World Health Emergencies and living guidelines

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Presenting on behalf of the WHO Emergencies Programme
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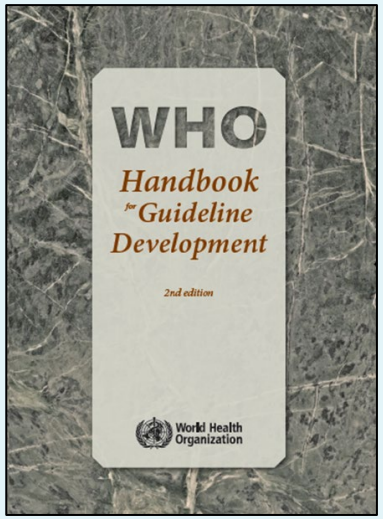
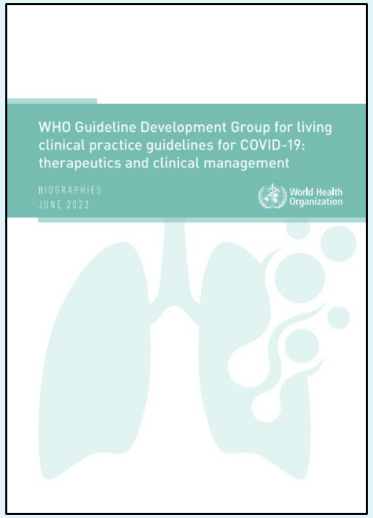
Guideline development process - robust methods

Evidence-to-Decision framework…

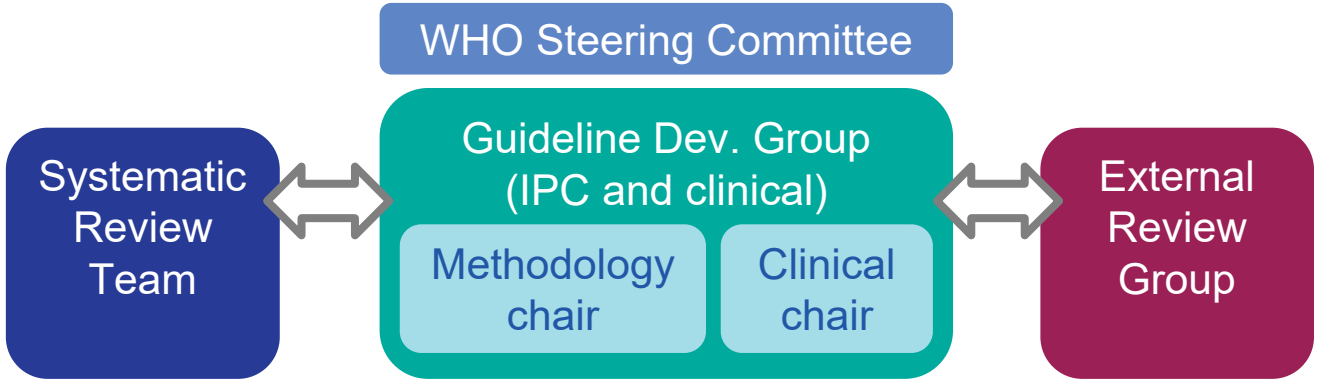


…for consensus on

- 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



WHO handbook for guideline development https://apps.who.int/iris/handle/10665/145714
Living guideline GDG https://www.who.int/publications/m/item/who-guideline-development-group-living-guidelines-for-covid-19-biographies

