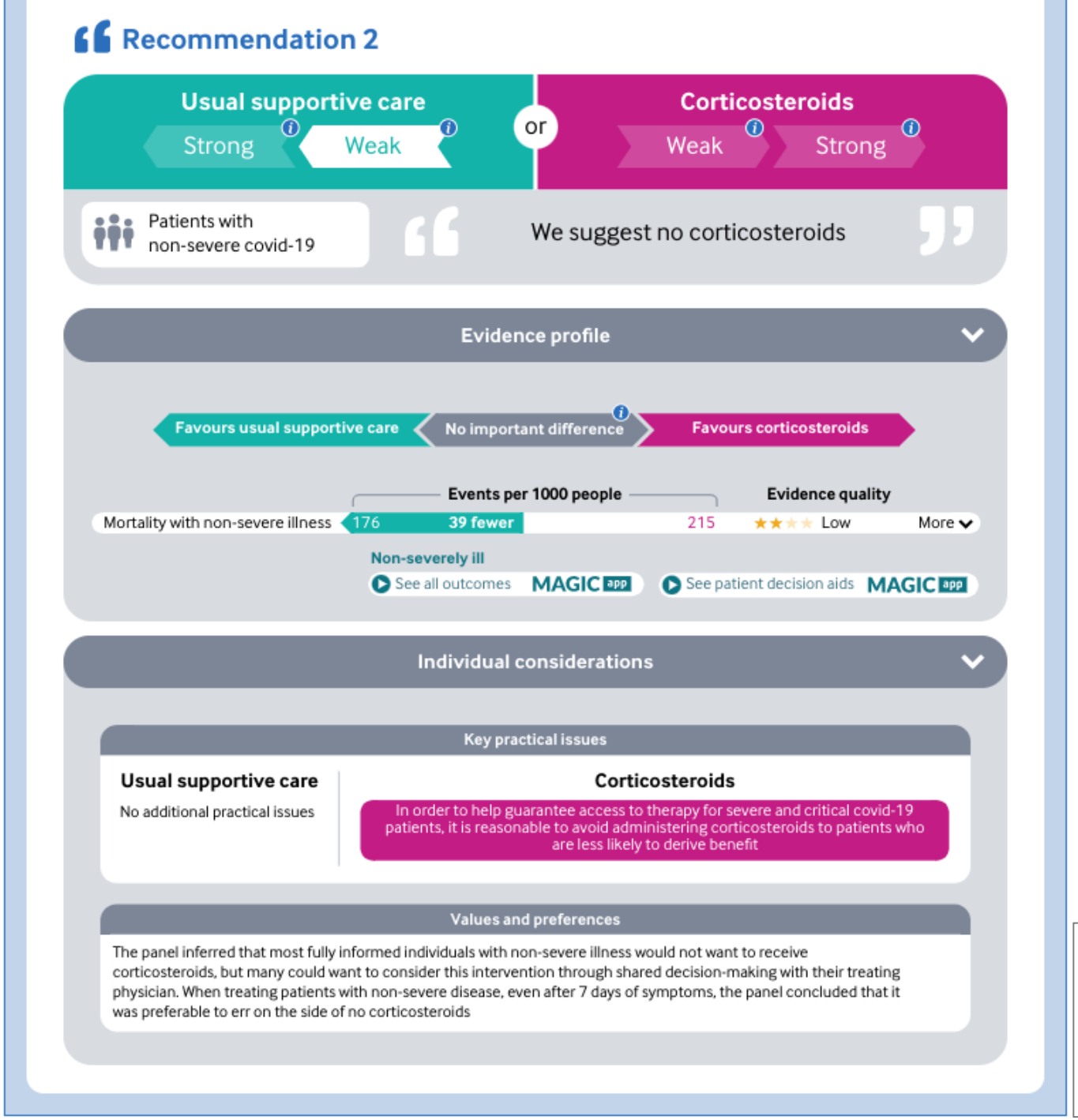
Disease severity

Non-severe	Severe	Critical
Absence of signs of severe or critical disease	SpO_2<90% on room air	Requires life sustaining treatment
	Respiratory rate >30 in adults	Acute respiratory distress syndrome
	Raised respiratory rate in children	Sepsis
	Signs of severe respiratory distress	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/

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.**

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

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Remdesivir in COVID-19: summary of recommendations

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.**

List of Trials that informed the Guidance (Remdesivir)

Table 2. Summary of trials and trial characteristics informing the remdesivir recommendation

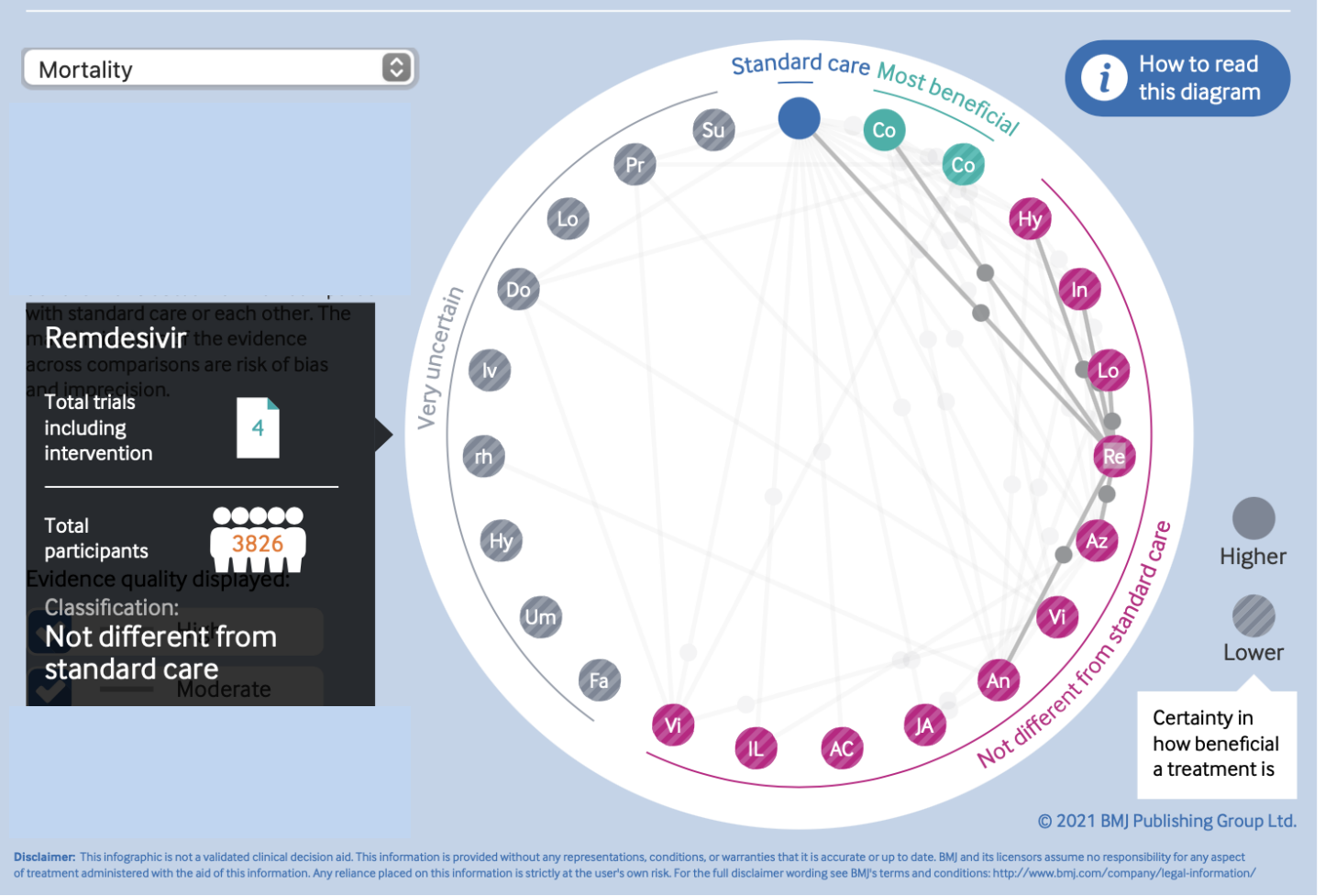
Study	N	Country	Mean age (years)	Severity (as per WHO criteria)	% IMV (at baseline)	Treatments (dose and duration)	Outcomes
Biegel (ACTT-1)	1063	United States, Europe, Asia	58.9	Non-severe (11.3%) Severe[a] (88.7%)	44.1%	Remdesivir IV (100 mg/day for 10 days)	-Mortality -Adverse events -Time to clinical 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

