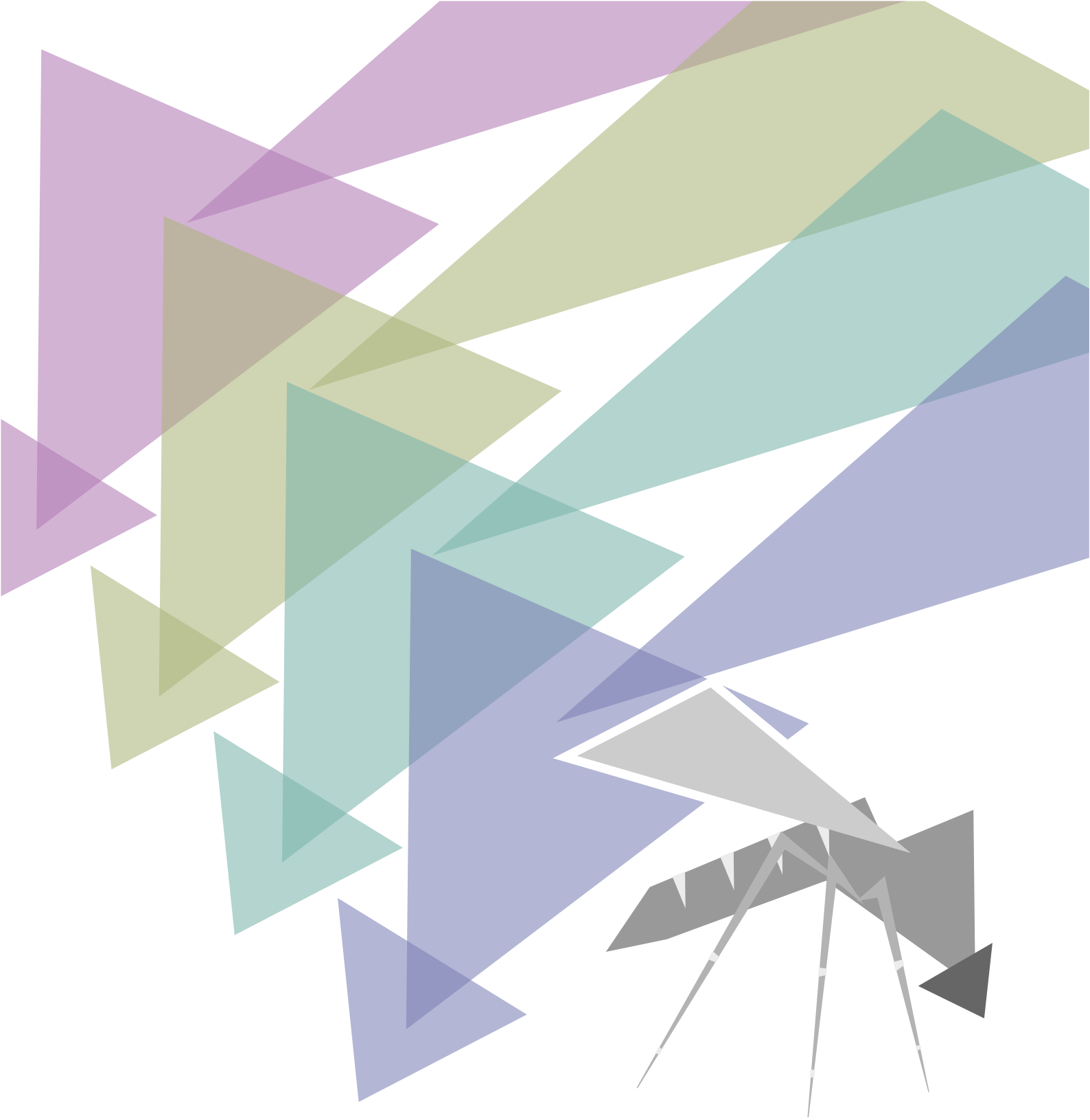

WHO guidelines for clinical management of arboviral diseases: dengue, chikungunya, Zika and yellow fever

World Health Organization

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Abbreviations

CI	confidence interval
CRT	capillary refill time
DOI	declaration of interest
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IV	intravenous
IVIG	intravenous immunoglobulin
ICU	intensive care unit
MAP	mean arterial pressure
MID	minimally important difference
NSAIDs	non-steroidal anti-inflammatory drugs
PLR	passive leg raise test
PICO	population, intervention, comparison, outcome
RCT	randomized controlled trial
WHO	World Health Organization

1 Executive summary

Scope: The purpose of this guideline is to assist health care providers caring for patients with suspected or confirmed arboviral disease caused by dengue, chikungunya, Zika or yellow fever viruses. This guideline includes recommendations on the management of patients admitted to health care facilities (defined for the purpose of this guidance as "severe disease") and those seen in outpatient facilities (defined for the purpose of this guidance as "non-severe disease").

Target audience: This guideline is designed primarily for health care providers who manage patients with clinically apparent arboviral infections. The guideline can be applied at all levels of the health system, including community-based care, primary care, emergency departments and hospital wards.

The guideline will also serve as a reference source for policymakers, health managers and health facility administrators to support the development of national, regional and local guidelines for epidemic and pandemic preparedness.

This guideline provides recommendations on the following:

- treatment for both severe and non-severe arboviral disease
- choice of fluid management and measurements to guide fluid administration.
- treatment with adjunctive therapies for patients with yellow fever

Knowledge gaps are highlighted as priority areas for future research.

Recommendations summary

Recommendations for patients with non-severe, suspected or confirmed arboviral diseases (dengue, chikungunya, Zika and yellow fever):

- WHO suggests the use of protocolized oral fluid treatment compared with non-protocolized oral fluid treatment in patients with suspected or confirmed non-severe arboviral disease. [Conditional recommendation, low certainty evidence]
- WHO suggests the use of paracetamol for the treatment of pain and/or fever in patients with suspected or confirmed non-severe arboviral disease. [Conditional recommendation, low certainty evidence]
- WHO suggests the use of metamizole for the treatment of pain and/or fever in patients with suspected or confirmed non-severe arboviral disease. [Conditional recommendation, low certainty evidence]
- WHO recommends against the use of non-steroidal anti-inflammatory medications (NSAIDs) in patients with acute suspected or confirmed arboviral disease, irrespective of severity. [Strong recommendation, low certainty evidence]

- WHO suggests against using corticosteroid treatment in patients with acute suspected or confirmed non-severe arboviral disease [Conditional recommendation, low certainty evidence]

Recommendations specific to patients with severe (hospitalized), suspected or confirmed arboviral disease (dengue, chikungunya, Zika and yellow fever):

- WHO suggests using crystalloid fluid rather than colloid fluid in patients who require intravenous fluid treatment for suspected or confirmed severe arboviral disease. [Conditional recommendation, low certainty evidence]
- WHO recommends the use of capillary refill time to guide intravenous fluid management in patients with suspected or confirmed severe arboviral disease. [Strong recommendation, low certainty evidence]
- WHO recommends the use of lactate measurement in addition to standard care to guide intravenous fluid management in patients with suspected or confirmed severe arboviral disease. [Strong recommendation, moderate certainty evidence]
- WHO suggests the use of passive leg raise test in patients in shock, with suspected or confirmed arboviral disease, when the clinician is uncertain if further intravenous fluid administration is warranted. [Conditional recommendation, low certainty evidence]
- WHO suggests against the use of systemic corticosteroids in the treatment of patients with suspected or confirmed severe arboviral disease. [Conditional recommendation, very low certainty evidence]
- WHO suggests against the use of immunoglobulins in the treatment of patients with suspected or confirmed severe arboviral disease. [Conditional recommendation, very low certainty evidence]
- WHO suggests against the use of prophylactic platelet transfusion in patients with suspected or confirmed severe arboviral disease and platelet count of <50,000 platelets/microlitre who have no active bleeding. [Conditional recommendation, low certainty evidence]
- WHO suggests the use of intravenous N-acetylcysteine in the treatment of patients with liver failure due to suspected or confirmed yellow fever. [Conditional recommendation, very low-certainty evidence]
- WHO recommends the use of monoclonal immunoglobulin TY014 in the treatment of patients with yellow fever only in research settings. [Use only in research]
- WHO recommends the use of sofosbuvir in the treatment of patients with yellow fever only in research settings. [Use only in research]

This guideline will be updated according to emerging evidence.

2 Introduction

2.1 Background

Arthropod-borne viruses (arboviruses) such as dengue, chikungunya and Zika viruses are transmitted by *Aedes* (*Stegomyia*) species mosquitoes. These mosquitoes can also transmit yellow fever virus in urban settings. *Aedes*-borne arboviruses currently pose a public health threat in areas where approximately 3.9 billion people live. Although *Aedes aegypti* and *Aedes albopictus* mosquitoes are more abundant in tropical and subtropical than in temperate climates, their geographic scope is expanding and so too the risk of introduction and spread of the viruses they transmit. The simultaneous circulation, frequency, and magnitude of outbreaks of these arboviruses are increasing globally, fuelled by the convergence of ecologic, economic and social factors, with consequent expansion of areas in which cases occur. This increasing incidence in endemic areas and occurrence of imported and autochthonous (sometimes referred to as indigenous) disease cases in new areas require clinician awareness to recognize disease and manage cases according to evidence-based guidance, a task complicated by the challenges in differentiating clinically between these infections, particularly in the early phases of illness.

In preparation for the 2022 Pan American Health Organization Guidelines for the Clinical Diagnosis and Treatment of Dengue, Chikungunya, and Zika, a systematic review was conducted using various electronic databases and manual searches *(1)*. Among other research questions, the review aimed to determine which clinical findings and basic complementary studies can differentiate diseases caused by arboviruses from each other and from other febrile diseases. The synthesis and evidence profiles were developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, with recommendations agreed upon by a panel of arbovirus experts. The methodology for these guidelines followed the WHO guideline development methods. Updated searches were not formally undertaken, as no recent large-scale studies were known to the panel; findings are incorporated here to aid end-users in refining their clinical judgements, but no formal recommendations have been made. For more detailed methodology information, please refer to the document *(2)*.

The Tables 1.1 and 1.2 detail the clinical and laboratory findings that are potentially useful for guiding the diagnosis of suspected arbovirus infection based on the systematic review for the Pan American Health Organization guidelines. In a subsequent publication of the multicentre, prospective, observational study of early diagnostic indicators of dengue versus other febrile illnesses in Asia and Latin America, platelet count, white blood cell count and a change in these counts from the previous day of illness, as well as bleeding, anorexia, and skin flushing were identified as significant predictors of dengue, while cough and rhinitis were negative predictors of dengue (3).

Table 2-1 Clinical manifestations of dengue, chikungunya and Zika which differentiate them from other causes of febrile illness[1]

Certainty of the evidence	Manifestations of arboviruses
HIGH (findings that differentiate them)	Rash Conjunctivitis Arthralgia (dengue or chikungunya) Myalgia or bone pain (dengue or chikungunya) Haemorrhage, including bleeding on the skin, mucous membranes, or both (dengue or chikungunya) Thrombocytopenia (dengue) Progressive increase in haematocrit (dengue) Leukopenia (dengue) Headache (dengue) Pruritus (Zika)
MODERATE (findings that probably differentiate them)	Fluid accumulation Arthritis (chikungunya) Chills (dengue or chikungunya) Dysgeusia (dengue)
LOW (findings that may differentiate them)	Asthenia Retro-ocular pain

[1]Adapted from the Pan American Health Organization guidelines for diagnosis and treatment of dengue, chikungunya, and zika in the Region of the Americas

Table 2-2. Clinical manifestations of dengue, chikungunya and Zika which might differentiate them from each other[1]

Certainty of the evidence	Manifestations of dengue	Manifestations of chikungunya	Manifestations of Zika
HIGH (findings that differentiate them)	Thrombocytopenia Progressive increase in haematocrit Leukopenia	Arthralgia	Pruritus
MODERATE (findings that probably differentiate them)	Anorexia or Vomiting Abdominal pain Chills Haemorrhage (includes bleeding on the skin, mucous membranes, or both)	Rash Conjunctivitis Arthritis Myalgia or bone pain	Rash Conjunctivitis
LOW (findings that may differentiate them)	Retro-ocular pain Hepatomegaly Headache Diarrhoea Dysgeusia Cough Elevated transaminases Positive tourniquet test	Haemorrhage (includes bleeding on the skin, mucous membranes, or both)	Adenopathy Pharyngitis or odynophagia

[1]Adapted from the Pan American Health Organization guidelines for diagnosis and treatment of dengue, chikungunya, and zika in the Region of the Americas

2.2 Dengue

Dengue is caused by infection with one of the dengue viruses (*Orthoflavivirus dengue*, serotypes 1-4), belonging to the family *Flaviviridae (4)*. Although most people infected with dengue virus will not have symptoms, those who do typically experience abrupt onset high fever, body aches, arthralgia, retro-orbital headache, rash, and nausea. If symptoms occur, they usually begin 4–10 days after infection and last for 2–7 days, starting with a febrile phase, after which most patients will recover (Figure 2-1)*(5)*. Other patients, often with increased capillary permeability, will enter the critical phase around the time of defervescence (fever reduction) on the 4th-5th day of illness, when warning signs become evident and when worsening of symptoms, organ dysfunction, and occasionally severe bleeding can occur; however, not all patients with severe dengue will have warning signs.

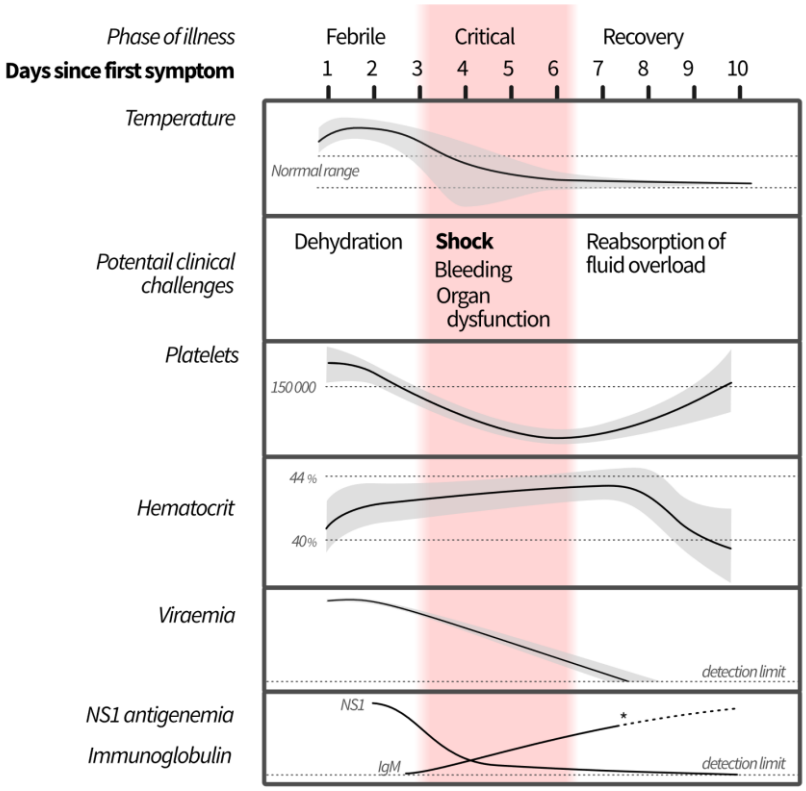
Severe dengue can be fatal, and patients need care in a hospital for careful fluid management and to address complications of infection *(6)*. Following the critical phase, patients typically enter the recovery phase with reabsorption of extravascular fluid. Most patients will recover in 1–2 weeks.

The risk of developing severe dengue increases when a person is infected with a second dengue virus serotype months to years after the initial infection. Risk can also be increased in patients with concomitant comorbidities or other conditions such as pregnancy, young age (particularly infants and young children) and advanced age. There are no known specific antiviral treatments for dengue virus infections. Medications can be used to manage pain and fever. However, non-steroidal anti-inflammatory drugs are typically avoided because of the risk of bleeding complications. Prevention of dengue hinges on avoidance of mosquito bites and community-level mosquito vector reduction.

Vaccines have been developed and received stringent regulatory approvals. Use of vaccines, however, has been limited to date *(7)*.

Reported dengue cases have increased markedly in the past decade, with cases roughly doubling annually since 2021. Globally, 136 countries or territories have reported current or prior autochthonous dengue transmission. In 2024, over 14.2 million dengue cases were reported to WHO, including 7.5 million confirmed cases, over 52 000 severe cases and more than 10000 deaths *(8)*. Most cases have been reported from the Region of the Americas where arbovirus surveillance is more consistent and robust than other Regions and all four dengue subtypes circulate *(9)*. Most cases are reported from Brazil, and all member states except Canada have reported prior autochthonous dengue transmission.

Figure 2-1. The course of dengue illness by days from onset



Source: updated from Yip, 1980 (2). Notes: IgM = immunoglobulin M. Temperature data are illustrative and represent the typical febrile and non-febrile phases. Sepsis or critical illness may be associated with hypothermia. Hematocrit values depend significantly on fluid therapy. IgM kinetics are variable and may depend on primary vs. secondary infection.
Hemocrit and platelet data from https://pmc.ncbi.nlm.nih.gov/articles/PMC6114047.
Viral count data from https://elifesciences.org/articles/92606.
NS1 data from https://www.embopress.org/doi/pdf/10.15252/embr.202153600.

In the African Region, there has been evidence of autochthonous transmission in more than 30 countries, with 19 reporting transmission in 2024. In the Eastern Mediterranean Region, seven countries have reported autochthonous transmission in 2024; dengue transmission in the Region is compounded by fragile, weakened health care systems, conflicts, and floods. In the South-East Asia Region, dengue is endemic in ten countries. From 2022-2023, the most significant increases in dengue cases were observed in Bangladesh and Thailand, and in 2024 the highest case numbers were reported by Indonesia and India. Dengue is endemic in 23 countries in the Western Pacific Region with recent large outbreaks in Malaysia and Viet Nam in 2023-2024. Although previously documented, large outbreaks have not been reported in Pacific Island Countries or territories in recent years. Sporadic autochthonous dengue cases and limited dengue outbreaks have been reported in the European Region since 2010 in France, Italy, Spain, Portugal (Madeira) and Croatia.

2.3 Chikungunya

Chikungunya is caused by infection with chikungunya virus *(Alphavirus chikungunya),* belonging to the family Togaviridae. More than half of patients with chikungunya virus infection will experience symptoms that typically include fever and severe, sometimes incapacitating arthralgia. In symptomatic patients, disease onset is typically 4 – 8 days (range 2 – 12 days) after the bite of an infected mosquito. Some patients develop severe chikungunya, which can be fatal, particularly in those with underlying medical conditions, elderly persons and neonates infected around the time of delivery in the presence of maternal viraemia or soon after birth through infected mosquito bites. Severe complications, including cardiovascular, neurological and multiorgan involvement, may require intensive medical care *(8 – 10)*. There are no known specific antiviral treatments for chikungunya virus infections. Medications can be used to manage pain and fever. There is one vaccine approved in the United States of America and Europe for use in travellers and laboratory workers, but the vaccine is not widely available for public health use in endemic or outbreak settings.

Chikungunya virus was first identified in the United Republic of Tanzania in 1952, and sporadic cases and outbreaks were reported in Africa and Asia from the 1950s and 1960s, respectively *(13)*. Since 2004 outbreaks have become more frequent and widespread with spread of the virus into non-immune populations that was associated, in some outbreaks, with viral adaptations that facilitate transmission by *Aedes albopictus* mosquitoes.

Autochthonous chikungunya virus transmission has been identified in 119 countries across all WHO regions. In 2024, more than 460 000 suspected cases of chikungunya were reported globally. Most cases were reported from the Region of the Americas, where systematic chikungunya surveillance is in place across Member States and Territories. Since 2018, chikungunya cases were reported from 14-15 countries in the region annually and transmission during 2023 marked geographic expansion of reported cases, including a large outbreak in Paraguay, resumption of transmission in Argentina and the first recorded autochthonous transmission in Uruguay. In the African Region, limited outbreaks and sporadic cases had been recorded periodically since the 1950s, with a marked increase starting with a 2004 outbreak in Kenya, which spread to Indian Ocean islands.

Outbreaks have been reported in countries across the African Region since that time. Chikungunya transmission has been reported from six countries in the Eastern Mediterranean Region, with outbreak activity reported in Pakistan in 2024. In the South-East Asia Region, cases are reported mostly from India on the Ministry of Health and Family Welfare website (14) and around 100 000 cases have occurred annually since 2020, with an increase noted in 2024; other countries in the Region have also experienced cyclical outbreaks within the past two decades*(15)*. Periodic chikungunya outbreaks, introduced by viraemic travellers, were reported in Italy and France (European Region) between 2007 and 2017. In 2024, a single

autochthonous chikungunya case was reported in mainland France, along with over ten cases in La Réunion, France. Autochthonous transmission has been reported in 20 countries in the Western Pacific Region, and large outbreaks of chikungunya were reported in several Pacific Island countries from 2011-2017.

2.4 Zika

Zika is caused by infection with Zika virus (*Orthoflavivirus zikaense*), belonging to the family *Flaviviridae*. Most people with Zika virus infection do not develop symptoms. Those who do typically have symptoms including rash with pruritus, conjunctivitis, fever, myalgia, arthralgia, malaise, and headache that last for 2 – 7 days. Although primarily transmitted by *Aedes* species mosquitoes, Zika virus can also be transmitted from mother to foetus during pregnancy, through sexual contact, transfusion of blood and blood products and organ transplantation. In 2016, WHO declared a public health emergency of international concern due to the association of Zika virus infection with clusters of microcephaly and other neurological disorders such as Guillain-Barré syndrome (GBS), encephalitis and myelitis *(16)*. No vaccine or antivirals are yet available for the prevention or treatment of Zika virus infection, but this remains an active area of research.

Cases of Zika virus disease declined from 2017 onwards globally, and many countries that instituted surveillance under the public health emergency have ceased testing and monitoring for transmission since then. However, Zika virus cases are still reported at low levels in several countries in the Region of the Americas and in other endemic regions, including outbreaks in India and Thailand.

To date, a total of 92 countries and territories have reported evidence of mosquito-transmitted Zika virus infection *(17,18)*. In 2024, over 30 000 Zika cases were reported, with most from the Region of the Americas, where there is good surveillance for the disease *(9)*. In the African Region, few countries are conducting testing for Zika; transmission was reported in multiple countries prior to 2024 but these have typically been sporadic cases detected during research projects *(19)*.

In the South-East Asia Region, autochthonous transmission of Zika occurs at low levels in several countries and periodic outbreaks have been reported, including in India (Maharashtra and Karnataka states) and in Thailand. In the European Region, Zika virus autochthonous transmission has only been reported in a single instance in France in 2019 and has not yet been reported from the Eastern Mediterranean Region. Sporadic Zika cases of have been reported in the mainland countries of the Western Pacific Region. Although the first recorded Zika outbreak occurred in Micronesia (Federated States of) in 2007, followed by a large outbreak in French Polynesia, France, in 2013, cases reported from Pacific Island countries have remained low since 2016.

2.5 Yellow fever

Yellow fever is caused by infection with yellow fever virus (*Orthoflavivirus flavi*) belonging to the family *Flaviviridae*. It is transmitted through the bites of infected mosquitoes, primarily from the *Aedes, Haemagogus* and *Sabethes* species. Yellow fever disease affects both humans and non-human primates.

Many infected people do not experience symptoms. For those who are symptomatic, symptoms appear after an incubation period of typically 3-6 days following a bite of an infected mosquito. The most common symptoms are fever, muscle pain with prominent backache, headache, loss of appetite and nausea or vomiting. In most cases, symptoms disappear after 3 – 4 days. A small percentage of patients enter a second, more toxic phase within 24 hours of recovering from initial symptoms. High fever returns and several body systems are affected, usually the liver and kidneys. In this phase, people are likely to develop jaundice, dark urine, and abdominal pain with vomiting. Bleeding can occur from the mouth, nose, eyes, or stomach. Half of these patients die within 7 – 10 days. More severe cases can be confused with severe malaria, leptospirosis, viral hepatitis (especially fulminant forms), other haemorrhagic fevers, infection with other flaviviruses (including dengue) and poisoning. Vaccination is the most effective preventive measure, providing lifelong immunity in most cases.