Accessible evidence synthesis

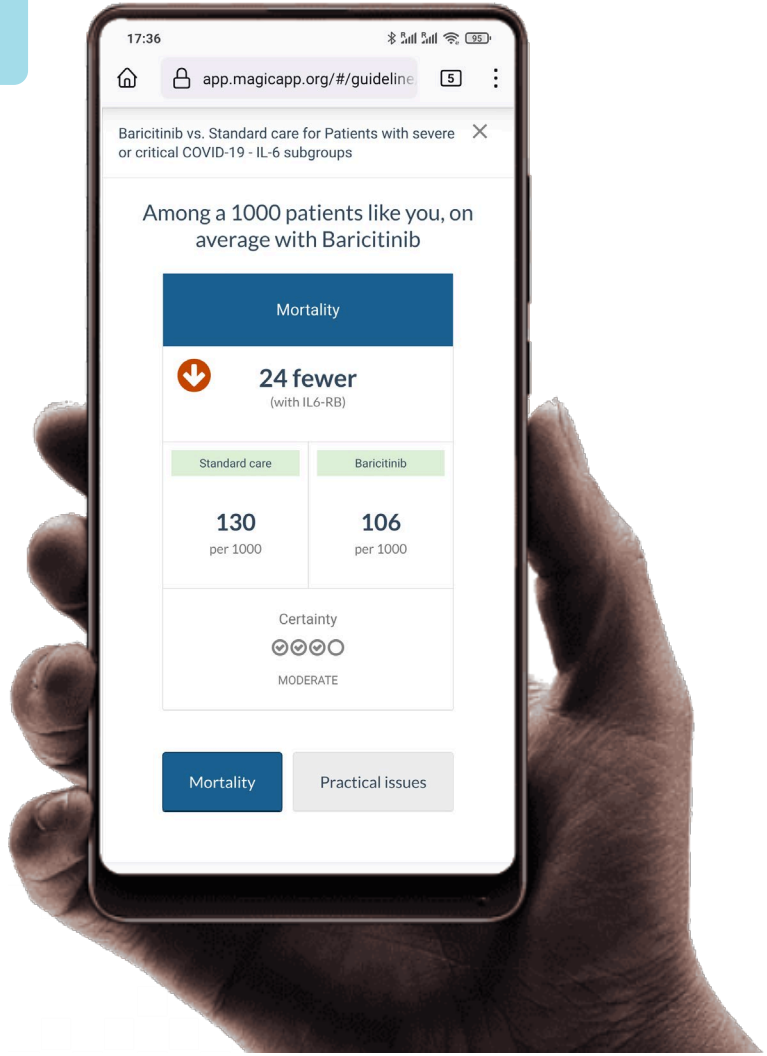
Summary of findings and comparisons

IL-6 receptor blockers vs Standard care
Patients with severe or critical COVID-19

6 Outcomes | Graphical view | Summary

	Results favor the comparator: Standard care		Results favor the intervention: IL-6 receptor blockers		
			Expected results with the intervention		
Mortality	130 per 1000		16 fewer per 1000	114 per 1000	⨁⨁⨁⨁ HIGH
Mechanical ventilation	86 per 1000		23 fewer per 1000	63 per 1000	⨁⨁⨁⨁ HIGH
Adverse events leading to drug discontinuation	9 per 1000	No important difference		5 per 1000	⨁◯◯◯ VERY LOW
Bacterial infections	101 per 1000	No important difference		96 per 1000	⨁⨁◯◯ LOW
			Direction not set		◯◯◯◯
Duration of mechanical ventilation	14.7 (Mean)	Scale: - Lower better	1.2 lower (MD)	13.5 (Mean)	⨁⨁◯◯ LOW
Duration of hospitalization	12.8 (Mean)	Scale: - Lower better	4.5 lower (MD)	8.3 (Mean)	⨁⨁◯◯ LOW

Mobile access



Therapeutics and COVID-19: living guideline (magicapp.org) https://app.magicapp.org/#/guideline/nBkO1E

