Clinical Practice Guideline

on the Diagnosis, Management and Prevention of Dengue for Adult and Pediatric Filipinos in the Primary Care Setting

May 2023

Disclaimer and Contact Information

This clinical practice guideline (CPG) is intended to be used by specialists and general practitioners who are primary care providers. Although adherence to this guideline is encouraged by the Department of Health (DOH), it should not restrict the clinicians in using their clinical judgment and considering patient's values, needs, and preferences while handling individual cases. Clinicians and relevant stakeholders must always exercise sound clinical decision-making as the individual patient's history, current physical status, and their responses to treatment may vary.

Payors and policymakers, including hospital administrators and employers, can also utilize this CPG, but nonconformance to this document should not be the sole basis for granting or denying financial assistance or insurance claims. Recommendations from this CPG should not be treated as strict rules to base legal action.

Several limitations of this CPG have been identified by the developers and users are therefore informed of these. Evidence summaries are based on the best available scientific evidence at the time of its formulation. As such, certain aspects of the interventions or diagnostic tests may not be completely addressed by the included studies. In fact, one of the questions identified (Question 3 on the frequency and timing of CBC determination) was addressed by formulating good practice statements because of the absence of direct evidence to support any recommendation statement.

This CPG is not intended to cover the entirety of the management of dengue. It provides recommendations on interventions where variability in clinical practice and some controversies in decision-making exist.

Contact Us

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Acknowledgments

The Dengue CPG Task Force would like to thank all the professionals who collaborated and shared their knowledge in one way or another during the entire guideline development process.

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Philippine College of Physicians (PCP)

List of Abbreviations

AGREE-II	Appraisal of Guidelines, Research and Evaluation
CBC	Complete blood count
CCT	Controlled clinical trials
CI	Confidence interval
COI	Conflict of interest
CP	Consensus panel
CPG	Clinical practice guideline
CPLE	*Carica papaya* leaf extract
DALY	Disability adjusted life years
DEET	N, N-Diethyl-meta-toluamide
DENV	Dengue virus
DF	Dengue fever
DHF	Dengue hemorrhagic fever
DOH	Department of Health
DPRI	Drug Price Reference Index
DSS	Dengue shock syndrome
ELISA	Enzyme-linked immunosorbent assay
ERE	Evidence review expert
FDA	Food and Drug Administration
GRADE	Grades of Recommendation, Assessment, Development and Evaluation
GI	Gastrointestinal
H2RA	Histamine 2 receptor antagonist
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IR3535	Ethyl butylacetylaminoproprionate
JEV	Japanese encephalitis virus
MAP	Mean arterial pressure
MD	Mean difference
NS1	Non-Structural protein 1
NPG	National Practice Guidelines

OIS	Oral isotonic solution
OR	Odds ratio
ORS	Oral rehydration solution
ORT	Oral rehydration therapy
PAHO	Pan American Health Organization
PCR	Polymerase Chain Reaction
PhilHealth	Philippine Health Insurance Corporation
PHP	Philippine peso
PNF	Philippine National Formulary
POCT	Point-of-care test
PPI	Proton pump inhibitor
PPV	Positive predictive value
PT	Prothrombin time
PTT	Partial thromboplastin time
RCT	Randomized control trial
RDT	Rapid diagnostic test
RITM	Research Institute for Tropical Medicine
RR	Risk ratio
RT-PCR	Reverse transcriptase-polymerase chain reaction
SC	Steering committee
Sn	Sensitivity
Sp	Specificity
WBC	White blood cell
WHO	World Health Organization
ZIKV	Zika virus

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Executive Summary

Dengue is an endemic, fast-spreading mosquito-borne viral disease in the Philippines, that is now being reported throughout the year – affecting more than 200,000 individuals this year which is almost 200% higher than previous years. Though it has been a common disease managed in the country, considerable variations in practices in diagnosis and management have been observed among clinicians and institutions.

This Clinical Practice Guideline (CPG) on dengue aims to give recommendations on the aspects of dengue diagnosis, management, and prevention in the primary care setting, where significant variability and controversy in clinical practice is noted. However, it does not aim to cover all aspects of the management of dengue infection. It is intended to be used by general physicians and specialists, other healthcare professionals, policymakers to improve dengue diagnosis and management. Its target beneficiaries are the patients with probable, suspected, and confirmed dengue infections, and indirectly the whole of society in the Philippines.

This guideline is based on the current best available evidence, local resources, infrastructure, and the practice context in the country. Guideline recommendations were developed following a standard guideline development methodology outlined in the DOH CPG Manual 2018. The CPG development was organized, directed and spearheaded by the Steering Committee, while current best available evidence were comprehensively searched and reviewed by the Technical Working Group to address nine key questions. Nine experts, comprised of multi-sectoral panel of representatives, crafted consensus recommendations. All of the members of the Dengue CPG Task Force were evaluated for any COI and any such COI identified were managed accordingly. The GRADE method was used to determine the direction and strength of each recommendation.

Fifteen recommendations were developed out of 8 clinical questions and their corresponding evidence summaries. Of these, a majority were strong recommendations and were based on very low certainty of evidence. Further research will very likely have an important impact in our confidence regarding the estimates of the effect of each intervention or accuracy of the diagnostic tests included in this CPG.

Summary of Recommendations

Table 1.0.1. Summary of Recommendations

No.	Recommendations	Certainty of Evidence	Strength of Recommendation
1A	Among those with suspected dengue infections, we recommend the use of dengue NS1 rapid diagnostic tests.	Low ⊕⊕◯◯	Strong
	Dengue NS1 RDT is most useful in the following situations: • individuals presenting within 3 days of symptom onset	Low ⊕⊕◯◯	Weak
	• patients with no previous history of dengue infection	Low ⊕⊕◯◯	Weak
1B1	Among patients with suspected dengue infection, we recommend the use of combined Dengue NS1/IgM/IgG rapid diagnostic test.	Low ⊕⊕◯◯	Strong
1B2	Among patients with suspected dengue infection who present more than 5 days from onset of symptoms, we recommend the use of rapid diagnostic test with Dengue IgM/IgG antibodies.	Low ⊕⊕◯◯	Strong
2A	Among adult and pediatric patients with dengue fever, we recommend using any one of the following clinical signs as a basis for in-hospital management: 1. Signs and symptoms a. Vomiting/persistent vomiting b. Abdominal pain/tenderness c. Lethargy/restlessness d. Mucosal bleeding e. Impaired consciousness f. Hepatomegaly g. Acute renal failure 2. Comorbidities a. Pregnancy b. Obesity c. Others (cardiac, renal, hematologic, pulmonary)	Very low ⊕◯◯◯	Strong
2B	Among adult and pediatric patients with dengue fever, we suggest using any one of the following laboratory parameters as a basis for in-hospital management:	Very low ⊕◯◯◯	Weak

	a. Increase in hematocrit with or without decrease in platelet count b. Elevation of transaminases c. Impaired PT or PTT d. Thrombocytopenia		
3	For outpatients with suspected, probable, or confirmed dengue: 1. An initial CBC should be requested on the first visit to establish baseline hematocrit and platelet count. 2. Daily CBC determination may be done as part of disease monitoring. 3. Subsequent CBCs may be done based on the clinical course/presentation (e.g., volume status, urine output, temperature, ability to tolerate feeding, presence of warning signs). 4. CBC monitoring may be discontinued when the patient is in the recovery phase (e.g. increasing platelet count trend, 48 hours afebrile, adequate urine output, and improved sense of well-being/appetite).	Very low ⊕◯◯◯	Not applicable (Good Practice Statement)
4	Among patients with probable or confirmed dengue fever, we recommend the use of oral rehydration solutions to prevent poor outcomes.	Very low ⊕◯◯◯	Strong
5	Among patients with confirmed or probable dengue fever, we recommend against the use of acid suppressants for the prevention of gastrointestinal bleeding or abdominal pain.	Very low ⊕◯◯◯	Strong
6	Among patients with dengue fever, we recommend against the use of acid suppressants for the treatment of gastrointestinal bleeding or pain.	Very low ⊕◯◯◯	Strong
7A	Among patients with confirmed dengue infection, we suggest giving papaya (*Carica papaya*) leaf extract or juice preparations as a supplement to standard therapy.	Very low ⊕◯◯◯	Weak
7B	Among patients with confirmed dengue infection, we suggest against giving tawa-tawa (*Euphorbia hirta*) preparations as a	Very low ⊕◯◯◯	Weak

	supplement to standard therapy due to insufficient evidence.		
7C	Among patients with confirmed dengue infection, we recommend against giving guava (*Psidium guajava*) preparations as a supplement to standard therapy due to insufficient evidence (lack of clinical trials in humans).	None	Strong
8A	Among individuals at risk for dengue infection, we suggest against the use of plant-based non-DEET extracts over DEET repellents for the prevention of dengue.	Low ⊕⊕◯◯	Weak
8B	Among individuals at risk for dengue infection, we suggest against the use of IR3535 over DEET repellents for the prevention of dengue.	Very low ⊕◯◯◯	Weak
8C	Among individuals at risk for dengue infection, we suggest against the use of Citronella over DEET repellents for the prevention of dengue.	Very low ⊕◯◯◯	Weak

Introduction

Background

Dengue is a mosquito-borne infection that causes symptoms ranging from asymptomatic to mild febrile illness to critical cases of multi-organ failure. In these cases of severe infection, patients exhibit blood plasma leakage, hence, the term dengue hemorrhagic fever (DHF).[1]

Hyperendemic in tropical and subtropical climates, dengue infection remains to be an important vector-borne disease in the Philippines. Over 270,000 cases of dengue were reported in 2019, prompting the declaration of a national dengue epidemic[2]. By mid-October of 2022, the DOH had reported 181,971 cases, a 91% increase over the same time period the previous year.[2] This has a case fatality rate of 0.3%. Dengue has been reported throughout the year in the Philippines and is expected to be the most important, most rapidly spreading mosquito-borne viral disease in the Philippines and throughout the world, making it a major public health concern.

Objectives

The objectives of this CPG are:

1. To provide evidence-based recommendations on the primary care management of dengue in Filipino adult and children on the following aspects:
    - diagnosis
    - management
    - prevention
2. To reduce practice variability among healthcare practitioners and improve clinical outcomes among dengue infected patients

Scope and Purpose

This CPG addresses specific questions on the diagnosis, management, and prevention of dengue in adults and children that have been identified as priority topics based on their relevance, inconsistencies, and controversies in the available evidence, leading to variable practices among clinicians. Specifically, it provides recommendations on essential diagnostic tests, clinical and laboratory parameters to identify patients at high risk for complications, the role of oral hydration, acid suppressants and herbal medicines for treatment, and the use of non-DEET based mosquito repellents in preventing dengue, in which a lot of variations in practice have been recognized. Given the limited resources in the Philippines, this guideline aims to recommend the most cost-effective strategies.

Target Population

This guideline is intended for the diagnosis, management, and prevention of suspected, probable, and confirmed dengue infection in both the adult and pediatric populations in the primary care setting in the Philippines. Most recommendations such as those on diagnostics and repellants are applicable for all subgroups of the population. The presence of co-morbidities were considered especially in Question 2 on the risk factors that may warrant in-hospital management of dengue.

Intended Users

This document is intended to guide healthcare providers and relevant stakeholders in primary and secondary/tertiary care in the management of dengue in adults and children including:

- Physicians, both primary care physicians and specialists, both adult or pediatric
- Nurses and other allied health professionals
- Medical and paramedical educators, trainees, and medical students
- Professional societies
- Department of Health, including the Philippine Health Insurance Corporation

Key Clinical Issues and Questions

The clinical issues tackled by this CPG include:

Question 1A. Should dengue NS1 rapid diagnostic tests be used to diagnose acute dengue infection in suspected patients?

Population	**Patients with suspected dengue infection**
Intervention/ Treatment	Dengue NS1 Rapid Diagnostic Tests (RDTs)
Comparison	Dengue RT-PCR or RT-PCR with Enzyme-linked immunosorbent assay (ELISA) IgM/IgG for dengue
Outcomes	Diagnostic accuracy (sensitivity, specificity, likelihood ratios) Harms and Benefits Cost / cost-effectiveness
Brief Rationale/ Context	This is to help decide which is the best test to request at the right time of disease presentation. Several RDTs are available, whether as single dengue NS1 tests or as combination, in different healthcare or diagnostic facilities locally. In addition, some self-administered dengue tests are even available online without any FDA approval yet. Recommendations can be made for or against the use of these dengue RDTs after careful review and assessment of the evidence.

Question 1B. Should dengue NS1/IgM/IgG and dengue IgM/IgG rapid diagnostic test (RDT) kits be used to diagnose dengue infection in suspected patients?

Population	**Patients with suspected dengue infection**
Intervention/ Treatment	Dengue NS1/IgM/IgG RDT kit Dengue IgM/IgG RDT
Comparison	Dengue RT-PCR ELISA IgM/IgG for dengue
Outcomes	Diagnostic accuracy (sensitivity, specificity) Cost / cost-effectiveness
Brief Rationale/ Context	This is to help decide which is the best test to request at the right time of disease presentation. Several RDTs are available, whether as single dengue NS1 tests or as combination, in different healthcare or diagnostic facilities locally. In addition, some self-administered dengue tests are even available online without any FDA approval yet. Recommendations can be made for or against the use of these dengue RDTs after careful review and assessment of the evidence.

Question 2. What clinical findings and laboratory parameters should be used to identify patients that require in-hospital management?

Population	**Patients with probable or confirmed dengue infection**
Intervention/ Treatment	Prognostic factors (whether clinical findings or laboratory parameters): • Headache, myalgia and/or arthralgia, rash, abdominal pain, bleeding, vomiting, anorexia • Narrow pulse pressure, prolonged capillary refill time, hypotension, neurologic changes (decreased sensorium, irritability, agitation, etc.), dyspnea • Pregnancy, malnutrition, obesity • Transaminitis, thrombocytopenia, leukopenia, hemoconcentration
Comparison	n/a
Outcomes	Development of severe dengue Respiratory distress Hospitalization Morbidity (Bleeding, Plasma leakage, hypotension or shock, clinical fluid accumulation) Mortality
Subgroups (If any)	Adult and pediatric populations

Brief Rationale/ Context	Warning signs listed in previous guidelines have been used as bases for hospital admission. This question would like to identify which symptoms, co-morbid conditions, physical findings or laboratory parameters (listed or not in the warning signs) are significantly and consistently associate with poor clinical outcomes and thus require in-hospital admission.

Question 3. Should regular CBC determination be done to monitor disease progression and improve outcomes among dengue patients in the primary care setting?

Population	**Patients with probable or confirmed dengue infection**
Intervention/ Treatment	CBC determination
Comparison	n/a
Outcomes	Progression to Severe dengue (shock/hypotension, plasma leakage, hemorrhage, severe organ impairment) Hospital admission Bleeding (gastrointestinal, etc.) Mortality Safety (local inflammation, site bleeding, pain, site infection, etc.) Cost/ cost-effectiveness
Brief Rationale/ Context	Variations exists on when and how frequent CBC determination should be done to monitor hemoconcentration, thrombocytopenia and assess need for in-hospital admission. Review of literature and evidence might provide guidance on the best timing for CBC determination for identification of and monitoring of dengue complications.