Yellow fever is transmitted through three distinct cycles: (1) sylvatic (or jungle); (2) intermediate or savannah yellow fever; and (3) urban yellow fever. The urban cycle involves the transmission of the virus between humans and *Aedes aegypti* mosquitoes in densely populated areas, potentially leading to large epidemics. As of 2023, 34 countries in Africa and 13 countries in Central and South America were either endemic for, or have regions that are endemic for, yellow fever. The threat of yellow fever outbreaks continues to affect countries in these regions. In the past six years, explosive outbreaks have seen yellow fever re-emerge as a major international public health threat in endemic areas, fuelled by insufficient vaccination coverage, climate factors, population growth and urbanization *(20,21)*.

In 2023, the African Region experienced yellow fever outbreaks in urban settings across three countries, cases with epidemic potential in three additional countries and sporadic cases in eight other countries. The transmission patterns in 2023 highlight the ongoing risk due to sylvatic transmission, spillover, and amplification into susceptible populations. In 2023, in the Region of the Americas, cases with exposure to sylvatic environment were reported from four countries (*22*).

The long-term Eliminate Yellow fever Epidemics (EYE) strategy (2017-2026) was developed by WHO and partners to respond to the increasing risk of large urban yellow fever outbreaks with risk of international spread and threat to global health security*(23)*. The EYE Strategy works

across the full continuum of prevention, preparedness, and outbreak response. Through the efforts of this partnership more than 377 million people in Africa, as of 2024, have been protected for life through vaccination campaigns and routine immunization since 2017.

Other resources

- Global Dengue Surveillance dashboard *(8)*
- Global distribution of Chikungunya virus *(24)*
- Countries and territories with current or previous Zika virus transmission *(25)*
- Yellow fever case distribution *(26)*

2.6 Laboratory confirmation

Aedes-borne arbovirus infections often cannot be distinguished clinically because they share non-specific clinical features. Laboratory confirmation is therefore needed to differentiate these infections from each other and from other circulating arboviral and non-arboviral pathogens. However, such testing is not readily available in many parts of the world where *Aedes*-borne arboviruses circulate, leading to frequent misdiagnoses, and clinical management is guided by the clinical syndrome and prevailing epidemiology.

Laboratory testing for arboviruses can be accomplished through either direct detection methods such as virus isolation, molecular detection of nucleic acid or antigen testing including rapid diagnostic tests (RDTs) within the first week of illness onset, or indirect detection methods such as IgM and IgG antibodies ELISAs and RDTs from the end of the first week after illness onset to the first three months up to years later *(27,28)*. Antigenic similarities within viral families can cause cross-reactivity on serologic testing that is notable among flaviviruses, particularly between Zika and dengue viruses *(29)*. Serologic cross-reactivity has also been noted between alphaviruses including chikungunya, Mayaro virus (*Alphavirus mayaro*) in the Americas and O'nyong'nyong virus (*Alphavirus onyong*) in Africa.

Laboratory guidance for the diagnosis of dengue in outbreak settings is under development, and updates are planned for Zika and chikungunya diagnostic testing. To guide countries in the selection of diagnostic tests, Expert Reviews for Procurement of Diagnostics are in progress for dengue.

Existing guidelines on laboratory diagnosis are found at:

- Laboratory manual for yellow fever (2024) *(30)*
- Recommendations for Laboratory Detection and Diagnosis of Arbovirus Infections in the Region of the Americas (2023) (*31*)
- Laboratory testing for Zika virus and dengue virus infections: interim guidance (2022) *(32)*
- Dengue guidelines for diagnosis, treatment, prevention and control: new edition (2009) *(33)*

2.7 Identifying severe arboviral disease

Dengue, chikungunya, Zika and yellow fever have unique WHO case definitions, and not all are accompanied by a classification of severity. The dengue severity classification outlined in the 2009 WHO Dengue guidelines for diagnosis, treatment, prevention, and control includes categories of non-severe (with or without warning signs) and severe dengue *(33)*. The case definitions for chikungunya proposed by an expert panel convened by WHO in 2015 included definitions for acute disease and severe acute disease *(34)*. The proposed case WHO case definitions for Zika and the surveillance case definition for yellow fever do not include categorization into severe and non-severe disease: for Zika, because severe disease manifestations are rare outside of congenital disease and neurological syndromes (which have their own case definitions) *(35)*; and for yellow fever because the case definition includes organ dysfunction (hepatic) resulting in jaundice that implies severe disease *(36)*. The Pan American Health Organization recently issued updated dengue, chikungunya and Zika case definitions and dengue severity classification for the Americas based on the systematic review of clinical features differentiating arboviral infections conducted in 2022 *(12)*.

Definitions of non-severe and severe arboviral disease in this guideline

The heterogeneity in available case definitions and classifications across viral diseases and variations in case definitions and classifications across Regions and WHO Member States necessitated the development of a working definition for the purposes of evaluating evidence and developing clinical recommendations. Consequently, for the purposes of clarity in this guideline, the following terminology is used.

Severe disease: those patients who clinicians assess as requiring hospitalization based on a clinical evaluation which includes assessment for the presence of warning signs and existing complications.

Non-severe disease: those who do not have features of severe disease and can be managed on an out-patient basis.

Based on the literature review from the 2022 Pan American Health Organization guidelines, the following criteria were identified that might encourage clinicians to hospitalize patients with dengue.

- Dengue with warning signs:
    - abdominal pain: progressive until it is continuous or sustained and intense, and at the end of the febrile stage
    - sensory disorder: irritability, drowsiness, and lethargy
    - mucosal bleeding: bleeding gums, epistaxis, vaginal bleeding not associated with menstruation or more menstrual bleeding than usual and haematuria
    - hepatomegaly: more than 2 cm below the costal margin and abrupt onset

    - vomiting: persistent (three or more episodes in one hour or four episodes in six hours)
    - progressive increase in haematocrit: on at least two consecutive measurements during patient monitoring.
- dengue with criteria of severe disease, according to the WHO 2009 definition
- oral intolerance
- difficulty breathing
- narrowing pulse pressure
- arterial hypotension
- acute renal failure
- prolonged capillary refill time
- pregnancy
- coagulopathy

In addition, clinicians in some settings may elect to admit to hospital those patients with other risk factors, such patients at the extremes of age (elderly, neonates) and those with underlying medical conditions at high risk for adverse disease outcomes.

For Zika, chikungunya, and yellow fever, the need for hospitalization will require individual assessment by the clinician.

2.8 Purpose

2.8.1 What are the guideline's objectives?

- Describe standards of clinical care to improve patient management and therefore clinical outcomes.
- Identify important uncertainties that require research and investigation.

2.8.2 Guideline principles

- Taking a patient perspective for outcomes, which entails prioritizing patient-important outcomes when assessing the certainty of evidence and making recommendations.
- Recommendations that pertain to across areas with arbovirus transmission globally.
- Recommendations that are inclusive and speak to the needs of vulnerable populations.

2.9 Scope and target audience

Scope: The purpose of these guidelines is to assist health workers caring for patients with suspected or confirmed arboviral disease caused by dengue, chikungunya, Zika, or yellow fever viruses. The guidelines include recommendations on the management of patients admitted to health care facilities (defined for the purpose of this guidance as "severe disease") and those seen in outpatient facilities (defined for the purpose of this guidance as "non-severe disease"). This guideline is not intended as an exhaustive clinical manual and should be read and implemented in the context of local clinical systems and arbovirus treatment practices. Prior WHO guidance includes more detailed information on clinical management *(5,33)*. All specific recommendations within this guideline supersede those from previous documents.

Target audience: The guidelines are designed primarily for health care providers who manage patients with clinically apparent arboviral infection. The guidelines can be applied at all levels of the health system including community-based care, primary care, emergency departments and hospital wards.

The guidelines will also serve as a reference source for policymakers, health managers and health facility administrators to support the development of national, regional, and local guidelines for epidemic and pandemic preparedness.

These guidelines provide recommendations on the following:

- Supportive and symptomatic treatment for non-severe and severe arboviral infection.
- Fluid management, including administration and monitoring of oral and intravenous fluids.
- Specific and adjunctive therapies for patients with yellow fever.

3 Guideline development and implementation

3.1 What triggered this update

Prior WHO guidance for the clinical management of dengue, chikungunya, Zika and yellow fever have been based mostly on expert opinion, clinical practice experience and reviews of available evidence but without applying GRADE methodology.

In 2022, the Pan American Health Organization and Member States developed and published guidelines emanating from the first GRADE-type evaluation of clinical management for dengue, chikungunya and Zika in the region *(2)*.

However, the considerations pertinent to the PAHO recommendations were specific to the Region of the Americas. There was thus a need for a similar process to be conducted at the global level and context, considering all WHO regions and Member States with endemic transmission and those where introduction is likely to occur over time. For those countries and subnational areas in which *Aedes*-borne arboviral diseases are now being detected for the first time, clinicians may be in particular need of guidance because of the lack of prior experience in caring for patients with these conditions.

From a health care resource planning and preparedness perspective, the increasing size and frequency of arbovirus epidemics is placing additional strain on available facilities and personnel, and the capacity to improve patient outcomes through reduced hospital admissions and shorter durations of hospital stay are becoming ever more important.

3.2 Guideline development process

Introduction

The development of these guidelines adheres to standards for trustworthy guidelines, including those of the United States Institute of Medicine *(37)*, WHO *(38)* and GRADE working group *(39,40)*.

Timeline

In May 2022, a WHO Steering Committee group was assembled (see authorship, contributions and acknowledgements section), with priority clinical questions related to arboviral disease management were identified. In April 2023, a written plan for the development of integrated clinical guidance for dengue, Zika, chikungunya and yellow fever was submitted to the WHO Guidelines Review Committee (GRC) for approval that included the proposed population, intervention, comparison, outcome (PICO) questions and Guideline Development Group (GDG) members. The plan was approved after one revision on May 23, 2023.

In 2023, the WHO Steering Committee appointed and convened the GDG for the clinical guidance of arboviruses approved by the GRC (see Authorship, contributions, and

acknowledgements section). The GDG is a multidisciplinary group comprised of 17 individuals from all WHO regions, including technical experts in arbovirus, researchers, primary care clinicians, paediatricians, emergency doctors, haematologists, neurologists, patient representatives and other stakeholders. For this guideline, the GDG also included specialists on ethics. WHO also ensured that the GDG was balanced for gender and representation from all WHO regions.

The initial meeting of the GDG was held online on July 2023. At this initial meeting the chair and co-chairs were proposed and elected by the other members of the GDG and the initial PICO questions were discussed. The GDG convened in person on July 2024 to review the data gathered in the systematic review to address the PICO questions.

3.2.1 Scope and formulation of PICOs

The population of interest included persons with suspected or confirmed arboviral disease. Disease caused by infections with the following arboviruses were considered:

- dengue
- Zika
- chikungunya
- yellow fever

The WHO Steering Committee and the GRC reviewed and revised this list and determined the clinical priorities and scope of the initial guideline.

Questions were codified using a PICO framework, which identifies the population, intervention, comparator and outcomes of interest. These questions were then refined by the methodologist, technical team, and clinical chairs. The outcomes of interest were chosen based on their perceived importance to patients, as agreed upon by the GDG.

3.2.2 Evidence identification and synthesis

3.2.2.1 Identification of existing evidence

An independent methodologist reviewed the proposed PICO questions and advised on refinement of the terminology and parameters and on optimal sequential ordering. PICOs previously framed as diagnostic identification of arbovirus illnesses compared with other febrile illnesses and differentiation of arboviruses were excluded from this systematic review, since the content was covered in the recent literature review conducted for the development of the PAHO guidance *(2)* that preceded this global guideline.

In 2023, an independent research group specializing in systematic reviews for application to GRADE methodology was commissioned to perform a systematic review of randomized controlled studies (RCTs) on clinical diagnoses and treatment for arboviral diseases. The systematic review team analysed RCTs in all major databases, from database inception to 30

April 2024 that enrolled patients with suspected or confirmed diagnosis of arboviral disease (chikungunya, dengue, yellow fever or Zika) and compared interventions against placebo, standard care, or alternative interventions. For most PICOs there were no RCTs identified that specifically addressed the questions in patients with Zika, chikungunya and yellow fever. Studies of patients with dengue were assessed as indirect evidence for the other arboviral diseases. Similarly, for some of the PICOs addressing fluid management in patients with severe disease, only indirect evidence could be obtained from studies of patients with sepsis *(6)*. The GDG considered the indirectness of this evidence as part of the GRADE evaluation.

3.2.2.2 *Additional evidence synthesis*

De novo reviews were undertaken where required using pre-defined protocol and search strategy. Evidence certainty was assessed using GRADE methodology *(38)*.

3.2.3 Values and preferences

There were insufficient evidence-based descriptions of patient experiences or values and preferences regarding decisions for treatment based on a literature search. The GDG, therefore, relied on their own judgments of what well-informed patients would value after balancing the benefits, harms, and burdens of treatment. Judgements on values and preferences were crucially informed through the experiences of former patients represented in the GDG.

The GDG agreed that the following values and preferences would be typical of well-informed patients:

- "Most patients suffering from a non-severe disease, given its good prognosis, would be reluctant to use an intervention when it is uncertain if they would receive an overall benefit."
- "Most patients suffering from a severe disease, given its poor prognosis, would wish to use an intervention even when it is uncertain whether or not it has an overall benefit."

In addition to taking an individual patient perspective, the GDG also considered a population perspective in which feasibility, acceptability, equity, and cost were important considerations. Specific deliberations on values and preferences and associated feasibility and resource-related considerations are presented for each recommendation.

3.2.4 Priority outcomes and minimal important differences

3.2.4.1 *Priority outcomes*

The GDG identified patient-important critical and important outcomes through a structured online survey in which they were asked to assign a relative important of each. A pooled analysis of the mandatory survey was presented to the panel highlighting the most frequently identified. Further discussion de-emphasised proxy endpoints and limited the list to eight

outcomes. The GDG collectively agreed to this list of endpoints before being presented with any evidence summaries. Outcomes of critical interest were identified as follows:

- duration of symptoms
- hospitalization
- length of hospital stay
- mechanical ventilation
- organ failure
- major bleeding
- severe adverse events
- mortality.

3.2.4.2 *Minimal important difference (MID)*

The MID is defined as the smallest difference in outcome that informed patients would perceive as significant, whether beneficial or harmful. An intervention with impact less than the MID would not usually prompt its use in patient management *(41)*. MIDs which are already in frequent use by other WHO clinical panels were presented to the GDG for ratification. In the case of organ failure and severe bleeding, no previous explicit MID had been used. The GDG were polled using a questionnaire which assessed the threshold for importance. The results were presented to the GDG for ratification. The final MIDs were agreed according to Table 3.1.

Table 3-1.Minimally important difference for outcomes of interest

Outcome	MID
Length of hospital stay	1 day
Hospitalization	15 per 1000
Duration of symptoms	1 day
Mortality	3 per 1000
Mechanical ventilation	15 per 1000
Organ failure	15 per 1000
Severe adverse events	15 per 1000

3.2.5 Defining baseline risks

To provide absolute risk estimates for the benefit of alternative interventions, this guideline used harmonized baseline rates of prioritized outcomes. Most of the evidence was obtained from studies involving participants with dengue, where the rates of most outcomes were lower for chikungunya and Zika, but similar or higher for yellow fever. However, following from the assumption that many patients will have unknown aetiology at the time of presentation, the guideline uses estimates from dengue.

To extract these, a systematic review obtained estimates of baseline absolute risks from observational studies for "mortality," "bleeding" and "hospitalization". This provided a wide range of estimates. To focus on a single point, the GDG panel were surveyed using discrete choices bounded by the outer estimates of observational studies (Annex 2). Using this survey, consensus of absolute risks was obtained and agreed at the meeting, as described in Table 3.2. For yellow fever specific PICOs, baseline risks from the primary evidence were used.

Table 3-2. Assumed absolute risks of prioritized outcomes

Outcome	**Non-severe disease** (per 1000 patients)	**Severe disease** (per 1000 patients)
Mortality	1	20
Bleeding	5	25
Admission to hospital	50	N/A
Organ failure	N/A	50

N/A: Not applicable

3.2.6 GDG meeting: GRADE considerations for evidence to decision in the making of recommendations

The GDG members (see authorship, contributions and acknowledgements) were convened in online meetings starting in July 2023. In July 2024, a hybrid (face-to-face and virtual) GDG meeting was held at WHO, Geneva, Switzerland, to review the results of the systematic review conducted by a consultant review team and formulate recommendations (Annex 3). At this meeting GRADE methodology was used to assess the overall certainty of evidence, which could not be higher than the lowest certainty rating for any outcome considered critical to informing a recommendation.

Standard approaches to lowering or raising the level of certainty or confidence were used, including the risk of bias, inconsistency, indirectness, imprecision, publication bias, confounding bias, dose response or large effect *(42)*. A GRADE methodologist was present at the July 2024 meeting to advise the GDG members on adherence to the methodology.

The GDG decided *a priori* not to consider costs in determining the strength and direction of recommendations, since cost-effectiveness analyses were not performed. Nonetheless, the cost of interventions and the resources required for the application of the guidelines were discussed by the GDG members, as feasibility is an important component of the evidence-to-decision framework.

The GDG noted that most of the intervention evidence originates from research on patients with dengue, making the evidence largely indirect for chikungunya, Zika and yellow fever. Furthermore, for PICOs regarding fluid administration, no eligible studies were identified in patients with any of these arboviral infections, and evidence from studies on patients with sepsis were considered, which is also indirect.

3.2.7 GDG decision-making

In making recommendations, the GDG considered the magnitude of benefits and harms, the certainty of evidence (very low, low, moderate and high) supporting estimates of the magnitude of benefits and harms and their belief regarding the values and preferences of stakeholders (in particular, patients with arboviral diseases). Interpretations of strong and conditional recommendations from the perspectives of patients, clinicians and policymakers appear in Table 3.3.

Table 3-3. Implications of strong and conditional recommendations for different users of guidelines

Implications for…	Strong recommendation "WHO recommends…"	Conditional recommendation "WHO suggests…"
Patients	Most individuals in this situation would want the recommended course of action; only a small proportion would not. Formal decision aides are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Most individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the intervention. Adherence to the recommendation could be used as a quality criterion or performance indicator.	Different choices will be appropriate for individual patients, who will require assistance in arriving at a management decision consistent with his or her values and preferences. Decision aides may be useful in helping individuals make decisions consistent with their values and preferences.
Policymakers	The recommendation can be adopted as policy in most situations.	Policymaking will require substantial debate and involvement of various stakeholders.

For more detail information, please refer to the WHO Handbook for guideline development *(38)*.

Deliberations on the direction and strength of recommendations were facilitated by the methodologist and clinical chairs. *A priori* voting rules (of 70% for consensus) informed procedures if the GDG failed to reach consensus by discussion, with the chairs absented from voting.

The following factors informed the formulation of recommendations:

- absolute benefits and harms for all patient-important outcomes through structured evidence summaries (e.g., GRADE summary of findings tables including effect estimates and confidence intervals or narrative summaries)
- certainty of the evidence
- values and preferences of patients
- resources and other considerations (including considerations of feasibility, applicability, and equity).

Consistent with recent advice to guideline panels, the GDG attempted to make recommendations even when there is limited evidence and in the face of considerable uncertainty. Whenever possible, the GDG used research evidence to inform discussion around those key factors. In the absence of such evidence, discussion of these factors was informed by expert opinion of GDG members.

Discussions on rationale, feasibility and accessibility, equity implications (if any) and implementation considerations were also documented. Equity implications included qualitative discussions of feasibility implications of any recommendations in favour of an intervention for constrained health care systems and in the context of other health care needs (such as supportive care) for the population of interest. This did not derive from empirical evidence of likely impact, but from principles of human rights and maximising public health impact.

All recommendations were made by consensus. Polling was used to trigger and guide ongoing debate but was not used to decide any recommendation.

3.2.8 Peer review and approval of the guidelines

An external review group reviewed the final guideline document to identify, correct and clarify errors, contextual issues, and implications for implementation.

The guideline was then reviewed and approved by the WHO Guideline Review Committee.

3.3 Managing declarations of interest

The technical unit collected and managed written statements of declarations of interest (DOI) (Annex 1). All DOI forms were reviewed by the WHO Secretariat. Consultation with WHO Quality Norms and Standards team and Ethics teams were obtained, when necessary. Conflicts of interest were declared by three panel members related to institutional research funding but were not deemed grounds for panel ineligibility. At the start of each meeting, the WHO Secretariat described the DOI process and GDG members were asked to verbally update any other DOI; no verbal conflicts were declared. Web searches did not identify any additional interests that would likely affect members' independence.

4 Recommendations for patients with non-severe, suspected or confirmed, arboviral diseases

In many settings, patients with symptoms that are common to co-circulating arboviral diseases will present to clinicians who often do not have access to reliable diagnostic tests, including those conducted at point of care, to differentiate between them. Thus, despite the differences in pathophysiology between arboviral infections and diseases, clinicians are often managing patients without certainty of the aetiology. *(43,44)*. The interventions thus need to be considered in terms of benefits and harms across the arboviral diseases included in the differential diagnosis.

4.1 Oral rehydration

Conditional recommendation for
WHO suggests **the use of protocolized oral fluid treatment** compared with non-protocolized oral fluid treatment in patients with suspected or confirmed non- severe arboviral disease. [*Conditional recommendation, low certainty evidence*]. • Monitoring of hydration, and prevention of dehydration, should be performed in all patients. Clinicians should provide a cup or other means of measuring oral intake and give advice on how to record the amount taken. • Volumes of fluids to be administered will depend on age (children vs adults) and underlying medical conditions (e.g. congestive heart failure, chronic kidney disease).

4.1.1 Evidence to decision

Benefits and harms

Benefits: In patients with non-severe disease, documenting the use of protocolized oral liquid intake may reduce hospital admission (22 fewer hospital admissions per 1000, 95% confidence interval (CI) 38 fewer to 15 more).

Harms: Specific groups with known intolerance to fluids (for example those with chronic kidney disease or chronic cardiac disease) may be more at risk of the harms from fluid.

Certainty of the evidence

Research evidence was limited to dengue. This evidence was indirectly applied to other arboviral infections.

A single RCT involved a patient population inferred to be non-severe. This population included 53.8% confirmed dengue cases, 11.2% probable dengue fever cases, 24.3% cases of other febrile illnesses and 10.5% undetermined cases. The evidence for non-dengue arbovirus infection was indirect.

Values and preferences

An overall summary of expected values and preferences is given in section 3.2.3. Given the possible benefits and minimal harms associated with the intervention in most patients, the GDG felt that most patients with non-severe disease would choose to use protocolized oral fluid treatment.

Resources and other considerations

Equity: The simplicity of the intervention is likely to promote accessible and equitability.

Acceptability: The intervention was simple and non-invasive, and therefore likely to be acceptable.

Feasibility: The potential positive impact of an intervention early in the treatment pathway was felt to be high.

The GDG concurred that the intervention would be expected to have similar benefits in pregnant women and children and that the recommendation should apply to these groups.

4.1.2 Justification

During dengue, chikungunya, and Zika outbreaks, this patient population is important because of the high proportion of individuals presenting with non-severe disease. This has substantial public health implications, especially when hospital services may be overwhelmed. The recommendation applies to patients who do not require intravenous fluid resuscitation for shock and dehydration treatment.

The GDG concluded that the balance of benefits and harms would favour the intervention, as the risks of over-hydration through oral fluids would be low, monitoring of intake would enable more careful fluid balance, and patients would typically take less fluid than would be optimal if not using protocolized oral fluid treatment.

The type of fluid was not specified in the RCT contributing data-to-evidence summary. The mean 24-hour fluid intake was 2500 ml in the control group and 3,000 ml in the intervention group. Both intervention and control groups were told to optimize their hydration (take five cups). The intervention provided, additionally:

- A means of measuring volume and administering fluid (a 200 ml cup).
- Advice on recording the volume administered.

Although the data are predominantly from patients with dengue, the GDG noted that in early disease, differentiation would be very difficult or impossible and concluded that the risk: benefit considerations would apply similarly to other arboviral infections.

