GUIDELINES FOR THE CLINICAL DIAGNOSIS AND TREATMENT OF DENGUE, CHIKUNGUNYA, AND ZIKA

PAHO
Pan American Health Organization
World Health Organization
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GUIDELINES FOR THE CLINICAL DIAGNOSIS AND TREATMENT OF DENGUE, CHIKUNGUNYA, AND ZIKA

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Guidelines for the Clinical Diagnosis and Treatment of Dengue, Chikungunya, and Zika

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Preface

This publication integrates, for the first time, the clinical diagnosis and treatment of three of the most important arboviruses in the Region of the Americas and the world: dengue, chikungunya, and Zika.

The manner in which these guidelines are presented differs markedly from the previously published clinical guidelines, since their development rigorously followed the steps of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology. These are the first GRADE guidelines for the clinical management of these three arboviruses in the Americas.

The groups of experts involved in their development combined, with great mastery, the scientific knowledge accumulated through medical practice in the Region with the results of an exhaustive systematic review that identified the principal best evidence published in the international specialized literature on these diseases.

Physicians, nursing professionals, health workers, and general scientists who consult these guidelines will find a clear, simple presentation of answers to key questions about the population, intervention, comparison, and outcome (PICO questions) related to the diagnosis and clinical management of these three diseases. The bibliographic references consulted as scientific evidence, which allowed the experts to formulate recommendations aimed at improving clinical management, are also identified.

The development of these guidelines is part of the work carried out by the Pan American Health Organization (PAHO) and the Region's countries over several years to reduce the severity of these diseases and prevent death as a first priority. It is necessary to recognize the complex epidemiological panorama in which the presence of multiple social and environmental determinants favors transmission dynamics and causes outbreaks and epidemics in the Region's countries every year, despite the tireless efforts deployed to prevent and control them.

Researching and developing the guidelines was a long and complex process supported by the World Health Organization (WHO), GRADE methodology experts and scholars, and the International Technical Group of Experts on Arboviral Diseases (International GT-Arbovirus). Thanks to these individuals, and their commitment and dedication, it was possible to answer all the questions proposed at the start of the development process and to formulate specific recommendations based on the greatest possible evidence.

We hope to provide readers with access to online guidelines that facilitate the resolution of many of the most challenging doubts and questions regarding the diagnosis and clinical management of arboviruses (dengue, chikungunya, and Zika), the main objective of this publication being to prevent severe disease and death.

Finally, it should be remembered that clinical management is only one of the components of integrated management strategies to prevent and control arboviruses. It is necessary to conduct concurrent actions on epidemiological surveillance, laboratory diagnosis, integrated vector control, environmental determinants, and health promotion and social communication, in order to achieve the greatest possible impact on prevention and control of arbovirus transmission.

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Special thanks to Drs. Raman Velayudhan of the World Health Organization and Luis Gerardo Castellanos of the Pan American Health Organization for their support throughout the guideline development process.

The review and final editing of this publication was overseen by Drs. Gamaliel Gutiérrez and José Luis San Martín, both from the Pan American Health Organization.

Summary

Rationale

Dengue, chikungunya, and Zika are arthropod-borne viral diseases (arboviruses) that pose a constant threat to public health worldwide. In the Americas, dengue fever is the most important arbovirus and one of the most frequent reasons for medical visits. Chikungunya fever and Zika fever are also present in the Americas, although the number of cases caused by both is currently much lower than those reported for dengue fever. Nevertheless, the three arboviruses (dengue, chikungunya, and Zika) can produce similar clinical manifestations, particularly in the first days of the disease. This similarity makes it challenging for the health personnel in charge of caring for the patient to establish an appropriate clinical diagnosis, which can lead to inadequate case management and cause patient death. In addition to this clinical difficulty, the cross-reactivity of the immunoglobulin M and G antibodies (IgM and IgG) of dengue and Zika viruses complicates laboratory confirmation and consequently compromises epidemiological surveillance.[1]

Faced with this situation, the Pan American Health Organization (PAHO), with the support of clinical experts from different countries and the International Technical Group of Experts on Arboviral Diseases (International GT-Arbovirus, from its acronym in Spanish), has developed and published several guidelines and instruments on the clinical diagnosis and management of dengue, chikungunya, and Zika.[2] These documents have been of great support for health personnel in charge of caring for cases of suspected arbovirus. However, it is important to mention that their development was based on expert opinion and a review of the scientific evidence.

Given the high burden of dengue, chikungunya, and Zika for health services in the countries and territories of the Americas, as well as the constant advance of available scientific information, it became necessary to develop clinical practice guidelines that covered the three arboviruses. This publication provides up-to-date, reliable scientific information and was developed based on the GRADE (Grading of Recommendations, Assessment, Development and Evaluation)[3] methodology, by answering key questions about the clinical diagnosis and treatment of dengue, chikungunya, and Zika, in order to prevent progression to severe forms of the diseases and fatal events.

Objective

These guidelines aim to provide recommendations for the diagnosis and treatment of dengue, chikungunya, and Zika in the Region of the Americas.

Methodology

These clinical practice guidelines were developed following the World Health Organization (WHO) guideline development methods.[4] A multidisciplinary group was formed for the guidelines' development, composed of thematic and methodological experts as well as users. Since no previously-developed guidelines or recommendations were identified that could be adapted, new guidelines were developed. Searches for systematic reviews and primary studies through July 2018 were carried out in various electronic databases (PubMed, EMBASE, Cochrane) and using manual searches.

Subsequently, the synthesis and evidence profiles were developed using the GRADE approach. The recommendations were adjusted by a panel of experts in arboviruses. The guidelines were evaluated by thematic and methodological peers. All panel participants and the guidelines development group signed a conflict of interest statement, which was evaluated by the guideline guidance group.

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1 Pan American Health Organization. Tool for the diagnosis and care of patients with suspected arboviral diseases. Washington, D.C.: PAHO; 2017. Available from: https://iris.paho.org/handle/10665.2/33895.

2 Pan American Health Organization. Dengue: guidelines for patient care in the Region of the Americas. 2nd edition. Washington, D.C.: PAHO; 2016. Available from: https://iris.paho.org/handle/10665.2/31207. World Health Organization. WHO handbook for guideline development, 2nd edition. Geneva: WHO; 2014. Available from: https://apps.who.int/iris/handle/10665/145714.

3 World Health Organization. WHO handbook for guideline development, 2nd edition. Geneva: WHO; 2014. Available from: https://apps.who.int/iris/handle/10665/145714.

4 See footnote 3.

Recommendations

These guidelines provide recommendations for the treatment of adult and pediatric patients. The following recommendations are for individuals with suspected or confirmed diagnosis of arbovirus infection (dengue, chikungunya, or Zika).

1	What clinical findings and basic complementary studies allow arboviruses to be differentiated from each other and from other febrile diseases?	Strength of recommendation:

Summary

The following table details the clinical and laboratory findings that are potentially useful for guiding the diagnosis of suspected arbovirus infection.

Certainty of the evidence	Manifestations of arboviruses
HIGH (findings that differentiate them)	Eruption Conjunctivitis Arthralgias (dengue or chikungunya) Myalgias or bone pain (dengue or chikungunya) Hemorrhages (includes bleeding on the skin, mucous membranes, or both) (dengue or chikungunya) Thrombocytopenia (dengue) Progressive increase in hematocrit (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

Certainty of the evidence	Manifestations of dengue	Manifestations of chikungunya	Manifestations of Zika
HIGH (findings that differentiate them)	Thrombocytopenia Progressive increase in hematocrit Leukopenia	Arthralgias	Pruritus
MODERATE (findings that probably differentiate them)	Anorexia or hyporexia Vomiting Abdominal pain Chills Hemorrhages (includes bleeding on the skin, mucous membranes, or both)	Eruption Conjunctivitis Arthritis Myalgias or bone pain	Eruption Conjunctivitis
LOW (findings that may differentiate them)	Retro-ocular pain Hepatomegaly Headache Diarrhea Dysgeusia Cough Elevated transaminases Positive tourniquet test	Hemorrhages (includes bleeding on the skin, mucous membranes, or both)	Adenopathies Pharyngitis or odynophagia

2	What clinical findings and basic complementary studies should be used to identify patients at risk of progression to severe disease (warning signs)?	Strength of recommendation: CONDITIONAL

Summary

It is suggested to use the following warning signs to identify patients with increased risk of progression to severe dengue:

- 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: gingivorrhagia, epistaxis, vaginal bleeding not associated with menstruation or more menstrual bleeding than usual, and hematuria
- Fluid accumulation: clinical, on imaging, or both, at the end of the febrile stage
- 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 hematocrit: on at least two consecutive measurements during patient monitoring

Quality of the evidence on the relationship between recommended prognostic factors and risk of severe disease: HIGH-MODERATE ⦿⦿⦿○

3	What clinical findings and basic complementary studies should be used to identify patients who require inpatient hospital management?	Strength of recommendation: CONDITIONAL

Summary

It is suggested to use the following criteria for the hospitalization of dengue patients:

- Dengue with warning signs (see recommendation 2)
- Dengue with criteria of severe disease, according to the WHO 2009 definition[5]
- Oral intolerance
- Difficulty breathing
- Narrowing pulse pressure
- Arterial hypotension
- Acute renal failure
- Prolonged capillary refill time
- Pregnancy
- Coagulopathy

Quality of the evidence: LOW to HIGH (depending on the prognostic factor) ⦿⦿○○

4	In patients diagnosed with arboviral infection, should an intense oral hydration scheme be used?	Strength of recommendation: STRONG

Summary

It is recommended to use an intense oral hydration scheme in dengue patients to decrease the progression to severe forms and the appearance of disease complications.

Quality of the evidence: LOW ⦿⦿○○

The STRONG recommendation does not adapt to any of the paradigmatic situations proposed to issue STRONG recommendations with LOW certainty of the evidence. However, considering that the intervention is not expensive, is easy to implement and operate, and would generate large benefits, especially in the context of an epidemic, the panel decided to issue a STRONG recommendation.

5	In dengue patients with warning signs, should parenteral hydration be indicated?	Strength of recommendation: STRONG

Summary

It is recommended to indicate parenteral hydration in dengue patients with at least one warning sign.

Quality of the evidence: VERY LOW ⦿○○○

The STRONG recommendation is based on the first paradigmatic situation, which justifies a STRONG recommendation with LOW certainty of the evidence (possible benefits in the context of a potentially catastrophic situation).

6	In patients with arboviral infection who receive parenteral hydration, should resuscitation with crystalloids or colloids be initiated?	Strength of recommendation: STRONG

Summary

It is recommended to use crystalloids instead of colloids in the initial management of patients with dengue shock.

Quality of the evidence regarding the effect: LOW ⦿⦿○○

The STRONG recommendation is based on the third paradigmatic situation, which justifies a STRONG recommendation with LOW certainty of the evidence (potential equivalence of beneficial effects, but one option is safer or less expensive).

[5] World Health Organization. Dengue guidelines for diagnosis, treatment, prevention and control: New edition. Geneva: WHO; 2009. Available from: https://apps.who.int/iris/handle/10665/44188.

7	In dengue patients with thrombocytopenia, should the transfusion of blood components (platelet concentrate or fresh frozen plasma) be indicated?	Strength of recommendation: STRONG

Summary

It is recommended to not transfuse blood components (platelet concentrate, fresh frozen plasma) to dengue patients with thrombocytopenia.

The recommendation applies to all patients with dengue and thrombocytopenia, regardless of platelet count.

The recommendation does not apply to patients with bleeding or additional conditions that predispose a person to bleeding (e.g., pregnancy). In these situations, the indication for the transfusion of blood components should be considered.

Quality of the evidence: VERY LOW ⊙○○○

The STRONG recommendation is based on the second paradigmatic situation, which justifies a STRONG recommendation with LOW certainty of the evidence (uncertainty about the benefits with MODERATE or HIGH certainty about the harms).

8	In patients with arboviral infection, what pharmacological interventions may be indicated to manage symptoms?	Strength of recommendation: CONDITIONAL

Summary

Paracetamol (acetaminophen) or metamizole is suggested instead of nonsteroidal anti-inflammatory drugs, antihistamines, or steroids for initial symptomatic management in patients with arboviral infection.

	Dosage in pediatrics	Dosage in adults
Paracetamol (orally)	10 mg/kg of body weight every 6 hours Maximum daily dose: 60 mg/kg	500 mg every 6 hours Maximum daily dose: 4 g
Metamizole (orally)	10 mg/kg of body weight every 6 hours	500 mg every 6 hours

Quality of the evidence: VERY LOW to LOW ⊙⊙○○

9	In patients with severe arboviral infection, should treatment with systemic steroids be indicated?	Strength of recommendation: CONDITIONAL

Summary

It is suggested to not administer systemic steroids to patients with dengue shock.

Quality of evidence: VERY LOW ⊙○○○

No reliable evidence was identified to determine the impact of this intervention on patients with severe dengue without shock, or with Zika or chikungunya.

10	In patients with severe arboviral infection, should treatment with immunoglobulins be indicated?	Strength of recommendation: CONDITIONAL

Summary

It is suggested to not indicate immunoglobulins for the treatment of severe dengue.

Quality of evidence: VERY LOW ⊙○○○

No reliable evidence was identified to determine the impact of this intervention on patients with Zika or chikungunya.

11	Should condom use be indicated to prevent non-vector-borne transmission of Zika virus?	Strength of recommendation: STRONG

Summary

Condom use is recommended for the prevention of sexual transmission of Zika virus infection.

Quality of evidence: VERY LOW ⊙○○○

The STRONG recommendation does not adapt to any of the paradigmatic situations proposed to issue STRONG recommendations with LOW certainty of the evidence. However, considering that the intervention is not expensive, is easy to implement, and was proven to work for the prevention of other sexually transmitted diseases, the panel decided to issue a STRONG recommendation.

12	Should the suppression of breastfeeding be indicated for women with suspected Zika virus infection?	Strength of recommendation: STRONG

Summary

It is recommended to maintain breastfeeding in women with suspected or confirmed diagnosis of Zika virus infection.

Quality of evidence: VERY LOW ⊙○○○

The STRONG recommendation is based on the second paradigmatic situation, which justifies a STRONG recommendation with LOW certainty of the evidence (doubtful benefits with established harms).

Acronyms

CI	confidence interval
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HIV	human immunodeficiency virus
HR	hazard ratio
IgG	immunoglobulin G
IgM	immunoglobulin M
NSAID	nonsteroidal anti-inflammatory drugs
OR	odds ratio
PAHO	Pan American Health Organization
PICO	question about population, intervention, comparison, and outcome
RD	risk difference
RR	relative risk
WHO	World Health Organization

PART I. Introduction

Evidence-based guidelines are currently one of the most useful tools for improving public health and clinical practice, delivering interventions with strong evidence of efficacy, avoiding unnecessary risks, making reasonable use of resources, reducing clinical variability, and, in essence, improving health and ensuring quality care, which is the purpose of health systems and services (*1*).

Their development, based on the methodology proposed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group (*2*), is based on the implementation of rigorous systematic reviews and the adequate summary of the body of evidence. In addition to analysis of the quality of the evidence, the GRADE methodology includes evaluation of the effectiveness of the recommended interventions and the balance between their desirable and undesirable consequences, and aspects such as the values and preferences of the individuals or populations that benefit from the interventions, the resources required to implement the recommendations, and the costs for the health system, among others.

This publication was prepared following this methodology, with the aim of providing health professionals with guidelines for managing patients with arboviral infection. Part One (I) presents the background to the guidelines and describes the scope and users, the theoretical framework and rationale, the objective, and the target population. Part Two (II) sets out the methodology used to develop the guidelines. Part Three (III) contains the questions and the recommendations formulated in response to the questions, with a summary of the judgments issued by the panel as rationale. Part Four (IV) presents the strategies for updating and implementation. The Annexes section contains additional information related to the process of constructing the recommendations (detailed description of the questions about the patient, intervention, comparison, and outcome [PICO format], the summary of findings tables, the GRADE tables for the translation of evidence into recommendations), and details about the composition of the guidelines development group.

Background

Arboviral diseases pose a constant threat to public health worldwide. In the Americas, dengue is the most important and most frequent arbovirus. This disease is caused by the dengue virus, for which four different serotypes (DENV 1, 2, 3, and 4) have been identified to date (*3*). The most common form of transmission is from the bite of the Aedes aegypti mosquito (*4*), which is present in almost all countries and territories of the Americas. Since the reintroduction of dengue in the Americas in the early 1980s, the number of dengue cases has been consistently increasing, with larger epidemics occurring cyclically every 3 to 5 years (*5*). In 2019, the highest number of dengue cases occurred in the Americas; there were more than 3.1 million cases, including 28,000 severe cases and 1,766 deaths (*6*). In addition, the four dengue virus serotypes that circulate in the Americas and in several countries do so simultaneously, which increases the risk of the emergence of epidemics and severe forms of this disease. In addition to this complex situation, there is the simultaneous presence of other arboviruses, such as chikungunya and Zika fevers, which are both transmitted by the same vector.

Chikungunya fever is caused by the chikungunya virus. This disease was introduced to the Americas in late 2013. The spread throughout the rest of the continent occurred quickly and reached nearly every country in the Region. By the end of 2014, 1.09 million cases had been reported. Although its incidence has decreased in recent years, the disease continues to be present in the Americas. In 2019, 184,787 cases of chikungunya were reported (*7*).

Zika fever is caused by the Zika virus (ZIKV). The first record of autochthonous transmission of this disease in the Americas occurred in March 2014 on Easter Island (Chile). However, in early 2015, an increasing number of

cases of an unknown disease began to be observed in Brazil, accompanied by a significant number of cases of congenital malformations a few months later. This led WHO to declare a public health emergency of international concern, as defined in the International Health Regulations, on 1 February 2016. By the end of 2016, over 650,000 cases of Zika fever had been reported in the Americas. As with chikungunya fever, the reported number of Zika virus cases has declined recently, with a total of 35,914 cases across the continent at the end of 2019 (*8*).

The three arboviruses (dengue, chikungunya, and Zika) can produce similar clinical manifestations, particularly in the first days following disease onset. This similarity makes it challenging for health personnel in charge of caring for the patient to establish a clinical diagnosis, which can lead to inadequate case management and fatal outcomes. In addition to this clinical difficulty, the cross-reactivity of the immunoglobulin M and G antibodies (IgM and IgG) for dengue and Zika viruses complicates laboratory confirmation and consequently compromises epidemiological surveillance (*9*).

Faced with this situation, PAHO, with the support of clinical experts from various countries and the International Technical Group of Experts on Arboviral Diseases (International GT-Arbovirus, by its acronym in Spanish), has developed guidelines and instruments for the diagnosis and clinical management of dengue, chikungunya, and Zika. In 2010, the first edition of the dengue guidelines for patient care in the Region of the Americas was published (*10*). Then, in 2016, a second edition of that guide was published. The second edition incorporated new elements of the approach to the disease that were not contemplated in the first edition, such as dengue during pregnancy, in newborns, and in older adults, as well as dengue and the presence of concomitant diseases (associated infections, systemic arterial hypertension, diabetes mellitus, acute renal failure, and osteoarticular diseases). This second edition also addressed elements related to epidemiological surveillance, the etiological agent, laboratory diagnosis, and the reorganization of health services in the different areas of medical care in outbreak or epidemic situations (*11*). In 2011, the document Preparedness and response for chikungunya virus: Introduction in the Americas was published (*12*). Subsequently, in 2017, the Tool for the diagnosis and care of patients with suspected arboviral diseases was published, which included relevant information on dengue, chikungunya, and Zika, as well as other arboviruses of importance for public health in the Americas (*9*). Although these documents have been of great support for health personnel, their development was based on expert opinion and the search for scientific evidence.

Given the disease burden of dengue, chikungunya, and Zika in the Americas, as well as the constant advance of available scientific information, it became necessary to have new clinical practice guidelines that both contain up-to-date scientific information and integrate the three diseases into a single publication. In addition, the guidelines presented here have been developed following the GRADE methodology, answering key questions about clinical diagnosis and treatment for dengue, chikungunya, and Zika, all in order to prevent progression to severe forms of the diseases and fatal outcomes.

Scope and users

These clinical practice guidelines provide evidence-based recommendations for pediatric, young adult, older adult, and pregnant female patients who are exposed or have a suspected or confirmed diagnosis of dengue, chikungunya, or Zika disease.

The recommendations are aimed at health professionals, including general physicians, resident physicians, specialist physicians (pediatricians, internists, infectious disease specialists, obstetrician-gynecologists, and emergency medicine physicians, among others), and nursing personnel, as well as medical and nursing students, who are involved in caring for patients with suspected dengue, chikungunya, or Zika in one capacity or another. These guidelines are also addressed to health unit managers and heads of national arboviral disease prevention and control programs, who are responsible for facilitating the process to implement the recommendations laid out in this publication.

Theoretical framework and rationale

Dengue, chikungunya, and Zika are viral infectious diseases that represent a high burden for health services in countries around the world (*13–17*). All three diseases are transmitted by arthropods (ARthropod-BOrne viruses or arboviruses), and the Aedes aegypti mosquito is the main vector responsible for their transmission. In addition to sharing the same vector, the clinical manifestations produced by the three arboviruses are also similar. The latter makes it challenging for the physician in charge of caring for cases to make an adequate clinical diagnosis and, in turn, determine appropriate treatment, which can lead to a fatal outcome.

In the Americas, dengue is the arbovirus that causes the highest number of cases, which represents a high demand on health services, as well as a large economic burden for the health systems of the countries of the Americas (*16, 17*). However, the simultaneous circulation of chikungunya and Zika viruses should put health personnel in charge of caring for cases with suspected arbovirus on constant alert.

Given this complex epidemiological situation, in which at least three arboviruses are circulating simultaneously, it became necessary for PAHO, together with Member States, to establish a comprehensive approach to these arboviral diseases. Thus, based on more than 15 years of experience working with the Integrated Management Strategy for Dengue Prevention and Control (IMS-dengue), Resolution CD55.R6 was adopted in 2016 (*18*). The resolution urges Member States to adopt the Strategy for Arboviral Disease Prevention and Control (IMS-arbovirus) (*19, 20*).

The IMS-arbovirus establishes four strategic lines of action:

1. Foster an integrated approach for arboviral disease prevention and control;
2. Strengthen health services capacity for the differential diagnosis and clinical management of arboviral diseases;
3. Evaluate and strengthen country capacity for surveillance and integrated vector control;
4. Establish and strengthen the technical capacity of the Arbovirus Diagnosis Laboratory Network in the Region of the Americas (RELDA).

Under the framework of the second strategic line of action, PAHO has carried out numerous actions aimed at strengthening national technical capacities in the field of the clinical diagnosis and management of dengue, chikungunya, and Zika cases. To this end, PAHO developed and published a second edition of clinical guidelines on dengue and the tool for the diagnosis and care of patients with suspected arboviral disease (*9, 11*). The preparation of these documents was accompanied by a training process at the regional and national levels. However, it is important to mention that the documents that were prepared and published, while based on published specialized scientific literature and the experience of clinical experts from different countries of the Americas, did not follow the GRADE methodology for their development, as currently recommended by PAHO and WHO for the publication of clinical guidelines.

The simultaneous circulation and constant threat to public health that dengue, chikungunya, and Zika pose in the Region, as well as the rapid advance of scientific publications related to clinical diagnoses and the challenges presented by the differential clinical diagnosis and treatment of the three arboviruses, underscored the need to develop new clinical practice guidelines for the diagnosis and treatment of these arboviruses.

The guidelines presented here include the three arboviruses (dengue, chikungunya, and Zika) and were developed by a panel of clinical experts from different countries who were all convened by PAHO. In addition, the guidelines were developed following the GRADE methodology, which guarantees the use of the most recent scientific information available at the time of their development.

Objectives and target population

These clinical practice guidelines were developed with the aim of presenting the strategies, resources, and capacities available for the management of patients with arboviral infection in the Americas and around the world.

How to use these guidelines

For each clinical question, a set of recommendations and good practices is presented, providing indications for the management of arboviruses. Each recommendation presents the quality of the evidence according to the GRADE system:

JUDGMENT	CHARACTERISTICS
HIGH ⦿⦿⦿⦿	Further research is very unlikely to change our confidence in the estimate of effect.
MODERATE ⦿⦿⦿○	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
LOW ⦿⦿○○	Further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
VERY LOW ⦿○○○	Any estimate of effect is very uncertain.

In addition, the strength of each recommendation according to the GRADE system is indicated:

STRENGTH OF THE RECOMMENDATION	MEANING
STRONG in favor	The desirable consequences clearly outweigh the undesirable consequences. **RECOMMENDED**.
CONDITIONAL in favor	The desirable consequences probably outweigh the undesirable consequences. **SUGGESTED**.
CONDITIONAL against	The undesirable consequences probably outweigh the desirable consequences. **NOT SUGGESTED**.
STRONG against	The undesirable consequences clearly outweigh the desirable consequences. **NOT RECOMMENDED**.

Updating of the guidelines

The recommendations in these guidelines should be updated when new evidence becomes available that modifies the recommendations noted herein.

The guidelines updating process will be carried out based on the following stages:

- Convening of a panel of thematic experts.
- Evaluation by a thematic expert panel of topics or questions that may need updating or require additional questions not considered in the previous version of the guidelines.
- Systematic review of the specialized literature on the questions or topics selected or the additional questions incorporated.
- Considering the evidence identified, the panel of thematic experts, in conjunction with methodologists, will decide which of the original recommendations will be updated.

The process of summarizing the evidence and translating it into the selected recommendations that need to be updated, or incorporating the questions, will be the same as the one described in the original guidelines.

PART II. Methodology

This section was adapted from the evidence-based guideline reporting template found in the tool for strengthening national programs' evidence-based guidelines (*1*).

Composition of the guidelines development group

Development group participants included thematic experts in arboviruses and experts in the methodology for developing clinical practice guidelines using the GRADE methodology. Annex 1 presents the full composition of the group.

Three groups participated in the development of the guidelines. First, the development group (PAHO members) fulfilled the functions of organization, direction, and coordination. Second, the group of experts, selected from among notable professionals with experience in the clinical diagnosis, management, and treatment of arboviruses, carried out these functions: 1) formulated the relevant questions that should be answered; 2) provided support to the methodological team in the search for and selection of the evidence that would be used to answer the questions; 3) made recommendations in response to the questions proposed; and 4) participated in the process of drafting the final document. Finally, the group of methodologists was selected from PAHO's specialized areas and their functions were to: 1) provide methodological support to the group of experts when formulating the questions, 2) conduct systematic reviews of the specialized literature with the aim of collecting the necessary evidence to answer the questions posed, 3) summarize the evidence, 4) provide methodological support to the group of experts for the formulation of recommendations, and 5) participate in the process of drafting the final guidelines.

Declaration of conflicts of interest

All members of the guidelines development group and the panel of experts, as well as those involved in both the expert collaboration and the external review, signed a conflict of interest statement. The general coordinators of the guidelines reviewed all statements in order to detect any conflicts that could affect value judgments and recommendations. Everyone involved stated that they had no conflicts of interest in the formulation of the recommendations, were not involved as researchers in ongoing clinical trials on the subject, and had not received donations or benefits from interest groups. Overall, no conflicts were identified with the potential to introduce bias into the guidelines' recommendations. Annex 2 presents the analysis of conflicts.

Declaration of editorial independence

PAHO provided support during the preparation of this publication to guarantee the transferability and applicability of its content into the clinical arena. The development group was independently responsible for the scientific research work and the formulation of the recommendations.

Definition of the scope and objectives of the clinical practice guidelines

PAHO defined the scope and objectives of these guidelines with the purpose of supporting health professionals, to enable them to provide homogeneous or standardized medical care with quality, equity, and efficiency. After reviewing the relevant specialized literature, the development group drafted a document with the themes and sub-themes, objectives, background, and rationale for developing these clinical practice guidelines. Heterogeneity

in clinical practice, the availability of new evidence, the existence of new therapeutic options, inadequate use of resources, and problems with quality in health care practice were all considered. The topics addressed and not addressed, the target population for the guidelines, and the main clinical aspects were also defined.

The objective of these guidelines is to update, organize, and assess the recommendations related to the management of patients with arboviral infection. Their development was led by the Pan American Health Organization (PAHO) and sought to strengthen technical and scientific interaction on this issue in the countries of the Region.

These guidelines make available to Member States and their partners the best available evidence for decision-making to reduce morbidity and mortality from arboviruses and contribute to the control of these neglected diseases that are considered a public health problem.

Decision on new development versus adaptation

The quality and clinical relevance of existing guidelines and guides were analyzed and no publications that could be adapted were identified. Therefore, new guidelines were developed.

Formulation of clinical questions

The guideline development group, composed of thematic experts and epidemiologists, reviewed the relevant clinical topics that should be addressed and formulated specific questions using the PICO format. The questions were formulated at an in-person meeting held in San Salvador from 7-9 August 2018. Annex 3 presents the PICO questions.

Identification and grading of the outcomes of clinical practice guidelines

The guideline development group conducted an outcome prioritization exercise with the aim of determining which outcomes were key and should be included. Clinical outcomes on safety, efficacy, and quality of life, as well as those that were important to patients, were identified and prioritized.

Each outcome was classified as “critical,” “important non-critical,” and “unimportant” for patients, based on a 9-unit scale proposed by the GRADE group (*21–23*).

Evidence review and summary

SYSTEMATIC REVIEWS

The methodological team performed rapid systematic reviews with the aim of compiling the available evidence to respond to the formulated questions. To achieve this, the search was structured in stages. All of the searches included all evidence available through 21 March 2019. In the first stage, the purpose of the search was to find clinical practice guides or guidelines and systematic reviews that answered questions that were the same or similar to the formulated questions, in order to extract primary studies. The search was performed using Medline (PubMed), Scielo, Google Scholar, and Epistemonikos. All of the bibliographic citations for the guides, guidelines, and systematic reviews retrieved were recorded and all potentially relevant primary studies were assessed, based on their title, to determine which should be included. The second stage of the search was designed to find primary studies that were not included in the guides, guidelines, and systematic reviews in the first stage. The search was performed using Medline (PubMed), Embase, Scielo, and Google Scholar. The inclusion of all relevant publications identified as primary studies was assessed. In a third stage, a list of all the selected

publications was sent to the group of experts, who were asked to assess whether there was relevant literature in addition to the references identified.

All studies identified and considered potentially relevant based on the title were analyzed in parallel by two methodologists, to decide whether they should be included. Discrepancies were resolved through deliberation.

The universal search terms (for all stages and questions) were: (Dengue OR Zika OR Chikungunya). Depending on the stage and question, additional terms were added as deemed necessary.

The criteria for selecting studies were as follows:

For clinical manifestations that differentiate between different arboviruses: cohort or cross-sectional studies that compared the clinical manifestations of patients diagnosed with dengue, chikungunya, or Zika.

For prognostic factors: cohort studies that reported the clinical evolution of patients with arboviral infection and described different variables considered to be potential prognostic factors.

For the efficacy and safety of therapeutic interventions: randomized controlled trials or non-randomized studies that included a control group comprised of patients from the same initial population.

The publications considered relevant were synthesized in summary of findings tables following the GRADE assumptions (*21–23*). To this end, the group of methodologists extracted and analyzed the information contained in the aforementioned publications as follows:

- To summarize the information on clinical manifestations or prognostic factors, the adjusted and unadjusted odds ratios (OR) of each variable evaluated were extracted. The results of the individual studies were meta-analyzed using the inverse variance statistical method and the metafor package in the R software® program (*24*).
- To summarize the efficacy and safety of therapeutic interventions, the relative risks (RR) were meta-analyzed using the Review Manager®[6] software or the metafor package in the R software® program (*24*), using the Mantel-Haenszel statistical method. In cases where it was not possible to obtain relative risks (e.g., no control group), the median or mean incidence of each relevant outcome in each group assessed was calculated, as appropriate.
- To summarize the baseline risks, the following were used as appropriate: the median or mean baseline risks or prevalences observed in the control groups of studies with two subgroups; or the median or mean baseline risks or prevalences described in observations of one group.

ASSESSMENT OF THE RISK OF BIAS OF INDIVIDUAL STUDIES

For the questions about prognostic factors or clinical manifestations, the group of methodologists assessed the risk of bias of individual studies using the Quality in Prognosis Studies (QUIPS) tool (*25*). For the questions about interventions, the group used the Cochrane RoB 1.0 tool (*26*).

EVALUATION OF CERTAINTY IN THE BODY OF EVIDENCE

The group of methodologists evaluated the evidence in the studies by separating the information by outcome evaluated, based on the methodology proposed by the GRADE working group (*27*). Certainty of the evidence was defined as the group's confidence that the desirable and undesirable consequences are within an interval that clearly justifies a recommendation in favor of or against a given intervention or management strategy (*28*). To assess the certainty of the evidence, the aspects proposed by the GRADE working group were considered, namely risk of bias, inconsistency, imprecision, indirect information, and risk of publication bias (*27*).

[6] RevMan, version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, Copenhagen.

MOVING FROM EVIDENCE TO RECOMMENDATIONS

The recommendations development process took place during an in-person meeting held in Panama 19-22 August 2019. The meeting was attended by coordinators, thematic experts, and methodology experts. To facilitate the entire process carried out during the meeting, described below, the GRADEpro GDT software® was used.[7]

To move from evidence to recommendations, the group of methodologists prepared forms to facilitate the process (evidence-to-decision frameworks) based on the recommendations of the GRADE working group (*29, 30*). These forms included: 1) the question formulated in PICO format; 2) the summary of findings table constructed with the evidence found; 3) information on patients' values and preferences; 4) information on resource use and costs; and 5) information related to the feasibility of implementation and equity.

The group of methodologists conducted a bibliographic search to identify additional relevant information pertaining to each of these aspects. The panel of experts evaluated the evidence compiled when discussing and defining the components that ultimately influenced each recommendation.

The group of experts issued a judgment for each aspect that was relevant to the recommendation to respond to each question. This judgment was made by group consensus and, if no consensus could be reached, it was decided by a show of hands. The results of each vote were recorded. However, the vast majority of decisions were made by consensus without the need for a vote.