COVID-19

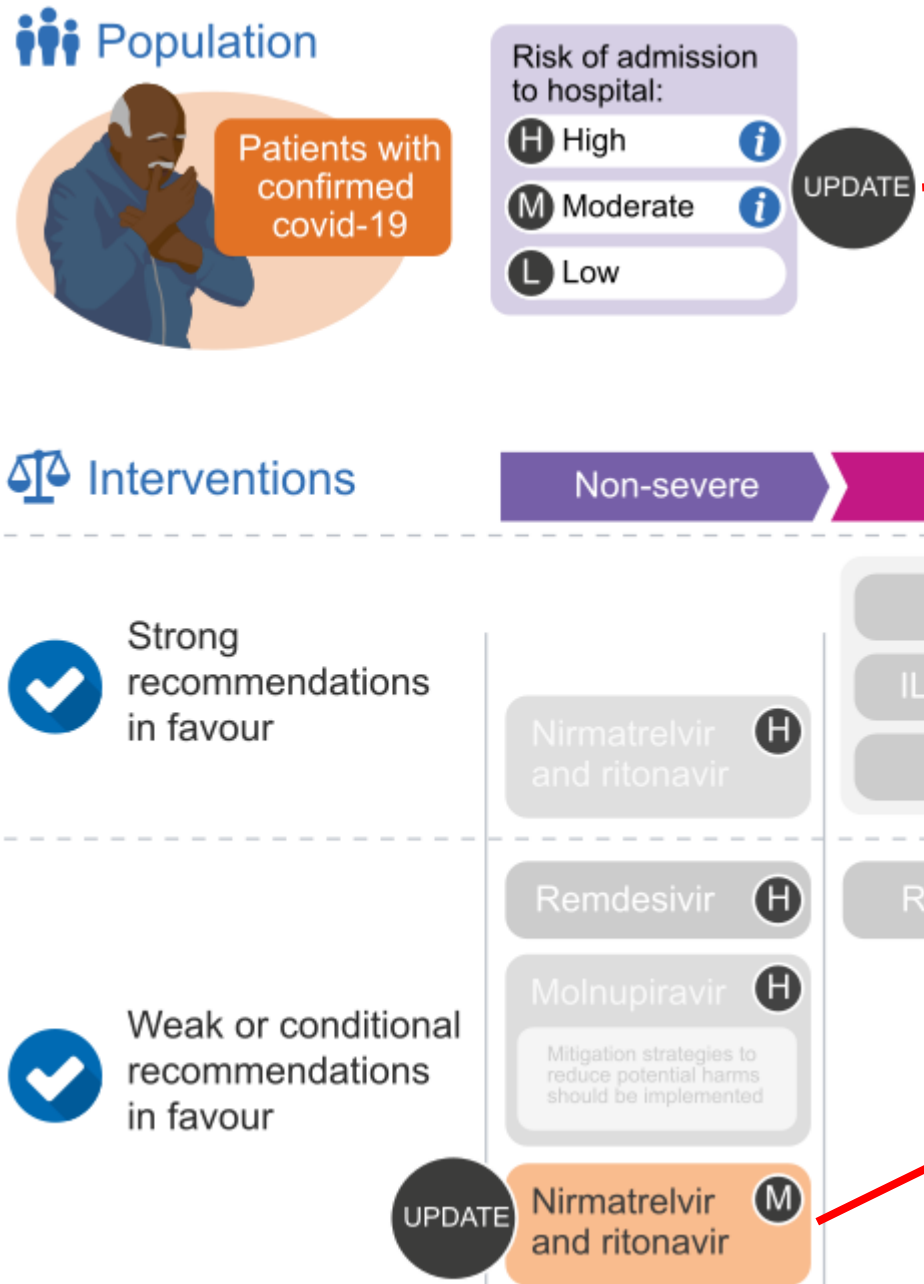
Last guideline update November 2023

- In view of changing epidemiology, **revised risk estimates** have been used to assess absolute effects of therapeutics

Current ongoing consideration of:

- **Anticoagulation** (heparins) in patients hospitalized with COVID-19
- **HMGCoA reductase inhibitors** (statins) in patients hospitalized with COVID-19
- **Metformin** to prevent long-COVID for patients with acute COVID-19