Notes: 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 SpO_2 < 94% on room air OR respiratory rate > 24 breaths /min; [b] defined severe as requiring oxygen support; [c] defined severe as SpO_2 < 94% on room air
*Only SIMPLE MODERATE was included in the analysis, as SIMPLE SEVERE *(14)* did not have a placebo/usual care arm.

WHO SOLIDARITY Trial on 15 October 2020
11,266 randomized patients

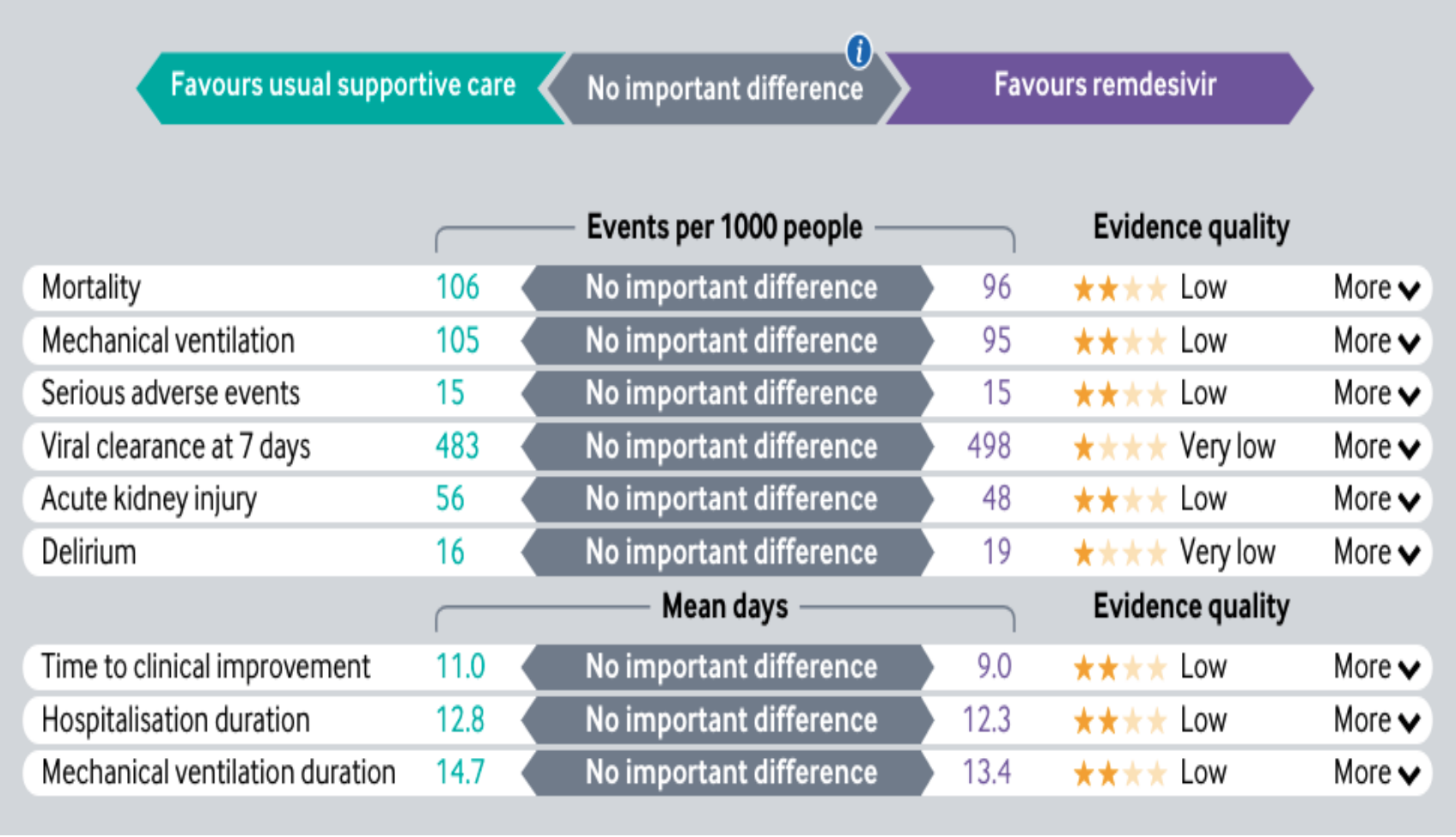
- 2570 to Remdesivir
- 954 to Hydroxychloroquine and
- 1411 to Lopinavir-Ritonavir,
- 6,331 to usual care)

