

### **World Health Emergencies and living guidelines**

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2 - 6 December 2024

### **Guideline development process - robust methods**



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• @ UNFPA

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

### **Accessible evidence synthesis**

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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	<b>130</b> per 1000		<b>16 fewer</b> per 1000	<b>114</b> per 1000		HIGH			
Mechanical ventilation	<b>86</b> per 1000		23 fewer per 1000	<b>63</b> per 1000		HIGH			
Adverse events leading to drug discontinuation	<b>9</b> per 1000	No importa	nt difference	<b>5</b> per 1000		<b>⊘</b> 000 VERY LOW			
Bacterial infections	<b>101</b> per 1000	No importa	ant difference	<b>96</b> per 1000					
	Direction not set			0000					
Duration of mechanical ventilation	<b>14.7</b> (Mean)	Scale: - Lower better	1.2 lower (MD)	<b>13.5</b> (Mean)					
Duration of hospitalization	<b>12.8</b> (Mean)	Scale: - Lower better	4.5 lower (MD)	<b>8.3</b> (Mean)					





### 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













### 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)



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



#### 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

*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



	Conditional recommendation for use	<b>Baloxavir</b> in patients with high risk of progression to severe influenza (65 years of age and over <b>or</b> 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	
		<i>adjunctive treatment</i> Concomitant antibiotics in patients with low probability of bacterial infection	

# Clinical practice guidelines for influenza: summary of recommendations 2



**Passive immune therapy** 

**Corticosteroids** 

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### **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: unicef@ Global production capacity assessment

- WHO will be reaching out to manufacturers to learn more about global production capacity of influenza antivirals
  - o 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, <u>taaffej@who.int</u>.





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### 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

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- 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 <b>or</b> pharyngitis <b>and</b> •Duration < 48 hours	20 000
<ul> <li>Nasopharyngeal disease (extensive pseudomembrane)</li> <li>and</li> <li>Duration &lt; 48 hours</li> </ul>	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 resourcelimited 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.



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- 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 optim 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 referrin atient specimens to international expert laboratories to ensure characterization and monitoring of outbreak strains, and to pr anid feedback to the referring laboratories

#### Hybrid Joint Meeting





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- Over the past decade, numbers of significant diphtheria outbreaks have increased, primarily affecting settings with low resource
- difficult to maintain in the settings described above. Hence, more detailed guidance is needed that builds on the principles o existing surveillance standards and provides laboratory systems with the information needed to prioritize and rationalize testing in
- 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
- 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

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### 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

