

# World Health Emergencies and living guidelines

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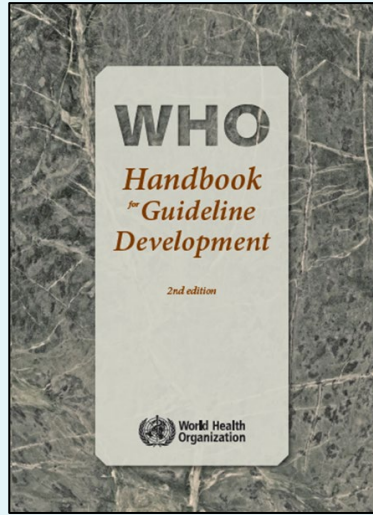
Lead Clinical management and operations

Presenting on behalf of the WHO Emergencies Programme

05 December 2024

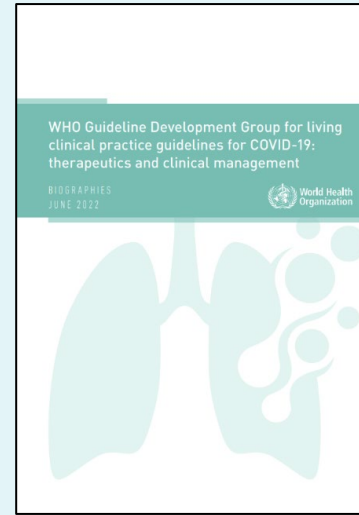
# Guideline development process - robust methods

