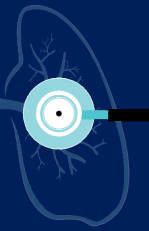


# COVID therapeutic guidance and the process for the new influenza guideline

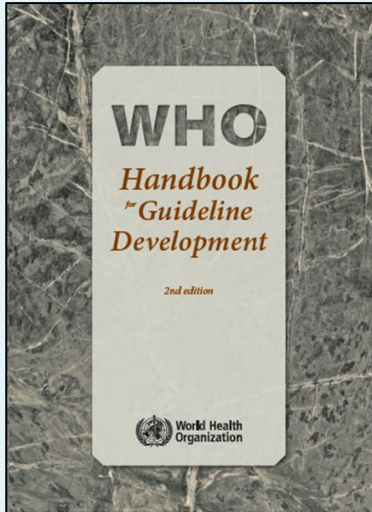
Dr Janet Diaz

Lead, Clinical Management Unit, Health Care Readiness,  
Health Emergencies Programme, WHO, Geneva

# Guideline Development Group

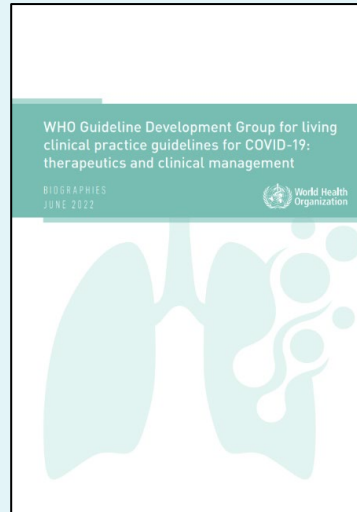


## Evidence-to-Decision framework...



...for consensus on

- Benefits and harms
- Values and preferences
- Equity
- Feasibility
- Cost and access