Question 4. Should ORS be given to patients with mild dengue or dengue without warning signs to prevent disease progression?

Population	**Patients with probable or confirmed mild dengue infection or dengue without warning signs**
Intervention/ Treatment	Oral rehydration solution (ORS)
Comparison	ORS vs IV hydration Oral isotonic solution vs water
Outcomes	Progression to severe disease (dengue shock syndrome, severe dengue) Dehydration

	Hospitalization Mortality Cost/ cost-effectiveness Adverse events (vomiting, congestion, electrolyte imbalance, etc.)
Subgroups (If any)	Adult and pediatric populations
Brief Rationale/ Context	Provision of hydration is a cornerstone in the management of dengue infection. The effectiveness of oral hydration among patients with mild dengue and the best form of oral rehydration, if any, were reviewed to ensure that these simple intervention are still appropriate for the outpatient management of dengue. If evidence to support oral rehydration is present, then the practice of IV hydration for mild dengue, which is done currently by some facilities or physicians, can be discouraged in the primary care setting.

Question 5. Should acid suppressants be used among probable or confirmed dengue patients to prevent abdominal pain or gastrointestinal (GI) bleeding?

Population	**Patients with probable or confirmed dengue infection**
Intervention/ Treatment	Acid suppressants [Proton pump inhibitors (PPIs) and H2-blockers]
Comparison	No acid suppressants
Outcomes	Prevention of abdominal pain Gastrointestinal bleeding Adverse events (thrombocytopenia, GI bleeding, others) Cost / cost-effectiveness
Subgroups (If any)	Adult and pediatric populations Drug class (e.g., PPI, H2-blockers) Dengue with vs. without warning signs
Brief Rationale/ Context	With abdominal pain and GI bleed as commonly reported occurrences in Dengue patients, clinicians routinely (or prophylactically) [over] prescribe PPI with hopes of preventing these complications. However, there seems to be no basis for this practice given the proposed mechanism for abdominal pain in dengue is not intestinal/gastric colic nor acid peptic disease related. Even patients who do not present with abdominal pain are started on these drugs.

Question 6. Should acid suppressants be used to treat abdominal pain or gastrointestinal bleeding among probable or confirmed dengue patients?

Population	**Dengue patients with abdominal pain or gastrointestinal bleeding**
Intervention/ Treatment	Acid suppressants (PPIs and H2-blockers)
Comparison	No medications
Outcomes	Resolution of abdominal pain Cessation of bleeding Adverse events (thrombocytopenia, GI bleeding, others) Cost / cost-effectiveness
Subgroups (If any)	Adult and pediatric populations
Brief Rationale/ Context	Abdominal pain and subsequent gastrointestinal bleeding in dengue is proposed to be from hypoperfusion or organ inflammation (gastric or hepatic swelling). However, acid suppressant drugs are being [over] prescribed for patients hoping to provide symptomatic relief or bleeding cessation despite these drugs having different mechanisms of action.

Question 7. Should herbal medicines available locally be used to treat probable or confirmed dengue patients?

Population	**Patients with probable or confirmed dengue fever**
Intervention/ Treatment	Herbal medicines available locally 1. Tawa-tawa 2. Papaya 3. Guava
Comparison	Standard treatment/ no treatment
Outcomes	Prevention of severe dengue / clinical deterioration Recovery time from dengue Duration of symptoms Length of hospitalization Preventing complications Adverse effects Cost/ cost-effectiveness
Subgroups (If any)	Adult and pediatric patients with dengue fever
Brief Rationale/ Context	In the absence of any effective antiviral, patients often ask clinicians whether they can take these traditional medicines to treat or prevent the dengue infection from worsening.

Question 8. Should non-DEET-based mosquito repellents be used for individuals at risk for dengue to prevent infection?

Population	**Patients at risk for dengue infection**
Intervention/ Treatment	N,N-diethyl-meta-toluamide (DEET)-based repellents (e.g. citronella and other herbal repellents)
Comparison	DEET-based repellants
Outcomes	Dengue infection rates Adverse effects Cost / cost-effectiveness
Brief Rationale/ Context	We would like to review/update evidence on the effectiveness of other types of mosquito repellants other than the recommended DEET. There are a lot of available mosquito repellant formulations claiming they are organic, child-safe or plant-based but the evidence on their effectiveness in preventing dengue has not been reviewed.

CPG Development Methodology

Guideline Preparation

Members of the CPG Task Force

The Research Institute for Tropical Medicine (RITM), being a national referral center for infectious diseases and tropical medicine was identified to lead in the preparation, identification of the Steering Committee (SC) members, and in providing administrative support throughout the guideline development process. The Chair of the 5-member Steering Committee nominated by RITM was one of its medical specialists and adult infectious disease and tropical medicine consultant while the rest are likewise experts in adult or pediatric infectious diseases. The SC then identified and invited relevant stakeholders including professional organizations, a patient group, and the Department of Health to nominate individuals with expertise and extensive experience in dengue management who can become part of the multisectoral consensus panel (CP). A group of Evidence Review Experts (EREs) were also identified and selected by the SC on the basis of their knowledge, content and technical expertise, and experience or background in critical appraisal and guideline development. The Task Force COI Review Committee (TFCOIRC) evaluated the conflicts of interest (COIs) of all members of the CPG task force by reviewing their submitted COI forms and made recommendations regarding the extent of their participation to the guideline development.

The full composition of the CPG task force on the Philippine Clinical Practice Guidelines on the Diagnosis, Management and Prevention of Dengue for Adult and Pediatric Filipinos in the Primary Care Setting together with their affiliations declarations of conflicts of interest are presented in Appendix 1.

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Evidence Synthesis

Search Methods and Strategies

Systematic literature searches were performed using the following electronic databases/platforms: MEDLINE via Ovid/PubMed, Embase, Cochrane CENTRAL, HERDIN, and clinical trial registries.

The search terms dengue, dengue fever, dengue hemorrhagic fever, combined with pertinent keywords based on the questions were used. The inclusion criteria were both adults and children with suspected and confirmed dengue infection, with preference for randomized clinical trial when appropriate. However, other study designs were considered especially when there are few searches for the higher quality evidence. The first search was limited to literature published in the last 14 years (2008 to 2022) and in humans. All languages were included. In addition, the reference lists of all retrieved literature and guidelines were searched and experts in the field contacted to identify relevant studies. All searches were conducted from 30 November 2022 to 30 December 2022. Literature search was repeated for all clinical questions at the end of the evidence synthesis allowing any recent relevant papers published in the interim to be included.

For therapeutic intervention questions, randomized controlled trials (RCTs), controlled clinical trials (CCTs), systematic reviews, or meta-analyses were sought. If there were none or too few, quasi-randomized and observational studies were considered. For questions on diagnostic tests, the included studies were those that report sensitivity and specificity or had data for their computation. Cost-effectiveness studies, if available, were included. Search strategies done per question can be seen in Appendix 2.

Inclusion and Exclusion Criteria

Studies including adult and pediatric patients with suspected and confirmed dengue infection were included. Meanwhile, duplicated studies, ongoing trials with no available data yet, and observational studies incompatible with the research question requirements were excluded. Animal studies were generally excluded especially for therapeutic questions but the questions on insect repellants included studies that involved insects since mean repellent activity and complete protection time (against the dengue insect vector) were used as surrogate marker to suggest efficacy in dengue prevention. See inclusion and exclusion criteria in Appendix 3.

Data extraction and Evidence retrieval

A group of evidence review experts (EREs) was tasked to perform the described literature search and to look for existing CPGs published over the past five years that can help in answering respective clinical questions assigned to them.

A data extraction tool which includes the type of study design, description of the clinical trial, type of RCT (superiority, inferiority, equivalence), results of the study, and other relevant information was used. Characteristics of all included studies are summarized in Appendix 4. The extraction tool was filled out by two EREs independently. For any discrepancies, a third reviewer was called to resolve the discrepancy.

Study Quality Assessment

Each study was independently appraised by two EREs for methodological quality and any discrepancies were resolved by a third ERE. The appraisal tools used for the assessment of methodological quality were Cochrane Risk of Bias Tool Version 1[3] for randomized trials, Newcastle Ottawa Scale (NOS) for non-randomized / observational studies[4], Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)[5] for studies on diagnostic accuracy, AMSTAR 2[6] for systematic reviews, Appraisal of Guidelines, Research and Evaluation (AGREE-II)[7] for CPGs.

The quality of evidence was assessed using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Framework[8]. GRADE is a transparent framework for developing and presenting summaries of evidence and provides a systematic approach for making clinical practice recommendations. The GRADE assesses the evidence based on several domains including risk of bias, imprecision, inconsistency, indirectness, and publication bias.[9] The assessment was as follows:

Table 1.0.2. Quality of evidence grades.

Certainty		What it means
Very Low	⊕◯◯◯	The true effect is probably markedly different from the estimated effect
Low	⊕⊕◯◯	The true effect might be markedly different from the estimated effect
Moderate	⊕⊕⊕◯	The authors believe that the true effect is probably close to the estimated effect
High	⊕⊕⊕⊕	The authors have a lot of confidence that the true effect is similar to the estimated effect

Evidence from randomized controlled trials (RCTs) were initially assigned a “high” quality, while evidence from observational studies was given a “low” rating. The initial assessment of RCTs was downgraded in case of serious risk of bias, inconsistency between studies, indirectness, imprecision, and publication bias. On the other hand, the ranking of observational studies was upgraded when there is a large and

consistent effect, a dose-response relationship between the outcomes and degree of exposure, or plausible confounders that are expected to diminish the observed effect.

The certainty of the evidence was determined by evidence reviewers by appraising the directness, methodological validity, results, and applicability of each relevant clinical study or guidelines included.

Data Synthesis

RevMan, STATA, and GRADE Pro were used for the quantitative synthesis of important clinical outcomes for each question. The ERE-generated evidence was summarized for each of the identified questions (see Appendix 4).

GRADEpro, a web-based application, was used to create, manage and share summaries of research evidence. All GRADE evidence profiles are available in Appendix 5.

Formulating Recommendations

Certainty of Evidence and Strength of Recommendations

The GRADE Evidence-to-Decision framework for decision making[10], with consideration of the following: 1.) burden of disease, 2.) balance between benefits and harm, 3.) cost implications, 4.) feasibility, 5.) acceptability, 6.) equity was used. It also included factors that need to be considered for preparing recommendations such as test accuracy, quality of the evidence presented, or resource use. These were used by the consensus panel to weigh the evidence and the possibility to recommend it.

Recommendations were rated as strong or weak, in favor or against an intervention. Strong recommendations suggest that all or almost all persons would choose that intervention. Weak recommendations imply that there is likely to be an important variation in the decision that informed persons are likely to make.

Recommendations are more likely to be weak rather than strong when the certainty in evidence is low, when there is a close balance between desirable and undesirable consequences, when there is substantial variation or uncertainty in patient values and preferences, and when interventions require considerable resources.

To reflect these decisions in the recommendations statement, the following sentence construction was adapted: the use of “We suggest” for conditional recommendations, and “We recommend” for strong recommendations.

Patients' Views and Preferences

There is no systematic or organized research undertaking that directly looked at the preferences of patients regarding the diagnostics, treatment and prevention measures of dengue and its complications. However, to ensure that patient's views and preferences were considered, a lay representative from a dengue patient group was include as a voting member of the consensus panel. The views and opinions of this patient group representative was actively sought during the consensus panel meetings. In addition, perceived patient concerns arising from past experiences of the other consensus panel members in their professional practice were given attention and rightful considerations across all the dengue CPG questions.

Resource Implications

Cost-effectiveness of dengue diagnostic and management strategies were included in all dengue CPG questions but there is lack of local studies on this area. However, some limited international studies that demonstrated the economic burden of dengue and the corresponding costs of the diagnostic and therapeutic strategies available for some were used to provide some context on cost-effectiveness. Additionally, costs of available interventions were summarized, presented and used as reference for cost or financial context during the consensus panel meetings.

The availability and accessibility of the diagnostic tests and treatments included in the development of this CPG were considered. Inquiries from healthcare facilities, diagnostic centers, manufacturing companies and practicing physicians were made to ensure that interventions reviewed were generally available locally, being offered in in government and private hospitals and laboratories, local drug stores, and online or other local sources.

Rating of Outcomes

For each of the guideline questions, outcomes were proposed by the Steering Committee and were presented to the consensus panel. Consensus panel members rated the outcomes according to the degree of importance in decision-making process. Outcomes are categorized as critical, important, and limited importance in decision-making. Those rated as CRITICAL were considered the most crucial for making recommendations and carry more weight in decision making than those rated as important, while outcomes of LIMITED IMPORTANCE did not have much of a bearing.

Consensus Process

A multidisciplinary Consensus Panel was created to vote, via en banc meetings, on the recommendations and the corresponding strengths of recommendations, taking into consideration (1) the quality of the evidence, (2) the value of the outcome, (3) the

balance between benefit and harm, and (4) the cost and resource availability. This was facilitated by a Technical facilitator. The direction and strength of the recommendation was carried if a consensus was reached, defined as 75% of the voting consensus panel members,. Panelists voted either "YES," "NO," or "ABSTAIN" on each draft statement. When consensus was not reached, each panelist was asked to explain the rationale behind their vote, then another round of voting was done. The process was repeated up to three times until a consensus was reached. If still a consensus was not reached, the issue was settled using the modified Delphi method. During the consensus panel meeting, each of the panel members including the patient representative were actively asked to express their and their group/society/colleagues' concerns about the issues at hand. These includes patient preferences, level of knowledge, accessibility, etc. In addition, the EREs were also requested to perform unofficial market surveys especially about availability and costing of certain tests or procedures to provide the task force about the actual scenario in the community.

Guideline Dissemination

The final recommendations are to be presented in scientific fora (including the annual conventions of the Philippine College of Physicians, Philippine Pediatric Society, and other professional societies) and presented to relevant stakeholders such as DOH and PhilHealth. Printed copies of the guidelines will be distributed to medical societies and posted online for wider coverage. Pocket references are also being considered. An executive summary and abridged version of the guideline will be published in a local, peer-reviewed journal such as the Philippine Journal of Internal Medicine. It will also be made available online.

Guideline Monitoring and Evaluation

The impact of this Clinical Practice Guideline is planned to be assessed by monitoring adherence to the recommendations, and more importantly, evaluate clinical outcomes such as reduction in mortality in quality assurance studies, pathway compliance review and operational research. This will be done in collaboration with the Department of Health, other professional societies and even healthcare institutions.

External Review

External reviewers representing stakeholders were identified and asked to perform a technical review of the draft CPG. The AGREE-REX checklist[11] was used for this purpose. At least 1 methodologist was asked to review on the methodological aspects of CPG development, including its reporting using the AGREE-II checklist.