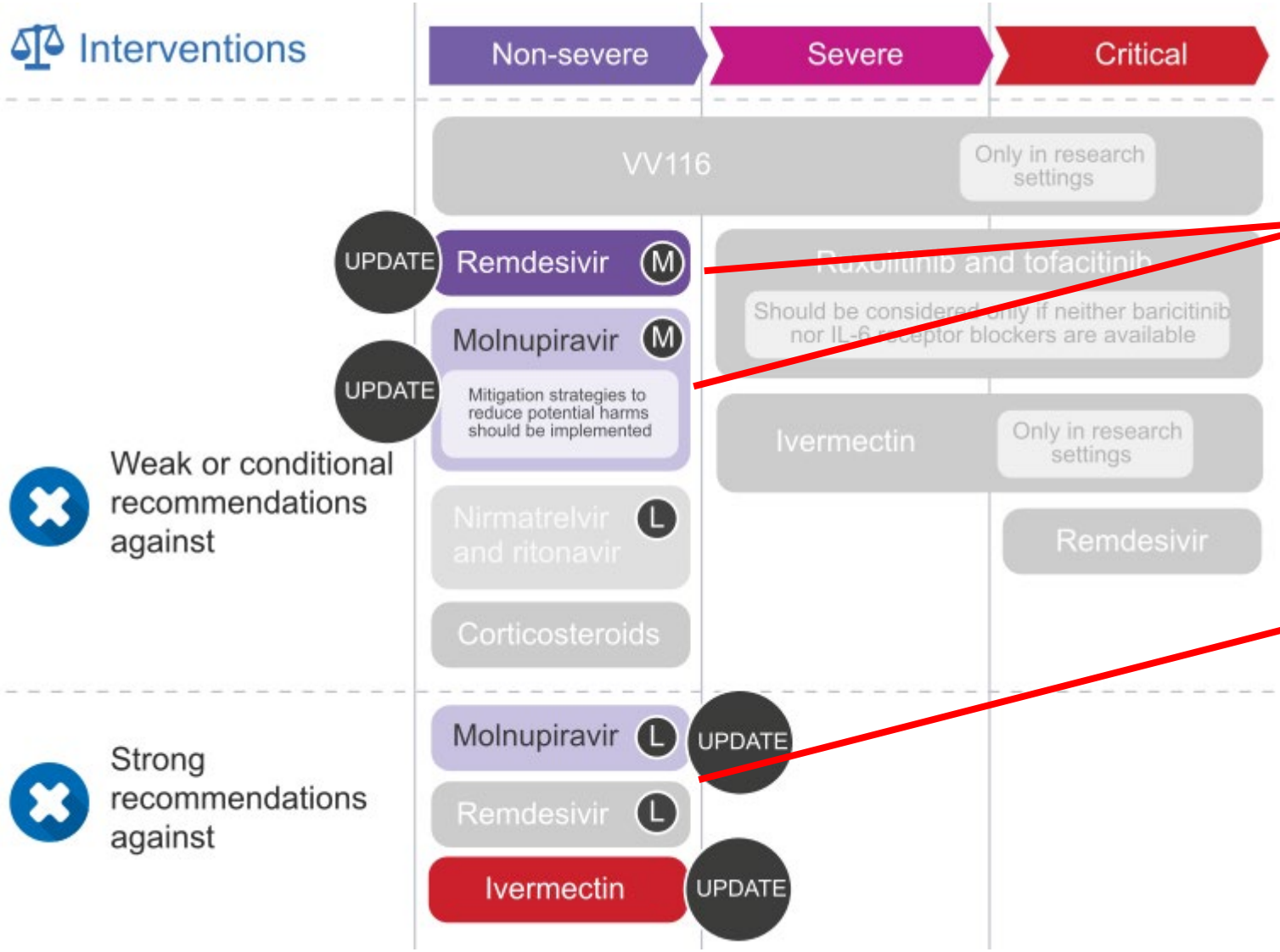
Next update publication in Q1 2025



new estimates of risk…

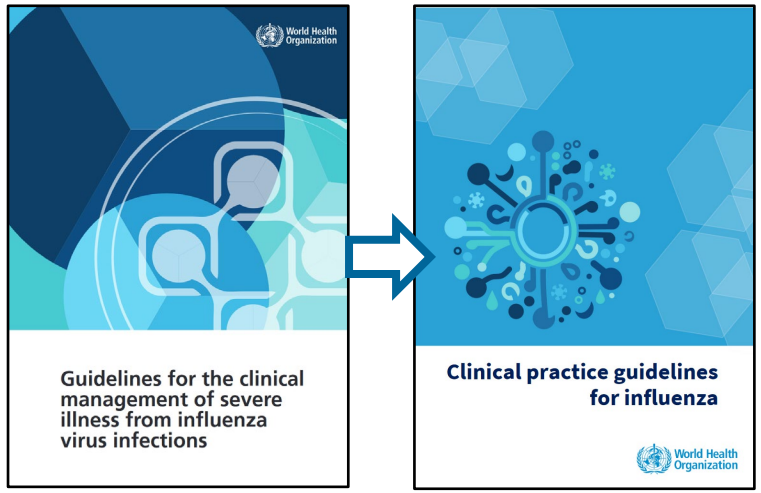
Patient risk group	Estimated hospitalisation rate
Low	0.5%
Moderate	3%
High	6%

conditional recommendation for nirmatrelvir-ritonavir for patients with non-severe COVID-19 at **moderate risk** of hospitalization



Remdesivir and molnupiravir
No longer recommended for moderate-risk patients

Molnupiravir
Strong recommendation against for low-risk patients



2022
(2019 data)

