COVID-19 Clinical Research Coalition

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WEBINAR

COVID-19 therapeutics in resource-constrained settings: Where are we and what do we need?

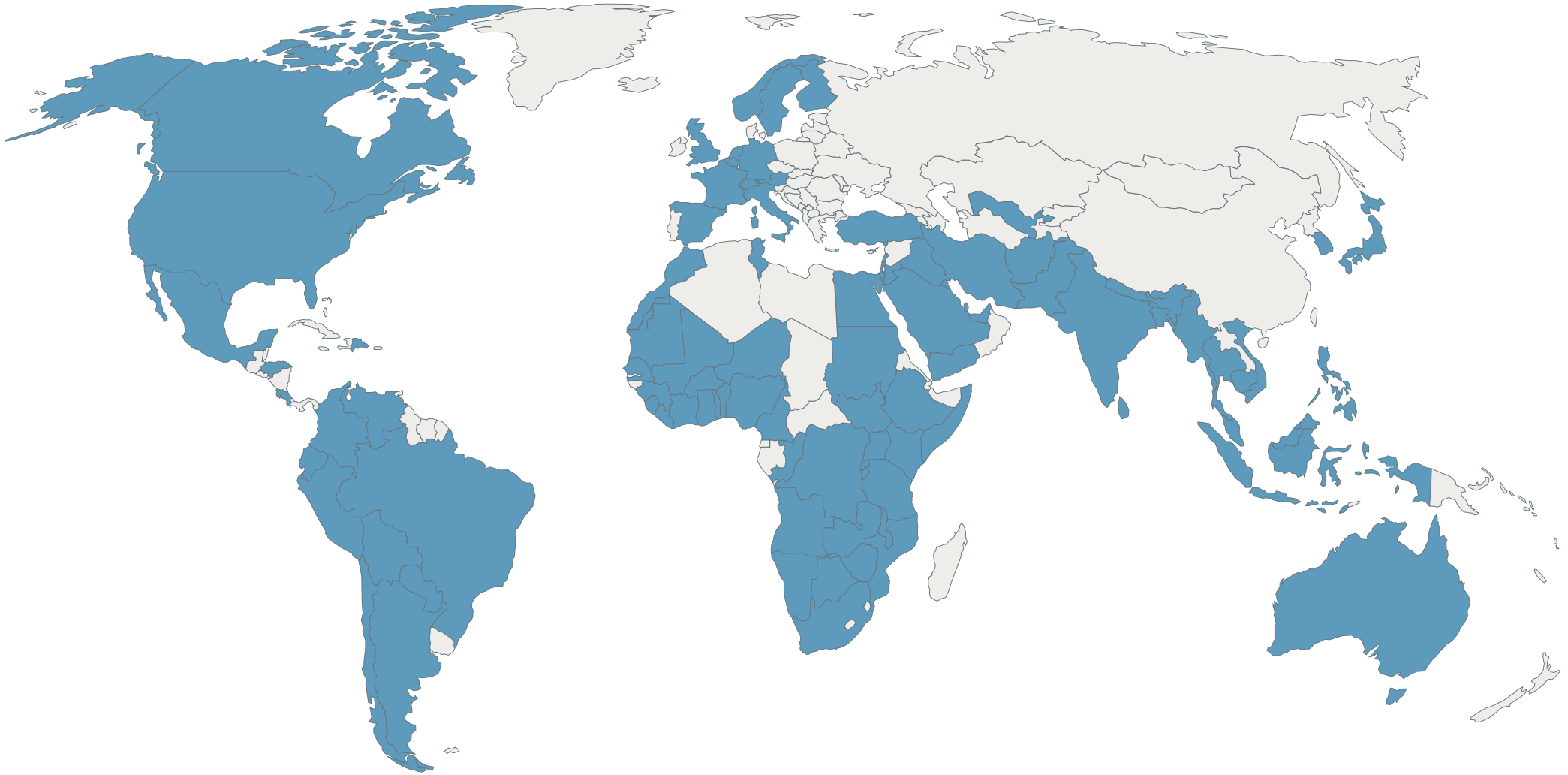
Thursday, 27 January 2022 (1h30')

WATCH THE RECORDING

Countries where coalition members are based

BECOME A COALITION MEMBER

bit.ly/3AyL42D



MODERATOR

COVID-19 Clinical Research Coalition Steering Committee Member

Prof. Patricia García

Cayetano Heredia University

Peru

Prof. Patty J. García, is a Professor at the School of Public Health at Cayetano Heredia University (UPCH) in Lima-Peru and member of the US National Academy of Medicine. She is the former Minister of Health of Peru, former Dean of the School of Public Health at UPCH, and former Chief of the Peruvian National Institute of Health (INS). She is recognized as a leader in Global Health. She is affiliate Professor of the Department of Global Health, at University of Washington and of the School of Public Health at Tulane University. She is actively involved in research and training in Global health, Reproductive health, STI/HIV, HPV and medical informatics. During the pandemic she is leading clinical trials as SOLIDARITY, Convalescent plasma and ivermectin use, and chairs the advising governmental committee on innovations to fight the pandemic.

SPEAKER

Dr Ludovic Reveiz

Pan American Health Organization (PAHO)

USA

Dr Ludovic Reveiz is the regional advisor on Health Research Management within the Department for Evidence and Intelligence for Action in Health at the Pan American Health Organization. He is also the coordinator of the Clinical Management team for the PAHO/WHO Incident Management System that was activated to provide direct emergency response to Ministries of Health and other national authorities for surveillance, laboratory capacity, support health care services, infection prevention control, clinical management and risk communication. He is a physician by training with a MSc in Clinical Epidemiology and a PhD in Public health.

SPEAKER

Dr Jeremy Nel

University of the Witwatersrand

South Africa

Dr Nel is a medical doctor, working as a specialist physician and infectious diseases specialist at the University of the Witwatersrand in Johannesburg, South Africa. He is a member of South Africa's COVID-19 clinical guidelines committee, and has been co-national principal investigator for the WHO Solidarity Trial and the Recovery Trial, among others.

SPEAKER

Prof. Samba Sow

Centre for Vaccine Development

Mali

Prof. Sow is a former Minister of Health for Mali and currently Director General of the National Institute of Public Health, Mali. He is also DG for Centre for Vaccine Development (CVD), Ministry of Health, Mali. In 2020, he was appointed by the Director General of WHO as one of six Special Envoys to WHO on COVID-19, to provide strategic advice and high-level political advocacy and engagement in different parts of the world. He also holds a faculty appointment as Professor at the University of Maryland, Division of Geographic Medicine. He has been Director of CVD-Mali since its inception in 2001. Prof. Sow has received the Prix Laviron de Médecine Tropicale, the Commemorative Fund Lectureship of the American Society of Tropical Medicine and Hygiene, and was also named to the rank of Officer of the National Order of Mali for his efforts in controlling outbreaks in the country. He has authored and co-authored more than 90 scientific articles and chapters.

SPEAKER

COVID-19 Clinical Research Coalition Steering Committee Member

Dr Nathalie Strub-Wourgaft

Drugs for Neglected Diseases *initiative* (DND*i*)

Switzerland

Dr Nathalie Strub-Wourgaft is part of the DND*i* team since 2009, and holds over 35 years of experience in R&D and public health since the past 11 years. Dr Strub-Wourgaft is currently the COVID-19 Response and Pandemic Preparedness Director.

Prior to her current appointment, Dr Strub-Wourgaft was the Director of Neglected Tropical Diseases (NTDs), where she provided strategic and technical oversight to a wide portfolio of R&D and access plans for therapeutic areas covering sleeping sickness, Chagas disease, cutaneous and visceral leishmaniasis, filarial diseases, mycetoma, answering unmet medical needs for neglected populations. Prior to that, Dr Strub-Wourgaft held the Medical Director position at DND*i*, where she oversaw clinical development of the DND*i* kinetoplastid and mycetoma portfolio, and was also responsible for developing and supervising the organization's quality, pharmaco-vigilance, and regulatory activities.

SPEAKER

Ms Leena Menghaney

MSF Access Campaign

India

Leena Menghaney is a lawyer and the Global IP Advisor with the Access Campaign in Médecins Sans Frontières/Doctors Without Borders. She works with other experts and in partnership with patient groups and civil society in the global south to increase access to affordable vaccines, medicines, and tests in low and middle-income countries for diseases like HIV, drug-resistant TB, Hepatitis, cancer, and COVID-19.

SPEAKER

Dr Podjanee Jittamala

Mahidol University

Thailand

Dr Jittamala is an Assistant Professor in the Department of Tropical Hygiene. She is a pediatrician with specialization in infectious diseases. She works in the Hospital for Tropical Diseases and also involved in teaching and research. She received her M.D. degree from Prince of Songkla University, Diploma in Thai Board of Pediatrics from Queen Sirikit National Institute of Child Health (QSNICH), and Diploma in Thai Board of Pediatrics Infections from Chiangmai University. Dr Jittamala's research expertise includes malaria epidemiology and conducting clinical trials to evaluate malaria treatment and elimination strategies in the region. She is also experienced in leading pragmatic trials, assessing the efficacy of treatments or therapies available for malaria in real-life routine practice conditions.

SPEAKER

COVID-19 Clinical Research Coalition Steering Committee Chair

Prof. Nick White

Mahidol-Oxford Research Unit

Thailand

Prof. White is a Wellcome Trust Principal Research Fellow who chairs the Wellcome Trust Tropical Medicine Research Programmes in Southeast Asia. He has lived and worked in Thailand since 1980. His research focus is the pathophysiology and treatment of malaria. He has concentrated on characterising antimalarial pharma-cokinetic-pharmacodynamic relationships to improve the treatment of malaria and reduce the emergence of resistance. This led to artemisinin-based combination treatment for falciparum malaria, and the change to artesunate for severe malaria. He has authored over 1000 scientific publications and 50 book chapters. He is on the Board of the WorldWide Antimalarial Resistance Network and Infectious Diseases Data Observatory, and he co-chairs the WHO GMP technical expert group on prevention and treatment of malaria and the WHO antimalarial treatment guidelines committee. He was appointed a Knight Commander of the Order of St Michael and St George (KCMG) for services to tropical medicine and global health in the 2017 New Year's Honours.

WELCOME AND INTRODUCTION

MODERATOR

Prof. Patricia García

Cayetano Heredia University

Peru

A GLOBAL RESEARCH RESPONSE TO COVID-19 DRIVEN BY THE NEEDS OF LOW RESOURCE SETTINGS

Member commitments:

- Promote **open sharing** of research knowledge & data
- Leverage **global expertise** for high-impact **COVID-19 research**
- Champion equitable & affordable **access** to COVID-19 vaccines, diagnostics & treatments

MEMBERSHIP

- **230 institutional members** (483 representatives) from **66 countries**
- **338 individual members** whose institutions have not joined yet (**75 countries**)
- More than **90 countries** represented

13 TOPIC-SPECIFIC WORKING AND ADVISORY GROUPS

- in ethics, data management & sharing, clinical epidemiology, and more, to address pressing needs identified by researchers in low-resource settings

COALITION OUTPUTS

- Webinars/workshops
- Priority research questions
- Working group projects
- Op-eds, comments & articles
- Protocol repository

COVID-19 Clinical Research Coalition

New Therapeutics Working Group – seeking expert members

- An **advisory role** for the coalition and its extended networks, providing a platform for relevant COVID-19 therapeutics discussions;
- An **advocacy role**, focusing on promoting the therapeutics research that will generate the most relevant evidence for low-resource settings;
- COVID-19 **therapeutics knowledge/evidence generation and synthesis** relevant for low-resource settings.

APPLY TO JOIN THE WORKING GROUP:

bit.ly/3tX3Kbf

COVID-19 Clinical Research Coalition

AGENDA

14:00 (CET)	**WELCOME AND INTRODUCTION**
	Prof. Patricia García, Cayetano Heredia University | Peru
14:05 (CET)	**WHERE ARE WE NOW WITH COVID-19 THERAPEUTICS? A LATIN AMERICAN PERSPECTIVE**
	Dr Ludovic Reveiz, PAHO| USA
14:16 (CET)	**WHERE ARE WE NOW WITH COVID-19 THERAPEUTICS? A SOUTH AFRICAN PERSPECTIVE**
	Dr Jeremy Nel, University of the Witwatersrand | South Africa
14:27 (CET)	**PRACTICAL REALITIES IN COVID-19 TREATMENT NOW. WHAT IS NEEDED?**
	Prof. Samba Sow, Centre for Vaccine Development | Mali
14:38 (CET)	**IMPACT OF RECENT CLINICAL TRIAL RESULTS ON CURRENT RESEARCH PRIORITIES**
	Dr Nathalie Strub-Wourgaft, Drugs for Neglected Diseases Initiative | Switzerland
14:49 (CET)	**IF MEDICINES WORK, HOW CAN WE ENSURE PEOPLE GET THEM?**
	Ms Leena Menghaney, MSF Access Campaign | India
15:00 (CET)	**ROUNDATABLE AND Q&A**
	All presenters **Moderated by Dr Podjanee Jittamala**, Mahidol University | Thailand & **Prof. Nick White**, Mahidol-Oxford Research Unit | Thailand
15:20 (CET)	**CLOSING REMARKS**
	Prof. Patricia García, Cayetano Heredia University | Peru