For concerns arising from the external review, the steering committee tried to resolve technical issues in the manuscript while concerns about content and recommendations was presented to the consensus panel for appropriate action.

Guideline Updating

The Steering Committee plans to update the guideline after five (5) years, or earlier, considering new evidence, availability of resources and interventions, and the results of the monitoring. Additional questions not included in this version can be included future updates.

Editorial Independence

Funding Source

The Department of Health provided funding for this endeavor, but were not involved in the decision-making process of the guideline development and only provided input when sought by the task force. Additional minor expenses were supplemented by the Philippine Society for Microbiology and Infectious Diseases.

Management of Conflicts of Interest

All members of the CPG Task Force, including the consensus panel members, were evaluated for potential conflicts of interest. This process was done to detect any conflicts that could affect value judgments and recommendations. For this, they were asked to accomplish, sign, and submit the prescribed conflict of interest (COI) form of the DOH NPG Program, together with their updated curriculum vitae. An independent Task Force COI Review committee was created which was composed of two individuals. The TFCOIRC reviewed the CVs and COI forms – identified and classified the financial and/or intellectual COIs, of all members, and made recommendations regarding the extent of participation of the CPG Task Force members.[12] For any disagreement between the two members of the TFCOIRC, a member of the NPG COI Review Committee evaluated and settled the disagreement.

Table 1.0.3. Classification and management of conflict of interests.

Conflict of Interest	Examples	Management
Primary	• Monetary relations with company within last 48 months; includes spouse (financial)	• Cannot be part of the Lead CPG Developers, or members of the Evidence Review Experts, Consensus Panel, Quality Review Panel, but

	• Authorship in papers with direct bearing on PICO question (intellectual)	• May participate in the discussion of evidence, e.g. with the Evidence Review Experts
Secondary	• Monetary relations with company, but covering interventions (e.g. drugs, in other areas) (financial) • Authorship in reviews or other related CPGs (intellectual)	• May participate in the entire CPG development process but must declare COI
None	• None of the above	• May be involved in all activities in the CPG development process

The evaluation by the TFCOIRC included analysis of each individual's specific or non-specific personal economic interest, specific or non-specific non-personal economic interest, personal non-economic interest, relative's specific or non-specific personal economic interest, research and research funding activities, donations and support,, and/or any other circumstances that could affect their objectivity or independence during the process was taken into consideration in the assessment of potential COI.

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Recommendations and Evidence Summaries

QUESTION 1A: Should dengue NS1 rapid diagnostic tests (RDT) be used to diagnose acute dengue infection in suspected patients?

Recommendation: Among those with suspected dengue infections, we recommend the use of dengue NS1 rapid diagnostic test. ***(Low certainty of evidence, Strong recommendation)***

Dengue NS1 RDT is most useful in the following situations:

- individuals presenting within 3 days of symptom onset ***(Low certainty of evidence, Weak recommendation)***
- patients with no previous history of dengue infection ***(Low certainty of evidence, Weak recommendation)***

KEY FINDINGS

There were 11 observational studies that assessed the diagnostic accuracy of NS1 rapid diagnostic tests (RDTs) against Reverse-Transcription Polymerase Chain Reaction (RT-PCR) as the reference standard. The studies included 11 test brands, with blood samples taken at various time periods from symptom onset. Subjects were affected with either primary or secondary infection, and infected by different dengue virus serotypes (DENV 1, 2, 3 and 4).

The pooled sensitivity of NS1 RDTs was moderate at 0.70 (95% CI 0.56-0.81) while the pooled specificity was high at 0.96 (95% CI 0.93-0.98). A positive NS1 result confirms dengue infection but a negative result does not exclude the diagnosis. Pooled sensitivity and specificity estimates must be interpreted with caution due to the substantial heterogeneity (I^2 Sn = 0.972, I^2 Sp = 0.82) across studies. Pooled sensitivity was high when only studies of high methodological quality or no serious risk of bias were included (Sn 0.83, 95% CI 0.68-0.92, n=3).

On subgroup analyses, NS1 RDT showed higher sensitivity when used in the following conditions:

- Primary infection (Sn 0.89, 95% CI 0.85-0.92; n=1155; 4 studies)
- Infection by DENV 3 serotype (Sn 0.92, 95% CI 0.87-0.96; n=412; 1 study) and DENV 1 serotype (Sn 0.77, 95% CI 0.68-0.84; n=144; 1 study)
- Samples taken at less than 3 days of symptom onset (Sn 0.91, 95% CI 0.85-0.95; n=1044, 4 studies)
- Specific brands of RDTs namely:
    - Dengue Day 1 J Mitra, India (Sn 0.94, 95% CI 0.88-0.97; n=249, 1 study),

    - SD Bioline NS1 Ag SD, South Korea (Sn 0.90-0.91, 95% CI 0.83-0.94; n=585, 2 studies),
    - CTK Biotech, USA (Sn 0.89-0.93, 95% CI 0.82-0.96; n=585, 2 studies),
    - Biosynex Dengue NS1 Ag Biosynex, France (Sn 0.80, 95% CI 0.73-0.86; n=471, 1 study), and
    - CareUS Dengue Combo Kit Wellsbio, Korea (Sn 0.72, 95% CI 0.64-0.79; n=202, 1 study)
- Studies with high methodological quality or no serious risk of bias (Sn 0.83, 95% CI 0.68-0.92, n=3)

The overall certainty of evidence for test sensitivity and specificity was low because of serious inconsistency (high heterogeneity; I^2 Sn = 0.97, I^2 Sp = 0.82) among studies, and high risk of bias (concerns in patient selection, n=7; reference standard, n=1; and flow and timing with selective reporting of outcome, n=5).

CONSIDERATIONS DURING THE CONSENSUS PANEL MEETING

The panel achieved consensus on strongly recommending the use of NS1 RDT despite low certainty of evidence because of the practicality and usefulness of NS1 for the early diagnosis of dengue infection, especially for areas that have no access to standard diagnostics like RT-PCR. As a result, early intervention can be initiated. As for its implementation, although it will entail moderate cost, the panel agreed that it will be a cost effective intervention and that it will be feasible and acceptable locally. However, some panel members emphasized the importance of the clinicians' ability to interpret the results properly – such that negative results will not rule out dengue, while a positive result confirms dengue infection even in the very early stages – for it to be fully beneficial.

BACKGROUND

In the year 2022, there have been 224,477 dengue cases and 729 deaths (with case fatality rate of 0.3%) in the Philippines, which is 184% higher compared to the 78,983 cases reported in the same period in 2021. The most prevalent dengue serotype was DEN-1 (361, 62%), followed by DEN-2 (135, 23%).[1]

Clinical examination complemented with the use of simple and rapid diagnostic tools is the cornerstone to the recognition and early diagnosis of dengue. The choice of test depends on the timing from onset of symptoms to presentation.

Virus isolation and RT-PCR are considered the gold standard for dengue diagnosis, with the ability to determine the circulating dengue serotypes. However, there are

limitations on their use such as: timing of the test since they are useful only during the viremic stage (up to day 5 of illness), available only in centers with specialized laboratory equipment, require special storage temperatures, require trained personnel, more expensive, and have a longer turnaround time.[2]

Because resources are limited in many dengue-endemic settings, RDTs have become more popular over the years. They require neither specific infrastructure nor technical expertise and allow for point-of-care diagnosis as they may be performed in clinics by health care providers or in community settings.[3] In 2016, DOH issued the Guideline for the Nationwide Implementation of Dengue Rapid Diagnostic Test. Following this, the introduction and adoption of RDTs for dengue Non-Structural protein 1 (NS1) antigen was started to support the clinical diagnosis of suspected dengue. NS1 is a non-structural glycoprotein produced by dengue virus during its replication process and can be detected in the serum starting 1 day before the onset of symptoms, until at least 5-7 days after symptoms.[4]

In general, the accuracy of NS1 antigen rapid test can change over the course of illness following the dynamics of viral antigen and antibody levels.[5] Reviews on their performance noted high specificity but with heterogenous sensitivities. Performance data are not always consistent from one study to another as viral serotype, serological status, clinical severity, and illness duration are confounding factors influencing diagnostic accuracy.[6] Acknowledging the significance of these variables, more recent guidelines suggest that Dengue NS1 antigen, IgM antibody and IgG antibody RDT be combined instead (such as those in Dengue Rapid Combo tests) to cover the entire temporal spectrum of patient presentation.[7]

While there are no Dengue NS1 RDTs that are FDA-approved, several kits are commercially available and already in use. A high level of accuracy is essential for rapid diagnostic tests to support their large-scale use.[8] This review aims to find evidence on diagnostic accuracy of NS1 RDTs in detecting dengue Infections, whether these assays are likely to be useful in making a diagnosis, and if so, when best to use them.

BENEFITS AND HARMS

Overall diagnostic accuracy

Pooled analysis of the 11 studies showed that RDTs had a moderate sensitivity at 0.70 (95% CI 0.56-0.81) with high heterogeneity (I^2=97%), and excellent specificity at 0.96 (95% CI 0.93-0.98) with high heterogeneity (I^2=83%). Appendix 7.1 shows the forest plots of the pooled sensitivity and pooled specificity of NS1 RDTs.

Subgroup Analysis

Table 1.1. Subgroup analysis for sensitivity of RDTs.

Variable	References	No. of Studies (No. of participants)	Sensitivity	95% CI	I^2 Sn
Nature of Infection					
Primary	[14, 16, 18, 19]	4 (1,155)	0.89	(0.85, 0.92)	0.77
Mixed	[9, 12]	2 (346)	0.71	(0.67, 0.75)	
Secondary	[10, 11, 13, 17]	4 (1,324)	0.36	(0.22, 0.53)	0.96
Dengue virus serotypes					
DENV 3	[16]	1 (412)	0.92	(0.87, 0.96)	
DENV 1,2,3	[13-15, 18, 19]	5 (1,352)	0.85	(0.79, 0.89)	0.80
DENV 1	[9]	1 (144)	0.77	(0.68, 0.84)	
DENV 1,2,3,4	[12]	1 (202)	0.69	(0.65, 0.74)	
DENV 2	[17]	1 (537)	0.49	(0.43, 0.55)	
DENV 4	[10, 11}	2 (649)	0.27	(0.17, 0.40)	
Symptom Onset					
3 days or less	[13, 16, 18, 19]	4 (1,044)	0.91	(0.85, 0.95)	0.80
more than 3 days	[13, 16, 18, 19]	4 (1,044)	0.78	(0.68, 0.86)	0.69
Test Brands					
Dengue Day 1 Test (J. Mitra & Co, India)	[14]	1 (249)	0.94	(0.88, 0.97)	
SD Bioline Dengue NS1 Ag (SD, South Korea)	[16,18]	2 (585)	0.91	(0.83, 0.94)	
Dengue Ag Rapid Test CTK (CTK Biotech USA)	[16,18]	2 (585)	0.91	(0.82, 0.96)	
Biosynex Dengue NS1 Ag RDT (Biosynex, France)	[15]	1 (471)	0.80	(0.73, 0.86)	

CareUs Dengue Combo Kit (WellsBio, Korea)	[12]	1 (202)	0.72	(0.64, 0.79)	
Humasis Dengue Combo Kit (Humasis, Korea)	[12]	1 (202)	0.69	(0.60, 0.76)	
Wondfo Dengue Combo Kit (Biotech, China)	[12]	1 (202)	0.67	(0.59, 0.75)	
Dengue NS1 Ag Strip (Bio-Rad, France)	[10, 13, 17-19]	5 (1,493)	0.62	(0.37, 0.82)	0.97
Dengue Eden Test NS1 Bioeasy (SD, South Korea)	[9-11]	3 (793)	0.56	(0.38, 0.73)	0.94
Dengue NS1-K130 (Bioclin, Brasil)	[10]	1 (324)	0.21	(0.15, 0.28)	
IVB Dengue Ag NS1 (Orangelife, Brasil)	[10]	1 (324)	0.14	(0.09, 0.21)	
Methodological Quality					
Studies with no serious risk of bias	[9, 13, 14]	3 (531)	0.832	(0.68. 0.92)	0.89
Studies with risk of bias					
Related to Patient Selection	[10-12, 15, 16,18,19]	7 (2,228)	0.68	(0.51, 0.81)	0.98
Related to Flow and Timing	[10-12,16,19]	5 (1,584)	0.58	(0.38, 0.76)	0.98
Related to Reference Standard	[17]	1 (537)	0.49	(0.43, 0.55)	

By nature of Infection

NS1 RDTs had high sensitivity in the detection of primary infections (Sn 0.89, 95% CI 0.85-0.92; n=1155; 4 studies), moderate sensitivity in mixed infections (Sn 0.71, 95% CI 0.67-0.75; n=346; 2 studies) but with low sensitivity in secondary infections (Sn 0.36, 95% CI 0.22-0.53; n=1324; 4 studies). According to Blacksell, this phenomenon of lowered NS1-antigen detection in secondary infections is caused by NS1 antigen complexing with anti-NS1 antibodies, resulting in an inability of the NS1-antigen RDT to detect complexed NS1 antigen.[8]

By DENV Serotype

The sensitivity of each NS1 RDT was considered in the context of the infecting serotype.

- Sensitivity was highest in infections caused by DENV-*3* (Sn 0.92, 95% CI 0.87-0.96; n=412; 1 study) and DENV-*1* (Sn 0.77, 95% CI 0.68-0.84; n=144; 1 study) serotypes.
- Sensitivity was relatively reduced in DENV-2 (Sn 0.49, 95% CI 0.43-0.55; n=537; 1 study).
- Sensitivity was lowest for DENV-4 (Sn 0.27, 95% CI 0.17-0.40; n=649; 2 studies) serotypes.
- Furthermore, NS1 RDT sensitivity was lower in the study that was represented by DENV 1,2,3, and 4 serotypes (Sn 0.69, 95% CI 0.65-0.74; n=202; 1 study) compared to the pooled sensitivity of those that tested DENV1, 2, 3 serotypes only (Sn 0.85, 95% CI 0.79-0.89; n=1352; 5 studies)

By Symptom Onset

NS1 tests are most sensitive in test samples collected within 3 days of illness onset (Sn 0.90, 95% CI 0.83-0.94; n-1515; 5 studies). The pooled sensitivity of NS1 detection gradually decreases beyond 3 days of illness (Sn 0.78, 95% CI 0.83-0.94; n-1515; 5 studies).

By Manufacturer

There was high variability in the performance of different brands of RDTs. The highest sensitivity value (Sn 0.94, 95% CI 0.88-0.97; n=249; 1 study) was noted with Dengue Day 1 Test (J. Mitra & Co, India) kits.

Four other brands had sensitivity of more than 0.70, and includes SD Bioline Dengue NS1 Ag (SD, Korea) (Sn 0.91, 95% CI 0.83-0.94; n=585; 2 studies), Dengue Ag Rapid Test CTK (CTK Biotech, USA) (Sn 0.91, 95% CI 0.82-0.96; n=585; 2 studies), Biosynex Dengue NS1 Ag RDT (Biosynex, France) (Sn 0.80, 95% CI 0.73-0.86; n=471; 1 study) and CareUs Dengue Combo Kit (WellsBio, Korea) (Sn 0.72, 95% CI 0.64, 0.79; n=202; 1 study).