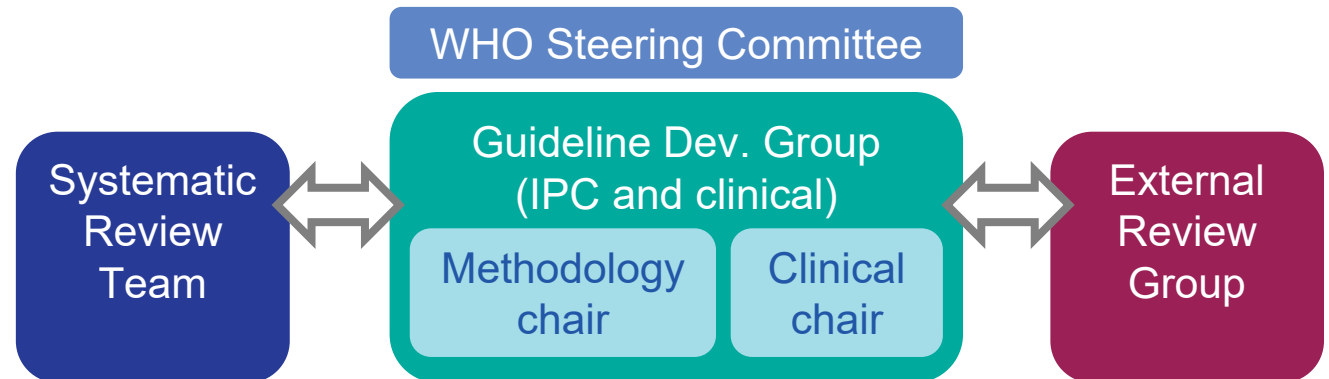


30 to 40 experts

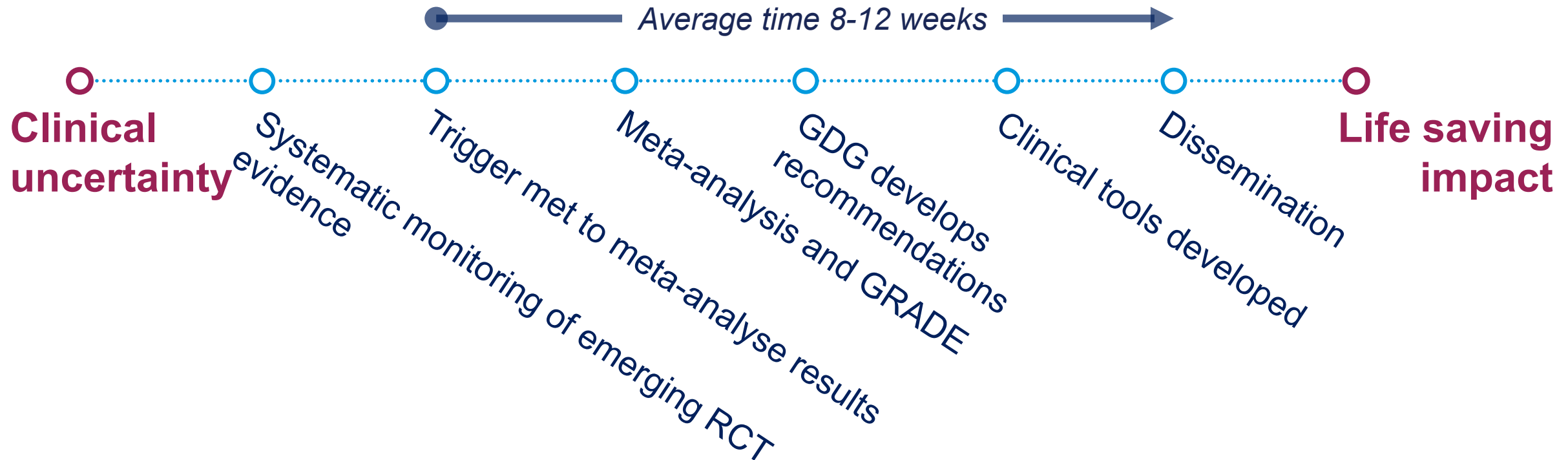
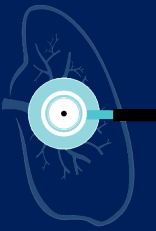
- All WHO regions
- Medical specialties
- Ethicists
- Patients

Unconflicted (financial and intellectual)

Standing virtual meetings



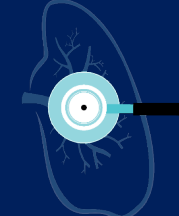
# Living guidelines: rapid, transparent and trustworthy evidence to the bedside