## Evidence-to-Decision framework...

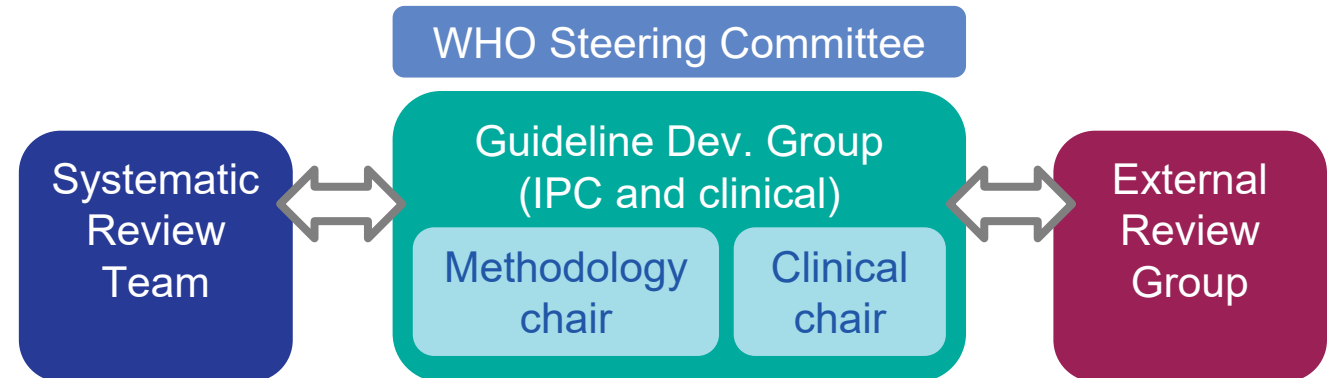


...for consensus on

- 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>

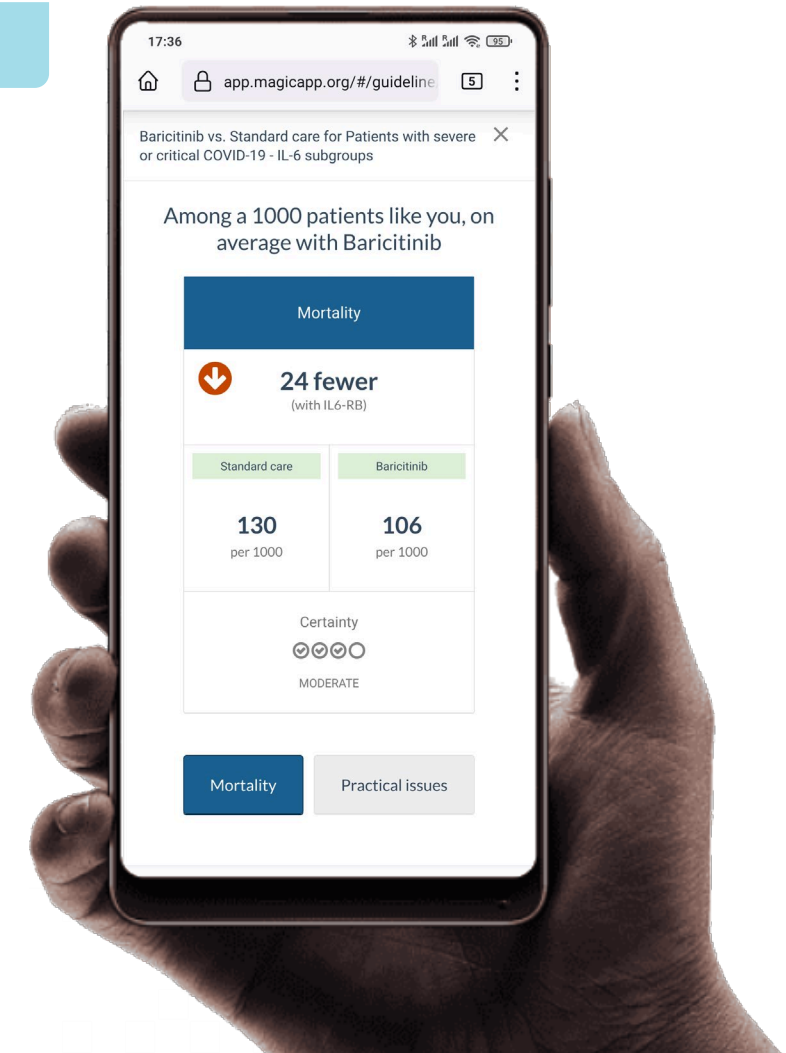
Living guideline GDG <https://www.who.int/publications/m/item/who-guideline-development-group-living-guidelines-for-covid-19-biographies>

# Accessible evidence synthesis

## Summary of findings and comparisons



## Mobile access



# 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

## Population



Risk of admission to hospital:

**H** High

**M** Moderate

**L** Low

UPDATE

**new estimates of risk...**

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

## Interventions

Non-severe

Severe

Critical



Strong recommendations in favour

Nirmatrelvir and ritonavir **H**

Corticosteroids

IL-6 receptor blockers

Baricitinib

All three may be combined



Weak or conditional recommendations in favour

Remdesivir **H**

Molnupiravir **H**

Mitigation strategies to reduce potential harms should be implemented

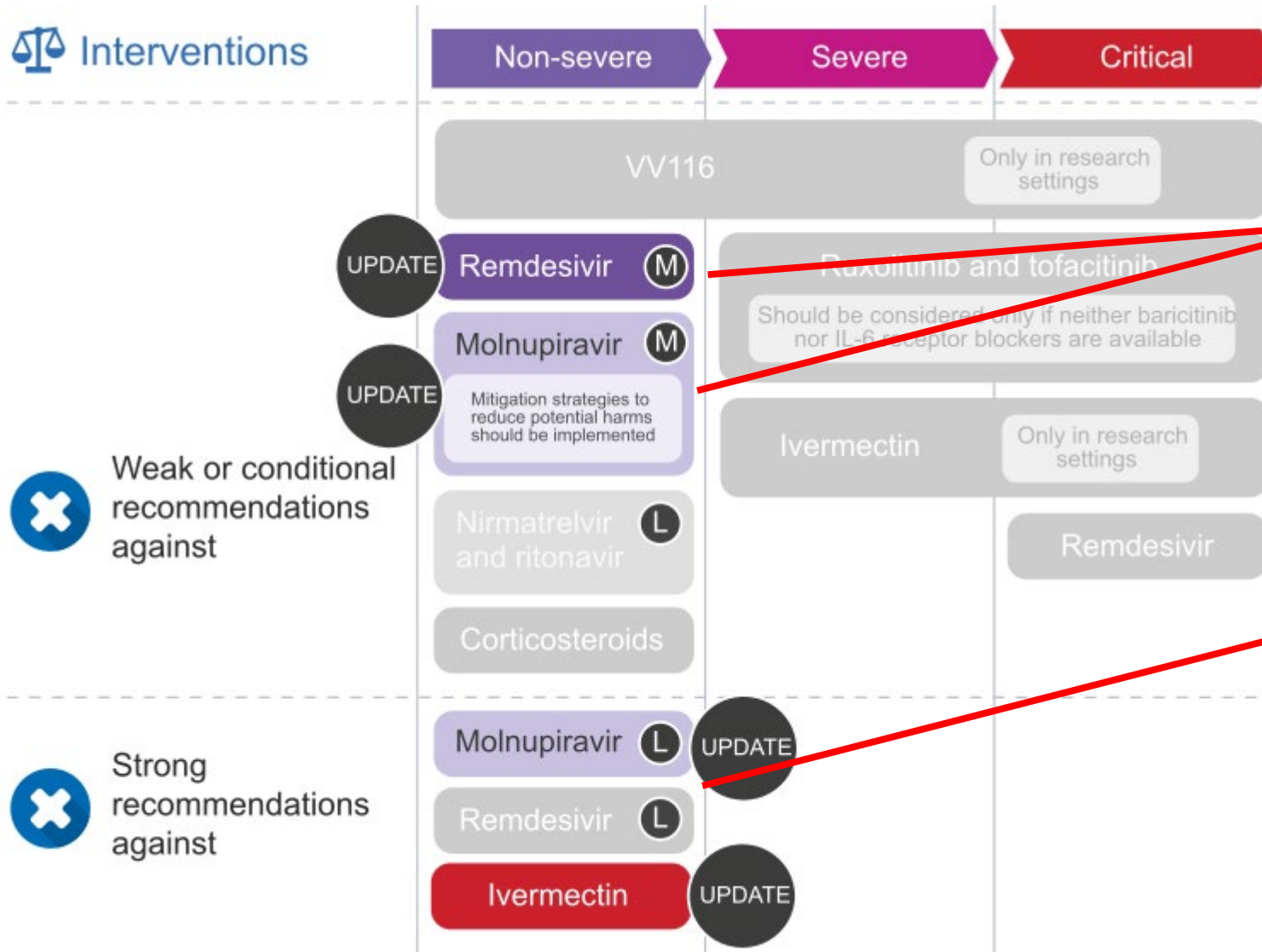
Remdesivir

UPDATE

Nirmatrelvir and ritonavir **M**

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

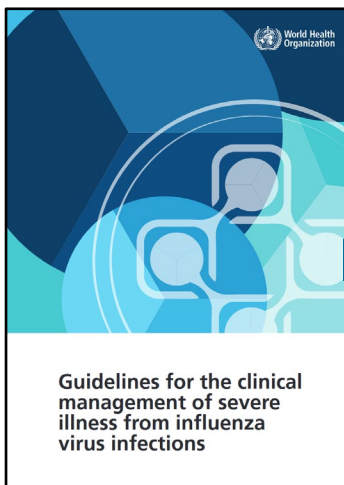
## Interventions



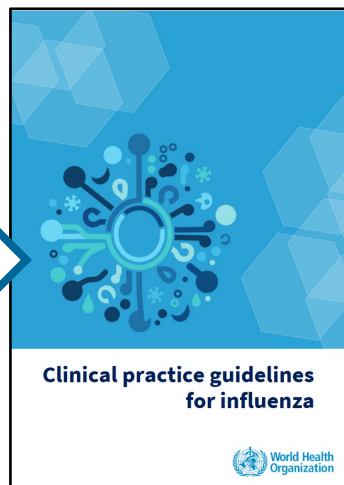
**Remdesivir and molnupiravir**  
No longer recommended for moderate-risk patients

**Molnupiravir**  
Strong recommendation against for low-risk patients





**2022**  
(2019 data)



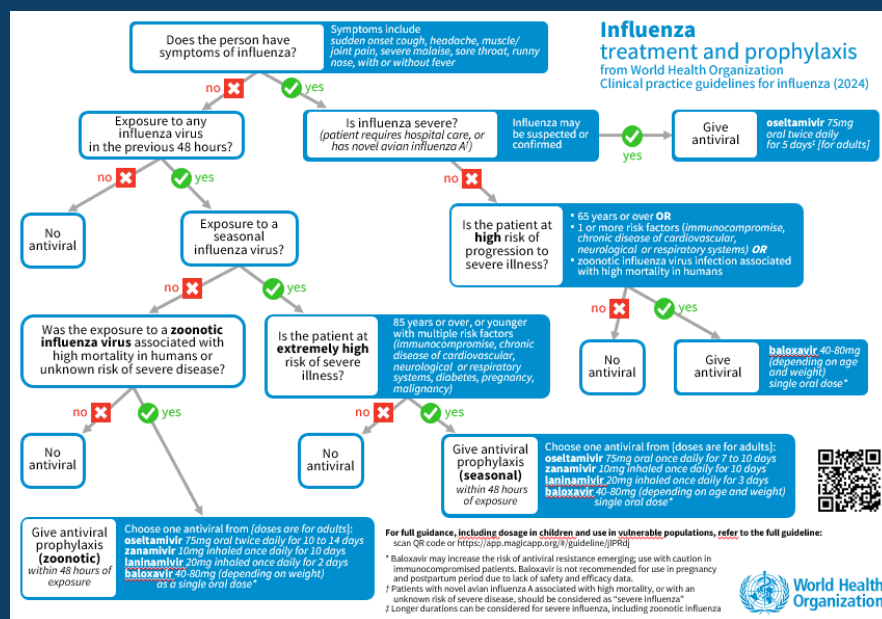
**2024**  
(2023 data)