The panel of experts defined the recommendations by considering the judgments reached on each relevant aspect. To do so, they decided on both the direction (in favor of or against the intervention) and the strength (strong or conditional), following the guidelines of the GRADE group (*30*). As with the individual components, the strength and direction of each recommendation were decided by consensus; in cases in which it was not possible to reach consensus, a vote was taken by a show of hands and the results of each vote were recorded. To define a recommendation as strong, at least 80% of the panel members needed to agree; if that percentage could not be reached, the recommendation was defined as conditional.

The GRADE methodology has two grades of strength for a recommendation: "strong" or "conditional." After considering the balance between risks and benefits, the quality of the evidence, patient values and preferences, and the Latin American context, the strength of each recommendation was determined based on the following structure:

STRENGTH OF THE RECOMMENDATION	MEANING
STRONG in favor	The desirable consequences clearly outweigh the undesirable consequences. **RECOMMENDED**.
CONDITIONAL in favor	The desirable consequences probably outweigh the undesirable consequences. **SUGGESTED**.
CONDITIONAL against	The undesirable consequences probably outweigh the desirable consequences. **NOT SUGGESTED**.
STRONG against	The undesirable consequences clearly outweigh the desirable consequences. **NOT RECOMMENDED**.

The process of defining the strength of the recommendation included a lengthy discussion by the panel of experts about the difficulty of conducting studies that provide accurate information on the efficacy and safety of interventions for the management of arboviruses. The emergence of these diseases in outbreaks makes it difficult, and often even impractical, to conduct controlled studies. This situation led the panel, in some of the proposed scenarios, to propose strong recommendations even in the absence of evidence with a moderate or high degree of certainty.

[7] GRADEpro Guideline Development Tool [software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from: gradepro.org.

Finally, it was verified that the panel of experts agreed with the final recommendations and that these recommendations incorporated the participants' perspectives.

INCORPORATION OF ISSUES RELATED TO COSTS, PATIENT PREFERENCES, EQUITY, AND IMPLEMENTATION

A review of the specialized literature was conducted to identify studies that described issues related to costs, preferences, values, and the social aspects of arboviruses. That information was summarized in narrative form and included in the evidence-to-decision frameworks.

When it was not possible to find evidence on these issues, the judgments were based on the experience and perceptions of the expert panel members.

INCLUSION OF EXTERNAL EVALUATOR COMMENTS

These clinical practice guidelines were independently reviewed by peer experts in methodology and thematic content.

PART III. Recommendations

QUESTION 1. What clinical findings and basic complementary studies allow arboviruses to be differentiated from each other and from other febrile diseases?

RECOMMENDATION 1

It is recommended to consider the clinical and laboratory findings described in Table 1, which are potentially useful for guiding the differential clinical diagnosis in the event of suspected arbovirus infection.

Summary of the evidence

Evidence considered: Thirty-nine potentially useful variables were identified to differentiate the different arboviruses and other febrile diseases: abdominal pain, sensory disorders, hemorrhages, progressive increase in hematocrit, thrombocytopenia (low platelet count), leukopenia (low white blood cell count), lymphopenia (low lymphocyte count), elevated transaminases, vomiting, hepatomegaly, positive tourniquet test, fluid accumulation (edema, ascites, and pleural effusion, among others), arthralgias, retro-ocular pain, anorexia or hyporexia, cough, rash, petechiae, diarrhea, headache, pruritus, rhinorrhea, jaundice, splenomegaly, high fever, dyspnea or difficulty breathing, asthenia, arthritis, prolonged fever, anemia, myalgias, bone pain, adenopathies, pharyngitis, conjunctivitis, dysgeusia, chills, photophobia, and ear pain.

Summary of the findings: Eighty studies were identified that included 70,160 people diagnosed with dengue, chikungunya, Zika, or other febrile illnesses. Of the variables evaluated, 16 were potentially useful for differentiating arboviruses from other febrile diseases. For 10 of the variables, the certainty of the evidence was judged as HIGH (rash, conjunctivitis, arthralgias, myalgias or bone pain, hemorrhages, thrombocytopenia, progressive increase in hematocrit, leukopenia, headache, and pruritus) while for the rest, it was judged as MODERATE or LOW (fluid accumulation, arthritis, chills, dysgeusia, asthenia, and retro-ocular pain). Of the variables evaluated, 24 were potentially useful for differentiating between the different arboviruses. For five of the variables, the certainty of the evidence was judged as HIGH (thrombocytopenia, progressive increase in hematocrit, leukopenia, arthralgias, and pruritus) while for the rest, it was judged as MODERATE or LOW (anorexia or hyporexia, vomiting, abdominal pain, chills, hemorrhages, rash, conjunctivitis, arthritis, myalgias or bone pain, retro-ocular pain, hepatomegaly, headache, diarrhea, dysgeusia, cough, elevated transaminases, positive tourniquet test, adenopathies, pharyngitis or odynophagia). Details on the data in the evidence identified for each of the 39 variables can be found in the summary of findings table 1 in Annex 4.

Table 1 details the findings described.

Table 1. Clinical manifestations that differentiate the arboviruses

Certainty of the evidence	Manifestations of arboviruses
HIGH (findings that differentiate them)	Eruption Conjunctivitis Arthralgias (dengue or chikungunya) Myalgias or bone pain (dengue or chikungunya) Hemorrhages (includes bleeding on the skin, mucous membranes, or both) (dengue or chikungunya) Thrombocytopenia (dengue) Progressive increase in hematocrit (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

Certainty of the evidence	Manifestations of dengue	Manifestations of chikungunya	Manifestations of Zika
HIGH (findings that differentiate them)	Thrombocytopenia Progressive increase in hematocrit Leukopenia	Arthralgias	Pruritus
MODERATE (findings that probably differentiate them)	Anorexia or hyporexia Vomiting Abdominal pain Chills Hemorrhages (includes bleeding on the skin, mucous membranes, or both)	Eruption Conjunctivitis Arthritis Myalgias or bone pain	Eruption Conjunctivitis
LOW (findings that may differentiate them)	Retro-ocular pain Hepatomegaly Headache Diarrhea Dysgeusia Cough Elevated transaminases Positive tourniquet test	Hemorrhages (includes bleeding on the skin, mucous membranes, or both)	Adenopathies Pharyngitis or odynophagia

QUESTION 2. What clinical findings and basic complementary studies should be used to identify patients at risk of progression to severe disease (warning signs)?

RECOMMENDATION 2

It is suggested to use the following warning signs to identify patients with increased risk of progression to severe dengue:

- 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: gingivorrhagia, epistaxis, vaginal bleeding not associated with menstruation or more menstrual bleeding than usual, and hematuria
- Fluid accumulation: clinical, on imaging, or both, at the end of the febrile stage
- 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 hematocrit: on at least two consecutive measurements during patient monitoring

(CONDITIONAL recommendation, based on MODERATE-HIGH certainty regarding the relationship between the prognostic factors and disease severity and LOW certainty regarding the impact of implementation of the recommended factors on clinically relevant outcomes).

Summary of the evidence and judgments issued by the panel

Interventions considered: Thirty-three potentially useful variables were found to identify those patients at risk of developing severe dengue (dengue with warning signs): narrowing pulse pressure (differential pressure), acute renal failure, arterial hypotension, increased capillary refill time, pregnancy (mainly in the third trimester), microscopic hematuria, coagulopathy, nausea, obesity, malnutrition, abdominal pain, sensory disorders, hemorrhages, progressive increase in hematocrit, thrombocytopenia, leukopenia, elevated transaminases, vomiting, hepatomegaly, positive tourniquet test, fluid accumulation, retro-ocular pain, anorexia or hyporexia, cough, rash, petechiae, diarrhea, headache, rhinorrhea, splenomegaly, high fever, dyspnea or difficulty breathing, and myalgias or arthralgias. No adequately designed studies were identified that assessed prognostic factors for the development of severe chikungunya or severe Zika. Given this, the panel decided to limit the recommendation to dengue patients.

Summary of the findings: No studies were identified that assessed the impact of using different variables or combinations of variables to identify patients at risk of severe arboviral infection on clinically relevant outcomes. There were 217 studies identified, which included 237,191 patients diagnosed with dengue, that assessed the relationship between different potential prognostic factors and progression to severe disease. Of the variables assessed, 21 were potentially useful for predicting severe dengue (see summary of findings table 2, Annex 4). For 12 of the variables, the certainty of the evidence was judged as MODERATE or HIGH (narrowing pulse pressure, arterial hypotension, abdominal pain, sensory disorder, hemorrhages including mucosal bleeding, fluid accumulation, dyspnea, hepatomegaly, thrombocytopenia, elevated transaminases, progressive increase in hematocrit, and vomiting) while, for the rest, it was judged as LOW (acute renal failure, increased capillary refill time, pregnancy, microscopic hematuria, coagulopathy, splenomegaly, high fever, positive tourniquet test, and diarrhea).

Reasons for reduced certainty in the body of evidence for some of the variables assessed included risk of bias (mainly due to lack of statistical adjustment to consider confounding variables), inconsistency, and imprecision (see summary of findings table 2, Annex 4).

Benefits and harms: Despite the lack of studies that have directly evaluated the effect of using different prognostic factors as warning signs on clinically relevant outcomes, the panel assumed that improving the ability to identify patients at higher risk of presenting serious disease has benefits, since there are effective, safe interventions that could substantially improve their prognosis. Given this, it was assumed that the use of the 12 prognostic factors that were shown to be associated with an increased risk of severe disease with MODERATE or HIGH certainty would result in important benefits. The results observed for these prognostic factors, in terms of their association with the risk of severe disease, were (OR and 95% confidence interval [95% CI]): narrowing pulse pressure (OR = 7.12; 95% CI: 3.02–16.76), arterial hypotension (OR = 5.38; 95% CI: 3.31–8.75), abdominal pain (OR = 2.02; 95% CI: 1.74–2.35), sensory disorder (OR = 5.23; 95% CI: 3.45–7.93), hemorrhages (OR = 5.21; 95% CI: 3.53–7.29), fluid accumulation (OR = 5.04; 95% CI: 3.56–7.14), dyspnea (OR = 3.93; 95% CI: 2.40–5.42), hepatomegaly (OR = 3.14; 95% CI: 2.38–4.15), thrombocytopenia (OR = 3.02; 95% CI: 2.45–3.73), elevated transaminases (OR = 2.55; 95% CI: 1.78–3.64), progressive increase in hematocrit (OR = 2.30; 95% CI 1.74–3.05), and vomiting (OR = 1.74; 95% CI: 1.48–2.05) (see summary of findings table 2, Annex 4).

Use of resources: Due to its high frequency, it was considered that the inclusion of thrombocytopenia among the warning signs for severe disease would be associated with a substantial increase in resource use, which could negatively impact the adequate development of strategies for managing this disease, especially in the context of an epidemic. Additionally, elevated transaminases, which requires a specific laboratory evaluation, is also likely to be associated with a substantial increase in costs.

Applicability: The panel considered that some of the prognostic factors identified could not be effectively implemented as warning signs given the stage at which they occur. The panel agreed that narrowing pulse pressure, dyspnea, major bleeding, and arterial hypotension occur late and are therefore part of the definition of severe dengue. Given this, implementation of these prognostic factors as warning signs is substantially less likely to have a positive impact on the prognosis of dengue patients. The panel considered that thrombocytopenia is not a warning sign (since it is **not a consequence of extravasation**, which can occur in patients with dengue) and that it is therefore not a useful guide for medical professionals in the management of parenteral liquids in these cases. The panel also considered that, although the progressive increase in hematocrit **is a consequence of extravasation**, medical professionals should immediately evaluate the CLINICAL warning signs in order not to delay resuscitation with parenteral liquids while waiting for laboratory results.

Balance between benefits and negative aspects: Considering the potential benefits of early, effective identification of those patients who may develop severe disease, and considering aspects related to implementation feasibility and costs, the panel determined that the prognostic factors that meet the necessary characteristics to be used as warning signs are: abdominal pain, sensory disorders, mucosal bleeding, fluid accumulation, hepatomegaly, progressive increase in hematocrit, and vomiting.

Annex 5 details the judgments issued by the panel of experts (framework 1).

QUESTION 3. What clinical findings and basic complementary studies should be used to identify patients who require inpatient hospital management?

RECOMMENDATION 3

It is suggested to use the following criteria for the hospitalization of dengue patients:

- Dengue with warning signs (see recommendation 2)
- Dengue with criteria for severe disease, according to the WHO 2009 definition[8]
- Oral intolerance
- Difficulty breathing
- Narrowing pulse pressure
- Arterial hypotension
- Acute renal failure
- Prolonged capillary refill time
- Pregnancy
- Coagulopathy

(CONDITIONAL recommendation, based on LOW to HIGH certainty [depending on the prognostic factor] regarding the relationship between the prognostic factors and disease severity, and LOW certainty regarding the impact of implementation of the recommended factors on clinically relevant outcomes).

Additional considerations:

- Other factors that may determine the need for the hospitalization of dengue patients include the presence of comorbidities other than those described above, the extremes of life, and social or environmental conditions. The decision to hospitalize patients with the aforementioned conditions should be individualized.
- In situations in which hospital capacity is exceeded (for example, an epidemic), dengue patients without criteria for severity, but who require hospitalization (for example, with warning signs), can be managed in special units of lower complexity for the management of dengue patients if they provide the necessary care (for example, parenteral hydration).

Summary of the evidence and judgments issued by the panel

Interventions considered: Thirty-three potentially useful variables were found to identify those patients at risk of developing severe dengue (dengue with warning signs): narrowing pulse pressure, acute renal failure, arterial hypotension, increased capillary refill time, pregnancy (mainly in the third trimester), microscopic hematuria, coagulopathy, nausea, obesity, malnutrition, abdominal pain, sensory disorders, hemorrhages, progressive increase in hematocrit, thrombocytopenia, leukopenia, elevated transaminases, vomiting, hepatomegaly, positive tourniquet test, fluid accumulation, retro-ocular pain, anorexia or hyporexia, cough, rash, petechiae, diarrhea, headache, rhinorrhea, splenomegaly, high fever, dyspnea or difficulty breathing, and myalgias or arthralgias. No adequately designed studies were identified that assessed prognostic factors for the development of severe chikungunya or severe Zika. Given this, the panel decided to limit the recommendation to dengue patients.

Summary of the findings: No studies were identified that assessed the impact of using different variables or combinations of variables to select patients that require hospitalization on clinically relevant outcomes.

[8] See definition in World Health Organization. Dengue guidelines for diagnosis, treatment, prevention and control: new edition. Geneva: WHO; 2009. Available from: https://apps.who.int/iris/handle/10665/44188.

There were 217 studies identified, which included 237,191 patients diagnosed with dengue, that assessed the relationship between different potential prognostic factors and progression to severe disease. Of the variables assessed, 21 were potentially useful for predicting severe dengue (see summary of findings table 2, Annex 4). For 12 of the variables, the certainty of the evidence was judged as MODERATE or HIGH (narrowing pulse pressure, arterial hypotension, abdominal pain, sensory disorders, hemorrhages including mucous membranes, fluid accumulation, dyspnea, hepatomegaly, thrombocytopenia, elevated transaminases, progressive increase in hematocrit, and vomiting) while, for the rest, it was judged as LOW (acute renal failure, increased capillary refill time, pregnancy, microscopic hematuria, coagulopathy, splenomegaly, high fever, positive tourniquet test, and diarrhea).

Reasons for reduced certainty in the body of evidence for some of the variables assessed included risk of bias (mainly due to lack of statistical adjustment to consider confounding variables), inconsistency, and imprecision (see summary of findings table 2, Annex 4).

Benefits and harms: Although there are no studies that have directly evaluated the effects of using different prognostic factors to indicate hospitalization on clinically relevant outcomes, the panel assumed that improving the ability to identify patients at higher risk of severe illness or death has benefits since there are effective, safe interventions that could substantially improve their prognosis. Thus, it was assumed that the use of the 12 prognostic factors that were shown to be associated with an increased risk of severe disease with MODERATE or HIGH certainty would result in important benefits (see question 2). In addition, the panel considered that the six prognostic factors that showed an association, but with LOW certainty, should also be considered as potential hospitalization criteria. The results observed for these prognostic factors, in terms of their association with the risk of severe disease, were: microscopic hematuria (OR = 3.12; 95% CI: 1.23–7.90), coagulopathy (OR = 2.83; 95% CI: 1.59–5.04), splenomegaly (OR = 2.64; 95% CI: 1.31–5.31), pregnancy (OR = 3.38; 95% CI: 2.10–5.42), increased capillary refill time (OR = 4.96; 95% CI 1.72–14.32), and acute renal failure (OR = 6.73; 95% CI: 1.66–27.2).

Use of resources: Due to its high frequency, it was considered that the inclusion of thrombocytopenia among the hospitalization criteria could be associated with a substantial increase in resource use, which could negatively impact the adequate development of strategies to manage this condition, especially in the context of an epidemic. Additionally, elevated transaminases and microscopic hematuria, which require specific laboratory evaluations, are also likely to be associated with a substantial increase in costs.

Applicability: Unlike warning signs (see question 2), time is not relevant in the definition of hospitalization criteria. For this reason, the panel considered all prognostic factors that demonstrated an association with severity, regardless of when they occur.

Balance between benefits and negative aspects: Considering the potential benefits of effectively identifying patients who require inpatient hospital management, and considering aspects related to implementation feasibility and costs, the panel determined that the prognostic factors that meet the characteristics necessary to be used as hospitalization criteria are: abdominal pain, sensory disorders, mucosal bleeding, fluid accumulation, progressive increase in hematocrit, vomiting, difficulty breathing, narrowing pulse pressure, arterial hypotension, acute kidney damage, increased capillary refill time, pregnancy, and coagulopathy. In addition, it was highlighted that there are other hospitalization criteria that must be considered, such as the accepted criteria for defining serious illness or oral intolerance.

Annex 5 details the judgments issued by the panel of experts (framework 1).

QUESTION 4. In patients diagnosed with arboviral infection, should an intense oral hydration scheme be used?

RECOMMENDATION 4

It is recommended to use an intense oral hydration scheme in dengue patients to decrease the progression to severe forms and the emergence of complications from this disease (STRONG recommendation based on LOW certainty of the evidence).

The STRONG recommendation does not adapt to any of the paradigmatic situations proposed for issuing STRONG recommendations with LOW certainty of the evidence; however, considering that the intervention is not expensive, is easy to implement and operate, and would generate great benefits, especially in the context of an epidemic, the panel decided to issue a STRONG recommendation.

Additional considerations:

- The intervention is implemented in the primary care arena, where different tools can be used, such as the provision of cups with volume quantification or forms to account for fluid intake. It should be kept in mind that dehydration is a complication of the febrile phase of dengue.
- Intense oral hydration could prevent dehydration, improving the evolution of these patients by maintaining an adequate circulating plasma volume.

  Intense hydration with oral rehydration salts:

- Healthy adults: up to 3,000 ml per day
- Pediatrics: Holliday-Segar formula plus 5%

  Holliday-Segar formula:

  - 4 ml/kg per hour for the first 10 kg of body weight
  - 2 ml/kg per hour for the next 10 kg of body weight
  - 1 ml/kg per hour for each kilogram of additional body weight

Summary of the evidence and judgments issued by the panel

Interventions considered: The panel of experts determined that interventions should involve active measures to promote an intense oral hydration scheme. Such schemes could be used with different strategies, but should result in a significant increase in fluid intake.

Summary of the findings: One randomized study was identified that evaluated the impact of an intervention on the risk of hospitalization and the need for parenteral hydration. The intervention was based on an intense hydration scheme, in which patients were told how much fluid they should consume and were given a cup with a tracker to be able to accurately determine the amount of liquid ingested. In addition, observational studies were identified that evaluated the impact of oral hydration volume on the risk of hospitalization. These studies compared the evolution of patients treated with oral versus parenteral hydration and those treated with isotonic solutions versus water for oral hydration.

Overall certainty in the body of evidence was judged as LOW due to the risk of bias (lack of blinding) and imprecision (see summary of findings table 3, Annex 4).

Benefits and harms: The body of available evidence suggests that intense oral hydration might reduce the risk of hospitalizations (randomized studies, OR = 0.52; 95% CI: 0.19–1.41; risk difference [RD] = −7.6%; 95% CI: −13.7–5.6%; observational studies, OR = 0.19; 95% CI: 0.11–0.35; RD = −13.7%; 95% CI: −15.6–10.3%), and the need for parenteral hydration (OR = 0.53; 95% CI: 0.21–1.29; RD = −8.3%; 95% CI : −15–4.4%). No significant differences were observed between dengue patients without shock who were treated with oral versus parenteral hydration or with oral hydration with isotonic solutions versus water. The identified studies reported no side effects of intense oral hydration. The panel considered that, if they do exist, such effects are negligible. Considering the simplicity of the intervention, the panel agreed that the vast majority of well-informed patients would choose intense oral hydration.

Use of resources: Considering that the direct costs of oral hydration are almost zero and that the intervention could reduce hospitalizations, the panel considered that there are potentially significant savings.

Applicability and impact on equity: Considering the simplicity of the intervention, the panel judged that it is acceptable and easy to implement. In addition, it was considered that, in those regions with less access to highly complex health services, a simple intervention that can be implemented in primary care and reduces more complex interventions favors equity.

Balance between benefits and negative aspects: The panel gave very significant weight to the possibility of reducing hospitalizations and the need for complex interventions, since in the context of an epidemic (when these diseases usually occur), these effects are of major importance at the individual and population levels. In addition, the panel highlighted the simplicity and safety of the intervention. Thus, despite not being strictly framed in any of the situations proposed for issuing STRONG recommendations based on LOW certainty of the evidence, the panel decided to formulate a STRONG recommendation considering the potential important positive effect that could exist with a simple and accessible intervention by reducing the need for hospitalizations in the context of an epidemic.

Annex 5 details the judgments issued by the panel of experts (framework 2).

QUESTION 5. In dengue patients with warning signs, should parenteral hydration be indicated?

RECOMMENDATION 5

It is recommended to indicate parenteral hydration in dengue patients with at least one warning sign (STRONG recommendation, based on VERY LOW certainty about the effects of the intervention).

The STRONG recommendation is based on the first paradigmatic situation, which justifies a STRONG recommendation with LOW certainty of the evidence (possible benefits in the context of a potentially catastrophic situation).

Additional considerations:

- The warning signs are those included in recommendation 2.
- In the context of an epidemic, the intervention can be implemented in hydration units with the aim of reducing hospitalizations and admissions to intensive care wards.

See recommendation 6 for further details on how to implement the intervention.

Summary of the evidence and judgments issued by the panel

Summary of the findings: No randomized or observational studies were identified in which the indication for parenteral hydration was compared to conservative management, without parenteral hydration, for dengue patients with warning signs, but without severity criteria. Four observational studies were included that reported on the evolution of dengue patients with warning signs who were managed using protocols that included parenteral hydration.

The overall certainty in the body of evidence was judged to be VERY LOW due to the risk of bias (observational studies with one group, so the comparison was made against a hypothetical control group) (see summary of findings table 4, Annex 4).

Benefits and harms: The body of evidence analyzed suggests that the indication of parenteral hydration for dengue patients with warning signs could be associated with significant benefits. In the absence of a control group, the panel interpreted the results of the identified studies in comparison to a hypothetical control. In this sense, the results showed that of 2,594 dengue patients managed according to a scheme in which those with warning signs received parenteral hydration, none died. The panel considered that mortality without parenteral hydration could have been higher. On the other hand, the risk of developing severe dengue was 2% to 5%. Similarly, the panel considered that this risk would have been significantly higher without parenteral hydration. In the case of side effects, an observational study was included that reported that the indication of parenteral hydration in patients with severe dengue or warning signs could increase the risk of difficulty breathing (hazard ratio (HR) = 2.9; 95% CI: 1.37–6.12). However, the panel of experts considered this complication to be exceptional since it occurs in patients with predisposing conditions (e.g., myocardial dysfunction) (see summary of findings table 4, Annex 4). In addition, the entire group of experts agreed that, as observed in their daily practice, early parenteral hydration could be the only effective measure to prevent progression to serious illness and death. Many of the panel members mentioned having information about this topic that they had recorded, but never published. Considering the relative simplicity of the intervention, the panel agreed that the vast majority of well-informed dengue patients with warning signs would choose to receive parenteral hydration.

Use of resources: Considering that the direct costs of parenteral hydration are low and that the intervention could reduce hospitalizations and the need for intensive care, the panel agreed that the intervention is likely to result in significant savings.

Applicability and impact on equity: Considering the simplicity of the intervention, the panel judged it as acceptable and easy to implement. In addition, it was considered that, in regions with less access to highly complex health services, a simple intervention that is applicable in primary care (for example, dengue patient care units implemented in epidemic areas) and that reduces the need for more complex interventions favors equity.

Balance between benefits and negative aspects: The panel gave greater weight to the potential large reduction in mortality and the possibility of implementing the intervention in a simple manner in the Region than to the risk of complications such as pulmonary edema. Although the certainty is VERY LOW, it was considered that experiences in daily practice strongly support the benefits of the intervention. Given this, it was considered that the situation proposed, especially in the context of an epidemic, corresponds to the first paradigmatic situation that justifies a STRONG recommendation in the context of LOW or VERY LOW certainty of the evidence (possible benefits in the context of a potentially catastrophic situation).

Annex 5 details the judgments issued by the panel of experts (framework 3).

QUESTION 6. In patients with arboviral infection who receive parenteral hydration, should resuscitation with crystalloids or colloids be initiated?

RECOMMENDATION 6

It is recommended to use crystalloids instead of colloids in the initial management of patients with dengue shock (STRONG recommendation based on LOW certainty regarding the effects of the intervention).

The STRONG recommendation is based on the third paradigmatic situation in which a STRONG recommendation is justified with LOW certainty of the evidence (potential equivalence of beneficial effects, but one option is safer or less expensive).

Additional considerations:

- It is advisable that the resuscitation be carried out in a controlled setting in which the hemodynamic parameters are evaluated periodically in order to determine whether the response is adequate.

Summary of the evidence and judgments issued by the panel

Summary of the findings: Four randomized studies were identified that compared the use of crystalloids and colloids in 694 people with dengue shock or severe dengue. In addition, indirect evidence was included from 69 randomized studies that compared crystalloids with colloids for resuscitation in people with shock from other causes.

The overall certainty in the body of evidence was rated as LOW. Certainty in the individual outcomes assessed was: death (LOW certainty), recurrent or treatment-resistant shock (MODERATE certainty), volume overload (MODERATE certainty), infusion-related reactions (HIGH certainty), and renal replacement therapy (LOW certainty).

Benefits and harms: The body of evidence analyzed suggests that the use of crystalloids would not impact mortality (no events were observed in either group in the four included studies and indirect evidence suggests an absence of significant differences), risk of recurrent or treatment-resistant shock (RR = 1.06; 95% CI: 0.82–1.37), or volume overload (RR = 1.01; 95% CI: 0.76–1.34). However, the use of crystalloids reduces the risk of infusion-related or allergic reactions (RR = 0.09; 95% CI: 0.01–0.64; DR = −3.7%; 95% CI: −4.1–1.5%), and could reduce the need for renal replacement therapy (DR = −24%; 95% CI: −11-−39) (see summary of findings table 5, Annex 4).

The panel considered that the vast majority of well-informed patients would possibly choose to receive crystalloids, considering the absence of differences in efficacy and the lower risk of adverse effects.

Use of resources: The direct cost of crystalloids is substantially lower than the cost of colloids. The panel considered that, although the volume of colloids to be infused is significantly lower than the volume of crystalloids, the implementation of crystalloids would result in moderate savings due to their lower cost.

Applicability and impact on equity: The panel agreed that crystalloids are more widely available than colloids in the Region. For this reason, the indication of crystalloids would be more feasible to implement and could improve equity.

Balance between benefits and negative aspects: The panel gave a very important weight to the possibility of avoiding infusion-related reactions, as well as to the benefits of resource savings and greater availability. Considering that the certainty regarding the reduced risk of infusion-related reactions is HIGH, and the differences in cost and availability, the decision was made to issue a STRONG recommendation, even though the overall certainty in the body of evidence is LOW. This recommendation is part of the third paradigmatic situation proposed by the GRADE group, which allows STRONG recommendations to be made with LOW certainty of the evidence.

Annex 5 details the judgments issued by the panel of experts (framework 4).

QUESTION 7. In dengue patients with thrombocytopenia, should the transfusion of blood components (platelet concentrate or fresh frozen plasma) be indicated?

RECOMMENDATION 7

It is recommended to not transfuse blood components (platelet concentrate or fresh frozen plasma) to dengue patients with thrombocytopenia (STRONG recommendation based on VERY LOW certainty regarding the effects of the intervention).

The STRONG recommendation is based on the second paradigmatic situation, which justifies a STRONG recommendation with LOW certainty of the evidence (uncertainty regarding the benefits with MODERATE or HIGH certainty regarding the harms).

Additional considerations:

- The recommendation applies to all dengue patients with thrombocytopenia, regardless of platelet count.
- The recommendation does not apply to patients with hemorrhage or additional conditions that predispose them to bleeding (e.g., pregnancy). In such situations, the indication for blood component transfusion should be considered.

Summary of the evidence and judgments issued by the panel

Summary of the findings: Three randomized studies were identified that assessed the effects of blood component transfusion in 565 people with dengue and thrombocytopenia. In addition, one observational study was included that provided additional information for the hemorrhage outcome.

The overall certainty in the body of evidence was judged to be VERY LOW, primarily because of the risk of bias (lack of blinding) and imprecision.

Benefits and harms: In the body of evidence analyzed, it was found that the effect of blood component transfusion on mortality (OR = 5.36; 95% CI: 0.25–115; RD = 4.7%; 95% CI: −0.9–55.9) and development of shock (OR = 0.71; 95% CI: 0.14–3.65; RD = −1.6%; 95% CI: −4.8–12.2) is uncertain. Moreover, the intervention could marginally reduce the risk of major bleeding (OR = 0.58; 95% CI: 0.18–1.90; RD= −1.3%; 95% CI: −2.5–2.6), and probably increases the risk of adverse effects (OR = 8.23; 95% CI: 1.84–36.8; RD = 2.5%; 95% CI: 0.3–11.2) (see summary of findings table 6, Annex 4). The panel considered that there are additional harms such as the risk of contracting Chagas disease, hepatitis B, hepatitis C, and AIDS. Although these risks are low, they are not zero, and their consequences are catastrophic.

The panel considered that all or almost all well-informed patients would possibly choose to not receive a blood transfusion, considering the uncertainty regarding its potential benefits and the risks associated with the procedure.

Use of resources: Considering the direct costs of a blood component transfusion, the panel considered that implementation of the intervention would be associated with high economic costs. It also considered that blood components are a limited resource and that their use as prophylaxis in patients with thrombocytopenia would probably result in less availability for other circumstances in which the benefits of blood transfusions are clear.

Applicability and impact on equity: The panel agreed that the intervention requires a level of complexity that is not universally available in the Region. This means that it is not feasible to implement blood transfusions in many health centers in the Region. Given this, a part of the population with less access to highly complex medical centers would not be able to receive the intervention, negatively impacting equity.

Balance between benefits and negative aspects: The panel prioritized the negative aspects of the intervention (infusion-related reactions, infections, increased costs) and the impossibility of implementation in regions with less access to health services, over the possible benefits of reducing the risk of hemorrhage. The STRONG recommendation is justified through the second paradigmatic situation (uncertainty regarding the benefits with MODERATE-HIGH certainty regarding the harms) since the panel considered that, in addition to MODERATE certainty regarding an increased risk of side effects, the intervention is associated with important costs and would probably have a negative impact on equity.

Annex 5 details the judgments issued by the panel of experts (framework 5).

QUESTION 8. In patients with arboviral infection, what pharmacological interventions may be indicated to manage symptoms?

RECOMMENDATION 8

It is suggested to use paracetamol (acetaminophen) or metamizole instead of nonsteroidal anti-inflammatory drugs (NSAIDs), antihistamines, or steroids for initial symptomatic management in patients with arboviral infection (CONDITIONAL recommendation based on VERY LOW to LOW certainty regarding the effects of the intervention).

Pharmacological intervention	Dosage in pediatrics	Dosage in adults
Paracetamol (orally)	10 mg/kg of body weight every 6 hours Maximum daily dose: 60 mg/kg	500 mg every 6 hours Maximum daily dose: 4 g
Metamizole (orally)	10 mg/kg of body weight every 6 hours	500 mg every 6 hours

Summary of the evidence and judgments issued by the panel

Summary of the findings: Regarding NSAIDS, five non-randomized studies were identified that assessed the safety of NSAID use in 2,692 dengue patients. In addition, information was included from 18 randomized studies involving 3,361 people with acute musculoskeletal injuries. Regarding paracetamol, two randomized studies with 167 dengue patients and four non-randomized studies with 3,053 dengue patients were included. Regarding the safety of metamizole use in patients with arboviral infection, one randomized study with 79 dengue patients and four non-randomized studies with 1,120 dengue patients were included. Information on the safety of metamizole was also included in 3,716 patients treated with this medicinal product for a short period for the management of other disorders. Regarding systemic steroids for the symptomatic treatment of dengue patients, two randomized studies involving 414 patients were identified. Finally, antihistamines were considered as a potential group of drugs to use in the symptomatic management of patients with arboviral infection. One randomized study involving 133 dengue patients was identified and additional information on the effect of antihistamine treatment was considered based on 2,624 patients with other conditions who were included in randomized studies.

The overall body of evidence was judged to have VERY LOW to LOW certainty, primarily due to the risk of bias, as much of the information used came from non-randomized studies, and due to imprecision (see summary of findings table 7, Annex 4).

Benefits and harms: In the absence of reliable studies that would have compared the efficacy of the different alternatives considered for symptomatic management, the panel – based mainly on its experience – considered that NSAIDs are probably the most effective option to achieve adequate symptomatic control, followed by paracetamol and metamizole. With regard to steroids and antihistamines, the panel considered their potential efficacy as negligible or uncertain. In the body of evidence identified, the estimates provided regarding the safety of the various alternatives suggest that the use of NSAIDs could be associated with gastrointestinal discomfort such as nausea and abdominal pain, while the risk of hemorrhage or liver injury is uncertain. Paracetamol may not increase the risk of bleeding or acute liver failure when given at normal doses, although it may be associated with a reversible increase in transaminases. Metamizole may not be associated with hemorrhages or other major complications, including idiosyncratic reactions such as marrow aplasia. Steroids may not be associated with major complications while antihistamines may be associated with sedation, but with no other major risks. In summary, the body of evidence identified suggests that all alternatives evaluated would be safe for the symptomatic management of dengue patients (see summary of findings table 7, Annex 4).