DENGUE GUIDELINES FOR DIAGN TREATMENT, PREVENTIC	Laboratory testing for 2 virus infections	Zika virus and	
	14 July 2022		Technical note Algorithm for laboratory confirmation of dengue cases
New edition 2009	Executive summary Zika virus (ZIKV) and dengue virus (DENV) remain significant public health threats. ZIKV infection is a cause of microcephaly and other congenital malformations and can cause neurological disease in children and adults. Persons infected with DENV are at this of severe disease and death if not managed appropriately. ZIKV and DENV infections neuron be readily distinguished clinically; infections neurons in the previous interim guidance published in 2016 on laboratory testing for ZIKV based on data and experience gathered during and after the Zika Public Health Emergency of International Concern (PHEIC) and incorporates current state of knowledge and guidance for DENV diagnosis (1,2). In the absence of diagnostic randomized control trails to determine outcomes of comparative testing strategies, recommendations are based on panel review of the performance data of assays and the experience and observations made within their institutions through	<ul> <li>Molecular assays ar method but the per following infection 1</li> <li>Interpretation of se challenging becaus prolonged detection their utility depend prior flav/virus expc</li> <li>Testing for antibodi be done with carefu epidemiologic and c</li> <li>For pregnant wome always be based on in these patients sh of samples, even du</li> <li>For pregnant wome particular importan in biood and urine r ZIKV infection in the</li> </ul>	December 1º, 2023 Dengue is transmitted through the bite of a mosquito infected with one of the four serotypes of the dengue virus (DENV-1, DENV-2, DENV-3, and DENV-4). DENV infection can affect people of all ages, occurring asymptomatically or producing various clinical manifestations that range from a mild fever to a disabiling fever, accompanied by severe headache, eye, muscle, and joint pain, erythema, and even progress to severe forms, characterized mainly by shock due to significant plasma leakage. There is neither specific medicine to treat dengue, nor a recommended vaccine in the Region to be incorporated into national immunization programs. The main vector responsible for transmitting dengue in the Americas is the Adees aegypti mosquito, and currently nearly 500 million people in the Region live at risk of contracting dengue. The number of dengue cases in the Americas has increased in the last four decades, going from 1.5 million cumulative cases in 1980- 1989 to 16 z million is 2010-2019. The four DENV scrotypes circulate throughout the Americas and in 1980- 1989 to 16 z million is clinical, and adequate suprise followed by another infection with a different serotype increases a person's risk of developing severe dengue and even dying (J). The initial diagnosis of DENV infections be analyzed in conjunction with demographic, clinical, and epidemiological information, for surveiliance purposes and not for making clinical decisions in the treatment of the patient.
For research on diseases of poverty uncut-unco-ward laws-ward	<ul> <li>Observations induct within their instructions infrographic extensive arborins testing.</li> <li>Updated key considerations, recommendations and good practices include:</li> <li>ZiKV and DENV infections need to be differentiated from each other, and from other circulating arboring and non-arboring laboratory tests.</li> <li>Laboratory tests performed and interpretation of results must be guided by the interval between symptom onset or exposure, and the collection of specimens.</li> <li>WHO recommends the use of whole blood, serum, or plasma routine diagnostic testing for arboriruses, and urine for ZIKV NAAT testing.</li> </ul>	<ul> <li>ZIKV ight festing in ; with caution, since- infection that occur</li> <li>ZIKV testing for asy remains challenging timing of specimen positive and faise n</li> <li>Only laboratory tesi independent, comp quality, safety and ; diagnosing arbovir</li> <li>Any testing for the ; other pathogens in be performed in app laboratories by staft technical and safety</li> </ul>	Laboratory confirmation of dengue infection is based on virological tests (RNA detection by RT-PCR, NS1 antigen detection by EUSA', and in some cases viral isolation) and serological tests (IgM and/or IgG detection by EUSA) (2). However, to confirm cases, virological tests that demonstrate the presence of the complete virus, its genetic material, or its proteins should be prioritized. In general, virological assays for dengue are performed on serum samples collected during the first 5 days after the onset of symptoms (acute phase), although highly sensitive molecular methodologies can detect viral RNA for up to 7 days depending on the viremia. Virus isolation is carried out mainly in cell culture or by inoculation of sucking mice and other rodents. However, viral isolation is not used for routine diagnosis nor is it a requirement for diagnostic confirmation and is primarily useful for additional characterization or reagent production. On the other hand, serological assays based on the detection of IgM (or IgG) must be analyzed carefully, considering the time that antibodies circulate in the blood after an infection (which can be several months for IgM antibodies and years for IgG antibodies), as well as the possibility of cross-reaction with other flavivruses (including Zika, yellow fever, and others) and nonspecific detection. Thus, a single IgM result in a patient only indicates possible recent contact with the virus, but this may have occurred up to 6 months before. Ascond paired sample, collected at least one week later, processed in parallel with the first using a quantitative serological assay (PRNT, for example) that shows a seroconversion or an increase in anilbody titer may be useful to carify the diagnostic because that processe in parallel with the first using a quantitative serological assay (PRNT, for example) that shows a seroconversion or an increase in a protessi travelue of IgG.

<sup>1</sup> The detection of the NS1 protein using the EUSA technique is not considered a rapid test. The detection of NS1 by rapid (immunochromatographic) test is not confirmatory and is described below.

nents in a single sample is limited. For the confirmation of an infection, it is necessary to detect

Laboratory diagnosis of dengue





### 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".





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)