## 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	<div>Peramivir</div> <div>Zanamvir</div> <div><i>adjunctive treatment</i></div> <div>Macrolide (for immunomodulatory therapy – recommendation not relevant to bacterial coinfection)</div> <div>NSAIDs</div> <div>mTOR inhibitors</div> <div>Passive immune therapy</div> <div>Corticosteroids</div>

# 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](mailto:taaffej@who.int).



# Mpox testing and testing strategies: interim guidance (4<sup>th</sup> 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.

## Diagnostic testing and testing strategies for mpox

Interim guidance  
12 November 2024



- 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)
<ul style="list-style-type: none"> <li>•Laryngitis <b>or</b> pharyngitis <b>and</b></li> <li>•Duration &lt; 48 hours</li> </ul>	20 000
<ul style="list-style-type: none"> <li>•Nasopharyngeal disease (extensive pseudomembrane) <b>and</b></li> <li>•Duration &lt; 48 hours</li> </ul>	40 000
One or more of: <ul style="list-style-type: none"> <li>•Diffuse swelling of the neck</li> <li>•Any disease ≥ 48 hours</li> <li>•Severe disease (respiratory distress, shock)</li> </ul>	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 diphtheria in outbreak settings

Interim guidance  
26 January 2024

#### Key points

- Over the past decade, numbers of significant diphtheria outbreaks have increased, primarily affecting settings with low resources and low vaccine coverage, and with vulnerable and conflict-affected populations.
- In ideal conditions, diphtheria testing is performed using an intensive case-based surveillance approach; however, this may be difficult to maintain in the settings described above. Hence, more detailed guidance is needed that builds on the principles of existing surveillance standards and provides laboratory systems with the information needed to prioritize and rationalize testing in accordance with the epidemiological situation and available resources.
- The development of testing strategies for diphtheria outbreak settings must support the public health response by characterizing the strain (or strains) responsible for the outbreak, and by providing information on those strains to guide public health measures (including antibiotic treatment), reduce further transmission, and monitor changes in strain patterns or epidemiology.
- Many laboratory tests recommended for diphtheria cases rely on the isolation of *Corynebacterium diphtheriae*. Hence, correct sampling of suspected cases and rapid transportation of specimens to the laboratory for testing is critical, to ensure the collection and maintenance of viability of sufficient *Corynebacterium*. Resources to support these activities should be highly prioritized as part of the outbreak response.
- Culture and identification of *C. diphtheriae*, followed by confirmation of toxin production by Elek testing, remains the gold standard of laboratory confirmation for diphtheria. However, methods including automated identification systems, molecular testing and genotyping can also play a role in informing public health decisions, sometimes more quickly and effectively than standard methods in an outbreak setting. Careful consideration of the benefits and limitations of each method is required to ensure the best use of available resources and alignment with public health goals.
- Although evidence remains limited, a growing number of *C. diphtheriae* isolates with antibiotic resistance have been detected. Thus, antimicrobial susceptibility testing is essential, not only to guide the selection of antibiotic treatment but also to contribute to global understanding of resistance mechanisms in *C. diphtheriae*.
- Much of the technical expertise required for laboratory testing for diphtheria is concentrated in the national reference laboratory. During large outbreaks, consideration should be given to the decentralization of some testing procedures and the optimization of laboratories that are in closer proximity to the epicentre of the outbreak.
- Where local resources are absent or insufficient to support the public health response, consideration should be given to referring patient specimens to international expert laboratories to ensure characterization and monitoring of outbreak strains, and to provide rapid feedback to the referring laboratories.

# 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)