Considering the lack of reliable evidence and the absence of side effects related to the mechanism of action of some of the drugs considered (e.g., hemorrhages and NSAIDs), the panel considered that there could be variability in the preferences of adequately informed patients, as some may prioritize the best symptomatic control while others may avoid the possibility of serious side effects.

Use of resources: The panel considered that, in general, the costs of the different options evaluated are accessible and would not generate a significant impact. However, there is variability in the Region and some options may be less expensive in some countries and more expensive in others.

Applicability and impact on equity: The panel considered that all of the alternatives evaluated, with the potential exception of some antihistamines, are universally available in the Region. Therefore, all alternatives could be implemented and their use would not significantly impact equity. However, the panel stressed that NSAIDs and glucocorticoids are probably not acceptable to some treating physicians due to the perception of serious side effects (e.g., hemorrhages) based on these medications' mechanisms of action.

Balance between benefits and negative aspects: The panel placed great importance on the common perception that NSAIDs are not safe for the management of dengue patients. Thus, in the absence of reliable evidence to certify the safety of this group of drugs for the circumstances proposed, the panel opted for other alternatives such as paracetamol or metamizole. With regard to steroids and antihistamines, it was considered that there is no evidence to justify their use. The strength of the recommendation was CONDITIONAL, as the certainty of the evidence was LOW to VERY LOW.

Annex 5 details the judgments issued by the panel of experts (framework 6).

QUESTION 9. In patients with severe arboviral infection, should treatment with systemic steroids be indicated?

RECOMMENDATION 9

It is suggested to not administer systemic steroids to patients with dengue shock (CONDITIONAL recommendation based on VERY LOW certainty regarding the effects of the intervention).

Summary of the evidence and judgments issued by the panel

Summary of the findings: Four randomized studies were identified that assessed the effects of systemic steroids in 284 people with dengue shock. In addition, 42 studies were considered that included patients treated for sepsis using systemic steroids.

The overall certainty in the body of evidence was judged to be VERY LOW, primarily because of the risk of bias and imprecision.

Benefits and harms: The body of evidence analyzed reported that the indication of systemic steroids could reduce mortality (RR = 0.68; 95% CI: 0.42–1.11; RD = −6.8%; 95% CI : −12.4–2.3). On the other hand, the intervention could increase the need for transfusions (RR = 1.08; 95% CI: 0.52–2.24; RD = 1.9%; 95% CI: −11.5–29.8) and hospital stays (mean difference: 1.1 days; 95% CI: −1.83–4.03). The risk of side effects associated with systemic steroid use in this particular population is uncertain due to limitations in the body of available evidence (see summary of findings table 8, Annex 4).

The panel considered that the potential benefits of steroid use in these circumstances are small and evaluated the fact that this intervention is not part of the usual treatment of these patients at the time that this document was prepared.

Use of resources: Considering that systemic steroids are a group of drugs with a modest economic cost, the panel agreed that there would be no high costs or high savings associated with the implementation of this intervention.

Applicability and impact on equity: The panel agreed that the intervention would be accessible if it were to be implemented in the Region and, possibly, would not have a significant impact on equity.

Balance between benefits and negative aspects: In the absence of reliable evidence to support the effect of systemic steroids on clinically relevant outcomes in patients with dengue shock, the panel prioritized the usual situation of non-routine use of this intervention. The possibility of benefits suggested by the body of evidence identified and the LOW certainty determined the CONDITIONAL strength of the recommendation.

Annex 5 details the judgments issued by the panel of experts (framework 7).

QUESTION 10. In patients with severe arboviral infection, should treatment with immunoglobulins be indicated?

RECOMMENDATION 10

It is suggested to not indicate immunoglobulins for the treatment of severe dengue (CONDITIONAL recommendation based on VERY LOW certainty regarding the effects of the intervention).

Summary of the evidence and judgments issued by the panel

Summary of the findings: Three randomized studies were identified that assessed the effects of immunoglobulins in 108 people with severe dengue. Two of the studies evaluated the use of anti-D immunoglobulin G and one evaluated the use of intravenous immunoglobulin G.

The overall certainty in the body of evidence was judged to be VERY LOW, primarily because of the risk of bias and imprecision.

Benefits and harms: The body of evidence analyzed reported that the effect of immunoglobulins on mortality (RR = 0.88; 95% CI: 0.06–13.25; RD = – 0.3%; 95% CI: –2.5–33.1) and the risk of bleeding is uncertain. On the other hand, no side effects associated with the intervention were identified, although the certainty was also VERY LOW (see summary of findings table 9, Annex 4).

The panel considered that the potential benefits of immunoglobulin use in these circumstances are negligible and evaluated the fact that this intervention is not part of the usual treatment of these patients at the time that this document was prepared.

Use of resources: Immunoglobulins have a prohibitive economic cost. The panel considered that implementation of this intervention would generate high economic costs.

Applicability and impact on equity: The panel agreed that the intervention requires a level of complexity that is not universally available in the Region. This means that it is not feasible to implement the immunoglobulin infusion in many health centers in the Region. Given this, a part of the population with less access to highly complex medical centers could not receive the intervention, which would negatively impact equity.

Balance between benefits and negative aspects: In the absence of reliable evidence to support the effect of immunoglobulin infusion on clinically relevant outcomes in patients with dengue shock, the panel prioritized the usual situation of non-routine use of this intervention. In addition, the panel considered that the implementation of immunoglobulins would lead to an excessive increase in the costs associated with care for these patients. The uncertainty regarding the effects of the intervention determined the CONDITIONAL strength of the recommendation.

Annex 5 details the judgments issued by the panel of experts (framework 8).

QUESTION 11. Should condom use be indicated to prevent non-vector-borne transmission of Zika virus?

RECOMMENDATION 11

Condom use is recommended for prevention of the sexual transmission of Zika virus infection (STRONG recommendation based on VERY LOW certainty regarding the effects of the intervention).

The STRONG recommendation does not adapt to any of the paradigmatic situations proposed to issue STRONG recommendations with LOW certainty of the evidence. However, considering that the intervention is not expensive, is easy to implement, and was proven to work for the prevention of other sexually transmitted diseases, the panel decided to issue a STRONG recommendation.

Summary of the evidence and judgments issued by the panel

Summary of the findings: Twenty-seven cases of possible sexual transmission of Zika virus were identified. In addition, a systematic review of population-based studies reported 72 cases of sexual transmission of Zika virus in the United States of America and Europe. In the absence of direct evidence on the efficacy of condoms for preventing Zika virus transmission, indirect information on human immunodeficiency virus (HIV) infection and other sexually transmitted diseases was used. Existing evidence supports the efficacy of condom use for preventing the transmission of these types of infections.

The overall certainty in the body of evidence was judged to be VERY LOW, primarily due to risk of bias and indirect information.

Benefits and harms: Based on indirect information on the effect of condom use on the prevention of sexually transmitted diseases such as HIV infection, the panel agreed that the potential benefits associated with condom use are moderate, while the negative aspects are negligible (see summary of findings table 10, Annex 4).

Use of resources: Although the direct costs of the intervention are not high, its mass implementation could have a significant impact on health systems. However, the panel considered that the potential benefits of condom use are not restricted to Zika prevention, making it difficult to determine the economic impact of such a measure.

Applicability and impact on equity: The panel agreed that guaranteeing access to condoms is a universal public health policy in the Region of the Americas and that it is generally accepted by users.

Balance between benefits and negative aspects: In the absence of reliable evidence on the benefits of condom use specifically for the prevention of Zika virus transmission, the panel based its decision on information related to the efficacy of this intervention for preventing other sexually transmitted diseases. Thus, the panel agreed that condoms could be effective for preventing the sexual transmission of Zika virus. Considering that condom use is a universally accepted intervention to prevent the spread of sexually transmitted diseases, the panel agreed to issue a STRONG recommendation in favor of condom use, to reduce the risk of transmission of these types of diseases, including Zika virus.

Annex 5 details the judgments issued by the panel of experts (framework 9).

QUESTION 12. Should the suppression of breastfeeding be indicated for women with suspected Zika virus infection?

RECOMMENDATION 12

It is recommended to maintain breastfeeding in patients with suspected or confirmed diagnosis of Zika virus infection (STRONG recommendation based on VERY LOW certainty regarding the effects of the intervention).

The STRONG recommendation is based on the second paradigmatic situation, which justifies a STRONG recommendation with LOW certainty of the evidence (doubtful benefits with established harms).

Summary of the evidence and judgments issued by the panel

Summary of the findings: The evidence identified is limited to two case reports for three mother-child pairs in which the mothers were infected with Zika virus during the postpartum period. In the three cases, the mothers started breastfeeding without negative consequences for the newborns, although in two of the cases, the newborns tested positive for Zika virus.

The overall certainty in the body of evidence was judged to be VERY LOW, primarily because of the risk of bias.

Benefits and harms: Considering the universally accepted and demonstrated benefits of breastfeeding, especially in low-resource settings, the panel considered that the suspension of breastfeeding would be associated with small benefits and large harms (see summary of findings table 11, Annex 4).

Use of resources: The suspension of breastfeeding could be related to significant costs associated with the acquisition of replacement feeding options.

Applicability and impact on equity: The panel considered that the suspension of breastfeeding is not acceptable and is likely to have a negative impact on equity in the Region of the Americas.

Balance between benefits and negative aspects: In the absence of reliable evidence demonstrating the existence of harms associated with maintaining breastfeeding in the context of acute maternal Zika virus infection, the panel decided that the demonstrated benefits of maintaining breastfeeding prevail. Thus, although the certainty of the evidence regarding the potential benefits of the suspension of breastfeeding is VERY LOW, the panel issued a STRONG recommendation based on the second paradigmatic situation, in which it would be reasonable to make STRONG recommendations with LOW or VERY LOW overall certainty in the evidence (doubtful benefits, but established harms related to implementation of the intervention).

Annex 5 details the judgments issued by the panel of experts (framework 10).

PART IV. Implementation plan

ACTIONS NEEDED TO IMPLEMENT THE RECOMMENDATIONS IN THE CLINICAL PRACTICE GUIDELINES

- Promote the dissemination, distribution, and recognition of clinical practice guidelines by countries and Member States, in compliance with Resolution CD55.R6 (*18*) in its strategic line 2 (strengthen health services capacity for the differential diagnosis and clinical management of arboviral diseases).
- Ensure the availability of guidelines in different formats (digital and printed) at all levels of health care.
- Strengthen national technical capacities for the management of arbovirus cases based on the content of the clinical practice guidelines.

BARRIERS TO IMPLEMENTATION

- Lack of human resources at different levels of health care.
- Lack of material supplies and accessibility to the clinical practice guidelines.
- Failure of health professionals (physicians, nurses, others) to comply with the recommendations contained in the clinical practice guidelines.
- Limited financial resources allocated to training processes (theoretical and practical) in the use of the clinical practice guidelines.

IMPLEMENTATION STRATEGIES

- Development of materials to support the training processes (clinical management flowcharts, updating of the instrument for the diagnosis and care of patients with suspected arbovirus).
- Use of the PAHO Virtual Campus for Public Health to train the trainers.
- Development of virtual courses on the diagnosis and clinical management of dengue, chikungunya, and Zika, which are accessible to all health personnel and available on the PAHO and WHO virtual public health campuses.
- Development of mobile applications for the diagnosis and management of patients with suspected arbovirus, based on the recommendations of the clinical practice guidelines.
- Monitoring and evaluation of the Strategy for Arboviral Disease Prevention and Control (*19*), including the patient care component.
- Establish alliances with strategic partners: academia, non-governmental organizations, donors, and private industry, among others, to promote training processes on the use of clinical practice guidelines.

INDICATORS

Below are the process and outcome indicators related to the implementation of the clinical practice guidelines.

Process indicators

- Number of countries that adapted their national guidelines for the clinical management of arboviruses based on the clinical practice guidelines over the total number of countries and territories in the Americas.
- Number of physicians and nursing personnel trained in the clinical diagnosis, differential diagnosis, and integrated management of cases with suspected dengue, chikungunya, Zika, or other arboviruses over the total number of physicians and nursing personnel in the training plan.

- Number of trained physicians and nurses who appropriately use the guidelines and protocols for the management of cases with suspected dengue, chikungunya, Zika, or other arboviruses over the total number of trained physicians and nurses.

Outcome and impact indicators

- Dengue case fatality rate at the regional and national levels.
- Proportion of severe dengue at the regional and national levels.

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ANNEXES

ANNEX 1. Professionals who collaborated on the development of the guidelines

1.1. GUIDANCE GROUP

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1.2 PANEL OF EXPERTS

The first step in developing the publication was to determine the scope and objectives of these clinical practice guidelines and the clinical questions to include in a systematic review. The second step was to form a panel of experts that included clinicians and epidemiologists, who were in charge of developing the recommendations following the highest methodological standards. The multidisciplinary team formed is detailed below.

Name	Specialty	Affiliation	Country
Anabelle Alfaro	Internist and emergency medicine physician	Latina University	Costa Rica
Yasmin Irina Alfaro Serrano*	Internist	San Juan de Dios National Hospital of San Miguel	El Salvador
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Leopoldo Córdova	Internist and infectious disease physician	Jackson Memorial Hospital	United States of America
Bladimir Cruz*	Pediatrician	Benjamin Bloom National Children's Hospital	El Salvador
Orlando Cuéllar**	Transfusion medicine	San Juan de Dios Hospital	Bolivia (Plurinational State of)
Pablo Durán*	Advisor on Perinatal Health	PAHO Latin American Center for Perinatology	
Virgen Gómez**	Pediatrician and infectious disease physician	Dr. Robert Reid Cabral Children's Hospital	Dominican Republic
Rodolfo Gómez Ponce*	Advisor on Reproductive Health	PAHO Latin American Center for Perinatology	
Franklin Hernández*	Advisor on Health Surveillance and Disease Prevention and Control	PAHO Country Office, El Salvador	

Name	Specialty	Affiliation	Country
Ronald Edgardo López*	Obstetrician-gynecologist	National Women's Hospital	El Salvador
Kleber Luz*	Pediatrician and infectious disease physician	Federal University of Rio Grande do Norte	Brazil
Eric Martínez	Pediatrician and infectious disease physician	Pedro Kouri Institute of Tropical Medicine	Cuba
Will Parada*	Clinical physician	San Juan de Dios National Hospital of Santa Ana	El Salvador
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André Ricardo Ribas de Freitas**	Physician epidemiologist	São Leopoldo Mandic School	Brazil
Liliana Sánchez**	Physician epidemiologist	Dengue Department, Centers for Disease Control and Prevention	Puerto Rico
Fabrice Simon**	Infectious disease physician	Laveran Military Teaching Hospital	France
Jaime Torres**	Internist and infectious disease physician	Tropical Medicine Institute, Central University of Venezuela	Venezuela (Bolivarian Republic of)
Sanet Torres Torres*	Pediatric infectious disease physician	San Jorge Children's Hospital	Puerto Rico

* Participated only in the writing of the guidelines scope and objectives, and the clinical questions that were part of the systematic review.

** Participated only in the development of the recommendations.

1.3 METHODOLOGISTS

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ANNEX 2. Summary of the analysis of conflicts of interest

Below is the analysis of the declarations of interest presented by each member of the guidelines development group.

Name	Role in the development of the guidelines	A. Specific or non-specific personal economic interest	B. Specific or non-specific non-personal economic interest	C. Personal non-economic interest	D. A relative's specific or non-specific personal economic interest	Are there any other circumstances that could affect your objectivity or independence during the process?
Anabelle Alfaro	Expert	No	No	No	No	No
Osvaldo Castro	Expert	No	No	No	No	No
Leopoldo Córdova	Expert	No	No	No	No	No
Orlando Cuéllar	Expert	No	No	No	No	No
Virgin Gómez	Expert	No	No	No	No	No
Ariel Izcovich	Methodologist	No	No	No	No	No
Eric Martínez	Expert	No	No	No	No	No
Martín Alberto Ragusa	Methodologist	No	No	No	No	No
André Ricardo Ribas de Freitas	Expert	No	No	No	No	No
Liliana Sánchez	Expert	No	No	No	No	No
Fabrice Simon	Expert	No	No	No	No	No
Jaime Torres	Expert	No	No	No	No	No
María Teresa Vallejo Ortega	Methodologist	No	No	No	No	No

ANNEX 3. Clinical questions: PICO

Below are the PICO questions as originally presented.

QUESTION 1. How should patients with suspected arbovirus be diagnosed?

ASPECT TO CONSIDER	KEY TERMS
Conditions of interest	Dengue Chikungunya Zika Other arboviruses
Type of tests	General clinical manifestations Signs and symptoms associated with infections: peri-orbital pain (yellow fever), joint pain (chikungunya virus) Differential diagnoses between arboviruses

QUESTIONS 2.1 AND 3.1. What is the best strategy to identify patients at risk of progressing to severe dengue?

POPULATION	FACTOR	OUTCOMES
Adults with dengue	Warning signs: – Irritability, drowsiness, lethargy – Severe abdominal pain – Persistent vomiting – Fluid accumulation – Mucosal bleeding – Postural hypotension – Hepatomegaly larger than 2 cm – Progressive increase in hematocrit Other signs and symptoms: – Decreased mean blood pressure – History or infection with Zika virus – Prolonged capillary refill time – Narrowing pulse pressure – Oliguria – Positive tourniquet test – Acute fetal distress (pregnant women) Laboratory results – Thrombocytopenia – Leukopenia Frequency of evaluation – Only at the time of the initial visit – Reevaluation	Dengue shock Severe dengue (includes organ failure) Death Length of hospital stay Hospitalization Admission to the intensive care unit Hyperhydration (safety) Bruising, bleeding Infection from venipuncture Compartment syndrome
Pregnant women with dengue		Risk of severe dengue Risk of dengue shock Obstetric outcomes Fetus: abortion, intrauterine death, prematurity, fetal malformations, intrauterine growth retardation Mother: postpartum hemorrhage
Children with dengue		Dengue shock Severe dengue (includes organ failure) Death Length of hospital stay Hospitalization Admission to the intensive care unit Hyperhydration Bruising, bleeding Infection from venipuncture Compartment syndrome
Infants with dengue		

QUESTIONS 2.2 AND 3.2: What are the factors related to a poor prognosis in Zika?

ASPECT TO CONSIDER	KEY TERMS
Groups of interest	General population Pregnant women Children
Type of factors	Comorbidities Neurological findings Congenital Zika syndrome Zika and Guillain-Barré syndrome Mortality

QUESTIONS 2.3 AND 3.3: What are the factors related to a poor prognosis in chikungunya?

ASPECT TO CONSIDER	KEY TERMS
Groups of interest	General population Pregnant women Children
Type of factors	Comorbidities Age Gestational age Signs and symptoms

QUESTION 4: What is the best orally administered fluid management scheme in patients with arboviral infection?

ASPECT TO CONSIDER	KEY TERMS
Conditions of interest	Dengue Chikungunya Zika Pregnant women
Alternatives	Water alone Oral hydration salts Local preparations (drinks)

QUESTIONS 5 AND 6: What is the best intravenous fluid management scheme in patients with arboviral infection?

POPULATION	TESTS	OUTCOMES
Patients with dengue and warning signs or with severe dengue	Type of solution Crystalloids (normal saline solution, lactate) Colloids (albumin, volume expansion solution)	Dengue shock Severe dengue (includes organ failure) Death Length of hospital stay Admission to the intensive care unit Hyperhydration Anaphylaxis Fluid overload
Patients with dengue or with resistance to initial management with crystalloids	Crystalloids (normal saline solution, lactate) Colloids (albumin, volume expansion solution) Blood Blood products	
Patients with severe chikungunya	Crystalloids (normal saline solution, lactate) Colloids (albumin, volume expansion solution)	
Patients with severe Zika	Crystalloids (normal saline solution, lactate) Colloids (albumin, volume expansion solution)	
Pregnant women with dengue	Blood Blood products	Dengue shock Severe dengue (includes organ failure) Death Length of hospital stay Admission to the intensive care unit Obstetric outcomes Hyperhydration Anaphylaxis Fluid overload
Children with arboviral infection	Hydration scheme by kilogram of weight Hydration scheme by ideal weight	Dengue shock Severe dengue (includes organ failure) Death Length of hospital stay Admission to the intensive care unit Hyperhydration Anaphylaxis Fluid overload

Subpopulations in which the original recommendation could be modified: 1) patients with cardiopathy, 2) patients with renal insufficiency, 3) immunocompromised patients, 4) patients with comorbidities, 5) obese population, and 6) pregnant women.

QUESTION 7: Should the transfusion of blood components be indicated for dengue patients with thrombocytopenia?

POPULATION	INTERVENTIONS/COMPARISONS	OUTCOMES
Dengue patients with thrombocytopenia	Blood components (e.g., platelets, fresh frozen plasma)	Death Hemorrhages Side effects

QUESTION 8: What is the efficacy and safety of the interventions used for the management of pain and fever (symptomatic management) in patients with acute arbovirus?

POPULATION	INTERVENTIONS/COMPARISONS	OUTCOMES
Dengue patients with no warning signs Dengue patients with warning signs Patients with severe dengue	Paracetamol Metamizole Aspirin NSAID Physical means Co-administered medicines No treatment	Fever control Pain control Side effects
Patients with chikungunya	Paracetamol Metamizole Aspirin Other NSAIDs Physical means Co-administered medicines Steroids Antihistamines Opioids No treatment	Fever control Pain control Side effects
Patients with Zika	Paracetamol Metamizole Aspirin Other NSAIDs Physical means Co-administered medicines Steroids Antihistamines No treatment Eye drops	Fever control Pain control Itch control Rash control Control of conjunctival irritation Side effects

Subpopulations in which the original recommendation could be modified: 1) patients with cardiopathy, 2) patients with renal insufficiency, 3) immunocompromised patients, 4) patients with comorbidities, 5) children, and 6) pregnant women.

QUESTIONS 9 AND 10: What additional interventions are useful for the management of patients with severe arboviral infection?

POPULATION	INTERVENTIONS/COMPARISONS	OUTCOMES
Patients with severe dengue, severe chikungunya, or severe Zika	Immunoglobulins Steroids	Death Side effects

QUESTIONS 11 AND 12: Which interventions are effective for preventing non-vector-borne transmission of Zika virus?

POPULATION	INTERVENTIONS/COMPARISONS	OUTCOMES
Patients with Zika	Condom use Breastfeeding Sexual abstinence	Transmission Congenital malformations Abortion Intrauterine fetal death

ANNEX 4. Summary of findings tables

SUMMARY OF FINDINGS TABLE 1. CLINICAL MANIFESTATIONS TO DIFFERENTIATE ARBOVIRAL DISEASES FROM EACH OTHER AND FROM OTHER FEBRILE DISEASES

Clinical and laboratory alterations to differentiate distinct arboviral diseases

Population: patients with suspected arbovirus infection

Intervention: clinical and laboratory alterations

Comparison: different arboviral diseases or other febrile diseases

Clinical and laboratory alterations	Dengue versus others OR (95% CI)	Chikungunya versus others OR (95% CI)	Zika versus others OR (95% CI)	Dengue versus chikungunya OR (95% CI)	Dengue versus Zika OR (95% CI)	Chikungunya versus Zika OR (95% CI)	Conclusions
Number of participants (studies)	**Certainty of the evidence**	**Certainty of the evidence**	**Certainty of the evidence**	**Certainty of the evidence**	**Certainty of the evidence**	**Certainty of the evidence**	
Abdominal pain Number of participants: 33,705 (41 observational studies)	1.09 [0.76, 1.56] MODERATE ⦿⦿⦿◯[a]	0.66 [0.53, 0.83] MODERATE ⦿⦿⦿◯[b]	0.25 [0.16, 0.40] MODERATE ⦿⦿⦿◯[b]	2.27 [1.68, 3.05] MODERATE ⦿⦿⦿◯[b]	3.16 [1.29, 7.71] MODERATE ⦿⦿⦿◯[b]	1.17 [0.32, 4.17] LOW ⦿⦿◯◯[a,b]	The presence of abdominal pain probably increases the likelihood of dengue.
Sensory disorder Number of participants: 22,063 (16 observational studies)	1.14 [0.83, 1.55] LOW ⦿⦿◯◯[a,b]	1.22 [0.86, 1.73] LOW ⦿⦿◯◯[a,b]	0.39 [0.24, 0.62] MODERATE ⦿⦿⦿◯[b]	0.92 [0.51, 1.66] LOW ⦿⦿◯◯[a,b]	- -	- -	The presence of sensory disorder may not allow for differentiation between the different arboviral diseases.
Mucosal bleeding Number of participants: 20,201 (12 observational studies)	1.93 [0.99, 3.78] MODERATE ⦿⦿⦿◯[a]	1.23 [1.09, 1.38] MODERATE ⦿⦿⦿◯[b]	0.32 [0.07, 1.38] LOW ⦿⦿◯◯[a,b]	0.70 [0.36, 1.48] LOW ⦿⦿◯◯[a,b]	0.45 [0.06, 3.54] LOW ⦿⦿◯◯[a,b]	- -	The presence of mucosal bleeding probably increases the likelihood of chikungunya and dengue.
Progressive increase in hematocrit Number of participants: 10,406 (8 observational studies)	1.46 [1.10, 1.94] HIGH ⦿⦿⦿⦿	0.35 [0.2, 0.64] MODERATE ⦿⦿⦿◯[b]	- -	- -	- -	- -	The presence of a progressive increase in hematocrit increases the likelihood of dengue.
Thrombocytopenia Number of participants: 35,017 (29 observational studies)	4.41 [2.68, 7.26] HIGH ⦿⦿⦿⦿	0.64 [0.29, 1.41] MODERATE ⦿⦿⦿◯[a]	- -	8.56 [2.68, 27.38] HIGH ⦿⦿⦿⦿	- -	- -	The presence of thrombocytopenia increases the likelihood of dengue.

Clinical and laboratory alterations	Dengue versus others OR (95% CI)	Chikungunya versus others OR (95% CI)	Zika versus others OR (95% CI)	Dengue versus chikungunya OR (95% CI)	Dengue versus Zika OR (95% CI)	Chikungunya versus Zika OR (95% CI)	Conclusions
Number of participants (studies)	Certainty of the evidence	Certainty of the evidence	Certainty of the evidence	Certainty of the evidence	Certainty of the evidence	Certainty of the evidence	
Leukopenia Number of participants: 39,716 (24 observational studies)	5.04 [3.72, 6.83] HIGH ⊕⊕⊕⊕	0.85 [0.64, 1.13] MODERATE ⊕⊕⊕◯[a]	-	5.51 [2.89, 10.50] HIGH ⊕⊕⊕⊕	- -	- -	The presence of leukopenia increases the likelihood of dengue.
Lymphopenia Number of participants: 3,081 (6 observational studies)	1.27 [0.65, 2.47] LOW ⊕⊕◯◯[a,b]	1.80 [1.07, 3.04] LOW ⊕⊕◯◯[a,b]	- -	2.1 [1.2, 3.9] MODERATE ⊕⊕⊕◯[b]	- -	- -	It is uncertain whether the presence of lymphopenia allows for differentiation between the different arboviral diseases.
Elevated transaminases Number of participants: 6,105 (10 observational studies)	2.48 [0.75, 8.20] MODERATE ⊕⊕⊕◯[b]	0.13 [0.04, 0.47] LOW ⊕⊕◯◯[a,b]	- -	6.94 [1.56, 30.84] MODERATE ⊕⊕⊕◯[b]	- -	- -	Elevated transaminases probably increase the likelihood of dengue.
Vomiting Number of participants: 38,553 (39 observational studies)	1.30 [1.15, 1.47] HIGH ⊕⊕⊕⊕	0.54 [0.47, 0.63] MODERATE ⊕⊕⊕◯[b]	0.14 [0.06, 0.32] MODERATE ⊕⊕⊕◯[b]	2.46 [1.73, 3.51] MODERATE ⊕⊕⊕◯[b]	5.14 [0.79, 33.18] LOW ⊕⊕◯◯[a,b]	3.54 [0.56, 21.85] LOW ⊕⊕◯◯[a,b]	The presence of vomiting probably increases the likelihood of dengue.
Hepatomegaly Number of participants: 7,948 (21 observational studies)	1.32 [0.88, 1.98] MODERATE ⊕⊕⊕◯[a]	0.75 [0.06, 8.16] LOW ⊕⊕◯◯[a,b]	0.19 [0.04, 0.88] MODERATE ⊕⊕⊕◯[b]	2.92 [0.56, 15.04] LOW ⊕⊕◯◯[a,b]	5.76 [0.009 , 3,392] LOW ⊕⊕◯◯[a,b]	- -	The presence of hepatomegaly may increase the likelihood of dengue.
Positive tourniquet test Number of participants: 35,905 (22 observational studies)	3.17 [2.42, 4.17] MODERATE ⊕⊕⊕◯[b]	- -	- -	4.16 [1.35, 12.66] LOW ⊕⊕◯◯[a,b]	- -	- -	A positive tourniquet test probably increases the likelihood of dengue.
Fluid accumulation Number of participants: (8 observational studies)	3.12 [1.56, 6.23] MODERATE ⊕⊕⊕◯[b]	5.10 [0.49, 52.99] LOW ⊕⊕◯◯[a,b]	3.33 [2.04, 5.42] MODERATE ⊕⊕⊕◯[b]	0.11 [0.01, 1.01] LOW ⊕⊕◯◯[a,b]	- -	- -	Fluid accumulation may not allow for differentiation between the different arboviral diseases.
Arthralgias Number of participants: 40,716 (47 observational studies)	2.07 1.68, 2.57] HIGH ⊕⊕⊕⊕	6.96 [3.32, 14.6] HIGH ⊕⊕⊕⊕	1.11 [0.60, 2.03] LOW ⊕⊕◯◯[a,b]	0.19 [0.09, 0.38] HIGH ⊕⊕⊕⊕	0.93 [0.32, 2.65] LOW ⊕⊕◯◯[a,b]	2.41 [0.41, 14.09] LOW ⊕⊕◯◯[a,b]	The presence of arthralgias increases the likelihood of chikungunya and, to a lesser extent, dengue.