The lowest sensitivities were demonstrated by IVB Dengue Ag NS1 (Orangelife, Brasil) (Sn 0.14, 95% CI 0.09-0.21; n=324; 1 study) and Dengue NS1-K130 (Bioclin, Brasil) (Sn 0.21, 95% CI 0.15-0.28; n=324; 1 study). In contrast, most of the samples where these kits were used for had Secondary Infection, and caused by DENV4 serotypes.

Sensitivity analysis

High heterogeneity was observed within studies and remained high even after subgroup analysis. NS1 RDTs showed higher sensitivity when only studies with high methodological quality were included in the analysis (Sn 0.832, 95% CI 0.68-0.92; n=531; 3 studies). Studies with potential risk of bias issues related to patient selection (Sn 0.68, 95% CI 0.51-0.81; n=2228; 7 studies), issues related to the choice of reference standard (Sn 0.49, 95% CI 0.43-0.55; n=537; 1 study), and issues with flow and timing (Sn 0.58, 95% CI 0.38-0.76; n=1584; 5 studies) decreased the sensitivity estimates.

RECOMMENDATIONS FROM OTHER GROUPS

Recommendations on the timing of NS1 Ag determination have been relatively consistent across groups: NS1 Ag test is requested in the acute phase of Dengue infection, at Day 1-5 or 1-7 of symptom onset. A positive NS1 Ag test confirms Dengue infection. Only DOH however classifies such cases as probable Dengue unless PCR, virus isolation or Hemagglutination inhibition tests is done for confirmation.[4]

A negative NS1 test result does not rule out infection. WHO suggests that even at primary-care level, people with negative NS1 Ag should also be tested for Dengue IgM antibodies to determine possible recent Dengue exposure. The Malaysian CPG for both adults and children recognizes that NS1 Ag test sensitivities vary hence includes the option of testing NS1 Antigen, IgM AND IgG in combination immediately, as soon as Dengue infection is suspected. This is done by use of Dengue Rapid Combo Kits. Such recommendation is based mostly on descriptive studies and case reports, and expert opinion.

Table 1.2. Summary of recommendations from other groups.

Group or Agency	Recommendation	Strength of Recommendation/ Certainty of Evidence
Malaysia CPG Management of Dengue sin Children (Second Edition) 2020.[7]	• Children suspected of dengue infection should be tested with a combination of NS1 Ag/ IgM/IgG rapid test (Dengue rapid combo test). • Rapid test of NS1 Ag alone may be used on day 1-5 of illness	Level III (Opinions of respected authorities based on clinical experience; descriptive studies, case reports or reports of expert committees)
Malaysia CPG Management of Dengue Infection In Adults	• Dengue rapid combo test or NS1 Ag should be taken as soon as dengue infection is suspected, 1-7 days of onset of symptoms in	Level III (Opinions of respected authorities based on clinical experience;

(Third Edition) 2015.[2]	Primary Dengue and 1-5 days after onset of symptoms in secondary Dengue • Positive NS1 Ag: Acute Dengue Infection • Negative NS1 Ag: Dengue infection cannot be ruled out, suggest to send 2nd sample for IgM after day 5 of fever	descriptive studies, case reports or reports of expert committees)
WHO Handbook for Clinical Management of Dengue.[25] 2012	• At primary-care level, rapid tests for NS1 Ag (suggestive of an acute dengue infection, 1-5 days of fever) and rapid tests for IgM (suggestive of a recent infection), are useful. • As patients access care independent of the period of infection suffered – some early, some late – a combination of both NS1 Ag and IgM markers is advisable.	Not specified
DOH AO 2016-0043 Guidelines for the Nationwide Implementation of Dengue Rapid Diagnostic Test (last reviewed 13June 2019)[4]	• Dengue NS1 RDT is requested between 1-5 days of illness (shall not be used beyond), as forefront diagnosis at the health center/ RHU level. • Dengue NSI RDT shall be used in support for the clinical diagnosis of suspected dengue. It shall not be the sole basis for the final diagnosis. • NS1 (+), IgM is used to identify probable dengue. • Confirmed dengue is a suspect case with positive (+) viral culture isolation and/or PCR. • RT-PCR, Hemagglutination Inhibition test, virus isolation remain to be the "confirmatory test" for the detection of dengue virus. PCR available only in dengue sub-national and national reference laboratories	Not specified

	• Dengue NSI RDT shall be performed by a health care worker (medical technologist, nurse, midwife, barangay health worker), and other health professional who has undergone appropriate training on its use. Performance shall be supported by a quality assurance system. • Test is for free in all health centers and selected public hospitals nationwide	

CERTAINTY OF EVIDENCE

The overall certainty of evidence for test sensitivity and specificity was low because of serious inconsistency (high heterogeneity; I2 Sn = 0.97, I2 Sp = 0.82) among studies and high risk of bias (concerns in patient selection n=7, reference standard n=1 and flow and timing with selective reporting of outcome n=5).

ONGOING STUDIES AND RESEARCH GAPS

As of February 18, 2023, there is one ongoing study on Dengue NS1 RDTs registered in clinicaltrials.gov. as seen in Table 1.3.

Table 1.3. Characteristics of ongoing studies.

Title/Study Design/ NCT	Population	Intervention	Comparator	Outcomes	Status
Evaluation of the Viro Track Dengue Acute NS1 Antigen Test • cross-sectional study • Institution: UP Manila • Sponsor: BluSense Diagnostics Denmark • PHRR200120-002435	Specimens from 2 dengue studies conducted in the Institute	ViroTrack Acute Dengue NS1 Ag	RT-PCR	Primary Outcome: Sn and Sp of the ViroTrack Acute Dengue NS1 Ag	Ongoing Start date: May 28, 2019 Target Completion Date: May 28, 2022

The list of validated kits for Dengue RDTs in the Philippines, and the specific brand used by different laboratories should be made readily accessible to researchers.

COST IMPLICATION

There are no local studies available in the Philippines on the cost-effectiveness of Dengue NS1 RDTs.

A study by Zubieta reviewed costs associated with case management for dengue fever patients in Mexico. Real medical expenses, reported to the Secretariat of Health, were USD 33 for outpatients, and USD 491 for inpatients.[20] In Cambodia, on average, the total cost of lab-confirmed dengue was USD 31.5 and the total cost per hospitalized dengue case was USD 40.1. Compared to an average one-week expenditure on food in Cambodia of about USD 9.5 per household, costs of treatment for dengue, whether outpatient or hospitalized, put enormous strain on the household. To finance the cost of a febrile illness, 67% of households incurred an average debt of USD 23.5 [21]

There is a need for studies to specifically measure economic impact of dengue RDTs. While Mitra concluded that RDT (brand Panbio) at USD 6.90 was cost-effective[22], Lubell concluded that Dengue RDT is associated with negative Disability Adjusted Life Years (DALYs) averted while resulting in higher costs than current practice of antibiotics prescription.[23] The 2 studies differ in design and findings. Such assessments must await future studies for more conclusive evidence.[24]

Table 1.4 shows the prices of dengue NS1 RDT kits while Table 1.5 shows the cost of various dengue tests that are available in different institutions.

Table 1.4. Price of Dengue NS1 RDT kits (as of March 14, 2023 search).

Brand	Unit Price per Test in Peso
Dengue Ag Rapid Test, CTK Biotech USA	P 685 (ctkbiotech.com)
Wondfo Dengue Combo Kit, Biotech China	P 360 (en.wondfo.com)
SD Bioline Dengue NS1 Ag, South Korea	P 275 (alliedhospitalsupply.com)
Dengue Day 1 Test, J. Mitra India	P 202 - 298 (jmitra.co.in)
Other NS1 RDTs Available Online	
Icheck Dengue NS1 Ag Rapid Test, Bluecross Biotech China	P 650 (philmedicalsupplies.com)

LabX Dengue NS1 Ag Self-Test Kit, Southstar Drug Philippines	P 350 - 570 (southstardrug.com.ph)
Mytest One Step Dengue NS1 Ag Test, Nano Entek South Korea	P 298 - 366 (biofootprintshealthcare.com)
SD Biosensor Dengue NS1 Ag, SD South Korea	P 225 (sdbiosensor.co.in)

Table 1.5. Costs of various dengue diagnostic tests that are available in different institutions.

Drug	Test	Cost
Government Hospitals*	Dengue NS1 Ag Rapid Test	P 350-700
	Dengue IgM IgG Rapid Test	P 700
	Dengue RT-PCR	P 4,000
Private Hospitals/Laboratories	Dengue NS1 Ag	P 1,505 – 5,480
	Dengue Duo (IgM/IgG)	P 2,310
	Dengue NS1/IgM/IgG RDT	P 3,210 - 5,990
	Dengue PCR	P 7,000 – 8,000

*Source: Research Institute for Tropical Medicine (ritm.gov.ph), prices are as of July 2022

ETHICAL, SOCIAL AND HEALTH SYSTEMS IMPACT

WHO recommends that Primary health care center should have at least NS1 Ag and IgM detection by RDT.[25] Since year 2016, the Philippine Department of Health suggested NS1 RDT as forefront diagnosis at the health center or Rural Health Unit level, and that testing is for free in all District Health Centers and selected public hospitals nationwide.[4] As of year 2022, PhilHealth pays PHP10,000 for each patient with Dengue fever and PHP16,000 each for severe cases that are admitted to hospitals.[26]

A qualitative study was conducted by Zongo in year 2014 to analyze the use of rapid diagnostic tests in six health and social promotion centers of Burkina Faso, Africa. Dengue rapid diagnostic tests were introduced into fever-related consultations. Prior to the introduction of the tests, most febrile cases were presumed to be malaria. In-depth interviews were conducted with 32 health professionals. They expressed that the test was laborious; the perceived complexity had to do with the type of test used and the quantity of blood it required. Health professionals in sites where no positive cases were found were more reserved about the reliability of the tests. Despite diverse opinions, they still considered Dengue RDTs as acceptable and useful, as it improved the ability to establish a differential diagnosis and manage cases more easily during

infection outbreaks. They wanted the Dengue RDTs scaled up as had been done for malaria RDTs. Those who had been specially trained in the use of the tests became more invested in the study's implementation.[27]

Peeling summarizes the characteristics of an ideal diagnostic test as defined by the ASSURED criteria: (1) Affordable by those at risk of infection; (2) Sensitive (few false-negatives); (3) Specific (few false-positives); (4) User-friendly (simple to perform and requiring minimal training); (5) Rapid (to enable treatment at first visit) and Robust (does not require refrigerated storage); (6) Equipment-free; (7) Delivered to those who need it [28]

Although Dengue NS1 tests are available in the Philippines as commercial diagnostic kits, there is no NS1 RDT cleared by the Philippine Food and Drug Administration.

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Question 1B: Should dengue NS1/IgM/IgG and dengue IgM/IgG rapid diagnostic test kits be used to diagnose dengue infection in suspected patients?

Recommendation: Among patients with suspected dengue infection, we recommend the use of combined dengue NS1/IgM/IgG rapid diagnostic test. ***(Low certainty of evidence, Strong recommendation)***

Recommendation: Among patients with suspected dengue infection who present more than 5 days from onset of symptoms, we recommend the use of rapid diagnostic test with dengue IgM/IgG antibodies. ***(Low certainty of evidence, Strong recommendation)***

KEY FINDINGS

There were 12 studies that assessed the diagnostic accuracy of combined Dengue NS1/IgM/IgG rapid diagnostic test (RDT) kits, and five studies for IgM/IgG RDT kits, testing against RT-PCR and/or ELISA NS1/IgG/IgM as the reference standard.

The pooled sensitivity and specificity of NS1/IgM/IgG RDTs was high at 0.86 (95% CI: 0.80 to 0.91) and 0.94 (95% CI: 0.89 to 0.96), respectively. Performance of the tests were based on a positive result on NS1 and/or IgM assay of the RDT. The certainty of evidence regarding these diagnostic accuracy estimates is downgraded to low due to serious risk of bias and inconsistency.

For combined IgM/IgG RDTs, the pooled sensitivity was moderate at 0.60 (95% CI 0.42-0.75), while pooled specificity was moderate at 0.79 (95% CI 0.65-0.88), with a positive IgM assay being considered a positive test result. The certainty of evidence regarding these diagnostic accuracy estimates is very low due to serious risk of bias, inconsistency, and imprecision. Subgroup analyses showed that IgM/IgG RDTs may be more accurate when used for:

- Secondary infection (Sn 0.77, 95% CI 0.59-0.89)
- Later in the course of illness, beyond 5 days (Sn 0.81, 95% CI 0.71-0.88)
- With the following test kit brands: Panbio Dengue Duo (Sn 0.67, 95% CI 0.62-0.71), Merlin (Sn 0.73, 95% CI 0.63-0.81), and Biosynex (Sn 0.80, 95% CI 0.71-0.87)

CONSIDERATIONS DURING THE CONSENSUS PANEL MEETING

Although the panel recognizes the low certainty of evidence suggesting that combination kits will yield net benefit, and that more studies are needed in the future, there was consensus among the panel members to recommend the use of combination kits in diagnosing dengue infection since available evidence shows high

sensitivity and specificity especially when it is used appropriately based on the day of illness. A strong recommendation was given because of the availability and accessibility of these combination kits especially to resource limited areas compared to standard tests that use specialized equipment like ELISA or RT-PCR.

BENEFITS AND HARMS

Overall diagnostic accuracy

Dengue NS1/IgM/IgG RDT

Pooled analysis of the 12 studies showed high sensitivity and specificity at 0.86 (95% CI: 0.80 to 0.91) and 0.94 (95% CI: 0.89 to 0.96) respectively, with high heterogeneity (Sn I^2 = 94%, Sp I^2=87%).

Dengue IgM/IgG RDT

Pooled analysis of the 5 studies showed sensitivity and specificity of dengue IgM/IgG RDTs to be moderate at 0.60 (95% CI: 0.42 to 0.75) and 0.79 (95% CI: 0.65 to 0.88) respectively, with high heterogeneity (Sn I^2 = 95%, Sp I^2=90%).

Subgroup analysis

Dengue NS1/IgM/IgG RDT

By nature of infection

Dengue NS1/IgM/IgG RDT had high sensitivity in the detection of primary (Sn 0.84, 95% CI 0.70-0.92), and secondary dengue infections ((Sn 0.85, 95% CI 0.75-0.91).