WHERE ARE WE NOW WITH COVID-19 THERAPEUTICS? A LATIN AMERICAN PERSPECTIVE

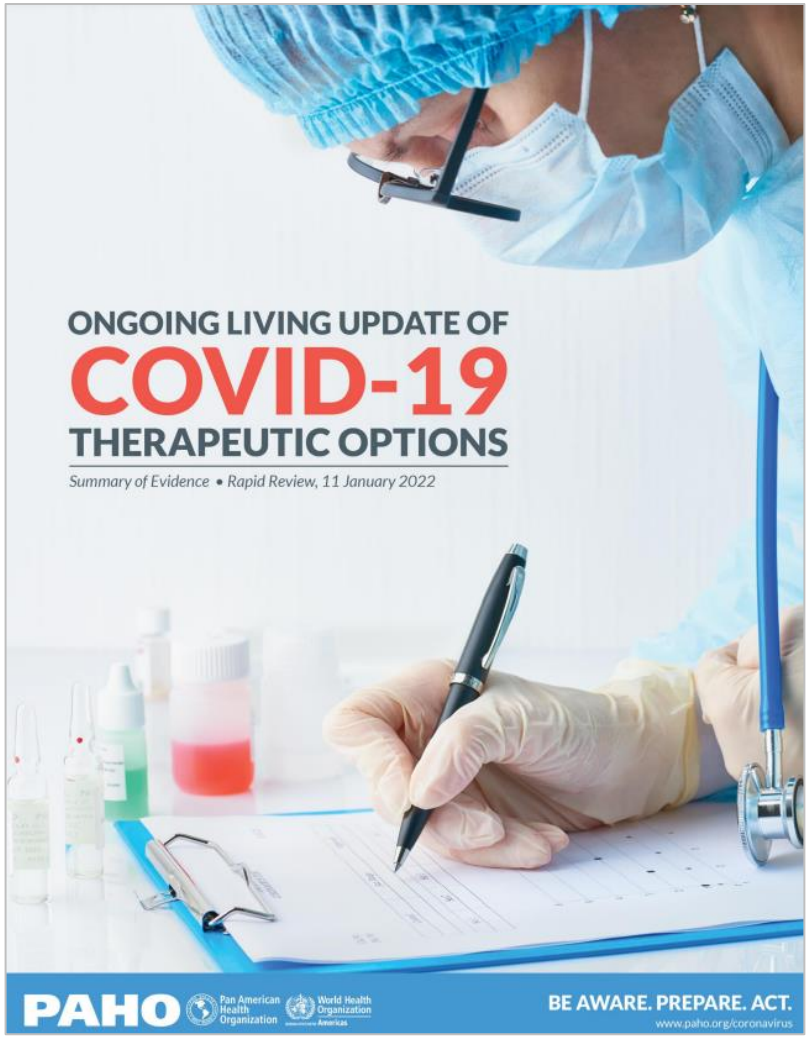
SPEAKER

Dr Ludovic Reveiz

Pan American Health Organization (PAHO)

USA

PAHO living review of potential COVID-19 therapeutics



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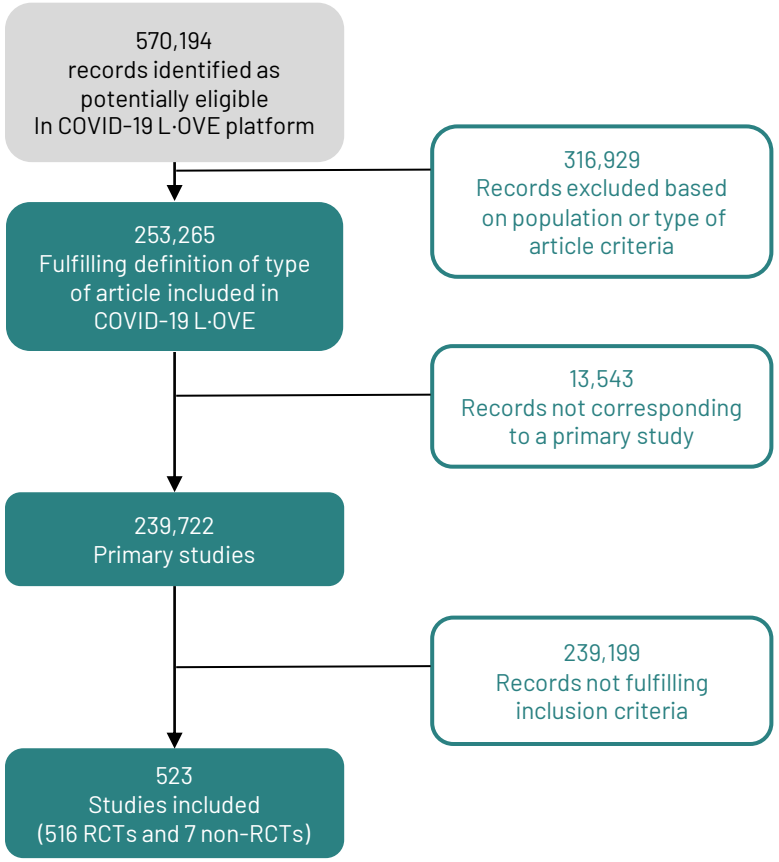
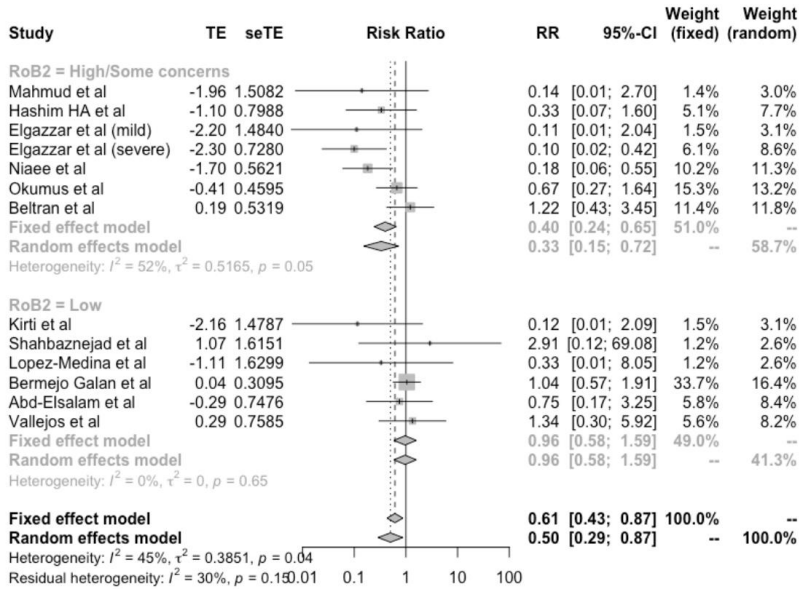
Methods



L·OVE repository

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Rob and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
99mTc-MDP Uncertainty in potential benefits and harms. Further research is needed.					
RCT					
Yuan et al.[10] Preprint; 2020	Patients with mild COVID-19 infection. 10 assigned to 99mTc-MDP 5/ml once a day for 7 days and 11 assigned to SOC	Median age 61 ± 20, male 42.9%	NR	High for mortality and invasive mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information



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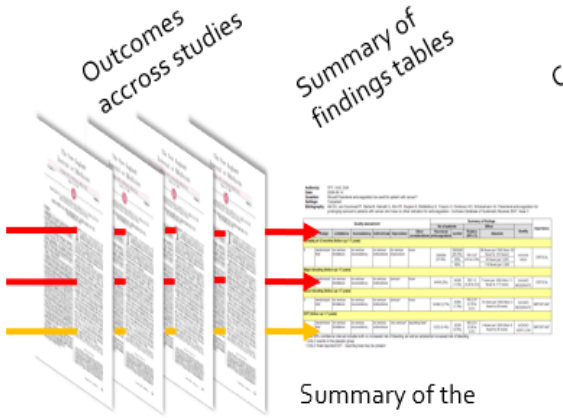
Methods

GRADE



High
Moderate
Low
Very Low

Downgrade
1. RoB
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias

Upgrade
1. Big effect
2. Dose-response gradient
3. Confounders

Summary of findings Table 12.

Population: Patients with COVID-19 infection
Intervention: Ivermectin
Comparator: Standard of care

Outcome Timeframe	Study results and measurements	Absolute effect estimates SOC	 Ivermectin	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality (Low risk of bias studies)[1]	Relative risk: 0.96 (CI 95% 0.58 - 1.59) Based on data from 1412 patients in 6 studies	**160** per 1000	**154** per 1000 Difference: **6 fewer per 1000** (CI 95% 67 fewer - 94 more)	**Low** Due to very serious imprecision[2]	Ivermectin may have little or no difference in mortality
Mechanical ventilation	Relative risk: 1.05 (CI 95% 0.64 - 1.72) Based on data from 1046 patients in 6 studies	**173** per 1000	**182** per 1000 Difference: **9 more per 1000** (CI 95% 62 fewer - 125 more)	**Low** Due to very serious imprecision[3]	Ivermectin may have little or no difference on mechanical ventilation
Symptom resolution or improvement (Low risk of bias studies)	Relative risk: 1.02 (CI 95% 0.96 - 1.1) Based on data from 635 patients in 3 studies	**606** per 1000	**618** per 1000 Difference: **12 more per 1000** (CI 95% 24 fewer - 61 more)	**Moderate** Due to serious imprecision[4]	Ivermectin probably has little or no difference on symptom resolution or improvement
Symptomatic infection[5]	Relative risk: 0.22 (CI 95% 0.09 - 0.53) Based on data from 1974 patients in 4 studies	**174** per 1000	**38** per 1000 Difference: **136 fewer per 1000** (CI 95% 158 fewer - 82 fewer)	**Very low** Due to very serious risk of bias, Due to serious imprecision[6]	We are uncertain whether ivermectin increases or decreases symptomatic infection
Severe adverse events	Relative risk: 1.29 (CI 95% 0.44 - 3.85) Based on data from 917 patients in 5 studies Follow up 28 days	**102** per 1000	**132** per 1000 Difference: **30 more per 1000** (CI 95% 57 fewer - 291 more)	**Very low** Due to very serious imprecision, Due to very serious risk of bias[7]	We are uncertain whether ivermectin increases or decreases severe adverse events
Hospitalization (in non-severe patients)	Relative risk: 0.67 (CI 95% 0.39 - 1.14) Based on data from 1179 patients in 5 studies Follow up 28 days	**48** per 1000	**32** per 1000 Difference: **16 fewer per 1000** (CI 95% 29 fewer - 7 more)	**Low** Due to very serious imprecision[8]	Ivermectin may have little or no difference on hospitalization (in non-severe patients

1. Base on low risk of bias studies
2. **Imprecision: very serious.** 95%CI includes significant benefits and harms;
3. **Imprecision: very serious.** Wide confidence intervals; **Publication bias: serious.**
4. **Imprecision: serious.** Wide confidence intervals;
5. Symptomatic infection in persons at risk or exposed to SARS-COV2
6. **Risk of Bias: very serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias,

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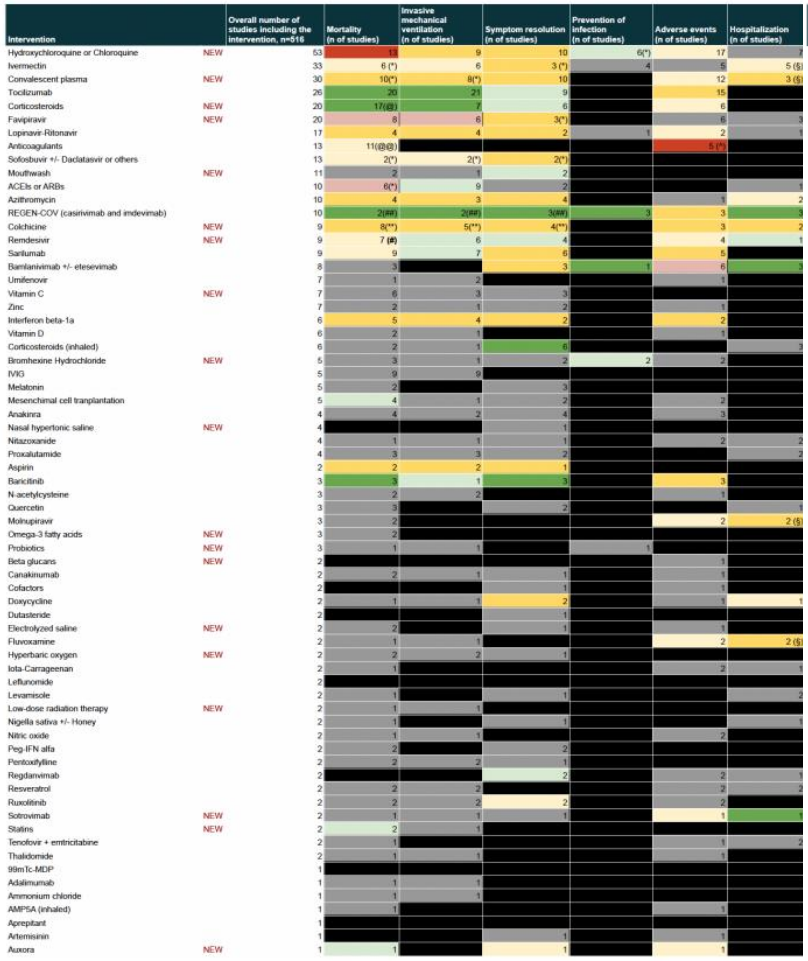
Key findings

Intervention		Overall number of studies including the intervention, n=516	Mortality (n of studies)	Invasive mechanical ventilation (n of studies)	Symptom resolution (n of studies)	Prevention of infection (n of studies)	Adverse events (n of studies)	Hospitalization (n of studies)
Hydroxychloroquine or Chloroquine	NEW	53	13	9	10	6(*)	17	7
Ivermectin		33	6 (*)	6	3 (*)	4	5	5 (§)
Convalescent plasma	NEW	30	10(*)	8(*)	10		12	3 (§)
Tocilizumab		26	20	21	9		15	
Corticosteroids	NEW	20	17(@)	7	6		6	
Favipiravir	NEW	20	8	6	3(*)		6	3
Lopinavir-Ritonavir		17	4	4	2	1	2	1
Anticoagulants		13	11(@@)				5 (^)	
Sofosbuvir +/- Daclatasvir or others		13	2(*)	2(*)	2(*)			
Mouthwash	NEW	11	2	1	2			
ACEIs or ARBs		10	6(*)	9	2			1
Azithromycin		10	4	3	4		1	2
REGEN-COV (casirivimab and imdevimab)		10	2(##)	2(##)	3(##)	3	3	3
Colchicine	NEW	9	8(**)	5(**)	4(**)		3	2
Remdesivir	NEW	9	7 **(#)**	6	4		4	1
Sarilumab		9	9	7	6		5	
Bamlanivimab +/- etesevimab		8	3		3	1	6	3
Umifenovir		7	1	2			1	

	GRADE High- Moderate certainty	GRADE Low certainty
Beneficial effect		
No significant effect		
Harmfull effect		
Uncertain effect		
No evidence or no estimable effect		