Clinical and laboratory alterations	Dengue versus others OR (95% CI)	Chikungunya versus others OR (95% CI)	Zika versus others OR (95% CI)	Dengue versus chikungunya OR (95% CI)	Dengue versus Zika OR (95% CI)	Chikungunya versus Zika OR (95% CI)	Conclusions
Number of participants (studies)	Certainty of the evidence	Certainty of the evidence	Certainty of the evidence	Certainty of the evidence	Certainty of the evidence	Certainty of the evidence	
Retro-ocular pain Number of participants: 41,596 (42 observational studies)	1.85 [1.60, 2.14]	1.46 [1.29, 1.64]	1.56 [0.77, 3.19]	1.44 [1.26, 1.65]	0.79 [0.47, 1.34]	0.81 [0.44, 1.49]	The presence of retro-ocular pain probably increases the likelihood of dengue.
	HIGH ⊕⊕⊕⊕	MODERATE ⊕⊕⊕◯[b]	LOW ⊕⊕◯◯[a,b]	MODERATE ⊕⊕⊕◯[b]	LOW ⊕⊕◯◯[a,b]	LOW ⊕⊕◯◯[a,b]	
Anorexia or hyporexia Number of participants: 26,000 (23 observational studies)	1.88 [1.47, 2.41]	0.76 [0.57, 1.01]	0.27 [0.16, 0.46]	2.31 [1.72, 3.11]	1.37 [0.75, 2.51]	0.4 [0.13, 1.27]	The presence of anorexia or hyporexia increases the likelihood of dengue.
	HIGH ⊕⊕⊕⊕	MODERATE ⊕⊕⊕◯[a]	MODERATE ⊕⊕⊕◯[b]	MODERATE ⊕⊕⊕◯[b]	LOW ⊕⊕◯◯[a,b]	LOW ⊕⊕◯◯[a,b]	
Cough Number of participants: 26,530 (26 observational studies)	0.54 [0.42, 0.71]	0.62 [0.17, 2.27]	0.57 [0.35, 0.91]	1.62 [1.16, 2.27]	2.74 [0.55, 13.5]	-	The presence of cough may increase the likelihood of dengue.
	HIGH ⊕⊕⊕⊕	LOW ⊕⊕◯◯[a,b]	MODERATE ⊕⊕⊕◯[b]	MODERATE ⊕⊕⊕◯[b]	LOW ⊕⊕◯◯[a,b]	-	
Cutaneous eruption Number of participants: 40,974 (50 observational studies)	3.20 [2.34, 4.38]	2.96 [1.60, 5.46]	8.20 [4.00, 16.81]	0.52 [0.45, 0.59]	0.25 [0.09, 0.63]	0.22 [0.07, 0.70]	The presence of cutaneous eruption probably increases the likelihood of Zika and, to a lesser extent, chikungunya.
	HIGH ⊕⊕⊕⊕	MODERATE ⊕⊕⊕◯[b]	HIGH ⊕⊕⊕⊕	HIGH ⊕⊕⊕⊕	MODERATE ⊕⊕⊕◯[b]	MODERATE ⊕⊕⊕◯[b]	
Petechiae Number of participants: 17,826 (13 observational studies)	2.67 [1.63, 4.37]	5.05 [4.45, 5.74]	0.29 [0.11, 0.73]	1.72 [0.11, 25.7]	-	-	It is uncertain whether petechiae allow for differentiation between the different arboviral diseases.
	HIGH ⊕⊕⊕⊕	HIGH ⊕⊕⊕⊕[c]	MODERATE ⊕⊕⊕◯[b]	LOW ⊕⊕◯◯[a,b]	-	-	
Diarrhea Number of participants: 29,238 (39 observational studies)	1.65 [0.94, 1.43]	0.59 [0.38, 0.93]	0.70 [0.46, 1.06]	2.35 [1.84, 3.02]	1.54 [0.38, 6.23]	-	The presence of diarrhea may increase the likelihood of dengue.
	MODERATE ⊕⊕⊕◯[a]	HIGH ⊕⊕⊕⊕	MODERATE ⊕⊕⊕◯[b]	HIGH ⊕⊕⊕⊕	LOW ⊕⊕◯◯[a,b]	-	
Headache Number of participants: 50,337 (54 observational studies)	1.53 [1.27, 1.85]	0.96 [0.64, 1.54]	0.60 [0.34, 1.06]	1.80 [1.25, 2.58]	2.25 [0.68, 7.38]	0.62 [0.30, 1.29]	The presence of headache probably increases the likelihood of dengue.
	HIGH ⊕⊕⊕⊕	MODERATE ⊕⊕⊕◯[a]	LOW ⊕⊕◯◯[a,b]	HIGH ⊕⊕⊕⊕	LOW ⊕⊕◯◯[a,b]	LOW ⊕⊕◯◯[a,b]	
Pruritus Number of participants: 15,219 (15 observational studies)	1.34 [0.85, 2.11]	1.35 [0.37, 4.89]	3.35 [1.28, 8.79]	0.87 [0.32, 2.36]	0.2 [0.05, 0.8]	0.08 [0.02, 0.26]	The presence of pruritus increases the likelihood of Zika.
	LOW ⊕⊕◯◯[a,b]	LOW ⊕⊕◯◯[a,b]	HIGH ⊕⊕⊕⊕	LOW ⊕⊕◯◯[a,b]	MODERATE ⊕⊕⊕◯[b]	MODERATE ⊕⊕⊕◯[b]	
Rhinorrhea Number of participants: 25,963 (12 observational studies)	0.44 [0.29, 0.68)	0.29 [0.05, 1.66)	1.32 [0.81, 2.14)	0.95 [0.83, 1.09)	-	-	The presence of rhinorrhea may not allow for differentiation between the different arboviral diseases.
	HIGH ⊕⊕⊕⊕	LOW ⊕⊕◯◯[a,b]	LOW ⊕⊕◯◯[a,b]	MODERATE ⊕⊕⊕◯[a]	-	-	

Clinical and laboratory alterations	Dengue versus others OR (95% CI)	Chikungunya versus others OR (95% CI)	Zika versus others OR (95% CI)	Dengue versus chikungunya OR (95% CI)	Dengue versus Zika OR (95% CI)	Chikungunya versus Zika OR (95% CI)	Conclusions
Number of participants (studies)	Certainty of the evidence	Certainty of the evidence	Certainty of the evidence	Certainty of the evidence	Certainty of the evidence	Certainty of the evidence	
Jaundice Number of participants: 14,326 (13 observational studies)	0.37 [0.11, 1.17]	0.55 [0.21, 1.48]	-	0.24 [0.01, 3.24]	-	-	The presence of jaundice may not allow for differentiation between the different arboviral diseases.
	LOW ⊕⊕◯◯[a,b]	LOW ⊕⊕◯◯[a,b]	-	LOW ⊕⊕◯◯[a,b]	-	-	
Splenomegaly Number of participants: 5,085 (12 observational studies)	0.41 [0.13, 1.31]	0.04 [0.005, 0.35]	-	0.48 [0.005, 45.7]	-	-	The presence of splenomegaly may not allow for differentiation between the different arboviral diseases.
	LOW ⊕⊕◯◯[a,b]	MODERATE ⊕⊕⊕◯[b]	-	LOW ⊕⊕◯◯[a,b]	-	-	
Hemorrhages Number of participants: 30,000 (27 observational studies)	2.56 [1.86, 3.53]	1.81 [1.65, 1.97]	0.26 [0.1, 0.67]	0.84 [0.52, 1.33]	1.68 [0.22, 2.05]	0.59 [0.07, 4.83]	The presence of hemorrhages may not allow for differentiation between the different arboviral diseases.
	HIGH ⊕⊕⊕⊕	MODERATE ⊕⊕⊕◯[b]	MODERATE ⊕⊕⊕◯[b]	LOW ⊕⊕◯◯[a,b]	LOW ⊕⊕◯◯[a,b]	LOW ⊕⊕◯◯[a,b]	
High fever Number of participants: 796 (3 observational studies)	0.37 [0.17, 0.82]	2.73 [1.35, 5.49]	-	-	-	-	It is uncertain whether high fever allows for differentiation between the different arboviral diseases.
	LOW ⊕⊕◯◯[b]	MODERATE ⊕⊕⊕◯[b]	-	-	-	-	
Dyspnea or difficulty breathing Number of participants: 4,763 (12 observational studies)	1.00 [0.60, 1.68]	1.81 [1.05, 3.13]	0.49 [0.24, 1.03]	1.83 [0.32, 10.36]	-	-	It is uncertain whether dyspnea or difficulty breathing allow for differentiation between the different arboviral diseases.
	MODERATE ⊕⊕⊕◯[b]	LOW ⊕⊕◯◯[a,b]	LOW ⊕⊕◯◯[a,b]	LOW ⊕⊕◯◯[a,b]	-	-	
Asthenia Number of participants: 11,292 (22 observational studies)	1.59 [1.14, 2.20]	2.64 [1.67, 4.15]	1.44 [0.25, 8.37]	1.00 [0.64, 1.55]	0.89 [0.31, 2.52]	-	Asthenia may not allow for differentiation between the different arboviral diseases.
	MODERATE ⊕⊕⊕◯[b]	MODERATE ⊕⊕⊕◯[b]	LOW ⊕⊕◯◯[a,b]	LOW ⊕⊕◯◯[a,b]	LOW ⊕⊕◯◯[a,b]	-	
Arthritis Number of participants: 12,273 (4 observational studies)	1.44 [0.97, 2.15]	6.49 [5.74, 7.34]	1.64 [0.68, 3.93]	0.36 [0.21, 0.63]	1.02 [0.26, 3.94]	1.48 [0.46, 4.73]	Arthritis probably increases the likelihood of chikungunya.
	LOW ⊕⊕◯◯[a,b]	MODERATE ⊕⊕⊕◯[b]	LOW ⊕⊕◯◯[a,b]	MODERATE ⊕⊕⊕◯[b]	LOW ⊕⊕◯◯[a,b]	LOW ⊕⊕◯◯[a,b]	
Prolonged fever Number of participants: 573 (2 observational studies)	0.45 [0.27, 0.73]	-	-	0.22 [0.02, 1.89]	-	-	It is uncertain whether prolonged fever allows for differentiation between the different arboviral diseases.
	LOW ⊕⊕◯◯[b]	-	-	LOW ⊕⊕◯◯[a,b]	-	-	

Clinical and laboratory alterations	Dengue versus others OR (95% CI)	Chikungunya versus others OR (95% CI)	Zika versus others OR (95% CI)	Dengue versus chikungunya OR (95% CI)	Dengue versus Zika OR (95% CI)	Chikungunya versus Zika OR (95% CI)	Conclusions
Number of participants (studies)	Certainty of the evidence	Certainty of the evidence	Certainty of the evidence	Certainty of the evidence	Certainty of the evidence	Certainty of the evidence	
Anemia Number of participants: 7,207 (9 observational studies)	0.35 [0.02, 5.74] LOW ⦿⦿○○[a,b]	1.10 [0.65, 1.87] LOW ⦿⦿○○[a,b]	- -	0.69 [0.07, 6.71] LOW ⦿⦿○○[a,b]	- -	- -	It is uncertain whether the presence of anemia allows for differentiation between the different arboviral diseases.
Myalgias or bone pain Number of participants: 42,485 (50 observational studies)	1.61 [1.36, 1.91] HIGH ⦿⦿⦿⦿	3.10 [2.75, 3.49] HIGH ⦿⦿⦿⦿	0.51 [0.39, 0.68] MODERATE ⦿⦿⦿○[b]	0.55 [0.48, 0.63] MODERATE ⦿⦿⦿○[b]	1.17 [0.67, 2.03] LOW ⦿⦿○○[a,b]	1.58 [0.48, 5.20] LOW ⦿⦿○○[a,b]	Myalgias probably increase the likelihood of chikungunya and dengue.
Adenopathies Number of participants: 6,812 (13 observational studies)	0.96 [0.61, 1.50] LOW ⦿⦿○○[a,b]	1.09 [0.38, 3.10] LOW ⦿⦿○○[a,b]	2.15 [1.44, 3.20] MODERATE ⦿⦿⦿○[b]	- -	- -	- -	The presence of adenopathies may increase the likelihood of Zika.
Pharyngitis or odynophagia Number of participants: 20,002 (23 observational studies)	0.61 [0.43, 0.87] HIGH ⦿⦿⦿⦿	0.21 [0.06, 0.69] HIGH ⦿⦿⦿⦿	1.57 [1.04, 2.37] MODERATE ⦿⦿⦿○[b]	1.53 [1.12, 2.10] MODERATE ⦿⦿⦿○[b]	1.06 [0.49, 2.27] LOW ⦿⦿○○[a,b]	0.43 [0.15, 1.25] LOW ⦿⦿○○[a,b]	The presence of pharyngitis or odynophagia may increase the likelihood of Zika.
Conjunctivitis or conjunctival hemorrhage Number of participants: 18,834 (18 observational studies)	1.50 [1.02, 2.19] HIGH ⦿⦿⦿⦿	1.19 [1.09, 1.29] HIGH ⦿⦿⦿⦿	1.67 [1.16, 2.40] HIGH ⦿⦿⦿⦿	0.81 [0.72, 0.91] MODERATE ⦿⦿⦿○[b]	0.15 [0.002, 0.80] MODERATE ⦿⦿⦿○[b]	0.72 [0.16, 3.23] LOW ⦿⦿○○[a,b]	The presence of conjunctivitis or conjunctival hemorrhage probably increases the likelihood of Zika and chikungunya.
Dysgeusia Number of participants: 2,883 (4 observational studies)	3.75 [2.85, 4.94] MODERATE ⦿⦿⦿○[b]	1.15 [0.59, 2.24] LOW ⦿⦿○○[a,b]	- -	- -	- -	- -	The presence of dysgeusia may increase the likelihood of dengue.
Chills Number of participants: 21,574 (20 observational studies)	2.18 [1.80, 2.63] MODERATE ⦿⦿⦿○[b]	1.46 [1.32, 1.62] MODERATE ⦿⦿⦿○[b]	0.44 [0.30, 0.64] MODERATE ⦿⦿⦿○[b]	1.55 [1.17, 2.06] MODERATE ⦿⦿⦿○[b]	- -	- -	It is uncertain whether the presence of chills allows for differentiation between the different arboviral diseases.
Photophobia Number of participants: 179 (1 observational study)	- -	0.64 [0.2, 1.97] LOW ⦿⦿○○[a,b]	- -	- -	- -	- -	It is uncertain whether photophobia allows for differentiation between the different arboviral diseases.

Clinical and laboratory alterations	Dengue versus others OR (95% CI)	Chikungunya versus others OR (95% CI)	Zika versus others OR (95% CI)	Dengue versus chikungunya OR (95% CI)	Dengue versus Zika OR (95% CI)	Chikungunya versus Zika OR (95% CI)	Conclusions
Number of participants (studies)	Certainty of the evidence	Certainty of the evidence	Certainty of the evidence	Certainty of the evidence	Certainty of the evidence	Certainty of the evidence	
Ear pain Number of participants: 659 (1 observational study)	-	-	1.13 [0.57, 2.23]	-	-	-	It is uncertain whether ear pain allows for differentiation between the different arboviral diseases.
	-	-	LOW ⦿⦿○○[a,b]	-	-	-	

Notes

CI: confidence interval; **OR:** odds ratio.

The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Grading of the certainty of the evidence from the GRADE working group

HIGH Certainty: we are very sure that the true effect approximates the estimated effect.

MODERATE Certainty: we have moderate confidence in the estimated effect. The true effect is probably close to the estimated effect, but there is a possibility that it is substantially different.

LOW Certainty: our confidence in the estimated effect is limited. The true effect may be substantially different from the estimated effect.

VERY LOW Certainty: we have very little confidence in the estimated effect. The true effect is probably substantially different from the estimated effect.

[a] The 95% CI includes the differentiation and the lack of differentiation between the different options. The size of the 95% CI may or may not be related to an inconsistency.

[b] Methodological problems were found in all or almost all included studies.

[c] The only study that reported this estimate did not provide an adjusted result for skin bleeding, but did provide one for any bleeding (OR = 1.69; 95% CI: 1.24–2.29).

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SUMMARY OF FINDINGS TABLE 2. PROGNOSTIC FACTORS IN PATIENTS WITH DENGUE

Prognostic factors in patients with dengue

Population: patients with dengue

Intervention: prognostic factors

Comparison: not applicable

Prognostic factors evaluated Number of participants (studies)	Relative effect OR (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Conclusions
		Risk without the prognostic factor	Risk with the prognostic factor	Difference		
Narrowing pulse pressure Number of participants: 5,096 (6 observational studies)	7.12 [3.02, 16.76]	**Low**			MODERATE ⊙⊙⊙○[b]	The presence of narrowing pulse pressure is probably a predictor of severe dengue.
		5.6%[i,a]	29.7% [15.2, 49.9]	24.1% [9.6, 44.3]		
		High				
		15.6%[ii]	56.8% [35.8, 75.6]	41.2% [20.2, 60]		
Acute renal failure Number of participants: 4,348 (8 observational studies)	6.73 [1.66, 27.20]	**Low**			LOW ⊙⊙○○[c,d]	Acute renal failure may be a predictor of severe dengue.
		5.6%[i]	28.5% [9, 61.7]	22.9% [3.4, 56.1]		
		High				
		15.6%[ii]	55.4% [23.5, 83.4]	39.8% [7.9, 67.8]		
Arterial hypotension Number of participants: 7,463 (19 observational studies)	5.38 [3.31, 8.75]	**Low**			MODERATE ⊙⊙⊙○[b]	Arterial hypotension is probably a predictor of severe dengue.
		5.6%[i]	24.2% [16.4, 34.2]	18.6% [10.8, 28.6]		
		High				
		15.6%[ii]	49.9% [38, 61.8]	34.3% [22.4, 46.2]		
Sensory disorder manifesting with encephalopathy, lethargy, irritability, drowsiness Number of participants: 76,881 (33 observational studies)	5.23 [3.45, 7.93]	**Low**			HIGH ⊙⊙⊙⊙[e,f]	Sensory disorder is a predictor of severe dengue.
		5.6%[i]	23.7% [17, 32]	18.1% [11.4, 26.4]		
		High				
		15.6%[ii]	49.2% [38.9, 59.4]	33.6% [23.3, 43.8]		
Hemorrhages Number of participants: 18,469 (59 observational studies)	5.21 [3.53, 7.69]	**Low**			HIGH ⊙⊙⊙⊙[e,f]	Hemorrhage is a predictor of severe dengue.
		5.6%[i]	23.6% [17.3, 31.3]	18.0% [11.7, 25.7]		
		High				
		15.6%[ii]	49.1% [39.5, 58.7]	33.5% [23.9, 43.1]		

Fluid accumulation manifesting with: edema, ascites, pleural effusion, pericardial effusion Number of participants: 26,241 (54 observational studies)	5.04 [3.56, 7.14]	**Low**			HIGH ⦿⦿⦿⦿[e,f]	Fluid accumulation is a predictor of severe dengue.
		5.6%[i]	23.0% [17.4, 29.8]	17.4% [11.8, 24.2]		
		High				
		15.6%[ii]	48.2% [39.7, 56.9]	32.6% [24.1, 41.3]		
Increased capillary refill time Number of participants: 210 (3 observational studies)	4.96 [1.72, 14.32]	**Low**			LOW ⦿⦿○○[b,g]	Increased capillary refill time may be a predictor of severe dengue.
		5.6%[i]	22.7% [9.3, 45.9]	17.1% [3.7, 40.3]		
		High				
		15.6%[ii]	47.8% [24.1, 72.6]	32.2% [8.5, 57]		
Third trimester of pregnancy assessed by comparing it with the first trimester Number of participants: 99 (1 observational study)	3.94 [2.10, 5.42]	**Low**			LOW ⦿⦿○○[b,g]	Being in the third trimester of pregnancy may be a predictor of severe dengue.
		5.6%[i]	18.9% [11.1, 24.3]	13.3% [5.5, 18.7]		
		High				
		15.6%[ii]	42.1% [28, 50]	26.5% [12.4, 34.4]		
Dyspnea or difficulty breathing Number of participants: 25,771 (12 observational studies)	3.93 [2.40, 6.42]	**Low**			HIGH ⦿⦿⦿⦿[e,f]	The presence of dyspnea or difficulty breathing is a predictor of severe dengue.
		5.6%[i]	18.9% [12.5, 27.6]	13.3% [6.9, 22]		
		High				
		15.6%[ii]	42.1% [30.7, 54.3]	26.5% [15.1, 38.7]		
Pregnancy Number of participants: not available (1 observational study)	3.38 [2.10, 5.42]	**Low**			LOW ⦿⦿○○[b,g]	Pregnancy may be a predictor of severe dengue.
		5.6%[i]	16.7% [11.1, 24.3]	11.1% [5.5, 18.7]		
		High				
		15.6%[ii]	38.5% [28, 50]	22.9% [12.4, 34.4]		
Hepatomegaly Number of participants: 25,989 (62 observational studies)	3.14 [2.38, 4.15]	**Low**			HIGH ⦿⦿⦿⦿[e,f]	The presence of hepatomegaly is a poor prognostic factor for dengue.
		5.6%[i]	15.7% [12.4, 19.8]	10.1% [6.8, 14.2]		
		High				
		15.6%[ii]	36.7% [30.6, 43.4]	21.1% [15, 27.8]		
Microscopic hematuria Number of participants: 1,831 (3 observational studies)	3.12 [1.23, 7.90]	**Low**			LOW ⦿⦿○○[b,h]	The presence of microscopic hematuria may be a predictor of severe dengue.
		5.6%[i]	15.6% [6.8, 31.9]	10.0% [1.2, 26.3]		
		High				
		15.6%[ii]	36.6% [18.5, 59.4]	21.0% [2.9, 43.8]		

Thrombocytopenia Number of participants: 50,586 (62 observational studies)	3.02 [2.45, 3.73]	**Low**			HIGH ⦿⦿⦿⦿[e,f]	Thrombocytopenia is a predictor of severe dengue.
		5.6%[i]	15.2% [12.7, 18.1]	9.6% [7.1, 12.5]		
		High				
		15.6%[ii]	35.8% [31.2, 40.8]	20.2% [15.6, 25.2]		
Coagulopathy assessed by alteration of laboratory parameters related to hemostasis Number of participants: 6,895 (10 observational studies)	2.83 [1.59, 5.04]	**Low**			LOW ⦿⦿○○[c,d]	Coagulopathy may be a predictor of severe dengue.
		5.6%[i]	14.4% [8.6, 23]	8.8% [3, 17.4]		
		High				
		15.6%[ii]	34.3% [22.7, 48.2]	18.7% [7.1, 32.6]		
Splenomegaly Number of participants: 2,367 (10 observational studies)	2.64 [1.31, 5.31]	**Low**			LOW ⦿⦿○○[c,d]	The presence of splenomegaly may be a predictor of severe dengue.
		5.6%[i]	13.5% [7.2, 24]	7.9% [1.6, 18.4]		
		High				
		15.6%[ii]	32.8% [19.5, 49.5]	17.2% [3.9, 33.9]		
Elevated transaminases Number of participants: 18,579 (39 observational studies)	2.55 [1.78, 3.64]	**Low**			HIGH ⦿⦿⦿⦿[e,f]	Elevated transaminases is a predictor of severe dengue.
		5.6%[i]	13.1% [9.6, 17.8]	7.5% [4, 12.2]		
		High				
		15.6%[ii]	32.0% [24.8, 40.2]	16.4% [9.2, 24.6]		
Progressive increase in hematocrit Number of participants: 17,462 (45 observational studies)	2.30 [1.74, 3.05]	**Low**			HIGH ⦿⦿⦿⦿[e,f]	The presence of a progressive increase in hematocrit is a predictor of severe dengue.
		5.6%[i]	12.0% [9.4, 15.3]	6.4% [3.8, 9.7]		
		High				
		15.6%[ii]	29.8% [24.3, 36.1]	14.2% [8.7, 20.5]		
Abdominal pain Number of participants: 85,769 (87 observational studies)	2.02 [1.74, 2.35]	**Low**			HIGH ⦿⦿⦿⦿[e,f]	Abdominal pain is a predictor of severe dengue.
		5.6%[i]	10.7% [9.4, 12.2]	5.1% [3.8, 6.6]		
		High				
		15.6%[ii]	27.2% [24.3, 30.3]	11.6% [8.7, 14.7]		
Mucosal bleeding Number of participants: 24,661 (50 observational studies)	1.96 [1.47, 2.69]	**Low**			HIGH ⦿⦿⦿⦿[e,f]	Mucosal bleeding is a predictor of severe dengue.
		5.6%[i]	10.4% [8, 13.8]	4.8% [2.4, 8.2]		
		High				
		15.6%[ii]	26.6% [21.4, 33.2]	11.0% [5.8, 17.6]		

Vomiting Number of participants: 72,312 (56 observational studies)	1.74 [1.48, 2.05]	**Low**			HIGH ⦿⦿⦿⦿[e,f]	The presence of vomiting is a predictor of severe dengue.
		5.6%[i]	9.4% [8.1, 10.8]	3.8% [2.5, 5.2]		
		High				
		15.6%[ii]	24.3% [21.5, 27.5]	8.7% [5.9, 11.9]		
High fever, assessed with at least one recorded temperature higher than 38.5 °C Number of participants: 2,125 (7 observational studies)	1.50 [0.97, 2.32]	**Low**			LOW ⦿⦿○○[c,d]	High fever may be a predictor of severe dengue.
		5.6%[i]	8.2% [5.4, 12.1]	2.6% [−0.2, 6.5]		
		High				
		15.6%[ii]	21.7% [15.2, 30]	6.1% [−0.4, 14.4]		
Positive tourniquet test Number of participants: 16,133 (32 observational studies)	1.48 [0.99, 2.20]	**Low**			LOW ⦿⦿○○[c,d]	A positive tourniquet test may be a predictor of severe dengue.
		5.6%[i]	8.1% [5.5, 11.5]	2.5% [−0.1, 5.9]		
		High				
		15.6%[ii]	21.5% [15.5, 28.9]	5.9% [−0.1, 13.3]		
Diarrhea Number of participants: 9,549 (33 observational studies)	1.33 [1.06, 1.68]	**Low**			LOW ⦿⦿○○[b,d]	The presence of diarrhea may be a predictor of severe dengue.
		5.6%[i]	7.3% [5.9, 9.1]	1.7% [0.3, 3.5]		
		High				
		15.6%[ii]	19.7% [16.4, 23.7]	4.1% [0.8, 8.1]		
Rhinorrhea Number of participants: 2,118 (4 observational studies)	1.24 [0.64, 2.42]	**Low**			LOW ⦿⦿○○[c,h]	Rhinorrhea may not be a predictor of severe dengue.
		5.6%[i]	6.9% [3.7, 12.6]	1.3% [−1.9, 7]		
		High				
		15.6%[ii]	18.6% [10.6, 30.9]	3.0% [−5, 15.3]		
Anorexia or hyporexia Number of participants: 2,089 (8 observational studies)	1.21 [0.68, 2.15]	**Low**			LOW ⦿⦿○○[b,d]	The presence of anorexia or hyporexia may not be a predictor of severe dengue.
		5.6%[i]	6.7% [3.9, 11.3]	1.1% [−1.7, 5.7]		
		High				
		15.6%[ii]	18.3% [11.2, 28.4]	2.7% [−4.4, 12.8]		
Petechiae or ecchymosis Number of participants: 9,663 (31 observational studies)	1.21 [0.96, 1.52]	**Low**			LOW ⦿⦿○○[c,h]	The presence of petechiae or ecchymosis may not be a predictor of severe dengue.
		5.6%[i]	6.7% [5.4, 8.3]	1.1% [−0.2, 2.7]		
		High				
		15.6%[ii]	18.3% [15.1, 21.9]	2.7% [−0.5, 6.3]		

Nausea Number of participants: 2,967 (12 observational studies)	1.21 [0.85, 1.71]	**Low**			LOW ⦿⦿○○[c,d]	Nausea may not be a predictor of severe dengue.
		5.6%[i]	6.7% [4.8, 9.2]	1.1% [−0.8, 3.6]		
		High				
		15.6%[ii]	18.3% [13.6, 24]	2.7% [−2, 8.4]		
Obesity Number of participants: 6,776 (17 observational studies)	1.18 [0.92, 1.52]	**Low**			LOW ⦿⦿○○[c,d]	Obesity may not be a predictor of severe dengue.
		5.6%[i]	6.5% [5.2, 8.3]	0.9% [−0.4, 2.7]		
		High				
		15.6%[ii]	17.9% [14.5, 21.9]	2.3% [−1.1, 6.3]		
Malnutrition Number of participants: 5,909 (13 observational studies)	1.09 [0.84, 1.42]	**Low**			LOW ⦿⦿○○[c,d]	Malnutrition may not be a predictor of severe dengue.
		5.6%[i]	6.1% [4.7, 7.8]	0.5% [−0.9, 2.2]		
		High				
		15.6%[ii]	16.8% [13.4, 20.8]	1.2% [−2.2, 5.2]		
Cutaneous eruption Number of participants: 71,994 (52 observational studies)	1.04 [0.79, 1.37]	**Low**			MODERATE ⦿⦿⦿○[h]	The presence of cutaneous eruption may not be a predictor of severe dengue.
		5.6%[i]	5.8% [4.5, 7.5]	0.2% [−1.1, 1.9]		
		High				
		15.6%[ii]	16.1% [12.7, 20.2]	0.5% [−2.9, 4.6]		
Cough Number of participants: 4,314 (14 observational studies)	1.02 [0.64, 1.64]	**Low**			LOW ⦿⦿○○[b,h]	The presence of cough may not be a predictor of severe dengue.
		5.6%[i]	5.7% [3.7, 8.9]	0.1% [−1.9, 3.3]		
		High				
		15.6%[ii]	15.9% [10.6, 23.3]	0.3% [−5, 7.7]		
Leukopenia Number of participants: 14,336 (29 observational studies)	0.88 [0.66, 1.17]	**Low**			MODERATE ⦿⦿⦿○[d,e]	Leukopenia is probably not a predictor of severe dengue.
		5.6%[i]	5.0% [3.8, 6.5]	−0.6% [−1.8, 0.9]		
		High				
		15.6%[ii]	14.0% [10.9, 17.8]	−1.6% [−4.7, 2.2]		
Retro-ocular pain Number of participants: 58,552 (28 observational studies)	0.88 [0.70, 1.10]	**Low**			LOW ⦿⦿○○[b,d]	The presence of retro-ocular pain may not be a predictor of severe dengue.
		5.6%[i]	5.0% [4, 6.1]	−0.6% [−1.6, 0.5]		
		High				
		15.6%[ii]	14.0% [11.5, 16.9]	−1.6% [−4.1, 1.3]		

Headache Number of participants: 61,520 (46 observational studies)	0.87 [0.76, 0.99]	**Low**			MODERATE ⦿⦿⦿○[c]	Headache is probably not a predictor of severe dengue.
		5.6%[i]	4.9% [4.3, 5.5]	−0.7% [−1.3, −0.1]		
		High				
		15.6%[ii]	13.9% [12.3, 15.5]	−1.7% [−3.3, −0.1]		
Myalgias or arthralgias Number of participants: 89,323 (43 observational studies)	0.79 [0.66, 0.95]	**Low**			HIGH ⦿⦿⦿⦿	The presence of myalgias or arthralgias is not a predictor of severe dengue.
		5.6%[i]	4.5% [3.8, 5.3]	−1.1% [−1.8, −0.3]		
		High				
		15.6%[ii]	12.7% [10.9, 14.9]	−2.9% [−4.7, −0.7]		

Notes

CI: confidence interval; **OR:** odds ratio.

The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Grading of the certainty of the evidence from the GRADE working group

HIGH Certainty: we are very sure that the true effect approximates the estimated effect.

MODERATE certainty: we have moderate confidence in the estimated effect. The true effect is probably close to the estimated effect, but there is a possibility that it is substantially different.

LOW Certainty: our confidence in the estimated effect is limited. The true effect may be substantially different from the estimated effect.

VERY LOW Certainty: we have very little confidence in the estimated effect. The true effect is probably substantially different from the estimated effect.

[a] An increase of at least 1.5% in the likelihood of severe illness was considered significant.

[b] All of the studies included in the meta-analysis had serious methodological problems.

[c] Most of the studies included in the meta-analysis had serious methodological problems. A subgroup analysis showed a significantly different estimate for studies that provided adjusted estimates or that had a low risk of bias.

[d] There is significant heterogeneity in the results of the included studies.

[e] The certainty was not reduced by the risk of bias because, although most of the studies included in the meta-analysis had methodological problems, there was no significant difference between the effect estimates of studies rated as having low risk of bias versus those rated as having moderate or high risk of bias.

[f] The certainty was not reduced due to inconsistency because, although significant heterogeneity was observed, it was related to a small proportion of the included studies.

[g] The optimal sample size was not reached.

[h] The 95% CI includes the possibility and absence of prediction of severe dengue.

Sources for the baseline risks

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ii Alexander N, Balmaseda A, Coelho IC, Dimaano E, Hien TT, Hung NT, et al. Multicentre prospective study on dengue classification in four South-east Asian and three Latin American countries. Tropical Medicine & International Health 2011;16(8):936-948. Available from: https://doi.org/10.1111/j.1365-3156.2011.02793.x.

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SUMMARY OF FINDINGS TABLE 3. ORAL HYDRATION FOR DENGUE PATIENTS

Orally-administered intense hydration compared to usual management of patients with arbovirus infection

Population: patients with arbovirus infections

Intervention: orally-administered intense hydration

Comparison: usual management

Result Number of participants (studies)	Relative effect OR (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Conclusions
		Risk without the intervention	Risk with the intervention	Difference		
Hospitalization assessed by the impact of a strategy to increase and record oral fluid intake in patients with fever (≥3 days) and thrombocytopenia, with a 2-month follow-up Number of participants: 143 (1 clinical trial)[1]	0.52 [0.19, 1.41]	17.6%	10.0% [3.9, 23.2]	−7.6% [−13.7, 5.6]	LOW ⦿⦿○○[a,b]	Increased orally-administered fluid intake may reduce the hospitalization of patients with arboviral diseases.
Hospitalization assessed by the consumption of more than 5 glasses of water in dengue patients without shock (dengue fever or dengue hemorrhagic fever) Number of participants: 992 (1 observational study)[2]	0.19 [0.11, 0.35]	Observed				Increased orally-administered fluid intake may reduce the hospitalization of patients with arboviral diseases.
		17.6%	3.9% [2.3, 7]	−13.7% [−15.3, −10.6]	LOW ⦿⦿○○	
The need for parenteral hydration assessed by the impact of a strategy to increase and record oral fluid intake in patients with fever (≥3 days) and thrombocytopenia, with a 2-month follow-up Number of participants: 143 (1 randomized clinical trial)[1]	0.53 [0.21, 1.29]	20.0%	11.7% [5, 24.4]	−8.3% [−15, 4.4]	LOW ⦿⦿○○[a,b]	Increased orally-administered fluid intake may reduce the number of patients who require parenteral hydration.
Clinical evolution, assessed by comparing oral and parenteral hydration, in dengue patients without shock (dengue hemorrhagic fever grade I-II) Number of participants: 49 (1 observational study)[3]	No significant difference was observed between the clinical or laboratory variables of patients treated with oral or parenteral hydration. The number of days of hospitalization was significantly lower in patients treated with parenteral hydration (5.3 vs. 7.4; p = 0.007).				VERY LOW ⦿○○○[c,d]	The effect of orally-administered versus parenteral hydration is uncertain.
Clinical evolution, assessed by comparing orally-administered isotonic solution and water, in addition to parenteral hydration, in patients with non-severe dengue Number of participants: 24 (1 randomized clinical trial)[4]	No important differences were observed in clinically relevant outcomes, such as death or development of shock. The intervention group had less nausea and vomiting, and a higher incidence of abdominal distention.				VERY LOW ⦿○○○[a,d,e]	The effect of isotonic solutions compared to water is uncertain.

Notes

CI: confidence interval; **OR:** odds ratio.

The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Grading of the certainty of the evidence from the GRADE working group

HIGH Certainty: we are very sure that the true effect approximates the estimated effect.

MODERATE Certainty: we have moderate confidence in the estimated effect. The true effect is probably close to the estimated effect, but there is a possibility that it is substantially different.

LOW Certainty: our confidence in the estimated effect is limited. The true effect may be substantially different from the estimated effect.

VERY LOW Certainty: we have very little confidence in the estimated effect. The true effect is probably substantially different from the estimated effect.

[a] Lack of blinding, significant information loss, or both.

[b] The 95% CI includes absence of benefits.

[c] Unadjusted estimates.

[d] The optimal sample size was not achieved.

[e] All patients were treated with parenteral hydration. For those who did not receive hydration, the effect of the intervention may be significantly different.

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SUMMARY OF FINDINGS TABLE 4. PARENTERAL HYDRATION OF DENGUE PATIENTS WITH WARNING SIGNS

Parenteral hydration of dengue patients with warning signs, compared to those with no parenteral hydration

Population: patients with dengue and with warning signs

Intervention: parenteral hydration

Comparison: no parenteral hydration

Result Number of participants (studies)	Impact	Certainty
Death Number of participants: 31,594 (2 observational studies)[1,2]	Of the 2,594 patients included in one of the studies evaluated, 482 received parenteral hydration. No patients died. Another study noted that the implementation of hydration units in the field was associated with a reduction in dengue mortality. In conclusion, the implementation of a dengue management scheme in which patients with at least one warning sign receive parenteral hydration may be effective for reducing dengue mortality.	VERY LOW ◉○○○[a]
Shock Number of participants: 32,294 (3 observational studies)[1-3]	The observed risk of progression to severe dengue in patients with at least one warning sign was 9%. In two cohorts in which a parenteral hydration scheme was implemented for patients with at least one warning sign, an incidence of shock of 2%-5% was reported. In conclusion, parenteral hydration of patients with at least one warning sign may reduce the risk of shock.	VERY LOW ◉○○○[a]
Hydrosaline overload Number of participants: 1,734 (1 observational study)[4]	In one study that evaluated the impact of intravenous hydration on the risk of hydrosaline overload with respiratory distress, it was reported that the indication of intravenous fluids was associated with a significant increase in the risk of respiratory distress due to fluid accumulation (HR = 2.90; 95% CI: 1.37–6.12). In conclusion, the indication of parenteral hydration may increase the risk of hydrosaline overload.	VERY LOW ◉○○○[b]

Notes

HR: hazard ratio; **OR:** odds ratio.