## Collaboration of hundreds of people...

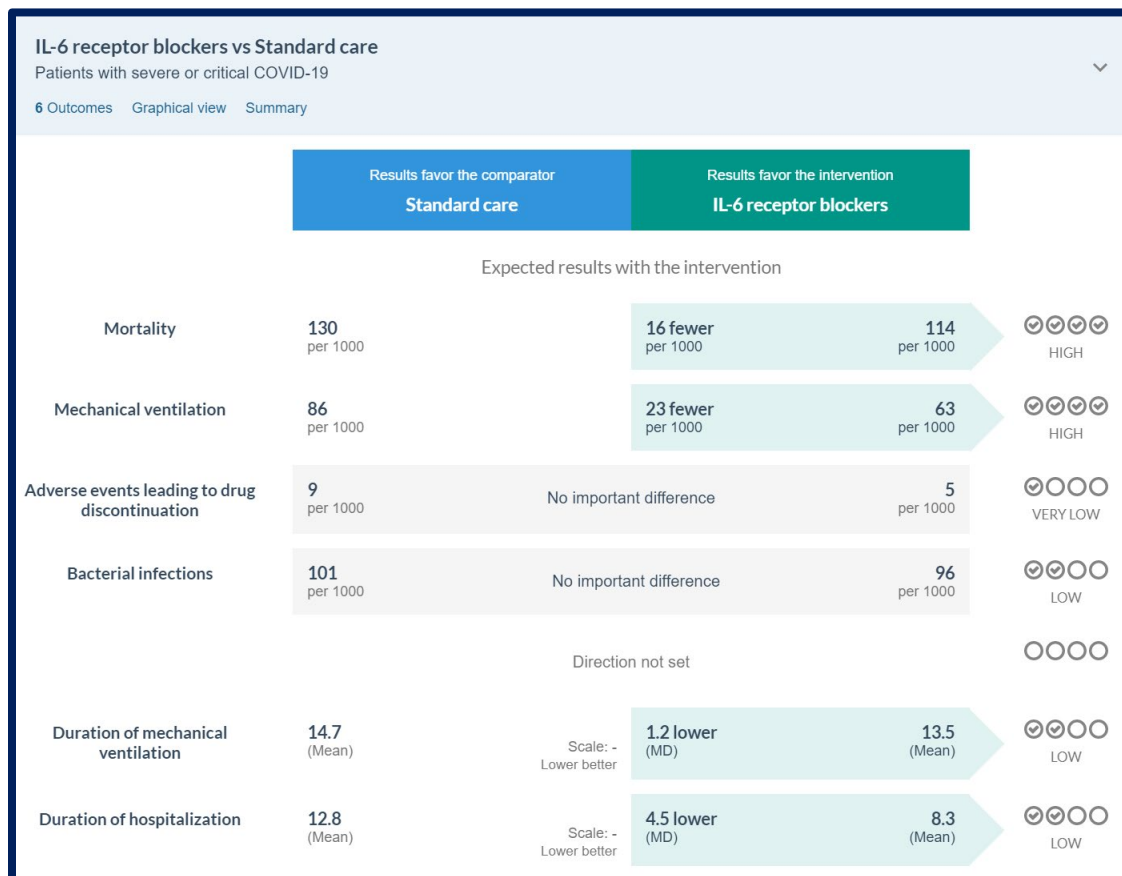
clinicians, researchers, methodologists, systematic reviewers, journal editors, patients and families



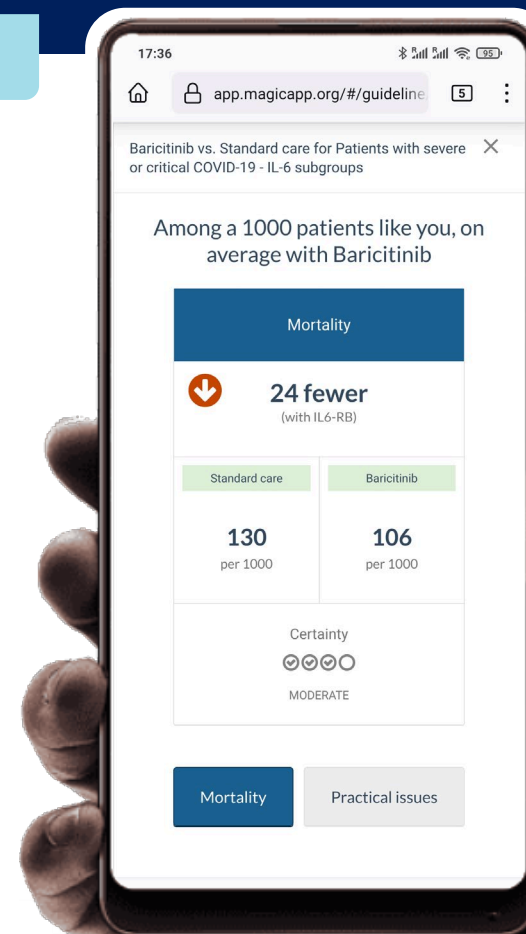


# Accessible evidence synthesis – MAGIC app

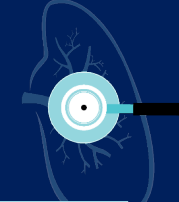
## Summary of findings and comparisons



## Mobile access







# Accessible evidence synthesis - BMJ

## Graphical summary

### Population

This recommendation applies only to people with these characteristics:



Patients with confirmed covid-19

### Interventions

Strong recommendations in favour

Weak or conditional recommendations in favour

Weak or conditional recommendations against

### Disease severity

| Non-severe   | Severe   | Critical  |
|--|--|---|
| Absence of signs of severe or critical disease                             | Oxygen saturation <90% on room air   | Requires life sustaining treatment                            |
| Risk of admission to hospital:<br>H High 5%<br>M Moderate 3%<br>L Low 0.5% | Signs of pneumonia<br>Signs of severe respiratory distress   | Acute respiratory distress syndrome<br>Sepsis<br>Septic shock |
| Nirmatrelvir and ritonavir H   | Corticosteroids<br>IL-6 receptor blockers<br>Baricitinib<br>All three may be combined                                    |   |
| Molnupiravir H<br>Requires mitigation strategies to reduce potential harms | Remdesivir   |   |
| Remdesivir H<br>Nirmatrelvir and ritonavir M                               |  |   |
| VV116 Only in research settings  |  |   |
| Corticosteroids  | Ruxolitinib and tofacitinib<br>Should be considered only if neither baricitinib nor IL-6 receptor blockers are available |   |
| Molnupiravir M<br>Requires mitigation strategies to reduce potential harms | Ivermectin Only in research settings   |   |

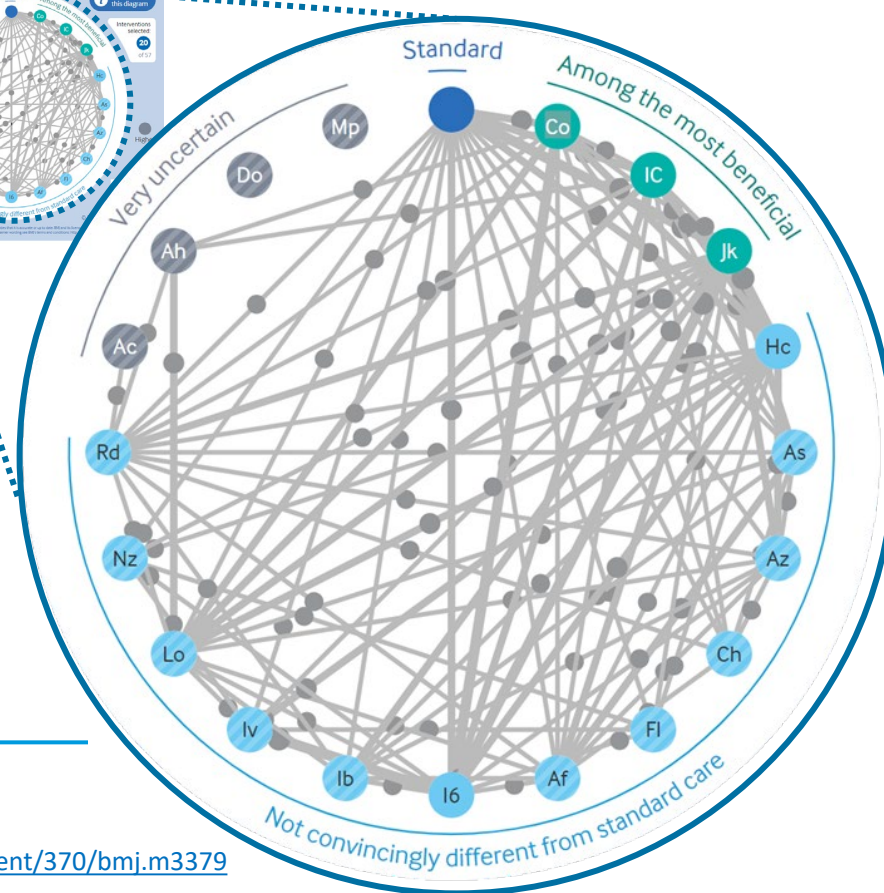
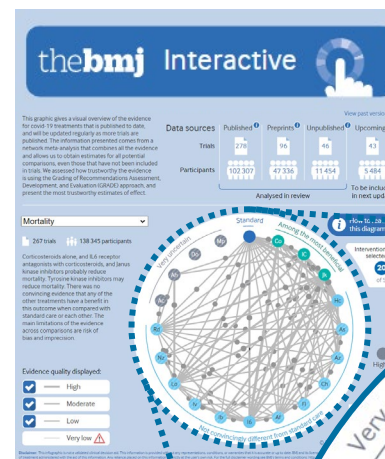
UPDATE