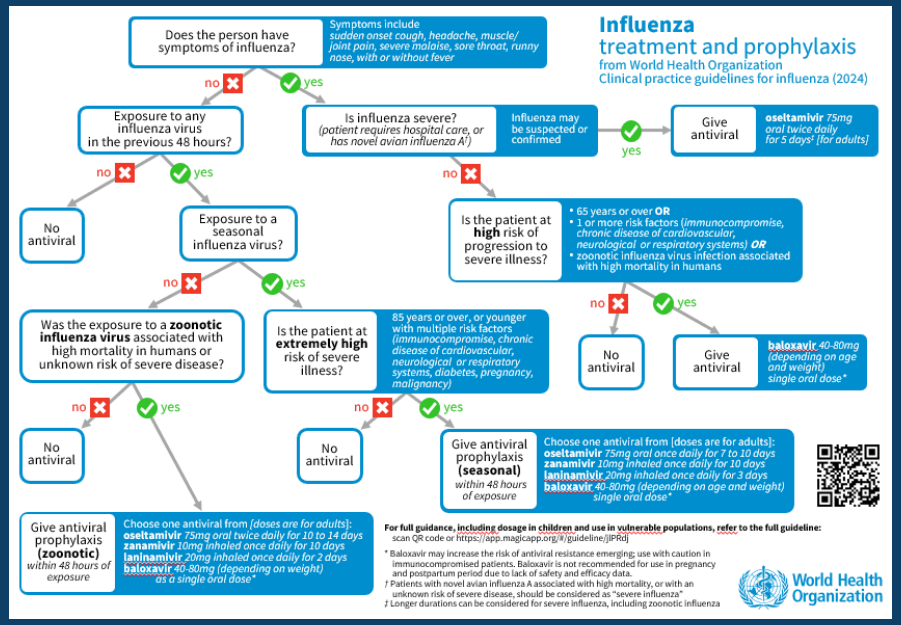
2024
(2023 data)

WHO Clinical guidelines for influenza (2024)

Considered all available therapeutics, privileging RCT evidence

Broadened scope to include recommendations on:

- non-severe influenza
- zoonotic influenza (novel influenza A)
- secondary prevention (in contacts of primary cases)
- adjunctive therapy (steroids, immunomodulators)
- routine use of antibiotics
- *assessment of severity (see bottom of page)*



Non-severe influenza

- Conditional for: baloxavir (high risk patients only)
- Conditional against: laninamivir, peramivir, umifenovir, (baloxavir in low risk patients)
- Strong against: oseltamivir, zanamivir, favipiravir
- Strong against: antibiotics in patients with a low probability of bacterial infection

Severe (hospitalized, or novel influenza A)

- Conditional for: oseltamivir
- Conditional against: peramivir, zanamivir
- Conditional against: macrolide as immunomodulator, NSAIDs, mTOR inhibitors, passive immune therapy, corticosteroids

Prophylaxis in seasonal influenza

- Conditional for (only in patients at extremely high risk): oseltamivir, zanamivir, laninamivir, baloxavir

Prophylaxis in zoonotic / novel influenza A

- Conditional for (all patients): oseltamivir, zanamivir, laninamivir, baloxavir

Major risk factors for severe disease: *Age 65+ years; immunocompromise; cardiovascular disease; neurological disease; chronic respiratory disease.*
Additional risk factors: *malignancy; pregnancy; diabetes.*

High risk for severe disease: *Age 65+ years and/or one or more major risk factors*
Extremely high risk for severe disease: *85 years or older, or under 85 years with multiple major and additional risk factors (as judged by clinician)*

Clinical practice guidelines for influenza: summary of recommendations 1

Patients with non-severe seasonal influenza		
	**Conditional recommendation for use**	**Baloxavir** in patients with high risk of progression to severe influenza (65 years of age and over **or** one or more major risk factors for severe influenza)
	**Conditional recommendation against use**	**Laninamivir** **Peramivir** **Umifenovir** **Baloxavir** in patients at low risk of progression to severe influenza.
	**Strong recommendation against use**	**Oseltamivir** **Zanamivir** **Favipiravir**
		adjunctive treatment Concomitant antibiotics in patients with low probability of bacterial infection