LNMA Diagram for Remdesivir



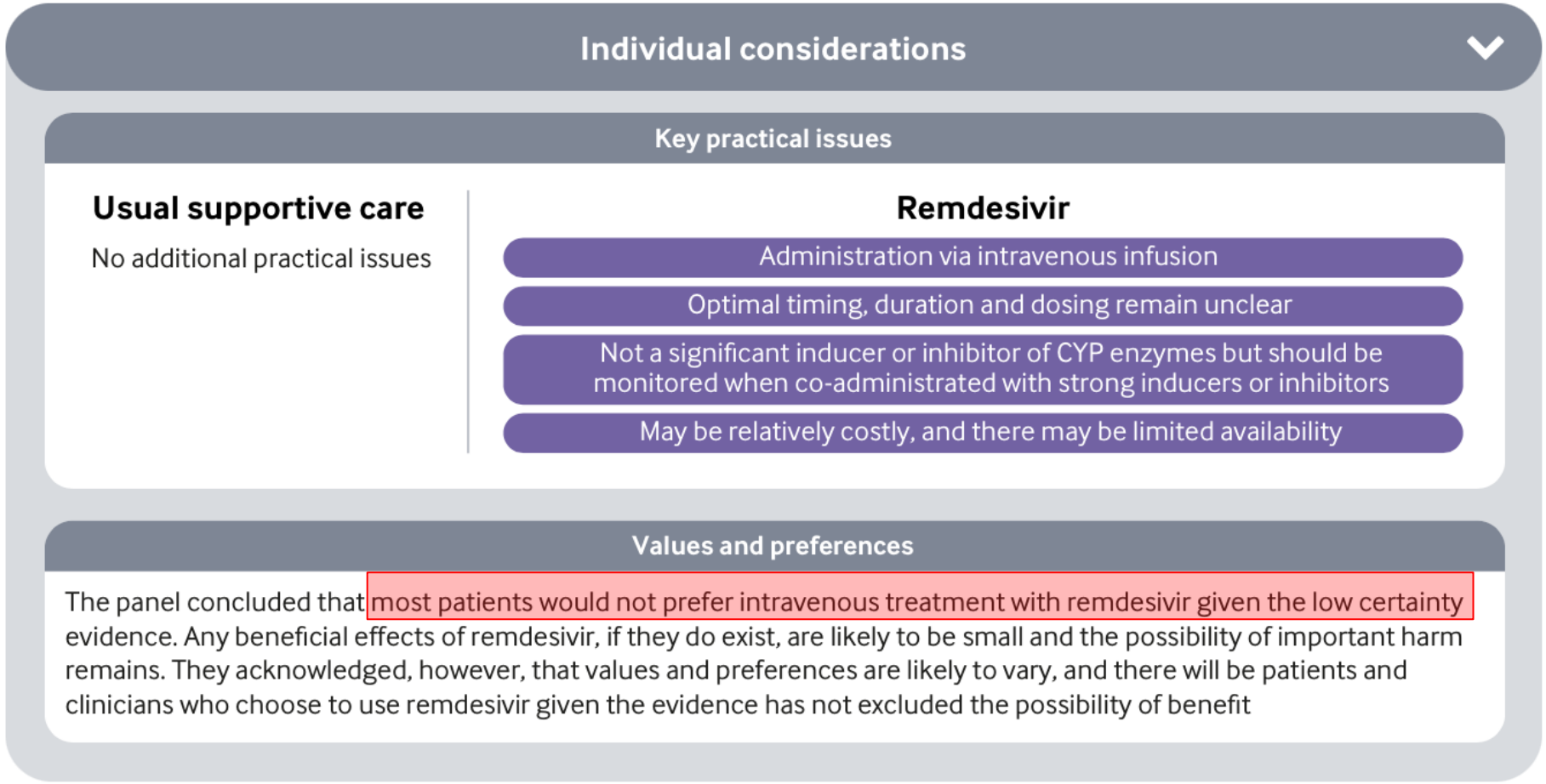
Remdesivir

4 randomized trials
7333 participants



	Events per 1000 people			Evidence quality	
Mortality	106	No important difference	96	★★☆☆ Low	More
Mechanical ventilation	105	No important difference	95	★★☆☆ Low	More
Serious adverse events	15	No important difference	15	★★☆☆ Low	More
Viral clearance at 7 days	483	No important difference	498	★☆☆☆ Very low	More
Acute kidney injury	56	No important difference	48	★★☆☆ Low	More
Delirium	16	No important difference	19	★☆☆☆ Very low	More
	Mean days			**Evidence quality**	
Time to clinical improvement	11.0	No important difference	9.0	★★☆☆ Low	More
Hospitalisation duration	12.8	No important difference	12.3	★★☆☆ Low	More
Mechanical ventilation duration	14.7	No important difference	13.4	★★☆☆ Low	More

Special Considerations



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

Recommendation as published in Guideline

Check for updates

For numbered affiliations see end of article.
Correspondence to: Bram Rochwerg rochwerg@mcmaster.ca or Michael Jacobs michael.jacobs@ucl.ac.uk
Additional material is published online only. To view please visit the journal online
Cite this as: *BMJ* 2020;370:m3379
http://dx.doi.org/10.1136/bmj.m3379

RAPID RECOMMENDATIONS

A living WHO guideline on drugs for covid-19

Bram Rochwerg, [1,2,a,c] Reed AC Siemieniuk, [1,2,a,*] Thomas Agoritsas, [1,3,4,*,b] François Lamontagne, [5,*,b] Lisa Askie, [6] Lyubov Lytvyn, [1,*] Arnav Agarwal, [7,*] Yee-Sin Leo, [8,a,b,c] Helen Macdonald, [9,*] Linan Zeng, [1,*] Wagdy Amin, [10,a,c] Erlina Burhan, [11,a,c] Frederique Jacquerioz Bausch, [12,a,c] Carolyn S Calfee, [13,b,c] Maurizio Cecconi, [14,a,b,c] Duncan Chanda, [15,a,c] Bin Du, [16,a,c] Heike Geduld, [17,a,b,c] Patrick Gee, [18,a,b,c] Nerina Harley, [19,c] Madiha Hashimi, [20,a,c] Beverly Hunt, [21,c] Sushil K Kabra, [22,a,c] Seema Kanda, [23,a,b,c] Leticia Kawano-Dourado, [24,a,b,c] Yae-Jean Kim, [25,a,b,c] Niranjan Kissoon, [26,a,b,c] Arthur Kwizera, [27,a,b,c] Imelda Mahaka, [28,a,c] Hela Manai, [29,a,b,c] Greta Mino, [30,a,c] Emmanuel Nsutebu, [31,a,c] Natalia Pshenichnaya, [32,a,c] Nida Qadir, [33,a,b,c] Saniya Sabzwari, [34,a,c] Rohit Sarin, [35,a,b,c] Manu Shankar-Hari, [36,c] Michael Sharland, [37,a,c] Yinzhong Shen, [38,a,b,c] Shalini Sri Ranganathan, [39,a,c] Joao P Souza, [40,a,c] Miriam Stegemann, [41,c] An De Sutter, [42,c] Sebastian Ugarte, [43,a,c] Sridhar Venkatapuram, [44,a,c] Vu Quoc Dat, [45,a,c] Dubula Vuyiseka, [46,a,c] Ananda Wijewickrama, [47,a,c] Brittany Maguire, [48,*] Dena Zeraatkar, [1,*] Jessica J Bartoszko, [1,*] Long Ge, [1,49,*] Romina Brignardello-Petersen, [1,*] Andrew Owen, [50,*] Gordon Guyatt, [1,2,*] Janet Diaz, [6,*,d] Michael Jacobs, [51,a,c,d] Per Olav Vandvik [4,52,*,d]

ABSTRACT

CLINICAL QUESTION
What is the role of drug interventions in the treatment of patients with covid-19?