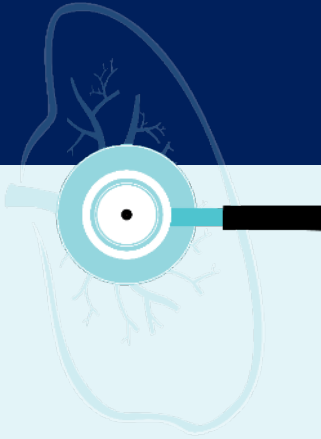
Several recommendations for people with non-severe disease are now stratified by how likely it is for someone to be admitted to hospital

UPDATE

New recommendation

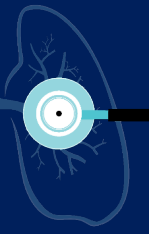
## Living network analysis



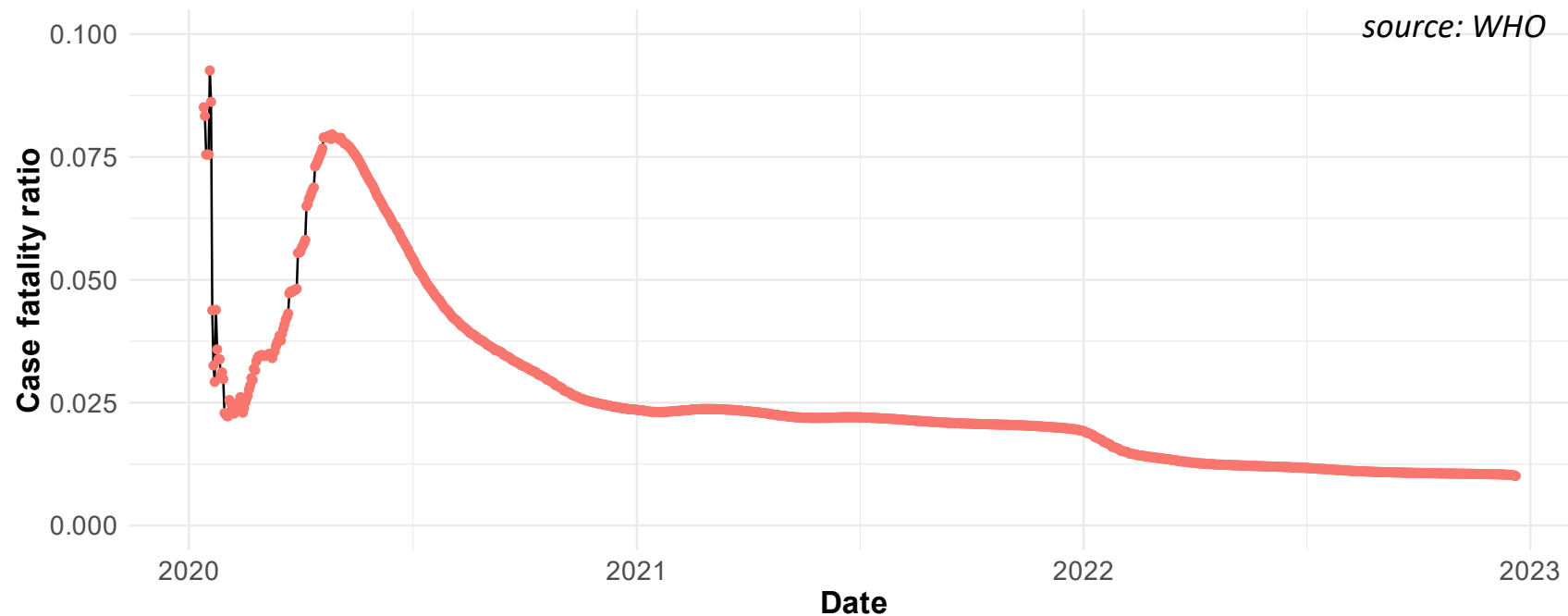


# Update on specific recommendations

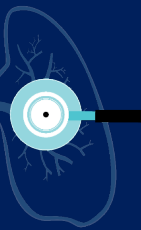
# Keeping the guideline responsive to changes in the pandemic



- Globally reducing mortality, and case fatality ratio
- Impacts the recommendations, especially for those with non-severe disease at clinical presentation



# Reducing absolute risks from COVID-19 alters the balance of risks and harms, and makes some risks trivial

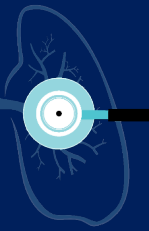











- GDG panel reassessed the likely **absolute risks of hospitalization** (a prioritized outcome) for patients with **non-severe COVID-19** at the time of clinical assessment...

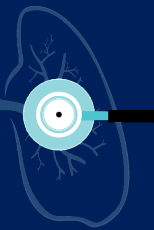
| Patient risk category | Estimated risk of hospitalisation | Includes patients such as...   |
|-----------------------|-----------------------------------|--|
| High                  | 6%                                | immunodeficiency syndromes<br>solid organ transplant receiving immunosuppressants<br>autoimmune illness receiving immunosuppressants   |
| Moderate              | 3%                                | over 65 years, obesity, diabetes, chronic cardiopulmonary disease, chronic kidney or liver disease, active cancer, those with disabilities, and those with comorbidities of chronic disease. |