Clinical practice guidelines for influenza: summary of recommendations 2

Patients with severe influenza		
	**Conditional recommendation for use**	**Oseltamivir**
	**Conditional recommendation against use**	**Peramivir** **Zanamvir**
		adjunctive treatment **Macrolide** (for immunomodulatory therapy – recommendation not relevant to bacterial coinfection) **NSAIDs** **mTOR inhibitors** **Passive immune therapy** **Corticosteroids**

Clinical practice guidelines for influenza: summary of recommendations 3

Preventing influenza among persons with exposure to seasonal influenza viruses in the prior 48 hours (with no known infection)

Conditional recommendation for use

Oseltamivir *or*
Zanamivir *or*
Laninamivir *or*
Baloxavir

Only in persons at ***extremely high risk*** *of severe illness (85 years of age and over* **or** *younger patients with multiple risk factors).*
In the absence of risk factors for developing severe disease the recommendation is against giving these therapeutics.

Clinical practice guidelines for influenza: summary of recommendations 4

Preventing influenza among persons with zoonotic influenza associated with high mortality or unknown risk of severe disease (with no known infection)		
	**Conditional recommendation for use**	**Oseltamivir** *or* **Zanamivir** *or* **Laninamivir** *or* **Baloxavir**

Influenza antivirals: Global production capacity assessment

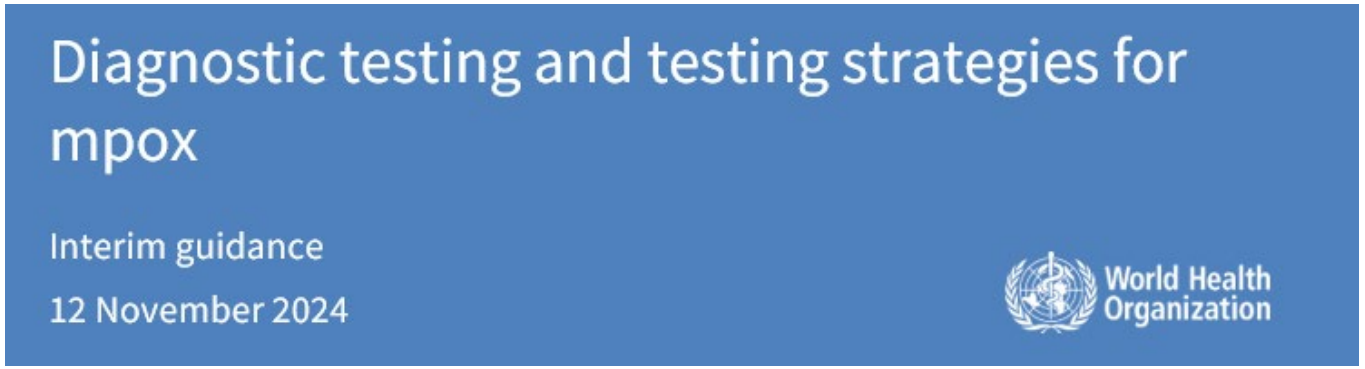
- **WHO will be reaching out to manufacturers to learn more about global production capacity of influenza antivirals**
  - Data on influenza antivirals are limited
  - WHO is developing a roadmap on seasonal influenza vaccination with a holistic approach to prevention and control
  - WHO is responsible for global estimates of vaccines and antivirals production capacities as part of influenza pandemic preparedness
- **WHO plans to send out a survey for antivirals information in March 2025** to manufacturers currently producing approved influenza antivirals
  - Information on product(s)
  - Estimate of maximum treatment courses that could be produced
  - Information provided by manufacturers will be kept confidential; only aggregate summaries will be published

If you are an influenza antiviral manufacturer and want to learn more, please contact Jessica Taaffe, taaffej@who.int.

Mpox testing and testing strategies: interim guidance (4th version)

Key updates

- Available molecular-based near patient Point-Of-Care Tests are able to demonstrate a high level of accuracy comparable to laboratory-based PCR.



- WHO does not recommend use of rapid antigen tests for detection of monkeypox virus (MPXV).
- Research on AgRDT strongly encouraged, so those would be game changers to provide access to Dx in remote areas
- Considerations on testing strategy depending on the epidemiological setting (no cases, sporadic cases, clusters, community transmission)

Diphtheria

Global shortage of antitoxin

(despite being 124 years after DAT was recognized in the Nobel prize for medicine!)