4.1.3 Practical information

- When oral hydration is possible, it is preferred over infusion of intravenous fluids *(45)*. When oral fluids are prescribed, they must be taken in sufficient amounts to address the fluid deficit and ongoing needs. (See Table 4.1 for a summary of findings.)
- To replace fluid loss from fever and vomiting, encourage frequent small amounts of oral fluids, especially for those experiencing nausea and anorexia.
- Record and review oral fluid intake daily in an ambulatory setting. Provide a cup or other means of measuring volume to ensure accurate fluid intake. Advise patients and caregivers to record the volume of fluids administered by noting the amount given each time and totalling it at the end of the day. Review this record daily to ensure adequate hydration.
- Adequate oral fluid intake should result in urination at least four to six times per day. Patients should aim for this threshold and monitor their urination frequency. If they notice any significant deviations from this pattern, they should promptly contact their health care provider for further guidance.
- Water should always be the main source of fluids. Choose fluids based on availability and ensure they come from a safe source of drinking water. For more information on fluid selection, please refer to other WHO guidelines *(46)*.
- Using standardised oral rehydration solution is a practical way of ensuring appropriate electrolyte replacement. In the absence of ORS, other fluids as locally available may be used in addition to water, including soups, unsweetened fluid juice, coconut water, yogurt drinks, and water used after cooking of rice or grains.
- Avoid commercial carbonated drinks that exceed the isotonic level (5% sugar) as they may exacerbate hyperglycaemia related to physiological stress from dengue and diabetes mellitus. Examples include commercial carbonated beverages, commercial fruit juices and sweetened tea *(5,45)*.
- For more detailed information on fluid therapy, please refer to other WHO guidelines *(45)*.

Table 4-1. Summary of findings for protocolized oral fluid treatment compared with non-protocolized oral fluid treatment in patients with non- severe arboviral disease

Clinical question/ PICO

- Population: patients who do not require intravenous resuscitation
- Intervention: protocolized oral hydration
- Comparator: non-Protocolized oral hydration

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Non-Protocolized oral hydration	Protocolized oral hydration		
Hospital admission	Relative risk: 0.55 (CI 95% 0.23-1.3) Based on data from 143 participants in 1 study in patients with dengue Follow-up 60 days	50 per 1000	28 per 1000	Low Due to serious risk of bias, due to serious imprecision[1]	Protocolized oral hydration may reduce hospital admission
		Difference: 22 fewer per 1000 (CI 95% 38 fewer - 15 more)			

1. ***Risk of bias: serious***: *Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;* ***imprecision: serious***: *95% CI including harms*

4.2 Symptom control

Pain and fever are common symptoms across all four arboviral infections. Effective management of these symptoms is important for ensuring patient wellbeing/comfort.

4.2.1 Paracetamol/acetaminophen

Conditional recommendation for
WHO suggests **the use of paracetamol** (acetaminophen) for the treatment of pain and/or fever in patients with suspected or confirmed non-severe arboviral disease. [*Conditional recommendation, low-certainty evidence*] • **This recommendation does not apply to yellow fever** • Use paracetamol (acetaminophen) with caution in patients with pre-existing or newly developing liver disease or transaminitis.

4.2.1.1 Evidence to decision

Benefits and harms

Benefits*:* The absolute benefit of paracetamol was not assessed; the panel examined comparative data between alternative therapies. Paracetamol (acetaminophen) probably has little or no impact on length of hospital stay (0.1 fewer days of length of stay, 95% CI 1.11 fewer days to 0.91 more days). It may be less efficacious in fever reduction than NSAIDs from indirect population (children with undifferentiated fever), low-certainty evidence.

Harms*:* In patients with non-severe disease, it is uncertain whether paracetamol (acetaminophen) increases or decreases severe bleeding and acute kidney injury. There was very low certainty evidence for liver failure as inferred from elevated liver enzymes resulting from paracetamol (192 more cases than standard care, 95% CI 4 more to 716 more), and possibly little or no impact on duration of illness (0.2 more days of duration of illness, 95% CI 0.2 fewer to 0.6 more).

Certainty of the evidence

Research evidence was limited to dengue. This evidence was indirectly applied to other arboviral infections.

A single RCT assessed length of hospital stay in 123 dengue patients (moderate certainty, downgraded for serious imprecision). Based on data from 587 participants in 5 studies, paracetamol (acetaminophen) may be less efficacious in reducing fever than NSAIDs (low certainty due to imprecision and indirectness in applying evidence from children younger than 2 years old with fever from various causes).

A single small study with 89 subjects provided very low certainty for adverse events related to paracetamol- (acetaminophen) related severe bleeding and acute kidney injury.

RCT evidence from 88 participants in one study provided very low certainty of evidence that paracetamol (acetaminophen) might elevate liver enzymes compared with standard of care (RR 2.92, 95% CI 1.04-8.16, serious imprecision, and very serious indirectness). Evidence from one RCT (n=123) with a follow-up period of seven days suggested there was probably little to no impact of paracetamol on duration of symptoms (moderate certainty due to serious imprecision).

Values and preferences

An overall summary of expected values and preferences is given in section 3.2.3. The GDG considered patients would choose to use a medication for pain and fever. Given the alternatives, patients might choose paracetamol as a treatment due to its accessibility.

Resources and other considerations

Equity and acceptability: No equity, availability or cost issues were identified, as paracetamol (acetaminophen) is widely available at low cost.

Feasibility: Paracetamol (acetaminophen) is included on the WHO Essential Medicines List *(47)*.

4.2.1.2 *Justification*

The overall body of evidence for paracetamol (acetaminophen) was considered of moderate to very low certainty, primarily due to imprecision and indirectness. The panel considered that paracetamol might not increase the risk of severe bleeding or acute kidney injury when given at recommended doses, although it may elevate liver enzymes. Mild rises in liver function tests in dengue may not indicate significant liver injury, and a holistic assessment should guide the choice of analgesia. The GDG inferred that paracetamol (acetaminophen) had few safety concerns when used for the symptomatic control of pain and fever. The panel noted that at the point of presentation, it might be impossible to distinguish between dengue and other arboviral diseases and that the potential for harm related to platelet inhibition caused by NSAIDs made paracetamol (acetaminophen) a safer alternative, despite low certainty evidence that it might be less effective.

4.2.1.3 Practical info

Mechanism of action

Understanding of the mechanism of action of paracetamol (acetaminophen) remains incomplete but appears to be derived mostly from action on the central nervous system. Hypotheses include: 1) inhibition of the cyclooxygenase (COX) enzyme because its analgesic and antipyretic effects are similar to those of nonsteroidal anti-inflammatory drugs (without anti-inflammatory anti-coagulation effects); 2) inhibition of the L-arginine-nitric oxide pathway and reinforcement of descending inhibitory serotonergic pain pathways; and 3) effect on cannabinoid receptors by active metabolites.

Potential indications and contraindications in arboviral infection

Pain and fever.

Route, dosage, and duration

Paracetamol (acetaminophen) is given orally as a dose, based on age and body weight, as below in Table 4.2. It is available in tablets of 500 mg and as oral powder for reconstitution and oral suspension. Indirect evidence from multiple systematic reviews shows it to be effective for pain (except for chronic lower back pain), and adverse events are not significantly higher than in placebo *(48)*.

Table 4-2. Dosing of Paracetamol (acetaminophen) for treatment

Age	Body weight	Dose and duration for non/severe, suspected or confirmed, arboviral diseases
Adults	> 50 kg	500 mg – 1 g every 4-6 hours (maximum daily dose: 4 g)
Paediatrics	10-15mg/kg	every 4-6 hours (maximum daily dose: 60 mg/kg)

Do not repeat the dose more frequently than every 4 hours.

Maximum daily dose to avoid hepatic toxicity is based on all routes of administration and all products containing paracetamol (acetaminophen) (49).

Dose adjustment

Renal impairment: It is recommended when giving paracetamol to patients with renal impairment, to reduce the dose and to increase the minimum interval between each administration to at least 6 hours unless directed otherwise by a physician (49), as below in Table 4.3.

Table 4-3. Dosing of Paracetamol for patients with renal impairment

Glomerular filtration rate	Dose
10-50 ml/min	500 mg every 6 hours
<10 ml/min	500 mg every 8 hours

Hepatic impairment: Reduce the dose or prolong the dosing interval in patients with hepatic impairment or Gilbert's Syndrome; the daily dose should not exceed 2g/day unless directed by a physician *(49)*. These doses should not be repeated more frequently than every four to six hours nor should more than four doses be given in any 24-hour period.

Other considerations

Children: Children should not be given paracetamol (acetaminophen) for more than three days without consulting a doctor *(49)*.

Pregnancy: A large amount of data on pregnant women indicates neither malformative nor foetal /neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, use paracetamol during pregnancy at the lowest effective dose, for the shortest possible time and at the lowest possible frequency.

Breastfeeding: Following oral administration, small amounts of paracetamol are excreted into breast milk. However, these are not clinically significant. To date, there are no known undesirable effects or side effects during breast-feeding. Paracetamol can be administered during lactation at therapeutic doses.

Table 4-4. Summary of findings for the use of paracetamol (acetaminophen) for the treatment of pain and/or fever in patients with suspected or confirmed non-severe arboviral disease

Clinical question/ PICO

- Population: patients with suspected or confirmed dengue fever
- Intervention: paracetamol (acetaminophen)
- Comparator: standard of care

Outcome timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		SOC	Paracetamol		
Duration of symptoms	Measured by: days scale: - lower better Based on data from 123 participants in 1 study Follow up 7 days	4.8 Mean	5 Mean	Moderate Due to serious imprecision[1]	Paracetamol (acetaminophen) probably has little or no impact on duration of illness
		Difference: MD 0.2 more (CI 95% 0.2 fewer - 0.6 more)			
Length of hospital stay	Measured by: days scale: - lower better Based on data from 123 participants in 1 study Follow-up 7 days	3.9 Mean	3.8 Mean	Moderate Due to serious imprecision[2]	Paracetamol (acetaminophen) probably has little or no impact on length of hospital stay
		Difference: MD 0.1 fewer (CI 95% 1.11 fewer - 0.91 more)			
Reduction of fever, inferred from comparison with NSAID in fever of any cause in young children	Relative risk: 0.54 (CI 95% 0.29 – 0.99) Based on data from 587 participants in 5 studies	536 per 1000 in NSAIDs	289 per 1000 in paracetamol	Low Due to concerns with imprecision and indirectness[3]	Paracetamol (acetaminophen) may be less efficacious in reducing fever than NSAIDs
		Difference: 247 fewer per 1000 (CI 95% 381 fewer – 5 fewer)			
Severe bleeding	Relative risk: 4.18 (CI 95% 0.21– 84.5) Based on data from 89 participants in 1 study Follow-up 7 days	5 per 1000	21 per 1000	Very low Due to extremely serious imprecision[4]	We are uncertain whether paracetamol (acetaminophen) increases or decreases severe bleeding
		Difference: 16 more per 1000 (CI 95% 15 fewer - 98 more)			
Acute kidney injury	Relative risk: 2.51 (CI 95% 0.1 – 59.8) Based on data from 89 participants in 1 study Follow-up 7 days	12 per 1000	30 per 1000	Very low Due to extremely serious imprecision[5]	We are uncertain whether paracetamol (acetaminophen) increases or decreases acute kidney injury
		Difference: 18 more per 1000 (CI 95% 19 fewer - 61 more)			
Liver failure as inferred by elevated liver enzymes (RCT)	Relative risk: 2.92 (CI 95% 1.04 – 8.16) Based on data from 88 participants in 1 study Follow up 7 days	100 per 1000	292 per 1000	Very Low Due to serious imprecision and very serious indirectness[6]	Paracetamol (acetaminophen) may increase elevated liver enzymes
		Difference: 192 more per 1000 (CI 95% 4 more - 716 more)			

1. ***Imprecision: serious.*** *123 patients*
2. ***Imprecision: serious.*** *123 patients*
3. ***Indirectness: serious.*** *Different population (young children with fever from any causes);* ***imprecision: serious.*** *95% CI including absence of important differences.*
4. ***Imprecision: extremely serious.*** *2 events overall*
5. ***Imprecision: extremely serious.*** *1 event overall*
6. ***Imprecision: very serious.*** *Optimal information size not met, 18 events overall*

4.2.2 Metamizole/dipyrone

Conditional recommendation for
WHO suggests **the use of metamizole (dipyrone) for the treatment of pain and/or fever** in patients with suspected or confirmed non-severe arboviral disease. [*Conditional recommendation, low certainty evidence*] • Metamizole has limited geographic availability and regulatory approval.

4.2.2.1 Evidence to decision

Benefits and harms

Benefits: Metamizole (dipyrone) causes similar fever reduction to NSAIDs (moderate certainty due to the indirectness of the patient population); in children with undifferentiated fever the effect is 0.03°C lower temperature, 95% CI 0.29°C lower to 0.24°C higher. It is uncertain whether metamizole (dipyrone) improves symptom control; 52 more patients improved with the intervention, 95% CI 151 fewer to 335 more.

Harms: Metamizole (dipyrone) probably has little or no impact on aplastic anaemia (1/1,000,000 fewer cases, 95% CI 3 fewer to 23 more, low certainty) compared with a baseline estimate of 3 per million cases of aplastic anaemia (0.5 per million of agranulocytosis). These data derive from a review of available evidence of effect in the largest published multicentre study in three Latin American countries, where researchers initially conducted a broad active search for cases from April 2002-April 2003 to determine background population incidence of agranulocytosis and aplastic anaemia, and then a multicentre case-control study in defined research sited to identify incident cases and risk factors for their development *(50,51)*. In patients with non-severe, suspected or confirmed arboviral disease, it is very uncertain whether metamizole (dipyrone) increases severe bleeding (3 more severe bleeding cases, 95% CI 3 fewer to 23 more).

Certainty of the evidence

Research evidence was limited to dengue. This evidence was indirectly applied to other arboviral infections.

The certainty of evidence for improvement in symptom control was also rated as very low, supported by one observational study with serious risk of bias and serious imprecision. However, the certainty of evidence for improvement of fever was rated as moderate. This rating was supported by three RCTs identified as indirect evidence, based on comparisons with the use of NSAIDs in young children with fever from any cause, and imprecision.

A systematic review of the rates of bone marrow suppression was not performed, and the GDG noted multiple different estimates exist. The GDG considered one large observational study, with the certainty of evidence for agranulocytosis was rated as low due to risk of bias and indirect evidence from patients without arboviral disease. However, there was high certainty in a very low baseline risk.

Based on three non-RCTs involving 1568 participants, the certainty of evidence for severe bleeding was rated as very low. This downgrade was due to inappropriate adjustments for potential confounders, resulting in a very serious risk of bias and serious imprecision.

The GDG concluded that metamizole (dipyrone) might not be associated with major complications such as agranulocytosis and severe bleeding. The evidence suggested its effect on fever was comparable to that of NSAIDs.

Values and preferences

Applying the agreed upon values and preferences (see 3.2.3) for patients with non-severe disease, the GDG inferred that most patients would use metamizole if there was good evidence of symptomatic benefit.

Resources and other considerations

Metamizole (dipyrone) is not included on the WHO Essential Medicines List *(47)*. Metamizole has limited geographic availability and licencing. Concerns about the safety of metamizole (dipyrone), particularly with respect to inducing agranulocytosis, prompted market withdrawals in several countries over the past four decades including the United Kingdom of Great Britain and Northern Ireland, Canada, the United States, Finland, Denmark, Sweden, and more recently, India. Metamizole remains readily available in Spain, Russia, Israel, and many countries in Latin America; in Germany access to the medication was restricted from over-the-counter to requiring a medical prescription. Primary research studies and meta-analyses have yielded a wide range of estimates of incidence of metamizole induced agranulocytosis, from 1.5-40 times more common when used vs not, and some authors concluded that there was no meaningful difference in overall rates of adverse events when compared with other widely used analgesics *(52,53)*.

4.2.2.2 Justification

Research evidence was derived only from studies addressing patients with dengue. The GDG did not feel this indirectness was significant enough to rate down.

The panel noted that metamizole (dipyrone) may not increase the risk of severe bleeding or agranulocytosis. For aplastic anaemia, the baseline risk estimate was derived from observational studies in Latin America (where metamizole is widely used) was found to be 3

cases per 1 million *(50)*. The panel recognised different regulatory approaches to metamizole, as above.

They inferred that its effect on fever is similar to NSAIDs in patients with non-severe arboviral disease. Therefore, the panel considered metamizole (dipyrone) as an alternative to paracetamol in countries where it is approved for the symptomatic control of pain and fever in patients with non-severe, suspected or confirmed arboviral disease.

4.2.2.3 Practical info

Mechanism of action

Metamizole (dipyrone) is classified as an atypical non-steroidal anti-inflammatory drug and is used as an antipyretic and analgesic. It has lower anti-inflammatory and anti-thrombotic activity than conventional non-steroidal anti-inflammatory drugs. Research suggests that metamizole (dipyrone) inhibits COX-3 with a higher affinity compared to COX-1 or COX-2.

Special considerations and adverse events related to metamizole (dipyrone)

Health care providers should inform patients about both the benefits and potential side effects, such as agranulocytosis, during the clinical decision-making process to help them make informed choices regarding their treatment plan. The choice of this medication depends on local epidemiology and resources, including availability and monitoring facilities.

Route, dosage, and duration

Metamizole (dipyrone) is given orally at a dose based on age and body weight, as below in Table 4.5. It is available as a tablet of 500 mg and as oral powder for reconstitution and oral suspension. Other routes of administration are available.

Table 4-5. Dosing of metamizole for treatment

Age category	Body weight	Single dose		Daily maximum dose	
	kg	tablets	mg	tablets	mg
Adults and adolescents *(≥ 15 years)*	> 53	1–2	500–1000	8	4000
Children and adolescents *(up to 14 years old)*	10 mg/kg	½–1	250–500	4	2000

Administer treatment as early as possible *(50,54)*.

Dose adjustment

Renal and hepatic impairment: Avoid multiple high doses when renal or hepatic function is impaired, as the elimination rate is reduced. To date, there has been insufficient experience with long-term use of metamizole (dipyrone) in patients with severe hepatic and renal impairment.

Other considerations

Children: For children and adolescents up to 14 years of age 8–16 mg metamizole (dipyrone) per kg body weight can be given as a single dose. A dose of 10 mg/kg body weight is suggested for fever. This single dose can be taken up to 4 times daily at intervals of 6–8 hours. Age-appropriate formulations (oral drops, solution for injection) are available.

Pregnancy: Although data are limited, no evidence shows teratogenic or embryotoxic effects of metamizole (dipyrone) when used during the first trimester. However, evidence indicates fetotoxicity, such as foetal renal impairment and ductus arteriosus constriction, when used in the third trimester. Therefore, the European Medicines Agency (EMA) considers metamizole contraindicated during the third trimester *(55,56)*.

Breastfeeding: Avoid using metamizole during breastfeeding because the relative infant dose may be high, and the overall evidence is scarce. Use of better investigated and characterized analgesics is advised *(56)*.

Table 4-6. Summary of findings for use of metamizole (dipyrone) for the treatment of pain and/or fever in patients with suspected or confirmed non-severe arboviral disease

Clinical question/ PICO

- Population: patients with suspected or confirmed dengue fever
- Intervention: metamizole (Dipyrone)
- Comparator: standard of care

Outcome timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		SOC	Metamizole (dipyrone)		
Improvement in symptom control	Relative risk: 1.08 (CI 95% 0.77 – 1.51) Based on data from 110 participants in 1 non-RCT	656 per 1000	708 per 1000 Difference: 52 more per 1000 (CI 95% 151 fewer - 335 more)	Very low Due to very serious risk of bias, due to serious imprecision[1]	We are uncertain whether metamizole (dipyrone) improves symptom control
Reduction of fever inferred from comparison with NSAID in fever of any cause in young children	Measured by: °C Lower better Based on data from 547 participants in 3 RCTs	37°C Mean in NSAID arm	37°C Mean in dipyrone arm Difference: MD 0.03 °C lower (CI 95% 0.29 °C lower to 0.24 °C higher)	Moderate Due to concerns with imprecision and indirectness[2]	There is probably little to no difference in fever reduction with metamizole (dipyrone) compared to NSAID treatment.
Severe bleeding	Relative risk: 1.61 (CI 95% 0.46 - 5.59) Based on data from 1568 participants in 3 non-RCTs Follow up 4.5 days	5 per 1000	8 per 1000 Difference: 3 more per 1000 (CI 95% 3 fewer - 23 more)	Very low Due to very serious risk of bias, due to serious imprecision[3]	We are uncertain whether metamizole(dipyrone) increases severe bleeding
Aplastic anaemia	Relative risk: 0.8 (CI 95% 0.54 – 1.14) Based on data from 1568 participants without arbovirus disease in 1 observational study	3 per 1 million	2 per 1 million Difference: 1 fewer per 1 million (CI 95% 2 fewer - 1 more)	Low Due to concerns with indirectness and risk of bias, upgraded due to high certainty in a very low baseline risk[4]	Metamizole (dipyrone) probably has little or no impact on aplastic anaemia.

1. ***Risk of bias: serious:*** *non-RCT with inappropriate adjustment for potential confounders;* ***imprecision: serious:*** *95% CI including important benefits and harms*
2. ***Indirectness: serious:*** *different population (Young children with fever from any cause);* ***imprecision: serious:*** *OIS not met.*
3. ***Risk of bias: serious:*** *non-RCT with inappropriate adjustment for potential confounders;* ***imprecision: serious;*** *95% CI including important harms*
4. ***Risk of bias:*** *non-RCT;* ***indirectness:*** *Patients without arboviral disease;* ***large magnitude of effect:*** *high certainty in a very low baseline risk*

4.2.3 Non-steroidal anti-inflammatory drugs (NSAIDs)

Strong recommendation against

WHO recommends against the use of non-steroidal anti-inflammatory medications (NSAIDs) in patients with acute suspected or confirmed arboviral disease, **irrespective of severity**. [*Strong recommendation, low certainty evidence*]

- For patients on established NSAID therapy (for example for ischaemic heart disease or inflammatory arthropathies), the decision to continue should be made according to anticipated risk/benefit balance.
- The recommendation does not apply in confirmed chikungunya and confirmed Zika where NSAID treatment may be considered for arthralgia and inflammation.

4.2.3.1 Evidence to decision

Benefits and harms

Benefits: NSAIDs probably improve fever compared with standard of care (0.45°C lower temperature, 95% CI 1°C lower to 0.11°C more, moderate certainty).

Harms: Whether NSAIDs treatment increases severe bleeding in patients with non-severe arbovirus disease is uncertain (1 more case per 1000 patients, 95% CI 1 fewer to 3 more, very low certainty). It is uncertain whether NSAIDs increases blood product requirement (2 more, 95% CI 2 fewer to 12 more, very low certainty).

Certainty of the evidence

Research evidence was limited to dengue. This evidence was indirectly applied to other arboviral infections.

There was moderate certainty in the evidence for fever improvement (0.45°C fewer temperature than standard care) based on two studies with 287 patients with respiratory viral infections, with consideration for indirect evidence (as the studies did not involve patients with arbovirus disease) and imprecision.

Four non-RCTs involving patients with arbovirus disease were identified. Additionally, three RCTs with 34 participants and one non-RCT with 2285 participants provided indirect evidence based on bleeding in haemophilic patients. There were several sources of bias in the studies, including indirectness (the RCTs did not involve patients with arbovirus disease) and the lack of adjustment for confounding variables in the non-RCTs.

A single non-RCT with 642 participants evaluated blood product requirement. The certainty of evidence was rated down from low (observational data) to very low due to inappropriate adjustment for potential confounders.

Values and preferences

Applying the agreed-upon values and preferences (see 3.2.3), for patients with non-severe disease, the GDG inferred that most patients suffering from a non-severe disease, given its good prognosis, would be reluctant to use NSAIDs with concerns of harm where there were alternative treatment options.

The GDG considered that patients would choose to avoid NSAID treatment as a precaution against the potential risks related to bleeding which although low and uncertain in frequency, could be very severe if they did occur.

Resources and other considerations

None noted.

4.2.3.2 Justification

The GDG panel decided that despite the very low certainty of the evidence, there were strong concerns around the possibility that NSAIDs, through their anti-platelet action, could contribute to mortality in dengue resulting from severe bleeding.