COVID-19 Clinical Research Coalition

Key findings



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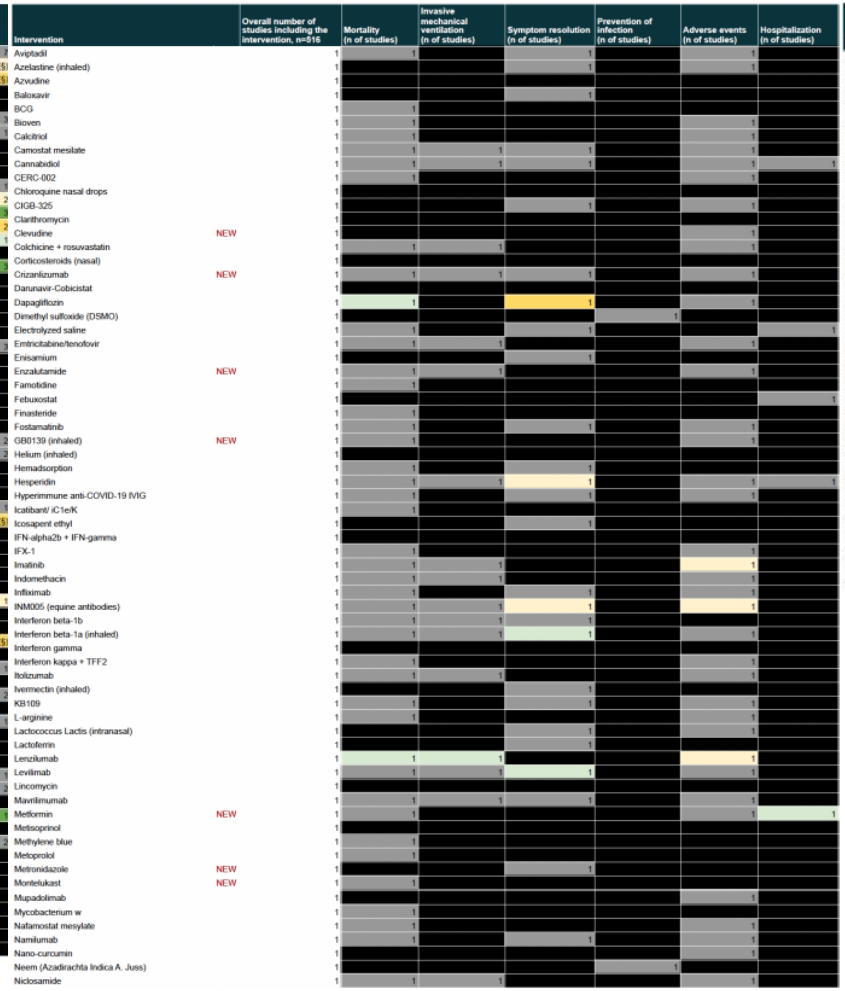
Hydroxychloroquine or Chloroquine	NEW	53	11	9	10	6(*)	17	2
Ivermectin		33	6 (*)	6	3 (*)	4	5	5 (§)
Convalescent plasma	NEW	30	10(*)	8(*)	10		12	3 (§)
Tocilizumab		26	20	21	9		15	
Corticosteroids	NEW	20	17(@)	7	6		6	
Favipiravir	NEW	20	8	6	3(*)		6	
Lopinavir-Ritonavir		17	4	4	2	1	2	
Anticoagulants		13	11(@@)				5 (*)	
Sofosbuvir +/- Daclatasvir or others		13	2(*)	2(*)	2(*)			
Mouthwash	NEW	11	2	1	2			
ACEIs or ARBs		10	6(*)	9	2			1
Azithromycin		10	4	3	4		1	2
REGEN-COV (casirivimab and imdevimab)		10	2(##)	2(##)	3(##)	3	3	3
Colchicine	NEW	9	8(**)	5(**)	4(**)		3	2
Remdesivir	NEW	9	7 (#)	6	4		4	1
Sarilumab		9	9	7	6		5	
Bamlanivimab +/- etesevimab		8	3		3	1	6	
Umifenovir		7	1	2			1	
Vitamin C	NEW	7	6	3	3			
Zinc		7	2	1	2		1	
Interferon beta-1a		6	5	4	2		2	
Vitamin D		6	2	1			1	
Corticosteroids (inhaled)		6	2	1	6			
Bromhexine Hydrochloride	NEW	5	3	1	2	2	2	
IVIG		5	5	5				
Melatonin		5	2		3			
Mesenchimal cell tranplantation		5	4	1	2		2	
Anakinra		4	4	2	4		3	
Nasal hypertonic saline	NEW	4			1			
Nitazoxanide		4	1	1	1		2	
Proxalutamide		4	3	3	2			
Aspirin		2	2	2	1			
Baricitinib		3	3	1	3		3	
N-acetylcysteine		3	2	2			1	
Quercetin		3	3		2			1
Molnupiravir		3	2				2	2 (§)
Omega-3 fatty acids	NEW	3	2					
Probiotics	NEW	3	1	1		1		
Beta glucans	NEW	2					1	
Canakinumab		2	2	1	1		1	
Cofactors		2			1		1	
Doxycycline		2	1	1	2		1	
Dutasteride		2			1			
Electrolyzed saline	NEW	2	2		1		1	
Fluvoxamine		2	1	1			2	2 (§)
Hyperbaric oxygen	NEW	2	2	2	1			
Iota-Carrageenan		2	1				2	
Leflunomide		2						
Levamisole		2	1		1			
Low-dose radiation therapy	NEW	2	1	1				
Nigella sativa +/- Honey		2	1		1			
Nitric oxide		2	1	1			2	
Peg-IFN alfa		2	2		2			
Pentoxifylline		2	2	2	1			
Regdanvimab		2			2		2	
Resveratrol		2	2	2			2	
Ruxolitinib		2	2	2	2		2	
Sotrovimab	NEW	2	1	1	1		1	
Statins	NEW	2	2	1				
Tenofovir + emtricitabine		2	1				1	
Thalidomide		2	1	1			1	
99mTc-MDP		1						
Adalimumab		1	1	1				
Ammonium chloride		1	1	1				
AMP5A (inhaled)		1	1				1	
Aprepitant		1						
Artemisinin		1			1		1	
Auxora	NEW	1	1		1		1	

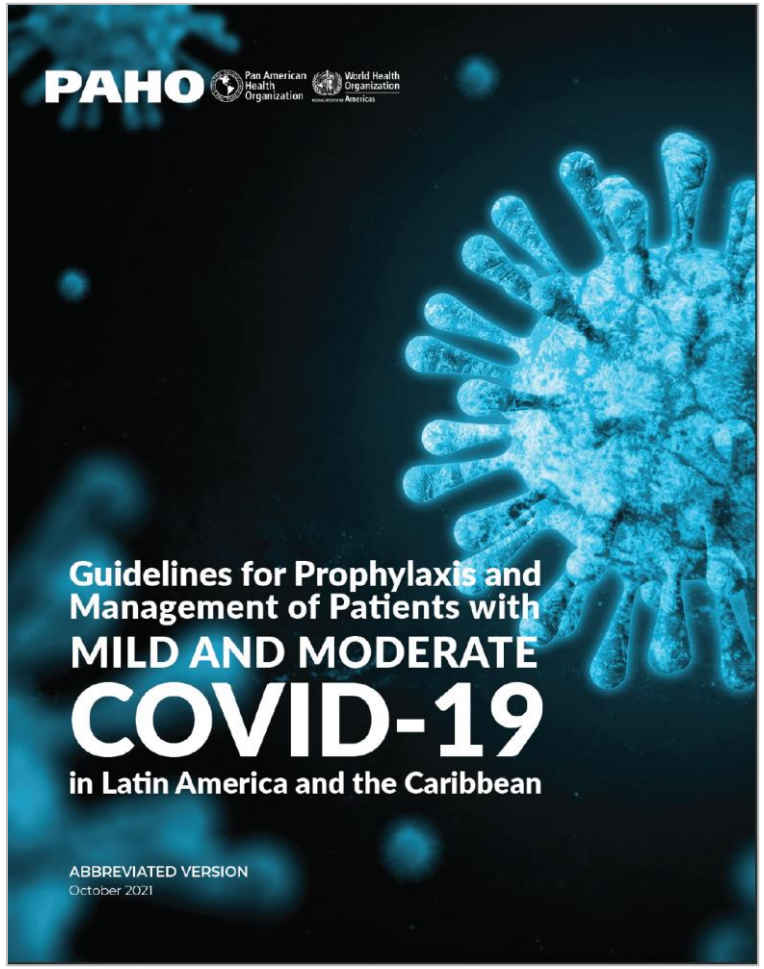


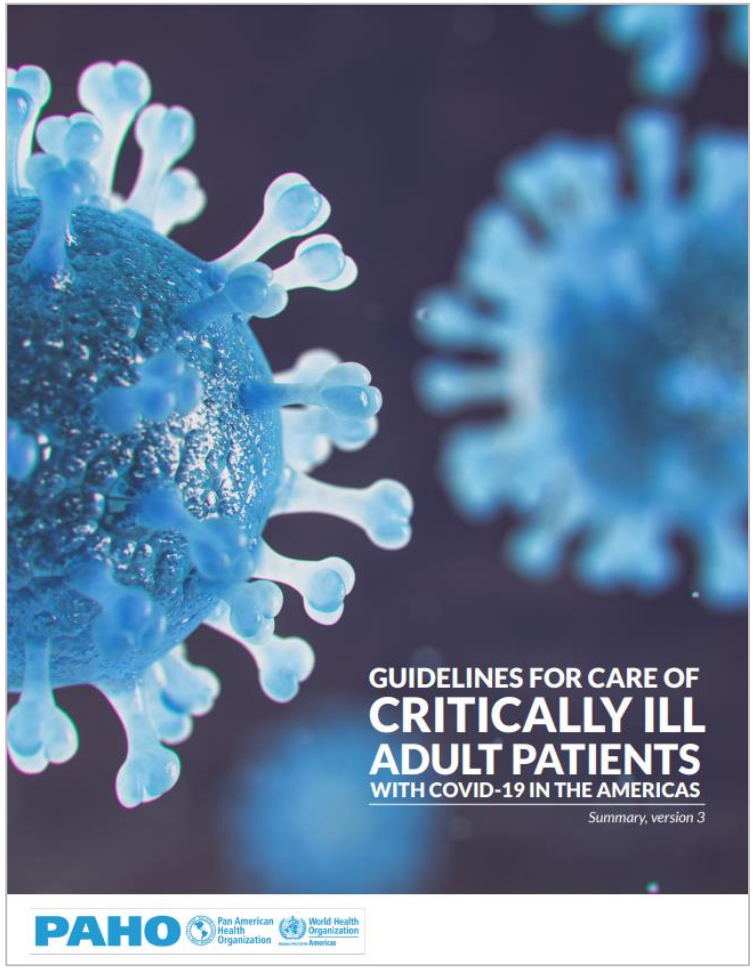
Intervention		Overall number of studies including the intervention, n=516	Mortality (n of studies)	Invasive mechanical ventilation (n of studies)	Symptom resolution (n of studies)	Prevention of infection (n of studies)	Adverse events (n of studies)	Hospitalization (n of studies)
Aviptadil		1	1		1		1	
Azelastine (inhaled)		1			1		1	
Azvudine		1						
Baloxavir		1			1			
BCG		1	1					
Bioven		1	1				1	
Calcitriol		1	1				1	
Camostat mesilate		1	1	1	1		1	
Cannabidiol		1	1	1	1		1	1
CERC-002		1	1				1	
Chloroquine nasal drops		1						
CIGB-325		1			1		1	
Clarithromycin		1						
Clevudine	NEW	1					1	
Colchicine + rosuvastatin		1	1	1			1	
Corticosteroids (nasal)		1						
Crizanlizumab	NEW	1	1	1	1		1	
Darunavir-Cobicistat		1						
Dapagliflozin		1	1		1		1	
Dimethyl sulfoxide (DSMO)		1				1		
Electrolyzed saline		1	1		1			1
Emtricitabine/tenofovir		1	1	1			1	
Enisamium		1			1			
Enzalutamide	NEW	1	1	1			1	
Famotidine		1	1					
Febuxostat		1						1
Finasteride		1	1					
Fostamatinib		1	1		1		1	
GB0139 (inhaled)	NEW	1	1				1	
Helium (inhaled)		1						
Hemadsorption		1	1			1		
Hesperidin		1	1	1	1		1	1
Hyperimmune anti-COVID-19 IVIG		1	1		1		1	
Icatibant/ iC1e/K		1	1					
Icosapent ethyl		1			1			
IFN-alpha2b + IFN-gamma		1						
IFX-1		1	1				1	
Imatinib		1	1	1			1	
Indomethacin		1	1	1			1	
Infliximab		1	1		1		1	
INM005 (equine antibodies)		1	1	1	1		1	
Interferon beta-1b		1	1	1	1			
Interferon beta-1a (inhaled)		1	1	1	1		1	
Interferon gamma		1						
Interferon kappa + TFF2		1	1				1	
Itolizumab		1	1	1			1	
Ivermectin (inhaled)		1			1		1	
KB109		1	1		1		1	
L-arginine		1	1				1	
Lactococcus Lactis (intranasal)		1			1		1	
Lactoferrin		1			1			
Lenzilumab		1	1	1			1	
Levilimab		1	1	1	1		1	
Lincomycin		1						
Mavrilimumab		1	1	1	1		1	
Metformin	NEW	1	1				1	1
Metisoprinol		1						
Methylene blue		1	1					
Metoprolol		1	1					
Metronidazole	NEW	1			1			
Montelukast	NEW	1	1					
Mupadolimab		1					1	
Mycobacterium w		1	1					
Nafamostat mesylate		1	1				1	
Namilumab		1	1		1		1	
Nano-curcumin		1					1	
Neem (Azadirachta Indica A. Juss)		1				1		
Niclosamide		1	1	1			1	