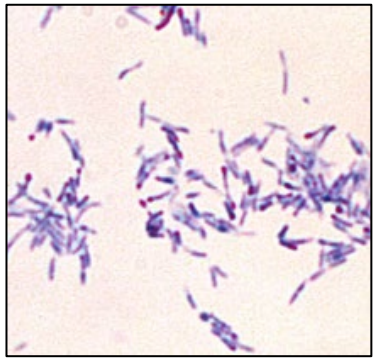
Under-utilization in epidemic settings due to

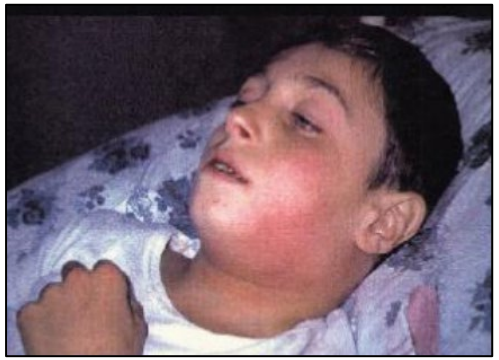
- **Lack of availability**
- Difficulties in administration and patient selection
- Reliance on antibiotics as a therapeutic
- WHO hosts small stockpile and supports with allocation during outbreaks

WHO Guideline recommendation (2024)

"In suspected or confirmed symptomatic diphtheria, WHO suggests administration of a single dose of diphtheria antitoxin"

[Conditional recommendation, very low certainty evidence]





Characteristic of diphtheria disease	DAT dose (IU)
•Laryngitis **or** pharyngitis **and** •Duration < 48 hours	20 000
•Nasopharyngeal disease (extensive pseudomembrane) **and** •Duration < 48 hours	40 000
One or more of: •Diffuse swelling of the neck •Any disease ≥ 48 hours •Severe disease (respiratory distress, shock)	80 000

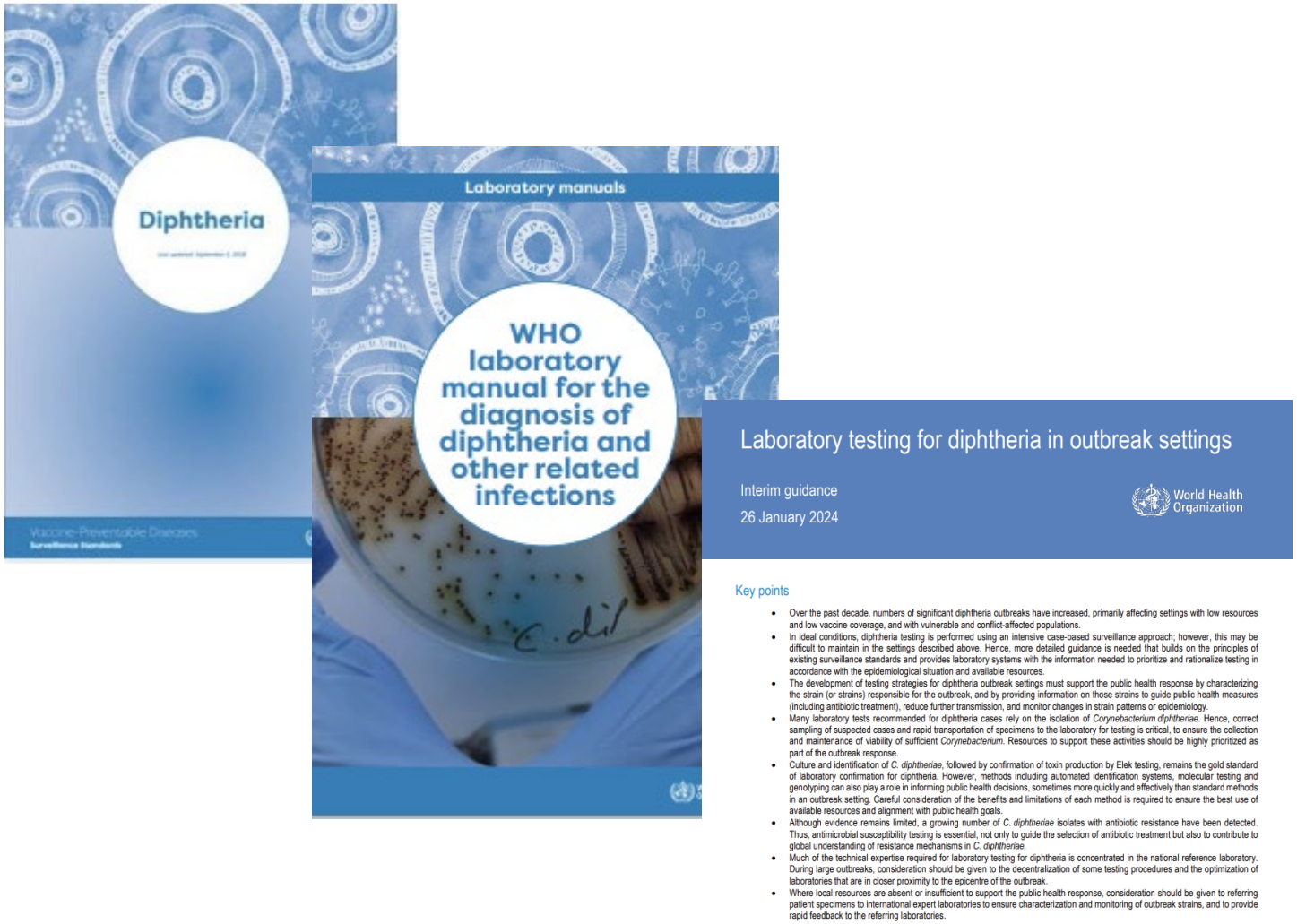
Interim Guidance: Laboratory Testing for Diphtheria in outbreak settings