The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Grading of the certainty of the evidence from the GRADE working group

HIGH Certainty: we are very sure that the true effect approximates the estimated effect.

MODERATE Certainty: we have moderate confidence in the estimated effect. The true effect is probably close to the estimated effect, but there is a possibility that it is substantially different.

LOW Certainty: our confidence in the estimated effect is limited. The true effect may be substantially different from the estimated effect.

VERY LOW Certainty: we have very little confidence in the estimated effect. The true effect is probably substantially different from the estimated effect.

[a] Includes studies of one subgroup without a comparison group.

[b] The estimate was not adjusted for all relevant prognostic factors.

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SUMMARY OF FINDINGS TABLE 5. CRYSTALLOIDS VERSUS COLLOIDS FOR THE INITIAL RESUSCITATION OF DENGUE PATIENTS

Crystalloids compared to colloids for dengue shock

Population: patients with dengue shock

Intervention: crystalloids

Comparison: colloids

Result Number of participants (studies)	Relative risk RR (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Conclusions
		With crystalloids	With colloids	Difference		
Death Number of participants: 694 (4 randomized clinical trials)[1-4,a]	There were no events in either group.				-	-
Death (indirect) Number of participants: 30,020 (69 randomized clinical trials)[5]	The reported effect estimates were ethyl hydroxide starch versus crystalloids, RR = 0.97 (0.86–1.09) [MODERATE certainty]; dextran versus crystalloids, RR = 0.99 (0.88–1.11) [MODERATE certainty); gelatins versus crystalloids, RR = 0.89 (0.74–1.08) [LOW certainty]; albumin or fresh plasma versus crystalloids, RR = 0.98 (0.92–1.06) [MODERATE certainty]. In conclusion, initial resuscitation with crystalloids and colloids may be associated with similar mortality.				LOW ⦿⦿○○[b,c]	-
Recurrent or treatment-resistant shock Number of participants: 694 (4 randomized clinical trials)	RR = 1.06 [0.82, 1.37]	25.9%	27.4% [21.2, 35.4]	1.6% [−4.7, 9.6]	MODERATE ⦿⦿⦿○[d]	The risk of recurrent or treatment-resistant shock is probably similar with crystalloids or colloids.
Volume overload Number of participants: 605 (2 randomized clinical trials)[2,3,a]	RR = 1.01 [0.76, 1.34]	26.8%	27.0% [20.3, 35.9]	0.3% [−6.4, 9.1]	MODERATE ⦿⦿⦿○[d]	The risk of volume overload is probably similar with crystalloids and colloids.
Infusion-related and allergic reactions Number of participants: 655 (3 randomized clinical trials)[1,2,3,a]	RR = 0.09 [0.01, 0.64]	4.1%	0.4% [0, 2.6]	−3.7% [−4.1, −1.5]	HIGH ⦿⦿⦿⦿[e]	The use of crystalloids reduces the risk of infusion-related and allergic reactions.
Renal replacement therapy (indirect) Number of participants: 11,555 (11 randomized clinical trials)[5]	The reported effect estimates were ethyl hydroxide starch versus crystalloids, RR = 1.30 (1.14–1.48); 24 more per 1,000 (11–39 more per 1,000) [MODERATE certainty]; albumin or fresh plasma versus crystalloids, RR = 1.11 (0.96–1.27) [LOW certainty]. In conclusion, colloid resuscitation may be associated with an increased risk of needing renal replacement therapy.				LOW ⦿⦿○○[b,c]	-

Notes

RR: relative risk; **OR:** odds ratio.

The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Grading of the certainty of the evidence from the GRADE working group

HIGH Certainty: we are very sure that the true effect approximates the estimated effect.

MODERATE Certainty: we have moderate confidence in the estimated effect. The true effect is probably close to the estimated effect, but there is a possibility that it is substantially different.

LOW Certainty: our confidence in the estimated effect is limited. The true effect may be substantially different from the estimated effect.

VERY LOW Certainty: we have very little confidence in the estimated effect. The true effect is probably substantially different from the estimated effect.

[a] All of the studies included pediatric patients and the intervention was implemented as initial resuscitation.

[b] Most of the included studies had relevant methodological limitations.

[c] Most of the included studies did not include patients with dengue.

[d] The 95% CI includes significant benefits and harms.

[e] The certainty of the evidence was not reduced because, although the optimal sample size was not reached, a large magnitude of effect was observed and the risk of crystalloid infusion-related reactions is assumed to be close to 0%.

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SUMMARY OF FINDINGS TABLE 6. TRANSFUSION OF BLOOD COMPONENTS FOR DENGUE PATIENTS WITH THROMBOCYTOPENIA

Comparison of the transfusion of blood products (platelet-rich plasma or fresh frozen plasma) with no transfusion of blood products in patients with arbovirus infection

Population: patients with arboviral infection

Intervention: transfusion of blood products (platelet-rich plasma or fresh frozen plasma)

Comparison: no transfusion of blood products (platelet-rich plasma or fresh frozen plasma)

Result Number of participants (studies)	Relative risk RR (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Conclusions
		Risk without the intervention	Risk with the intervention	Difference		
Death Number of participants: 456 (2 randomized clinical trials)[1,2,a,b]	5.36 [0.25, 115.00]	**Low**			VERY LOW ◉○○○[c,d]	The effect of the transfusion of blood products (platelet-rich plasma) on mortality is uncertain.
		1.1%[3]	5.8% [0.3, 57]	4.7% [−0.9, 55.9]		
Shock Number of participants: 478 (2 randomized clinical trials)[2,4,b,e]	0.71 [0.14, 3.65][f]	**Study population**			VERY LOW ◉○○○[c,d]	The effect of the transfusion of blood products (platelet-rich plasma or fresh frozen plasma) on shock is uncertain.
		1.3%	0.9% [0.2, 4.5]	−0.4% [−1.1, 3.2][f]		
		Low				
		5.6%[5]	4.0% [0.8, 17.8]	−1.6% [−4.8, 12.2]		
		High				
		15.6%[6]	11.6% [2.5, 40.3]	−4.0% [−13.1, 24.7]		
Major bleeding Number of participants: 456 (2 randomized clinical trials)[1,2,a,b]	0.58 [0.18, 1.90]	3.1%	1.8% [0.6, 5.7]	−1.3% [−2.5, 2.6]	LOW ◉◉○○[c,d]	The transfusion of blood products (platelet-rich plasma) may marginally reduce the risk of major bleeding.
Bleeding (observations) Assessed with: clinically evident bleeding Number of participants: 788 (1 observational study)[7,a]	1.01 [0.94, 1.07]	18.2%	18.4% [17.3, 19.2]	0.1% [−0.9, 1]	LOW ◉◉○○	The transfusion of platelets may not decrease the risk of bleeding.
Side effects Number of participants: 565 (3 randomized clinical trials)[1,2,4,b,e]	8.23 [1.84, 36.81][f]	0.4%	2.8% [0.7, 11.6]	2.5% [0.3, 11.2][f]	MODERATE ◉◉◉○[c]	The transfusion of blood products (platelet-rich plasma or fresh frozen plasma) probably increases the risk of side effects.

Notes

CI: confidence interval; **OR:** odds ratio.

The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Grading of the certainty of the evidence from the GRADE working group

HIGH Certainty: we are very sure that the true effect approximates the estimated effect.

MODERATE Certainty: we have moderate confidence in the estimated effect. The true effect is probably close to the estimated effect, but there is a possibility that it is substantially different.

LOW Certainty: our confidence in the estimated effect is limited. The true effect may be substantially different from the estimated effect.

VERY LOW Certainty: we have very little confidence in the estimated effect. The true effect is probably substantially different from the estimated effect.

[a] In all of the studies, the intervention was the transfusion of platelet-rich plasma.

[b] The patients included in the studies were adults with dengue and thrombocytopenia below 40,000.

[c] Lack of blinding.

[d] The 95% CI includes significant benefits and harms.

[e] In the two studies, the intervention was the transfusion of: in one, platelet-rich plasma; and in the other, fresh frozen plasma.

[f] There were no significant differences between studies with the infusion of platelet-rich plasma and those with the infusion of fresh frozen plasma.

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SUMMARY OF FINDINGS TABLE 7. SYMPTOMATIC MANAGEMENT OF ACUTE ARBOVIRUS INFECTION

Comparison of interventions for symptomatic control of arbovirus infection

Population: patients with arbovirus infection

Intervention: medications for symptomatic control

Comparison: medications for symptomatic control

Result Number of participants (studies)	Impact	Certainty
Side effects of NSAIDs	**Side effects of NSAIDs in dengue patients.** There is uncertainty about the impact of NSAID use on the risk of bleeding in dengue patients: 1 non-randomized study,[1] which included 683 dengue patients and 154 with bleeding of clinical impact that was not described, reported an adjusted OR of 0.86 (95% CI: 0.51–0.97); 4 non-randomized studies, which included 2,054 dengue patients and 368 with bleeding without adjustment for confounding variables, reported discordant results, with 2 indicating a higher incidence in patients who received NSAIDs[2,3] and 2 indicating no higher incidence.[4,5] There is uncertainty about the impact of NSAID use on abdominal pain in dengue patients: 1 non-randomized study, which included 238 dengue patients and 91 events, observed similar incidences in patients exposed (36%) and not exposed (37%) to NSAIDs.[3] There is uncertainty about the impact of NSAIDs on liver injury in dengue patients: 1 non-randomized study,[2] which included 977 dengue patients, reported an increased risk of alanine aminotransferase (ALT) >300 U/L [OR = 2.1; 95% CI: 0.89–5], while ALT levels >1,000 U/L were observed in 1.5% of patients who received NSAIDs and in no patient who did NOT receive NSAIDs. **Side effects of NSAIDs in general.** Busse notes an increased risk of gastrointestinal events such as nausea and abdominal pain in 3,361 patients with acute musculoskeletal injury included in 18 randomized studies (RR = 1.78; 95% CI: 1.33–2.39) in patients who received NSAIDs, compared to those who did not receive them.[6] **In summary:** The use of NSAIDs in dengue patients may be associated with gastrointestinal discomfort, such as nausea and abdominal pain, while the impact on the risk of bleeding and liver injury is uncertain. The certainty of the evidence is VERY LOW to LOW, mainly due to methodological problems and inconsistencies.[1–6]	VERY LOW ⦿○○○[a-d]
Side effects of acetaminophen	**Side effects of paracetamol in dengue patients.** There is uncertainty about the impact of paracetamol on the risk of bleeding in dengue patients: 2 randomized studies[7,8] observed a total of 2 gastrointestinal bleeding events and 3 minor bleeding events in 104 patients randomized to paracetamol and no events in 63 patients randomized to the control group (placebo or metamizole), respectively; 1 non-randomized study, which included 729 dengue patients and 86 events, recorded similar proportions of events in patients receiving paracetamol (12%), NSAIDs (12.5%), or metamizole (9%).[5] No relevant direct or indirect evidence was identified that informs the impact of paracetamol use on abdominal pain. Paracetamol may increase the risk of elevated transaminases and may not significantly increase the risk of acute liver failure: 1 randomized study,[7] which included 125 dengue patients, recorded an increased risk of transaminase values greater than 3 times the upper normal limit compared to placebo (incidence rate ratio: 3.77; 95% CI: 1.36–10.5); 1 randomized study that included 79 dengue patients indicated no significant differences in transaminase values compared to metamizole;[8] 1 non-randomized study with adjustment for confounding variables, which included 77 dengue patients and 31 events, reported an increased risk of elevated transaminases 3 times their normal value (adjusted OR = 4.62; 95% CI: 1.37–13) when compared to complete treatment doses greater than and less than 8 grams;[9] 2 non-randomized studies with adjustment for confounding variables, which included 2,134 dengue patients and 115 events, indicated an increased risk of transaminase values greater than 10 times their normal value (adjusted HR = 2.6; 95% CI: 1.1–6) when compared with not using paracetamol in the previous 24 hours (adjusted OR = 3.4; 95% CI: 1.2–9.6), comparing doses greater and less than 60 mg/kg/day, respectively;[10,11] 1 randomized study that included 125 dengue patients with baseline transaminase values less than 3 times the upper normal limit, of whom 48 received at least 1 dose of paracetamol, indicated that there were no cases of liver failure;[7] 1 non-randomized study that included 113 hospitalized patients with dengue and transaminase values higher than 3 times the upper normal limit, who received paracetamol despite this increase, reported that there were no cases of acute liver failure.[12] **In summary:** Paracetamol may not increase the risk of bleeding or acute liver failure in dengue patients at the usual daily doses (up to 60 mg/kg or 4 g/day), although it may increase the risk of elevated transaminases. There is no reliable information to assess the impact of paracetamol on abdominal pain or other gastrointestinal discomfort. The certainty of the evidence is LOW to VERY LOW, mainly due to methodological problems in the included studies and imprecision.[5,7–11]	VERY LOW ⦿○○○[e,f]

Side effects of metamizole	**Side effects of metamizole in dengue patients.** Díaz-Quijano et al. compared the evolution of 17 dengue patients treated with metamizole within the first 4 days of illness with 93 patients not treated with metamizole.[4] The results showed a higher rate of dengue hemorrhagic fever (RR = 7.29; 95% CI: 1.8–29.7) and accentuated thrombocytopenia (RR = 10.94; 95% CI: 1.05–114.05) in the group that received metamizole. However, the study's notable methodological limitations (retrospective observational study without adjustment for potential confounding variables) mean that the aforementioned findings are not reliable. Díaz-Quijano et al. looked for predictors of spontaneous bleeding in a cohort of 890 dengue patients.[5] Metamizole consumption was not associated with an increased risk of spontaneous bleeding. However, the study's notable methodological limitations (retrospective observational study without adjustment for potential confounding variables) mean that the aforementioned findings are not reliable. Céspedes et al. conducted a randomized study in which they compared paracetamol and metamizole for the symptomatic treatment of 79 pediatric dengue patients with warning signs.[8] No significant differences were observed in the risk of adverse effects or in disease progression. The certainty in the aforementioned results is LOW due to imprecision, since the number of patients and events included was insufficient to exclude the possibility of significant differences. Rosaldo et al. recorded the response to metamizole for 50 dengue patients, 4 of whom met the criteria for dengue hemorrhagic fever.[13] All were treated with metamizole and had a good therapeutic response and no relevant side effects. The certainty in the observed results was LOW due to the absence of a control group and the small sample size. Gutierres-Lesmes et al. reported an association between treatment with metamizole and mortality in 70 pediatric dengue patients.[14] However, the study has notable methodological limitations (lack of adjustment for potential confounders, insufficient sample size) that mean that the aforementioned results are not reliable. **Side effects of metamizole in general.** Kotter et al., in a systematic review of the specialized literature, identified 79 studies that included 3,716 patients who received short-term metamizole.[15] The results show that metamizole was safe, with no difference in comparison to paracetamol or NSAIDs. No cases of agranulocytosis or death were observed. **In summary:** The existing body of evidence suggests that metamizole may be safe for the symptomatic treatment of dengue patients. The certainty of the evidence is VERY LOW to LOW due to methodological problems in the identified studies and to imprecision.[4,5,8,13–15]	VERY LOW ◉○○○[g,h]
Side effects of steroids	**Side effects of steroids in dengue patients.** Zhang et al. conducted a systematic review of the specialized literature about studies that evaluated the efficacy and safety of steroids for the treatment of dengue patients.[16] Two studies, involving 414 patients, included adverse effects as an outcome, with no significant difference between steroids and placebo. **Side effects of steroids in general.** Steroids are commonly used in the treatment of various diseases and conditions, so their adverse effects are known. The most relevant include hyperglycemia, infections, and thromboembolic events. However, these are rare when steroids are used in anti-inflammatory doses and for limited periods. **In summary:** The scarce available evidence on steroid use in dengue patients suggests that steroids would be safe. Therefore, they could be considered as an alternative for managing symptoms related to this disease.[16–18]	LOW ◉◉○○[g,h]
Side effects of antihistamines	**Side effects of antihistamines in dengue patients.** The use of antihistamines in dengue patients may not be associated with increased risk of gastrointestinal side effects, bleeding, or liver damage (in 1 randomized study that included 133 dengue patients, with 38 episodes of abdominal pain, 42 episodes of vomiting, 21 elevated transaminase events, 8 bleeding events, and 2 liver failure events, similar incidences of detailed effects were reported).[19] **Side effects of antihistamines in general.** Sutter et al. indicated an increased risk of sedation (OR = 1.64; 95% CI: 0.69–3.85; 6 randomized studies, 2,624 patients, and 190 events) and gastrointestinal discomfort (OR = 1.46; 95% CI: 0.84–2.56; 5 randomized studies, 1,586 patients, and 53 events) in patients with a common cold who received antihistamines, compared to those who did not receive them.[20] **In summary:** The body of evidence suggests that in dengue patients, antihistamines may increase the risk of sedation, while they may not impact the risk of bleeding or liver damage. The impact on gastrointestinal discomfort is uncertain. The certainty of the evidence is LOW, mainly due to imprecision, methodological problems, and indirect evidence.[19,20]	LOW ◉◉○○[i,j]

Notes

HR: hazard ratio; **OR:** odds ratio; **RR:** relative risk; **95% CI:** 95% confidence interval.

The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Grading of the certainty of the evidence from the GRADE working group

HIGH Certainty: we are very sure that the true effect approximates the estimated effect.

MODERATE Certainty: we have moderate confidence in the estimated effect. The true effect is probably close to the estimated effect, but there is a possibility that it is substantially different.

LOW Certainty: our confidence in the estimated effect is limited. The true effect may be substantially different from the estimated effect.

VERY LOW Certainty: we have very little confidence in the estimated effect. The true effect is probably substantially different from the estimated effect.

[a] The certainty in the estimates for bleeding is VERY LOW, considering: 1) fragility and failure to report the severity of the bleeding in the adjusted estimate; and 2) lack of adjustment for other variables and heterogeneity in the estimates from the remaining studies.

[b] The certainty in the evidence for abdominal pain based on studies of dengue patients is VERY LOW, considering that they are supported by NON-randomized studies with no adjustment for confounding variables.

[c] The certainty in the evidence for gastrointestinal side effects based on the evidence about musculoskeletal injury is LOW, considering: 1) the risk of bias in the studies; and 2) indirect evidence, as these are not dengue patients.

[d] The certainty in the estimates for liver damage is VERY LOW, considering: 1) that they are based on a non-randomized study with no adjustment for confounding variables; and 2) the fragility of the estimates.

[e] The certainty in the estimate for bleeding is VERY LOW, considering that it is based on: 1) 2 randomized studies with no details on the randomization methods and without a reported assessor for blinding, with 2 major events (see sources 7 and 8); and 2) 1 non-randomized study with no adjustment for confounding variables and 86 events.

[f] The certainty in the evidence for the estimates of liver damage is LOW, considering that: 1) 1 randomized study was stopped early following 23 events of elevated transaminases (3 times their upper normal limit) and excluded patients with an altered hepatogram at admission (see source 7); and 1 randomized study that did not provide details about the randomization process, did not report assessors for blinding, and had unclear loss to follow-up (see source 8); and 2) 4 non-randomized studies have methodological problems (the 4 studies do not specify a control group, defined by the NON-use of paracetamol), and the 3 studies that described a model adjusted for confounding variables did not incorporate other treatments such as NSAIDs or metamizole into the regression models and did not include parameters that define dengue severity, such as shock or major bleeding, in the regression models (see source 11); and, in another study, there was frequent loss of data regarding paracetamol use (see source 10).

[g] There are methodological limitations in the primary studies identified.

[h] There are insufficient side effects, from patients or both groups.

[i] The certainty in the estimates based on the study of dengue patients is LOW, considering the risk of bias (unreported method of allocation concealment and, in addition, it is not clear whether the event assessors were blinded to the allocation) and imprecision due to fragility (small number of events).

[j] The certainty in the estimate based on people with a common cold is LOW, considering imprecision due to fragility (small number of events) and indirect evidence.

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SUMMARY OF FINDINGS TABLE 8. CORTICOSTEROIDS FOR PATIENTS WITH SEVERE ARBOVIRUS INFECTION

Steroids for patients with severe arbovirus infection

Population: patients with severe arbovirus infection

Intervention: with steroids

Comparison: without steroids

Result Number of participants (studies)	Relative effect RR (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Conclusions
		Without steroids	With steroids	Difference		
Death Assessed by death, without other specification, due to dengue Number of participants: 284 (4 randomized clinical trials)[a]	0.681 [0.42, 1.11]	**Study population**			LOW ⦿⦿○○[b-e]	Steroid use may decrease mortality due to dengue shock.
		21.3%[1]	14.5% [9, 23.7]	−6.8% [−12.4, 2.3]		
		Low				
		13.0%[1]	8.8% [5.5, 14.4]	−4.2% [−7.5, 1.4]		
		High				
		18.0%[1]	12.2% [7.6, 20]	−5.8% [−10.4, 2]		
Death Assessed by death and, in the long term, sepsis Follow-up: range from 60 days to 1 year Number of participants: 6,438 (9 randomized clinical trials)	0.94[2] [0.89, 1.00]	**Study population**			VERY LOW ⦿○○○[f,g]	Steroid use may not increase mortality in patients with dengue shock.
		37.2%[2]	35.0% [33.1, 37.2]	−2.2% [−4.1, 0]		
		Low				
		13.0%[1]	12.2% [11.6, 13]	−0.8% [−1.4, 0]		
		High				
		18.0%[1]	16.9% [16, 18]	−1.1% [−2, 0]		
Need for transfusion Number of participants: 89 (2 randomized clinical trials)[a]	1.08[1] [0.52, 2.24]	**Study population**			LOW ⦿⦿○○[b,d,e]	Steroid use may not impact the need for transfusion in patients with dengue shock.
		24.0%[1]	25.9% [12.5, 53.8]	1.9% [−11.5, 29.8]		
		Low				
		21.0%[1]	22.7% [10.9, 47]	1.7% [−10.1, 26]		
		High				
		26.0%[1]	28.1% [13.5, 58.2]	2.1% [−12.5, 32.2]		
Hospital stay Assessed by: days in hospital Number of participants: 63 (1 randomized clinical trial)[a]	-	The average hospital stay was 6.2 days[1]	-	MD = 1.1 days longer[1] [1.83 shorter to 4.03 longer]	LOW ⦿⦿○○[d,g]	Steroid use may not impact the length of the hospital stay of patients with dengue shock.

Side effects: gastrointestinal bleeding Assessed by: number of cases with gastrointestinal bleeding Number of participants: 4,243 (17 randomized clinical trials)[a]	1.09[2] [0.86, 1.38]	5.5%[2]	6.0% [4.7, 7.5]	0.5% [−0.8, 2.1]	VERY LOW ⦿○○○[h,i]	There is uncertainty about the effect of steroids on gastrointestinal bleeding.
Side effects: neuropsychiatric alterations Number of participants: 1,004 (5 randomized clinical trials)[a]	0.58[2] [0.33, 1.03]	5.9%[2]	3.4% [2, 6.1]	−2.5% [−4, 0.2]	VERY LOW ⦿○○○[j,k]	There is uncertainty about the effect of steroids on neuropsychiatric alterations.
Side effects: acute myocardial infarction Assessed by: number of patients with acute myocardial infarction Number of participants: 1,080 (3 randomized clinical trials)[a]	0.91[2] [0.45, 1.82]	2.6%[2]	2.4% [1.17, 4.7]	−0.2% [−1.23, 2.1]	VERY LOW ⦿○○○[j,k]	There is uncertainty about the effect of steroids on acute myocardial infarction.

Notes

CI: confidence interval; **RR:** relative risk; **MD:** mean difference.

The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Grading of the certainty of the evidence from the GRADE working group

HIGH Certainty: we are very sure that the true effect approximates the estimated effect.

MODERATE Certainty: we have moderate confidence in the estimated effect. The true effect is probably close to the estimated effect, but there is a possibility that it is substantially different.

LOW Certainty: our confidence in the estimated effect is limited. The true effect may be substantially different from the estimated effect.

VERY LOW Certainty: we have very little confidence in the estimated effect. The true effect is probably substantially different from the estimated effect.

[a] This was not specified in the review.

[b] Studies with uncertain risk of selection bias. The review authors did not identify a high risk of bias in any of the items for the included trials.

[c] The included studies have methodological problems.

[d] The classification used in the selection of the population does not correspond to the current classification. The population included corresponds to patients with dengue shock and the population of interest corresponds to cases of severe arbovirus infection.

[e] Wide confidence interval that includes the null value, reduced number of events, and low percentage of risk reduction.

[f] 1 of 9 studies conducted in dengue patients.

[g] Wide confidence interval that includes the null value, in which the range of the interval affects the clinical decision.

[h] Only includes one study conducted in dengue patients.

[i] Number of events: 115, relative risk reduction of 0.5%. It is considered as not meeting the optimal sample size.

[j] It does not include studies conducted in the population with severe dengue.

[k] Wide confidence interval that includes the null value, less than 100 events, and a relative risk reduction of less than 30%.

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SUMMARY OF FINDINGS TABLE 9. IMMUNOGLOBULINS FOR PATIENTS WITH SEVERE ARBOVIRUS INFECTION

Intravenous immunoglobulin for patients with severe arbovirus infection (modified version)

Population: patients with severe arbovirus infection

Intervention: with intravenous immunoglobulin

Comparison: without immunoglobulin

Result Number of participants (studies)	Relative effect RR (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Conclusions
		Without immunoglobulins	With immunoglobulins	Difference		
Death Number of participants: 77 (2 randomized clinical trials)	0.88 [0.06, 13.25][1,2]	3%[2]	2.7% [0.2, 35.8]	−0.4% [−2.8, 37.1][a]	VERY LOW ⦿○○○[b-d]	There is uncertainty about the impact of immunoglobulins on mortality in patients with severe dengue.
Clinically significant bleeding Assessed with: WHO scale grade 2 Follow-up: 6 days Number of participants: 30 (1 randomized clinical trial)	In all patients included in the study, hemorrhagic manifestations improved within 36 hours of starting treatment (with or without immunoglobulin).[1]				VERY LOW ⦿○○○[b-d]	
Side effects (extravascular hemolysis) Assessed with: hemoglobin value following the intervention Follow-up: 2-6 days Number of participants: 77 (2 randomized clinical trials)	The studies assessed extravascular hemolysis, through the maximum decrease in the hemoglobin value. In one of the studies,[2] the maximum values of hemoglobin decrease were not different between groups (mean for anti-D group: 19.6 g/L; mean for placebo: 17.2 g/L). In the second trial,[1] the baseline hemoglobin values were 14.1 g/L in the anti-D group and 14.3 g/L in the control group. At 48 hours after the application of the intervention, the mean hemoglobin value in the group that received anti-D was 13.7 g/L (p = 0.253), with no mean hemoglobin values at 48 hours reported for the control group.				VERY LOW ⦿○○○[b,c,e,f]	
Increase in the number of platelets Assessed with: increase greater than 20,000/mm^3 to 50,000/mm^3 relative to the baseline[1,2] Follow-up: 5-6 days	Two of the studies reported no difference in the changes in the number of platelets between patients who received and those who did not receive immunoglobulins.[1,3] Another study reported that in the pediatric population that participated,[2] 80% of the patients who received anti-D improved with treatment, compared to 40% of the placebo group (significance values not reported by the studies), while the reaction in the adult population was 71% for both arms; when compared by the baseline number of platelets: in the population with counts below 50,000/mm^3, the improvement was 75% in the anti-D group and 58% in the placebo group (significance values not reported); and in the group of patients with counts between 50,000/mm^3 and 100,000/mm^3, the frequency of improvement was 92% in the anti-D group and 90% in the placebo group (significance values not reported).				VERY LOW ⦿○○○[b,d]	

Notes

CI: confidence interval; **RR:** relative risk.

The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Grading of the certainty of the evidence from the GRADE working group

HIGH Certainty: we are very sure that the true effect approximates the estimated effect.

MODERATE Certainty: we have moderate confidence in the estimated effect. The true effect is probably close to the estimated effect, but there is a possibility that it is substantially different.

LOW Certainty: our confidence in the estimated effect is limited. The true effect may be substantially different from the estimated effect.

VERY LOW Certainty: we have very little confidence in the estimated effect. The true effect is probably substantially different from the estimated effect.

[a] Information obtained from the two studies through a summary estimator, from the RevMan program, through a random-effects meta-analysis for relative risk (RR).

[b] There were studies with limitations in the risk of bias of selective reporting of outcomes.

[c] The study population was classified using a previous system (hemorrhagic dengue) rather than the current classification (severe dengue or dengue with warning signs).

[d] The sample size was small with a wide interval that includes the null value.

[e] It was not possible to determine the degree of heterogeneity due to the incomplete information published by the studies.

[f] Small sample size. Due to the absence of details regarding the dispersion of the information, it was not possible to estimate precision through an optimal sample size or the calculation of confidence intervals.

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SUMMARY OF FINDINGS TABLE 10. CONDOM USE FOR THE PREVENTION OF NON-VECTOR TRANSMISSION OF ZIKA VIRUS

Condom use for the prevention of non-vector transmission of Zika virus

Population: people exposed to non-vector transmission of Zika virus

Intervention: sexual intercourse with a condom

Comparison: sexual intercourse without a condom

Result Number of participants (studies)	Impact	Certainty
Sexual transmission Assessed with: confirmed cases of sexual transmission of Zika virus infection (18 observational studies)	A qualitative systematic review assessed the risk of transmission of Zika virus infection through sexual intercourse. The review compiled 18 studies that indicated person-to-person transmission, for a total of 27 episodes of probable or confirmed Zika virus infection. The most frequent mechanisms recorded were man to woman (25/27), man to man (1/27), and woman to man (1/27). Cases were confirmed through serological testing or polymerase chain reaction (PCR); the authors did not report confirmatory methods for the population that had sexual intercourse with the index cases.[1]	VERY LOW ⦿○○○[a,b]
Sexual transmission (67 observational studies)	A systematic review[1] described the outcomes for sexual transmission of Zika. The reported frequency of sexual transmission was 52/5,627 cases in the United States of America (CDC) and 20/1,737 cases in Europe. In addition to notifications from health agencies, the review included 24 notifications with a total of 36 couples with primary sexual transmission of Zika virus; transmission from partners was from index cases returning from areas where Zika was endemic. Similar to the other included review, the most frequent transmission mechanisms were from man to woman and through penile-vaginal sex, although oral sex and anal sex were also reported as possible routes of transmission.[2]	VERY LOW ⦿○○○[c]
Sexual transmission: condom use (10 randomized clinical trials)	One systematic review that included 10 randomized clinical trials that evaluated the efficacy of complex condom promotion interventions showed a significant reduction in the risk of sexually transmitted infections.[3]	MODERATE ⦿⦿⦿○[d]
Transmission associated with condom use (14 observational studies)	Seroconversion in users classified as "always use condoms": frequency, 11/587 people; incidence, 1.14 per 100 people/year. Seroconversion in users classified as "never use condoms": frequency, 40/276 people; incidence, 6.68 per 100 people/year.[4]	VERY LOW ⦿○○○[d,e]

Notes

The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Grading of the certainty of the evidence from the GRADE working group

HIGH Certainty: we are very sure that the true effect approximates the estimated effect.

MODERATE Certainty: we have moderate confidence in the estimated effect. The true effect is probably close to the estimated effect, but there is a possibility that it is substantially different.

LOW Certainty: our confidence in the estimated effect is limited. The true effect may be substantially different from the estimated effect.

VERY LOW Certainty: we have very little confidence in the estimated effect. The true effect is probably substantially different from the estimated effect.

[a] The review authors indicate MODERATE overall quality of the evidence, without specifying the quality of the included case reports.

[b] Lack of a comparison given the design.

[c] In the assessment of the risk of bias, there were 7/66 reports with the concept of "high diagnostic certainty" for the sexual partners of the index cases.

[d] The evidence came from studies that evaluated the role of condom use in the seroconversion of people with HIV.

[e] Although there is no quantitative information on the degree of heterogeneity, the authors note significant heterogeneity in the cohorts included to assess seroconversion in a population that never used condoms.

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SUMMARY OF FINDINGS TABLE 11. BREASTFEEDING IN PATIENTS WITH ZIKA

Suspension of breastfeeding compared to maintenance of breastfeeding for the prevention of non-vector transmission of Zika virus

Patient or population: people exposed to non-vector transmission of Zika virus

Intervention: suspend breastfeeding

Comparison: maintain breastfeeding

Result Number of participants (studies)	Impact	Certainty
Disease transmission Assessed by: number of confirmed Zika cases Number of participants: 3 (2 observational studies)	A systematic review of the specialized literature[1] assessed the risk of non-vector transmission of Zika virus associated with breastfeeding. As a result, the review found two case reports corresponding to a total of 3 mother-child pairs. The first mother: began breastfeeding on day 1 postpartum; on day 2 postpartum, the Zika virus infection was confirmed by PCR in saliva and serum; and on day 3, infection in the newborn was confirmed by PCR in serum and saliva. The second mother: obtained confirmation of infection through PCR in serum on days 1 and 5 postpartum; and began breastfeeding on day 3 postpartum. The newborn's PCR test in serum on days 0 and 3 was negative, but turned positive on the evaluations on days 4 and 7. The third mother began breastfeeding on the day of delivery and developed a fever and rash on subsequent days. On day 3, the infection was confirmed through PCR in serum. The newborn data were reported as ambiguous. Based on these results, the WHO guidelines on infant feeding in areas with Zika virus transmission contain a recommendation in favor of breastfeeding in mothers with suspected, probable, or confirmed Zika virus infection.[2]	VERY LOW ◉○○○[a]

Notes

[a] The evidence corresponds to case reports.