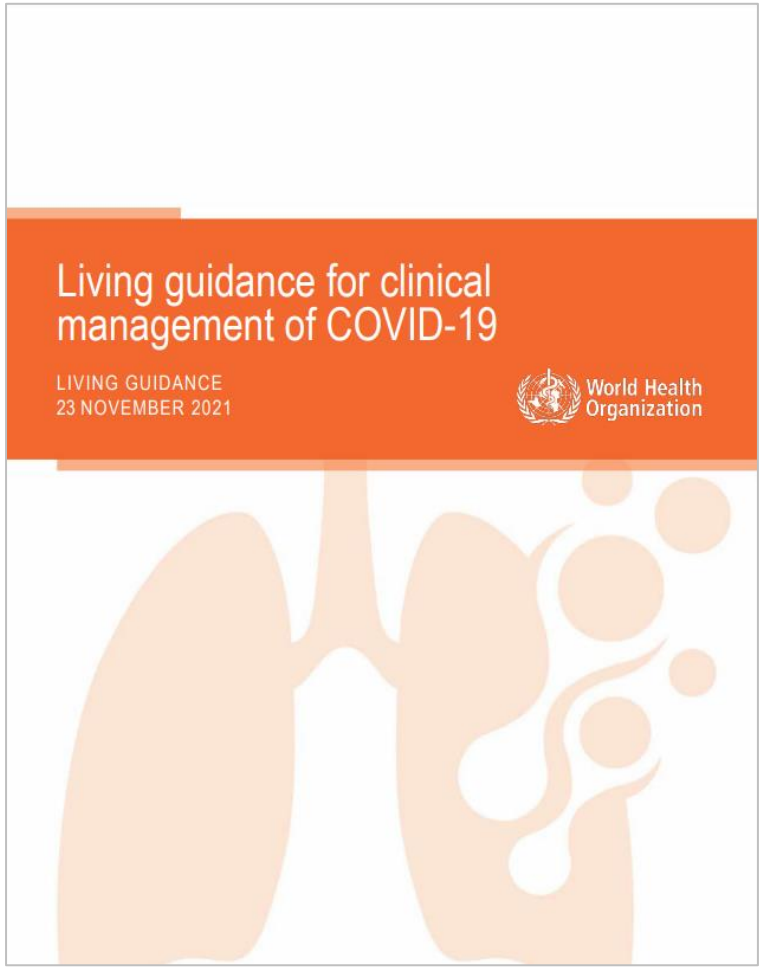
Intervention		Overall number of studies including the intervention, n=516	Mortality (n of studies)	Invasive mechanical ventilation (n of studies)	Symptom resolution (n of studies)	Prevention of infection (n of studies)	Adverse events (n of studies)	Hospitalization (n of studies)
Novaferon		1						
NSAIDS		1	1		1		1	
Nutritional support		1	1	1				
Opaganib		1	1	1	1		1	
Otilimab		1	1				1	
Peg-IFN lambda		1					1	
PNB001 (CCK-A antagonist)		1	1		1			
Polymerized type I collagen (PT1C)		1						1
Povidone iodine		1	1				1	1
Progesterone		1	1	1			1	
Prolectin-M		1	1	1			1	
Propolis		1	1	1	1			
Prostacyclin		1	1				1	
Pyridostigmine		1	1	1	1		1	
Ramipril		1	1			1		
RD-X19 (light therapy)		1			1			
Recombinant Super-Compound IFN		1	1		1			
Ribavirin		1						
Ribavirin + Interferon beta-1b		1						
rhG-CSF		1	1		1		1	
rhG-CSF (inhaled)		1	1	1	1		1	
Secukinumab		1	1	1			1	
Short-wave diathermy		1	1		1		1	
Sildenafil	NEW	1	1	1			1	
Siltuximab		1	1	1				
Sitagliptin		1	1	1				
Spironolactone		1	1	1				
Stem-cell nebulization		1	1		1		1	
Sulodexide		1	1	1			1	1
TD-0903 (inhaled JAK-inhibitor)		1	1				1	
Tissue-plasminogen activator (tPA)		1	1				1	
Triazavirin		1	1		1		1	
Tofacitinib		1	1		1		1	
XAV-19 (swine polyclonal antibodies)		1	1				1	
α-Lipoic acid		1	1					

COVID-19 Clinical Research Coalition

Clinical management guideline







COVID-19 Clinical Research Coalition

Therapeutics for severe and critical

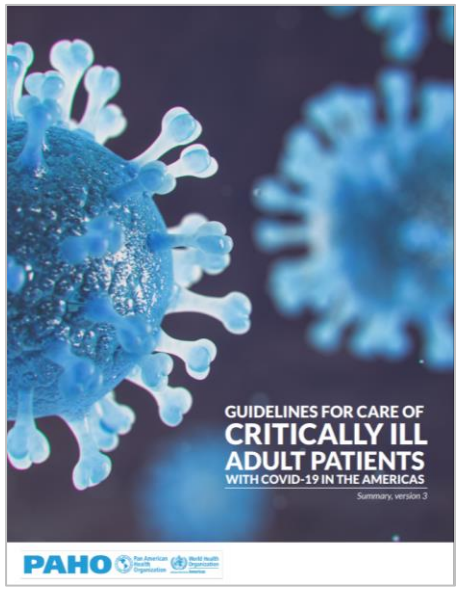
Intervention	Effect on mortality		Safety considerations	Implementation	Other key considerations
	Patients with severe disease (baseline risk 16%)	GRADE certainty of the evidence			
Corticosteroids (8000 patients in 12 trials)	16 fewer per 1000	Moderate ⨁⨁⨁◯	Well known safety profile. Severe AE rare (hyperglycemia, hypertension, infections)	Intravenous infusion (standard dose dexamethasone 6mg a day).*	
Tocilizumab (8455 patients in 20 trials)	24 fewer per 1000	High ⨁⨁⨁⨁	No signal of AE in trials. Theoretical risk of infections and intestinal perforation.	Intravenous infusion. One or two doses.	Limited availability.
Baricitinib (2659 patients in 3 trials)	58 fewer per 1000	Moderate ⨁⨁⨁◯	No signal of AE in trials. Theoretical risk of infections, blood clots and infusion reactions.	Orally. One a day.	Limited availability.
REGEN-COV (16667 patients in 4 trials)	32 fewer per 1000	Moderate ⨁⨁⨁◯	No signal of AE in trials. Theoretical risk of anaphylaxis and infusion reactions.	Intravenous infusion. Single dose. #	May not be effective against Omicron based on in-vitro studies. Limited availability.

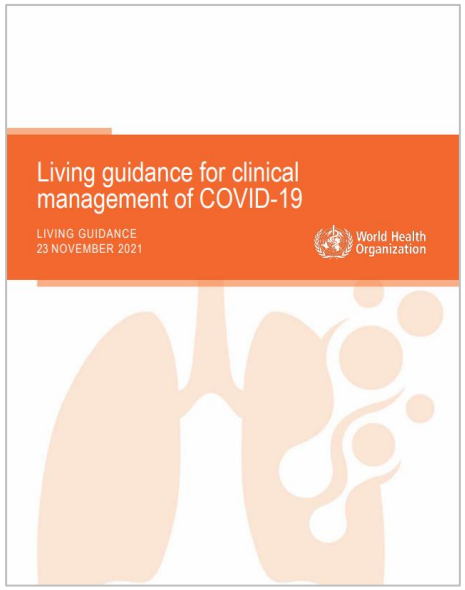
* Higher dosage schemes apparently not more effective

Seronegative patients

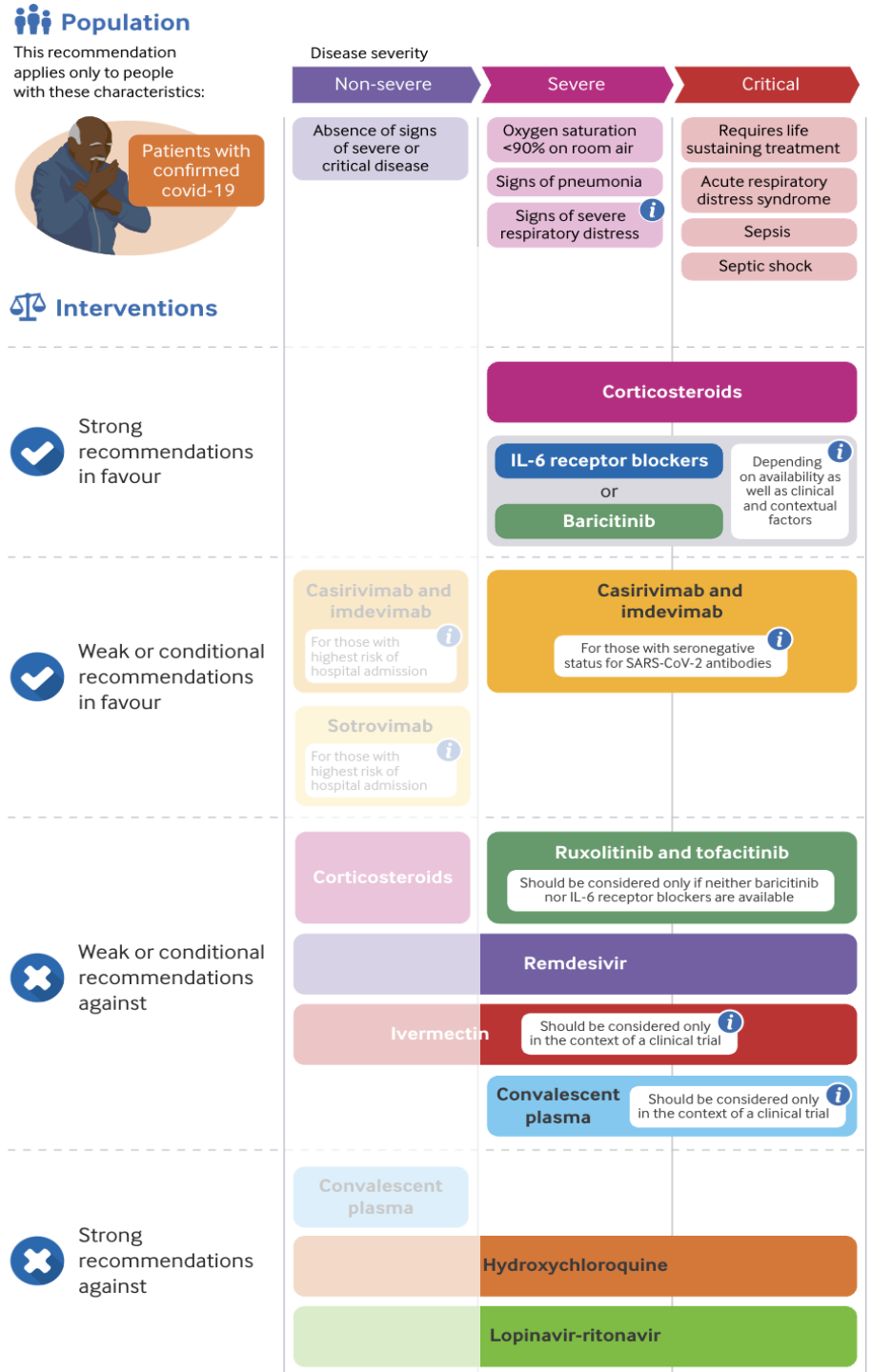
Pan American Health Organization. Ongoing Living Update of Potential COVID-19 Therapeutics Options: Summary of Evidence. Rapid Review. Available at: https://iris.paho.org/handle/10665.2/52719

Therapeutics for severe and critical





Covid-19: WHO recommends baricitinib and sotrovimab to treat patients
BMJ 2022; 376 doi: https://doi.org/10.1136/bmj.o97



Therapeutics for non-severe COVID-19

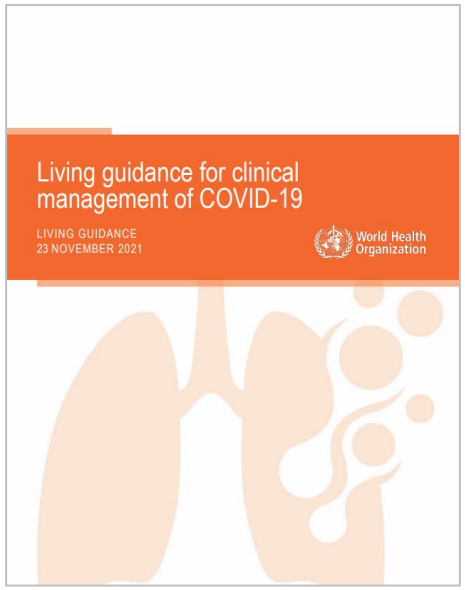
Intervention		Effect on hospitalizations			Safety considerations	Dosage, route	Other key considerations
		Unvaccinated high-risk patients (baseline risk 4.8%)	Vaccinated patients (baseline risk 0.5%)	GRADE certainty of the evidence			
Monoclonal antibodies	REGEN-COV (5049 patients in 3 trials)	34 fewer per 1000	3 fewer per 1000	Moderate ⊕⊕⊕◯	No signal of AE in trials. Theoretical risk of anaphylaxis and infusion reactions.	Intravenous infusion.* Single dose.	May not be effective against Omicron based on in-vitro studies. Limited availability.
	Sotrovimab (1622 patients in 2 trials)	41 fewer per 1000	4 fewer per 1000	Moderate ⊕⊕⊕◯	No signal of AE in trials. Theoretical risk of anaphylaxis and infusion reactions.	Intravenous infusion. Single dose.	Limited availability.
	Bamlanivimab (1804 patients in 3 trials)	30 fewer per 1000	3 fewer per 1000	Moderate ⊕⊕⊕◯	No signal of AE in trials. Theoretical risk of anaphylaxis and infusion reactions.	Intravenous infusion. Single dose.	May not be effective against Omicron based on in-vitro studies. Limited availability.
Antivirals	Remdesivir (562 patients in 1 trial)	35 fewer per 1000	3 fewer per 1000	Low ⊕⊕◯◯	Hepatotoxicity.	Intravenous infusion. Three doses (days 1-3)	Limited availability.
	Molnupiravir (1610 patients in 2 trials)	14 fewer per 1000	1 fewer per 1000	Moderate ⊕⊕⊕◯	No signal of AE in trials. Theoretical risk of mutagenesis, hepatotoxicity, and hematologic risks.	Orally. Twice a day for 5 days	Limited availability.
	Paxlovid (2940 patients in 2 trials)#	54 fewer per 1000	5 fewer per 1000	Moderate ⊕⊕⊕◯	No information available. Drug to drug interactions.	Orally. Twice a day for 5 days	Limited availability.
Other	Fluvoxamine (1649 patients in 2 trials)	11 fewer per 1000	1 fewer per 1000	Moderate ⊕⊕⊕◯	No signal of AE in trials for COVID-19. Commonly observed AE in other clinical scenarios include abnormal ejaculation, anorexia, asthenia, dyspepsia, insomnia, nausea, nervousness, somnolence, sweating, tremor and vomiting	Orally. Twice a day for 10 days	

* Can be administered subcutaneously
\# Unpublished information

References:

1. Pan American Health Organization. Ongoing Living Update of Potential COVID-19 Therapeutics Options: Summary of Evidence. Rapid Review. Avalable at: https://iris.paho.org/handle/10665.2/52719
2. https://www.pfizer.com/news/press-release/press-release-detail/pfizers-novel-covid-19-oral-antiviral-treatment-candidate