The panel reasoned that in many circumstances during the acute presentation, differentiation of the causative aetiology would not be possible. At the time of prescription, therefore, unless dengue could be ruled out, there would be safer alternatives available (paracetamol and metamizole). Despite the low certainty evidence, the panel issued a strong recommendation on the basis of similar benefits but fewer risks according to rationale outlined in the GRADE framework *(38,57)*.

For those patients already taking non-steroidal anti-inflammatory medications for their anti-platelet effect - for example, those receiving aspirin for coronary heart disease - the GDG noted that risk and benefits would need to be assessed on an individual basis.

The panel acknowledged that where the aetiology is known, clinicians might use NSAIDs, for example in the inflammatory arthralgia and arthritis caused by chikungunya.

4.2.3.3 Practical information

Mechanism of action

NSAIDs include drugs like aspirin, ibuprofen, ketorolac, indomethacin, naproxen, and others, which influence the enzyme cyclo-oxygenase (COX) responsible for producing prostaglandins.

At least two isoforms of COX enzymes exist, coded by separate genes. The constitutive isoform (COX-1) has multiple actions, including, for example, the production of prostacyclin, which has a cytoprotective effect on the gastric mucosa.

The inducible isoform (COX-2) is upregulated and produced in response to inflammatory stimuli and cytokines in migratory and other cells.

Effect on platelets: Aspirin and other NSAIDs inhibit platelet activation, aggregation, and secretion by reducing the production of thromboxane A2 (TxA2).

Table 4-7. Summary of findings for use of non-steroidal anti-inflammatory medications (NSAIDs) in patients with acute suspected or confirmed arboviral disease, irrespective of severity

Clinical question/ PICO

- Population: patients with suspected or confirmed dengue fever
- Intervention: non-steroidal anti-inflammatory drugs
- Comparator: standard of care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence	Summary
		SOC	NSAIDs		
Fever reduction	Measured by: °C Scale: Lower is better Based on data from 287 participants in 2 studies	37.5°C Mean Difference: MD 0.45°C fewer (CI 95% 1°C less – 0.11°C more)	37°C Mean	Moderate Due to concerns about indirectness and imprecision[1]	NSAIDs probably reduce fever compared to standard of care
Severe bleeding	Relative risk: 1.14 (CI 95% 0.85 – 1.53) Based on data from 2247 participants in 4 non-RCT Follow-up 3.5 days	5 per 1000 Difference: 1 more per 1000 (CI 95% 1 fewer – 3 more)	6 per 1000	Very low Due to serious risk of bias[2]	We are uncertain whether NSAIDs increases severe bleeding
Blood product requirement	Relative risk: 1.48 (CI 95% 0.65 – 3.38) Based on data from 642 participants in 1 non-RCT	5 per 1000 Difference: 2 more per 1000 (CI 95% 2 fewer – 12 more)	7 per 1000	Very low Due to serious risk of bias, due to serious imprecision[3]	We are uncertain whether NSAIDs increases blood product requirement
Severe bleeding (indirect evidence on bleeding in haemophilic patients) RCTs[4]	Relative risk: 1 (CI 95% 0.02 – 47.7) Based on data from 34 participants in 3 studies Follow-up 12 to 16 weeks	5 per 1000 Difference: 0 fewer per 1000 (CI 95% 217 fewer – 217 more)	5 per 1000	Very low Due to very serious imprecision, due to serious indirectness[4]	We are uncertain whether NSAIDs increases severe bleeding
Severe bleeding (indirect evidence on bleeding in haemophilic patients) non-RCT	Hazard ratio: 0.8 (CI 95% 0.3 – 2.2) Based on data from 2285 participants in 1 study Follow-up 17.4 months	5 per 1000 Difference: 1 fewer per 1000 (CI 95% 3 fewer - 6 more)	4 per 1000	Very low Due to serious risk of bias, Due to very serious indirectness[5]	We are uncertain whether NSAIDs increases severe bleeding

1. ***Imprecision:*** *95% CI including no temperature reduction****; indirectness:*** *different population (patients with acute viral respiratory infection).*
2. ***Risk of bias: serious:*** *non-RCT with inappropriate adjustment for potential confounders*
3. ***Risk of bias: serious:*** *Non-RCT with Inappropriate adjustment for potential confounders;* ***imprecision: very serious:*** *95% CI including important harms*
4. ***Imprecision: very serious:*** *2 events in 34 participants;* ***indirectness: serious:*** *subjects without arbovirus diseases*
5. ***Risk of bias: serious:*** *non-RCT with inappropriate adjustment for potential confounders;* ***imprecision: serious;*** *95% CI includes important harms, 42 events;* ***indirectness: serious;*** *different population (patients with haemophilia)*

4.3 Corticosteroids (for non-severe arboviral disease)

Conditional recommendation against
WHO suggests against using corticosteroid treatment in patients with acute suspected or confirmed non-severe arboviral disease. *[Conditional recommendation, low certainty evidence]* • For patients on established corticosteroid therapy, the decision to continue should be made according to anticipated risk: benefit balance.

4.3.1 Evidence to decision

Benefits and harms

Benefits*:* There was very low certainty of evidence of any benefit of corticosteroids in non-severe arboviral disease (18 fewer hospital admissions, 95% CI 35 fewer to 18 more).

Harms: Corticosteroids probably have little or no impact on gastrointestinal bleeding. It is uncertain if they cause severe bleeding.

Certainty of the evidence

A single randomized trial assessed corticosteroid use in 179 dengue outpatients, but only hospital admission could be extracted from the systematic review publication, with very low certainty of evidence.

Indirect data on adverse events in participants without arboviral diseases provided data from 245 participants in two randomized controlled trials and for gastrointestinal bleeding, from 33 253 participants in 159 randomized controlled trials (moderate certainty of no effect) and severe bleeding (very low certainty due to serious imprecision). The median duration of corticosteroid treatment was 8.5 days (IQR 3.3–28.0), and the appreciation that short and longer course of steroids might have different adverse events contributed to the very low certainty rating.

Values and preferences

Applying the agreed upon values and preferences (see 3.2.3), for patients with non-severe disease, the GDG inferred that most patients, given their good prognosis, would be reluctant to use corticosteroids when it is uncertain if they would receive an overall benefit.

Resources and other considerations

Corticosteroids are widely available at low cost worldwide, particularly oral preparations. Multiple corticosteroids are included on the WHO Essential Medicines List *(47)*, such as dexamethasone, hydrocortisone, and prednisolone.

4.3.2 Justification

Due to the very low certainty of evidence, and acknowledging the lack of direct research findings to inform them, the panel argued that the principle of non-maleficence would justify a recommendation against the use of corticosteroids.

Two panel members felt that a recommendation should be a "strongly against," specifically for dengue based on the putative harm of immunosuppression in acute infectious disease; a conditional recommendation was made on consensus with these concerns noted.

For patients already on corticosteroid therapy at the time of infection, an individualized clinical determination of the risk and benefit balance is required.

The panel intended that this recommendation apply to chikungunya, dengue, yellow fever and Zika. The GDG noted that compared to dengue, other arboviral infections (e.g. chikungunya and yellow fever) may be more frequently associated with complications such as uveitis, myocarditis, or severe pruritus, for which the use of corticosteroids may be indicated, although patients with these complications would more likely be classified as having severe disease.

4.3.3 Practical information

Mechanism of action

Corticosteroids bind glucocorticoid receptors mediating changes in gene expression that lead to multiple downstream effects over hours to days. Non-genomic effects through interactions between the intracellular glucocorticoid receptor or a membrane-bound glucocorticoid receptor can result in changes in shorter timeframes.

Corticosteroids have very broad activity, including alteration of immune cell function such as reducing neutrophil apoptosis and demargination; reduction of arachidonic acid derivatives through inhibition of phospholipase A2; inhibition of transcription factors such as NF-κB and AP-1, with multiple subsequent changes in gene expression; and promotion of anti-inflammatory genes such as interleukin-10.

Lower doses of corticosteroids tend to have an anti-inflammatory effect, while higher doses are more profoundly immunosuppressive, for example inhibiting the production of B cells and T cells (58). The short-term effects of corticosteroids are decreased vasodilation and permeability of capillaries, as well as decreased leukocyte migration to sites of inflammation.

Corticosteroids also exhibit mineralocorticoid activity, impacting water, salt, and mineral homeostasis.

Adverse event profile

Adverse effects due to corticosteroids are dose and duration dependent and affect multiple body systems. The incidence and severity of adverse events are also affected by patient age, underlying medical conditions (such as diabetes mellitus) and concomitant medication use. A systematic review of 22 RCTs in children who received ≤14 days of systemic corticosteroids published in 2016 described vomiting, behavioural changes, and sleep disturbances as the most common adverse events reported, and increased susceptibility to infection as the most serious *(59)*. Although not measured in all patients, 43 of 53 patients demonstrated hypothalamic-pituitary-adrenal axis suppression.

In adults treated with ≤ 30 days of corticosteroids, the most common adverse events noted in a large retrospective cohort and self-controlled case series in the United States included sepsis, venous thromboembolism, and fracture *(60)*.

Table 4-8. Summary of findings for corticosteroid treatment compared with no corticosteroid treatment in patients with acute non-severe arboviral disease

Clinical question/ PICO

- Population: patients with acute arboviral disease (non-severe)
- Intervention: corticosteroids
- Comparator: standard of care

Outcome timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence	Summary
		SOC	Steroids		
Hospital admission	Relative risk: 0.63 (CI 95% 0.36 – 1.08) Based on data from 179 participants in 1 RCT	50 per 1000	32 per 1000 Difference: 18 fewer per 1000 (CI 95% 32 fewer - 4 more)	Very low Due to risk of bias, due to very serious imprecision[1]	We are uncertain whether corticosteroids increase or decrease hospitalization
Severe bleeding	Relative risk: 1.13 (CI 95% 0.07 – 17.61) Based on data from 245 participants in 2 RCTs	5 per 1000	6 per 1000 Difference: 1 more per 1000 (CI 95% 26 fewer - 28 more)	Very low Due to serious risk of bias, due to very serious imprecision, due to concerns with indirectness[2]	We are uncertain whether corticosteroids increase or decrease severe bleeding
Gastro-intestinal bleeding	Relative risk: 1.43 (CI 95% 1.22 – 1.66) Based on data from 33 253 participants in 159 study RCTs	5 per 1000	7 per 1000 Difference: 2 more per 1000 (CI 95% 1 more - 3 more)	Moderate Due to serious indirectness[3]	Corticosteroids probably have little or no impact on gastrointestinal bleeding

1. ***Imprecision: very serious.*** *95% CI including absence of benefits; 24 events overall,* ***risk of bias: serious:*** *complete risk of bias assessment not possible as full text unavailable*
2. ***Risk of bias: serious:*** *inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;* ***imprecision: very serious:*** *95% CI including important benefits and harms;* ***indirectness:*** *different population (severe patients)*
3. ***Indirectness:*** *different population (patients without arboviral diseases)*

5 Recommendations specific to patients with severe, suspected or confirmed, arboviral disease (hospitalized)

Clinical management should be based on the suspected aetiology and the patient's needs. For a definition of severe disease used in this guideline, refer to section 2.6.

The approach to treat severe cases must involve thorough training of health care personnel. Practices may differ among regions, but standardization of procedures in hospitalized patients is the best option to ensure consistent and effective care.

Users of the guideline are strongly encouraged to educate patients to recognize warning signs and present to a health care facility quickly if they occur.

5.1 Choice of intravenous fluid

Conditional recommendation for
WHO suggests **using crystalloid fluid rather than colloid fluid** in patients who require intravenous fluid treatment for suspected or confirmed severe arboviral disease. [*Conditional recommendation, low certainty evidence*] • Clinicians must personalise treatment decisions due to complex fluid and resuscitation requirements, and the dynamic nature of severe arboviral disease. This applies particularly to choices of fluid subsequent to the initial resuscitation.

5.1.1 Evidence to decision

Benefits and harms

Benefits*:* In patients with severe, suspected, or confirmed arboviral disease requiring hospitalization, colloids may have little to no impact on mortality (no difference between the two intervention groups, 95% CI 24 fewer to 24 more). There was low certainty evidence that compared with crystalloids, colloids did not have impact on organ failure (2 fewer cases of organ failure per 1000 patients, 95% CI 17 fewer to 22 more), or on clinical bleeding, defined as mucosal or major soft-tissue bleeding (3 more cases of bleeding per 1000 patients, 95% CI 15 fewer to 53 more). Colloids probably have little to no impact on hospital length of stay (no difference between the two intervention groups, 95% CI 0.47 fewer to 0.47 more).

Harms: Colloids may increase severe adverse events, such as infusion reactions (27 more cases of severe adverse events, 95% CI 1 more to 180 more). Adverse events associated with colloid (dextran) were typified by rigors and temperature usually occurring within 6 hours of starting the study fluid.

Certainty of the evidence

Research evidence was limited to dengue. This evidence was indirectly applied to other arboviral infections.

Three RCTs involving 313 participants evaluated mortality and organ failure among children with dengue receiving intravenous fluid infusion, providing low certainty evidence due to serious imprecision (the confidence interval includes both important benefits and harms).

A single RCT of 383 participants evaluated clinical bleeding in children with dengue (low certainty due to serious imprecision).

The certainty of the evidence for the length of hospital stay is rated moderate due to serious risk of bias. Children with dengue receiving intravenous fluid infusion had a similar average hospital stay of four days, regardless of whether they were treated with crystalloids or colloids.

Three studies involving 658 children with dengue evaluated serious adverse events. The certainty of the evidence is rated low due to serious imprecision, as all events occurred in the intervention group, not in the control group. Absolute effect estimates were 27 more cases of severe adverse events per 1000 patients in the colloid group compared to the crystalloid group (95% CI 1 more to 180 more).

Values and preferences

Applying the agreed-upon values and preferences (see 3.2.3) for severe disease, the GDG inferred that most patients, given the uncertain benefits of colloids and the possibility of harms, would choose to receive crystalloids.

Resources and other considerations

Equity: Colloids are more expensive than crystalloids, although the panel had insufficient quantitative information, and believed that a single universal estimate would not apply to all regions. Equity concerns arose about colloids because of increased costs.

Acceptability: The intervention was judged as likely to be acceptable.

Feasibility: Crystalloids are frequently more available than colloids.

5.1.2 Justification

Research evidence was limited to dengue. This evidence was indirectly applied to other arboviral infections. All studies were conducted on hospitalized children, encompassing the following number of patients.

The preference for crystalloids was driven mostly based on the higher rate of severe adverse events with colloids, and the absence of evidence of benefit. The GDG panel appreciated the heterogeneity of colloid interventions which were tested, and that there would be situations where the initial choice of one intravenous fluid might be changed for a different fluid later, driven by individualized patient-clinician decisions.

Table 5-1. Choice of intravenous fluid assessed

Interventions assessed	Studies	Patients
Balanced crystalloids *(Ringer's lactate)*	7	484
Dextran *(dextran 40 – 10% and 70 – 6% variously)*	5	577
Starch *(hydroxyethyl starch 3%, 6% and 10% variously)*	5	388
Isotonic saline *(0.9% w/v sodium chloride)*	3	266
Gelatins *(gelafusine 3% and 4% variously)*	2	207
Hypertonic saline *(hypertonic lactated saline)*	1	48
Albumin	0	0

The GDG judged that the recommendation should apply similarly to adults, during pregnancy, and to children. Similarly, that the recommendation would also apply to arboviral diseases other than dengue.

5.1.3 Practical information

The manufacturer's summary of product characteristics provides additional details on contraindications, special warnings, precautions for use and interactions with other medicinal products *(61,62)*.

Table 5-2. Summary of findings for administration of crystalloid fluid rather than colloid fluid in patients who require intravenous fluid treatment for severe arboviral disease

Clinical question/ PICO

- Population: patients with suspected or confirmed arbovirus infection that will receive intravenous fluid infusion
- Intervention: colloids
- Comparator: crystalloids

Outcome timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Crystalloids	Colloids		
Mortality	Relative risk: 1 (CI 95% 0.11 – 9.6) Based on data from 313 participants in 3 studies in children with dengue Follow-up 30 days	20 per 1000	20 per 1000 Difference: 0 fewer per 1000 (CI 95% 24 fewer - 24 more)	Low Due to very serious imprecision[1]	Colloids may have little or no impact on mortality
Organ failure	Relative risk: 0.96 (CI 95% 0.65 – 1.44) Based on data from 311 participants in 3 studies in children with dengue Follow-up 30 days	50 per 1000	48 per 1000 Difference: 2 fewer per 1000 (CI 95% 17 fewer - 22 more)	Low Due to very serious imprecision[2]	Colloids may have little or no impact on organ failure
Clinical bleeding (mucosal or major soft-tissue bleeding)	Relative risk: 1.1 (CI 95% 0.39 –3.11) Based on data from 383 participants in 1 study in children with dengue Follow-up 7 days	25 per 1000	28 per 1000 Difference: 3 more per 1000 (CI 95% 15 fewer - 53 more)	Low Due to very serious imprecision[3]	Colloids may have little or no impact on severe bleeding
Severe adverse events (mostly infusion reactions)	Relative risk: 7.75 (CI 95% 1.31 – 46.0) Based on data from 658 participants in 3 studies in children with dengue Follow-up 7 days	4 per 1000	31 per 1000 Difference: 27 more per 1000 (CI 95% 1 more - 180 more)	Low Due to very serious imprecision[4]	Colloids may increase severe adverse events
Hospital length of stay	Measured by: Days Scale: lower better Based on data from 383 participants in 1 study in children with dengue Follow-up 7 days	4 Mean	4 Mean Difference: MD 0 fewer (CI 95% 0.47 fewer - 0.47 more)	Moderate Due to serious risk of bias[5]	Colloids probably have little or no impact on hospital length of stay

1. ***Imprecision: very serious;*** *95% CI including important benefits and harms (0 events overall);*
2. ***Imprecision: very serious.;*** *95% CI including important benefits and harms (70 events overall)*
3. ***Imprecision: very serious;*** *95% CI including important benefits and harms*
4. ***Imprecision: very serious;*** *18 events overall; all in intervention arm.*
5. ***Risk of bias: serious;*** *possible selective reporting as only one trial reported this outcome.*

5.2 Guiding the administration of intravenous fluid volume

The purpose of fluid resuscitation in shock is to improve oxygen delivery to vital organs. Briefly, shock may be **hypovolemic** (loss of intravascular volume, with resulting low cardiac preload), **distributive** (pathological reduction in systemic vascular resistance due to vasodilatation), **cardiogenic** (reduction of systolic or diastolic cardiac function), **obstructive** (physical obstruction of the great vessels or the heart, either internally within the vessels themselves or through extrinsic compression). *(63,64)*

Dengue and plasma leakage

Some patients with dengue experience a clinically significant degree of plasma leakage due to increased vascular permeability, which manifests as fluid accumulation and intravascular fluid depletion, during the critical phase. This typically occurs around day 4–6 of illness and often coinciding with defervescence*(65)*. This phase typically improves spontaneously after 48–72 hours *(66)*.

Differences in management between arboviruses

Pathophysiological differences between arboviral diseases require adaptation of clinical approaches. For example, plasma leakage in dengue may be profound and require significant initial volumes of intravenous fluid, with subsequent de-escalation to minimise accumulation of interstitial fluid. In contrast, chikungunya can lead to myocarditis and cardiac insufficiency, especially in infants and older adults, making iatrogenic pulmonary oedema more likely; although myocarditis can occur in dengue, this is rare in comparison with the rate of dengue related shock. In each case, monitoring of the effect of intravenous fluid administration should be performed to maximise benefit and minimise harm.

Patient monitoring

Routine patient monitoring for fluid balance includes regular and frequent monitoring of physiological variables, urine output, and laboratory values (notably haematocrit) *(5)*. Clinical measures of response include blood pressure (including pulse pressure and mean arterial pressure), heart rate, urine output and mental status. Imminent or worsening respiratory compromise, such as pulmonary oedema, may be detected by rising respiratory rate and/or decreasing oxygen saturation.

Fluids should be given to improve targets of perfusion, at volumes and rates which may be modified based on age, weight, clinical and biological conditions (such as acid-base balance) and concomitant therapy. Careful monitoring is essential.

5.2.1 Current guidelines on fluid volume and administration

The GDG acknowledged that there is heterogeneity across the Regions regarding practice and current guidelines. Clinicians are encouraged to use appropriate guidelines based on Regional and national experience.

- World Health Organization:
    a. Dengue guidelines, for diagnosis, treatment, prevention and control
- Pan American Health Organization/Regional Office for the Americas of the World Health Organization:
    a. Guidelines for the Clinical Diagnosis and Treatment of Dengue, Chikungunya and Zika - PAHO/WHO | Pan American Health Organization
    b. Algorithms for the Clinical Management of Dengue Patients - PAHO/WHO | Pan American Health Organization
    c. Tool for the diagnosis and care of patients with suspected arboviral diseases
    d. Clinical Management of Yellow Fever in the Region of the Americas. Experiences and Recommendations for Health Services
- Regional Office for South-East Asia:
    a. Comprehensive Guideline for Prevention and Control of Dengue and Dengue Haemorrhagic Fever. Revised and expanded edition
    b. Guidelines on Clinical Management of Chikungunya Fever
    c. SEARO IMAI district clinician manual: hospital care for adolescents and adults: guidelines for the management of illnesses with limited-resources.
- Regional Office for the Western Pacific:
    a. Dengue clinical management: facilitator's training manual

5.2.2 Capillary refill time

Strong recommendation for
WHO recommends the use of capillary refill time to guide intravenous fluid management in patients with suspected or confirmed arboviral disease in addition to standard care/monitoring. [*Strong recommendation, low certainty evidence*]

5.2.2.1 Evidence to decision

Benefits and harms

Benefits*:* From two RCTs involving a total of 466 participants, there was high-certainty evidence that capillary refill time (CRT)-guided resuscitation did not increase mortality compared to lactate-guided resuscitation (2 fewer deaths per 1000 patients than lactate; 95% CI 6 fewer to 2 more).

Harms*:* In one RCT involving 30 participants, fluid replenishment was guided using fluid challenges followed by reassessment. Peripheral perfusion was monitored using CRT and other parameters. This approach was compared to a standard care group where fluid administration followed fixed clinical guidelines. The outcomes on mortality (3 more deaths per 1000 patients than standard care; 95% CI 10 fewer to 33 more), hospital length of stay (27 fewer days than standard care; 95% CI 43 fewer to 11 more) and intensive care unit (ICU) length of stay (2 more days than standard care; 95% CI: 1.5 fewer to 5.5 more) were uncertain due to very low certainty of evidence.

Certainty of the evidence

Evidence for CRT with standard care-guided resuscitation was very low certainty due to extremely serious imprecision and indirectness (it was based on a single RCT involving 30 participants with sepsis). For hospital and ICU lengths of stay, certainty was also very low, with additional concerns of serious risk of measurement bias.

By contrast, high certainty evidence informed comparisons of CRT with lactate-guided resuscitation (two RCTs involving over 400 participants). The panel noted concerns about indirectness from sepsis patients but felt the monitoring aspects of circulatory compromise were similar in dengue. The certainty of evidence for renal replacement therapy is rated moderate due to indirectness and imprecision, as the 95% CI includes significant benefits. The certainty of evidence for hospital length of stay is rated very low due to indirectness, potential performance and detection biases, resulting in a serious risk of bias and very serious imprecision, as the 95% CI includes both significant benefits and harms. For ICU length of stay certainty was low due to potential measurement bias, indirectness, and imprecision.

Values and preferences

Applying the agreed-upon values and preferences (see 3.2.3) for patients with severe disease, the GDG inferred that most patients, given the possible benefit and lack of harm, would choose to have capillary refill time measured to guide intravenous fluid management.

Resources and other considerations

Equity, acceptability, and feasibility: The panel expected that the use of CRT would require training to ensure the correct methods of measurement and interpretation. However, the use of a simple, widely available, and low-cost intervention would be feasible and increase equity. The GDG concluded that this recommendation would apply to all arboviral diseases.

The GDG judged that the recommendation would apply similarly in pregnancy and in children.

5.2.2.2 *Justification*

The GDG considered evidence comparing CRT with the standard of care, and CRT with lactate levels. Based on strong evidence of superiority of lactate monitoring over standard care, see 5.2.2 lactate, and high certainty evidence of non-inferiority of CRT versus lactate in terms of mortality, the GDG panel recommends measuring CRT over not measuring CRT to guide intravenous fluid resuscitation.