Sources

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ANNEX 5. GRADE tables: from evidence to recommendations

FRAMEWORK 1. WARNING SIGNS AND HOSPITALIZATION CRITERIA FOR DENGUE PATIENTS

Evaluation

PROBLEM **Is the problem a priority?**	
Research evidence	**Additional considerations**
A systematic review identified 291,964 cases associated with dengue outbreaks reported in the specialized literature. Most were from China, Singapore, and Malaysia, while 19.4% of these cases were recorded in the Region of the Americas. Half of the outbreaks occurred in urban areas and the average age of infection was 30 years old.[1] The annual incidence of dengue cases worldwide is 58.4 million, of which 10.53 million are hospitalized and 13,586 die from this disease.[2] In endemic areas, approximately 10% of fever episodes correspond to confirmed dengue, of which 11.1% require hospitalization.[3] A systematic review that evaluated the seroprevalence of dengue, chikungunya, and Zika reported prevalences of: 22%-99% (mean 65%) for asymptomatic dengue; 4%-65% (mean 26%) for asymptomatic chikungunya; and 29%-80% (mean 55%) for asymptomatic Zika. These estimates did not differ significantly across continents for any of the arboviruses.[4]	The panel made no observations.
DESIRABLE EFFECTS **How significant are the anticipated desirable effects?**	
Research evidence	**Additional considerations**
See the summary of findings table 2 (Annex 4).	The following prognostic factors or markers of severe dengue were identified: Narrowing pulse pressure Acute renal failure Arterial hypotension Sensory disorder Bleeding (including mucous membranes) Fluid accumulation Prolonged capillary refill time Pregnancy (especially the third trimester) Dyspnea or difficulty breathing Hepatomegaly Abdominal pain Microscopic hematuria Thrombocytopenia Coagulopathy Splenomegaly Elevated transaminases Progressive increase in hematocrit Vomiting

UNDESIRABLE EFFECTS
How significant are the anticipated undesirable effects?

Research evidence	Additional considerations
See the summary of findings table 2 (Annex 4).	The following factors were identified as NON-predictors or markers of severe dengue: High fever Positive tourniquet test Diarrhea Rhinorrhea Anorexia or hyporexia Petechiae or ecchymosis Nausea Obesity (considered as a potential risk factor and not a potential predictor) Malnutrition Rash Cough Leukopenia Retro-ocular pain Headache Myalgias or arthralgias

CERTAINTY OF THE EVIDENCE
What is the overall certainty of the evidence regarding effects?

Research evidence	Additional considerations
See the summary of findings table 2 (Annex 4).	The panel agreed that the predictive variables that were not supported by MODERATE or HIGH certainty of the evidence would not be considered as warning signs or criteria for hospitalization. Of the potential prognostic factors identified, those that met this condition were: Microscopic hematuria Coagulopathy Splenomegaly Pregnancy Prolonged capillary refill time Acute renal failure

Table 1. Predictors of severe disease in patients with dengue, chikungunya, or Zika

Certainty of the evidence	Dengue	Chikungunya	Zika
HIGH (confirmed prognostic factors)	– Abdominal pain – Sensory disorders – Bleeding (including mucous membranes) – Fluid accumulation – Dyspnea or difficulty breathing – Hepatomegaly – Thrombocytopenia – Elevated transaminases – Progressive increase in hematocrit – Vomiting	-	-
MODERATE (probable prognostic factors)	– Narrowing pulse pressure – Arterial hypotension	-	-
LOW (possible prognostic factors)	– Acute renal failure – Prolonged capillary refill time – Pregnancy – Third trimester of pregnancy (vs. first trimester) – Microscopic hematuria – Coagulopathy – Splenomegaly – High fever – Positive tourniquet test – Diarrhea	– Acute renal failure – Sensory disorder – Bleeding – Dyspnea or difficulty breathing – Elevated transaminases – Abdominal pain – Rhinorrhea – Anorexia or hyporexia – Petechiae or ecchymosis – Rash – Cough – Initial severe rheumatic involvement	– Headache – Nausea

VALUES
Is there high uncertainty or variability regarding how much patients value key outcomes?

Judgment	Research evidence	Additional considerations
○ High uncertainty or variability. ○ There may be high uncertainty or variability. ○ There is probably no high uncertainty or variability. ⊘ There is no high variability or uncertainty.	No evidence was identified.	The panel considered that all or almost all patients would prefer to use the prognostic factors that best predict the risk of progression to severe disease.

RESOURCE REQUIREMENTS
How large are the resource requirements (costs)?

Research evidence	Additional considerations
Multiple systematic reviews reported that the economic impact of dengue is significant, both in Latin America (US$ 1.73 billion-US$ 3 billion per year) and on other continents (approximately US$ 9 billion worldwide).[2,5–7] The largest impact would correspond to costs associated with lost productivity[5] and costs associated with hospitalization.[8] The estimated overall cost per dengue case was US$ 70.1 for patients requiring hospitalization, US$ 51.16 for outpatients, and US$ 12.94 for cases outside the health system.[2] In a study that evaluated the economic impact of dengue in Vietnam, it was reported that 47.2% of families had to borrow money to treat the disease, and 72.9% said that the disease impacted the family economy.[9]	Given its high frequency, it was considered that the inclusion of thrombocytopenia among the warning signs or hospitalization criteria would probably be associated with a substantial increase in resource use, which could negatively impact the adequate development of strategies for managing this disease, especially in the context of an epidemic. The case of elevated transaminases requiring specific laboratory evaluation is also probably associated with a substantial increase in costs.

EQUITY
What would be the impact on health equity?

Research evidence	Additional considerations
Multiple studies conducted in Latin American and Caribbean countries suggest, as a whole, that people from lower socioeconomic strata are at a disadvantage. This group has less access to medical services, medicines, and education.[10–24] According to the analysis of information obtained from 2005-2010, it was reported that, in the different countries in the Region, health inequities were worse in Haiti, Guatemala, Bolivia (Plurinational State of), Venezuela (Bolivarian Republic of), and Honduras. In contrast, the five countries with the best health status were Cuba, Argentina, Uruguay, Chile, and Mexico.[21] For a large part of society, drug expenditures continue to be an important component of out-of-pocket expenses due to lack of adequate coverage by health services. The average out-of-pocket expenditures on drugs in the Region was estimated at US$ 97 per capita, ranging from US$ 7 in Bolivia (Plurinational State of) to more than US$ 160 in Argentina and Brazil.[25] The seroprevalence of dengue, chikungunya, and Zika was mainly associated with age and socioeconomic, environmental, and behavioral factors. People from the lowest social classes and those living in urban areas and in conditions that favor vector development are the ones who presented the highest probability of positive seroprevalences.[4] In a systematic review that included 12 studies, it was found that in 9 of the studies, there was an association between at least one variable related to low socioeconomic status and dengue risk.[26] In a study that analyzed exposure to violence by geographical area within the city of Cali, Colombia, it was reported that this exposure was associated with arbovirus infection.[27]	Most of the prognostic factors identified are easily applicable in any setting so it is unlikely that there will be a negative impact on equity. However, the inclusion of elevated transaminases, which requires specific laboratory analysis, may reduce equity.

FEASIBILITY
Is it feasible to implement the intervention?

Research evidence	Additional considerations
No evidence was identified.	It was considered that it would not be feasible to establish some of the potential prognostic factors identified as warning signs, due to the time at which they occur. The panel agreed that narrowing pulse pressure, dyspnea, major bleeding, and arterial hypotension occur late and are part of the definition of severe dengue. Therefore, they would not be appropriate clinical manifestations to use as warning signs, but instead as hospitalization criteria.

Conclusions

Recommendations

1. The following factors should be used as warning signs for progression to severe dengue:

- Abdominal pain
  - Justification: due to the progression to dengue shock.
  - Clarification: progressive until it is continuous or sustained and intense and at the end of the febrile stage.
- Sensory disorder
  - Clarification: irritability, drowsiness, lethargy.
- Mucosal bleeding
  - Clarification: gingivorrhagia, epistaxis, vaginal bleeding not associated with menstruation, hematuria.
- Fluid accumulation
  - Justification: the decision was made to include this as a warning sign because its mere discovery or detection does not define or indicate the severity of the disease.
  - Clarification: detected through clinical review, imaging studies, or both, at the end of the febrile stage.
- Hepatomegaly
  - Clarification: abrupt onset. Greater than 2 cm below the costal margin.
- Progressive increase in hematocrit
  - Justification: cardinal sign of extravasation.
  - Clarification: it will be reinforced that physicians should be trained to assess other CLINICAL warning signs early so as not to delay resuscitation while waiting for laboratory results.
- Vomiting
  - Clarification: recurrence should be assessed to define it as a warning sign, considered as the presence of three or more episodes in one hour or four episodes in six hours.

2. The following factors should NOT be used as warning signs of progression to severe dengue:

- Clinically relevant bleeding (does not include mucosal bleeding)
  - Justification: is part of the definition or is a manifestation of severe dengue.
- Difficulty breathing
  - Justification: is part of the definition or is a manifestation of severe dengue.
- Thrombocytopenia
  - Justification: 1) the frequency of the event and problems with feasibility in hospital admissions and 2) it was considered that it is not a sign of extravasation that represents the need for immediate parenteral hydration.
- Elevated transaminases
  - Justification: 1) ALT values greater than 1,000 U/L are part of the definition or are a manifestation of severe dengue; 2) variability in the definition of "elevated" made it difficult to apply this risk factor as a warning sign; and 3) the costs of systematic determination in the assessment of the suspected dengue case.
- Shortened pulse pressure
  - Justification: is part of the definition or is a manifestation of severe dengue.
- Arterial hypotension
  - Justification: is part of the definition or is a manifestation of severe dengue.
- Microscopic hematuria
  - Justification: LOW certainty of the evidence.
- Coagulopathy
  - Justification: LOW certainty of the evidence.
- Splenomegaly
  - Justification: LOW certainty of the evidence.

3. The following criteria should be used to decide on hospitalization or admission to a dengue unit:

- Patients with the warning signs set out in these guidelines
- Patients with severe dengue, according to the WHO 2009 definition[1]

Other criteria:

- Difficulty breathing
  - Justification: is part of the definition or is a manifestation of severe dengue.
- Shortened pulse pressure
  - Justification: is part of the definition or is a manifestation of severe dengue.
- Arterial hypotension
  - Justification: is part of the definition or is a manifestation of severe dengue.
- Acute renal failure
  - Justification: the presence of acute renal failure was a prognostic factor for severe disease.
- Prolonged capillary refill time
  - Justification: is part of the definition or is a manifestation of severe dengue.
- Pregnancy
  - Justification: Pregnancy, especially in the third trimester, was a prognostic factor for severe illness.
- Coagulopathy
  - Justification: despite being supported by LOW certainty of the evidence, the panel considered that coagulopathy may be a manifestation of serious disease, which is why it was included as an admission criterion.
- Oral intolerance
  - Oral hydration is a fundamental pillar of the management of dengue patients.
- Others
  - Other factors that may determine the need for the hospitalization of dengue patients include the presence of comorbidities other than those described above, the extremes of life, and social or environmental conditions. The decision to hospitalize patients with the aforementioned conditions should be individualized.

Subgroup considerations

No subgroup considerations were proposed.

Implementation considerations

No implementation considerations were proposed.

Research priorities

Evaluate comorbidities as prognostic factors.

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FRAMEWORK 2. INTENSE ORAL HYDRATION FOR DENGUE PATIENTS

Evaluation

PROBLEM **Is the problem a priority?**		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ⊘ Yes ○ Varies ○ Don't know	In addition to the risk of plasma extravasation, dengue patients may become dehydrated due to fever, vomiting, diarrhea, and anorexia. Therefore, if management is not adequate, they can progress to severe forms of the disease.[1] Intense oral hydration may improve the evolution of these patients by maintaining an adequate circulating plasma volume.[2]	The panel made no observations.
DESIRABLE EFFECTS **How significant are the anticipated desirable effects?**		
Judgment	**Research evidence**	**Additional considerations**
○ Insignificant ○ Small ○ Moderate ⊘ Large ○ Varies ○ Don't know	See the summary of findings table 3 (Annex 4).	The panel considered as very relevant the effects on hospitalization and the need for parenteral hydration.
UNDESIRABLE EFFECTS **How significant are the anticipated undesirable effects?**		
Judgment	**Research evidence**	**Additional considerations**
○ Large ○ Moderate ○ Small ⊘ Insignificant ○ Varies ○ Don't know	See the summary of findings table 3 (Annex 4).	The panel made no observations.

CERTAINTY OF THE EVIDENCE
What is the overall certainty of the evidence regarding effects?

Judgment	Research evidence	Additional considerations
○ VERY LOW ⊘ LOW ○ MODERATE ○ HIGH ○ No studies included	See table below	The panel made no observations.

Outcomes	Importance	Certainty of the evidence
Hospitalization assessed by: impact of a strategy to increase and record oral fluid intake in patients with 3 or more days of fever and thrombocytopenia Follow-up: 2 months	CRITICAL	LOW ⊙⊙○○[a,b]
Hospitalization assessed by: consumption of more than 5 glasses of water in dengue patients without shock (dengue fever or dengue hemorrhagic fever)	CRITICAL	LOW ⊙⊙○○
Need for parenteral hydration assessed by: impact of a strategy to increase and record oral fluid intake in patients with 3 or more days of fever and thrombocytopenia Follow-up: 2 months	HIGH	LOW ⊙⊙○○[a,b]
Clinical evolution assessed by: comparison of oral and parenteral hydration in dengue patients without shock (dengue hemorrhagic fever grade I-II)	CRITICAL	VERY LOW ⊙⊙○○[c,d]
Clinical evolution assessed by: comparison of orally-administered isotonic solution and water, in addition to parenteral hydration, in patients with NON-severe dengue	CRITICAL	VERY LOW ⊙⊙○○[a,d,e]

Notes

[a] Lack of blinding, significant information loss, or both.
[b] The 95% confidence interval includes the absence of benefits.
[c] Unadjusted estimates.
[d] The optimal sample size was not achieved.
[e] All patients were treated with parenteral hydration. In patients who do not receive parenteral hydration, the effect of the intervention may be significantly different.

VALUES
Is there high uncertainty or variability regarding how much patients value key outcomes?

Judgment	Research evidence	Additional considerations
○ High uncertainty or variability. ○ There may be high uncertainty or variability. ○ There is probably no high uncertainty or variability. ⊘ There is no high variability or uncertainty.	No evidence was identified.	The panel deemed that, considering the characteristics of the intervention, all or almost all people would prefer to receive it.

BALANCE OF EFFECTS **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**		
Judgment	**Research evidence**	**Additional considerations**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor the intervention or the comparison ○ Probably favors the intervention ✓ Favors the intervention ○ Varies ○ Don't know	Not applicable.	The panel made no observations.

RESOURCE REQUIREMENTS **How high are the costs?**		
Judgment	**Research evidence**	**Additional considerations**
○ High costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ✓ High savings ○ Varies ○ Don't know	Multiple systematic reviews reported that the economic impact of dengue is significant, both in Latin America (US$ 1.73-US$ 3 billion per year) and on other continents (approximately US$ 9 billion worldwide).[3-6] The largest impact would correspond to costs associated with lost productivity[3] and costs associated with hospitalization.[7] The estimated overall cost per dengue case was US$ 70.1 for patients requiring hospitalization, US$ 51.16 for outpatients, and US$ 12.94 for cases outside the health system.[6] In a study that evaluated the economic impact of dengue in Vietnam, it was reported that 47.2% of families had to borrow money to treat the disease, and 72.9% said that the disease impacted the family economy.[8] A study in Brazil reported a significant cost associated with dengue hospitalizations (2.5% of the gross domestic product of the locality in which the observation was conducted).[9]	Given the lower direct costs of oral hydration and that hospitalizations may be reduced, the panel considered that the intervention may be associated with significant savings.

EQUITY **What would be the impact on health equity?**		
Judgment	**Research evidence**	**Additional considerations**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ✓ Increased ○ Varies ○ Don't know	Multiple studies conducted in Latin American and Caribbean countries suggest, as a whole, that people from lower socioeconomic strata are at a disadvantage. This group has less access to medical services, medicines, and education.[10–23] According to the analysis of information obtained from 2005-2010, it was reported that, in the different countries in the Region, health inequities were worse in Haiti, Guatemala, Bolivia (Plurinational State of), Venezuela (Bolivarian Republic of), and Honduras. In contrast, the five countries with the best health status were Cuba, Argentina, Uruguay, Chile, and Mexico.[21] For a large part of society, drug expenditures continue to be an important component of out-of-pocket expenses due to lack of adequate coverage by health services. The average out-of-pocket expenditure on drugs in the Region was estimated at US$ 97 per capita, ranging from US$ 7 in Bolivia (Plurinational State of) to more than US$ 160 in Argentina and Brazil.[24]	In regions with less access to highly complex health services, a simple intervention that is applicable in primary care and reduces the most complex interventions favors equity.

ACCEPTABILITY Is the intervention acceptable to stakeholders?		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ⊘ Yes ○ Varies ○ Don't know	In a study in which the intervention consisted of providing patients with a cup and an oral hydration record sheet, it was possible to increase orally-consumed liquid intake by 500 ml per day.[25]	The panel considered the intervention to be acceptable.

FEASIBILITY Is it feasible to implement the intervention?		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ⊘ Yes ○ Varies ○ Don't know	In a study in which the intervention consisted of providing patients with a cup and an oral hydration record sheet, it was possible to increase orally-consumed liquid intake by 500 ml per day.[25]	The panel considered that it is feasible to implement the intervention.

Summary of judgments

	JUDGMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Insignificant	Small	Moderate	**Large**		Vary	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Insignificant**		Vary	Don't know
CERTAINTY OF THE EVIDENCE	VERY LOW	**LOW**	MODERATE	HIGH			No studies included
VALUES	High uncertainty or variability.	There may be high uncertainty or variability.	There is probably no high uncertainty or variability.	**There is no high variability or uncertainty.**			
BALANCE OF EFFECTS	Favors the comparison.	Probably favors the comparison.	Does not favor the intervention or the comparison.	Probably favors the intervention.	**Favors the intervention.**	Varies	Don't know
RESOURCE REQUIREMENTS	High costs	Moderate costs	Negligible costs and savings	Moderate savings	**Extensive savings**	Vary	Don't know
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	**Increased**	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of recommendation

STRONG recommendation against the intervention	Additional recommendation against the intervention	CONDITIONAL recommendation in favor of the intervention or the comparison	CONDITIONAL recommendation in favor of the intervention	**STRONG recommendation in favor of the intervention**
○	○	○	○	◉

Conclusions

Recommendation

It is recommended to use an intense oral hydration scheme in dengue patients (STRONG recommendation supported with LOW certainty of the evidence). The STRONG recommendation does not adapt to any of the paradigmatic situations proposed for issuing STRONG recommendations with LOW certainty of the evidence.[26] However, considering that the intervention is not expensive, is easy to implement and operate, and would generate significant benefits, especially in the context of an epidemic, the panel decided to issue a STRONG recommendation.

Justification

The panel gave a very important weight: to the potential benefits in terms of reducing hospitalizations and the need for parenteral hydration; to the simplicity of the intervention, which facilitates its implementation (even in the primary care setting); and to its positive impact on equity. In this context, the panel decided to issue a STRONG recommendation, knowing that it does not conform to the GRADE system guidelines.

Subgroup considerations

The panel considered that the recommendation should apply to all patients with dengue virus infection.

Implementation considerations

The intervention is implemented in the primary care setting. For this, different tools can be used, such as the provision of cups with volume quantification or forms to record the ingestion of liquids.

Research priorities

No research priorities were proposed.

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FRAMEWORK 3. PARENTERAL HYDRATION FOR DENGUE PATIENTS WITH WARNING SIGNS

Evaluation

PROBLEM
Is the problem a priority?

Judgment	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ⊘ Yes ○ Varies ○ Don't know	The adequate restoration of circulating plasma volume is the cornerstone of managing patients with severe shock. The WHO 1975 and PAHO 2016 guidelines, currently in force, recommend the initial infusion of crystalloids for patients with dengue shock, followed by colloid boluses for treatment-resistant cases.[1,2] However, resuscitation with intravenous fluids may be initiated at even earlier stages of the disease, for example, in patients with warning signs. The implementation of different resuscitation protocols may have an impact on clinically relevant outcomes in this situation.	The panel made no observations.

DESIRABLE EFFECTS
How significant are the anticipated desirable effects?

Judgment	Research evidence	Additional considerations
○ Insignificant ○ Small ○ Moderate ⊘ Large ○ Varies ○ Don't know	See the summary of findings table 4 (Annex 4). Several panel members stated that there are multiple unpublished cohorts in which results similar to those included in the table were observed.	The panel considered the evidence included in the table, in addition to their personal experience. There was agreement among the panel members that, as observed in their individual practice, early hydration of cases with warning signs has an important positive impact on the clinical evolution of dengue patients.

UNDESIRABLE EFFECTS
How significant are the anticipated undesirable effects?

Judgment	Research evidence	Additional considerations
○ Large ○ Moderate ⊘ Small ○ Insignificant ○ Varies ○ Don't know	See the summary of findings table 4 (Annex 4). Several panel members stated that there are multiple unpublished cohorts in which results similar to those included in the table were observed.	The panel considered acute respiratory distress syndrome or pulmonary edema to be complications in: 1) prolonged or recurrent shock; 2) myocardial dysfunction (as a manifestation of severe dengue); and 3) comorbidities that increase the risk of this outcome.

CERTAINTY OF THE EVIDENCE
What is the overall certainty of the evidence regarding effects?

Judgment	Research evidence	Additional considerations
⊘ VERY LOW ○ LOW ○ MODERATE ○ HIGH[b1] ○ No studies included		The panel made no observations.

Outcomes	Importance	Certainty of the evidence (GRADE)
Death	CRITICAL	VERY LOW ◉○○○[a]
Shock	CRITICAL	VERY LOW ◉○○○[a]
Hydrosaline overload	CRITICAL	VERY LOW ◉○○○[b]

Notes

[a] Studies of one group without a comparison group.
[b] The estimate was not adjusted for all relevant prognostic factors.

VALUES
Is there high uncertainty or variability regarding how much patients value key outcomes?

Judgment	Research evidence	Additional considerations
○ High uncertainty or variability. ○ There may be high uncertainty or variability. ○ There is probably no high uncertainty or variability. ⊘ There is no high variability or uncertainty.	No evidence was identified.	The panel deemed that, considering the potential benefits of avoiding progression to severe disease and the relative simplicity of the intervention, all or almost all people would choose to receive the intervention.

BALANCE OF EFFECTS
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

Judgment	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor the intervention or the comparison ○ Probably favors the intervention ⊘ Favors the intervention ○ Varies ○ Don't know	Not applicable.	The panel made no observations.

RESOURCE REQUIREMENTS
How high are the costs?

Judgment	Research evidence	Additional considerations
○ High costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ⊘ High savings ○ Varies ○ Don't know	The prices of the different interventions compared, according to the International Drug Price Indicator:[3] Saline solution: US$ 0.001/ml Ringer's lactate: US$ 0.001/ml Dextran: US$ 0.01/ml Polygeline: US$ 0.01/ml Multiple systematic reviews reported that the economic impact of dengue is significant, both in Latin America (US$ 1.73 billion-US$ 3 billion per year) and on other continents (approximately US$ 9 billion worldwide).[4-7] The greatest impact would correspond to the costs associated with lost productivity[A] and the costs associated with hospitalization.[8]	The panel considered that the intervention is likely to be associated with high savings due to the reduced need for costly interventions such as hospitalization or admission to the intensive care unit.

EQUITY
What would be the impact on health equity?

Judgment	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ⊘ Increased ○ Varies ○ Don't know	Multiple studies conducted in Latin American and Caribbean countries suggest, as a whole, that people from lower socioeconomic strata are at a disadvantage. This group has less access to medical services, medicines, and education.[9-22] According to the analysis of information obtained from 2005-2010, it was reported that, in the Region's different countries, health inequities were worse in Haiti, Guatemala, Bolivia (Plurinational State of), Venezuela (Bolivarian Republic of), and Honduras. In contrast, the five countries with the best health status were Cuba, Argentina, Uruguay, Chile, and Mexico.[21] For a large part of society, drug expenditures continue to be an important component of out-of-pocket expenses due to lack of adequate coverage by health services. The average per capita out-of-pocket expenditure on medicines in the Region was estimated to be US$ 97, ranging from US$ 7 in Bolivia (Plurinational State of) to more than US$ 160 in Argentina and Brazil.[23]	Since it is a universally accessible intervention that may reduce the need for complex and costly interventions, the panel considered that equity would be increased.

ACCEPTABILITY Is the intervention acceptable to stakeholders?		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ⊘ Yes ○ Varies ○ Don't know	In two studies in Brazil in the context of an epidemic, a parenteral hydration strategy using tents installed at strategic points was successfully implemented, with the aim of caring for all symptomatic patients and avoiding hospital visits.[24,25]	The panel considered that the intervention is acceptable to those involved.

FEASIBILITY Is it feasible to implement the intervention?		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ⊘ Yes ○ Varies ○ Don't know	In two studies in Brazil in the context of an epidemic, a parenteral hydration strategy using tents installed at strategic points was successfully implemented, with the aim of caring for all symptomatic patients and avoiding hospital visits.[24,25]	The panel considered that it is feasible to provide parenteral hydration in most settings or regions.

Summary of judgments

	JUDGMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Insignificant	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Insignificant		Varies	Don't know
CERTAINTY OF THE EVIDENCE	**VERY LOW**	LOW	MODERATE	HIGH			No studies included
VALUES	High uncertainty or variability.	There may be high uncertainty or variability.	There is probably no high uncertainty or variability.	**There is no high variability or uncertainty.**			
BALANCE OF EFFECTS	Favors the comparison.	Probably favors the comparison.	Does not favor the intervention or the comparison.	Probably favors the intervention.	**Favors the intervention.**	Varies	Don't know
RESOURCE REQUIREMENTS	High costs	Moderate costs	Negligible costs and savings	Moderate savings	**High savings**	Varies	Don't know
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	**Increased**	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of recommendation

STRONG recommendation against the intervention	CONDITIONAL recommendation against the intervention	CONDITIONAL recommendation in favor of the intervention or the comparison	CONDITIONAL recommendation in favor of the intervention	STRONG recommendation in favor of the intervention
◉	○	○	○	○

Conclusions

Recommendation

Parenteral hydration is recommended in dengue patients with at least one warning sign (STRONG recommendation based on VERY LOW certainty of the evidence). The STRONG recommendation is based on the first paradigmatic situation, which justifies a STRONG recommendation with LOW certainty of the evidence[26] (possible benefits in the context of a potentially catastrophic situation).

Additional considerations: the warning signs are those set out in this document (see related recommendations).

1. The following factors should be used as warning signs for progression to severe dengue:

- Abdominal pain
- Sensory disorders
- Mucosal bleeding
- Fluid accumulation
- Hepatomegaly
- Progressive increase in hematocrit
- Vomiting

2. It is recommended to use crystalloids instead of colloids in the initial management of patients with dengue shock (STRONG recommendation based on LOW to MODERATE certainty of the evidence).

Additional considerations: depending on the reaction to the initial resuscitation scheme, the use of colloids (for example, in patients with persistent shock) may be considered.

Justification

In recommending the early use of parenteral hydration, the panel gave more weight to the potential large reduction in mortality and the possibility of easily implementing the intervention in the Region than to the risk of pulmonary edema. Although the certainty is VERY LOW, it was considered that the circumstances raised, especially in the context of an epidemic, correspond to the first paradigmatic situation, which justifies a STRONG recommendation when there is LOW certainty of the evidence (possible benefits in a potentially catastrophic situation).

Subgroup considerations

No subgroup considerations were proposed.

Implementation considerations

In the context of an epidemic, the intervention can be implemented in hydration units with the aim of reducing hospitalizations and admission to intensive care units.

Research priorities

The panel considers that it would be unethical to develop new intervention studies in which parenteral hydration is not offered to patients with warning signs.

Sources

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FRAMEWORK 4. CRYSTALLOIDS VERSUS COLLOIDS FOR THE INITIAL RESUSCITATION OF DENGUE PATIENTS

Evaluation

PROBLEM **Is the problem a priority?**		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ⊘ Yes ○ Varies ○ Don't know	The adequate restoration of circulating plasma volume is the cornerstone of managing patients with severe shock. The WHO 1975 and PAHO 2016 guidelines, currently in force, recommend the initial infusion of crystalloids for patients with dengue shock, followed by colloid boluses for treatment-resistant cases.[1,2] In recent decades, an intense debate has developed related to the use of crystalloids or colloids in critically ill patients. In theory, colloids would offer benefits to patients with increased vascular permeability; however, in clinical practice, this benefit has not been demonstrated.[3] In addition, colloids may be associated with significant side effects.[4]	The panel made no observations.
DESIRABLE EFFECTS **How significant are the anticipated desirable effects?**		
Judgment	**Research evidence**	**Additional considerations**
○ Insignificant ○ Small ⊘ Moderate ○ Large ○ Varies ○ Don't know	See the summary of findings table 5 (Annex 4).	The panel gave weight to the possibility of reducing the risk of renal failure with crystalloids and the infusion-related reactions reported with colloids. Vote: 5 (LOW), 6 (MODERATE)
UNDESIRABLE EFFECTS **How significant are the anticipated undesirable effects?**		
Judgment	**Research evidence**	**Additional considerations**
○ Large ○ Moderate ○ Small ⊘ Insignificant ○ Varies ○ Don't know	See the summary of findings table 5 (Annex 4).	The panel made no observations.

CERTAINTY OF THE EVIDENCE
What is the overall certainty of the evidence regarding effects?

Judgment	Research evidence	Additional considerations
○ VERY LOW ⊘ LOW ○ MODERATE ○ HIGH ○ No studies included	See table below	Considering that the certainty of the effect on mortality was LOW, it was agreed that the overall certainty should be LOW. However, the panel considered that there is MODERATE and HIGH certainty about the effects of the intervention on other critical and important outcomes. For this reason, the overall certainty of the evidence was considered to be LOW to MODERATE.

Outcomes	Importance	Certainty of the evidence
Death	CRITICAL	-
Death (indirect)	CRITICAL	LOW ⦿⦿○○[a,b]
Recurrent or treatment-resistant shock	CRITICAL	MODERATE ⦿⦿⦿○[c]
Fluid overload	HIGH	MODERATE ⦿⦿⦿○[c]
Infusion-related reactions and allergies	HIGH	HIGH ⦿⦿⦿⦿[d]
Renal replacement therapy (indirect)	HIGH	LOW ⦿⦿○○[a,b]

Notes

[a] Most of the included studies had relevant methodological limitations.
[b] Most of the studies considered did not include dengue patients.
[c] The 95% confidence interval includes significant benefits and harms.
[d] The certainty of the evidence was not reduced because, although the optimal sample size was not reached, a large magnitude of effect was observed and the risk of crystalloid infusion-related reactions is assumed to be close to 0%.

VALUES
Is there high uncertainty or variability regarding how much patients value key outcomes?

Judgment	Research evidence	Additional considerations
○ High uncertainty or variability. ○ There may be high uncertainty or variability. ⊘ There is probably no high uncertainty or variability. ○ There is no high variability or uncertainty.	No evidence was identified.	The panel considered that most people who are well informed about the effects of the intervention would prefer to receive crystalloids.

BALANCE OF EFFECTS
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

Judgment	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor the intervention or the comparison ○ Probably favors the intervention ⊘ Favors the intervention ○ Varies ○ Don't know	Not applicable.	The panel made no observations.

RESOURCE REQUIREMENTS
How high are the costs?

Judgment	Research evidence	Additional considerations
○ High costs ○ Moderate costs ○ Negligible costs and savings ⊘ Moderate savings ○ High savings ○ Varies ○ Don't know	The prices of the different interventions compared, according to the International Drug Price Indicator:[5] Saline solution: US$ 0.001/ml Ringer's lactate: US$ 0.001/ml Dextran: US$ 0.01/ml Polygenline: US$ 0.01/ml Polygeline: US$ 0.01/ml Multiple systematic reviews reported that the economic impact of dengue is significant, both in Latin America (US$ 1.73 billion-US$ 3 billion per year) and on other continents (approximately US$ 9 billion worldwide).[6-9] The greatest impact would correspond to the costs associated with lost productivity[6] and the costs associated with hospitalization.[10]	Despite the fact that the volume of colloids to be infused is significantly lower than the volume of crystalloids, the panel considered that, due to the substantial difference in cost, the use of crystalloids would likely result in savings.

EQUITY
What would be the impact on health equity?

Judgment	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ⊘ Increased ○ Varies ○ Don't know	Multiple studies conducted in different Latin American and Caribbean countries suggest that people from lower socioeconomic strata are at a disadvantage. This group has less access to medical services, medicines, and education.[11–24] According to the analysis of information obtained from 2005-2010, it was reported that, in the different countries in the Region, health inequities were worse in Haiti, Guatemala, Bolivia (Plurinational State of), Venezuela (Bolivarian Republic of), and Honduras. In contrast, the five countries with the best health status were Cuba, Argentina, Uruguay, Chile, and Mexico.[22] For a large part of society, drug expenditures continue to be an important component of out-of-pocket expenses due to lack of adequate coverage by health services. The average out-of-pocket expenditure on drugs in the Region was estimated to be US$ 97 per capita, ranging from US$ 7 in Bolivia (Plurinational State of) to more than US$ 160 in Argentina and Brazil.[25]	In some contexts, colloids may not be available.

ACCEPTABILITY
Is the intervention acceptable to stakeholders?

Judgment	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ⊘ Yes ○ Varies ○ Don't know	In two studies in Brazil in the context of an epidemic, a parenteral hydration strategy using tents installed at strategic points was successfully implemented, with the aim of caring for all symptomatic patients and avoiding hospital visits.[26,27]	The panel considered crystalloid infusion to be an acceptable intervention.

FEASIBILITY
Is it feasible to implement the intervention?

Judgment	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ⊘ Yes ○ Varies ○ Don't know	In two studies in Brazil in the context of an epidemic, a parenteral hydration strategy using tents installed at strategic points was successfully implemented, with the aim of caring for all symptomatic patients and avoiding hospital visits.[26,27]	The panel considered that it is feasible to provide parenteral hydration in most settings or regions.

Summary of judgments

	JUDGMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Insignificant**	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Insignificant**		Varies	Don't know
CERTAINTY OF THE EVIDENCE	VERY LOW	**LOW**	MODERATE	HIGH			No studies included
VALUES	High uncertainty or variability.	There may be high uncertainty or variability.	**There is probably no high uncertainty or variability.**	There is no high variability or uncertainty.			
BALANCE OF EFFECTS	Favors the comparison.	Probably favors the comparison.	Does not favor the intervention or the comparison.	Probably favors the intervention.	**Favors the intervention.**	Varies	Don't know
RESOURCE REQUIREMENTS	High costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Extensive savings	Varies	Don't know
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	**Increased**	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of recommendation

STRONG recommendation against the intervention	CONDITIONAL recommendation against the intervention	CONDITIONAL recommendation in favor of the intervention or the comparison	CONDITIONAL recommendation in favor of the intervention	**STRONG recommendation in favor of the intervention**
○	○	○	○	◉

Conclusions

Recommendation

It is recommend to use crystalloids or colloids in the initial management of patients with dengue shock (STRONG recommendation, based on LOW to MODERATE certainty of the evidence).