Therapeutics for non-severe COVID-19



Covid-19: WHO recommends baricitinib and sotrovimab to treat patients
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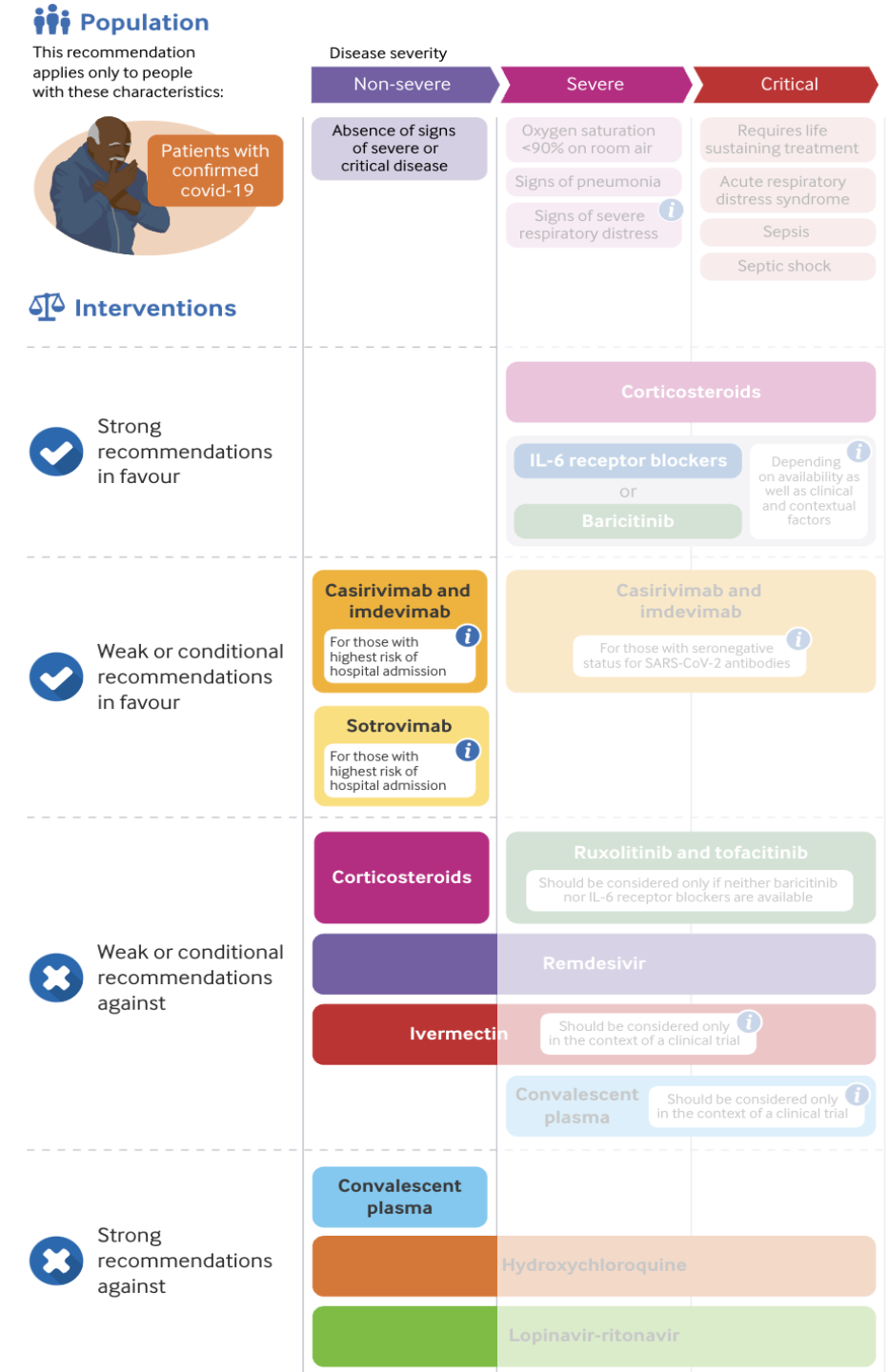


Statement on Patient Prioritization for Outpatient Therapies

National Institutes of Health
The COVID-19 Treatment Guidelines Panel's Interim Statement on Patient Prioritization for Outpatient Anti-SARS-CoV-2 Therapies or Preventive Strategies When There Are Logistical or Supply Constraints

Tier	Risk Group
1	• Immunocompromised individuals not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to their underlying conditions, regardless of vaccine status (see Immunocompromising Conditions below); *or* • Unvaccinated individuals at the highest risk of severe disease (anyone aged ≥75 years or anyone aged ≥65 years with additional risk factors).
2	• Unvaccinated individuals at risk of severe disease not included in Tier 1 (anyone aged ≥65 years or anyone aged <65 years with clinical risk factors)
3	• Vaccinated individuals at high risk of severe disease (anyone aged ≥75 years or anyone aged ≥65 years with clinical risk factors) **Note:** Vaccinated individuals who have not received a COVID-19 vaccine booster dose are likely at higher risk for severe disease; patients in this situation within this tier should be prioritized for treatment.
4	• Vaccinated individuals at risk of severe disease (anyone aged ≥65 years or anyone aged <65 with clinical risk factors) **Note:** Vaccinated individuals who have not received a COVID-19 vaccine booster dose are likely at higher risk for severe disease; patients in this situation within this tier should be prioritized for treatment.

COVID-19 Clinical Research Coalition

WHERE ARE WE NOW WITH COVID-19 THERAPEUTICS? A SOUTH AFRICAN PERSPECTIVE

SPEAKER

Dr Jeremy Nel

University of the Witwatersrand

South Africa

Pharmaceutical interventions

Post-exposure prophylaxis

- Monoclonal antibodies
  - e.g., bamlanivimab + etesevimab
  - e.g., casirivimab + imdevimab

Early intervention

- Monoclonal antibodies
  - e.g., sotrovimab
- Oral antivirals
  - Molnupiravir
  - Nirmatrelvir/ritonavir
- Remdesivir

Treatment for severe disease

- Steroids
- Tocilizumab
- Baricitinib

Monoclonals in a LMIC?

- **Logistics** make this a nightmare
  - Infusion centres
  - Staffing
  - In early treatment, patients are highly infectious
  - Cold chain
  - Access
  - Expense
  - Treatment: only if seronegative (another logistic hurdle)

- Monoclonals directed at spike protein are highly **vulnerable to new variants**

Oral antivirals

- Oral formulation is the way to go!
- Challenges of early identification (need to be started within 3-5 days of symptoms)
- Drug-drug interactions with nermatrelvir/ritonavir
- Efficacy of molnupiravir – cost-effectiveness calculations
- Access a challenge in 2022
  - Lots of generics for molnupiravir though
- Indication creep

Inpatient therapies

- We got lucky with **steroids**
  - Cheap, widely-available, multiple formulations, big effect on mortality

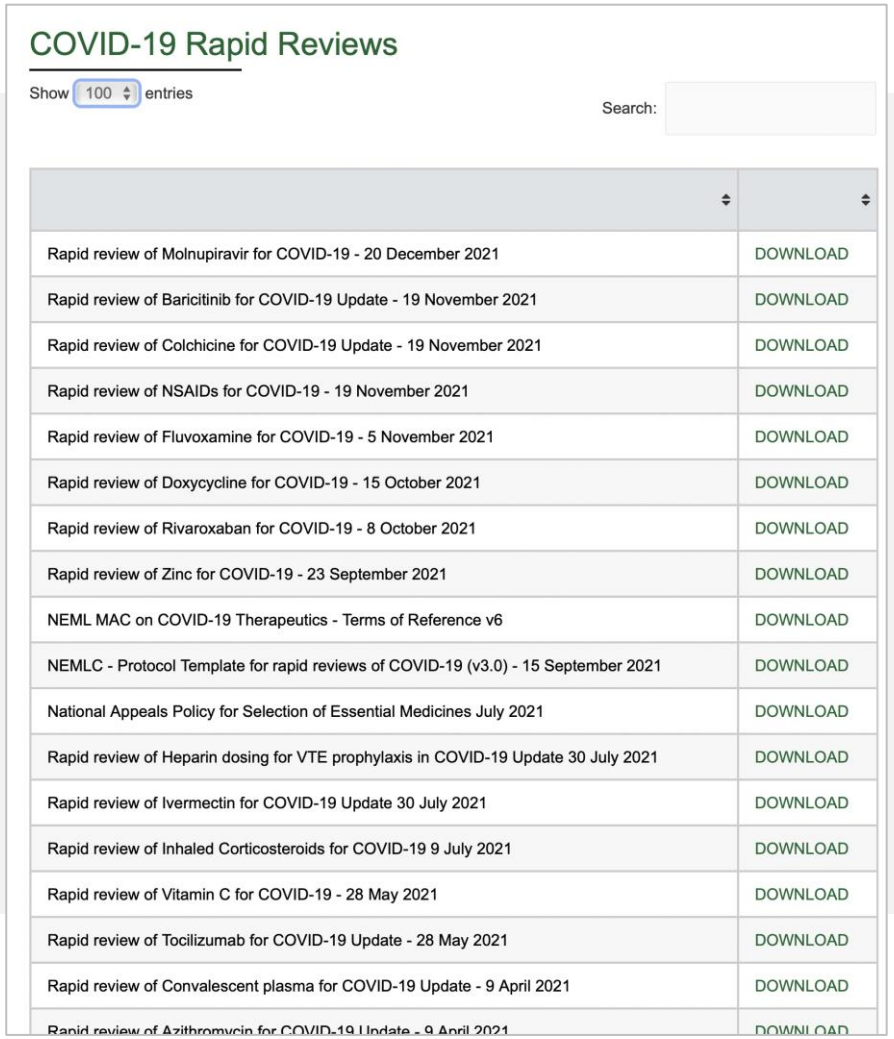
BMJ. A living WHO guideline on drugs for covid-19. doi: https://doi.org/10.1136/bmj.m3379

- **Tocilizumab** – cost, access
- **Baricitinib** – access

COVID-19 Clinical Research Coalition

Finding the right strategy for your own country

- Tidal wave of evidence
- Rapidly changing market conditions
- SA established a dedicated ministerially-appointed COVID-19 therapeutics committee
  - EBM experts
  - Physicians
  - Pharmacologists



COVID-19 Rapid Reviews

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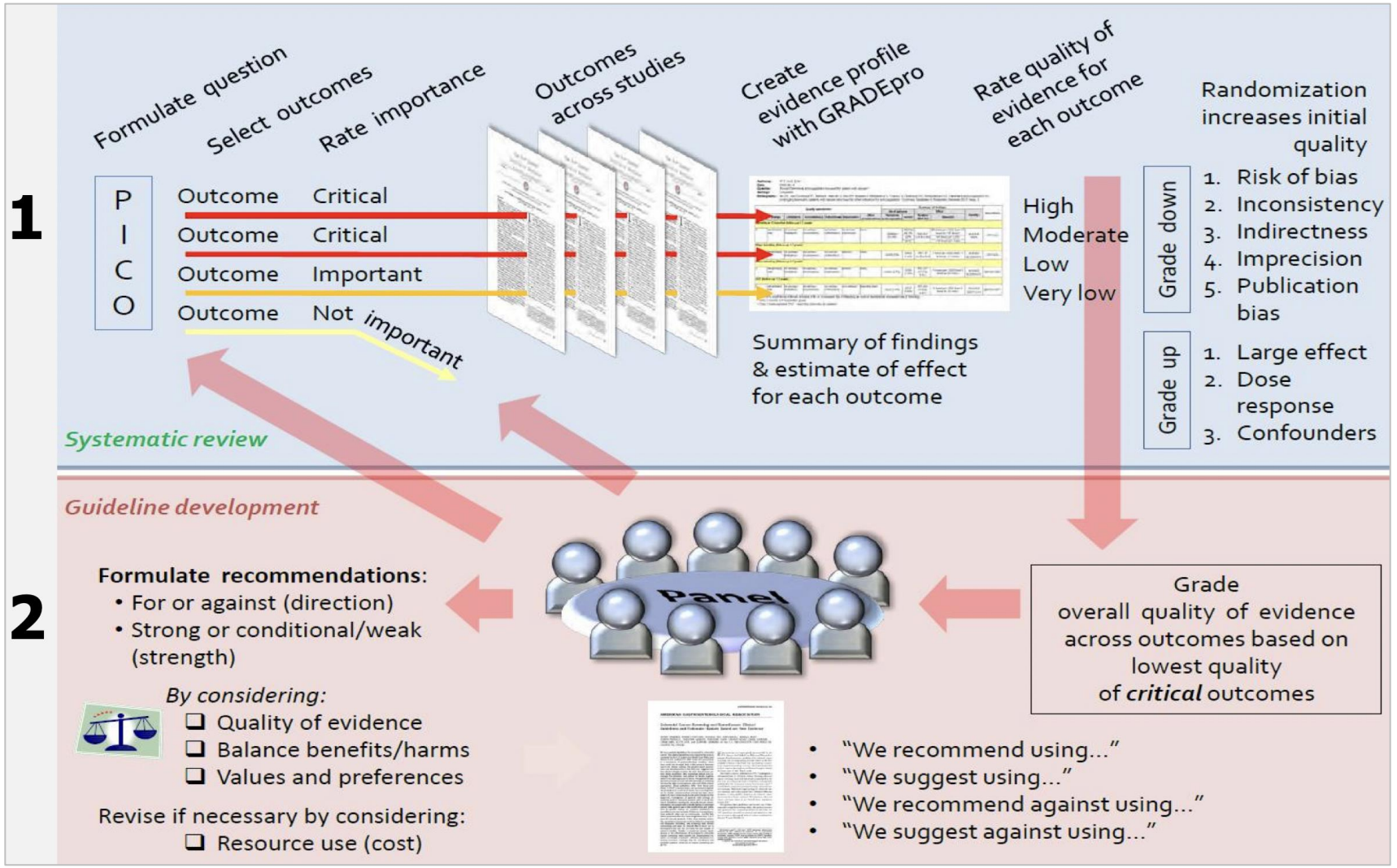
Rapid review of Convalescent plasma for COVID-19 Update - 9 April 2021	DOWNLOAD
Rapid review of Azithromycin for COVID-19 Update - 9 April 2021	DOWNLOAD

From evidence to recommendations…



COVID-19 Clinical Research Coalition

Finding the right strategy for your own country

- Evidence **feeds into guidelines**
- **Publicly available** – open to review, critique, feedback
- **Updated** regularly
- **Publicised** – webinars, articles, training

COVID-19 Clinical Research Coalition

The outcome…

Summary of COVID-19 treatments
Click on the name of the medicine to see the full evidence review.

We recommend for treatment of COVID-19:

- Corticosteroids for hospitalised patients with COVID-19 requiring oxygen support.
- Heparin at prophylactic doses for hospitalised patients with COVID-19.
- Baricitinib for hospitalized patients with COVID-19 reuqiring oxygen support.