| Low                   | 0.5%                              | <i>those who are not moderate or high risk</i>   |



# Recommendations for COVID-19 therapeutics



|                        | <i>High risk<br/>patients</i>   | <i>Moderate risk<br/>patients</i>   | <i>Low risk<br/>patients</i>   |
|------------------------|---|---|--|
| Molnupiravir           |  <b>Conditional<br/>For</b>  |  <b>Conditional<br/>Against</b>  |  <b>Strong<br/>Against</b>      |
| Nirmatrelvir-ritonavir |  <b>Strong<br/>For</b>       |  <b>Conditional<br/>for</b>      |  <b>Conditional<br/>Against</b> |
| Remdesivir             |  <b>Conditional<br/>for</b> |  <b>Conditional<br/>against</b> |  <b>Strong<br/>against</b>     |



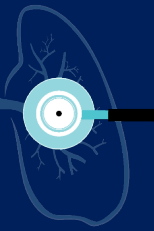
# Nirmatrelvir-ritonavir (1) – November 2023

## Strong recommendation for use of nirmatrelvir-ritonavir in patients with non-severe COVID-19 at **high** risk of hospitalization

- ...**nirmatrelvir-ritonavir in general represents a superior choice to molnupiravir** because it probably has a greater reduction in hospitalization and because of concerns about potential harms of molnupiravir.
- ...**nirmatrelvir-ritonavir in general represents a superior choice to remdesivir** because of the practical difficulty that arises from the intravenous administration of remdesivir.
- consider possible dangerous drug interactions or nirmatrelvir-ritonavir
- Given possible benefit and residual uncertainty regarding potential undesirable effects, clinicians should engage pregnant or breastfeeding individuals fully informed shared decision-making regarding the use of nirmatrelvir-ritonavir.