Additional considerations: depending on the reaction to the initial resuscitation scheme, the use of colloids (e.g., in patients with treatment-resistant shock) may be considered.

Justification

The panel gave weight to the benefits of the intervention in terms of lower risk of infusion-related reactions and possibly, kidney failure. In addition, it considered the benefits of the intervention in terms of lower cost and greater accessibility. The strength of the recommendation is justified based on LOW to MODERATE certainty of the evidence and the third paradigmatic situation, which supports STRONG recommendations with LOW certainty of the evidence (LOW certainty of the equivalence between both options in terms of benefits, but MODERATE-HIGH certainty in terms of fewer risks or costs).[28]

Subgroup considerations

No subgroup considerations were proposed.

Implementation considerations

It is advisable that resuscitation be carried out in a controlled setting in which the hemodynamic parameters are evaluated periodically in order to determine whether the response was adequate.

Research priorities

No research priorities were proposed.

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FRAMEWORK 5. TRANSFUSION OF BLOOD COMPONENTS FOR DENGUE PATIENTS WITH THROMBOCYTOPENIA

Evaluation

PROBLEM
Is the problem a priority?

Judgment	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ⊘ Yes ○ Varies ○ Don't know	The presence of thrombocytopenia has been reported in 79%-100% of patients hospitalized for dengue.[1,2] Platelet transfusion may be associated with benefits by reducing hemorrhages and preventing progression to shock, while fresh frozen plasma may reduce immune-mediated platelet destruction. Both interventions may be associated with side effects such as hydrosaline overload or transfusion-related reactions.	The panel made no observations.

DESIRABLE EFFECTS
How significant are the anticipated desirable effects?

Judgment	Research evidence	Additional considerations
⊘ Insignificant ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	See the summary of findings table 6 (Annex 4).	The magnitude of the benefit may be greater in patients with an elevated baseline risk of bleeding.

UNDESIRABLE EFFECTS
How significant are the anticipated undesirable effects?

Judgment	Research evidence	Additional considerations
○ Large ○ Moderate ⊘ Small ○ Insignificant ○ Varies ○ Don't know	See the summary of findings table 6 (Annex 4).	In addition to those included in the table, these other undesirable effects were considered: Risk of acute and chronic infection (Chagas, 1 in 300,000; hepatitis B virus and HIV, 1 in 1 million; hepatitis C virus) due to platelet transfusion in particular and in general (multiple donors as a source of blood components in the Region).

CERTAINTY OF THE EVIDENCE
What is the overall certainty of the evidence regarding effects?

Judgment	Research evidence	Additional considerations
⊘ VERY LOW ○ LOW ○ MODERATE ○ HIGH[b1] ○ No studies included	See table below	The panel made no observations.

Outcomes	Importance	Certainty of the evidence (GRADE)
Death	CRITICAL	VERY LOW ◉○○○[a,b]
Shock	CRITICAL	VERY LOW ◉○○○[a,b]
Major bleeding	CRITICAL	LOW ◉◉○○[a,b]
Side effects	CRITICAL	MODERATE ◉◉◉○[a]

Notes

[a] Lack of blinding.
[b] The 95% confidence interval includes significant benefits and harms.

VALUES
Is there high uncertainty or variability regarding how much patients value key outcomes?

Judgment	Research evidence	Additional considerations
○ High uncertainty or variability. ○ There may be high uncertainty or variability. ⊘ There is probably no high uncertainty or variability. ○ There is no high variability or uncertainty.	No evidence was identified.	The panel considered that the vast majority of patients who are correctly informed about the benefits and harms would decide not to receive a blood component transfusion. Vote: probably (9); definitely (3)

BALANCE OF EFFECTS
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

Judgment	Research evidence	Additional considerations
○ Favors the comparison ⊘ Probably favors the comparison ○ Does not favor the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Not applicable.	The panel made no observations.

RESOURCE REQUIREMENTS
How high are the costs?

Judgment	Research evidence	Additional considerations
⊘ High costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ High savings ○ Vary ○ Don't know	A study conducted in Brazil reported a significant cost associated with hospitalizations due to dengue (2.5% of the gross domestic product of the locality in which the observation was carried out) and that the use of blood products was associated with a significant increase in these costs.[3]	The panel considered that implementation of the intervention would be associated with high economic costs. It also considered that blood components are a limited resource and that their use as prophylaxis in patients with thrombocytopenia would probably result in less availability for other circumstances.

EQUITY
What would be the impact on health equity?

Judgment	Research evidence	Additional considerations
⊘ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Multiple studies conducted in Latin American and Caribbean countries suggest, as a whole, that people from lower socioeconomic strata are at a disadvantage. This group has less access to medical services, medicines, and education.[4–17] According to the analysis of information obtained from 2005-2010, it was reported that, in the different countries in the Region, health inequities were worse in Haiti, Guatemala, Bolivia (Plurinational State of), Venezuela (Bolivarian Republic of), and Honduras. In contrast, the five countries with the best health status were Cuba, Argentina, Uruguay, Chile, and Mexico.[15] For a large part of society, drug expenditures continue to be an important component of out-of-pocket expenses due to lack of adequate coverage by health services. The average per capita out-of-pocket expenditure on medicines in the Region was estimated to be US$ 97, ranging from US$ 7 in Bolivia (Plurinational State of) to more than US$ 160 in Argentina and Brazil.[18]	The intervention requires a level of complexity that is not universally available in the Region.

ACCEPTABILITY Is the intervention acceptable to stakeholders?		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ⊘ Probably yes ○ Yes ○ Varies ○ Don't know	The transfusion of blood components as part of the management of dengue patients is usual care in many contexts and regions.[1,19-21]	The intervention may be acceptable to most of the actors involved, although there are exceptions (e.g., Jehovah's Witnesses).

FEASIBILITY Is it feasible to implement the intervention?		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ○ Yes ⊘ Varies ○ Don't know	The transfusion of blood components as part of the management of dengue patients is usual care in many contexts and regions.[1,19-21]	The intervention requires a level of complexity that is not universally available in the Region.

Summary of judgments

	JUDGMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Insignificant**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	**Insignificant**		Varies	Don't know
CERTAINTY OF THE EVIDENCE	**VERY LOW**	LOW	MODERATE	HIGH			Does not include studies
VALUES	High uncertainty or variability.	There may be high uncertainty or variability.	**There is probably no high uncertainty or variability.**	There is no high variability or uncertainty.			
BALANCE OF EFFECTS	Favors the comparison.	**Probably favors the comparison.**	Does not favor the intervention or the comparison.	Probably favors the intervention.	Favors the intervention.	Varies	Don't know
RESOURCE REQUIREMENTS	**High costs**	Moderate costs	Negligible costs and savings	Moderate savings	Extensive savings	Varies	Don't know
EQUITY	**Reduced**	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

Type of recommendation

STRONG recommendation against the intervention	CONDITIONAL recommendation against the intervention	CONDITIONAL recommendation in favor of the intervention or the comparison	CONDITIONAL recommendation in favor of the intervention	STRONG recommendation in favor of the intervention
◉	○	○	○	○

Conclusions

Recommendation

It is recommended to not transfuse blood components (platelet concentrate or fresh frozen plasma) to dengue patients with thrombocytopenia (STRONG recommendation based on VERY LOW certainty regarding the effects of the intervention). The STRONG recommendation is based on the second paradigmatic situation, which justifies a STRONG recommendation with LOW certainty of the evidence (uncertainty regarding the benefits with MODERATE or HIGH certainty regarding the harms).[22]

Justification

The panel prioritized the negative aspects of the intervention (reactions to infusions, infections, increased costs) and the impossibility of its implementation in regions with less access to health services over the possible benefits of reducing the risk of hemorrhage. The certainty of the evidence was VERY LOW for benefits and MODERATE for side effects. The STRONG recommendation is justified through the second paradigmatic situation (uncertainty regarding the benefits with MODERATE-HIGH certainty regarding the harms)[22] since the panel considered that there is MODERATE-HIGH certainty that the intervention has high costs and would probably have a negative impact on equity.

Subgroup considerations

The recommendation applies to all patients with dengue and thrombocytopenia, regardless of platelet count.

In certain subgroups with indication for transfusion due to associated conditions (pregnancy, life-threatening bleeding), platelet transfusion should be considered.

Implementation considerations

No implementation considerations were proposed.

Research priorities

The panel considered that, in the situation proposed, there is a need to evaluate other interventions, such as the administration of fibrinogen, cryoprecipitates, or tranexamic acid.

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FRAMEWORK 6. SYMPTOMATIC TREATMENT

Evaluation

PROBLEM
Is the problem a priority?

Judgment	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ⊘ Yes ○ Varies ○ Don't know	A systematic review identified 291,964 cases associated with dengue outbreaks reported in the specialized literature. Most were from China, Singapore, and Malaysia, while 19.4% of these cases were recorded in the Region of the Americas. Half of the outbreaks occurred in urban areas and the average age of infection was 30 years old.[1] The annual incidence of dengue cases worldwide is 58.4 million, of which 10.53 million are hospitalized and 13,586 die from this disease.[2] In endemic areas, approximately 10% of fever episodes correspond to confirmed dengue, of which 11.1% require hospitalization.[3] A systematic review that evaluated the seroprevalence of dengue, chikungunya, and Zika reported prevalences of: 22%-99% (mean 65%) for asymptomatic dengue; 4%-65% (mean 26%) for asymptomatic chikungunya; and 29%-80% (mean 55%) for asymptomatic Zika. These estimates did not differ significantly across continents for any of the arboviruses.[4] Arboviruses are usually associated with significant morbidity, mainly due to fever, myalgias, and arthralgias. Symptomatic treatment is one of the pillars for managing these patients.	The panel made no observations.

DESIRABLE EFFECTS
How significant are the anticipated desirable effects?

Judgment	Research evidence	Additional considerations
○ Insignificant ○ Small ○ Moderate ○ Large ⊘ Varies ○ Don't know	See the summary of findings table 7 (Annex 4).	The benefits were judged: as moderate for NSAIDs, considering the panel's experience with the use of these drugs for the treatment of acute pain due to other causes; and as small for paracetamol and metamizole, based on the panel's experience with these drugs in patients with arbovirus. On the other hand, the benefit was considered insignificant for glucocorticoids and uncertain for antihistamines, noting that arboviruses have no pathophysiological basis for histamine release. Metamizole vs. paracetamol: small NSAIDs: moderate Glucocorticoids: insignificant Antihistamines: unknown

UNDESIRABLE EFFECTS
How significant are the anticipated undesirable effects?

Judgment	Research evidence	Additional considerations
○ Large ○ Moderate ○ Small ○ Insignificant ⊘ Varies ○ Don't know	See the summary of findings table 7 (Annex 4).	For the case of NSAIDS, the harms were judged to be uncertain, noting, in addition, that they could be confused with severe dengue (for example, bleeding). For metamizole and paracetamol, the panel considered the harms to be minor, on the basis that the reported side effects are not life-threatening. On the other hand, the harm was considered insignificant for glucocorticoids and uncertain for antihistamines, noting that arboviruses have no pathophysiological basis for histamine release. Metamizole vs. paracetamol: small NSAIDs: unknown Glucocorticoids: minimal Antihistamines: unknown

CERTAINTY OF THE EVIDENCE
What is the overall certainty of the evidence regarding effects?

Judgment	Research evidence	Additional considerations
☑ VERY LOW ○ LOW ○ MODERATE ○ HIGH ○ No studies included	See table below	The certainty of the overall evidence was rated as VERY LOW to LOW. Metamizole vs. paracetamol: LOW NSAIDs: VERY LOW Metamizole: VERY LOW Glucocorticoids: LOW Antihistamines: LOW

Outcomes	Importance	Certainty of the evidence
Side effects of NSAIDs		VERY LOW ◉○○○[a-d]
Side effects of paracetamol		VERY LOW ◉○○○[e,f]
Side effects of metamizole		VERY LOW ◉○○○[g,h]
Side effects of steroids		LOW ◉◉○○[g,h]
Side effects of antihistamines		LOW ◉◉○○[i,j]

Notes

[a] VERY LOW certainty for the bleeding estimates considering: 1) fragility and the failure to report the severity of the bleeding in the adjusted estimate, and 2) lack of adjustment for other variables and heterogeneity in the estimates from the remaining studies.

[b] VERY LOW certainty in the evidence for abdominal pain based on studies of dengue patients, considering that they are supported by NON-randomized studies with no adjustment for confounding variables.

[c] LOW certainty in the evidence for gastrointestinal side effects based on the evidence about musculoskeletal injury, considering: 1) the risk of bias in the studies, and 2) indirect evidence, as these are not dengue patients.

[d] VERY LOW certainty in the estimates for liver damage, considering: 1) that they are based on a non-randomized study with no adjustment for confounding variables, and 2) the fragility of the estimates.

[e] VERY LOW certainty for the bleeding estimate, considering that it is based on: 1) 2 randomized studies, with no details about the randomization methods and without a reported assessor for blinding,[5] with 2 major events,[6] and 2) 1 non-randomized study with no adjustment for confounding variables and 86 events.

[f] The certainty in the evidence for the estimates of liver damage is LOW, considering that: 1) 1 randomized study[6] was stopped early after 23 events of elevated transaminases (3 times their upper normal limit) and excluded patients with an altered hepatogram at admission, and 1 randomized study[5] did not present details about randomization, does not report assessors for blinding, and had unclear loss-to-follow-up; 2) 4 non-randomized studies have methodological problems (the 4 studies did not specify a control group, defined by the NON-use of paracetamol; the 3 studies that described a model adjusted for confounding variables did not incorporate other treatments such as NSAIDs or metamizole into the regression models; 1 study did not include parameters that define dengue severity such as shock or major bleeding in the regression model,[7] and also indicated frequent loss of data related to paracetamol ingestion).[8]

[g] Insufficient number of events, patients, or both.

[h] There are methodological limitations in the primary studies identified.

[i] LOW certainty in the estimates based on the study of dengue patients, considering the risk of bias (unreported method of allocation concealment and, in addition, it is not clear whether the event assessors were blinded to the allocation) and imprecision due to fragility (small number of events).

[j] LOW certainty in the estimate based on patients with a common cold, considering imprecision due to fragility (small number of events) and indirect evidence.

VALUES
Is there high uncertainty or variability regarding how much patients value key outcomes?

Judgment	Research evidence	Additional considerations
○ High uncertainty or variability. ☑ There may be high uncertainty or variability. ○ There is probably no high uncertainty or variability. ○ There is no high variability or uncertainty.	No evidence was identified.	High variability was considered possible, as some patients may judge the potential side effects of the drugs assessed to be more relevant than symptom control, while other patients may judge the opposite (e.g., chikungunya patients with severe joint pain). Metamizole vs. paracetamol: possible uncertainty NSAIDs: possible uncertainty Metamizole: possible uncertainty Glucocorticoids: there is no high variability. Antihistamines: possible uncertainty

BALANCE OF EFFECTS
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

Judgment	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ⊘ Varies ○ Don't know	Not applicable.	The balance was considered to favor the use of paracetamol or metamizole (with no preference for one over the other) compared to NSAIDs, glucocorticoids, and antihistamines. The panel based its judgment on the side effect profile presented in the summary of findings table and the perspectives gained from clinical experience with the use of these drugs in patients with arbovirus. Metamizole vs. paracetamol: does not favor either. NSAIDs: probably favors the comparison. Glucocorticoids: favors the comparison. NSAIDs: probably favors the comparison.

RESOURCE REQUIREMENTS
How high are the costs?

Judgment	Research evidence	Additional considerations
○ High costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ High savings ⊘ Varies ○ Don't know	No evidence was identified.	The costs for each of the drugs analyzed were considered to be variable in the different countries of the Region. Metamizole: variable Paracetamol: variable NSAIDs: moderate costs Glucocorticoids: moderate costs Antihistamines: moderate savings

EQUITY
What would be the impact on health equity?

Judgment	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ⊘ •Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No evidence was identified.	The panel considered that, with the exception of antihistamines, the choice of metamizole, paracetamol, NSAIDs, or glucocorticoids does not impact equity. The availability of some antihistamines may be restricted in some of the Region's countries and their choice may have a negative impact on equity.

ACCEPTABILITY
Is the intervention acceptable to stakeholders?

Judgment	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ○ Yes ⊘ Varies ○ Don't know	No evidence was identified.	The panel unanimously considered that paracetamol is a universally accepted drug for the symptomatic treatment of arboviruses, while metamizole is also probably accepted, although some doctors may consider NOT using it in order to avoid serious idiosyncratic side effects. On the other hand, it was considered that NSAIDs and glucocorticoids are probably not acceptable to treating physicians due to perceived side effects (e.g., hemorrhages).

FEASIBILITY Is it feasible to implement the intervention?		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ⊘ Probably yes ○ Yes ○ Varies ○ Don't know	No evidence was identified.	The panel considered that it is feasible to use antihistamines, metamizole, paracetamol, NSAIDs, and glucocorticoids in patients with arboviruses. The availability of some antihistamines may be restricted in some of the Region's countries.

Summary of judgments

	JUDGMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Insignificant**	Small	Moderate	Large		**Varies**	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Insignificant**		**Varies**	Don't know
CERTAINTY OF THE EVIDENCE	**VERY LOW**	LOW	MODERATE	HIGH			No studies included
VALUES	High uncertainty or variability.	**There may be high uncertainty or variability.**	There is probably no high uncertainty or variability.	There is no high variability or uncertainty.			
BALANCE OF EFFECTS	Favors the comparison.	Probably favors the comparison.	Does not favor the intervention or the comparison.	Probably favors the intervention.	Favors the intervention.	**Varies**	Don't know
RESOURCE REQUIREMENTS	High costs	Moderate costs	Negligible costs and savings	Moderate savings	High savings	**Varies**	Don't know
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

STRONG recommendation against the intervention	CONDITIONAL recommendation against the intervention	CONDITIONAL recommendation in favor of the intervention or the comparison	**CONDITIONAL recommendation in favor of the intervention**	STRONG recommendation in favor of the intervention
○	○	○	◉	○

Conclusions

Recommendation

It is suggested to use paracetamol or metamizole, instead of NSAIDs, antihistamines, or steroids, for the initial symptomatic management of patients with arbovirus (CONDITIONAL recommendation, supported by VERY LOW certainty of the evidence).

Justification

The panel based its recommendation on:

The absence of reliable evidence on the comparative effect of the different options in terms of efficacy, but primarily in terms of safety.

- The fact that usual practice, so far, is to avoid the use of NSAIDs due to the possibility of serious side effects, primarily those related to bleeding.

- The existing body of evidence suggests that the side effect profile of paracetamol and metamizole is not life-threatening, and that both drugs are acceptable to treating physicians and patients.

Subgroup considerations

In patients who do not obtain adequate symptomatic control with the suggested interventions, the use of NSAIDs may be considered; for example, in patients with chikungunya who do not achieve pain control, the use of NSAIDs may be considered.

Implementation considerations

Pharmacological measures may be accompanied by other interventions, such as the use of physical means (use of compresses or baths with water) as alternatives for controlling fever in dengue patients.

Research priorities

No research priorities were proposed.

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FRAMEWORK 7. STEROIDS FOR PATIENTS WITH SEVERE ARBOVIRUS

Evaluation

PROBLEM Is the problem a priority?		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ⊘ Yes ○ Varies ○ Don't know	Dengue is a mosquito-borne disease that is widely disseminated around the world. According to WHO,[1] the incidence of dengue is considered to have increased in recent years, but since most cases are asymptomatic, there is underreporting of cases. Bhatt et al. published the global estimate of the burden of dengue in 2013. They found that, of the 96 million dengue infections with symptomatic manifestations, 13.3 million correspond to cases distributed in the Region of the Americas. In addition to the significant number of symptomatic cases, they found that nearly 20,000 deaths associated with this disease may occur in developing countries.[2] Regarding the burden of this disease, mortality associated with dengue has been observed in countries such as Brazil, where 62 deaths were recorded out of a total of 105,459 cases. Sixty-one of these deaths occurred in the 1,605 patients with severe dengue (3.8%).[3] Similar behavior was reported by Castrillón et al., who found that in Colombia in 2011, 203 deaths were associated with 30,694 dengue cases, including 1,303 cases of severe dengue.[4]	The panel made no observations.

DESIRABLE EFFECTS How significant are the anticipated desirable effects?		
Judgment	**Research evidence**	**Additional considerations**
○ Insignificant ⊘ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Corticosteroids in patients with dengue shock** A systematic review of the specialized literature evaluated the efficacy and safety of corticosteroid use in adults and children diagnosed with dengue.[5] For the severe dengue component, the authors included studies of patients with dengue-related shock. The intervention of interest consisted of the oral or intravenous administration of any type of steroid orally, compared to the use of a placebo or non-corticosteroids. The primary outcome was mortality and secondary outcomes for dengue-related shock were the need for transfusion, the presence of complications such as pulmonary hemorrhage or seizures, the duration of the shock, the length of the hospital stay, and the frequency of side effects. The review found four clinical trials with a total of 284 pediatric patients under age 15. The types of corticosteroids used were intravenous hydrocortisone (three studies) and methylprednisolone (one study). When comparing corticosteroid use versus placebo or no intervention, the authors found no difference in the risk of death (RR = 0.68; 95% CI: 0.42–1.11; four studies, 284 participants), the need for transfusion (RR = 1.08; 95% CI: 0.52–2.24; two studies, 89 patients), the frequency of pulmonary hemorrhage (RR = 0.97; 95% CI: 0.06–14.82; one study, 63 patients), the frequency of seizures (RR = 6.79; 95% CI: 0.36–126.24; one study, 63 patients), or the length of the hospital stay (MD = 1.1; 95% CI: −1.83–4.03; one study, 63 patients).[5] **Corticosteroids in patients with sepsis** A systematic review of the specialized literature evaluated the efficacy and safety of corticosteroids in patients with sepsis.[6] The review authors included clinical trials conducted in adults and children diagnosed with sepsis, severe sepsis, or septic shock, according to definitions established by expert consensus. As interventions, the review included the use of any corticosteroid administered at any dosage. It established as high doses the administration of greater than 400 mg/day of hydrocortisone or its equivalent, and defined as long-term administration an administration time equal to or greater than 3 days. Outcomes of interest were 90-day mortality, 28- and 30-day intensive care stay, 28- and 30-day mortality, long-term mortality, probability of shock reversal at 7 days, organ failure at 7 days as measured by the sequential organ failure assessment (SOFA) score, hospital stay in intensive care, frequency of side effects, and quality of life.[6] The review included 42 clinical trials, of which 24 were conducted in patients with septic shock, 5 in patients with sepsis and community-acquired pneumonia, and 13 with acute respiratory distress syndrome and sepsis. Interventions included the use of hydrocortisone (28 studies), methylprednisolone (6 studies), prednisolone (3 studies), dexamethasone (3 studies), and the combination of hydrocortisone with fludrocortisone (2 studies). The authors concluded that corticosteroid use was associated with a higher likelihood of shock reversal (RR = 1.26; 95% CI: 1.12–1.42; 13 studies, 2,802 patients) and an improvement in SOFA organ failure scores (MD = −1.39; 95% CI: −1.88-–0.89; 9 studies, 1,986 patients), but they found no differences in short-term mortality (RR = 0.93; 95% CI: 0.84–1.03; 36 studies, 9,433 patients), long-term mortality (RR = 0.94; 95% CI: 0.89–1; 9 studies, 6,438 patients), intensive care stay (MD = –0.73; 95% CI : −1.78–0.31; 20 studies, 7,463 patients), or hospital stay (MD = –0.73; 95% CI: −2.06–0.6; 18 studies, 7,706 patients). Regarding side effects, the review found that corticosteroid use was associated with an increased risk of muscle weakness (RR = 1.21; 95% CI: 1.01–1.45; 7 studies, 6,178 patients), hypernatremia (RR = 1.64; 95% CI: 1.32–2.03; 6 studies, 5,015 patients), and hyperglycemia (RR = 1.16; 95% CI: 1.08–1.24; 15 studies, 7,563 patients), with no differences between comparisons detected for the risk of gastrointestinal bleeding, neuropsychiatric events, superinfection, myocardial infarction, or cerebrovascular event.[6] See the summary of findings table 8 (Annex 4).	In everyday practice, corticosteroids are not used as part of the management of severe dengue.

UNDESIRABLE EFFECTS How significant are the anticipated undesirable effects?		
Judgment	**Research evidence**	**Additional considerations**
○ Large ○ Moderate ○ Small ⊘ Insignificant ○ Varies ○ Don't know	**Corticosteroids in patients with dengue shock** A systematic review of the specialized literature evaluated the efficacy and safety of corticosteroid use in adults and children diagnosed with dengue.[5] For the severe dengue component, the authors included studies of patients with dengue-related shock. The intervention of interest consisted of the administration of any type of corticosteroid orally or intravenously and, as a comparison, the use of a placebo or a non-corticosteroid. The primary outcome was mortality and the secondary outcomes for dengue shock were the need for transfusion, the presence of complications such as pulmonary hemorrhage or seizures, the duration of the shock, the length of the hospital stay, and the frequency of side effects. The review identified four clinical trials with 284 pediatric patients under age 15. The types of corticosteroids used were intravenous hydrocortisone (three studies) and methylprednisolone (one study). When comparing corticosteroid use versus placebo or no intervention, the authors found no difference in the risk of death (RR = 0.68; 95% CI: 0.42–1.11; four studies, 284 participants), the need for transfusion (RR = 1.08; 95% CI: 0.52–2.24; two studies, 89 patients), the frequency of pulmonary hemorrhage (RR = 0.97; 95% CI: 0.06–14.82; one study, 63 patients), the frequency of seizures (RR = 6.79; 95% CI: 0.36–126.24; one study, 63 patients), or the length of the hospital stay (MD = 1.1; 95% CI: −1.83–4.03; one study, 63 patients).[5] **Corticosteroids in patients with sepsis** A systematic review of the specialized literature evaluated the efficacy and safety of corticosteroid use in patients with sepsis.[6] The review authors included clinical trials conducted in adults and children diagnosed with sepsis, severe sepsis, or septic shock, according to definitions established by expert consensus. For interventions, the review included the use of any corticosteroid administered at any dosage. It established as high doses administration greater than 400 mg/day of hydrocortisone or its equivalent and defined as long-term administration an administration time equal to or greater than 3 days. Outcomes of interest were 90-day mortality, 28- and 30-day intensive care stay, 28- and 30-day mortality, long-term mortality, probability of shock reversal at 7 days, organ failure measured with the SOFA score at 7 days, hospital stay in intensive care, frequency of side effects, and quality of life.[6] The review included 42 clinical trials, of which 24 were conducted in patients with septic shock, 5 in patients with sepsis and community-acquired pneumonia, and 13 with acute respiratory distress syndrome and sepsis. Interventions included the use of hydrocortisone (28 studies), methylprednisolone (6 studies), prednisolone (3 studies), dexamethasone (3 studies), and the combination of hydrocortisone with fludrocortisone (2 studies). The authors concluded that corticosteroid use was associated with a higher likelihood of shock reversal (RR = 1.26; 95% CI: 1.12–1.42; 13 studies, 2,802 patients) and an improvement in SOFA organ failure scores (MD = −1.39; 95% CI: −1.88–−0.89; 9 studies, 1,986 patients), but they found no differences in short-term mortality (RR = 0.93; 95% CI: 0.84–1.03; 36 studies, 9,433 patients), long-term mortality (RR = 0.94; 95% CI: 0.89–1; 9 studies, 6,438 patients), intensive care stay (MD = −0.73; 95% CI: −1.78–0.31; 20 studies, 7,463 patients), or hospital stay (MD = −0.73; 95% CI: −2.06–0.6; 18 studies, 7,706 patients). Regarding side effects, the review found that corticosteroid use was associated with an increased risk of muscle weakness (RR = 1.21; 95% CI: 1.01–1.45; 7 studies, 6,178 patients), hypernatremia (RR = 1.64; 95% CI: 1.32–2.03; 6 studies, 5,015 patients), and hyperglycemia (RR = 1.16; 95% CI: 1.08–1.24; 15 studies, 7,563 patients), with no differences between comparisons for the risk of gastrointestinal bleeding, neuropsychiatric events, superinfection, myocardial infarction, or cerebrovascular event.[6] See the summary of findings table 8 (Annex 4).	The panel made no observations.

CERTAINTY OF THE EVIDENCE What is the overall certainty of the evidence regarding effects?		
Judgment	**Research evidence**	**Additional considerations**
⊘ VERY LOW ○ LOW ○ MODERATE ○ HIGH ○ No studies included	See the summary of findings table 8 (Annex 4).	The panel made no observations.

VALUES
Is there high uncertainty or variability regarding how much patients value key outcomes?

Judgment	Research evidence	Additional considerations
○ High uncertainty or variability. ○ There could be high uncertainty or variability. ⊘ There is probably no high uncertainty or variability. ○ There is no high variability or uncertainty.	No evidence was identified.	The panel made no observations.

BALANCE OF EFFECTS
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

Judgment	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ⊘ Don't know	Not applicable.	One panel member proposed the alternative of not favoring either option.

RESOURCE REQUIREMENTS
How high are the costs?

Judgment	Research evidence	Additional considerations
○ High costs ○ Moderate costs ⊘ Negligible costs and savings ○ Moderate savings ○ High savings ○ Varies ○ Don't know	Multiple systematic reviews reported that the economic impact of dengue is significant, both in Latin America (US$ 1.73 billion-US$ 3 billion per year) and on other continents (approximately US$ 9 billion worldwide).[7-10] The greatest impact corresponds to the costs associated with lost productivity.[7] Another publication concluded that the most important costs were those related to hospitalization.[11] The estimated overall cost per dengue case was US$ 70.1 for patients requiring hospitalization, US$ 51.16 for outpatients, and US$ 12.94 for cases outside the public health system.[10] A study that evaluated the economic impact of dengue in Vietnam reported that 47.2% of families had to borrow money to treat the disease and 72.9% said that the disease impacted the family economy.[12]	The panel made no observations.

EQUITY What would be the impact on health equity?		
Judgment	**Research evidence**	**Additional considerations**
○ Reduced ○ Probably reduced ○ Probably no impact ⊘ Probably increased ○ Increased ○ Varies ○ Don't know	Multiple studies conducted in Latin American and Caribbean countries suggest, as a whole, that people from lower socioeconomic strata are at a disadvantage. This group has less access to medical services, medicines, and education.[13-27] According to the analysis of information obtained from 2005-2010, it was reported that, in the different countries in the Region, health inequities were worse in Haiti, Guatemala, Bolivia (Plurinational State of), Venezuela (Bolivarian Republic of), and Honduras. In contrast, the five countries with the best health status were Cuba, Argentina, Uruguay, Chile, and Mexico.[24] For a large part of society, drug expenditures continue to be an important component of out-of-pocket expenses due to lack of adequate coverage by health services. The average per capita out-of-pocket expenditure on medicines in the Region was estimated to be US$ 97, ranging from US$ 7 in Bolivia (Plurinational State of) to more than US$ 160 in Argentina and Brazil.[28] The seroprevalence of dengue, chikungunya, and Zika was primarily associated with age and socioeconomic, environmental, and behavioral factors. People from the lowest social classes and those living in urban areas and in conditions that favor the development of the vector had the highest probability of positive seroprevalences.[29] A systematic review that included 12 studies found that in 9 of the studies, there was an association between at least one variable related to low socioeconomic status and dengue risk.[30] A study that analyzed exposure to violence by geographic area within the city of Cali, Colombia, reported that exposure to violence is associated with arbovirus infection.[31]	The panel made no observations.

ACCEPTABILITY Is the intervention acceptable to stakeholders?		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ⊘ Probably yes ○ Yes ○ Varies ○ Don't know	No evidence was identified.	In everyday practice, corticosteroids are not used as part of the management of severe dengue.

FEASIBILITY Is it feasible to implement the intervention?		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ⊘ Probably yes ○ Yes ○ Varies ○ Don't know	No evidence was identified.	In everyday practice, corticosteroids are not used as part of the management of severe dengue.

Summary of judgments

	JUDGMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Insignificant	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Insignificant**		Varies	Don't know
CERTAINTY OF THE EVIDENCE	**VERY LOW**	LOW	MODERATE	HIGH			No studies included
VALUES	High uncertainty or variability.	There may be high uncertainty or variability.	**There is probably no high uncertainty or variability.**	There is no high variability or uncertainty.			
BALANCE OF EFFECTS	Favors the comparison.	Probably favors the comparison.	Does not favor the intervention or the comparison.	Probably favors the intervention.	Favors the intervention.	Varies	**Don't know**
RESOURCE REQUIREMENTS	High costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Extensive savings	Vary	Don't know
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

STRONG recommendation against the intervention	**CONDITIONAL recommendation against the intervention**	CONDITIONAL recommendation in favor of the intervention or the comparison	CONDITIONAL recommendation in favor of the intervention	STRONG recommendation in favor of the intervention
○	◉	○	○	○

Conclusions

Recommendation

It is suggested to not administer systemic steroids to patients with dengue shock (CONDITIONAL recommendation based on VERY LOW certainty regarding the effects of the intervention).

Additional considerations: The panel decided not to issue a recommendation for patients with severe dengue without shock, severe acute chikungunya, or severe Zika, due to the absence of evidence.

Justification

The panel gave weight to the uncertainty of the effects of the intervention in the usual situation of non-routine use of this intervention.

Subgroup considerations

No subgroup considerations were proposed.

Implementation considerations

No implementation considerations were proposed.

Research priorities

Use of corticosteroids in patients with chronic and neurological joint manifestations from chikungunya.