We recommend against the following medicines for COVID-19:

- Chloroquine or hydroxychloroquine for treatment or prevention
- Lopinavir/ritonavir
- Interferon-beta-1a (subcutaneous or intravenous)
- Azithromycin
- Colchicine
- Doxycycline
- Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin

We suggest against use the following medicines for COVID-19:

- Tocilizumab (due to concerns about cost-effectiveness in the state sector)
- Remdesivir

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

2030 NDP

COVID-19 Clinical Research Coalition

PRACTICAL REALITIES IN COVID-19 TREATMENT NOW. WHAT IS NEEDED?

SPEAKER

Prof. Samba Sow

Centre for Vaccine Development

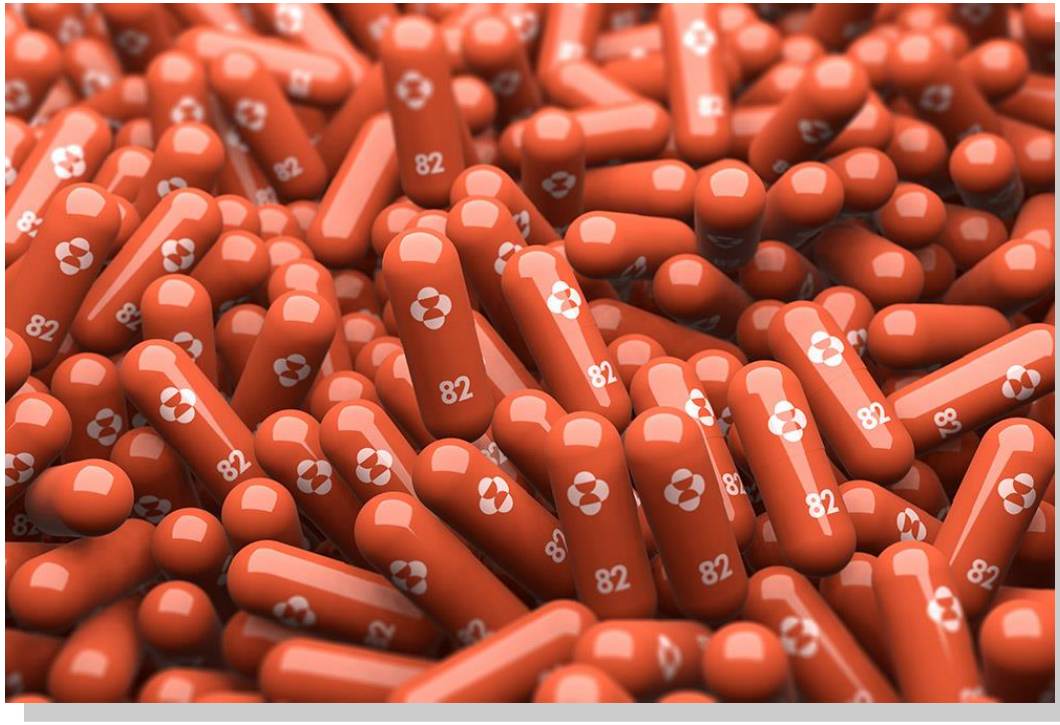
Mali

The impact of COVID-19

- The poorest and most marginalized in society have been hit hardest by the pandemic
- Many low-income countries already had fragile and under-resourced health systems
- Two years of pandemic have made things even worse

Vaccines & therapeutics

- African continent critically under-vaccinated
- No equitable vaccine distribution yet
- Oral antiviral treatments offer hope of relieving burden on fragile communities and health systems



Quality Stock Arts - stock.adobe.com

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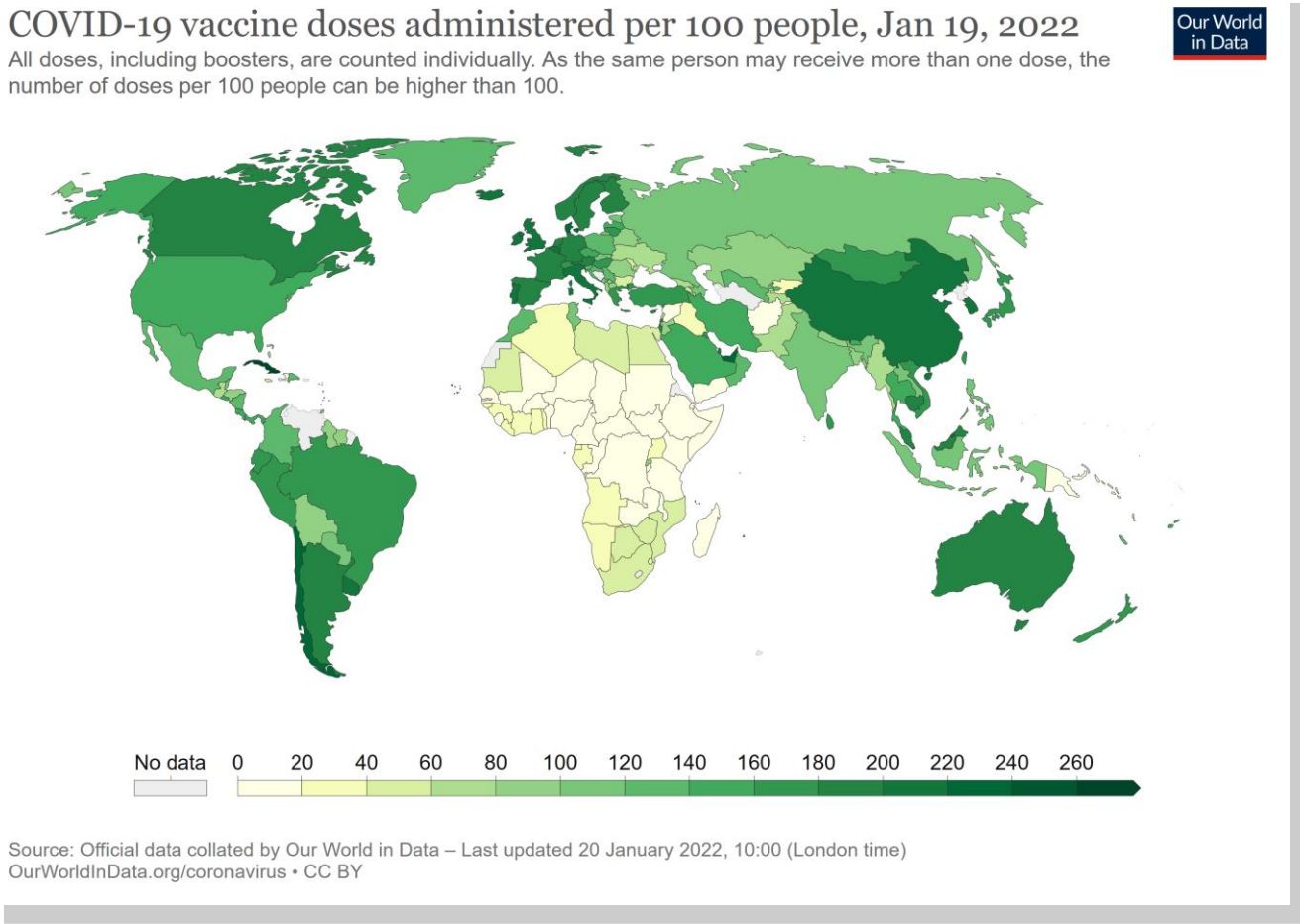
Vaccine inequity

- < 10% of African population fully vaccinated (3% in Mali)
- True rate of infection and death unknown
- With fragile health systems, those who do contract COVID-19 are more likely to be more badly affected
- As new variants emerge, treatments & therapeutics have an increasingly important role



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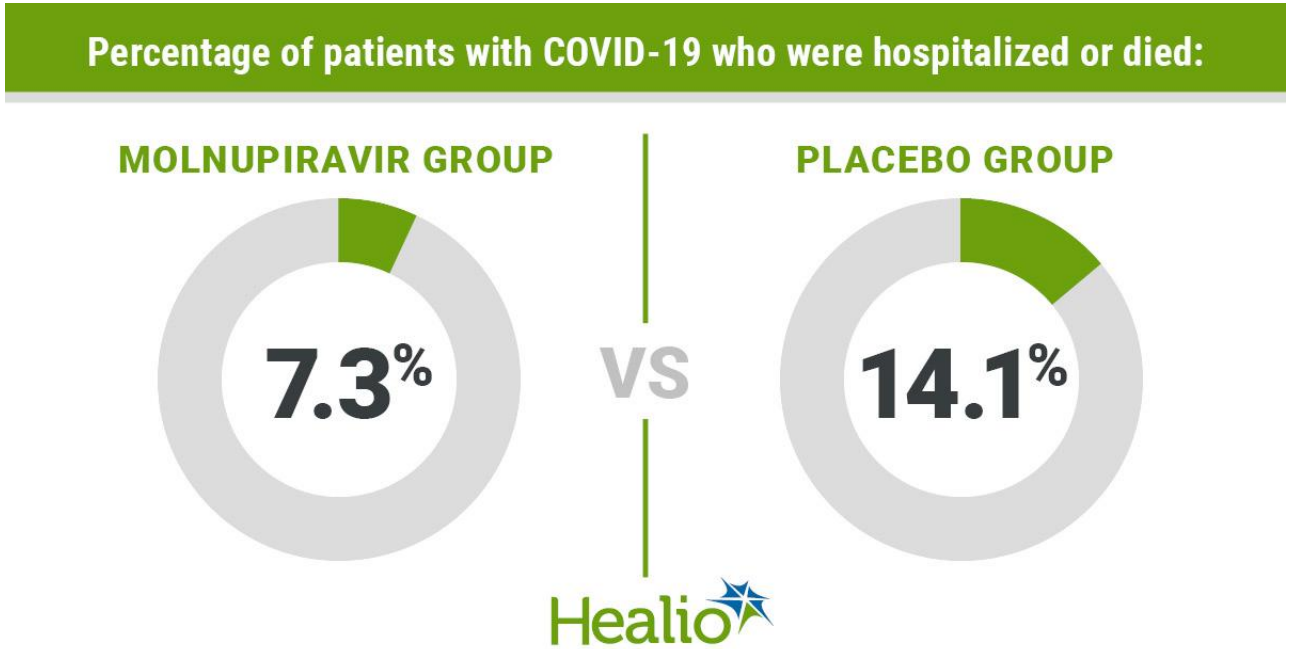
Wider impact on health services

- Treating patients to keep them out of hospitals reduces burden on health system and workers
- Additionally reduces mortality due to COVID-19 itself
- In Mali, maternal & child mortality has increased due to impact of COVID-19 on routine services
- The disease has potential to undo all hard-won gains of last decade

Oral antiviral treatments

- Oral antiviral treatments are proving to be effective, even in unvaccinated populations
- Most of African population currently has no protection against COVID-19
- Pills could be a life-saver for high-risk unvaccinated patients



Interim analysis of a phase 3 study of 775 at-risk, non-hospitalized adults with mild to moderate COVID-19 on or before 5 Aug 2021. Source: healio.com

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Oral antiviral treatments

- Quick and easy to administer
- Can be taken at home
- Require less medical supervision
- Professional assessment still required for advice on suitability and dosage – adherence to dosing instructions is vital in reducing possibility of resistance to medications

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Oral antiviral treatments

- Cheaper than other treatments such as monoclonal antibodies
- In poor countries with stretched health budgets, this is significant
- Potential for equitable COVID-19 treatment
- Potential for relief of pressure on overwhelmed health systems and personnel

Mike Mareen - stock.adobe.com

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Challenges

- Opportunity can only be taken if African nations are able to ensure adequate supplies
- Familiar challenges:
  - Access to treatment
  - Testing infrastructure
  - Timing of drug administration
- Also need to monitor resistance

COVAX shipment. Image: Gavi/2021/Olga Khrustaleva

COVID-19 Clinical Research Coalition

Cautious optimism

- Main issue is with equitable access
- Under-vaccination is only due to limited supply, not lack of willingness or ability
- Need to ensure inequity of vaccine distribution is not repeated

COVID-19 Clinical Research Coalition

IMPACT OF RECENT CLINICAL TRIAL RESULTS ON CURRENT RESEARCH PRIORITIES

SPEAKER

Dr Nathalie Strub-Wourgaft

Drugs for Neglected Diseases *initiative* (DND*i*)

Switzerland

Preamble … during a pandemic in a rapidly evolving environment, information on treatment selection should be easily accessible

Treatment guidelines should be

- easy to identify
- developed from results of well-conducted studies
- showing results based on agreed scientific methodologies
- responding to therapeutic needs as laid out e.g., in Target Product Profiles
- transparent, robust and consistent across regions

COVID-19 Clinical Research Coalition

1. WHO recommendation (R) and regulatory status (MA) vary

PHEIC

Conditional R against systemic steroids in non severe Sep 2020

Strong R for systemic steroids for severe/ critical Sept 2020

Conditional R against remdesivir in hospitalised Nov 2020

Strong R against lopi/r and HCQ in patients with any severity Dec 2020

R not to use IVM except in clinical trials March 2021

Strong R for IL& blockers (tocilizumab and sarilumab) in severe/ critical July 2021

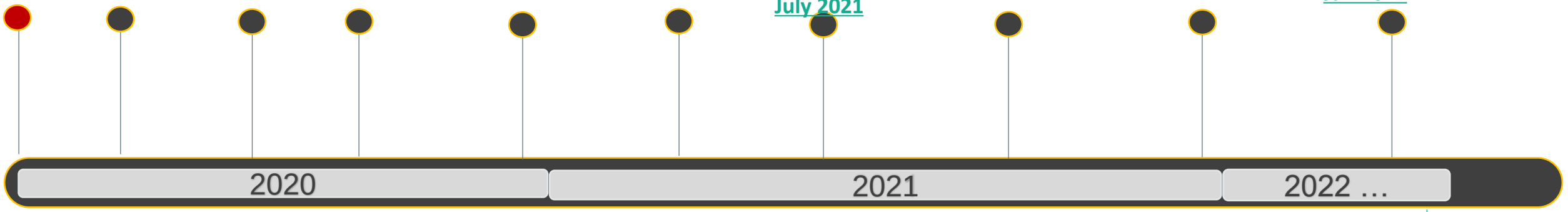
Conditional R for casirivimab & imdevimab severe/critical seronegative Sept 2021

R against convalescent plasma in severe/critical except in clinical trials Dec 2021

Conditional R for sotrovimab for non severe

conditional R against ruxolitinib and tofacitinib for severe/critical

Strong R for baricitinib with steroids for severe/critical Jan 2022



EMA Conditional MA for remdesivir (Velklury) July 2020


Sun Pharmaceutical Industries Limited
SUN HOUSE, CTS No. 201 B/1,
Western Express Highway, Goregaon (E),
Mumbai 400063, India
Tel.: (91-22) 4324 4324 Fax.: (91-22) 4324 4343
CIN: L24230GJ1993PLC019050
www.sunpharma.com