## Conditional recommendation for use of nirmatrelvir-ritonavir in patients with non-severe COVID-19 at **moderate** risk of hospitalization

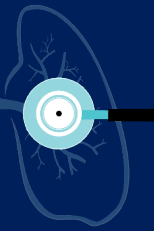
- Because their risk of hospitalization is sufficiently high such that they will receive an appreciable reduction in hospitalization with the drug, the GDG concluded that a majority of well-informed moderate-risk patients would choose to use nirmatrelvir-ritonavir.



# Nirmatrelvir-ritonavir (2) – November 2023

## Conditional recommendation against use of nirmatrelvir-ritonavir in patients with non-severe COVID-19 at moderate risk of hospitalization

- The marginal benefits of nirmatrelvir-ritonavir for patients at low risk of hospitalization suggest most patients would not want to use this treatment, but a minority may still be inclined to do so.
- The GDG noted the uncertainty in baseline risk estimates and uncertainty and variability in patient values and preferences when deciding on a conditional recommendation, rather than a strong recommendation, against nirmatrelvir-ritonavir.
- Given considerations regarding resources and equity, the GDG concluded that health care systems may reasonably not offer this drug to patients at low risk of hospitalization.



# Molnupiravir – November 2023

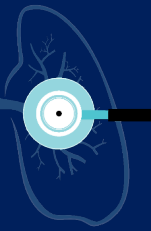
## **Conditional recommendation for use of molnupiravir** in patients with non-severe COVID-19 at **high** risk of hospitalization

- Nirmatrelvir-ritonavir is a superior choice to molnupiravir (due to greater reduction in hospitalization and because of safety concerns with molnupiravir).
- Remdesivir is a superior choice to molnupiravir because it possibly has a greater reduction in hospitalization in high-risk patients.
- The longer term harms of molnupiravir remain unknown in the absence of clinical evidence, both for individual patients and at the population level. These include potential mutagenesis, emergence of resistance, and emergence of new variants
- Use of molnupiravir should be accompanied by mitigation strategies such as avoiding the drug in younger adults, children and pregnant patients, active pharmacovigilance programmes, and monitoring viral polymerase and spike sequences



## **Conditional recommendation against use of molnupiravir** in patients with non-severe COVID-19 at **moderate** risk of hospitalization

## **Strong recommendation against use of molnupiravir** in patients with non-severe COVID-19 at **low** risk of hospitalization



# Remdesivir – November 2023

## **Conditional recommendation for use of remdesivir** in patients with non-severe COVID-19 at **high** risk of hospitalization

- The GDG concluded that nirmatrelvir-ritonavir may represent a superior choice to remdesivir because of the practical difficulty that arises from the intravenous administration of remdesivir.
- Remdesivir is likely to be the desirable option in patients for whom nirmatrelvir-ritonavir or molnupiravir are not options. For nirmatrelvir, this will be patients who are using drugs with problematic interactions with nirmatrelvir-ritonavir. For molnupiravir, these will be individuals in whom concerns regarding mutagenesis are particularly great, which would include pregnancy and children. For both drugs, it will include those for whom, for whatever reason, the drugs are unavailable.

## **Conditional recommendation against use of remdesivir** in patients with non-severe COVID-19 at **moderate** risk of hospitalization

## **Strong recommendation against use of remdesivir** in patients with non-severe COVID-19 at **low** risk of hospitalization

# Update on specific recommendations

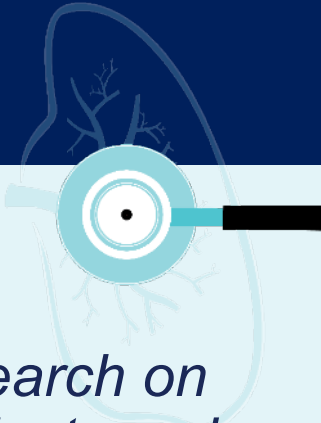
... reviewed and  
**not recommended...**