NEW RECOMMENDATION
Increased attention on ivermectin as a potential treatment for covid-19 triggered this recommendation. The panel made a recommendation against ivermectin in patients with covid-19 regardless of disease severity, except in the context of a clinical trial.

PRIOR RECOMMENDATIONS
(*a*) a strong recommendation against the use of hydroxychloroquine in patients with covid-19, regardless of disease severity; (*b*) a strong recommendation against the use of lopinavir-ritonavir in patients with covid-19, regardless of disease severity; (*c*) a strong recommendation for systemic corticosteroids in patients with severe and critical covid-19; (*d*) a conditional recommendation against systemic corticosteroids in patients with non-severe covid-19, and (*e*) a conditional recommendation against remdesivir in hospitalised patients with covid-19.

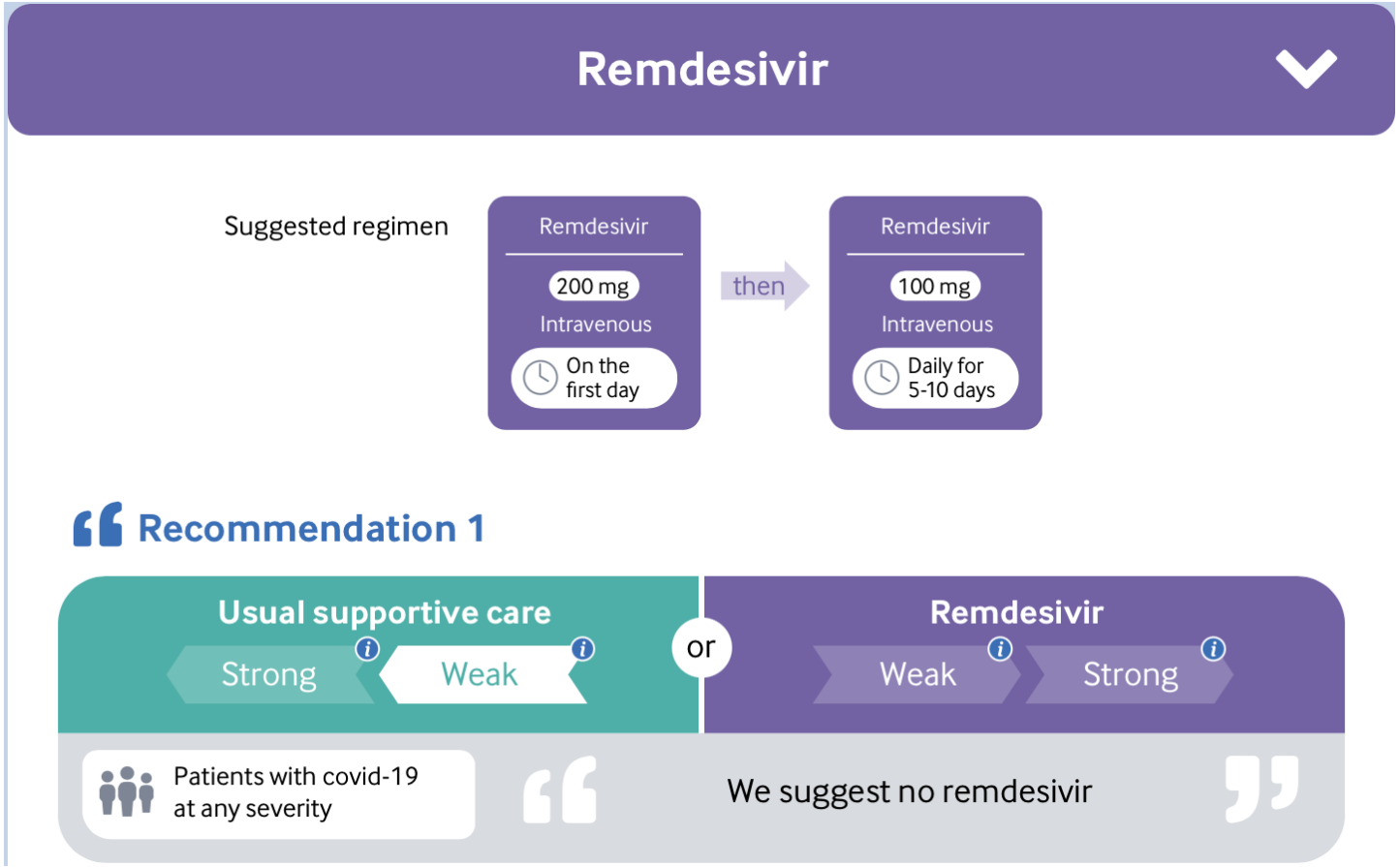
HOW THIS GUIDELINE WAS CREATED
This living guideline is from the World Health Organization (WHO) and provides up to date covid-19 guidance to inform policy and practice worldwide. Magic Evidence Ecosystem Foundation (MAGIC) provided methodological support. A living systematic review with network analysis informed the recommendations. An international guideline development group (GDG) of content experts, clinicians, patients, an ethicist and methodologists produced recommendations following standards for trustworthy guideline development using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

UNDERSTANDING THE NEW RECOMMENDATION
There is insufficient evidence to be clear to what extent, if any, ivermectin is helpful or harmful in treating covid-19. There was a large degree of uncertainty in the evidence about ivermectin on mortality, need for mechanical ventilation, need for hospital admission, time to clinical improvement, and other patient-important outcomes. There is potential for harm with an increased risk of adverse events leading to study drug discontinuation. Applying pre-determined values and preferences, the panel inferred that almost all well informed patients would want to receive ivermectin only in the context of a randomised trial, given that the evidence left a very high degree of uncertainty on important effects.

UPDATES
This is a living guideline. It replaces earlier versions (4 September, 20 November, and 17 December 2020) and supersedes the *BMJ* Rapid Recommendations on remdesivir published on 2 July 2020. The previous versions can be found as data supplements. New recommendations will be published as updates to this guideline.