SUN PHARMA

FOR IMMEDIATE RELEASE

Sun Pharma receives DCGI approval for Molxvir® (Molnupiravir) in India

Mumbai, December 28, 2021: Sun Pharmaceutical Industries Limited (Reuters: SUN.BO, Bloomberg: SUNP IN, NSE: SUNPHARMA, BSE: 524715, "Sun Pharma" and includes its subsidiaries and/or associate companies) today announced that one of its wholly owned subsidiaries has received Emergency Use Authorization (EUA) from the Drugs Controller General of India (DCGI) to manufacture and market a generic version of MSD (a trade name of Merck & Co., Inc, Kenilworth, NJ, USA) and Ridgeback's molnupiravir under the brand name Molxvir® in India. Earlier this year, Sun Pharma had signed a non-


FDA Takes Actions to Expand for Outpatients with Mild-to-M

Share Tweet LinkedIn Email

For Immediate Release: January 21, 2022

Español

Today, the U.S. Food and Drug Administration took two ac
antiviral drug Veklury (remdesivir) to certain non-hospital
patients for the treatment of mild-to-moderate COVID-19

EMA - MA for casirivimab / imdevimab (Ronapreve) & regdanvimab (Regkirona) Nov 2021 and cond use for molnu

EMA - MA for sotrovimab (Xevudy) for tocilizumab (RoActemra) Anankira (Kineret) Dec 2021

EMA – Paxlovid & January 2022

Extension for remdesivir to patients not requiring O2

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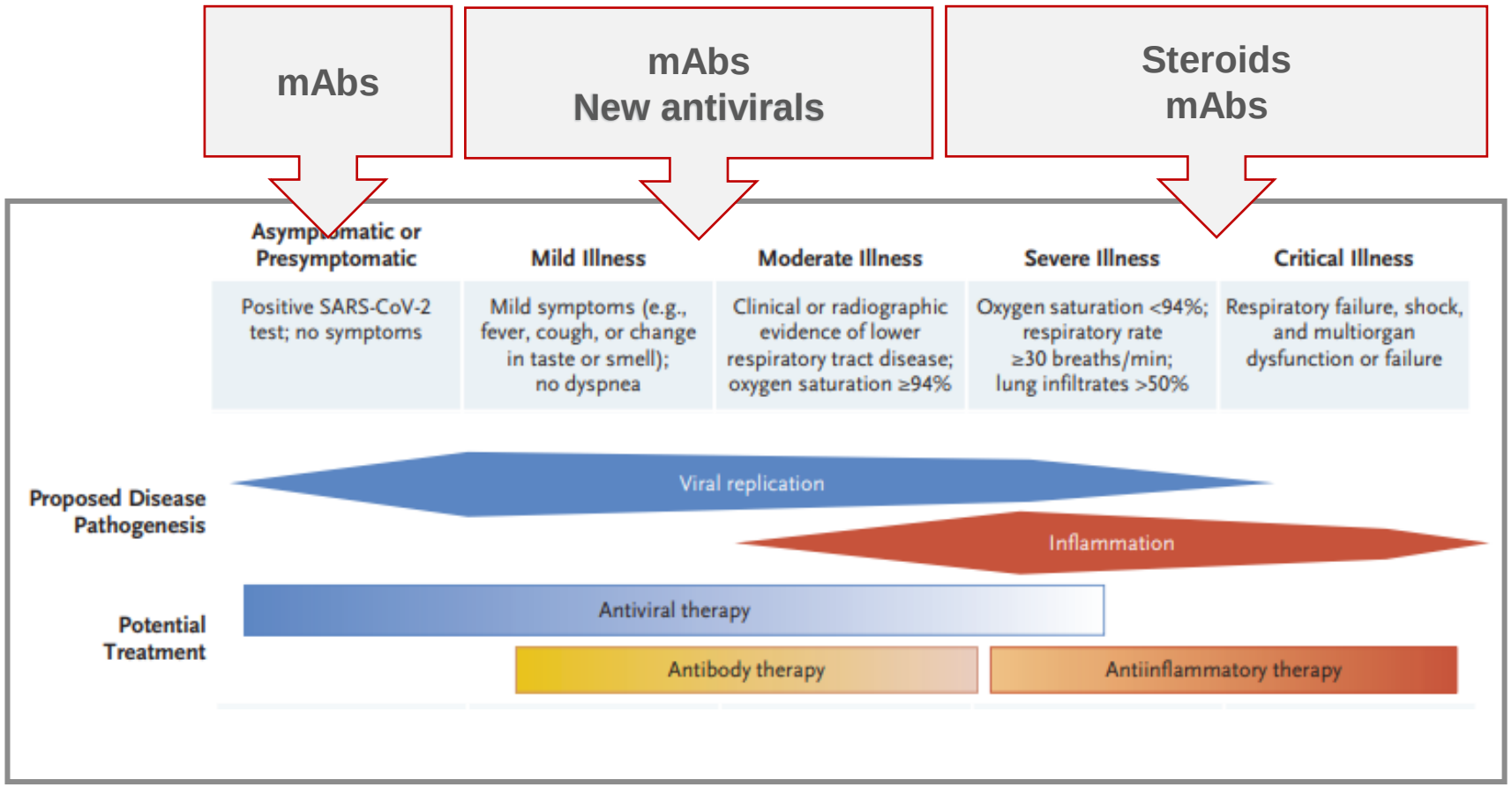
2. We need safe, effective, affordable & field-adapted treatments: where are we?



Source: Rajesh T. Gandhi et al, *NEJM* 383;18 nejm.org October 29, 2020

Limited by

1. Cost
   - MaBs … 600 to > 3000 USD / course
     Note: manufacturing costs of monoclonal antibodies are often < $100 per gram large scale - (MSF – July 2021)
   - NAVs … 700 + USD
2. IV route for mAbs and remdesivir
3. Variant sensitivity: either lack of data or from documented preclinical
4. Generalisability
5. Resistance potential?

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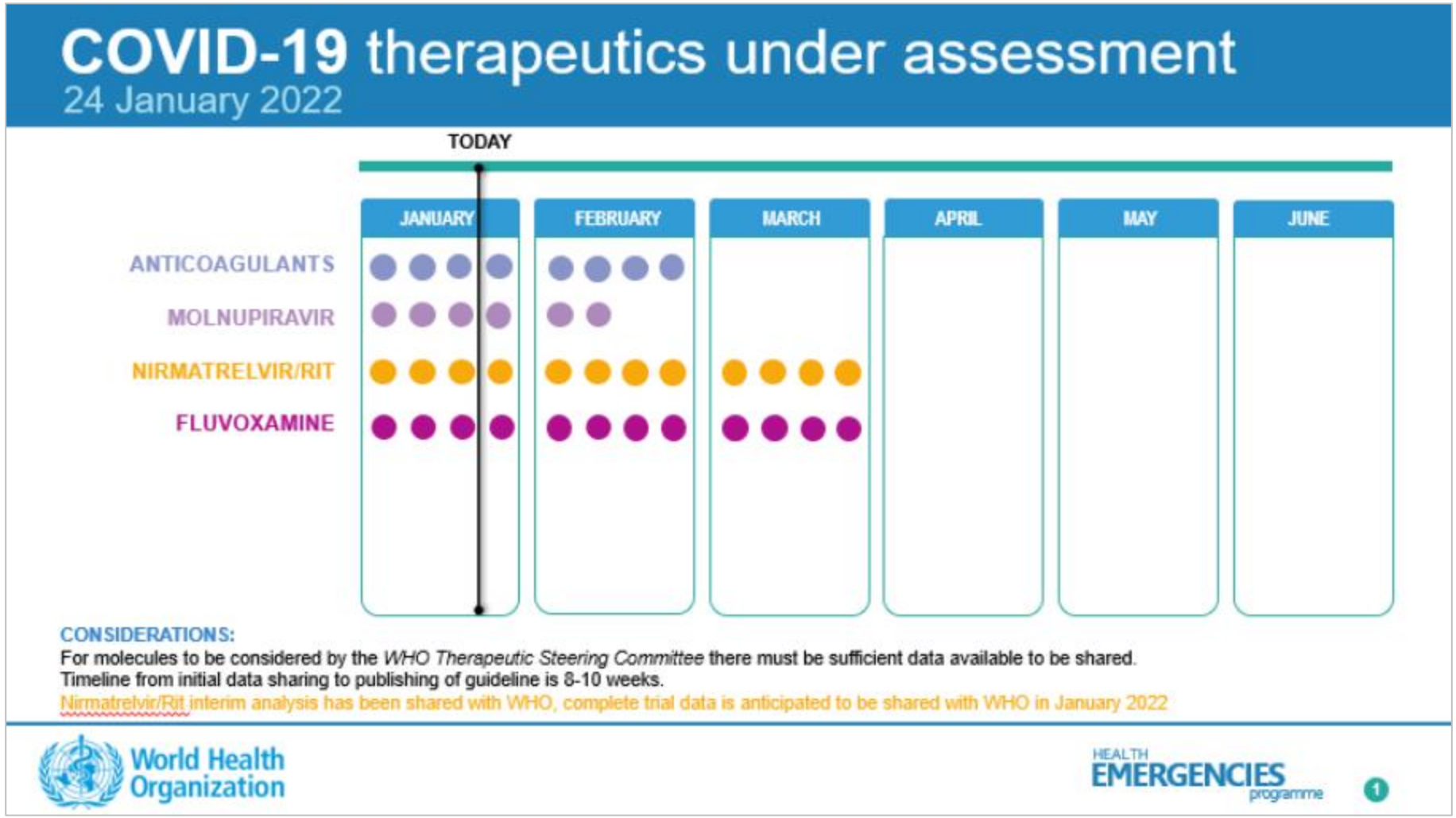
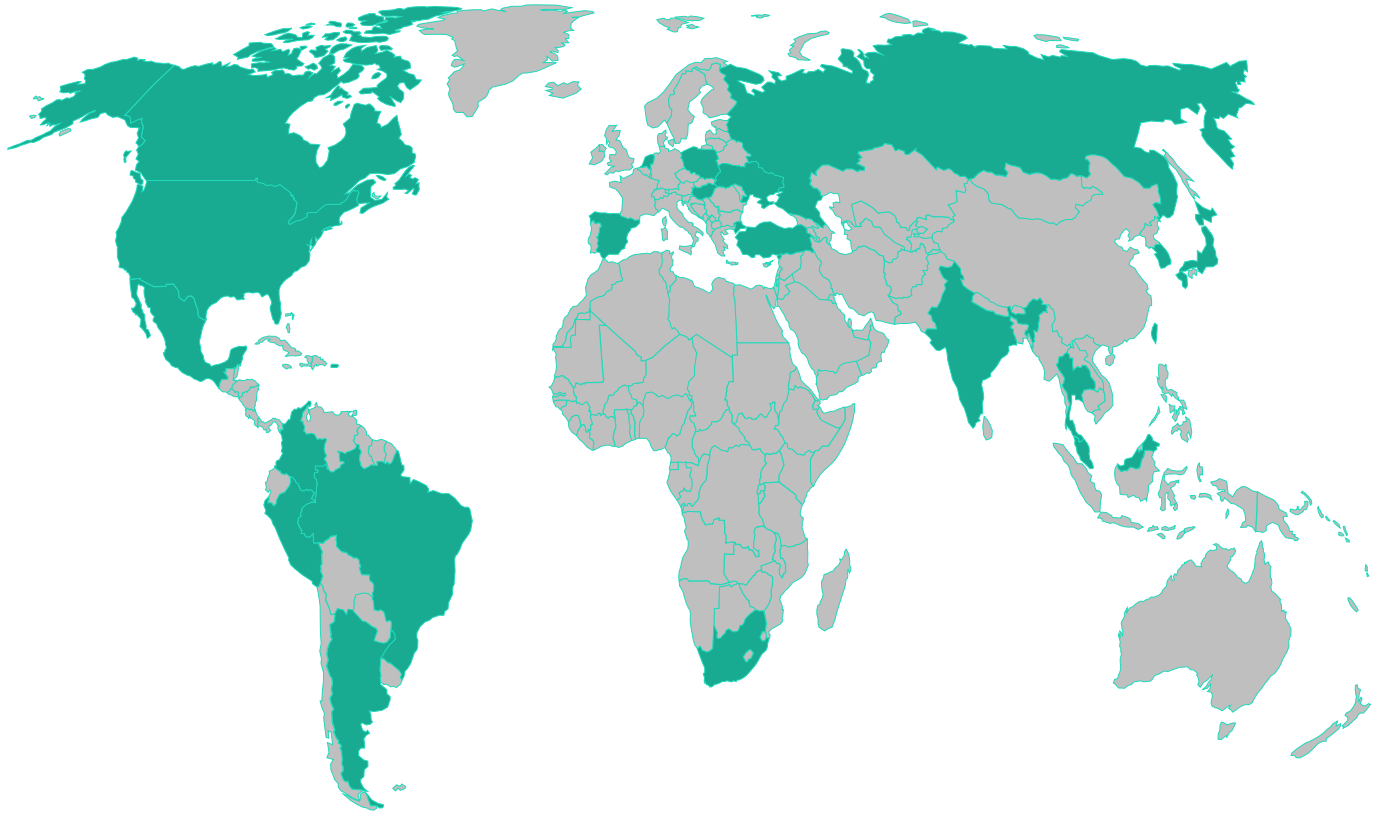
3. What is coming next from the WHO - GDG



Source: https://www.who.int/teams/health-care-readiness-clinical-unit/covid-19/therapeutics

4. Most recent updates: nirmatrelvir/r (study in High-Risk patients)

- **Moa**: 3C-like protease inhibitor
- **Route of administration**: (2+1) tablets every 12 hours for 5 days
- **Study design**:
  - Randomized, DB versus placebo
  - Patients: non-hospitalized adult patients, at high risk
  - Primary endpoint: risk of COVID-19-related hospitalization or death compared to placebo in patients treated within three days of symptom onset



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4. Most recent updates Nirmatrelvir/r – primary efficacy results- interim

Table 31 - Primary Analysis of Proportion of Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28 - mITT, Kaplan-Meier Method

	PF-07321332 300 mg + Ritonavir 100 mg	Placebo
N	389	385
Participants with event, n (%)	3 (0.8)	27 (7.0)
Participants with COVID-19 hospitalization	3 (0.8)	27 (7.0)
Participants with death	0	7 (1.8)
Average time at risk for event (Days)[a]	27.2	25.9
Average study follow-up (Days)[b]	27.3	26.9
Estimated proportion (95% CI), %	0.776 (0.251, 2.386)	7.093 (4.919, 10.174)
Difference from Placebo (SE)	-6.317 (1.390)	
95% CI of difference	-9.041, -3.593	
p-value	<.0001	

Results also statistically significant in patients enrolled after 5 days of symptoms, w/out mAbs (8%), w/out India patients (90% positive seropositive status at baseline).