The panel emphasized the importance of contextualizing CRT results for each patient and ensuring that health care personnel are adequately trained in both performing the test and interpreting its results.

5.2.2.3 *Practical info*

What is capillary refill time (CRT)?

CRT is an accessible marker of end organ perfusion. It measures the time for blood to return to the skin capillaries after they have been emptied by applying pressure. It is quick, visual, and non-invasive test *(41)*, although education of health care workers is paramount to ensure correct measurement and interpretation. It is used for recognition of hypoperfusion and for monitoring of fluid administration. Detailed guidelines from there are available from WHO*(68,69)*.

What factors affect CRT?

CRT can be affected by multiple factors, including room temperature, skin temperature, age, sex, room lighting, procedural technique, presence of underlying vascular disease, and the site of testing. Variability can be minimized through training, education, and standardized protocols to mitigate the impact of ambient factors *(67,70)*.

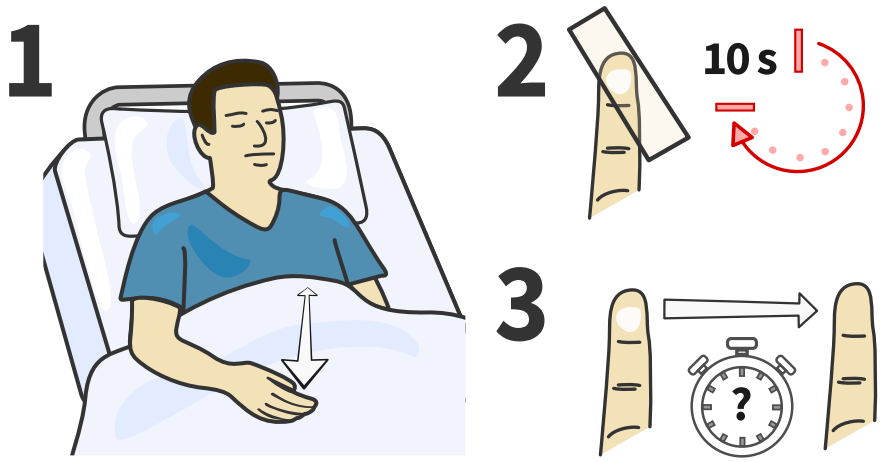
CRT standardization protocol

Standardized procedures can enhance reliability and reduce interobserver variability (Figure 5.1). To reflect the procedure in the research studies, in infants, children and adults:

- Check the environment:
  - Ensure a warm room.
  - Choose a site free from skin abnormalities.
  - Place the patient's hand at the level of the thorax / heart.
- Apply firm pressure to the ventral surface of the distal phalanx of the index finger for 10 seconds.
- Remove the pressure.
- Measure the time for the return of pre-existing skin colour.
- Use a chronometer *(71)*.
- A CRT longer than 3 seconds should be considered abnormal. *(70,72)*

A microscope slide was used to apply pressure in the RCTs as this enables visualisation of skin blanching and ensures even pressure. The GDG panel recognized that usual clinical practice does not require a glass slide.

Figure 5-1. Suggested way to measure standardized capillary refill time (67)



Notes: 1 – Place the patient's hand at the level of their heart (mid chest). 2 – Apply firm pressure to the ventral surface of the distal phalanx of one finger for 10 seconds. This can be done using your thumb, or if available a glass microscope slide so that blanching of the skin underneath can be confirmed. 3 – Release the pressure and measure the time taken for the skin colour to return to the same as before.

Table 5-3. Summary of findings for capillary refill time-guided resuscitation compared with standard of care in patients with suspected or confirmed arbovirus infection who will receive intravenous fluid infusion

Clinical question/ PICO

- Population: patients with suspected or confirmed arbovirus infection
- Intervention: capillary refill time guided resuscitation [a]
- Comparator: standard of care[b]

a. Fluid repletion was guided using intravenous fluid challenge and subsequent re-evaluation of peripheral perfusion to assess the further need of fluid challenges. Capillary refill time, the peripheral perfusion index, the forearm-to-fingertip body temperature gradient, and the tissue oxygenation saturation were measured. Only patients with "poor peripheral perfusion" (i.e., three of four parameters altered) were considered suitable for fluid repletion. The intervention also included fluid targeted to a minimum cardiac index of 2.5 L/min/m2, irrespective of peripheral perfusion and a minimum mean arterial pressure (MAP) of 65 mmHg.

b. Fluid repletion was guided using fluid challenges and after challenge, stroke volume was re-evaluated to assess further need of fluid challenges. Hemodynamic goals were based on the 2012 Surviving Sepsis guidelines: Give volume until CI ≥ 2.5 L/min/m2; mean arterial pressure ≥ 65 mmHg; CVP ≥ 8 – 12 mmHg; SaO2 ≥ 92%; heart rate ≤ 100/min; UO ≥ 0.5 ml/kg/hr

Outcome timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		SOC	CRT		
Mortality	Relative risk: 1.17 (CI 95% 0.51 – 2.66) Based on data from 30 participants in 1 study Follow-up 10 days	20 per 1000	23 per 1000 Difference: 3 more per 1000 (CI 95% 10 fewer – 33 more)	Very low Due to concerns with indirectness, due to extremely serious imprecision[1]	We are uncertain whether capillary refill time-guided resuscitation increases or decreases mortality
Hospital length of stay	Measured by: Days (mean) Scale: - Lower better Based on data from 30 participants in 1 study	43 days	16 days Difference: Mean Difference 27 fewer (CI 95% 43.3 fewer - 10.7 more)	Very low due to serious risk of bias, Due to concerns with indirectness, due to very serious imprecision[2]	We are uncertain whether capillary refill time-guided resuscitation increases or decreases hospital length of stay
ICU length of stay	Measured by: Days (mean) Scale: - Lower better Based on data from 30 participants in 1 study	8 days	10 days Difference: MD 2 more (CI 95% 1.5 fewer –5.5 more)	Very low Due to serious risk of bias, due to concerns with indirectness, due to very serious imprecision[3]	We are uncertain whether capillary refill time-guided resuscitation increases or decreases ICU length of stay

1. **Indirectness:** Estimates of effects calculated from a body of evidence that included patients with sepsis. The mortality baseline risk for patients with dengue requiring IV infusion was used to calculate absolute effects; **imprecision: extremely serious:** 95% CI including important benefits and harms. 16 events and 30 patients overall
2. **Risk of bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **indirectness:** estimates of effects calculated from a body of evidence that included patients with sepsis.; **imprecision: very serious;** 30 patients overall
3. **Risk of bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **indirectness:** Estimates of effects calculated from a body of evidence that included patients with sepsis.; **imprecision: very serious.** 30 patients overall.

Table 5-4. Summary of findings for capillary refill time-guided resuscitation compared with lactate-guided resuscitation in patients with suspected or confirmed arbovirus infection

Clinical question/ PICO

- Population: patients with suspected or confirmed arbovirus infection
- Intervention: capillary refill time guided resuscitation[a]
- Comparator: lactate-guided resuscitation[b]

a. Fluids were repeated until the perfusion target was achieved (CRT ≤ 3 seconds) (Castro 2020; Hernández 2019). Intervention also included assessing fluid responsiveness (pulse pressure variation, inferior vena cava variation or passive leg raising with velocity – time integral in Castro 2020 and Hernández 2019 and stroke volume and end-expiratory occlusion test in Hernández 2019) or a safety limit of an increase in central venous pressure ≥ 5 mmHg after a fluid bolus was reached (Castro 2020; Hernández 2019).

b. Fluids were repeated until the perfusion target was achieved (arterial lactate ≤ 2 mmol/l or a decrease> 20% every 2 h) (Castro 2020; Hernández 2019). assessing fluid responsiveness (pulse pressure variation, inferior vena cava variation or passive leg raising with velocity – time integral in Castro 2020 and Hernández 2019 and stroke volume and end-expiratory occlusion test in Hernández 2019) or a safety limit of an increase in CVP ≥ 5 mmHg after a fluid bolus was reached (Castro 2020; Hernández 2019).

Outcome timeframe	Study results + measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Lactate	CRT		
Mortality	Relative risk: 0.89 (CI 95% 0.72 - 1.1) Based on data from 466 participants in 2 studies Follow up 59 days	20 per 1000	18 per 1000 Difference: 2 fewer per 1000 (CI 95% 6 fewer - 2 more)	High In spite of concerns with indirectness[1]	Capillary refill time-guided resuscitation does not increase mortality in comparison with lactate-guided resuscitation
Renal replacement therapy	Relative risk: 0.71 (CI 95% 0.47 – 1.1) Based on data from 424 participants in 1 study Follow-up 90 days	60 per 1000	43 per 1000 Difference: 17 fewer per 1000 (CI 95% 32 fewer - 6 more)	Moderate Due to concerns with imprecision and indirectness[2]	Capillary refill time-guided resuscitation probably does not increase renal replacement therapy in comparison to lactate-guided resuscitation
Hospital length of stay	Measured by: Days (mean), lower better Based on data from 466 participants in 2 studies	22.2 days	24.2 days Difference: MD 2 more (CI 95% 8.4 fewer – 12.5 more)	Very low Due to concerns with indirectness, Due to serious risk of bias, Due to very serious imprecision[3]	We are uncertain whether capillary refill time guided resuscitation increases or decreases hospital length of stay in comparison to lactate- guided resuscitation
ICU length of stay	Measured by: Days (mean), lower better Based on data from 466 participants in 2 studies	10 days	9.8 days Difference: 0.2 fewer mean days (CI 95% 1.8 fewer – 1.4 more)	Low Due to serious risk of bias, Due to concerns with indirectness and imprecision[4]	Capillary refill time-guided resuscitation may not increase ICU length of stay in comparison to lactate-guided resuscitation

1. ***Indirectness:*** *Estimates of effects calculated from a body of evidence that included patients with sepsis. The mortality baseline risk for patients with dengue requiring IV infusion was used to calculate absolute effects.*
2. ***Indirectness:*** *Estimates of effects calculated from a body of evidence that included patients with sepsis. The baseline risk of acute kidney injury in patients with acute arboviral disease for patients was used to calculate absolute effects.* ***Imprecision:*** *95% CI including important benefits. 72 events overall*
3. ***Risk of bias: serious:*** *inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;* ***indirectness:*** *estimates of effects calculated from a body of evidence that included patients with sepsis.;* ***imprecision: very serious.*** *95% CI including important benefits and harms*

4. ***Risk of bias: serious:*** *inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;* ***indirectness:*** *estimates of effects calculated from a body of evidence that included patients with sepsis.;* ***imprecision:*** *95% CI including important benefits and harms.*

5.2.3 Lactate

Strong recommendation for
WHO recommends the use of lactate measurement in addition to standard care to guide intravenous fluid management in patients with suspected or confirmed severe arboviral disease. [*Strong recommendation, moderate certainty evidence*] • Measurement and interpretation must occur in conjunction with routine patient monitoring. • The recommendation is intended to support clinical decisions once intravenous fluid resuscitation has been commenced. It is not intended as routine monitoring for all patients. • Lactate is not useful for fluid monitoring in the context of liver failure, including yellow fever.

5.2.3.1 *Evidence to decision*

Benefits and harms

Lactate-guided resuscitation, compared with standard of care in two trials reporting data from 430 participants, probably decreases mortality (4 fewer deaths per 1000, CI 95% 8 fewer - 0 more). Lactate-guided resuscitation, compared with standard of care in one trial reporting data from 82 participants, may decrease ICU length of stay (1.5 fewer mean days, CI 95% 3 fewer - 0.1 fewer).

Lactate-guided resuscitation, compared with central venous oxygen saturation (ScvO2)-guided resuscitation, probably decreases mortality based on 4 randomized control trials reporting data from 772 participants (7 fewer deaths per 1000, CI 95% 10 fewer - 3 fewer by 29 days post-intervention) and may decrease mechanical ventilation based on one study reporting data from 360 participants (14 fewer patients needing mechanical ventilation per 1000, CI 95% 27 fewer - 7 more).

The GDG inferred that serum lactate is beneficial both when compared to standard of care and when compared with central venous oxygen saturation monitoring.

Certainty of the evidence

Research evidence was only available for patients with sepsis. Two trials compared serum lactate with “standard of care” which was variably implemented by facility but included monitoring of hydration and haemodynamic status. Certainty of evidence for mortality was moderate due to imprecision (95% CI included no benefit, 180 events overall) and indirectness (data derived from patients with sepsis). Certainty of evidence for ICU length of stay,

compared with standard of care, was rated as low due to serious risk of bias (inadequate/lack of blinding with possible performance and detection biases), concerns with indirectness (data derived from patients with sepsis) and serious imprecision (82 patients overall).

For ScvO2, certainty of evidence for mortality was moderate due to imprecision (180 events overall) and indirectness (data derived from patients with sepsis). Certainty of evidence for mechanical ventilation was low due to indirectness (data derived from patients with sepsis) and very serious imprecision (95% CI including benefits and harms, 60 events overall).

Values and preferences

Applying the agreed-upon values and preferences (see 3.2.3) for patients with severe disease, the GDG inferred that most patients, given the likely mortality benefit would choose to have lactate measurement in addition to standard care to guide intravenous fluid management.

Resources and other considerations

Resources and availability: Lactate is not readily measurable in many low-resource settings. The costs of measuring lactate include those of equipment and consumables (when used as either point-of-care, or through laboratory measurement). In the context of the recommendation, the GDG urged WHO to advance availability of lactate measurement through essential device mechanisms and other channels.

The GDG agreed that the recommendation applies to arboviral disease in the absence of liver failure (which can occur in yellow fever) as the lactate measurement can be unreliable under these circumstances. Similarly, the panel judged that the recommendation would apply to pregnant and breastfeeding women and to children.

5.2.3.2 Justification

The GDG considered lactic-acid guided resuscitation with standard of care (as defined by the two respective studies). Evidence was presented to the GDG on ScvO2-guided resuscitation, although this was treated as secondary to comparisons of lactate with standard of care. All studies enrolled patients with sepsis, and outcomes for arboviral disease were not specifically available. Lactate was measured at intervals of two to three hours.

The GDG agreed a strong recommendation for lactate-guided resuscitation but emphasised the non-inferiority of capillary refill time and its greater accessibility and lower costs. The panel judged that multiple comparisons which were favourable for lactate allowed a strong recommendation in favour of use, although noted some indirectness as the evidence did not derive from studies of patients with arbovirus.

The GDG noted limitations in the use and interpretation of lactate, especially in liver failure.

5.2.3.3 Practical info

What does blood lactate concentration indicate?

Lactate is produced during anaerobic metabolism. Patients in shock typically have hypoperfusion, whereby lactate is produced and released into the circulation. Higher blood lactate levels are associated with poor patient outcomes. However, production of lactate may occur for many reasons, and changes in blood concentrations lag behind other physiological improvements.

When guiding fluid resuscitation, blood lactate has been typically measured at 2 – 4 hourly intervals.

Routine patient monitoring

Lactate can be used as an adjunct to routine patient monitoring in severe disease including shock. However, it is mandatory to regularly and frequently measure physiological variables and urine output, and laboratory values where appropriate (such as haematocrit). Clinical measures of fluid response include blood pressure (including pulse pressure and mean arterial pressure), heart rate and urine output. Clinical indicators of imminent or worsening respiratory compromise, such as pulmonary oedema, include respiratory rate and oxygen saturations.

How to use lactate to guide fluid therapy

Different protocols have been used. Examples of successful haemodynamic resuscitation using lactate targets include:

- lactate decrease of 10 or 30% measured every 2 hours (73),
- lactate decrease of 10% measured every 3 hours (74),
- lactate kinetics at 2 hours up to 10%, 4 hours up to 20% and 6 hours up to at least 30% (75),
- targeted lactate clearance of at least 10% (76).

Specific protocols for lactate-guided fluid administration should be based on relevant local or international guidance *(38)*.

Cautions for use of lactate

In general, clinical management of patients with dengue should be as minimally invasive as possible due to the bleeding associated with interventions. Care should be taken where more invasive sampling techniques (such as arterial lines) are used for lactate measurement. Capillary measurement provides an alternative.

Lactate monitoring is unreliable in patients with liver failure, which is a feature of advanced yellow fever disease and can occur in severe dengue.

Table 5-5. Summary of findings for lactate-guided resuscitation compared with Central Venous Oxygen saturation-guided resuscitation in patients with suspected or confirmed arbovirus infection that will receive intravenous fluid infusion

Clinical question/ PICO

- Population: patients with suspected or confirmed arbovirus infection
- Intervention: lactate-guided resuscitation[a]
- Comparator: central Oxygen saturation guided resuscitation[b]

a. Lactate decrease of 10 or 30% measured every 2 hours (Tian 2012), Lactate decrease of 10% measured every 3 hours (Yu 2013), lactate kinetics at 2 hours up to 10%, 4 hours up to 20% and 6 hours up to at least 30% (Zhou 2017), targeted lactate clearance of at least 10% (Jones 2010). Intervention arm also included EGDT (Tian 2012); CVP ≥8 mm Hg, MAP ≥65 mm Hg (Yu 2013; Zhou 2017; Jones 2010)

b. CVP ≥8 mm Hg, MAP ≥65 mm Hg and ScvO2≥0.70 (Tian 2012; Yu 2013; Zhou 2017; Jones 2010)

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence	Summary
		Scv02	Lactate		
Mortality	Relative risk: 0.65 (CI 95% 0.5 - 0.84) Based on data from 772 participants in 4 studies Follow-up 29 days	20 per 1000	13 per 1000 Difference: 7 fewer per 1000 (CI 95% 10 fewer - 3 fewer)	Moderate Due to concerns with imprecision and indirectness[1]	Lactate-guided resuscitation probably decreases mortality in comparison to ScvO2 guided resuscitation
Mechanical ventilation	Relative risk: 0.71 (CI 95% 0.45 - 1.14) Based on data from 360 participants in 1 study Follow-up 60 days	50 per 1000	36 per 1000 Difference: 14 fewer per 1000 (CI 95% 27 fewer - 7 more)	Low Due to concerns with indirectness, Due to very serious imprecision[2]	Lactate-guided resuscitation may decrease mechanical ventilation in comparison to Scv02

1. ***Indirectness:*** *estimates of effects calculated from a body of evidence that included patients with sepsis. The mortality baseline risk for patients with dengue requiring IV infusion was used to calculate absolute effects.;* ***Imprecision: serious.*** *180 events overall*
2. ***Indirectness:*** *estimates of effects calculated from a body of evidence that included patients with sepsis. The baseline risk for organ failure in patients with dengue requiring IV infusion was used to calculate absolute effects.* ***imprecision: very serious.*** *95% CI including benefits and harms. 60 events overall*

Table 5-6. Summary of findings for lactate-guided resuscitation compared with standard of care in patients with suspected or confirmed arbovirus infection that will receive intravenous fluid infusion.

Clinical question/ PICO

- Population: patients with suspected or confirmed arbovirus infection
- Intervention: lactate-guided resuscitation [a]
- Comparator: standard of care[b]

a. Decrease lactate levels by at least 20% per 2 hours (Jansen 2010) or 30% every 2 hours (Chen 2021). Intervention also included heart rate less than 100 beats/min (Jansen 2010; Chen 2021), MAP at or above 60 mm Hg (Jansen 2010; Chen 2021), CVP 8 – 12 mm Hg (12 – 15 in mechanically ventilated) (Jansen 2010; Chen 2021), with the use of CVP as a dynamic safety limit during fluid challenges (Jansen 2010) , urinary output more than 0.5 ml/kg/h (Jansen 2010; Chen 2021), arterial oxygen saturation (SaO2) at or above 92% (Jansen 2010; Chen 2021) and haemoglobin level at or above 7.0 g/dl (>10.0 g/dl in case of cardiac ischemia) (Jansen 2010; Chen 2021). ScvO2 was measured continuously (Jansen 2010). When ScvO2 was at or above 70% and (Jansen 2010) /or (Chen 2021) lactate levels did not decrease by at least 20% during a 2-hour time interval, vasodilator therapy was started

b. Heart rate less than 100 beats/min (Jansen 2010; Chen 2021), MAP at or above 60 mm Hg (Jansen 2010; Chen 2021), CVP 8 – 12 mm Hg (12 – 15 in mechanically ventilated) (Jansen 2010; Chen 2021), with the use of CVP as a dynamic safety limit during fluid challenges (Jansen 2010) , urinary output more than 0.5 ml/kg/h (Jansen 2010; Chen 2021), arterial oxygen saturation (SaO2) at or above 92% (Jansen 2010; Chen 2021) and haemoglobin level at or above 7.0 g/dl (>10.0 g/dl in case of cardiac ischemia) (Jansen 2010; Chen 2021). The use of ScvO2 and clinical assessment of peripheral perfusion allowed at the discretion of the attending clinician (Jansen 2010).

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		SOC	Lactate		
Mortality	Relative risk: 0.79 (CI 95% 0.62 – 1.01) Based on data from 430 participants in 2 studies	20 per 1000	16 per 1000 Difference: 4 fewer per 1000 (CI 95% 8 fewer – 0 more)	Moderate Due to concerns with imprecision and indirectness[1]	Lactate-guided resuscitation probably decrease mortality
ICU length of stay	Measured by: Days (mean), lower better Based on data from 82 participants in 1 study	6 days	4.5 days Difference: MD 1.5 fewer (CI 95% 3 fewer - 0.1 fewer)	Low Due to serious risk of bias, due to concerns with indirectness, due to serious imprecision[2]	Lactate-guided resuscitation may have decrease ICU length of stay

1. ***Indirectness:*** *estimates of effects calculated from a body of evidence that included patients with sepsis. The mortality baseline risk for patients with dengue requiring IV infusion was used to calculate absolute effects;* ***imprecision:*** *95% CI including no benefits, 180 events overall*
2. ***Risk of bias: serious.*** *inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;* ***indirectness:*** *estimates of effects calculated from a body of evidence that included patients with sepsis.;* ***imprecision: serious:*** *82 patients overall.*

5.2.4 Passive leg raise test

Conditional recommendation for
WHO suggests the use of passive leg raise test in patients in shock, with suspected or confirmed arboviral disease, when the clinician is uncertain if further intravenous fluid administration is warranted. [*Conditional recommendation, low certainty evidence*] • The recommendation is intended to support clinical decisions once intravenous fluid resuscitation has been commenced. It is not intended as routine monitoring for all patients. • Real-time monitoring of cardiac output is required to most accurately interpret the results of a passive leg raise test.

5.2.4.1 *Evidence to decision*

Benefits and harms

Benefits: In patients with suspected or confirmed arbovirus infection who will receive intravenous fluid infusion in an inpatient setting, cardiac output monitoring during passive leg raise may reduce mortality (2 fewer deaths per 1,000 patients than standard of care, 95% CI 5 fewer - 5 more), and the need for mechanical ventilation (24/1000 fewer events, 95% CI 36 fewer to 1 fewer).

Harms: Prevention of pulmonary oedema was the GDGs primary concern in terms of over-treatment with intravenous fluids, although specific data on this endpoint were not available. Overall, the panel judged there was unlikely to be harm from the use of passive leg raise.

Certainty of the evidence

The certainty of the evidence for mortality is rated as moderate, based on data from 462 participants with sepsis across five studies (95% CI 7 fewer deaths to 6 more deaths). For mechanical ventilation, certainty was low, derived from a single study involving 120 participants, downgraded due to serious risk of bias from inadequate blinding, imprecision due to the low number of events *(28),* and indirectness. The outcomes for renal replacement therapy, hospital length of stay and ICU length of stay were very low certainty.

Values and preferences

Applying the agreed-upon values and preferences (see 3.2.3), for patients with severe disease, the GDG inferred that most, given the possible benefit and lack of harm, would choose to have the passive leg raise test performed to guide intravenous fluid management.

Resources and other considerations

Equity, acceptability, and feasibility: Ultrasound equipment is expensive, frequently unavailable and requires considerable training and maintenance of skills. Competence of the user will be an important determinant of accuracy and utility.

5.2.4.2 *Justification*

Six RCTs were identified that tested passive leg raise or bolus infusion-guided resuscitation vs standard of care, n=664 patients with sepsis.