READERS NOTE
This is the fourth version (update 3) of the living guideline (*BMJ* 2020;370:m3379). When citing this article, please consider adding the update number and date of access for clarity.
This living guideline responds to emerging evidence from randomised controlled trials (RCTs) on existing and new drug treatments for covid-19. Although case numbers are falling in some regions, they are rising in others. Vaccines are linked to falling case numbers and hospitalisations, but most people remain unvaccinated. It is unclear how long protection following vaccination or natural infection will last, or how this might alter with the emergence of new variants. Therefore, the potential for drugs to treat people infected with covid-19 remains of interest and is the focus of this guideline. A linked guideline addresses the role of drugs in the prevention of covid-19 among people who are not infected.[1]

More than 3800 trials on covid-19 interventions have been registered or are ongoing (see section on



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

Remdesivir in COVID-19: summary of recommendations

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

World Health Organization

HEALTH EMERGENCIES programme

Lopinavir/ritonavir in COVID-19: Summary of recommendations

In December 2020, the following WHO recommendation released:[4]

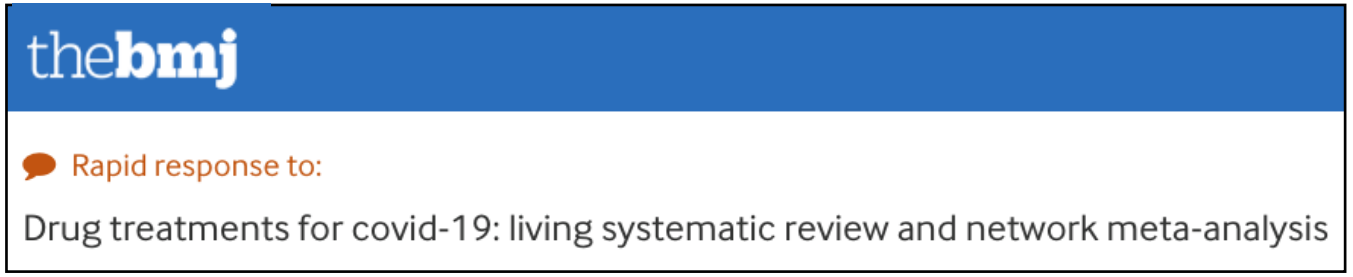
Strong recommendation against

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.

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**



BMJ 2020 ; 370 doi: https://doi.org/10.1136/bmj.m2980

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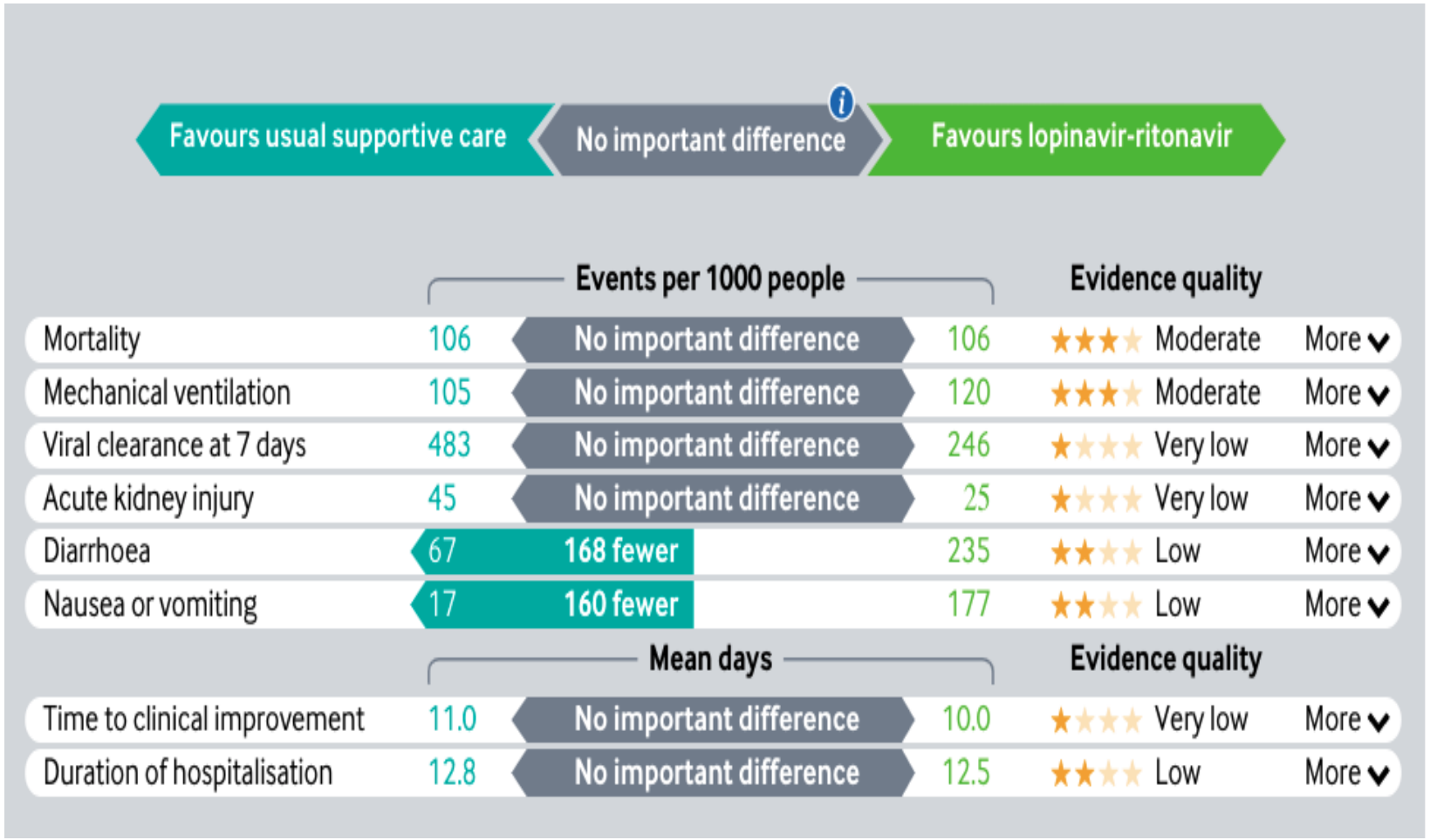
Lopinavir/ritonavir

7 randomized trials
8061 participants



Recommendation 1

Usual supportive care		or	Lopinavir-ritonavir	
Strong	Weak		Weak	Strong

Patients with covid-19 at any severity

We recommend against administering lopinavir/ritonavir

Evidence profile

Favours usual supportive care | No important difference | Favours lopinavir-ritonavir

	Events per 1000 people			Evidence quality	
Mortality	106	No important difference	106	★★★☆ Moderate	More
Mechanical ventilation	105	No important difference	120	★★★☆ Moderate	More
Viral clearance at 7 days	483	No important difference	246	★☆☆☆ Very low	More
Acute kidney injury	45	No important difference	25	★☆☆☆ Very low	More
Diarrhoea	67	168 fewer	235	★★☆☆ Low	More
Nausea or vomiting	17	160 fewer	177	★★☆☆ Low	More
	Mean days			**Evidence quality**	
Time to clinical improvement	11.0	No important difference	10.0	★☆☆☆ Very low	More
Duration of hospitalisation	12.8	No important difference	12.5	★★☆☆ Low	More