By DENV serotype

One study assessed the accuracy of the RDTs among the 4 DENV serotypes.[12] DENV3 was associated with the highest test sensitivity (0.97, CI 95% 0.82-0.99). When stratified by serotype, all NS1 assays, whether alone or in combination, had higher sensitivity in detecting DENV-3.[12] The study by Gan and Kyaw were unable to prove equivalent performance between dengue serotypes since the small number of each DENV serotype cases did not lead to statistically significant results, because of limitation in the dengue serotype distribution in Singapore and the single-site field trial design.[13,14]

By day of illness

Accuracy of combination assays for dengue NS1/IgM/IgG had high sensitivity and specificity (Sn 0.97, 95% CI 0.86-0.98; Sp 0.91, 95% CI 0.83-0.95). NS1 assays alone

are most sensitive when collected earlier in the disease course (<3 days) and gradually decrease thereafter. However, when combined with serology IgM/IgG, pooled sensitivity remains high even beyond day 3 of illness.[15]

By kit brand

The brand SD Bioline was the most tested dengue RDT kit with 10 studies assessing its accuracy (see Table 1.6). All test kits demonstrated a test sensitivity > 0.80 (SD Bioline: SN 0.85, 95% CI 0.77-0.91; CareUS: Sn 0.88 95% CI 0.79, 0.93; Humasis: Sn 0.89, 95% CI 0.64, 0.98; Wondfo: Sn 0.83, 95% CI 0.72, 0.90; CTK: Sn 0.95, 95% CI 0.92, 0.97), except for Dengue Day 1 (Sn 0.77, 95% CI 0.49, 0.92).

Table 1.6. Subgroup analysis for sensitivity of dengue NS1/IgM/IgG RDTs.

Variable	References	No. of Studies (No. of participants)	Sensitivity	95% CI	I^2 Sn
Nature of Infection					
Primary	(12) (11) (16) (17) (15) (14) (9) (10)	8 (1,281)	0.81	0.81-0.92	0.849
Secondary		8 (857)	0.84	0.75, 0.90	0.86
Dengue virus serotypes					
DENV 1	(12) (13) (14)	3 (224)	0.84	0.73, 0.92	0.726
DENV 2	(12) (13)	2 (118)	0.92	0.86, 0.96	0.487
DENV 3	(12)	1 (30)	0.97	0.82, 0.99	
DENV 4	(12)	1 (1)	0	0, 0.97	
Symptom Onset					
3 days or less	(15) (9) (10)	3 (470)	0.97	0.86, 0.98	0.905
more than 3 days		3 (249)	0.91	0.83, 0.95	0.606
Test Brands					
SD Bioline Dengue Duo (SD, South Korea)	(17) (12) (13) (11) (18) (19) (9) (10) (16) (15)	10 (1,899)	0.85	0.77, 0.91	0.948
Dengue Day 1 Test (J. Mitra & Co, India)	(20) (19)	2 (567)	0.77	0.49, 0.92	0.979

CareUs Dengue Combo Kit (WellsBio, Korea)	(11) (14)	2 (249)	0.88	0.79, 0.93	0.83
Humasis Dengue Combo Kit (Humasis, Korea)	(11) (14)	2 (249)	0.89	0.64, 0.98	0.939
Wondfo Dengue Combo Kit (Biotech, China)	(14)	1(202)	0.83	0.72, 0.90	
Dengue Ag Rapid Test CTK (CTK Biotech USA)	(9) (10)	2 (378)	0.95	0.92, 0.97	0

Dengue IgM/IgG RDT

By nature of infection

Sensitivity of dengue IgM/IgG RDTs was low when tested among patients with primary dengue infection and moderate among those with secondary infection (Sn 0.46, 95% CI 0.28-0.66; Sn 0.77, 95% CI 0.59-0.89 respectively). The higher sensitivity of patients with secondary infection could be attributed to the relative abundance of secondary infections.[21]

By DENV serotype

None of the studies provided data to allow subgroup analysis according to DENV serotype.

By day of illness

Among patients tested on days 0-5 of illness, the sensitivity of IgM (Panbio Dengue Duo IgM/IgG) was moderate (Sn 0.60, 95% CI 0.53-0.68). Later in the course of illness beyond day 5, the sensitivity for IgM was higher (Sn 0.81, 95% CI 0.71-0.88). Accordingly, anti-dengue IgM specific antibodies can be detected 3−6 days after fever onset. On average, IgM is detected in 50% of cases by days 3–5 after the onset of illness, this figure increasing to 95–98% for days 6−10.[22]

By kit brand

Moderate sensitivity was observed among the kits Panbio Dengue Duo (Sn 0.67, 95% CI 0.62-0.71), Merlin (Sn 0.73, 95% CI 0.63-0.81), and Biosynex (Sn 0.80, 95% CI 0.71-0.87). The remaining test brands demonstrated poor sensitivity (Acon, SD Bioline Dengue IgG/IgM).

Table 1.7. Subgroup analysis for sensitivity of dengue IgM/IgG RDTs.

Variable	References	No. of Studies (No. of participants)	Sensitivity	95% CI	I^2 Sn
Nature of Infection					
Primary	(21) (23) (24)	3 (138)	0.46	0.28, 0.66	0.833
Secondary		3 (340)	0.77	0.59, 0.89	0.898
Symptom Onset					
3 days or less	(21) (25)	2 (153)	0.60	0.53, 0.68	0
more than 3 days		2 (88)	0.81	0.71, 0.88	0
Test Brands					
Biosynex	(21)	1 (259)	0.80	0.71, 0.87	
Merlin	(21)	1 (259)	0.73	0.63, 0.81	
Panbio Dengue Duo	(21) (23) (25)	3 (413)	0.67	0.62, 0.71	0
Acon	(27)	1 (239)	0.49	0.41, 0.58	
SD Bioline Dengue IgG/IgM	(25) (26)	2 (212)	0.34	0.06, 0.81	0.98

Cross-reactivity with other flaviviruses of the dengue serologic tests

Cross-reactivity with other flaviviruses, malaria, and leptospirosis have been reported when testing Anti-DENV IgM.[45] However, in a study by Jang et al. evaluating the Humasis, CareUS, and SD Bioline NS1/IgM/IgG RDT kits, SD Bioline IgG kits showed no cross-reactivity with Chikungunya virus infected serum.[44] All three NS1/IgM kits showed no cross reactivity with Chikungunya virus infected serum. However, in cross-reactivity test of three RDT kits against Chikungunya virus infected serum samples (n= 15) among other flaviviruses, Humasis and CareUS IgG tests showed cross-reactivities of 80% and 73.3%, respectively. Cross-reactivity testing of the three test kits for other flavivirus samples such as Japanese encephalitis virus (JEV), or Zika virus (ZIKV), which are common in Southeast Asia, Humasis and CareUS IgG test might have cross-reactivity with other flavivirus infected samples. Therefore, for confirmation of dengue infection, IgG alone is not recommended without additional NS1 Ag and IgM antibody testing, and evaluation for other flavivirus infections as differential diagnoses was suggested.[44]

Impact of prior dengue vaccination with dengue serologic tests

Prior dengue vaccination, such as with Dengvaxia, may confound the interpretation of dengue IgM and IgG serologic tests. In a phase IIb randomized, placebo-controlled trial efficacy trial of the tetravalent CYD-TDV dengue vaccine among school children, high false positive rates were observed when IgM/IgG serologic tests are used particularly in the 2 months after vaccination. This is demonstrated by the low PPV of 29.7% for probable dengue using the dengue serologic tests.[47] Another study that performed a post hoc pooled analysis of febrile episodes during the first 25 months after the administration of CYD-TDV dengue vaccine in 2 phase III, placebo-controlled trials that involved more than 31,000 children aged 2–16 years in 10 countries, a low specificity and PPV using probable dengue definition (defined using positive serologic tests) compared with virologically-confirmed dengue were reported at 77.2% and 22.9%, respectively.[46] These two studies highlight the need to exercise caution when using serologic tests in the diagnosis of dengue among previously vaccinated individuals. The timing of disease presentation, results and pattern of other ancillary tests such as the CBC in relation to fever and other symptoms, and dengue NS1 test results can help in interpreting dengue serologic test results in the context of prior dengue vaccination.

RECOMMENDATIONS FROM OTHER GROUPS

The Malaysia Clinical CPG on the management of dengue in children and adults both recommended the use of dengue rapid combo tests, citing well-designed analytic studies and opinions and clinical experience of respected authorities as bases for their recommendations.

Table 1.8. Summary of recommendations from other groups.

Group or Agency	Recommendation	Strength of Recommendation/ Certainty of Evidence
CPG Management of Dengue Infection In Adults (Third Edition). 2015.[17] Malaysia Health Technology Assessment Section (MaHTAS)	• **Dengue rapid combo test** or non-structural protein 1 antigen (NS1 Ag) should be taken as soon as dengue infection is suspected. • If dengue IgM is negative before day seven, a repeat sample must be taken in recovery phase	Level II-2 Evidence obtained from well-designed cohort or case control analytic studies[12,13,32], preferably from more than one center or research group
Management of Dengue in Children (Second Edition). 2020.[18]	• Children suspected of dengue infection should be tested with a combination of NS1 Antigen/	Level III Opinions of respected authorities based on clinical experience;

Malaysia Health Technology Assessment Section (MaHTAS)	IgM/IgG rapid test (dengue rapid combo test). • Rapid test of NS1 Antigen alone may be used on day 1 to day 5 of illness	descriptive studies and case reports; or reports of expert committees
World Health Organization. 2012. Handbook for Clinical Management of Dengue.[20]	Rapid tests for NS1 Ag, IgM detection are recommended among primary health care centers, district health centers, and reference centers.*	Not mentioned

** Whether to test these separately or simultaneously (by combo kits, or separate kits NS1 and IgM simultaneously) was not particularly stated.*

CERTAINTY OF EVIDENCE

Dengue NS1/IgM/IgG RDT

Overall, there is **low certainty of evidence** supporting that combined NS1/IgM/IgG RDTs have **high accuracy.** Reasons for downgrading certainty included serious risk of bias in patient selection and high heterogeneity. Seven out of 12 studies has risk of bias due to unclear patient selection criteria – one study excluded patients in need of emergency care or patients with preexisting conditions that were prone to complications from blood sampling,[15] while another study excluded pregnant women.[13]

Dengue IgM/IgG RDT

There is **very low** certainty of evidence suggesting that IgM/IgG RDTs have **moderate** accuracy. Certainty of evidence was downgraded due to risk of bias, inconsistency, and imprecision (confidence intervals ranged from poor to moderate accuracy). Of the five studies, two studies had serious risk of bias due to unclear patient selection. The study by Nga excluded patients with severe systemic or organ-specific disease.[16]

COST IMPLICATION

There are no local health economic studies assessing the costs, benefits, or impact of using dengue RDTs. A study by Camprubi-Ferrer assessing reduction of hospitalizations, healthcare costs, and antibiotic prescriptions in Spain showed that the use of dengue RDTs were associated with 53.5% (95% CI 33.9-72.5) reduction of hospital admissions and were estimated to save 289.08-389.31€ per traveler tested.[35] Moreover, RDTs would have avoided the use of antibiotics in 46.4% of dengue patients (95% CI 27.5-66.1).[28]

A systematic review done in 2017 on the economic impact of rapid diagnostic tests for dengue showed limited data to demonstrate an economic impact. There were only 2 studies selected for data extraction. One study found satisfactory performance of IgM-based Panbio RDT, concluding that it would be cost-effective in endemic settings. The second study was a modeling analysis and showed that a dengue RDT would not be advantageous in terms of cost and effectiveness compared to current practice of antibiotics prescription for acute febrile illness. Evidence of such an impact would require further quantitative economic studies.[29]

Table 1.9. Estimated cost of dengue NS1/IgM/IgG and dengue IgM/IgG RDT kits (direct from supplier).

Brand	Unit Price per Test in Peso
SD Dengue Duo (NS1 Ag + IgM/IgG), Abbott	PHP 500.00 Abbott Philippines
Panbio Dengue Duo Test Kit (IgM/IgG), Abbott	PHP 500.00 Abbott Philippines

Table 1.10. Estimated cost of various dengue diagnostic tests in institutions.

Test	Price
NS1 rapid dengue test	PHP 1,500.00
IgG/IgM rapid dengue test	PHP 1,100.00
NS1/IgG/IgM rapid dengue test (Abbott)	PHP 3,900.00
Dengue virus culture	PHP 12,650.00
Dengue virus RT PCR	PHP 10,974.00
Trioplex RT PCR (Dengue/Zika/Chikugunya)	PHP 4,000.00

ETHICAL, SOCIAL AND HEALTH SYSTEMS IMPACT

The WHO recommends that primary health care centers should have at least NS1 Ag and IgM detection by RDT. A study was done by Tan in Singapore on assessing the understanding of the health care workers' and patients' experience on the introduction of dengue RDT during a surge.[34] Results showed that RDTs did not do much to help in its current implementation at that time in 2017. Healthcare workers expressed that public perceptions of dengue in recent years was a major factor in changing patient management, and that the point-of-care-test (POCT) kit was helpful in improving the speed and accuracy of diagnoses. Health service delivery for dengue patients was enhanced by the introduction of dengue RDTs. However as presented in the Dengue AWARE model of care delivery, improvements can be focused on adapting to outbreaks by (1) reducing and rendering waiting experiences more comfortable, (2) advancing education about symptom recognition, while also recognising better

communication strategies, and (3) expanding follow-up care options.[34] Dengue RDTs in combination kits (NS1/IgM/IgG and IgM/IgG) are readily available in laboratory centers. However, none is approved by the Philippine Food and Drug Administration to be self-administered nor for home use.[34]

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QUESTION 2: What clinical findings and laboratory parameters should be used to identify patients that require in-hospital management?

Recommendation: Among adult and pediatric patients with dengue fever, we recommend using any one of the following clinical signs as a basis for in-hospital management ***(Very low certainty of evidence, Strong recommendation)***:

1. Signs and symptoms
    a. Vomiting/persistent vomiting
    b. Abdominal pain/tenderness
    c. Lethargy/restlessness
    d. Mucosal bleeding
    e. Impaired consciousness
    f. Hepatomegaly
    g. Acute renal failure
2. Comorbidities
    a. Pregnancy
    b. Obesity
    c. Others (cardiac, renal, hematologic, pulmonary)

Recommendation: Among adult and pediatric patients with dengue fever, we suggest using any one of the following laboratory parameters as a basis for in-hospital management ***(Very low certainty of evidence, Weak recommendation)***:

a. Increase in hematocrit with or without decrease in platelet count
b. Elevation of transaminases
c. Impaired PT or PTT
d. Thrombocytopenia

KEY FINDINGS

Eight systematic reviews that investigated prognostic factors for severe dengue were included in this evidence synthesis. A total of 13 variables were identified to be associated with progression to severe dengue (based on the WHO 2009 Dengue Classification): impaired consciousness, increasing hematocrit with concurrent decrease in platelet count, thrombocytopenia, acute renal failure, hepatomegaly, vomiting and persistent vomiting, lethargy/restlessness, mucosal bleeding, elevated transaminases, pregnancy, coagulopathy, and abdominal pain or restlessness. For children, the presence of petechiae was also a significant predictor of severe dengue. Overall, the degree of association of these variables with severe dengue was found to be moderate based on low to very low certainty of evidence.