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FRAMEWORK 8. IMMUNOGLOBULINS FOR PATIENTS WITH SEVERE ARBOVIRUS

Evaluation

PROBLEM **Is the problem a priority?**		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ⊘ Yes ○ Varies ○ Don't know	Dengue is a mosquito-borne disease that is widely disseminated around the world. According to WHO,[1] dengue incidence is considered to have increased in recent years, but since most cases are asymptomatic, there is underreporting of cases. Bhatt et al. published the global estimate of the burden of dengue in 2013. They found that, of the 96 million dengue infections with symptomatic manifestations, 13.3 million correspond to cases distributed in the Region of the Americas. In addition to the significant number of symptomatic cases, they found that nearly 20,000 deaths associated with this disease may occur in developing countries.[2] Regarding the burden of this disease, mortality associated with dengue has been observed in countries such as Brazil, where, although the frequency of overall mortality is 62 per 105,459 cases, 61 of these occurred in the 1,605 patients with severe dengue (3.8%).[3] Similar behavior was reported by Castrillón et al., who found that in Colombia in 2011, 203 deaths were associated with 30,694 dengue cases, including 1,303 cases of severe dengue.[4]	The panel made no observations.

DESIRABLE EFFECTS How significant are the anticipated desirable effects?		
Judgment	**Research evidence**	**Additional considerations**
◉ Insignificant ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Anti-D immunoglobulin in dengue patients** A review conducted by the guidelines development group evaluated the efficacy and safety of immunoglobulin use in patients with severe arbovirus. Studies in adults or children with dengue were included and the definitions used by the primary study authors to classify arbovirus severity were considered. As a result of the process, two studies that evaluated the use of anti-D immunoglobulin in children and adults with dengue, which included 108 participants, were identified and included.[5,6] One study compared as interventions the administration of anti-D plus platelets versus the administration of only platelets[6] and the other study evaluated the use of anti-D versus placebo, with no other specification.[5] Regarding the assessment of mortality (two studies), one study reported no fatal cases[6] and the other found no statistically significant difference in the risk of death (RR = 0.88, calculated with the reported data; 95% CI: 0.06–13.25).[5] Regarding changes in platelet count, one study found that in the transfusion of platelets plus anti-D group, there was a greater number of platelets at 24 hours (intervention: 28,666 ± 8,925; platelets alone: 17,866 ± 6,706; p = 0.001), 36 hours (intervention: 41,866 ± 10,315; platelets alone: 25,266 ± 9,601; p = 0.001), and 48 hours (intervention: 55,666 ± 12,697; platelets alone: 31,400 ± 11,343; p = 0.001), but that these differences were not maintained at the time of discharge.[6] The other study concluded that, in the pediatric population that participated in the study, 80% of patients who received anti-D improved with treatment, compared to 40% of the placebo group (significance values were not reported by the studies), while the reaction in the adult population was 71% for both groups. When compared by baseline platelet count: in the population with platelet counts below 50,000/mm^3, the reaction was 75% in the anti-D group and 58% in the placebo group (significance values not reported); and in patients with counts between 50,000/mm^3 and 100,000/mm^3, the frequency of reaction was 92% in the anti-D group and 90% in the placebo group (significance values not reported).[5] One study assessed hospital stay and found no differences between the groups (mean for: anti-D, 5.7 days; control, 5.8 days; p = 0.89).[6] Regarding side effects, one study measured hemoglobin values within 48 hours of drug administration and found no differences between the interventions (anti-D: 13.7 g/dl; control: not reported; p = 0.25),[6] while the other study reported hemoglobin values of 19.6 g/dl in the anti-D group and 17.2 g/dl in the placebo group (significance values not reported).[5] **Immunoglobulin G in dengue patients** One randomized clinical trial evaluated the efficacy and safety of high-dose immunoglobulin G in dengue patients. The study included 31 patients with dengue infection, the severity of which was defined according to the WHO 1997 classification.[7] The interventions used by the study were intravenous immunoglobulin G at daily doses of 0.4 g/kg for 4 days compared with usual care consisting of intravenous fluid administration. In the results, the study authors found no statistically significant differences between the treatments in platelet count (mean immunoglobulin: 54,900/mm^3; control: 48,000/mm^3; p = 0.15), the duration of severe thrombocytopenia (mean immunoglobulin: 3.1 days; control: 2.5 days; p = 0.11), or the frequency of side effects. See the summary of findings table 9 (Annex 4).	The panel made no observations.

UNDESIRABLE EFFECTS How significant are the anticipated undesirable effects?		
Judgment	**Research evidence**	**Additional considerations**
○ Large ○ Moderate ○ Small ⊘ Insignificant ○ Varies ○ Don't know	**Anti-D immunoglobulin in dengue patients** A review conducted by the guidelines development group evaluated the efficacy and safety of immunoglobulin use in patients with severe arbovirus. Two studies in adults or children with dengue were included and the definitions used by the primary study authors to classify arbovirus severity were considered. As a result of the process, two studies that evaluated the use of anti-D immunoglobulin in children and adults with dengue, which included 108 participants, were identified and included.[5,6] One study compared the administration of anti-D plus platelets versus the administration of only platelets[6] and the other study evaluated the use of anti-D versus placebo, with no other specification.[5] Regarding the assessment of mortality (two studies), one study reported no fatal cases[6] and the other found no statistically significant difference in the risk of death (RR = 0.88, calculated with the reported data; 95% CI: 0.06–13.25).[5] Regarding changes in platelet count, one study found that in the transfusion of platelets plus anti-D group, there was a greater number of platelets at 24 hours (intervention: 28,666 ± 8,925; platelets alone: 17,866 ± 6,706; p = 0.001), 36 hours (intervention: 41,866 ± 10,315; platelets alone: 25,266 ± 9,601; p = 0.001), and 48 hours (intervention: 55,666 ± 12,697; platelets alone: 31,400 ± 11,343; p = 0.001), but that these differences were not maintained at the time of discharge.[6] The other study concluded that, in the pediatric population that participated in the study, 80% of patients who received anti-D improved with treatment, compared to 40% of the placebo group (significance values were not reported by the studies), while the reaction in the adult population was 71% for both groups; when compared by baseline platelet count, in the population with platelet counts below 50,000, the reaction was 75% in the anti-D group and 58% in the placebo group (significance values not reported) and in patients with counts between 50,000/mm^3 and 100,000/mm^3, the frequency of reaction was 92% in the anti-D group and 90% in the placebo group (significance values not reported).[5] One study assessed hospital stay and found no differences between the groups (mean for: anti-D, 5.7 days; control, 5.8 days; p = 0.89).[6] Regarding side effects, one study measured hemoglobin values within 48 hours of drug administration, finding no difference between interventions (anti-D: 13.7 g/dl; control: not reported; p = 0.25),[6] while the other study reported hemoglobin values of 19.6 g/dl in the anti-D group and 17.2 g/dl in the placebo group (significance values not reported).[5] **Immunoglobulin G in dengue patients** One randomized clinical trial evaluated the efficacy and safety of high-dose immunoglobulin G in dengue patients. The study included 31 patients with dengue infection, the severity of which was defined according to the WHO 1997 classification.[7] The interventions used by the study were intravenous immunoglobulin G at daily doses of 0.4 g/kg for 4 days compared with usual care consisting of intravenous fluid administration. In the results, the study authors found no statistically significant differences between the treatments in the platelet count (mean immunoglobulin: 54,900/mm^3; control: 48,000/mm^3; p = 0.15), the duration of severe thrombocytopenia (mean immunoglobulin: 3.1 days; control: 2.5 days; p = 0.11), or the frequency of side effects. See the summary of findings table 9 (Annex 4).	The panel made no observations.

CERTAINTY OF THE EVIDENCE What is the overall certainty of the evidence regarding effects?		
Judgment	**Research evidence**	**Additional considerations**
⊘ VERY LOW ○ LOW ○ MODERATE ○ HIGH ○ No studies included	See the summary of findings table 9 (Annex 4).	The panel made no observations.

VALUES Is there high uncertainty or variability regarding how much patients value key outcomes?		
Judgment	**Research evidence**	**Additional considerations**
○ High uncertainty or variability. ○ There may be high uncertainty or variability. ⊘ There is probably no high uncertainty or variability. ○ There is no high variability or uncertainty.	No evidence was identified.	The panel made no observations.

BALANCE OF EFFECTS Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Judgment	**Research evidence**	**Additional considerations**
⊘ Favors the comparison ○ Probably favors the comparison ○ Does not favor the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Not applicable.	The panel made no observations.

RESOURCE REQUIREMENTS How high are the costs?		
Judgment	**Research evidence**	**Additional considerations**
⊘ High costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ High savings ○ Varies ○ Don't know	Multiple systematic reviews reported that the economic impact of dengue is significant, both in Latin America (US$ 1.73 billion-US$ 3 billion per year) and on other continents (approximately US$ 9 billion worldwide).[8-11] The greatest impact corresponds to the costs associated with lost productivity.[8] Another publication indicated that the most important costs were those related to hospitalization.[12] The estimated overall cost per dengue case was US$ 70.1 for patients requiring hospitalization, US$ 51.16 for outpatients, and US$ 12.94 for cases outside the public health system.[11] A study that evaluated the economic impact of dengue in Vietnam reported that 47.2% of families had to borrow money to treat the disease and 72.9% said that the disease impacted the family economy.[13] A study conducted in Brazil reported a significant cost associated with hospitalizations due to dengue (2.5% of the gross domestic product of the locality in which the observation was carried out) and that the use of blood products was associated with a significant increase in these costs.[14]	The panel made no observations.

EQUITY What would be the impact on health equity?		
Judgment	**Research evidence**	**Additional considerations**
☑ Reduced ☐ Probably reduced ☐ Probably no impact ☐ Probably increased ☐ Increased ☐ Varies ☐ Don't know	Multiple studies conducted in Latin American and Caribbean countries suggest, as a whole, that people from lower socioeconomic strata are at a disadvantage. This group has less access to medical services, medicines, and education.[15–29] According to the analysis of information obtained from 2005-2010, it was reported that, in the different countries in the Region, health inequities were worse in Haiti, Guatemala, Bolivia (Plurinational State of), Venezuela (Bolivarian Republic of), and Honduras. In contrast, the five countries with the best health status were Cuba, Argentina, Uruguay, Chile, and Mexico.[26] For a large part of society, drug expenditures continue to be an important component of out-of-pocket expenses due to lack of adequate coverage by health services. The average per capita out-of-pocket expenditure on medicines in the Region was estimated to be US$ 97, ranging from US$ 7 in Bolivia (Plurinational State of) to more than US$ 160 in Argentina and Brazil.[30] The seroprevalence of dengue, chikungunya, and Zika was primarily associated with age and socioeconomic, environmental, and behavioral factors. People from the lowest social classes and those living in urban areas and in conditions that favor the development of the vector had the highest probability of positive seroprevalences.[31] A systematic review that included 12 studies found that in 9 of the studies, there was an association between at least one variable related to low socioeconomic status and dengue risk.[32] A study that analyzed exposure to violence by geographic area within the city of Cali, Colombia, reported that exposure to violence was associated with arbovirus infection.[33]	The panel indicates that patients who have an Rh-negative blood type cannot receive anti-D.

ACCEPTABILITY Is the intervention acceptable to stakeholders?		
Judgment	**Research evidence**	**Additional considerations**
☐ No ☑ Probably no ☐ Probably yes ☐ Yes ☐ Varies ☐ Don't know	No evidence was identified.	The panel made no observations.

FEASIBILITY Is it feasible to implement the intervention?		
Judgment	**Research evidence**	**Additional considerations**
☐ No ☑ Probably no ☐ Probably yes ☐ Yes ☐ Varies ☐ Don't know	No evidence was identified.	Immunoglobulins are not available at all levels of care.

Summary of judgments

	JUDGMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Insignificant**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Insignificant**		Varies	Don't know
CERTAINTY OF THE EVIDENCE	**VERY LOW**	LOW	MODERATE	HIGH			No studies included
VALUES	High uncertainty or variability.	There may be high uncertainty or variability.	**There is probably no high uncertainty or variability.**	There is no high variability or uncertainty.			
BALANCE OF EFFECTS	**Favors the comparison.**	Probably favors the comparison.	Does not favor the intervention or the comparison.	Probably favors the intervention.	Favors the intervention.	Varies	Don't know
RESOURCE REQUIREMENTS	**High costs**	Moderate costs	Negligible costs and savings	Moderate savings	Extensive savings	Varies	Don't know
EQUITY	**Reduced**	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

Type of recommendation

STRONG recommendation against the intervention	**CONDITIONAL recommendation against the intervention**	CONDITIONAL recommendation in favor of the intervention or the comparison	CONDITIONAL recommendation in favor of the intervention	STRONG recommendation in favor of the intervention
○	◉	○	○	○

Conclusions

Recommendation

It is recommended to not administer immunoglobulins for the treatment of severe dengue (CONDITIONAL recommendation based on VERY LOW certainty regarding the effects of the intervention).

Additional considerations: the panel decided not to issue a recommendation for patients with severe acute chikungunya or severe Zika, due to lack of evidence.

Justification

The review of the available evidence demonstrates that there is no important clinical benefit that justifies the use of immunoglobulins in patients with severe dengue. In addition to its small benefit, the review also showed that this substance is not available at all levels of care and that its costs are high.

Regarding the recommendation to use immunoglobulins in patients with chikungunya or severe Zika, the panel decided to not issue any recommendation due to lack of evidence.

Subgroup considerations

No recommendations were generated for people with chikungunya or severe Zika, due to lack of evidence.

Implementation considerations

No implementation considerations were proposed.

Research priorities

No research priorities were proposed.

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FRAMEWORK 9. CONDOM USE FOR THE PREVENTION OF NON-VECTOR TRANSMISSION OF ZIKA VIRUS

Evaluation

PROBLEM **Is the problem a priority?**		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ⊘ Yes ○ Varies ○ Don't know	Zika virus infection has gained relevance in recent years thanks to the epidemic outbreaks that have occurred in the Region, in addition to the emergence of cases with obstetric complications such as the presence of microcephaly. Given this, WHO declared complications associated with Zika virus infection to be a public health emergency of international concern.[1] Along with the associated complications, another aspect of global interest has been the appearance of cases whose transmission mechanism was not vector based. To date, cases of vertical (mother-to-fetal) transmission during pregnancy or lactation and sexual transmission have been reported. Considering the potential complications associated with this infection, it is necessary to formulate recommendations on how to prevent non-vector transmission.	The panel made no observations.

DESIRABLE EFFECTS How significant are the anticipated desirable effects?		
Judgment	**Research evidence**	**Additional considerations**
○ Insignificant ○ Small ⊘ Moderate ○ Large ○ Varies ○ Don't know	**Sexual transmission** In a systematic review of the specialized literature,[2] the behavior of the sexual transmission of Zika virus was described by reviewing cases reported through May 2018. The authors included observational studies and in vitro and in vivo modeling studies that described the mechanism of sexual transmission of Zika virus and other flavivirus infections in humans. The authors considered: as primary outcomes, the incubation period, serial interval, and duration of infection; and as secondary outcomes, vulnerability, the number of reproduction events due to sexual transmission, the probability of transmission through sexual intercourse, and the rate of transmission. For results, the authors reported the frequency of sexual transmission in 52 of 5,627 cases in the United States of America (CDC) and in 20 of 1,737 cases in Europe. In addition to notifications from health agencies, the review included 24 reports with a total of 36 couples with primary sexual transmission of Zika virus; transmission from partners was from index cases returning from areas where Zika was endemic. The most frequent mechanisms of transmission were from man to woman and through penile-vaginal sex, although oral sex and anal sex were also reported as possible routes of transmission. It was confirmed in 14 of 36 cases of primary couples and in 18 of 36 secondary couples, by PCR in blood, urine, saliva, or semen.[2] In addition, another systematic review[2] assessed reported cases of sexually acquired Zika virus infection and the time to decline in virus levels in semen. The review compiled 18 studies that recorded human-to-human transmission; these studies collected a total of 27 episodes of probable or confirmed Zika virus infection. The most frequent mechanisms recorded were man to woman (25/27), man to man (1/27), and woman to man (1/27). Cases were confirmed either by serological tests or PCR; the authors did not report the confirmatory methods for the population that had sexual intercourse with the index cases. The range of days in which Zika virus was found through positive PCR tests was 3 to 188 days.[3] **Condom use for the prevention of sexually transmitted infections** A systematic review of the specialized literature[4] evaluated the efficacy of condom use for the prevention of sexual transmission of HIV in serodiscordant heterosexual couples. The review included longitudinal or cohort observational studies conducted in serodiscordant couples who reported condom use habits classified as "always" or "never," had at least two HIV serology measurements, and had measurements showing that the participant was HIV-negative at baseline and had seroconverted during the follow-up period. The outcomes assessed by the review were HIV incidence, measured through serology and the exposure-free period measured in people/year. For results, the review found 13 cohorts in which participants reported "always" using condoms (587 participants, 964.3 people/year of observation). Among the 587 participants in these studies, 11 cases of seroconversion were found, representing an incidence rate of 1.14 per 100 people/year. On the other hand, the review found 10 cohorts of participants who reported "never" using condoms (276 participants, 2,169 people/year of observation, 598.61 people/year of disease-free observation); in this population of 276 participants, 40 seroconversions were presented, representing an incidence rate of 6.68 per 100 people/year. Using these values, the review authors calculated an overall efficacy of condoms of 82.9% for reducing the risk of HIV infection. See the summary of findings table 10 (Annex 4).	The panel states that models of sexual transmission of Zika virus and HIV infections may be different. Given this, the degree of indirect evidence is important and makes it difficult to interpret the results. The HIV and Zika virus models may be different, making the evidence indirect and difficult to interpret.

UNDESIRABLE EFFECTS
How significant are the anticipated undesirable effects?

Judgment	Research evidence	Additional considerations
○ Large ○ Moderate ○ Small ⊘ Insignificant ○ Varies ○ Don't know	**Sexual transmission** In a systematic review of the specialized literature,[2] the behavior of the sexual transmission of Zika virus was described by reviewing cases reported through May 2018. The authors included observational studies and in vitro and in vivo modeling studies that described the mechanism of sexual transmission of Zika virus and other flavivirus infections in humans. The authors considered: as primary outcomes, the incubation period, serial interval, and duration of infection; and as secondary outcomes, vulnerability, the number of reproduction events due to sexual transmission, the probability of transmission by sexual intercourse, and the rate of transmission. For results, the authors reported the frequency of sexual transmission in 52 of 5,627 cases in the United States of America (CDC) and in 20 of 1,737 cases in Europe. In addition to notifications from health agencies, the review included 24 notifications with a total of 36 couples with primary sexual transmission of Zika virus; transmission from partners was from index cases returning from areas where Zika was endemic. The most frequent mechanisms of transmission were from man to woman and through penile-vaginal sex, although oral sex and anal sex were also reported as possible routes of transmission. It was confirmed in 14 of 36 cases of primary couples and in 18 of 36 secondary couples, by PCR in blood, urine, saliva, or semen.[2] In addition, another systematic review[2] assessed reported cases of sexually acquired Zika virus infection and the time to decline in virus levels in semen. The review compiled 18 studies that recorded human-to-human transmission; these studies collected a total of 27 episodes of probable or confirmed Zika virus infection. The most frequent mechanisms recorded were man to woman (25/27), man to man (1/27), and woman to man (1/27). Cases were confirmed either by serological tests or PCR; the authors did not report the confirmatory methods for the population that had sexual intercourse with the index cases. The range of days in which Zika virus was found through positive PCR tests was 3 to 188 days.[3] **Condom use for the prevention of sexually transmitted infections** A systematic review of the specialized literature[4] evaluated the efficacy of condom use for the prevention of sexual transmission of HIV in serodiscordant heterosexual couples. The review included longitudinal or cohort observational studies conducted in serodiscordant couples who reported condom use habits classified as "always" or "never," had at least two HIV serology measurements, and had measurements showing that the participant was HIV-negative at baseline and had seroconverted during the follow-up period. The outcomes assessed by the review were HIV incidence measured by serology and the exposure-free period measured in people/year. For results, the review found 13 cohorts in which participants reported "always" using condoms (587 participants, 964.3 people/year of observation). Among the 587 participants in these studies, 11 cases of seroconversion were found, representing an incidence rate of 1.14 per 100 people/year. On the other hand, the review found 10 cohorts of participants who reported "never" using condoms (276 participants, 2,169 people/year of observation, 598.61 people/year of disease-free observation); in this population of 276 participants, 40 seroconversions were presented, representing an incidence rate of 6.68 per 100 people/year. Using these values, the review authors calculated an overall efficacy of condoms of 82.9% for reducing the risk of HIV infection. See the summary of findings table 10 (Annex 4).	The panel made no observations.

CERTAINTY OF THE EVIDENCE
What is the overall certainty of the evidence regarding effects?

Judgment	Research evidence	Additional considerations
⊘ VERY LOW ○ LOW ○ MODERATE ○ HIGH ○ No studies included	No direct evidence was found on this topic.	The panel made no observations.

VALUES
Is there high uncertainty or variability regarding how much patients value key outcomes?

Judgment	Research evidence	Additional considerations
○ High uncertainty or variability. ○ There may be high uncertainty or variability. ⊘ •There is probably no high uncertainty or variability. ○ There is no high variability or uncertainty.	No direct evidence was found on this topic.	The panel made no observations.

BALANCE OF EFFECTS
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

Judgment	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor the intervention or the comparison ⊘ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Not applicable.	Results of the panel vote: 7 to 5 in favor of the intervention.

RESOURCE REQUIREMENTS
How high are the costs?

Judgment	Research evidence	Additional considerations
○ High costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ High savings ○ Varies ⊘ Don't know	No direct evidence was found on this topic.	The panel made no observations.

EQUITY
What would be the impact on health equity?

Judgment	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ⊘ Don't know	No direct evidence was found on this topic.	The panel made no observations.

ACCEPTABILITY
Is the intervention acceptable to stakeholders?

Judgment	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ⊘ Yes ○ Varies ○ Don't know	No direct evidence was found on this topic.	Condom use is a practice used and implemented to prevent other sexually transmitted infections.

FEASIBILITY Is it feasible to implement the intervention?		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ⊘ Probably yes ○ Yes ○ Varies ○ Don't know	No direct evidence was found on this topic.	Condom use is a practice used and implemented to prevent other sexually transmitted infections.

Summary of judgments

	JUDGMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Insignificant	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Insignificant**		Varies	Don't know
CERTAINTY OF THE EVIDENCE	**VERY LOW**	LOW	MODERATE	HIGH			No studies included
VALUES	High uncertainty or variability.	There may be high uncertainty or variability.	**There is probably no high uncertainty or variability.**	There is no high variability or uncertainty.			
BALANCE OF EFFECTS	Favors the comparison.	Probably favors the comparison.	Does not favor the intervention or the comparison.	**Probably favors the intervention.**	Favors the intervention.	Varies	Don't know
RESOURCE REQUIREMENTS	High costs	Moderate costs	Negligible costs and savings	Moderate savings	Extensive savings	Varies	**Don't know**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

STRONG recommendation against the intervention	CONDITIONAL recommendation against the intervention	CONDITIONAL recommendation in favor of the intervention or the comparison	CONDITIONAL recommendation in favor of the intervention	**STRONG recommendation in favor of the intervention**
○	○	○	○	◉

Conclusions

Recommendation

Condom use is recommended for the prevention of sexual transmission of Zika virus infection.

Justification

Evidence was identified that supports the risk of sexual transmission of Zika virus. Although the evidence on condom use does not correspond to Zika virus, and although it was considered that there is a high degree of indirect evidence, it is considered that the efficacy of condoms may not be inferior. In addition to this, condom use is a practice that is implemented and available in the Region.

Given that the panel considers that condom use represents more desirable than undesirable effects, the decision was made to recommend condoms to prevent the sexual transmission of Zika virus.

Subgroup considerations

Not applicable.

Implementation considerations

No implementation considerations were proposed.

Research priorities

No research priorities were proposed.

Sources

1. World Health Organization. WHO Director-General summarizes the outcome of the Emergency Committee regarding clusters of microcephaly and Guillain-Barré syndrome. Geneva: WHO; 2016. Available from: https://www.who.int/news/item/01-02-2016-who-director-general-summarizes-the-outcome-of-the-emergency-committee-regarding-clusters-of-microcephaly-and-guillain-barr%C3%A9-syndrome.
2. Counotte MJ, Kim CR, Wang J, Bernstein K, Deal CD, Broutet NJN, Low N. Sexual transmission of Zika virus and other flaviviruses: A living systematic review. PLoS Medicine 2018;15(7):e1002611. Available from: https://doi.org/10.1371/journal.pmed.1002611.
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4. Weller SC, Davis- Beaty K. Condom effectiveness in reducing heterosexual HIV transmission. Cochrane Database of Systematic Reviews 2002;1:CD003255. Available from: https://doi.org/10.1002/14651858.CD003255.

FRAMEWORK 10. SUPPRESSION OF BREASTFEEDING IN WOMEN WITH SUSPECTED OR CONFIRMED DIAGNOSIS OF ZIKA VIRUS INFECTION

Evaluation

PROBLEM
Is the problem a priority?

Judgment	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ⊘ Yes ○ Varies ○ Don't know	Breastfeeding is one of the main strategies formulated to reduce infant mortality in the world,[1] especially in newborns. To date, the possibility of disease transmission through breastfeeding has been proposed. Therefore, it is necessary to determine the breastfeeding-related recommendations that should be proposed in order to prevent non-vector transmission of Zika virus infection.	The panel made no observations.

DESIRABLE EFFECTS
How significant are the anticipated desirable effects?

Judgment	Research evidence	Additional considerations
○ Insignificant ⊘ Small ○ Moderate ○ Large ○ Varies ○ Don't know	A systematic review of the specialized literature assessed the risk of nonvector transmission of Zika virus associated with breastfeeding.[2] As a result, the review found two case reports corresponding to a total of 3 mother-child pairs. The first mother: began breastfeeding on day 1 postpartum; on day 2 postpartum, the Zika virus infection was confirmed by PCR in saliva and serum; and on day 3, infection in the newborn was confirmed by PCR in serum and saliva. The second mother: obtained confirmation of infection through PCR in serum on days 1 and 5 postpartum; and began breastfeeding on day 3 postpartum. The newborn's PCR test in serum on days 0 and 3 was negative, but turned positive on the evaluations on days 4 and 7. The third mother began breastfeeding on the day of delivery and developed a fever and rash on subsequent days. On day 3, the infection was confirmed through PCR in serum. The newborn data were reported as ambiguous. See the summary of findings table 11 (Annex 4).	For this question, the following were considered as outcomes of interest: – Disease transmission. – The presence of congenital malformations. – The risk of abortion. – Intrauterine fetal death. The evidence presents the results of three mother-child cases. No evidence on long-term outcomes was found. The panel considers that there is no certainty regarding the potential harm of Zika virus infection in childhood, given that the available evidence only confirmed the presence of the infection.

UNDESIRABLE EFFECTS
How significant are the anticipated undesirable effects?

Judgment	Research evidence	Additional considerations
⊘ Large ○ Moderate ○ Small ○ Insignificant ○ Varies ○ Don't know	A systematic review of the specialized literature assessed the risk of non-vector transmission of Zika virus associated with breastfeeding.[2] As a result, the review found two case reports corresponding to a total of 3 mother-child pairs. The first mother: began breastfeeding on day 1 postpartum; on day 2 postpartum, Zika virus infection was confirmed by PCR in saliva and serum; and on day 3, infection in the newborn was confirmed by PCR in serum and saliva. The second mother obtained confirmation of infection through PCR in serum on days 1 and 5 postpartum and began breastfeeding on day 3 postpartum. The newborn's PCR test in serum on days 0 and 3 was negative, but turned positive in the evaluations on days 4 and 7. The third mother began breastfeeding on the day of delivery and developed fever and rash on subsequent days. On day 3, infection was confirmed through PCR in serum. The newborn data were reported as ambiguous. Based on these results, the WHO guidelines on infant feeding in areas with Zika virus transmission contain a recommendation in favor of breastfeeding in mothers with suspected, probable, or confirmed Zika virus infection.[4] See the summary of findings table 11 (Annex 4).	The panel considered the following elements: – One of the models that contains specific recommendations on breastfeeding is for the prevention of HIV infection. In that specific case, there are countries where breastfeeding is recommended for the first 6 months. – Based on the review presented, WHO published guidance on breastfeeding in the context of Zika virus infection in 2016.[3] As a result, the guidance recommends initiating breastfeeding within the first hour of delivery, maintaining exclusive breastfeeding for the first 6 months, and initiating the transition to complementary feeding while continuing breastfeeding until age 2 or older. The reasons for supporting the recommendation are based on the benefits of breastfeeding in children in low-, middle-, and high-income countries, and the lack of information on the long-term consequences of infection. – The panel considered that, in Latin America, breastfeeding is essential to the adequate nutrition of children.

CERTAINTY OF THE EVIDENCE
What is the overall certainty of the evidence regarding effects?

Judgment	Research evidence	Additional considerations
☑ VERY LOW ○ LOW ○ MODERATE ○ HIGH ○ No studies included	Disease transmission: VERY LOW Presence of congenital malformations: no evidence was found. Risk of abortion: not applicable. Intrauterine fetal death: not applicable.	The panel made no observations.

VALUES
Is there high uncertainty or variability regarding how much patients value key outcomes?

Judgment	Research evidence	Additional considerations
○ High uncertainty or variability. ○ There may be high uncertainty or variability. ○ There is probably no high uncertainty or variability. ☑ There is no high variability or uncertainty.	No direct evidence was found on this topic.	The panel made no observations.

BALANCE OF EFFECTS
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

Judgment	Research evidence	Additional considerations
☑ Favors the comparison ○ Probably favors the comparison ○ Does not favor the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Not applicable.	The panel made no observations.

RESOURCE REQUIREMENTS
How high are the costs?

Judgment	Research evidence	Additional considerations
☑ High costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ High savings ○ Varies ○ Don't know	No direct evidence was found on this topic.	The panel made no observations.

EQUITY
What would be the impact on health equity?

Judgment	Research evidence	Additional considerations
○ Reduced ☑ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Breastfeeding contributes to the Sustainable Development Goals related to maternal and child health, nutrition, education, poverty reduction, and economic growth.[3]	The panel made no observations.

ACCEPTABILITY Is the intervention acceptable to stakeholders?		
Judgment	**Research evidence**	**Additional considerations**
◉ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No additional evidence was considered.	The panel made no observations.

FEASIBILITY Is it feasible to implement the intervention?		
Judgment	**Research evidence**	**Additional considerations**
◉ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No additional evidence was considered.	The panel made no observations.

Summary of judgments

	JUDGMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Insignificant	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	**Large**	Moderate	Small	Insignificant		Varies	Don't know
CERTAINTY OF THE EVIDENCE	**VERY LOW**	LOW	MODERATE	HIGH			No studies included
VALUES	High uncertainty or variability.	There may be high uncertainty or variability.	There is probably no high uncertainty or variability.	**There is no high variability or uncertainty.**			
BALANCE OF EFFECTS	**Favors the comparison.**	Probably favors the comparison.	Does not favor the intervention or the comparison.	Probably favors the intervention.	Favors the intervention.	Varies	Don't know
RESOURCE REQUIREMENTS	**High costs**	Moderate costs	Negligible costs and savings	Moderate savings	Extensive savings	Varies	Don't know
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	**No**	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	**No**	Probably no	Probably yes	Yes		Varies	Don't know

Type of recommendation

STRONG recommendation against the intervention	CONDITIONAL recommendation against the intervention	CONDITIONAL recommendation in favor of the intervention or the comparison	CONDITIONAL recommendation in favor of the intervention	STRONG recommendation in favor of the intervention
◉	○	○	○	○

Conclusions

Recommendation

It is recommended to maintain breastfeeding in women with suspected or confirmed diagnosis of Zika virus infection.

Justification

The panel gave more weight to the known benefits of breastfeeding than to the uncertainty of the potential harm to the child's health.

Subgroup considerations

No subgroup considerations were proposed.

Implementation considerations

No implementation considerations were proposed.

Research priorities

No research priorities were proposed.

Sources

1. World Health Organization. Newborns: Improving survival and well-being. Geneva: WHO; 2020. Available from: https://www.who.int/news-room/fact-sheets/detail/newborns-reducing-mortality.
2. Colt S, Garcia-Casal MN, Peña-Rosas JP, Finkelstein JL, Rayco-Solon P, Weise Prinzo ZC, et al. Transmission of Zika virus through breast milk and other breastfeeding-related bodily-fluids: A systematic review. PLoS Neglected Tropical Diseases 2017;11(4):e0005528. Available from: https://doi.org/10.1371/journal.pntd.0005528.
3. World Health Organization. Breastfeeding in the context of Zika virus: Interim guidance. Geneva: WHO; 2016. Available from: https://www.who.int/publications/i/item/WHO-ZIKV-MOC-16.5.
4. World Health Organization. WHO Director-General summarizes the outcome of the Emergency Committee regarding clusters of microcephaly and Guillain-Barré syndrome. Geneva: WHO; 2016. Available from: https://www.who.int/news/item/01-02-2016-who-director-general-summarizes-the-outcome-of-the-emergency-committee-regarding-clusters-of-microcephaly-and-guillain-barr%C3%A9-syndrome.

Evidence-based guidelines are one of the most useful tools for improving public health and clinical practice. Their purpose is to formulate interventions based on strong evidence of efficacy, avoid unnecessary risks, use resources efficiently, reduce clinical variability, and, in essence, improve health and ensure quality care, which is the purpose of health systems and services.

These guidelines were developed following the GRADE methodology, with the support of a panel of clinical experts from different countries, all convened by the Pan American Health Organization. By responding to 12 key questions about the clinical diagnosis and treatment of dengue, chikungunya, and Zika, evidence-based recommendations were formulated for pediatric, youth, adult, older adult, and pregnant patients who are exposed to these diseases or have a suspected or confirmed diagnosis of infection. The purpose of the guidelines is to prevent progression to severe forms of these diseases and the fatal events they may cause.

The recommendations are intended for health professionals, including general, resident, and specialist physicians, nursing professionals, and medical and nursing students, who participate in caring for patients with suspected dengue, chikungunya, or Zika. They are also intended for health unit managers and the executive teams of national arboviral disease prevention and control programs, who are responsible for facilitating the process of implementing these guidelines.

We hope that this publication will benefit not only health personnel, who will have up-to-date scientific information of the best possible quality, but also children and youth, adults, pregnant women, older adults, and the general population, who will receive better health care provided by properly trained medical personnel.

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