See all outcomes MAGIC app See patient decision aids MAGIC app

Individual considerations

Key practical issues

Usual supportive care	lopinavir-ritonavir
No additional practical issues	Should be used with caution in those with severe hepatic impairment
	Contraindicated in breastfeeding mothers
	Risk of drug-drug interactions with potent CYP3A inducers

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/bm

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

World Health Organization

HEALTH EMERGENCIES programme

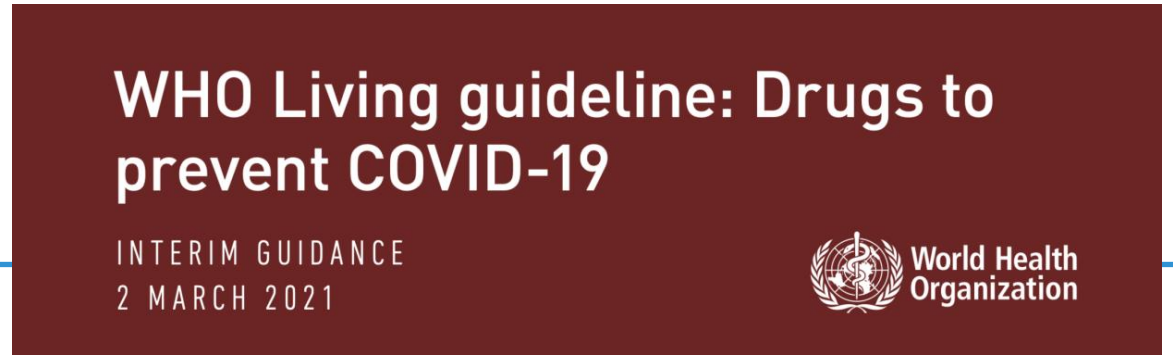
Hydroxychloroquine as prophylaxis for COVID-19: Summary of recommendations

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.



Research trials that included hydroxychloroquine as potential prophylactic agent

- The Guideline Decision Group (GDG) requested an update of the living network meta-analysis of randomized controlled trials of prophylactic interventions for COVID-19.
- The resulting systematic review[2] pooled data from six trials, with a total of 6059 participants who did not have COVID-19 and received hydroxychlroquine.[3,4,5,6,7,8]
  - Three of those trials enrolled participants with known exposure to COVID-19.

medRxiv THE PREPRINT SERVER FOR HEALTH SCIENCES

Prophylaxis for covid-19: living systematic review and network meta-analysis

Jessica J Bartoszko, Reed AC Siemieniuk, Elena Kum, Anila Qasim, Dena Zeraatkar, Long Ge, Mi Ah Han, Behnam Sadeghirad, Arnav Agarwal, Thomas Agoritsas, Derek K Chu, Rachel Couban, Andrea J Darzi, Tahira Devji, Maryam Ghadimi, Kimia Honarmand, Ariel Izcovich, Assem Khamis, Francois Lamontagne, Mark Loeb, Maura Marcucci, Shelley L McLeod, Shahrzad Motaghi, Srinivas Murthy, Reem A Mustafa, John D Neary, Hector Pardo-Hernandez, Gabriel Rada, Bram Rochwerg, Charlotte Switzer, Britta Tendal, Lehana Thabane, Per O Vandvik, Robin WM Vernooij, Andrés Viteri-García, Ying Wang, Liang Yao, Zhikang Ye, Gordon H Guyatt, Romina Brignardello-Petersen

doi: https://doi.org/10.1101/2021.02.24.21250469

Summary of Findings Table (Hydroxychloroquine Prophylaxis)

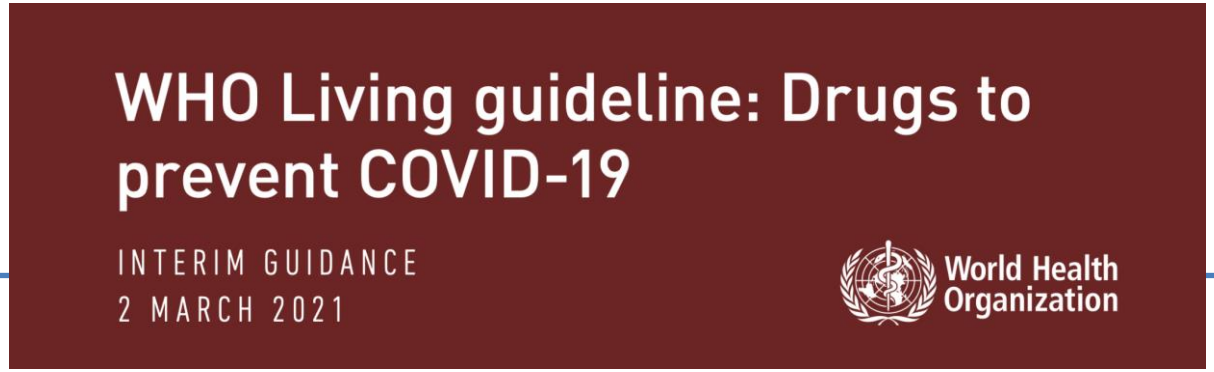
Clinical question/PICO

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

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	 Hydroxychloroquine	Certainty of the evidence (Quality of evidence)	Plain text summary
Mortality	Odds Ratio 0.7 (CI 95% 0.24 - 1.99) Based on data from 4849 patients in 4 studies. (Randomized controlled)	3 per 1000	2 per 1000 Difference: 1 fewer per 1000 (CI 95% 2 fewer - 3 more)	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 per 1000	4 per 1000 Difference: 1 fewer per 1000 (CI 95% 3 fewer - 4 more)	High	Hydroxychloroquine has a small or no effect on hospital admission.
Lab-confirmed COVID-19 diagnosis	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 Difference: 2 more per 1000 (CI 95% 18 fewer - 28 more)	Moderate Due to serious risk of bias [1]	Hydroxychloroquine probably has a small or no effect on lab-confirmed COVID-19 diagnosis.
Adverse events leading to discontinuation	Odds Ratio 2.34 (CI 95% 0.93 - 6.08) Based on data from 3616 patients in 4 studies.	15 per 1000	34 per 1000 Difference: 19 more per 1000 (CI 95% 1 fewer - 70 more)	Moderate Due to serious imprecision [2]	Hydroxychloroquine probably increases adverse events leading to discontinuation.

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.