Builds on existing WHO laboratory guidance documents:

- WHO Laboratory Manual for the diagnosis of diphtheria & other related infections (2021)
- WHO Diphtheria: Vaccine Preventable Diseases Surveillance Standards (2018)

Focuses on key issues related to laboratory testing during outbreak events & resource-limited settings:

- Rationalization of Elek (toxin) testing in resource-limited settings.
- Considerations and use-cases for the use of automated identification systems or molecular methods.
- The importance of antimicrobial susceptibility testing to guide clinical care & knowledge of emergence of resistance mechanisms.



Laboratory testing for Dengue
Interim Guidance

Builds on previous WHO laboratory guidance documents

- Dengue specific 2009
- Zika and Dengue 2022
- PAHO Dengue Technical note and Algorithm 2023 (RDTs not recommended in PAHO)

Updated dengue-specific interim laboratory testing guidance

- Include diagnostic algorithms - low resource settings
- Include recommendations on genomic surveillance

Laboratory testing for Dengue
Key Messages

- In primary infections, during the acute phase, following symptom onset
  - 0-5 days, viral RNA and NS1 antigens are detectable;
  - day 5 +, IgM and IgG are detectable
- In secondary infections,
  - NS1 detection is reduced due to antigen-antibody complexes, IgM responses are reduced or absent, and IgG rises earlier and dominates.
- Serological tests for IgM and IgG are known to be affected by cross-reactivity in areas where multiple orthoflaviviruses are circulating.
- The preferred diagnostic tools may vary according to the context, capacity of the national laboratory system and intended use:
  - For clinical management of patients, fast and accurate tests such as RT-PCR, NS1 ELISA, or a combination of NS1 and IgM (+/-IgG) (ELISA or RDTs) are preferred.
  - For field investigations for suspected outbreaks, near-patient NAAT, NS1 ELISA, or a combination of NS1 and IgM (RDTs) can be most efficiently deployed to confirm or exclude DENV as the etiologic pathogen.
  - For surveillance, high-throughput , high-sensitivity, and specific methods are preferred; these include RT-PCR and next-generation sequencing (NGS). IgG/IgM ELISA can be used to monitor areas of transmission.
- DENV can be detected in a range of patient samples including whole blood, plasma, serum, and urine samples.
- For shipping purposes, dengue diagnostic samples are classified as UN 3373 "Biological Substance Category B," while DENV cultures are classified as Category A, with UN2184 and proper shipping name “Infectious substance, affecting humans”.

Thank you for your attention

Slides contribution from various departments and teams within WHO Health Emergencies Programme

- Philomena Raftery (Department of Country Readiness Strengthening)
- Jamie Rylance (Department of Country Readiness Strengthening)
- Lorenzo Subissi (Department of Epidemic and Pandemic Threat Management)