Known limitations of the test are severe hypovolaemia (where volumes of venous blood in the legs are small), and where intra-abdominal pressure is raised.

A sensitivity analysis that only looked at the passive leg raise test was highly similar (n=462 septic patients, in 5 RCTs) but with lower quality of evidence. The GDG decided to recommend separately for passive leg raise and monitored fluid bolus approaches.

The panel noted that measures of responsiveness to passive leg raise tests were heterogeneous across studies, and a specific recommendation on which technique to use could not be made.

The GDG noted differences in arboviral disease pathophysiology, but also the difficulty of clinical differentiation in the absence of rapidly available laboratory diagnostics. They noted specifically that chikungunya patients may be more prone to myocarditis, especially at extremes of age, and that plasma leakage in dengue can be profound.

5.2.4.3 *Practical info*

What is evaluated by the passive leg raise test (PLR)?

PLR is used to predict whether further volume expansion will increase cardiac output (and therefore potentially end-organ perfusion). During PLR, approximately 150-300 ml of venous blood from the legs is transferred quickly to the central circulation. An immediate increase in cardiac output demonstrates preload responsiveness. This mimics a fluid challenge without actual fluid infusion; hemodynamic effects are quickly reversible the risk of fluid overload is minimized *(77,78)*.

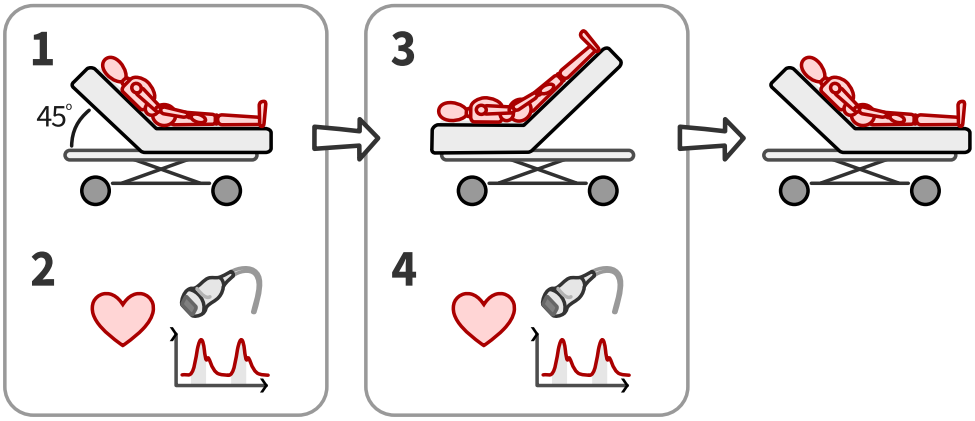
How to measure cardiac output response to passive leg raise or bolus intravenous fluid

Possible measures of cardiac output include visualisation by ultrasound / echocardiography and thermodilution techniques. Blood pressure is an indirect measure, and a less reliable indicator of preload responsiveness. The choice of measure will depend on specific clinical contexts and available resources. Other measures of venous filling, such as static measures of inferior vena cava diameter may be helpful in some circumstances but are not considered here.

PLR test protocol

- Positioning the patient semi-recumbent at 45°
- Record the cardiac output at baseline. This may be an average of multiple measurements.
- Quickly lower the patient flat, and lift both legs to at least 45° from the horizontal.
- Record the cardiac output again, as soon as possible after the manoeuvre (maximal effect takes place between 30 and 90 seconds).
- Reposition the patient according to clinical need.

Figure 5-2. Suggested way to perform standardized passive leg raise test



Notes: Ensure you are using a bed in which the patient can be rapidly repositioned without discomfort. 1 - Position the patient semi-recumbent at 45 degrees. 2 – Record the patient's cardiac output. The chosen modality of measurement will depend on equipment, training and resources. The most direct and reproducible measurements employ echocardiography or thermodilution techniques. 3 – Lower patient's torso to horizontal position and lift both legs to 45 degrees. 4 – Repeat the measurement of cardiac output within 30 to 90 seconds. When complete, return the patient to a clinically appropriate position.

How to interpret the result

In the context of shock, preload responsiveness is indicated by a PLR-related increase in cardiac output from baseline of more than 10% (79,80). Being a less reliable measure, thresholds for improvements in other more indirect measures of cardiac output are not known.

How to act on the result

The decision to administer fluids should be individualized, using a cycle of assessment, intervention, and reassessment.

In a patient with haemodynamic instability and/or signs of circulatory shock:

- a positive PLR test indicates preload responsiveness and a lower risk of fluid overload. A positive PLR should give the clinician more confidence to proceed with a fluid bolus, with appropriate monitoring and reassessment.
- a negative PLR test indicates that further fluid administration may not result in physiological improvement and may increase the risk of fluid overload. A negative PLR should prompt evaluation of non-hypovolaemic causes of shock, and act as a caution that further intravenous fluids that alternative approaches, such as vasoactive medication may be more immediately appropriate *(81)*.

After any fluid administration, the PLR can be repeated.

Cautions and contraindications

- Known limitations of the test are severe hypovolaemia (where volumes of venous blood in the legs are small), and where discomfort or adrenergic stimulation is provoked by the test *(82)*.
- Moving of patients before, during and after PLR requires care to minimise discomfort, and to ensure the appropriate positioning is maintained during the rest of care (for example supine or semi-recumbent as clinically indicated).
- PLR is contraindicated for patients with:
    - traumatic brain injuries due to the risks of increasing intracranial pressure.
    - deep vein thrombosis of the lower limbs due to the risk of dislodging a clot.
    - fractures of the lower extremities or leg amputations due to effects on the volume of blood recruited by the test.
    - venous compression stockings

Training and competency

Proper training and competence are essential for accurate assessment and patient safety. Health care professionals should receive comprehensive training on the procedure, including the correct positioning of the patient, accurate recording of hemodynamic parameters and interpretation of results. Regular competency assessments and refresher courses are recommended to maintain high standards of practice.

Table 5-7. Summary of findings for cardiac output response to leg raise test (LRT) or bolus infusion-guided resuscitation compared with standard of care in patients with suspected or confirmed arbovirus infection who will receive intravenous fluid infusion

Clinical question/ PICO

- Population: patients with suspected or confirmed arbovirus infection
- Intervention: cardiac output response to leg raise test (LRT) or bolus infusion guided resuscitation. [a]
- Comparator: standard of care[b]

a. Fluid challenge was performed by PLR (Chen 2015; Douglas 2020; Li 2019; Richard 2015) or IV fluids (Chen 2015; Kuan 2016; Musikatavorn 2021). Fluid responsiveness was assessed by pulse pressure variability (Chen 2015; Richard 2015), IVC distension (Chen 2015; Musikatavorn 2021), stroke volume (Chen 2015; Douglas 2020; Kuan 2016; Li 2019; Richard 2015)

b. SOC was rapid fluid replacement (Li 2019), 30 mL/kg loading of NSS (Musikatavorn 2021), intravascular volume expansion administered by aliquots of 500 ml to achieve a CVP of at least 8 cm H2O in the control group (Richard 2015) or described as clinician discretion/per clinician criteria (Chen 2015; Douglas 2020; Kuan 2016),

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		SOC	LRT or Bolus		
Mortality	Relative risk: 0.96 (CI 95% 0.74 – 1.25) Based on data from 664 participants in 6 studies Follow-up 10 days	20 per 1000	19 per 1000 Difference: 1 fewer per 1000 (CI 95% 5 fewer - 5 more)	Moderate Due to concerns with imprecision and indirectness[1]	Cardiac output response LRT or bolus-guided resuscitation may have little or no impact on mortality
Renal replacement therapy	Relative risk: 0.8 (CI 95% 0.35 – 1.83) Based on data from 403 participants in 3 studies	60 per 1000	48 per 1000 Difference: 12 fewer per 1000 (CI 95% 39 fewer-–50 more)	Very low Due to serious risk of bias, due to concerns with indirectness, due to very serious imprecision[2]	We are uncertain whether cardiac output response to LRT or bolus-guided resuscitation increases or decreases renal replacement therapy
Mechanical ventilation	Relative risk: 0.66 (CI 95% 0.46 – 0.97) Based on data from 322 participants in 2 studies	50 per 1000	33 per 1000 Difference: 17 fewer per 1000 (CI 95% 27 fewer – 1 fewer)	Low Due to serious risk of bias, due to concerns with imprecision and indirectness[3]	Cardiac output response LRT or bolus-guided resuscitation may decrease mechanical ventilation
Hospital length of stay	Measured by days, lower better Based on data from 522 participants in 4 studies	13 Days	11 Days Difference: MD 2 fewer (CI 95% 5.4 fewer – 1.3 more)	Very low Due to serious risk of bias, due to concerns with indirectness, due to serious inconsistency, due to serious imprecision[4]	We are uncertain whether cardiac output response to LRT or bolus-guided resuscitation increases or decreases hospital length of stay
ICU length of stay	Measured by days, lower better Based on data from 169 participants in 2 studies	8 Days	8 Days Difference: MD 0 fewer (CI 95% 6.7 fewer – 6.6 more)	Very low Due to serious risk of bias, due to concerns with indirectness, due to very serious imprecision[5]	We are uncertain whether cardiac output response to LRT or bolus-guided resuscitation increases or decreases ICU length of stay

1. ***Indirectness:*** *Estimates of effects calculated from a body of evidence that included patients with sepsis. The baseline risk for patients with dengue requiring IV infusion was used to calculate absolute effects.* ***Imprecision:*** *95% CI including benefits and harms*
2. ***Risk of bias: serious****: inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;* ***indirectness:*** *estimates of effects calculated from a body of evidence that included patients with sepsis. The baseline risk of acute kidney injury in patients with acute arboviral disease for patients was used to calculate absolute effects.* ***Imprecision: very serious:*** *95% CI including important benefits and harms*
3. ***Risk of bias: serious****: inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;* ***indirectness:*** *estimates of effects calculated from a body of evidence that included patients with sepsis. The baseline risk for organ failure in patients with dengue requiring IV infusion was used to calculate absolute effects.* ***Imprecision:*** *67 events overall.*
4. ***Risk of bias: serious.*** *Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;* ***inconsistency: serious.*** *The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies.* ***Indirectness:*** *estimates of effects calculated from a body of evidence that included patients with sepsis.;* ***imprecision: serious.*** *95% CI including benefits and harms*
5. ***Risk of bias: serious:*** *inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;* ***indirectness:*** *estimates of effects calculated from a body of evidence that included patients with sepsis.;* ***imprecision: very serious.*** *95% CI including benefits and harms.*

Table 5-8. Summary of findings for cardiac output response to leg raise test (LRT) guided resuscitation compared with standard of care in patients with suspected or confirmed arbovirus infection who will receive intravenous fluid infusion.

Clinical question/ PICO

- Population: patients with suspected or confirmed arbovirus infection
- Intervention: cardiac output response to leg raise test (LRT).
- Comparator: standard of care

Outcome timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		SOC	LRT		
Mortality	Relative risk: 0.91 (CI 95% 0.64 –1.3) Based on data from 462 participants in 5 studies Follow-up 10 days	20 per 1000	18 per 1000 Difference: 2 fewer per 1000 (CI 95% 7 fewer – 6 more)	Moderate Due to concerns with indirectness and imprecision[1]	Cardiac output response to LRT guided resuscitation probably has little or no impact on mortality.
Renal replacement therapy	Relative risk: 0.59 (CI 95% 0.19 – 1.82) Based on data from 201 participants in 2 studies	60 per 1000	35 per 1000 Difference: 25 fewer per 1000 (CI 95% 49 fewer – 49 more)	Very low Due to serious risk of bias, due to very serious imprecision[2]	We are uncertain whether cardiac output response to LRT-guided resuscitation increases or decreases renal replacement therapy.
Mechanical ventilation	Relative risk: 0.52 (CI 95% 0.27 – 0.98) Based on data from 120 participants in 1 study	50 per 1000	26 per 1000 Difference: 24 fewer per 1000 (CI 95% 36 fewer – 1 fewer)	Low Due to serious risk of bias, due to concerns with imprecision and indirectness[3]	Cardiac output response to LRT guided resuscitation may decrease mechanical ventilation.
Hospital length of stay		13 days	10.2 days	Very low	We are uncertain whether cardiac output response

	Measured by days (mean), lower better Based on data from 320 participants in 3 studies	Difference: MD 2.78 fewer (CI 95% 7.04 fewer – 1.47 more)		Due to serious risk of bias, due to serious inconsistency, due to serious imprecision, due to concerns with indirectness[4]	to LRT guided resuscitation increases or decreases hospital length of stay.
ICU length of stay	Measured by days (mean), lower better Based on data from 169 participants in 2 studies	8 days Difference: MD 0 fewer (CI 95% 6.7 fewer – 6.6 more)	8 days	Very low Due to serious risk of bias, due to very serious imprecision, due to concerns with indirectness[5]	We are uncertain whether cardiac output response to LRT or bolus-guided resuscitation increases or decreases ICU length of stay.

1. ***Indirectness:*** *estimates of effects calculated from a body of evidence that included patients with sepsis. The baseline risk for patients with dengue requiring IV infusion was used to calculate absolute effects.* ***Imprecision:*** *95% CI including benefits and harms*
2. ***Risk of bias: serious.*** *Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;* ***indirectness: not serious.*** *Estimates of effects calculated from a body of evidence that included patients with sepsis. The baseline risk of acute kidney injury in patients with acute arboviral disease was used to calculate absolute effects.;* ***imprecision: very serious:*** *95% CI including important benefits and harms*
3. ***Risk of bias: serious****: inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;* ***indirectness:*** *estimates of effects calculated from a body of evidence that included patients with sepsis. The baseline risk for organ failure in patients with dengue requiring IV infusion was used to calculate absolute effects.* ***imprecision:*** *28 events overall*
4. ***Risk of bias: serious:*** *inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;* ***inconsistency: serious:*** *The confidence interval of some of the studies does not overlap with those of most included studies/ the point estimate of some of the included studies;* ***indirectness:*** *estimates of effects calculated from a body of evidence that included patients with sepsis.;* ***imprecision: serious:*** *95% CI including benefits and harms*
5. ***Risk of bias: serious:*** *inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;* ***indirectness:*** *estimates of effects calculated from a body of evidence that included patients with sepsis.;* ***imprecision: very serious.*** *95% CI including benefits and harms.*

5.3 Corticosteroids (for severe disease)

Conditional recommendation against
WHO suggests against the use of systemic corticosteroids in the treatment of patients with suspected or confirmed severe arboviral disease. [*Conditional recommendation, very low certainty evidence*] • For patients on established corticosteroid therapy, the decision to continue should be made according to anticipated risk/benefit balance.

5.3.1 Evidence to decision

Benefits and harms

Benefits*:* In patients with severe arboviral disease, it is uncertain whether steroids increase or decrease mortality (6 fewer deaths per 1000, 95% CI 12 fewer – 3 more, at 5-day follow up) based on data from 258 participants in 3 studies. Corticosteroids have little or no impact on length of hospital stay (0.55 mean days longer, 95% CI 0.53 fewer – 1.63 more) based on data from 124 participants in 2 studies.

Harms*:* Corticosteroids probably increase gastrointestinal bleeding (11 more per 1000, 95% CI 6 more-17 more) based on data from 33 253 participants without arboviral disease in 159 RCTs. Corticosteroids may increase severe adverse events (28 more per 1000, 95% CI 40 fewer – 145 more) based on data from 468 participants in 3 studies. It is uncertain whether steroid use increases or decreases organ failure or severe bleeding.

Certainty of the evidence

Certainty of evidence was rated as low for effect on length of hospital stay, based on data from 124 participants in 2 studies due to serious inconsistency and serious imprecision.

Certainty was rated as very low for mortality, organ failure and severe bleeding. Certainty of evidence was rated as moderate for gastrointestinal bleeding, based on data from 33 253 participants in 159 RCTs; however, these were patients without arboviral disease and there were thus concerns with indirectness and imprecision. The median duration of corticosteroid treatment was 8.5 days (IQR 3.3–28.0), and the appreciation that short and longer course of steroids might have different adverse events contributed to the very low certainty rating. Certainty of evidence was rated as low for severe adverse events, based on data from 468 participants in three studies, due to very serious imprecision.

Values and preferences

Applying the agreed-upon values and preferences (see 3.2.3) for patients with severe disease, the GDG inferred that most patients would choose to avoid corticosteroids because of overall evidence suggesting potential harm without strong evidence of benefit.

Resources and other considerations

The panel intended that the recommendation apply to chikungunya, dengue, yellow fever and Zika.

5.3.2 Justification

The GDG noted that corticosteroids are variably and inconsistently used in the management of several non-arboviral acute infections and sepsis, and there is little evidence for benefit in the published data on use in arboviral infections, particularly dengue. Members were concerned about the adverse event profile of corticosteroids and the potential for negative effects of immunosuppression.

Some panel members noted that corticosteroids have been used in the management of patients with certain disease manifestations and sequelae caused by arboviral infections. Examples cited included acute viral myocarditis and chikungunya encephalitis. In the absence of robust specific evidence, individual judgement should be made for these and other manifestations of severe arboviral disease.

The panel identified evaluation of corticosteroids in dengue as a research priority.

5.3.3 Practical information

Mechanism of action, adverse event profile and availability

Please, refer to Section 4.3 for further information.

The recommendation refers only to systemic (not local or topic) corticosteroids. Additionally, some patients develop conditions complicating their arboviral infection that may, in the clinician’s assessment, benefit from corticosteroids, for example, uveitis, myocarditis, or severe pruritus.

Table 5-9. Summary of findings for corticosteroids compared to standard of care in patients with acute severe arboviral disease

Clinical question/ PICO

- Population: patients with acute arboviral disease (severe patients)
- Intervention: corticosteroids
- Comparator: standard of care

Outcome timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		SOC	Steroids		
Mortality	Relative risk: 0.68 (CI 95% 0.41 – 1.14) Based on data from 258 participants in 3 studies Follow-up 5 days	20 per 1000	14 per 1000 Difference: 6 fewer per 1000 (CI 95% 12 fewer – 3 more)	Very low Due to serious risk of bias, due to serious imprecision, due to serious inconsistency[1]	We are uncertain whether corticosteroids increase or decrease mortality.
Organ failure	Relative risk: 1.3 (CI 95% 0.66 – 2.58) Based on data from 288 participants in 2 studies Follow up 17.5 days	50 per 1000	65 per 1000 Difference: 15 more per 1000 (CI 95% 17 fewer – 79 more)	Very low Due to serious risk of bias, due to very serious imprecision[2]	We are uncertain whether corticosteroids increase or decrease organ failure.
Severe bleeding	Relative risk: 1.13 (CI 95% 0.07 – 17.61) Based on data from 245 participants in 2 studies Follow-up 47	25 per 1000	28 per 1000 Difference: 3 more per 1000 (CI 95% 26 fewer – 28 more)	Very low Due to serious risk of bias, due to very serious imprecision[3]	We are uncertain whether corticosteroids increase or decrease severe bleeding.
Gastro-intestinal bleeding	Relative risk: 1.43 (CI 95% 1.22 – 1.66) Based on data from 33 253 participants without arboviruses in 159 RCTs	25 per 1000	36 per 1000 Difference: 11 more per 1000 (CI 95% 6 more – 17 more)	Moderate Due to concerns with indirectness and imprecision[4]	Corticosteroids probably increase gastrointestinal bleeding.
Severe adverse events	Relative risk: 1.21 (CI 95% 0.7 – 2.09) Based on data from 468 participants in 3 studies Follow-up 13 days	133 per 1000	161 per 1000 Difference: 28 more per 1000 (CI 95% 40 fewer – 145 more)	Low Due to very serious imprecision[6]	Corticosteroids may increase severe adverse events.
Length of hospital stay (days)	Measured by: Days, lower better Based on data from 124 participants in 2 studies	4.1 days	4.65 days Difference: MD 0.55 more (CI 95% 0.53 fewer – 1.63 more)	Low Due to serious inconsistency, due to serious imprecision[7]	Corticosteroids may have little or no impact on length of hospital stay (days).

1. ***Risk of bias: serious.*** *Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias;* ***inconsistency: serious:*** *best point estimate of one study showing mortality reduction while two studies showed no effect;* ***imprecision: serious.*** *95% CI including absence of benefits*
2. ***Risk of bias: serious.*** *Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; incomplete data and/or large loss to follow up;* ***imprecision: very serious:*** *95% CI including important benefits and harms*

3. ***Risk of bias: serious.*** *Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias* ***imprecision: very serious:*** *95% CI including important benefits and harms*
4. ***Imprecision:*** *95% CI includes unimportant increase in gastrointestinal bleeding. MID used was 10 per 1000;* ***indirectness:*** *different population (patients without arboviruses). The median duration of corticosteroid treatment was 8.5 days (IQR 3.3–28.0), and the appreciation that short and longer course of steroids might have different adverse events contributed to the very low certainty rating.*
5. ***Imprecision: very serious:*** *95% CI including important benefits and harms; 23 events overall*
6. ***Imprecision: very serious:*** *95% CI including benefits and harms*
7. ***Inconsistency: serious.*** *The confidence interval of some of the studies does not overlap with that of most included studies/ the point estimate of some of the included studies.;* ***imprecision: serious:*** *95% CI include important harms.*

5.4 Immunoglobulins

Conditional recommendation against
WHO suggests against the use of immunoglobulins in the treatment of patients with suspected or confirmed severe arboviral disease. [*Conditional recommendation, very low certainty evidence*]

5.4.1 Evidence to decision

Benefits and harms

It is unclear whether the use if immunoglobulins increases or decreases mortality, based on data from 77 participants in 2 studies (13 fewer deaths per 1000, CI 95% 19 fewer – 52 more), bleeding based on data from 31 participants in 1 study (22 fewer events per 1000, CI 95% 39 fewer – 3 more), or adverse events based on data from 31 participants in one study (64 more events per 1000, CI 95% 59 fewer – 152 more).

Certainty of the evidence

Three RCTs were identified that evaluated the effect of administration of either anti-D Rho hyperimmune globulin (two studies) or intravenous immunoglobulin (IVIG) (one study). There were two studies that assessed mortality based on data from 79 participants; one study that assessed severe bleeding based on data from 31 participants; and one that assessed any adverse events based on data from 31 participants. Certainty across outcomes was rated as very low because of serious risk of bias and very serious imprecision.

Values and preferences

Applying the agreed-upon values and preferences (see 3.2.3) for patients with severe disease, the GDG inferred that most patients would choose to avoid immunoglobulins because of overall evidence suggesting absence of evidence of benefit.

Resources and other considerations

Immunoglobulin preparations are expensive and not readily available in resource-limited settings. Given the paucity of supplies, the GDG emphasized the importance of using available immunoglobulins for indications with evidence of beneficial effect, e.g., IVIG in patients with Guillain-Barré syndrome.

5.4.2 Justification

The GDG noted the lack of evidence demonstrating benefit in the routine use of immunoglobulins in patients with arboviral disease and the need to reserve use for indications with evidence of clinical benefit.

The GDG used indicative voting during the debate, where the initial position of 'research-only' was the most popular. However, a significant minority felt that this was too restrictive for clinicians, as it would be closer to a ‘strong against’ recommendation than a ‘conditional against’ one. Further discussions led to a consensus on a 'conditional against' stance among all members, allowing clinicians the latitude to consider its use in a minority of patients.

5.4.3 Practical Information

Mechanism of action

Immunoglobulins are used therapeutically to bind to epitopes on infectious agents in the absence of host immunity, or to bind antibodies responsible for adverse immune or autoimmune conditions. IVIG is a blood product derived from pooled human sera, intravenously administered, which contains a broad array of antibodies. Anti-D Rho hyperimmune globulin is the IgG fraction of plasma from pooled D-positive red-cell-immunized donors that is used primarily for Rh isoimmunization suppression in obstetric settings and for immune thrombocytopenic purpura.

Immunoglobulins have been used in the management of patients with some clinical sequelae of arboviral infections, such as Guillain-Barré syndrome, for which IVIG has been shown to be of benefit *(83)*.