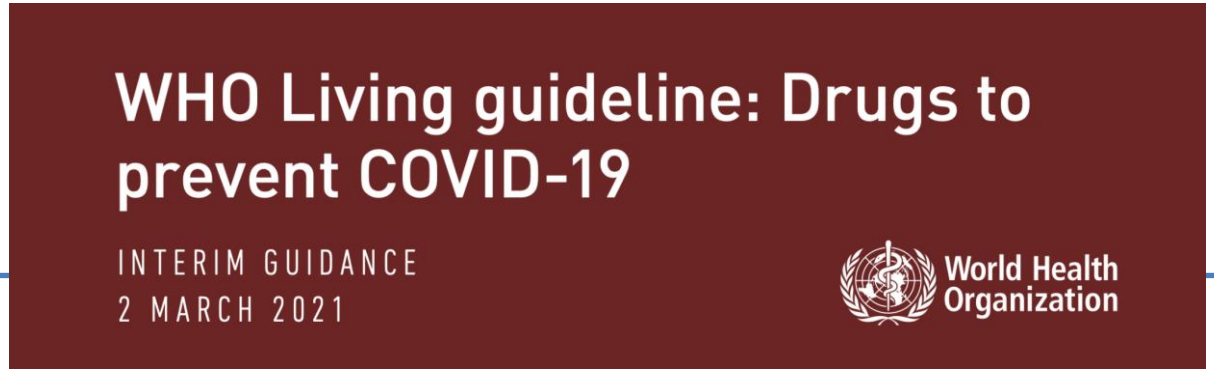
Hydroxychloroquine as prophylaxis for COVID-19: Summary of recommendations

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

World Health Organization

HEALTH EMERGENCIES programme

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

Hydroxychloroquine as a therapeutic for COVID-19: Summary of recommendations

In December 2020, the following WHO recommendation was released:[13]

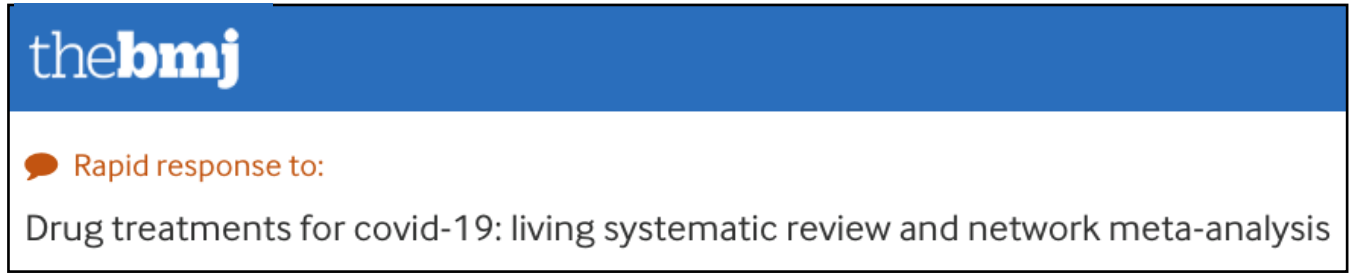
Strong recommendation against

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.

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

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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

Hydroxychloroquine as a therapeutic for COVID-19: Summary of recommendations

In December 2020, the following WHO recommendation was released:[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)

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HEALTH EMERGENCIES programme

Ivermectin in COVID-19: Summary of recommendations

In March 2021, the following WHO recommendation released:

Only in research settings

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.

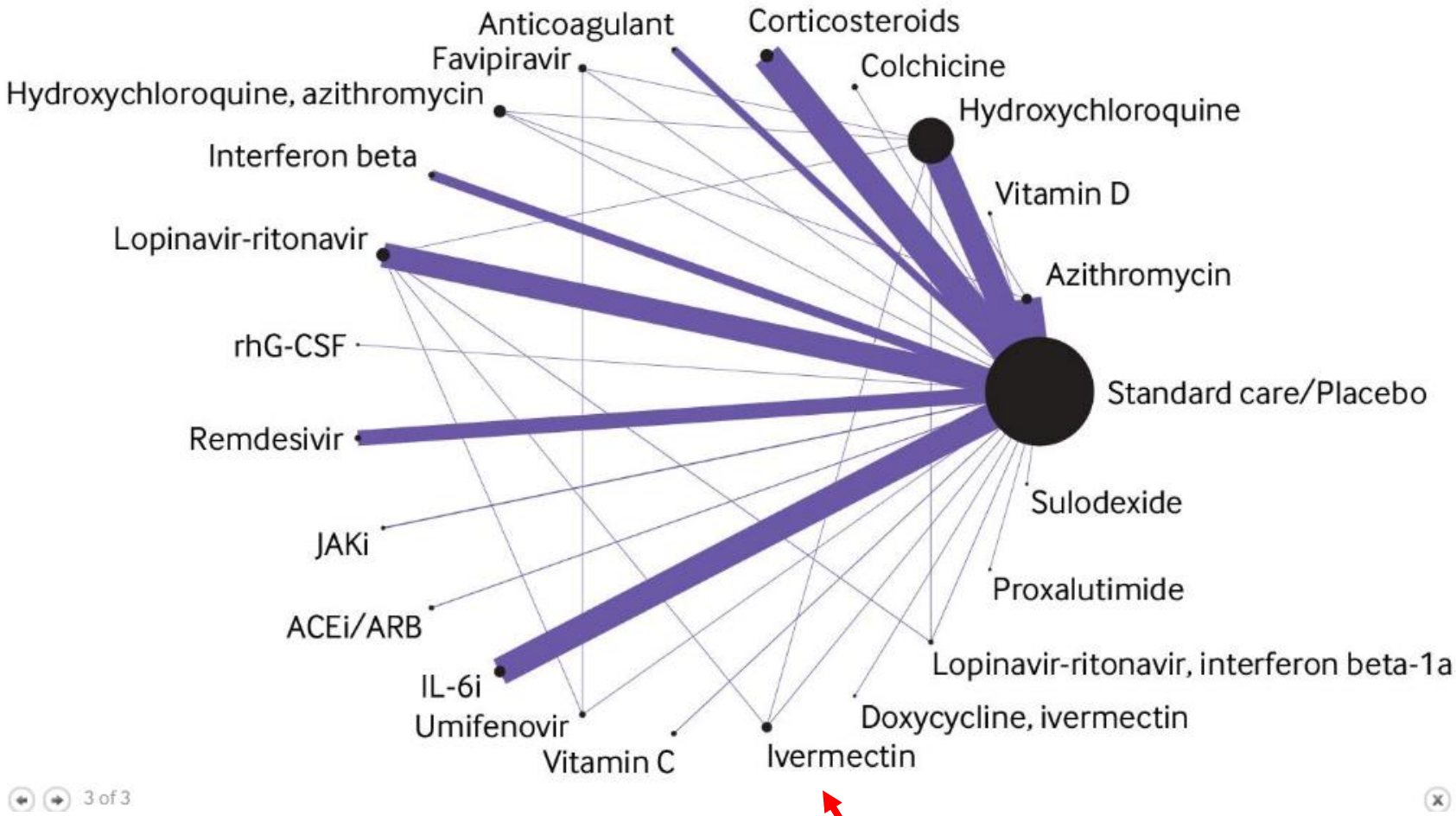
Recommendation: Use ivermectin only in research settings