*...in 2023...*

- ✗ VV116 (only in research)
- ✗ Ivermectin (*only for use in research on severe or critical disease, against use in non-severe disease*)

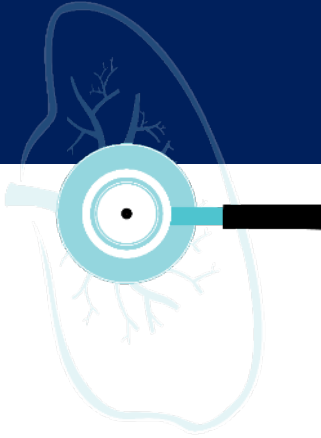
*...and previously...*

- ✗ Hydroxychloroquine
- ✗ Lopinavir-ritonavir
- ✗ Ruxolitinib and tofacitinib
- ✗ Convalescent plasma (*only for use in research on severe or critical disease*)
- ✗ Casirivimab-indevimab





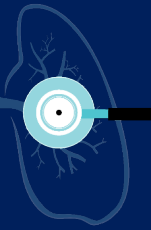
# Being reviewed



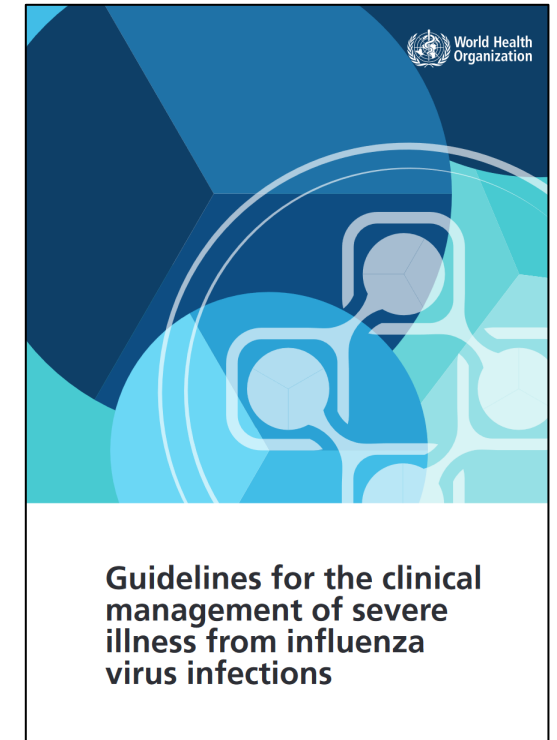
- Anticoagulation (heparin)
  - based on prospective systematic review of multiple trials
- VV116 (oral antiviral)
  - Based on recent RCT publication (n=1369) on 2 November 2023  
(DOI:[https://doi.org/10.1016/S1473-3099\(23\)00577-7](https://doi.org/10.1016/S1473-3099(23)00577-7))

# Influenza guideline under development

# Scope and timeline of influenza guidelines



- Previous WHO guidance from 2022 (SR from 2019)
- Multiple requests for update, which will include
  - Antivirals for non-severe and severe/critical patients
  - Antivirals for seasonal and zoonotic flu
  - Antivirals for secondary prevention (in high-risk contacts of primary cases)
  - Adjunctive therapies (such as immunosuppressives)
  - Use of antibiotics
  - Diagnostic testing strategy to guide treatment
- Guideline Development Group meeting 18-20 December 2023
- Expected publication Q2 2024



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# Thank you!

[Health Care Readiness \(who.int\)](#)

[Therapeutics and COVID-19 \(who.int\)](#)

[The WHO Global Clinical Platform for COVID-19](#)

[COVID-19 Clinical Care Pathway \(who.int\)](#)

[A living WHO guideline on drugs for covid-19 | The BMJ](#)

[Therapeutics and COVID-19: living guideline \(magicapp.org\)](#)