Table 5-10. Summary of findings for Intravenous immunoglobulins compared with standard of care in patients with acute arboviral disease

Clinical question/ PICO

- Population: patients with acute arboviral disease,
- Intervention: intravenous immunoglobulins
- Comparator: standard of care

Outcome timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		SOC	Lactate		
Mortality	Relative risk: 0.34 (CI 95% 0.03 – 3.58) Based on data from 77 participants in 2 studies[1]	20 per 1000	7 per 1000 Difference: 13 fewer per 1000 (CI 95% 19 fewer - 52 more)	Very low Due to serious risk of bias, due to very serious imprecision[1]	We are uncertain whether immunoglobulins increase or decrease mortality.
Severe bleeding	Relative risk: 0.11 (CI 95% 0.01 – 1.89) Based on data from 31 participants in 1 study	25 per 1000	3 per 1000 Difference: 22 fewer per 1000 (CI 95% 39 fewer - 3 more)	Very low Due to serious risk of bias, due to very serious imprecision[2]	We are uncertain whether immunoglobulins increase or decrease severe bleeding.
Adverse events (any)	Relative risk: 3.0 (CI 95% 0.13 – 68.0) Based on data from 31 participants in 1 study	32 per 1000	96 per 1000 Difference: 64 more per 1000 (CI 95% 59 fewer - 152 more)	Very low Due to serious risk of bias, due to very serious imprecision[3]	We are uncertain whether immunoglobulins increase or decrease adverse events.

1. ***Risk of bias: 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; inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;* ***imprecision: very serious:*** *95% CI including important benefits and harms*
2. ***Risk of bias: 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; inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;* ***imprecision: very serious:*** *95% CI including absence of benefits, 4 events overall*
3. ***Risk of Bias: 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; inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;* ***imprecision: very serious:*** *95% CI including important benefits and harms*

5.5 Platelet transfusion

Conditional recommendation against
WHO suggests against the use of prophylactic platelet transfusion in patients with suspected or confirmed severe arboviral disease and platelet count of <50,000 platelets/microlitre who have no active bleeding. [*Conditional recommendation, low certainty evidence*] • The panel noted the specific circumstances in which platelet transfusion may be indicated, including prevention of haemorrhage in surgery or other invasive procedure and pre-existing anticoagulation treatment.

5.5.1 Evidence to decision

Benefits and harms

Benefits: Based on data from 372 participants in one observational study comparing outcomes in patients who received platelet transfusions with those who did not, platelet transfusion may decrease length of hospital stay (1 fewer mean days' duration, CI 95% 1.32 fewer – 0.7 fewer).

Harms*:* It was uncertain whether platelet transfusion increases or decreases mortality (11 more events per 1000 based on data from 460 participants in 2 studies, CI 95% 13 fewer – 34 more), severe bleeding (7 fewer events per 1000 based on data from 460 participants in 2 studies, CI 95% 22 fewer – 75 more), clinical bleeding (23 fewer events per 1000, CI 95% 13 fewer – 34 more based on data from 450 patients in two randomized control trials; 2 more per 1000, CI 95% 11 fewer – 13 more based on data from 788 participants in a non-randomized study) organ failure (1 fewer per 1000 based on data from 372 participants in one study, CI 95% 21 fewer – 21 more) or severe adverse events (15 more events per 1000 based on data from 460 participants in 2 studies, CI 95% 2 fewer – 32 more).

In addition to the data summarized from the systematic review, the GDG noted that platelet transfusion can be associated with the transmission of additional blood-borne pathogens, and results in additional intravenous volumes of fluid.

Certainty of the evidence

Research evidence was limited to dengue. This evidence was indirectly applied to other arboviral infections.

The evidence summary on administration of platelets to patients with dengue and thrombocytopenia was informed by two randomized controlled trials and one retrospective

non-randomized observational study, and the number of patients informing estimates varied across outcomes from 372 to 788 patients. There was very low certainty of effect on mortality, severe bleeding, clinical bleeding, organ failure and severe adverse events because of serious imprecision and serious risk of bias.

Values and preferences

Applying the agreed-upon values and preferences (see 3.2.3), for patients with severe disease, the GDG inferred that most patients suffering severe arboviral disease, given the lack of benefit and considering possible harms, would not choose to receive platelet transfusion.

Resources and other considerations

Platelet availability may be low in many settings due to cost, the availability of donors or inadequate laboratory and storage facilities. Ensuring safety of blood products, and prevention of viral transmission from donors is also a concern in resource-limited settings.

Blood products may not be acceptable to all patients, for example, patients with religious objections to receiving them.

The recommendation applies to pregnant and breastfeeding women and to children.

5.5.2 Justification

The conditional recommendation against the administration of platelets in patients with thrombocytopenia and with no active bleeding rests on the lack of demonstrated benefit and consequent irrational use of scarce resources. In addition, the use of platelets introduces risk of transfusion-transmitted infections and further risk of fluid overload.

The use of platelets in the absence of bleeding may be appropriate in specific circumstances, for example preceding a surgical procedure with anticipated blood loss. A threshold of 10 000 platelets per microlitre was discussed for prophylactic platelet transfusion based on earlier WHO recommendations *(33)*

The GDG intended this recommendation to apply to dengue, chikungunya, Zika and yellow fever.

5.5.3 Practical info

Dengue infections are frequently accompanied by thrombocytopenia from day 3 and day 8 following onset of illness. The mechanism is multifactorial but remains incompletely understood.

For conditions other than dengue, platelet transfusions are usually administered to treat or prevent bleeding in patients with thrombocytopenia or platelet dysfunction, depending on the patient's clinical condition and accompanying platelet concentration thresholds. However, considerations are different in dengue accounting for the pathophysiology of the

disease, the expected spontaneous resolution of thrombocytopenia and the low likelihood of thrombocytopenia-induced haemorrhage in most patients with dengue.

In patients who do have bleeding, additional work-up is required, including other markers of coagulation dysfunction (for example, prothrombin time, activated partial thromboplastin time and fibrinogen level).

Table 5-11. Summary of findings for platelet transfusion compared to no platelet transfusion in patients with confirmed or suspected dengue fever and thrombocytopenia.

Clinical question/ PICO

- Population: patients with suspected or confirmed dengue fever and thrombocytopenia
- Intervention: platelet transfusion
- Comparator: no platelet transfusion

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		No platelet transfusion	platelet transfusion		
Length of hospital stay	Measured by: Days (mean) Scale: - Lower better Based on data from 372 participants in 1 study Follow up 21 days	5 days	4 days Difference: MD 1 fewer (CI 95% 1.32 fewer – 0.7 fewer)	Low Due to serious risk of bias, Due to serious imprecision[1]	Platelet transfusion may decrease length of hospital stay.
Mortality	Relative risk: 2.89 (CI 95% 0.27 – 31.4) Based on data from 460 participants in 2 studies Follow up 10.5	20 per 1000	31 per 1000 Difference: 11 more per 1000 (CI 95% 13 fewer – 34 more)	Very low Due to extremely serious imprecision[2]	We are uncertain whether platelet transfusion increases or decreases mortality.
Severe bleeding (RCT) **(Mostly melaena and haemoptysis)**	Relative risk: 0.7 (CI 95% 0.23 – 4.02) Based on data from 460 participants in 2 studies Follow up 21 days	25 per 1000	18 per 1000 Difference: 7 fewer per 1000 (CI 95% 22 fewer - 75 more)	Very Low Due to serious risk of bias, due to very serious imprecision[3]	We are uncertain whether platelet transfusion increases or decreases severe bleeding.
Clinical bleeding (RCT) **(Excluding petechiae, mostly gingival)**	Relative risk: 0.83 (CI 95% 0.57 – 1.19) Based on data from 460 participants in 2 studies Follow-up 21 days	137 per 1000	114 per 1000 Difference: 23 fewer per 1000 (CI 95% 59 fewer – 26 more)	Very Low Due to serious risk of bias, due to very serious imprecision[4]	We are uncertain whether platelet transfusion increases or decreases clinical bleeding.
Clinical bleeding (non-RCT) **(Any bleeding excluding the presence of petechiae)**	Relative risk: 1.01 (CI 95% 0.94 – 1.07) Based on data from 788 participants in 1 study	182 per 1000	184 per 1000 Difference: 2 more per 1000 (CI 95% 11 fewer – 13 more)	Low Non-RCT without additional limitations	Platelet transfusion may have little or no impact on clinical bleeding (non-RCT).
Organ failure	Relative risk: 0.97 (CI 95% 0.146.84)	50 per 1000	49 per 1000	Very low	We are uncertain whether platelet

	Based on data from 372 participants in 1 study Follow up 21 days	Difference: 1 fewer per 1000 (CI 95% 21 fewer – 21 more)		Due to serious risk of bias, Due to very serious imprecision[5]	transfusion increases or decreases organ failure.
Severe adverse events	Relative risk: 4.63 (CI 95% 0.78 – 27.4) Based on data from 460 participants in 2 studies Follow up 10.5 days	8 per 1000 Difference: 15 more per 1000 (CI 95% 2 fewer – 32 more)	23 per 1000	Very low Due to serious risk of bias, Due to very serious imprecision[6]	We are uncertain whether platelet transfusion increases severe adverse events.

1. ***Risk of bias: serious:*** *inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;* ***imprecision: serious:*** *95% CI including unimportant effect.*
2. ***Imprecision: extremely serious:*** *2 events overall*
3. ***Risk of bias: serious.*** *Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;* ***imprecision: very serious:*** *95% CI including harms; 11 events*
4. ***Risk of bias: serious:*** *inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;* ***imprecision: very serious:*** *95% CI including harms, 89 events*
5. ***Risk of bias: serious:*** *Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;* ***imprecision: very serious:*** *95% CI including important benefits and harms*
6. ***Risk of bias: serious.*** *inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;* ***imprecision: very serious:*** *95% CI including absence and important harms; 8 events*

5.6 Specific management of yellow fever

Most individuals with yellow fever are asymptomatic or have mild disease which can be mistaken for other nonspecific febrile illness. In a minority of patients, after a period of remission, illness reappears in a more severe form, with high fever, vomiting, prostration, and dehydration.

Hepatic-induced coagulopathy produces severe haemorrhagic manifestations, including petechiae, ecchymoses, epistaxis and hematemesis. Yellow fever is distinguished from other viral haemorrhagic fevers by the characteristic severity of liver damage and the appearance of jaundice. Acute kidney injury frequently leads to extreme albuminuria. Late central nervous system manifestations such as confusion, seizure and coma are often associated with death.

5.6.1 N-acetylcysteine

Conditional recommendation for
WHO suggests the use of intravenous N-acetylcysteine in the treatment of patients with liver failure due to probable or confirmed yellow fever. [*Conditional recommendation, very low certainty evidence*] • This recommendation applies when the use of N-acetylcysteine is in adequate supply within the health system and does not compromise its availability to patients who have therapeutic need for it and where there is greater certainty of efficacy (e.g. paracetamol overdose).

5.6.1.1 Evidence to decision

Benefits and harms

Benefits*:* It is unclear whether N-acetylcysteine treatment might improve the prognosis for patients with liver failure secondary to yellow fever virus infection. It is uncertain whether N-acetylcysteine treatment decreases mortality, reduces the use of mechanical ventilation, decreases the chance of liver transplant, and reduces severe bleeding or length of hospital stay.

Harms: It is uncertain if N-acetylcysteine effects the occurrence of severe adverse events based on one study of 184 patients with 11 more adverse events (95% CI 28 fewer to 151 more) at 365 days following treatment. Retrospective studies (in patients with liver failure) reported that anaphylactoid reactions led to treatment interruption in a very small percentage of patients (2%). Harms of anaphylactoid reactions were noted and felt to be relatively unimportant considering the stated expected values and preferences for patients with severe disease.

Certainty of the evidence

The evidence summary on use of N-acetylcysteine for patients with liver failure secondary to yellow fever was informed by five randomized and non-randomized studies on patients with liver failure secondary to infectious diseases other than yellow fever and on patients with liver failure secondary to non-infectious diseases.

Certainty of evidence was rated low for severe adverse events and very low for all other outcomes based primarily on very serious imprecision. Indirect evidence was available for studies on outcomes of severe bleeding, length of hospital stay and mechanical ventilation.

Values and preferences

Applying the agreed upon values and preferences (see 3.2.3), for patients with severe disease, the GDG inferred that most, given the possible benefit and minimal harms, would choose to use intravenous N-acetylcysteine for liver failure due to yellow fever.

Resources and other considerations

N-acetylcysteine is a highly effective antidote to treat paracetamol (acetaminophen) overdose. The GDG were cognizant of the risk of shortage of this extremely valuable countermeasure in case of widespread use. Given the uncertainty of its benefit in patients with liver failure secondary to yellow fever, it was noted that the use of N-acetylcysteine requires an adequate supply within the health system, and that its use in this context should not compromise the availability to other patients. N-acetylcysteine is on the WHO's List of Essential Medicines *(47)* and is available as an inexpensive generic drug.

5.6.1.2 *Justification*

The GDG specified that the target population for this recommendation is adult patients with severe yellow fever. There were no RCTs on the use of N-acetylcysteine for treatment of liver failure in this population.

Indirect evidence from patients with other infectious disease-induced liver failure provided low certainty evidence for mortality, severe bleeding and length of hospital stay. In general, the WHO does not make strong recommendations when evidence of critical outcomes is only low certainty. In this situation, the GDG felt that the potential benefits in a disease with particularly poor prognosis outweighed the minimal harms and costs. The panel encouraged evaluation of N-acetylcysteine in yellow fever as a research priority.

5.6.1.3 *Practical info*

Mechanism of action

N-acetylcysteine is frequently used to prevent free – radical-related hepatotoxicity resulting from paracetamol overdose. Molecular mechanisms may include direct oxidant scavenging,

glutathione replenishment, reduction of disulfides and increased H_2S and sulfane sulfur species inside cells*(84)*.

Adverse event profile

The most commonly reported adverse effects of intravenous acetylcysteine are anaphylactoid reactions, including rash, pruritus, angioedema, bronchospasm, tachycardia, and hypotension. Within a trial of loading doses in the treatment of paracetamol overdose, these have been seen to occur in approximately 15% (of total n=180), although discontinuation due to adverse reaction occurred in 2%*(85)*. Retrospective study has found adverse event rates of 5% (4/76 participants).

Route, dosage, and duration

This recommendation concerns N-acetylcysteine as an intravenous medication (200 mg/mL, in a 10 mL ampoule) *(47)*.

Different dosage and administration schedules have been adopted for various conditions. However, the panel endorsed the use according to established protocols for acute acetaminophen ingestion, as follows:

Table 5-12. N-acetylcysteine dosing

Body weight	Loading dose	Second dose	Third dose
5 kg to 20 kg	150 mg/kg in 3 ml/kg of diluent infused over 1 hour	50 mg/kg in 7 ml/kg of diluent infused over 4 hours	100 mg/kg in 14 ml/kg of diluent infused over 16 hours
21 to 40 kg	150 mg/kg in 100 ml of diluent infused over 1 hour	50 mg/kg in 250 ml of diluent infused over 4 hours	100 mg/kg in 500 ml of diluent infused over 16 hours
41 kg or greater	150 mg/kg in 200 ml of diluent1 infused over 1 hour	50 mg/kg in 500 ml of diluent infused over 4 hours	100 mg/kg in 1000 ml of diluent infused over 16 hours

Dilute N-acetylcysteine in one of the following three solutions: sterile water for injection, 0.45% w/v sodium chloride or 5% w/v dextrose.

For detailed weight-based dosage and dilution instructions, please refer to the summary of product information *(86)* and the indication for N-acetylcysteine in cases of non-acetaminophen-induced liver failure *(87)*.

Dose adjustment

Renal impairment: No data are available to determine if dose adjustment in moderate or severe renal impairment is required.

Hepatic impairment: Although there was a threefold increase in acetylcysteine plasma concentrations in patients with hepatic cirrhosis, no data are available to determine if a dose adjustment in these patients is required.

Other considerations

Children: The mean elimination ($t_{1/2}$) of acetylcysteine is longer in newborns (11 hours) than in adults (5.6 hours). Pharmacokinetic information is not available in other age groups.

Pregnancy: In four pregnant women with paracetamol (acetaminophen) toxicity, oral or IV acetylcysteine was administered at the time of delivery. Acetylcysteine was detected in the cord blood of three viable infants and in cardiac blood of a fourth infant, sampled at autopsy.

Breastfeeding: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when acetylcysteine is administered to a nursing woman.

Table 5-13. Summary of findings for N-acetylcysteine compared to standard of care in patients with acute liver failure caused by infectious diseases

Clinical question/ PICO

- Population: patients with acute liver failure caused by infectious diseases
- Intervention: n-acetylcysteine
- Comparator: standard of care

Outcome timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		SOC	N- acetyl-cysteine		
Mortality	Relative risk: 0.62 (CI 95% 0.35 – 1.09) Based on data from 81 participants in 2 studies Follow-up 15 days	488 per 1000	303 per 1000	Very low Due to extremely serious imprecision[3]	We are uncertain whether N-acetylcysteine improves or worsen mortality.
		Difference: 185 fewer per 1000 (CI 95% 317 fewer –44 more)			
Mechanical ventilation	Relative risk: 0.8 (CI 95% 0.23 – 2.76) Based on data from 80 participants in 1 study Follow-up 9 days	125 per 1000	100 per 1000	Very low Due to serious risk of bias, due to serious indirectness, due to very serious imprecision[4]	We are uncertain whether N-acetylcysteine improves or worsen mechanical ventilation.
		Difference: 25 fewer per 1000 (CI 95% 160 fewer –110 more)			
Liver transplant	Relative risk: 0.48 (CI 95% 0.26 – 0.89) Based on data from 37 participants in 1 study Follow-up 21 days	750 per 1000	360 per 1000	Very Low Due to extremely serious imprecision[7]	We are uncertain whether N-acetylcysteine improves or worsen liver transplant.
		Difference: 390 fewer per 1000 (CI 95% 555 fewer – 82 fewer)			

Severe adverse events	Relative risk: 1.25 (CI 95% 0.35 – 4.51) Based on data from 184 participants in 1 study Follow-up 365 days	43 per 1000	54 per 1000 Difference: 11 more per 1000 (CI 95% 28 fewer – 151 more)	Low Due to very serious imprecision[11]	N- acetylcysteine may have little or no impact on severe adverse events.
Severe bleeding	Relative risk: 0.67 (CI 95% 0.2 – 2.18) Based on data from 80 participants in 1 study Follow-up 9 days	150 per 1000	101 per 1000 Difference: 49 fewer per 1000 (CI 95% 120 fewer – 177 more)	Very low Due to serious risk of bias, due to serious indirectness, due to very serious imprecision[12]	We are uncertain whether n-acetylcysteine increases or decreases severe bleeding
Length of hospital stay	Measured by: Days (mean). Scale: 0 – 30, lower better Based on data from 121 participants in 2 studies Follow-up 94.5 days	15 days	12.6 days Difference: MD 2.37 fewer (CI 95% 3.48 fewer – 1.25 fewer)	Very Low Due to serious risk of bias, due to serious indirectness, due to serious imprecision[13]	N- acetylcysteine may reduce length of hospital stay

3. ***Imprecision: extremely serious.*** *95% CI include no benefits*
4. ***Risk of bias: serious*** *inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias* ***Indirectness: serious:*** *Studies included patients with infectious and non-infectious hepatitis;* ***imprecision: very serious:*** *95% CI includes important benefits and harms*
7. ***Imprecision: very serious:*** *18 events overall*
11. ***Imprecision: very serious:*** *95% CI including important benefits and harms*
12. ***Risk of bias: serious:*** *inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;* ***indirectness: serious:*** *studies included patients with infectious and non-infectious hepatitis;* ***imprecision: very serious:*** *95% CI including important benefits and harms*
13. ***Risk of bias: serious:*** *Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;* ***indirectness: serious:*** *Studies included patients with infectious and non-infectious hepatitis;* ***imprecision: serious.*** *121 patients overall.*

5.6.2 Intravenous monoclonal immunoglobulin TY014 for yellow fever

Only in research settings
WHO recommends the use of monoclonal immunoglobulin TY014 for the treatment of patients with suspected or confirmed yellow fever only in research settings. [*Use only in research, very low certainty evidence*] • Given the challenge of a randomized controlled trial in rare diseases, clinical trials could be conducted during outbreaks through pre-positioned trial protocols and under the monitored emergency use of unregistered and investigational interventions (MEURI) framework *(88)*.

5.6.2.1 *Evidence to decision*

Benefits and harms

In patients with yellow fever disease, it is unknown whether monoclonal immunoglobulin TY014 may improve prognosis. The use of monoclonal immunoglobulin TY014 has not been assessed in humans infected with yellow fever virus.

Benefit: Experimental human challenge (phase I) of healthy subjects demonstrated no viraemia in 8 individuals given the TY014 and the yellow fever vaccine, but detectable virus in 2 individuals receiving placebo.

Harm: From 37 participants, RR 1.02 (95% CI 0.71-1.46), 16 more events per 1000 would be expected in those treated with TY014 (95% CI 232 fewer to 368 more).

Certainty of the evidence

There were no published data from studies on the use of monoclonal immunoglobulin TY014 in humans infected with yellow fever virus. Evidence on critical outcomes in patients with yellow fever disease is absent.

Evidence of viral clearance in experimental human challenge data was very low certainty due to serious indirectness and imprecision.

Evidence of adverse events was low certainty due to serious risk of bias and very serious imprecision.

Values and preferences

The GDG inferred that almost all informed patients would choose not to have TY014 as a treatment except in the context of a clinical trial.

Resources and other considerations

There is lack of availability of monoclonal immunoglobulin TY014 in most settings, particularly low resource settings. Monoclonal immunoglobulin TY014 is an unlicensed, unregistered medication.

5.6.2.2 *Justification*

Given the absence of specific treatment options for yellow fever, the high mortality in patients progressing to the toxic phase and developing severe disease, there is a need for improved understanding of potential therapeutics such as monoclonal immunoglobulin TY014 to improve patient outcomes. Given that monoclonal immunoglobulin TY014 is an unregistered drug without regulatory approval for treating yellow fever, the panel recommended for research settings only. Clinical trials will help inform the impact of critical outcomes as well as the timing of administration during disease progression. Because yellow fever is a rare disease, the optimal period for a trial would be during outbreaks, especially those occurring in urban areas. Pre-established protocols, and appropriate ethical and regulatory clearance will be required.

Currently, there is no licensed antiviral therapy for yellow fever virus. Therefore, managing severe cases, particularly in at-risk groups, relies on supportive care. This highlights an unmet need for both therapeutic and prophylactic measures to effectively manage yellow fever *(89)*.

5.6.2.3 *Practical Information*

Mechanism of action

TY014 is a fully engineered human IgG1 monoclonal antibody designed to combat the yellow fever virus. It is produced using Chinese hamster ovary cells. TY014 targets the envelope (E) protein on the virus's surface, preventing the virus from entering and replicating within host cells. Non-clinical *in vitro* and *in vivo* studies have demonstrated the safety profile and efficacy in inhibiting yellow fever virus infection. TY014 is currently being explored as a post-infection therapy for yellow fever *(89)*.

Table 5-14. Summary of findings for yellow fever-specific monoclonal antibody TY014 compared with placebo in patients with yellow fever

Clinical question/ PICO

- Population: patients with yellow fever
- Intervention: yellow fever-specific monoclonal antibody (TY014)
- Comparator: placebo

Outcome timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Placebo	Yellow fever-specific monoclonal antibody (TY014)		
Adverse events (any)	Relative risk: 1.02 (CI 95% 0.71 – 1.46) Based on data from 37 participants in 1 study Follow-up 84 days	800 per 1000	816 per 1000 Difference: 16 more per 1000 (CI 95% 232 fewer– 368 more)	Very low Due to serious risk of bias, due to very serious imprecision[1]	We are uncertain whether yellow fever-specific monoclonal antibody (TY014) increases or decreases adverse events (any).
Viral clearance	Based on data from 10 participants in 1 study Follow-up 15 days	Viraemia was observed in none of the participants who received TY014 and in 2 of the participants who received placebo at 48 hours after the infusion (72 hours after the live-attenuated yellow fever vaccine [YF17D] challenge)		Very low Due to serious indirectness, due to serious risk of bias, due to very serious imprecision[2]	We are uncertain whether yellow fever-specific monoclonal antibody (TY014) increases or decreases viral clearance.