CONSIDERATIONS DURING THE CONSENSUS PANEL MEETING

A very low certainty of evidence was found regarding the use of prognostic factors in determining the need for in-hospital management. While evidence is not robust, the

panel emphasizes that these prognostic factors are the actual clinical signs, symptoms and laboratory parameters that are observed in, actively looked for and/or monitored in dengue patients in clinical practice. Any of these manifestations might already be indicators of dengue plasma leakage in patients who are about to enter the critical phase; hence, they should be easily utilized as alarm signals and recognized by general practitioners, pediatricians, and internists. The panel was therefore in agreement to give a strong recommendation, despite the very low certainty of evidence, as it will certainly result in timely management decisions and better clinical outcomes for the patient. It was also mentioned that the use of these prognostic factors has high stakeholder acceptability, easy implementation, and anticipated positive effects when training clinicians in the timely recognition of dengue complications.

It is important to note that during the discussion, the panel unanimously agreed to provide greater emphasis on the clinical signs and symptoms than laboratory parameters; hence the strong recommendation for the clinical signs and symptoms and and weak recommendation for the laboratory parameters. At the primary care setting, a clinical diagnosis of dengue infection can be made and patients can be managed as dengue and monitored for its complications. Laboratory findings may supplement, but are not critical for diagnosing dengue. Laboratory results are not used as the only basis/bases for intervention and hospital admission of dengue patients; these are always to be interpreted in the context of clinical parameters. Moreover, the panel believes that a weak recommendation for the use of certain laboratory parameters gives the clinicians more flexibility in ordering appropriate tests to guide patient care and decision-making regarding prognostication.

Some panel members brought up the need to specify actual values of laboratory findings that may suggest hospital management to prevent unnecessary admissions and shortage of resources in primary care centers. However, this suggestion faces some issues for implementation like 1) variability of hematocrit values with age, 2) absence of studies indicating reference values for admission, and 3) inconsistency of laboratory results and patient's clinical appearance; since some patients may present with low hemoglobin and hematocrit who clinically look fine, but are actually bleeding internally. Correspondingly, there is a very low certainty of evidence regarding its use.

Lastly, the panel suggested adding other comorbidities aside from pregnancy like obesity, heart, renal, hematologic and pulmonary conditions as prognostic factors for hospital admission since these patients are considered high risk for morbidity and require hospital monitoring. These are based on their shared experiences, from other studies and from recommendations from other groups such as the Malaysia CPG.

BACKGROUND

Clinical manifestations of dengue vary in severity, with outcomes ranging from mild to severe. While most patients experience a self-limiting disease, a small portion may

develop severe symptoms characterized by plasma leakage and potential bleeding.[1] Accurate prognostic estimation is crucial for effective clinical management, enabling prompt intervention for those at high risk of severe dengue. Identifying predictors of progression to severe disease is essential for triage and early management and serves as a defining criterion for classifying severe dengue according to the 2009 WHO Dengue Classification.[2]

Figure 1. 2009 WHO dengue case classification and levels of severity.

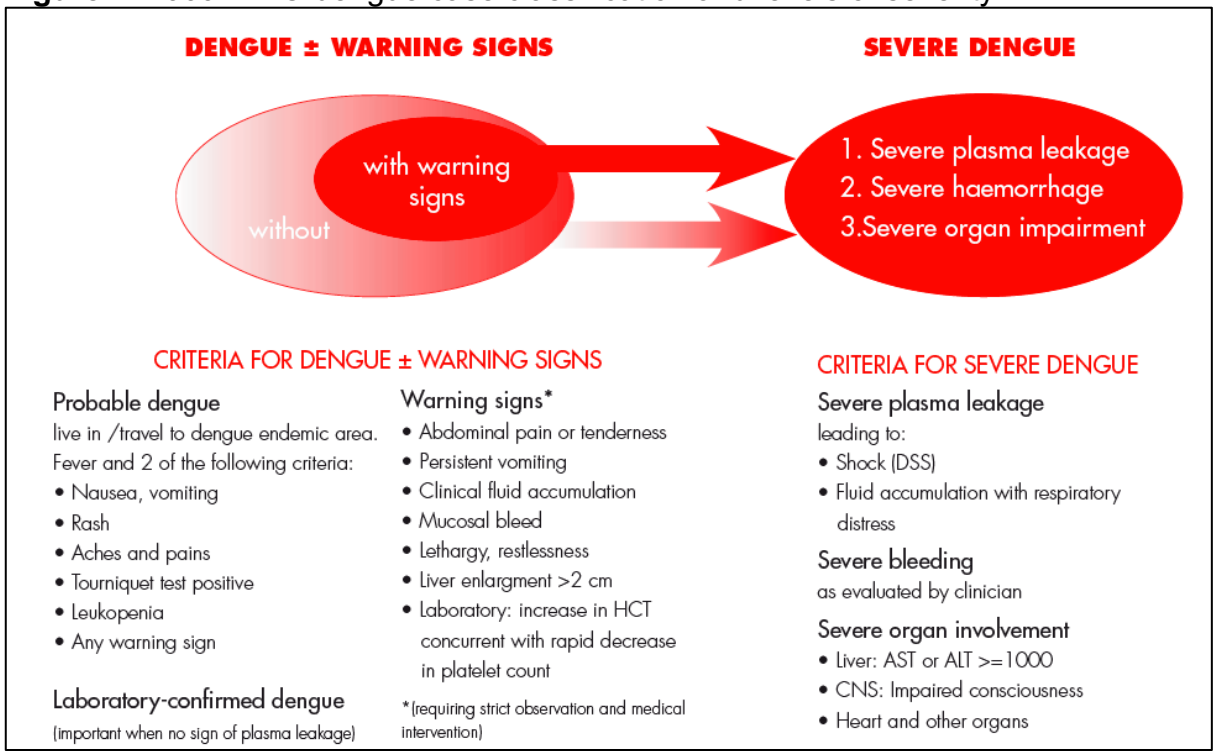

Figure from the 2009 WHO Dengue guidelines, for diagnosis, treatment, prevention and control

BENEFITS AND HARMS

Degree of association with severe dengue progression

Based on 8 systematic reviews, 13 prognostic factors (or warning signs according to WHO 2009 Dengue severity classification) had varying associations with severe dengue. Some factors lacked clear definitions or had inconsistent definitions across reviews (e.g., persistent vomiting, impaired consciousness, lethargy, or restlessness), which could explain the discrepancies in reported effect estimates. Table 2.1 provides a summary of prognostic factors found in this evidence synthesis.

Table 2.1. Summary of prognostic factors for severe dengue progression.

Prognostic Factor	Basis *(No. and type of studies, total participants)*	Effect Estimates (95% Confidence Interval)	Certainty of Evidence
Impaired consciousness	Htun 2021; 5 studies, n=37 PAHO 2022; 33 studies, n=76881	**OR 29.81 [4.08, 217.94]** OR 5.23[3.45,7.93]	⊕◯◯◯ Very low
Increasing hematocrit +/- concurrent decrease in platelet count	Yuan 2022; 7 studies, n=18180 Tsheten 2021; 7 studies, n/a PAHO 2022; 45 studies, n=17462	**OR 12.39[6.20, 25.20]** OR 5.14 [1.51, 16.34] OR 2.30[1.74,2.35]	⊕◯◯◯ Very low
Thrombo-cytopenia	Yuan 2022; 12 studies, n=1238 PAHO 2022; 62 studies, n=50586	**OR 8.15[3.37,19.67**] OR 3.02[2.45,3.73]	⊕◯◯◯ Very low
Acute renal failure	PAHO 2022; 8 studies, n=4,348	**OR 6.73** [1.66, 27.20]	⊕◯◯◯ Very low
Hepatomegaly	Tsheten 2021; 47 studies, n/a Yuan 2022; 17 studies, n=20581 Htun 2021; 25 studies, n=796 PAHO 2022; 62 studies, n=25989	**OR 5.92[3.29, 10.65]** OR 4.403[3.02, 6.43] OR 3.34[2.38, 4.68] OR 3.14[2.38, 4.15]	⊕◯◯◯ Very low
Vomiting	Sangkaew 2021; 9 studies, n=6,229 Htun 2021; 9 studies, n=849 PAHO 2022; 56 studies, n=72312 Yuan 2022; 26 studies, n=9,417	**OR 2.25 [**1.87, 2.71] OR 2.18[1.5, 3.16] OR 1.74[1.48, 2.05] **OR 1.53** [1.20, 1.95]	⊕⊕◯◯ Low
Persistent vomiting	Yuan 2022; 3 studies, n=813 Htun 2021; 12 studies, n=296	**OR 5.57 [3.04, 10.2]** OR 2.57 [1.40, 4.73]	⊕◯◯◯ Very low
Lethargy/ restlessness	Htun 2021; 13 studies, n=464 Tsheten 2021; 10 studies Yuan 2022; 8 studies, n=29412	**OR 4.32[1.86, 10.04]** OR 2.73[1.05, 7.10] OR 2.56[1.517, 4.33]	⊕⊕◯◯ Low
Mucosal bleeding (epistaxis, gum bleeding, hematuria, melena)	Tsheten 2021; 9 studies Htun 2021; 10 studies, n=48 PAHO 2022; 3 studies, n=1831 Htun 2021; 9 studies, n=73 Htun 2021; 19 studies, n=386	**OR 4.05[1.64, 10.00]** OR 3.34[1.6, 6.98] OR 3.12[1.23,7.9] OR 2.23[1.04, 4.77] OR 2.12[1.53, 3.19] OR 1.96[1.47, 2.69] OR 1.87[1.23, 2.84]	⊕◯◯◯ Very low

	PAHO 2022; 50 studies, n=24661 Sangkaew 2021; 4 studies, n=7057 PAHO 2022; 31 studies, n=9663	OR 1.21[0.96, 1.52]	
Elevated transaminases	Yuan 2022; 8 studies, n=1069 PAHO 2022; 39 studies, n=18579 Htun 2021; 25 studies, n=796	**OR 4.030[2.41,6.75]** OR 2.55[1.78,3.64] OR 3.24[2.38, 4.68]	⊕◯◯◯ Very low
Pregnancy (All trimester; 3rd Trimester)	PAHO 2022; 1 study, n=99 PAHO 2022; 1 study, n/a	**OR 3.94[2.10,5.42]** OR 3.38[2.10,5.42]	⊕⊕◯◯ Low
Coagulopathy (PT, PTT or both)	PAHO 2022; 10 studies, n=6895	OR 2.83[1.59, 5.04]	⊕◯◯◯ Very low
Abdominal pain or tenderness	PAHO 2022; 87 studies, n=85769 Tsheten 2021; 55 studies Htun 2021; 63 studies, n=1338 Sangkaew 2021; 9 studies, n=7171 Yuan 2022; 33 studies, n=27727	**OR 2.02[1.74,2.35]** OR 2.00[1.49, 2.68] OR 2.00[1.49, 2.68] OR 1.92[1.35, 2.74] OR 1.85[1.47, 2.34]	⊕⊕◯◯ Low

The following factors exhibited a strong association with risk for progression to severe dengue: impaired consciousness, acute renal failure, thrombocytopenia and increasing hematocrit with concurrent decrease in platelet counts. Other warning signs and severe classifications had weak to moderate associations as predictors for developing severe dengue.

Vomiting/Persistent vomiting

Vomiting showed a moderate association, with moderate certainty of evidence, in identifying patients at risk for severe dengue, ranging from OR 1.53 (95% CI 1.20-1.95) (Yuan 2022, 26 studies, n=9417) to OR 2.25 (95% CI 1.8-2.71) (Sangkaew 2021, 9 studies, n=6229). Persistent vomiting also appeared to be a moderate-to-strong predictor based on two systematic reviews with very low certainty of evidence, with OR 2.57 (95% CI 1.4-4.73) (Htun 2021, 12 studies, n=296) to OR 5.57 (95% CI 3.04-10.2) (Yuan 2022, 3 studies, n=813). However, the definition of persistent vomiting in the WHO 2009 criteria for severe dengue, remains unclear.

Abdominal pain or tenderness

Abdominal pain or tenderness showed a moderate association, with low certainty of evidence, as a predictor for severe dengue, ranging from OR 1.85 (95% CI 1.46-2.33) (Yuan 2022, 33 studies, n=27727) to OR 2.02 (95% CI 1.74-2.35) (PAHO 2022, 87 studies, n=85769).

Mucosal bleeding

Mucosal bleeding (such as epistaxis, gum bleeding, hematuria, and melena) or bleeding that does not require transfusion, as defined in one systematic review[2], demonstrated a moderate association with severe dengue, ranging from OR 1.87 95% CI 1.23-2.84) (Sangkaew 2021, 4 studies, n=7057) to OR 3.34 (95% CI 1.6-6.98) (Htun 2021, 10 studies, n=48). Due to variations in inclusions and definitions of bleeding, the certainty of evidence for this association is very low.

Lethargy/restlessness and Impaired consciousness

Varying states of consciousness, ranging from lethargy and restlessness to impaired consciousness, showed moderate to strong associations in identifying patients at risk for severe disease, respectively, with low to very low certainty of evidence. Lethargy had a pooled effect estimate ranging from OR 2.56 (95% CI 1.517-4.329) (Yuan 2022, 8 studies, n=29412) to OR 4.32 (95% CI 1.86-10.04) (Htun 2021, 13 studies, n=464). Impaired consciousness had a pooled effect estimate ranging from OR 5.23 (95% CI 3.45-7.93) (PAHO 2022, 33 studies, n=76881) to OR 29.81 (95% CI 4.08-217.94) (Htun 2021, 5 studies, n=37).

Hepatomegaly

Hepatomegaly as a warning sign showed moderate to strong association in identifying patients at risk for severe dengue, ranging from OR 3.14 (95% CI 2.38-4.15) (PAHO 2022, 62 studies, n=25989) to OR 5.92 (95% CI 3.29-10.65) (Tsheten 2021, 47 studies).

Increasing hematocrit with decrease in platelet count

Progression to severe dengue was associated with increasing hematocrit along with a concurrent decrease in platelet count. The strength of association varied from moderate to strong, with OR 2.3 (95% CI 1.74-2.35) (PAHO 2022, 62 studies, n=17462) to OR 5.14 (95% CI 1.61-16.34) (Tsheten 2021, 7 studies). Both variables had very low certainty of evidence.

Severe organ involvement

Severe organ involvement as a criterion for severe dengue showed a moderate to strong association with the development of severe dengue. Acute renal failure had an effect estimate of OR 6.73 (95% CI 1.66-27.20) (PAHO 2022, 8 studies, n=4348).

Liver involvement, manifested as coagulopathy or increased transaminases, showed a moderate association as a predictor of severe dengue. The range of effect estimates was from OR 2.55 (95% CI 1.78-3.64) (PAHO 2022, 39 studies, n=18579) to OR 4.05 (95% CI 2.25-7.287) (Yuan 2022, 4 studies, n=366) and OR 2.83 (95% CI 1.59-5.04) (PAHO 2022, 10 studies, n=6895). Both factors had a very low certainty of evidence.