"In patients with positive serology status at baseline (55.6%), results make difficult to conclude on the efficacy, with an absolute reduction of -1.22% (95% CI: -2.66% to -0.21%; p=0.0947)"

Potential for DDIs – well tolerated

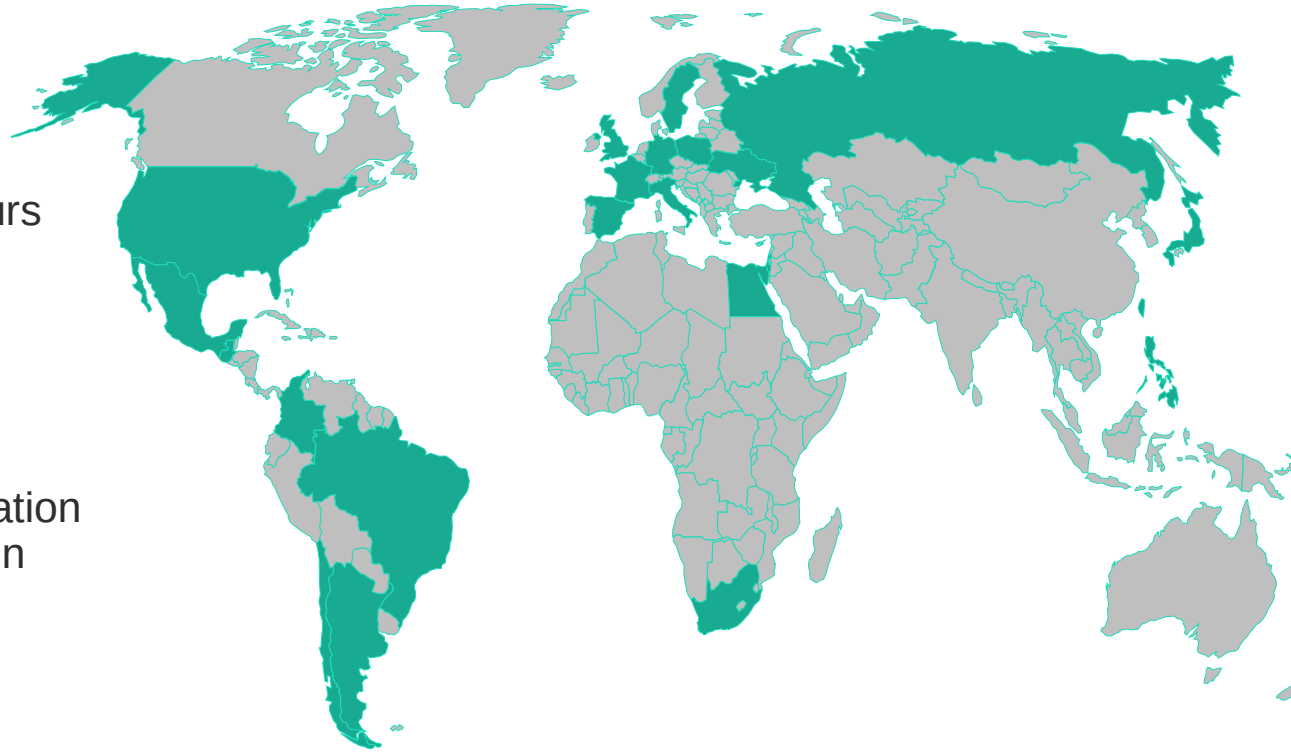
Source: EMA – Assessment Report EMA/783153/2021

https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/article-53-opinions#use-of-paxlovid-(pf-07321332-and-ritonavir)-for-treating-covid-19-section

COVID-19 Clinical Research Coalition

4. Most recent updates: molnupiravir

- **Moa**: inhibits viral replication by causing errors in the viral genome
- **Route of administration**: 4 capsules tablets every 12 hours for 5 days
- **Study design**:
  - Randomized, DB versus placebo
  - Patients: non-hospitalized adult patients, at high risk
  - Primary endpoint: risk of COVID-19-related hospitalization or death compared to placebo in patients treated within three days of symptom onset



4. Most recent updates: molnupiravir results (full dataset)

FDA

P002 Efficacy Analysis

	Interim Analysis Population Enrollment Dates: 5/7/2021 – 08/5/2021		Post-Interim Analysis Population[a] Enrollment Dates: 8/6/2021 – 10/2/2021		Full Population Enrollment Dates: 5/7/2021 – 10/2/2021	
	MOV	PBO	MOV	PBO	MOV	PBO
Hospitalization or death by Day 29	28/385 (7.3%)	53/377 (14.1%)	20/324 (6.2%)	15/322 (4.7%)	48/709 (6.8%)	68/699 (9.7%)
Death by Day 29	0 (0%)	8/377 (2.1%)	1/324 (<1%)	1/322 (<1%)	1/709 (<1%)	9/699 (1.3%)

[a]The Post-Interim Analysis Population includes those participants who had not reached Day 29 by the interim analysis data cutoff date of 9/18/2021.
Abbreviations: MOV, molnupiravir; PBO placebo

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Well tolerated

Potential for enhanced viral evolution

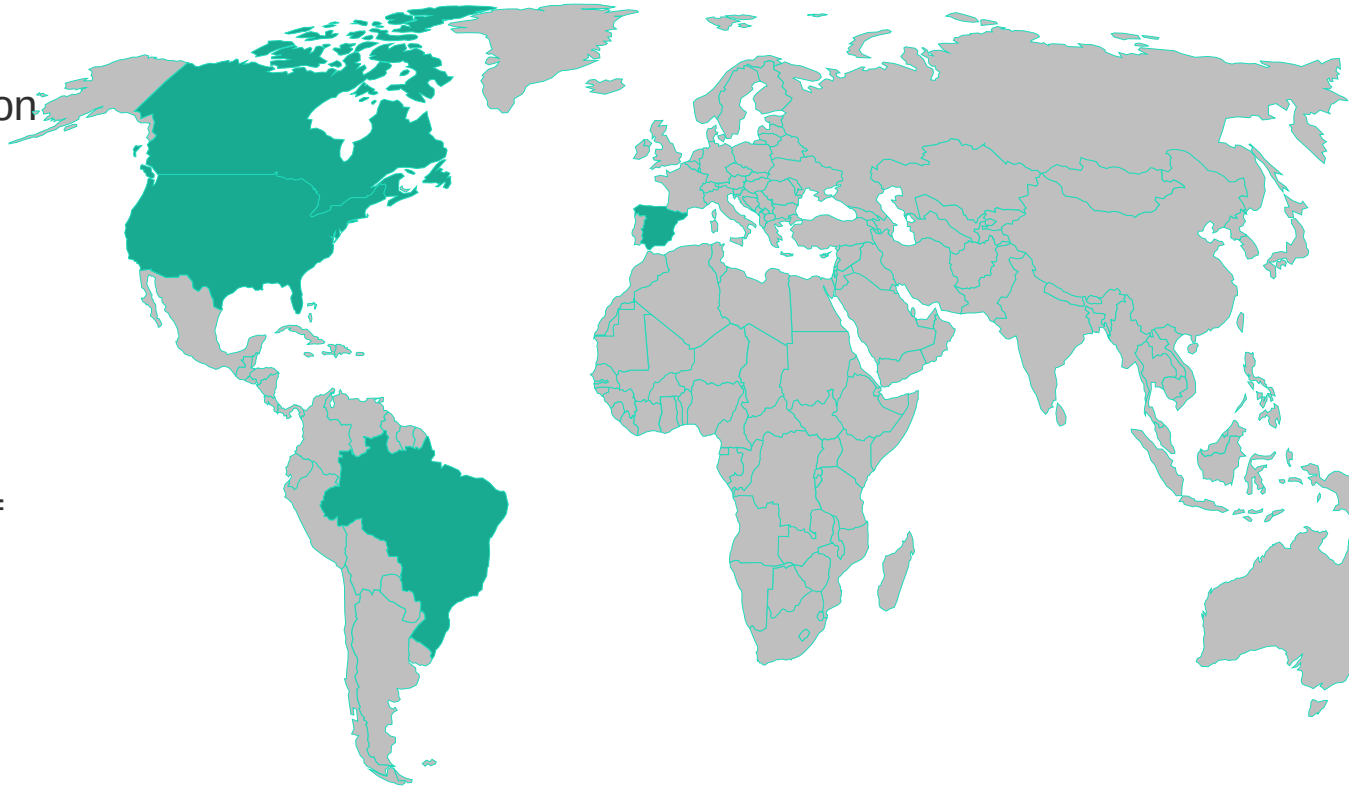
Requires male and female contraception

Source:
November 30, 2021: Antimicrobial Drugs Advisory Committee Meeting Announcement - 11/30/2021 - 11/30/2021 | FDA

COVID-19 Clinical Research Coalition

4. Most recent updates: sotrovimab (COMET-ICE)

- **Moa**:engineered human monoclonal antibody
- **Route of administration**: one single intravenous infusion of 500 mg over 30 minutes
- **Study design**
  - Multicenter, double-blind, phase 3 trial, 1:1 ratio
  - Non-hospitalized patients with symptomatic Covid-19 (≤5 days after the onset of symptoms) and at least one risk factor for disease progression to receive a single infusion of sotrovimab at a dose of 500 mg or placebo.
  - The primary efficacy outcome was hospitalization (for >24 hours) for any cause or death
  - Within 29 days after randomization



4. Most recent update: sotrovimab: interim analysis results (COMET-ICE) N=583

* CI denotes confidence interval, and ICU intensive care unit.

† The contributing event in Patient K was hospitalization for more than 24 hours; this patient later was included in the category "death from any cause."

‡ Inferential testing of secondary outcomes was not performed at this interim analysis.

§ "Emergency department visit for any cause" was defined as any inpatient or outpatient emergency department visit (regardless of whether the patient was hospitalized).

¶ One patient was hospitalized for less than 24 hours for diabetes management.

‖ The contributing event in Patient L was an "emergency department visit for any cause"; this patient later was included in the category "hospitalization for any cause."

** "Emergency department visit without hospitalization, or hospitalization for less than 24 hours for any cause" was defined as any emergency department visit without hospitalization, or hospitalization for less than 24 hours for any cause.

†† Severe or critical progression was manifested by the use of supplemental oxygen.

Source: Anil Gupta et al, *NEJM* 385;21 nejm.org November 18, 2021

Table 2. Efficacy Outcomes through Day 29 (Intention-to-Treat Population).*

Outcome	Sotrovimab (N = 291)	Placebo (N = 292)
Primary outcome		
Hospitalization for >24 hr for any cause or death from any cause — no. (%)	3 (1)	21 (7)
Hospitalization for >24 hr for any cause	3 (1)	21 (7)
Death from any cause	0	1 (<1)†
Alive and not hospitalized — no. (%)	284 (98)	270 (92)
Data missing — no. (%)		
All patients with missing data	4 (1)	1 (<1)
Patients with missing data because of withdrawal of consent before receipt of sotrovimab or placebo	3 (1)	1 (<1)
Relative risk reduction (97.24% CI)	85 (44–96)	—
P value	0.002	—
Other clinical outcomes‡		
Emergency department visit or hospitalization for any cause or death from any cause — no. (%)	6 (2)	28 (10)
Emergency department visit for any cause§	2 (<1)	8 (3)
Hospitalization for any cause	4 (1)¶	21 (7)‖
Death from any cause	0	1 (<1)†
Emergency department visit without hospitalization, or hospitalization for <24 hr for any cause — no. (%)**	3 (1)	7 (2)
Severe or critical progression — no. (%)††	2 (<1)	19 (7)
Low-flow nasal cannula or face mask	2 (<1)	11 (4)
Nonrebreather mask, high-flow nasal cannula, or noninvasive ventilation	0	5 (2)
Invasive mechanical ventilation	0	2 (<1)
Death from any cause	0	1 (<1)
Admission to ICU for any cause — no. (%)	0	5 (2)

5. Patient population from clinical trials of recommended outpatient treatments … and gaps…

	Published	Age	Symptom onset	vaccinated	Inclusion of Immunocompromised	Inclusion period or VoCs	Post-COVID follow-up
Molnupiravir [(a)]	YES (MSD) NO? (India)	≥18	up to 5 days	NO	Active cancer (1.8%)	33% delta, 12% mu, 45% UNK	NO
Nirmatrelvir/r	NO	≥18	up to 5 days	NO	YES (*)	16/07/21 - 26/10/21 97% delta	NO?
Sotrovimab [(b)]	YES	>18	Up to 5 days	NO	NO	27/08/2020 – 04/03/2021	24 weeks (no data yet)

(*) " poorly represented [chronic lung disease, CVD], immunosuppressive disease …] making difficult to conclude on the relevance of the results in these subpopulations "

[(a)] A. Jayk Bernal et al, *NEJM*, December 16, 2021, 10.1056/NEJMoa2116044
[(b)] Anil Gupta et al, *NEJM*, November 18, 2021, 10.1056/NEJMoa2107934

Conclusion

1. Access to **recent** evidence **difficult**
2. Regulatory opinions and treatment guidelines **not fully aligned –** criteria vary – not all relevant
3. There are **promising innovative** treatments for outpatients, not suitable to all settings
4. Access to new compounds for clinical research **mostly limited to originators**
5. Still **many therapeutic gaps: symptom onset > 5 days, regional generalisability, vaccinated, immunosuppressed, pregnant, children, post-COVID, asymptomatic... with other or resistant strains...**
6. **Access for patients is limited**
   - geographically
   - due to cost and/or route of administration
   - based on contraception needs… DDIs …

Still **pressing need to (access and) test** the **new compounds** as well as other **repurposed** drugs for **adapted "test and treat" strategy for all patients in need,** especially in LRS.

IF MEDICINES WORK, HOW CAN WE ENSURE PEOPLE GET THEM?

SPEAKER

Ms Leena Menghaney

MSF Access Campaign

India

No slides. Please refer to Ms Menghaney's presentation in the webinar recording.

ROUNDTABLE AND Q&A

CO-MODERATOR

Dr Podjanee Jittamala

Mahidol University

Thailand

CO-MODERATOR

Prof. Nick White

Mahidol-Oxford Research Unit

Thailand

CLOSING

How to connect

Become a **COVID-19 Clinical Research Coalition** member:

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Apply to join the coalition's new **Therapeutics Working Group**:

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