1. ***Risk of bias: serious:*** *inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias* ***Imprecision: very serious:*** *95% CI including important benefits and harms*
2. ***Risk of bias: serious:*** *inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias* ***indirectness: serious:*** *experimental inoculation of yellow fever vaccine virus and monoclonal antibody administration 24 hours later;* ***imprecision: very serious.*** *10 patients.*

5.6.3 Sofosbuvir

Only in research settings
WHO recommends the use of sofosbuvir in the treatment of patients with suspected or confirmed yellow fever only in research settings. [*Use only in research, very low certainty evidence*] • Given the challenge of a randomized controlled trial in rare diseases, clinical trials could be conducted during outbreaks through pre-positioned trial protocols and under the monitored emergency use of unregistered and investigational interventions (MEURI) framework.

5.6.3.1 *Evidence to decision*

Benefits and harms

In patients with yellow fever disease, it is unknown whether sofosbuvir may improve prognosis.

There are no data on adverse effects of sofosbuvir in patients with yellow fever.

Certainty of the evidence

The evidence summary was informed by one single-arm intervention study of patients with yellow fever. There was no information on important clinical outcomes. Certainty of evidence was rated very low for viral clearance due to serious risk of bias and imprecision.

Values and preferences

The GDG inferred that almost all informed patients would choose not to have sofosbuvir as a treatment except in the context of a clinical trial.

Resources and other considerations

Sofosbuvir is available in some areas where it has been developed and tested for viral hepatitis C. It is not licensed for use in yellow fever.

5.6.3.2 *Justification*

There are no published data from randomized control trials on the use of sofosbuvir in patients with yellow fever *(90)*.

Given the absence of specific treatment options for yellow fever, the high mortality in patients progressing to the toxic phase and developing severe disease, there is a need for improved understanding of potential antivirals to improve patient outcomes. Given that sofosbuvir is an antiviral used to treat hepatitis C (also in the *Flavivirus* family) it may improve outcomes of

patients with yellow fever. Given the lack of evidence, the panel recommended for research settings only. Clinical trials will help inform the impact of critical outcomes as well as the timing of administration during disease progression. As yellow fever is a rare disease, the optimal period for a trial would be during outbreaks, especially those occurring in urban areas. Pre-established protocols, and appropriate ethical and regulatory clearance will be required.

5.6.3.3 *Practical Information*

Mechanism of action

Sofosbuvir is a pan-genotypic inhibitor of the hepatitis C virus (HCV) NS5B RNA-dependent RNA polymerase, which is essential for viral replication. It is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. GS-461203 (the active metabolite of sofosbuvir) is not an inhibitor of human DNA and RNA polymerases or an inhibitor of mitochondrial RNA polymerase *(91)*.

Rationale

No specific treatment options for yellow fever exist, and patients receive solely intensive palliative care. Therefore, antivirals with anti-flavivirus activity may represent an important alternative for drug repurposing in an attempt to improve patient outcomes*(92)*.

Table 5-15. Summary of findings for Sofosbuvir compared to standard of care in patients with yellow fever

Clinical question/ PICO

- Population: Patients with yellow fever
- Intervention: Sofosbuvir
- Comparator: Standard of care

Outcome timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		SOC	Sofosbuvir		
Viral clearance	Based on data from 67 participants in 1 study Follow-up 10 days	Statistically significant differences in viremia between treated and untreated patients that survived were observed on days 5 and 6 but not on days 4, 7, 8, 9 and 10. Statistically significant differences in viremia between treated and untreated patients that did not survive were observed on days 4, 7, 8 and 9 but not on days 5, 6 and 10.		Very low Due to serious risk of bias, due to serious imprecision[1]	We are uncertain whether sofosbuvir increases or decreases viral clearance.

1. ***Risk of bias: serious:*** *non-RCT with no adjustment for potential confounders;* ***imprecision: serious.*** *67 patients.*

6 How to access and use the guideline

WHO website in PDF format: this is a full PDF version of the MAGICapp content. It can also be downloaded directly from MAGICapp (see cogwheel on top right).

How to navigate this guideline

The guideline is disseminated and updated in MAGICapp online.

End-users will also need to understand what is meant by strong and conditional recommendations (see below) and certainty of evidence (the extent to which the estimates of effect from research represent true effects from treatment) *(38,42)*.

Additional educational modules and implementation tools for health workers

- Global vector control response 2017 – 2030
- Eliminate yellow fever epidemics (EYE) strategy 2017-2026
- Global Arbovirus Initiative
- Laboratory testing for Zika virus and dengue virus infections: interim guidance
- Guidelines on the Clinical Management of Sepsis
- Guidelines for the Clinical Diagnosis and Treatment of Dengue, Chikungunya, and Zika - PAHO/WHO | Pan American Health Organization
- Integrated Management Strategy for Arboviral Disease Prevention and Control in the Americas
- Establishing syndromic surveillance and event-based surveillance systems for zika, dengue and other arboviral diseases
- Comprehensive Guideline for Prevention and Control of Dengue and Dengue Haemorrhagic Fever. Revised and expanded edition
- Zika virus and emerging mosquito-borne diseases: the European emergency risk communication challenge: a response guide
- Yellow Fever: Vaccine Preventable Diseases Surveillance Standards
- Dengue clinical management : facilitator's training manual
- Tool for the diagnosis and care of patients with suspected arboviral diseases
- WHO guidelines for the prevention of sexual transmission of Zika virus
- Case definitions, clinical classification, and disease phases Dengue, Chikungunya, and Zika - PAHO/WHO | Pan American Health Organization

7 Guideline-relevant research needs and limitations

The GDG identified the following questions as priorities for research to improve the care of patients with arbovirus infection:

1. Disease progression and classification:

- What are the clinical features, laboratory tests and biomarkers that can accurately identify patients at high risk of progressing from non-severe to severe disease (e.g. dengue and other arboviruses) and which can lead to clinically actionable interventions?
- What are the clinical features that allow accurate identification of patients at high risk of poor outcomes, especially those with severe disease (e.g., dengue and other arboviruses)?
- Develop tools to predict the progression from non-severe to severe disease (beyond commonly observed warning signs, which may occur with high prevalence and overwhelm health systems).
- Investigating discriminant clinical and biological markers between diseases, potentially incorporating the kinetics and durations of associated features, could enhance the development of predictive scores and improve diagnostic accuracy

2. Disease management:

- Compare the efficacy of crystalloid versus colloid solutions in managing severe arboviral diseases.
- Investigate subgroups of patients in whom colloids may be clinically advantageous.
- Compare the efficacy of different fluid resuscitation protocols to determine the most effective approach for patient outcomes.
- How should multiple measures of fluid resuscitation such as capillary refill and lactate levels, be incorporated into patient management?
- Evaluate the efficacy of corticosteroids for the treatment of severe disease, especially in dengue, to determine their impact on patient outcomes.
- Evaluate of corticosteroids for treatment and fluid management for neonates with shock.

3. Arbovirus-specific research:

    - *Dengue:*
        - Identify disease phenotypes which have utility in guiding patient management
        - Understand the phases of volume resuscitation in dengue and dengue shock syndrome

    - Explore the role haematocrit in modifying patient management strategies.
- *Chikungunya:*
    - Evaluate the use of NSAIDs and control of pain in the post-acute phases of disease
    - Assess optimal strategies for using disease-modifying antirheumatic drugs (DMARDs) in the chronic stage.
    - Assess the potential benefits of immunoglobulins in neonates, including the evaluation of specific IgG versus non-specific IgG.
    - Investigate the effectiveness of immunoglobulins in preventing vertical transmission.
    - Investigate shock mechanisms in chikungunya and its management.
- *Zika:*
    - Evaluate the role of antipruritic medications.
    - Evaluate the role of corticosteroids and immunoglobulins in Zika-associated neurological disease (encephalitis, Guillain-Barré syndrome).
    - Investigate the potential use of medical countermeasures during pregnancy to mitigate the risk of congenital diseases, with a specific focus on the efficacy and safety of monoclonal antibodies.
- *Yellow fever:*
    - Accelerate evidence generation by having pre-established research protocols for evaluating potential therapeutics.
    - Research monoclonal antibody treatment.
    - Assess the efficacy of N-acetylcysteine in yellow fever.
    - Evaluate the effect of plasmapheresis on severe yellow fever.
    - Evaluate the effect of sofosbuvir on severe yellow fever.

4. Inclusive evidence generation:

- Ensure that evidence generation includes all patient populations, including those frequently excluded from trials (children, immunocompromised, pregnant women).

8 Publication, dissemination, monitoring and evaluation

Guidelines will be disseminated through WHO 3-level structures, and to partner organizations as both electronic document and online resources.

The impact of the guidelines will at high level be monitored through international data on clinical outcomes of arboviral diseases. Member states and guideline users will be encouraged to report where guidelines have been systematically deployed. In subsequent country and regional implementation projects, WHO arbovirus teams will ascertain specifically which guidelines are in use.

Facilities and end-users are encouraged to perform clinical audit of the use of the guideline recommendations amongst their patients. Within this guideline, no specific targets are set so that the independence of localisation and national strategies are not compromised; local targets should be set before audit.

Several implementation tools are being developed to help end-users, specifically clinicians, to make decisions and support quality-improvement in arbovirus care.

There is no planned obsolescence date for the guideline, but the WHO arbovirus team will monitor the evolving research landscape for large-impact clinical studies which would precipitate a guideline review. We will use our internal steering group, GDG and broader networks to consult on such changes.

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Annex 1. Declarations of Interest

The technical unit collected and managed written statements of declarations of interest (DOI). All DOI forms were reviewed by the WHO Secretariat. Consultation with WHO Quality Norms and Standards team and Ethics teams were obtained, when necessary. Conflicts of interest were declared by three panel members related to institutional research funding but were not deemed grounds for panel ineligibility. At the start of each meeting, the WHO Secretariat described the DOI process and GDG members were asked to verbally update any other DOI; no verbal conflicts were declared. Web searches did not identify any additional interests that would likely affect members' independence.

A declarations of interest noted by the GDG members and methodologist are shown in the table below.

Member (First name)	Role	DOI	Description
Ashutosh Biswas	GDG	No	
Orlando Cuellar	GDG	No	
Ismael Diallo	GDG	No	
Christina Domingo Carrasco	GDG	No	
Gordon Guyatt	Methodologist	No	
Pillaveetil Indu	GDG	No	
Ariel Izcovich	Sys rev	No	
Emilie Javelle	GDG	No	
Mikaela Kabore	GDG	No	
Marta Lado	GDG	No	
Lucy Lum	GDG	Yes	Sysmex Asia Pacific; $35,000; 2021
Pisake Lumbiganon	GDG	No	
Kleber Luz	GDG	No	
Tajeldin Mohameddein Abdallah	GDG	No	
Carlos Pardo	GDG	Yes	Research funding from United States National Institutes of Health
Mostafa Salehi-Vaziri	GDG	No	
J Erin Staples	GDG	Yes	Employed by United States CDC
Maria Esterlita Uy	GDG	No	
Michal Van Herp	GDG	No	
Liya Wassie	GDG	Yes	Institutional AFI research funding from ITM Belgium; 40,000 Euros; work institution paid for travel insurance
Leo Yee Sin	GDG	No	

Annex 2. Arbovirus baseline risk estimates survey

A short survey to determine which baseline absolute rates of clinical outcomes should be used when considering evidence for the WHO Clinical management of arbovirus guidelines.

Many thanks in advance for taking the time to complete this short survey. It is of critical importance that the GDG respond, because it will determine how information on the effect of interventions is presented to them. That information will be used during deliberations to create the guideline recommendations.

The aim

- To produce a guideline which is cohesive, and which clinicians and patients can use to understand the benefits and harms they might receive.

The issues

1. Research study participants are often different than the wider patient population. They are always selected, and so differences might be expected in, for example, the severity of their disease and their outcomes (amongst other things).
2. Research studies looking at one aspect of disease treatment may not include patients with exactly the same risk/severity as studies which look at another aspect.

The solution

- We use the treatment effect found in the research studies as our starting place.
- We select a "baseline absolute risk" for each outcome which is the same throughout the guideline. This is the risk associated with standard care, or placebo. It is how frequently we expect to see this outcome in "normal" (or non-study) patients. We usually give this as a number per 1000 patients.
- We apply the treatment effect from the studies to this baseline absolute risk, which shows how frequently we expect to see that outcome in treated patients. This gives us an estimate of the actual difference a treatment will make (per 1000 patients, for example).

One more small problem!

- We don't have baseline estimates of absolute rates of the outcomes in "normal" patients. Of course, there will be some variability. We have looked for data from observational and randomised studies, and so we can describe the range which has been seen.

This survey asks you to make a decision about what baseline rates we should use.

How does this survey work?

- We will present you every outcome in turn.
- For each outcome, we will give you 5 different values of potential baseline rates. They will span the lowest and highest rates from existing studies.
- We ask you to think "what is the rate I would expect in real patient populations". We will give you information about *where* the patients are being seen. For example, those presenting to primary care clinics, and those admitted to hospital will be different. The same is true for disease. For example, dengue patients have different outcomes from zika patients.
- You should select one value which represents the rate you think is most relevant for that population.

If you need any more information, please email glai@who.int.

There are 6 questions in this survey.

Dengue

For patients with dengue, presenting to primary care facilities (or out-patient departments), what is a reasonable estimate of the mortality?

Please choose **only one** of the following:

- 0.25 per 1000 (0.025%)
- 1 per 1000 (0.1%)
- 5 per 1000 (0.5%)
- 10 per 1000 (1%)
- 25 per 1000 (2.5%)
- From my experience, I am unable to estimate

Range informed by WHO reporting of cases and mortality, and observational studies of low risk patients.

For patients with dengue already admitted to hospital, what is a reasonable estimate of the mortality?

Please choose **only one** of the following:

- 5 per 1000 (0.6%)
- 20 per 1000 (2%)
- 50 per 1000 (5%)
- 100 per 1000 (10%)
- 180 per 1000 (18%)
- From my experience, I am unable to estimate

Range informed by observational studies of high risk patients.

For patients with dengue, already admitted to hospital, what is a reasonable estimate of the organ failure?

Please choose **only one** of the following:

- 10 per 1000 (1%)
- 30 per 1000 (3%)
- 60 per 1000 (6%)
- 100 per 1000 (10%)
- 150 per 1000 (15%)
- From my experience, I am unable to estimate

Range informed by observational studies of high risk patients.

Organ failure is a life-threatening reduction in function of any of [brain, cardiovascular system, coagulation, heart, liver, lung, kidney] which requires specific medical support to replace that function or mitigate the risk associated with dysfunction

For patients with dengue, already admitted to hospital, what is a reasonable estimate of the severe (major) bleeding?

Please choose **only one** of the following:

- 10 per 1000 (1%)
- 25 per 1000 (2.5%)
- 50 per 1000 (5%)
- 100 per 1000 (10%)
- 200 per 1000 (20%)
- From my experience, I am unable to estimate

Range informed by observational studies of high risk patients.

"major bleeding" is one or more of:

- a fall in hemoglobin level of 2 g/dL
- need for transfusion of at least 2 units of packed red blood cells
- involvement of a critical anatomical site (intracranial, spinal, ocular, pericardial, articular, intramuscular with compartment syndrome, retroperitoneal)."

For patients with dengue presenting to primary healthcare facilities (or outpatient departments), what is a reasonable estimate of the severe (major) bleeding?

Please choose **only one** of the following:

- 1 per 1000 (0.1%)
- 5 per 1000 (0.5%)
- 15 per 1000 (1.5%)
- 30 per 1000 (3%)
- 60 per 1000 (6%)

- From my experience, I am unable to estimate

Range informed by observational studies of low risk patients.

"major bleeding" is one or more of:

- a fall in hemoglobin level of 2 g/dL
- need for transfusion of at least 2 units of packed red blood cells
- involvement of a critical anatomical site (intracranial, spinal, ocular, pericardial, articular, intramuscular with compartment syndrome, retroperitoneal)."

For patients with dengue, presenting to primary care facilities (or out-patient departments), what is a reasonable estimate of hosptial admission?

Please choose **only one** of the following:

- 5 per 1000 (0.5%)
- 20 per 1000 (2%)
- 50 per 1000 (5%)
- 100 per 1000 (10%)
- 200 per 1000 (20%)
- From my experience, I am unable to estimate

Range informed by observational studies of low risk patients.

You have completed the survey.

Many thanks for taking the time to help us.

Annex 3. Protocol for the systematic review to inform a clinical practice guideline on the management of arboviral diseases

Title: Systematic Review and Meta-analysis of Interventions for the Management of Arboviral Diseases: Informing Clinical Practice Guidelines for Dengue, Zika, Chikungunya, and Yellow Fever

1. Introduction

1.1 Background and Rationale:

Arboviral diseases, including Dengue, Zika, Chikungunya, and Yellow Fever, continue to present significant challenges in terms of morbidity, mortality, and economic burden. The objective of this systematic review is to comprehensively evaluate and synthesize the existing evidence on interventions for the management of arboviral diseases, providing a foundation for the development of evidence-based clinical practice guidelines.

1.2 Objectives:

- To identify and evaluate the effectiveness of medical interventions for the management of Dengue, Zika, Chikungunya, and Yellow Fever.
- To assess the safety and adverse effects associated with these interventions.
- To determine the impact of interventions on clinical outcomes, including symptom resolution, disease progression, and mortality.
- To provide a robust evidence base for the development of clinical practice guidelines.

2. Methods

2.1 Eligibility Criteria:

The populations, interventions, comparators, and outcomes of interest will be selected by de guideline development group (GDG).

The question development process will include:

- Identification of populations, interventions, comparators, and outcomes of interest
- Identification of subgroups of interest (effect modification and different baseline risks)
- Outcome prioritization and definition of outcome relevance (i.e. utilities)

For questions on the health effects of interventions we will search for randomized controlled studies (RCT) (primary search described below). In cases in we don’t find RCT or the overall certainty of the evidence results very low we will consider conducting additional searches to

identify high quality non-RCT.[1] For questions about other aspects of the evidence to decision process, not related to health effects of interventions (e.g. resource utilization) we will search for systematic reviews.

2.2 Search Strategy:

A comprehensive systematic search will be conducted in electronic databases (Medline, Embase, Cochrane Library and LILACS) from inception to [insert end date].

Table 1. Search strategy for MEDLINE though Pubmed

1	"dengue"[MeSH Terms] OR "dengue"[All Fields] OR "dengue s"[All Fields] OR ("zika virus"[MeSH Terms] OR ("zika"[All Fields] AND "virus"[All Fields]) OR "zika virus"[All Fields] OR "zika"[All Fields] OR "zika virus infection"[MeSH Terms] OR ("zika"[All Fields] AND "virus"[All Fields] AND "infection"[All Fields]) OR "zika virus infection"[All Fields]) OR ("chikungunya fever"[MeSH Terms] OR ("chikungunya"[All Fields] AND "fever"[All Fields]) OR "chikungunya fever"[All Fields] OR "chikungunya"[All Fields]) OR "Yellow fever"[All Fields] OR "Yellow fever"[All Fields]
2	"randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "randomly"[Title/Abstract] OR "trial"[Title/Abstract] OR "groups"[Title/Abstract]
3	"animals"[MeSH Terms] NOT "humans"[MeSH Terms]
4	#2 NOT #3
5	"metaanalys*"[Title] OR ("meta"[Title] AND "analys*"[Title]) OR ("systematic"[Title] AND "review*"[Title])
6	#1 AND (#4 OR #5)

Table 2. Search strategy for Embase

1	'dengue'/exp OR dengue OR 'yellow fever'/exp OR 'yellow fever' OR zika OR 'chikungunya'/exp OR chikungunya
2	'randomized controlled trial'/de
3	'controlled clinical trial'/de
4	random*:ti,ab,tt
5	'randomization'/de
6	'intermethod comparison'/de
7	placebo:ti,ab,tt
8	compare:ti,tt OR compared:ti,tt OR comparison:ti,tt
9	(evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab)
10	(open NEXT/1 label):ti,ab,tt
11	((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt
12	'double blind procedure'/de
13	(parallel NEXT/1 group*):ti,ab,tt
14	crossover:ti,ab,tt OR 'cross over':ti,ab,tt
15	((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt
16	assigned:ti,ab,tt OR allocated:ti,ab,tt
17	(controlled NEAR/8 (study OR design OR trial)):ti,ab,tt

18	volunteer:ti,ab,tt OR volunteers:ti,ab,tt
19	'human experiment'/de
20	trial:ti,tt
21	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
22	((random* NEXT/1 sampl* NEAR/8 ('cross section*' OR questionnaire* OR survey OR surveys OR database OR databases)):ti,ab,tt) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'randomly assigned':ti,ab,tt)
23	'cross-sectional study' NOT ('randomized controlled trial'/de OR 'controlled clinical study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'control group':ti,ab,tt OR 'control groups':ti,ab,tt)
24	'case control*':ti,ab,tt AND random*:ti,ab,tt NOT ('randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt)
25	'systematic review':ti,tt NOT (trial:ti,tt OR:ti,tt)
26	nonrandom*:ti,ab,tt NOT random*:ti,ab,tt
27	'random field*':ti,ab,tt
28	('random cluster' NEAR/4 sampl*):ti,ab,tt
29	'we searched':ab AND (review:ti,tt OR review:it)
30	'update review':ab
31	(databases NEAR/5 searched):ab
32	(rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de
33	'animal experiment'/de NOT ('human experiment'/de OR 'human'/de)
34	#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33
35	review:ab AND review:it NOT trial:ti,tt
36	#34 OR #35
37	#21 NOT #36
38	systematic AND review*:ti
39	meta AND analys*:ti
40	metaanalys*:ti
41	#38 OR #39 OR #40
42	#1 AND (#41 OR #37)

Table 3. Search strategy for Cochrane CENTRAL and LILACS

1	dengue OR 'yellow fever' OR zika OR chikungunya

2.3 Study Selection:

Two independent reviewers will screen titles and abstracts for eligibility. Full-text articles of potentially relevant studies will be assessed for inclusion. Discrepancies will be resolved through discussion and, if necessary, by a third reviewer.

2.4 Data Extraction:

A standardized data extraction form will be developed, including study characteristics, interventions, comparators, outcomes, and key findings. Two reviewers will independently extract data from included studies.

2.5 Data Synthesis:

We will conduct meta-analysis, when feasible, using frequentist random-effects models. We will perform subgroup analyses considering potential effect modifiers identified during the question development process. In addition, we will perform sensitivity analysis excluding high risk of bias studies when feasible.

We will conduct a frequentist random-effects network meta-analysis (NMA) when multiple interventions are available for a specific scenario. This approach allows for the comparison of multiple treatments simultaneously while accounting for both direct and indirect evidence. To estimate the between-study variance, we will use the restricted maximum likelihood (REML) method, which provides robust variance estimates and improves the precision of effect estimates in the presence of heterogeneity.

2.6 Certainty of the evidence Assessment:

We will assess the certainty of evidence using the grading of recommendations assessment, development and evaluation (GRADE) approach.[2] Two methodologists with experience in using GRADE will rate each domain for each comparison separately and will resolve discrepancies by consensus. We will rate the certainty for each comparison and outcome as high, moderate, low, or very low, based on considerations of risk of bias, inconsistency, indirectness, publication bias and imprecision. To assess risk of bias we will use the Cochrane 2.0 tool.[3] To assess the risk of bias resulting from missing data we will perform sensitivity analysis including missing participants and assuming more and less plausible event rates.[4] We will make judgements of imprecision using a minimally contextualised approach with the null effect as a threshold. This minimally contextualised approach considers whether the CI includes the null effect, or, when the point estimate is close to the null effect, whether the CI lies within the boundaries of small but important benefit and harm.[5] To define severe or very severe imprecision we will considered if the CI included not only the null effect, but important benefits and harms.[6] Additionally we will analyse if the total number of patients included in the meta-analysis is less than the required number of patients generated by a conventional sample size calculation for a single adequately powered trial to define if optimal information

size (OIS) is met.[7] We will created GRADE evidence summaries (Summary of Findings tables) using the MAGIC Authoring and Publication Platform (www.magicapp.org) to provide user friendly formats for clinicians and patients and to allow re-use in the context of clinical practice guidelines for COVID-19. We will calculate the absolute risks and RD from the RRs (and their CIs) and the mean risk in the control groups across all of the included trials.

To communicate our findings and conclusions using statements we followed published guidance.[8]

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