Other Clinical Factors

Thrombocytopenia

Thrombocytopenia showed varying associations (weak to strong) as a factor in identifying patients at risk for the development of severe dengue, with high heterogeneity observed across all systematic reviews. Subgroup analysis by age revealed varying effect estimates but a positive association with the development of severe dengue. Effect estimates ranged from OR 2.71 (95% CI 1.6-4.55) (Htun 2021, 18 studies, n=893) to OR 8.146 (95% CI 3.374-19.66) (Yuan 2022, 12 studies, n=1238).

Pregnancy

Pregnancy up to the 3rd trimester was moderately associated with severe dengue, with an effect estimate of OR 3.94 (95% CI 2.10-5.42) (PAHO 2022, 1 study, n=99).

Obesity and malnutrition

Obesity and malnutrition showed weak to no association as predictors of severe dengue, with effect estimates ranging from OR 0.76 (95% CI 0.41-1.40) (Tsheten 2021, 5 studies) to OR 1.38 (95% CI 1.10-1.73) (Zulkipli 2018, 15 studies, n=579).

Other constitutional symptoms

Other constitutional symptoms, such as headache (OR 0.84 (95% CI 0.7-1.0) (Htun 2021, 18 studies, n=2893), myalgia or arthralgia (OR 1.01 (95% CI 0.83,-1.24), Htun 2021, 17 studies, n=2949), rash or cutaneous eruption (OR 1.04, PAHO 2022, 14 studies, n=4314), and anorexia (OR 1.21 (95% CI 0.68-2.15), PAHO 2022, 8 studies, n=2089), were not associated with identifying patients at risk for the development of severe dengue. Similarly, the presence of purpura and ecchymosis had no association in identifying patients at risk for severe dengue (OR 1.21 (95% CI 0.96-1.52), PAHO 2021).

Subgroup analysis: Prognostic factors for pediatric populations

Several clinical and laboratory signs were identified as predictors of severe dengue in children based on the systematic review by Sandinirwan et al. 2023.[5] Of the clinical signs, neurological signs (i.e., varying manifestations of decreasing levels of consciousness) appeared to be the strongest predictor for severe dengue (OR 6.88

(95% CI 2.91-16.25), 7 studies, n/a). Unlike in adults, it was only in the pediatric population where the presence of petechiae showed an association with severe dengue. Other clinical signs that exhibited moderate strength of association with severe dengue were:

- hepatomegaly (OR 2.28 (95% CI 1.54-3.38); 16 studies, n=not reported)
- vomiting (OR 2.28 (95% CI 1.54-3.38); 16 studies, n=not reported)
- abdominal pain (OR 1.58 (95% CI 1.07-2.35); 12 studies, n=not reported)
- petechiae (OR 1.62 (95% CI 1.31-2.02); 5 studies, n=not reported; OR 1.57 (95% CI 1.1-2.25), n=not reported)

Laboratory markers found to be moderately associated with severe dengue in children included the following:

- elevated partial thromboplastin time [PTT] (OR 4.59 (95% CI 2.24-9.37;3 studies, n/a)
- increasing hematocrit (OR 3.14 (95% CI 2.03-4.85); 16 studies, n/a)
- elevated aspartate transferase [AST] (OR 3.08 (95% CI 2.18-4.36); 10 studies, n/a)
- elevated alanine transaminase [ALT] (OR 1.98 (95% CI 1.27-3.08); 9 studies, n/a)
- low platelet count (OR 1.76 (95% CI 1.50-2.06); 20 studies, n/a).

All reported ORs were based on very low to low certainty of evidence.

Safety Outcomes

None of the included studies in this review have specifically assessed the potential harms or adverse effects (e.g., number or proportion of patients incorrectly classified as having high risk for severe dengue) associated with using any of the identified prognostic factors for predicting dengue progression.

RECOMMENDATIONS FROM OTHER GROUPS

Other guidelines and groups also recommend using the WHO 2009 Dengue Case Classification and severity levels as a basis for in-hospital management of dengue. These guidelines also consider additional factors, such as environmental and social conditions, as well as the patient's ability to tolerate oral fluids, when making decisions about in-hospital management. These factors can provide valuable information for healthcare providers to determine the appropriate level of care and interventions needed for patients with dengue.

Table 2.2. Summary of recommendations from other groups.

Group or Agency	Recommendation	Strength of Recommendation/ Certainty of Evidence
PAHO 2022	For identifying patients at risk of progression to severe disease, it is suggested to use the following criteria for the hospitalization of dengue patients: • Dengue with criteria for warning signs 2009 WHO definition • Dengue with criteria for severe disease 2009 WHO definition • Oral intolerance • Difficulty breathing • Narrowing of pulse pressure • Arterial hypotension • Acute renal failure* • Prolonged capillary refill time • Pregnancy* • Coagulopathy*	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).
Malaysia Dengue CPG 2015	• Dengue with Warning Signs • Bleeding Manifestations • Inability to tolerate oral fluids • Reduced urine output • Seizure • Dehydration • Shock • Bleeding • Any Organ failure Special Situations • Patients with co-morbidity (diabetes, hypertension, ischemic heart disease, coagulopathy, morbid obesity, renal failure, chronic liver disease, COPD • Elderly >65 years old • Patients who are on anti-platelet and/or anticoagulants • Pregnancy • Social factors that limit follow-up e.g. living far from health facility, no transports, patient living alone, etc. Laboratory Criteria • Rising hematocrit accompanied by reducing platelet count	None

CERTAINTY OF EVIDENCE

The certainty of evidence regarding the reported estimates of association across various prognostic factors was assessed to be low to very low. This downgrading of evidence was commonly attributed to several reasons. First, high risk of bias was reported among the included studies across the systematic reviews. Serious inconsistency was also noted for some prognostic factors, particularly due to unclear definitions of variables across studies. Furthermore, serious imprecision was noted for studies that found a wide range of confidence intervals for the odds ratios.

ONGOING STUDIES AND RESEARCH GAPS

No studies were found specifically investigating the effectiveness and adverse effects of using prognostic factors / indices on hospitalization rates or clinical outcomes among patients with dengue. Current clinical practice related to hospitalization decisions is typically based on the physician's judgement of the overall clinical presentation, disease severity, and other patient-related factors.

There is growing interest in exploring the role of novel biomarkers and genetic factors as potential predictors of severe dengue infection and how these can provide additional insights into the pathogenesis of the disease. The utility of these new biomarkers for improving risk stratification and guiding clinical management decisions, including the need for hospitalization and intensive care, need further validation from well-designed cohort studies.

COST IMPLICATION

The inclusion of prognostic factors such as thrombocytopenia, elevated transaminases, and tests for coagulation as criteria for hospitalization in dengue management may indeed result in increased utilization of healthcare resources. This could have implications, particularly in the context of an epidemic or during periods of high healthcare demand.

The decision to hospitalize patients should consider various factors, including the severity of the disease, risk of complications, and the availability of resources. While these prognostic factors may provide valuable information in assessing disease severity and predicting the risk of progression to severe dengue, their utilization should be balanced with the overall healthcare situation.

During an epidemic or when healthcare resources are strained, healthcare systems may need to optimize resource allocation and prioritize cases based on the severity of illness and available capacity. This may require careful consideration of multiple factors beyond individual prognostic markers.

ETHICAL, SOCIAL AND HEALTH SYSTEMS IMPACT

In addition to clinical evaluation, several social and other factors may be considered in the management of patients with dengue fever, particularly when making decisions about hospitalization. These factors can provide important insights into the patient's overall health and circumstances that may impact their disease outcome. Some of these factors include:

1. Chronic use of anticoagulants: Patients on long-term anticoagulant therapy may require close monitoring and specialized care in a hospital setting due to the potential risk of bleeding complications associated with dengue.
2. Significant comorbid illness: Patients with underlying medical conditions, such as cardiovascular disease, respiratory disorders, or immunosuppression, may be at higher risk for severe dengue complications and may benefit from hospital-based management.
3. Limited access to the nearest healthcare facility: Patients who have limited access to healthcare facilities or live in remote areas may face challenges in accessing timely medical care. In such cases, hospitalization may be considered to ensure close monitoring and prompt intervention if needed.
4. Living alone: Patients who live alone and lack adequate support or caregiving resources may require hospitalization to ensure their safety and access to medical assistance.

These social factors, along with clinical assessment, can help healthcare providers make informed decisions about the appropriate level of care and management setting for patients with dengue fever. By considering these factors, healthcare professionals aim to provide optimal care and support tailored to the individual needs of each patient.

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QUESTION 3: Should regular complete blood count (CBC) determination be done to monitor disease progression and improve outcomes among dengue patients in the primary care setting?

Good Practice Statements:
For outpatients with suspected, probable, or confirmed dengue:

1. An initial CBC should be requested on the first visit to establish baseline hematocrit and platelet count.

2. Daily CBC determination may be done as part of disease monitoring.

3. Subsequent CBCs may be done based on the clinical course/presentation (e.g., volume status, urine output, temperature, ability to tolerate feeding, presence of warning signs).

4. CBC monitoring may be discontinued when the patient is in the recovery phase (e.g., increasing platelet count trends, 48 hours afebrile, adequate urine output, and improved sense of well-being/appetite).

KEY FINDINGS

No studies were found directly comparing the efficacy and safety of different schedules of CBC monitoring among patients with dengue. Evidence from 8 observational studies that mentioned a specific schedule of CBC monitoring among dengue-confirmed patients provided data on clinical outcomes.

The values of a complete blood count vary during the different phases of dengue infection. Thrombocytopenia was the most common hematological feature, and the decline is lowest at the critical phase or at the onset of defervescence. The hematocrit, on the other hand, displays an increasing trend during the critical phase of dengue or at the onset of defervescence. Most of the included studies, however, did not intentionally investigate the value of a daily CBC monitoring compared to a more frequent CBC determination. Only 1 study investigated sequential daily platelet counts to help identify patients at risk for shock.

CONSIDERATIONS DURING THE CONSENSUS PANEL MEETING

The steering committee suggested and the panel agreed to provide good practice statements instead of recommendations because of the absence of direct evidence to support a recommendation regarding the frequency of CBC determination. Consequently, the panel members suggested unanimously that baseline CBC for

outpatients with dengue infection should be done on the first visit, and that CBC should be done daily to monitor disease progression. Also, CBC monitoring should proceed or be stopped based on the clinical presentation.

However, CBC like other laboratory findings should not be used as a basis for admission and in-hospital management since clinicians should decide using clinical signs and symptoms instead. Although CBC will help clinicians correlate the severity of plasma leakage, CBC alone will not be able to tell if dengue patients are proceeding to critical phase.

BACKGROUND

The key to good clinical outcomes of dengue is early detection and a clear understanding of the clinical problems that may arise during the different phases.[1] The CBC parameters such as hemoglobin, hematocrit, WBC count, differential percentages of the WBCs, and platelet counts are dynamic throughout the course of dengue infection although certain patterns have been observed especially in relation to the fever. For example, more profound hemoconcentration and thrombocytopenia are usually observed before the lysis of fever and onset of shock.[2,4] Because thrombocytopenia and hemoconcentration have always been a common finding in dengue, serial daily platelet counts at the early stage of the disease may help identify patients who are likely to develop shock.[3]

The frequency of doing these tests is usually based on the clinician's discretion. [2,5] Thus, the advantage of doing more frequent (i.e., more than once a day) versus daily CBC monitoring in improving clinical outcomes remains to be established.

BENEFITS AND HARMS

Efficacy Outcomes

Based on two studies, those that were monitored daily, 57.7% were classified as dengue hemorrhagic fever and 12.6% progressed to dengue shock syndrome DSS[6] in one study; in another study, 48.2% were classified as dengue hemorrhagic fever and 11.6% progressed to DSS.[8] Both studies[6,8] showed increased circulating inflammatory proteins during febrile episodes can be used to predict progression to severe dengue infection. In 1 study, 6% of the population developed DSS and eventually recovered[3] and in another 33 (8.8%) developed shock and recovered.[7] Twenty-five percent had severe dengue in one study, 4% of which succumbed to death.[9]

In another study involving adult patients who were monitored less frequently (only Days 2, 3, 5), 64.66% progressed to DHF with thrombocytopenia noted at days 2-3

and declining significantly at day 5 yet no mention of death among those who had DHF.[10] Patients in 2 studies however were not classified to non-severe dengue and severe dengue.[2,5]

Bleeding is a common symptom of dengue fever, occurring in about 5.8% of cases and higher than the rate of bleeding in patients with other febrile illnesses.[2] Mucosal bleeding, such as bleeding from the gums, nose, or eyes, is seen in about 55% of dengue patients.[7] The risk of bleeding is higher in patients with dengue shock syndrome (DSS), with about 2% of patients with DSS experiencing bleeding.[3] In contrast, none of the patients in a study of non-severe dengue had bleeding.[9] These findings suggest that bleeding is a serious complication of dengue fever and should be monitored closely in all patients.

Safety Outcomes

None of the included observational studies reported on the incidence of adverse events associated with frequent CBC monitoring, such as rates of local inflammation, site bleeding, pain, site infection, among others.

In a 3-year study done on venipuncture in an outpatient setting on 4050 insurance applicants, bruising and hematoma were the top two most common reactions (12.3%) and these were followed by diaphoresis or near syncope. There were no serious local reactions observed in this study.[20] In one small case series, the potentially most serious adverse events associated with venipuncture relate to nerve injury.[21]

RECOMMENDATIONS FROM OTHER GROUPS

Frequency of CBC monitoring varies across guidelines depending on patients' clinical presentations. CBC monitoring may be done daily or every 3 days to observe and detect early disease progression.

Table 3.1. Summary of recommendations from other groups.

Group or Agency	Recommendation	Strength of Recommendation/ Certainty of Evidence
2009 World Health Organization (WHO) Dengue: Guidelines for Diagnosis,	**For ambulatory patients in the outpatient setting:** • Reviewed daily for disease progression until they are out of the critical period.	No available evidence base, strength of recommendation, and certainty rating

Treatment, Prevention, and Control[4]	**For patients in compensated shock:** • If with improvement after 1 hour of fluid resuscitation, monitor hematocrit every 6 to 8 hours. • If without improvement after 1 hour of fluid resuscitation, repeat hematocrit. If the hematocrit is high, give a second bolus of fluid and if hematocrit is low, consider overt bleeding. **For patients in hypotensive shock:** • If with improvement after 15 minutes of fluid resuscitation, monitor hematocrit every 6 hours. • If without improvement after 15 minutes of fluid resuscitation, repeat hematocrit every hour.	
2012 Ministry of Health Sri Lanka Guidelines on Management of Dengue Fever and Dengue Hemorrhagic Fever in Children and Adolescents.[17]	**For outpatients:** • First full blood count (FBC) should be done at least on the third day of fever/illness and daily thereafter if the platelet count is >150,000/ mm^3 and twice daily if the platelet count is <150,000/mm^3. • However, a FBC should be done on the first day of fever/contact during pregnancy and in patients with co-morbidities. **For inpatients with DF/DHF:** • FBC daily or twice daily if platelet <130,000/mm^3 and hematocrit once or twice daily **For inpatients in the critical phase:** • Regular hematocrit measurements (4-6 hourly) in non-shock patients and more regularly in patients who develop shock	No available evidence base, strength of recommendation, and certainty rating
2012 Ministry of Health Sri Lanka Guidelines on Management of Dengue Fever and Dengue Haemorrhagic	**For outpatients:** • First full blood count (FBC) should be done at least on the third day of fever/illness and daily thereafter if the platelet count is >150,000/ mm^3 and twice daily if the platelet count is <150,000/mm^3. • However, a FBC should be done on the first day of fever in pregnant	No available evidence base, strength of recommendation, and certainty rating

Fever in Adults [18]	patients and in patients with co-morbidities. **For inpatients who are clinically stable and DF/DHF is suspected:** • FBC on admission and then daily • FBC twice daily if platelet <130,000/mm^3 and hematocrit every 6 hours. **For inpatients in the critical phase:** • Do hematocrit every 3 hours or more.	
2014 Royal College Physician of Thailand Practical Guideline for Management of Dengue in Adults [19]	**For outpatients:** • CBC every 1-3 days **For inpatients:** • Hematocrit should be monitored 1-4 hours per day according to clinical presentations.	No available evidence base, strength of recommendation, and certainty rating

ONGOING STUDIES AND RESEARCH GAPS

Currently, there are no ongoing studies or clinical trials comparing the effects of different schedules of CBC determination among patients with dengue infection.