- 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)

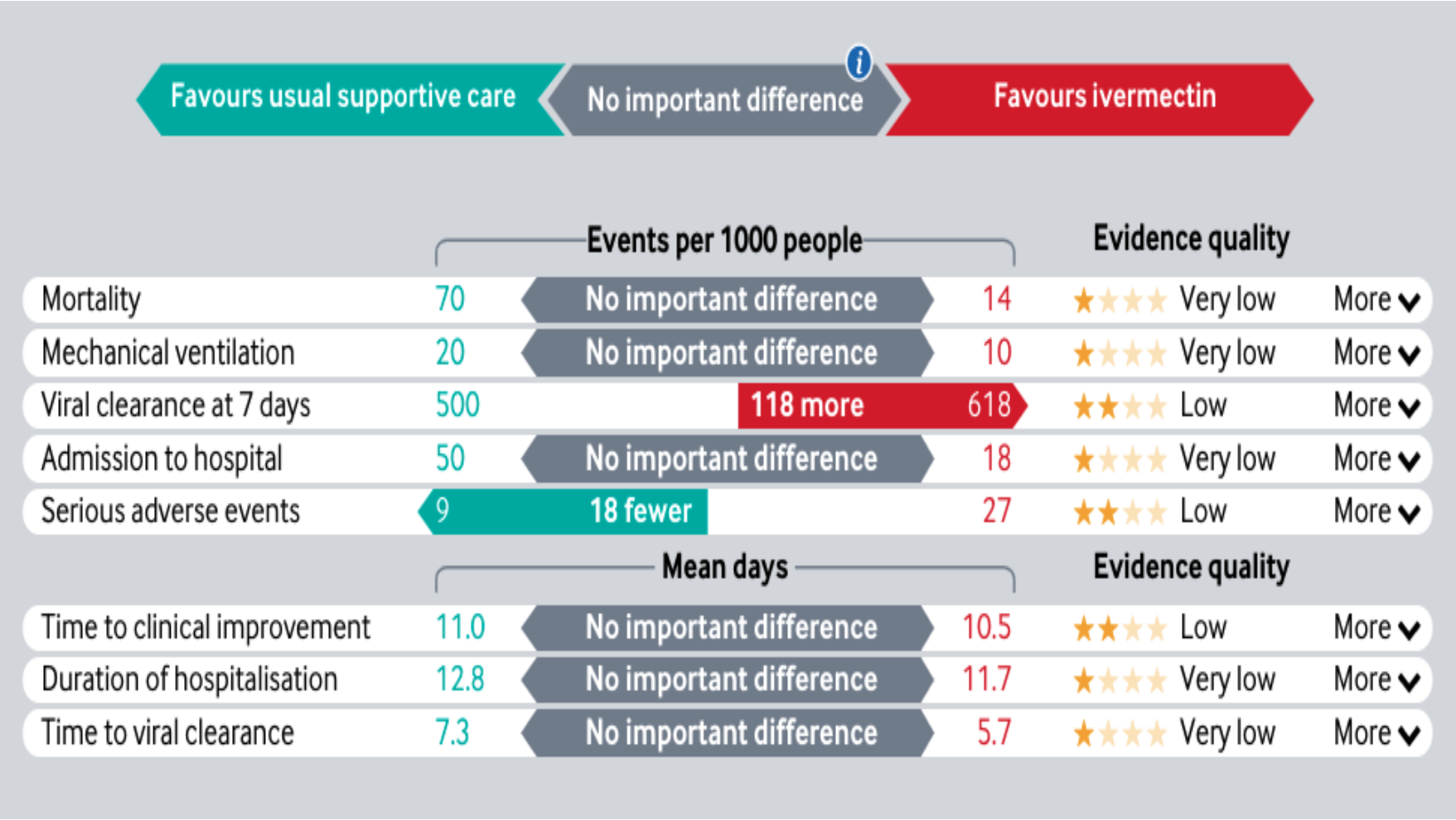
- 16 RCTs contributed to the evidence summary informing this drug
  - Only five directly compared ivermectin with standard of care and reported mortality
  - Quasi-randomized trials, or any RCT that did not use explicit randomization techniques were excluded
  - Of these five RCTs, two were at high risk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

Living Network Meta Analysis (Ivermectin)



Ivermectin

7 randomized trials
1419 participants



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:

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

Future Drugs

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In process

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

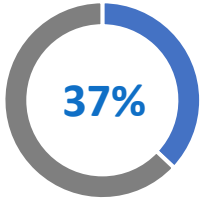
Prospective meta-analysis aim to estimate the effect of anti IL-6 therapy vs usual care in hospitalised patients with COVID-19

- 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

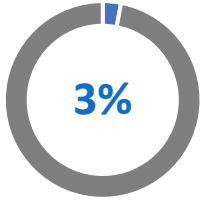
Tocilizumab, sarilumab and siltuximab

(30 RCTs with 10,618 participants)

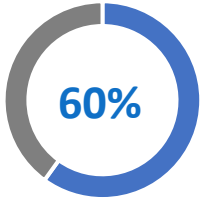
Data sources



Journal



Preprint

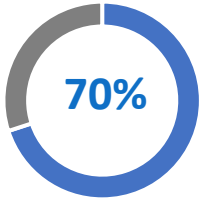


Unpublished data

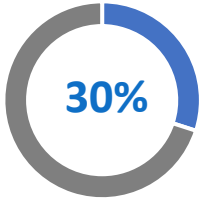
Trial registration

Registered

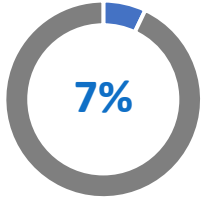
Drug



Tocilizumab

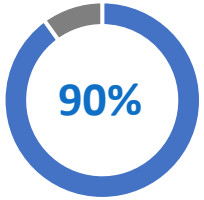


Sarilumab

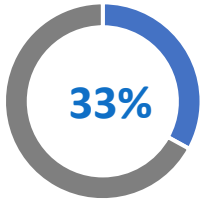


Siltuximab

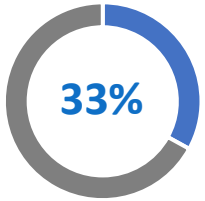
Outcomes reported



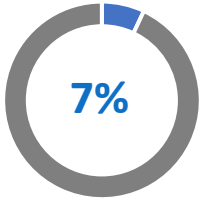
Mortality



Mechanical ventilation



Duration of mechanical ventilation



Adverse effects

30 RCTs- Two large trials RECOVERY and REMAP-CAP contributed the majority of power
Sources – Journals , 1 preprint, unpublished data from PMA
All trials registered and no publication bias
Majority of trials Tocilizumab or Sarilumab , some both

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

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Thank You

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