COST IMPLICATION

Based on estimates from local laboratories and hospitals, a complete blood count may cost between PHP 175-380.[11] Though widely available, more frequent CBC monitoring may incur more fees and misutilization of clinical laboratory testing can lead to increased health care costs.[15] In one study that assessed the direct costs of managing in-ward dengue patients in Sri Lanka, most money had been spent on laboratory investigations especially on full blood counts and it accounted for more than 50% of the total cost for hospitalized dengue patients. This study implies that frequent CBC monitoring may incur more costs.[16] No cost-effectiveness studies were found directly comparing different frequencies of CBC monitoring.

ETHICAL, SOCIAL AND HEALTH SYSTEMS IMPACT

There are no existing local studies on patients' perceptions or attitudes toward frequent blood extraction, particularly among dengue patients. One survey study in Turkey reported that 30.1% of the patients and 19.5% of the healthy adults reported that they had fear of blood/injection.[12]

More frequent CBC monitoring could also be more difficult in children than in adults. In a qualitative study from a Swedish pediatric hospital care, it stated that nurses are more challenged when blood samples are taken from children than from adults.[13] There is a need to build the children's confidence to ensure the blood sampling procedure went smoothly and more often the children's parents could interfere and make the nurse's relationship with the child difficult.[13] This was also supplemented with an American study investigating phlebotomist experiences that described anxious patients and parents as a primary problem in relation to blood sampling in children.[14]

CBC is widely available in most hospitals in the Philippines hence frequent CBC monitoring may be done in dengue patients.

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QUESTION 4: Should oral rehydration solution (ORS) be given to patients with mild dengue or dengue without warning signs to prevent disease progression?

Recommendation: Among patients with probable or confirmed dengue fever, we recommend the use of oral rehydration solution to prevent poor outcomes.
(Very low certainty of evidence, Strong recommendation)

KEY FINDINGS

Two studies were included in this evidence summary review on different types of oral rehydration therapy.

One observational study showed that oral hydration in patients with non-shock dengue hemorrhagic fever may be as effective as intravenous hydration in reducing the length of hospital stay – 2 days shorter. Results suggested that those given intravenous hydration may be more prone to fluid overload. The certainty of evidence is low to very low because of risk of bias and imprecision.

One RCT compared oral isotonic solution (OIS) versus water as therapy for patients with dengue. This study showed better tolerability for OIS and showed an increase in the fluid intake and a decrease in parenteral fluid administration after day 5 of the illness. The certainty of evidence is downgraded to low because of risk of selection bias.

CONSIDERATIONS DURING THE CONSENSUS PANEL MEETING

Based on evidence alone, there was a *weak* strength of recommendation because of the very low certainty of evidence regarding the effectiveness of oral rehydration. However, the panel decided to strongly recommend ORS for hydration of patients with mild dengue infections because of its potential to prevent disease progression to critical phase and poor outcomes, cheap cost, acceptability to most clinicians taking care of dengue, accessibility, and feasibility of implementation at the community level, with low anticipated related adverse events. It was also emphasized that the absence of evidence neither means it is not beneficial nor does it equate to harm.

BACKGROUND

The pathophysiology of dengue illness proceeds via two key processes: increase vascular permeability leading to vascular leakage and abnormal homeostasis due to vascular changes and thrombocytopenia.[1] Consequently, interventions directed to

address these processes would prevent complications like congestion and organ hypoperfusion; hence replacement of fluid losses is a priority in the management of dengue. However, the plasma leakage is transient and lasts only for 24 to 48 hours and should be taken in consideration so as not to cause fluid overload.[2]

BENEFITS AND HARMS

Efficacy and safety outcomes of oral rehydration therapy vs intravenous therapy

Length of hospital stay

The mean (±SD) length of hospital stay for patients given oral therapy was shorter at 5.3±2.2 days compared to 7.4±2.7 days in the intravenous therapy group (mean difference [MD] -2.10 days [95%CI -3.48 to -0.72 days]; *P*=0.007). Although this result was statistically significant, the certainty of this estimate is low due to the very serious risk of bias in the included study (non-randomized design, unclear assessor blinding, and unclear volume of fluids taken by the oral hydration group).[3]

Laboratory parameters

There were no significant differences in both group's mean pulse pressure, mean hematocrit level, and mean platelet count for the duration of the 7 days of hospital stay.[3] All the patients in this study survived.

Adverse events

Less patients developed pulmonary edema or pleural effusion in the ORS group (14/30 or 47%) compared to those in the oral hydration group (3/16 or 19%) (OR 0.26 [95%CI 0.06 to 1.12], P=0.07). The ORS group also was associated with less gall bladder swelling (43.8% vs 55.6%; OR 0.62 [95%CI 0.18 to 2.16], P=0.46), ascites (6.3% vs 11.1%; OR 0.53 [95%CI 0.05 to 5.61], P=0.60), or parenteral furosemide use (5.3% vs 16.7%; OR 0.28 [95%CI 0.03 to 2.59], P=0.26).[3] All differences were not statistically significant.

The certainty of this estimate is very low due to very serious risk of bias (non-randomized design, unclear assessor blinding, unclear volume of fluids taken by the oral hydration group, and exclusion of 3/19 patients in ORS group) as well as imprecision in the confidence intervals.

Efficacy and safety outcomes of oral isotonic solution vs water

Laboratory parameters

In the RCT comparing oral isotonic solution (OIS) to water[4], there were no significant differences in the hematocrit levels (P = 0.60) as well as the sodium (P = 0.707) and potassium levels (P = 0.581) for both groups. Effect estimates could not be calculated as the study did not report actual values for these laboratory parameters.

Fluid balance parameters

In terms of fluid balance parameters, patients in the OIS group had positive fluid balance and higher mean arterial pressure (MAP, P = 0.711), and became afebrile faster (Day 3) compared to those in the control group. However, the difference was deemed not significant. All patients were treated with parenteral hydration. The OIS group received fewer intravenous fluids (MD -457 mL [95%CI -1173 to 259 mL]) and a higher oral fluid intake (MD 194 mL [95%CI *not estimatable*]) compared to the control group.[4]

Adverse effects

The OIS group experienced less nausea and vomiting but had more bloating.[4] No actual values were reported. The certainty of evidence for all these estimates is very low due to serious risk of bias (reporting, lack of blinding), indirectness (did not compare ORS with IV), and imprecision (wide confidence intervals, small sample size).

Table 4.1. Benefits and harms of oral rehydration therapy among patients with dengue fever.

Critical Outcomes	Basis *(No. and type of studies, total participants)*	Effect Size	95% Confidence Interval	Interpretation	Certainty of Evidence
Length of hospital stay (number of days)	1 observational study (N = 49)	mean difference [MD] -2.10 days	[95%CI 3.48 to -0.72 days], P=0.007	Benefit	⊕◯◯◯ Very low

Table 4.2. Adverse events among patients given oral versus intravenous therapy.

Critical Outcomes	Basis *(No. and type of studies, total participants)*	Effect Size	95% Confidence Interval	Interpretation	Certainty of Evidence
Pleural effusion and/or pulmonary edema	1 observational study (N = 49)	OR 0.26	[95%CI 0.06 to 1.12], P=0.07	Benefit	⊕◯◯◯ Very low
Gallbladder swelling	1 observational study (N = 49)	(43.8% vs 55.6%; OR 0.62	[95%CI 0.18 to 2.16], P=0.46	Benefit	⊕◯◯◯ Very low
Ascites	1 observational study (N = 49)	(6.3% vs 11.1%; OR 0.53	[95%CI 0.05 to 5.61], P=0.60	Benefit	⊕◯◯◯ Very low
Patients receiving furosemide	1 observational study (N = 49)	(5.3% vs 16.7%; OR 0.28	[95%CI 0.03 to 2.59], P=0.26	Benefit	⊕◯◯◯ Very low

RECOMMENDATIONS FROM OTHER GROUPS

Table 4.3. Summary of recommendations from other groups.

Group or Agency	Recommendation	Strength of Recommendation/ Certainty of Evidence
WHO Dengue Guidelines (2009)[5]	**Encourages** patients with dengue fever with no warning signs to have adequate oral fluid intake with oral rehydration solution (ORS), fruit juice and other fluids containing electrolytes and sugar to replace losses from fever and vomiting.	Not mentioned
Pan American Health Organization (PAHO) Guidelines (2022)[6]	**Recommends** to use an intense oral hydration scheme in dengue patients to decrease the progression to severe forms and the appearance of disease complications. Additional considerations were given: • Implemented in primary care setting using various tools to	Strong recommendation (due to low cost, easy implementation, expected benefits especially in epidemic contexts)

	account for fluid intake (e.g., cups with volume quantification)
	• Intense hydration with oral rehydration salts for healthy adults: up to 3,000 ml per day
	• For pediatrics: apply Holliday-Segar formula plus 5%:
	  ○ 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
		Low quality of evidence (1 RCT, 3 observational)

National guidelines for clinical management of dengue fever, India[7]	Oral fluid and electrolyte therapy is **recommended** for patients with excessive sweating or vomiting. Oral rehydration solution (ORS) is preferable to plain water. For infants with dengue fever with no warning signs, oral rehydration with ORS, fruit juice, and other fluids containing electrolytes and sugar, together with breastfeeding or formula feeding is **encouraged**.	Not mentioned
Management of Dengue Infection in Adults Clinical Practice Guidelines (2015), Malaysia[8]	The home care card included in the guidelines mentioned the following: • Adequate fluid intake (more than 8 glasses or 2 liters for an average person). • Milk, fruit juice (caution with diabetes patient) and isotonic electrolyte solution (ORS) and barley water. • Plain water alone is not sufficient and may cause electrolyte imbalance.	Not mentioned
World Health Organization. Regional Office for South-East Asia. Guidelines for treatment of dengue fever/dengue hemorrhagic fever in small	Oral rehydration therapy is **recommended** for patients with moderate dehydration caused by vomiting and high temperature. In children, with signs of some dehydration, oral rehydration solution which is commonly used in the treatment of diarrheal diseases and/or fresh juices are preferable(50ml/kg bodyweight fluids	Not mentioned

hospitals (1999) [9]	should be given during the first 4-6 hrs. After correction of dehydration, the child should be given maintenance fluids orally at the rate of 80-100 ml/kg bodyweight in the next 24 hrs. Children who are breastfed should continue to be breastfed in addition to ORS administration. In adults, oral fluid intake of 2.5-4.0 liters should be given per day.	

A randomized controlled study done in Malaysia in 2017 compared the outcomes of patients who were given an outpatient fluid chart compared to a standard dengue home care treatment card. The treatment group was associated with fewer hospital admissions, lesser requirement for intravenous fluids, and higher average fluid intake. These effects, however, were not statistically significant. [10]

CERTAINTY OF EVIDENCE

The study by Lee et al. has a serious risk of bias (non-randomized design, unclear assessor blinding, unclear volume of fluids taken by the oral hydration group, exclusion of 3/19 patients in ORS group) as well as imprecision in the confidence intervals. The study by Nainggolan et. al has a low certainty of evidence due to selection bias and unavailability of some data which were presented as a chart format in the study. Overall certainty of evidence is downgraded to low.

ONGOING STUDIES AND RESEARCH GAPS

There are no ongoing research studies on dengue fever and oral rehydration therapy. Possible research gaps include what type of oral fluids to use and the amount needed to prevent poor outcome. More studies comparing oral therapy to the standard IV therapy are also needed.

COST IMPLICATION

Costs of the intervention

An oral rehydration salt solution costs PHP 15.40 to 17.50 per sachet in pharmacies.[11] The Department of Health Drug Price index priced it at PHP 3.64 per sachet. One sachet is dissolved in 200 mL of water. Five sachets dissolved in one liter of water will provide the following which is consistent with the latest WHO and UNICEF recommendations of reduced osmolarity ORS: Sodium 75 mmol, Potassium 20 mmol, Chloride 65 mmol, Citrate 10 mmol, Glucose 75 mmol, Total Osmolarity 245 mmol.

Cost-effectiveness studies

There are currently no local cost-effective studies on oral rehydration use in dengue fever.

ETHICAL, SOCIAL AND HEALTH SYSTEMS IMPACT

A systematic review done by Ezekika et. al. described the barriers in the implementation of oral rehydration therapy (ORT) in low-to -middle income countries. Successful implementation was dependent on the availability and accessibility of the oral rehydration therapy (supply and demand in the community setting and costs), awareness and education among communities (awareness of what oral rehydration therapy is and training of health workers), strong partnership engagement strategies (external entities that work to increase ORT uptake), and adaptable design to enhance acceptability (existence of other treatments, more culturally adapted designs of ORT, acceptance amongst communities and taking cultural norms into account).[12]

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QUESTION 5: Should acid suppressants be used among probable or confirmed dengue patients to prevent abdominal pain or gastrointestinal bleeding?

Recommendation: Among patients with confirmed or probable dengue fever, we recommend against the use of acid suppressants for the prevention of gastrointestinal bleeding or abdominal pain. ***(Very low certainty of evidence, Strong recommendation)***

KEY FINDINGS

There were no randomized controlled trials or observational studies that examined the efficacy of acid suppressants in preventing abdominal pain or gastrointestinal bleeding in patients with confirmed or probable dengue. One observational study showed the incidence of diarrhea at 7.4% among dengue patients receiving omeprazole. The certainty of evidence is very low due to very serious issues on imprecision, risk of bias, and indirectness.

CONSIDERATIONS DURING THE CONSENSUS PANEL MEETING

The panel reached consensus on recommending against the use of omeprazole in preventing abdominal pain or gastrointestinal bleeding in dengue patients, but initially disagreed on the strength of recommendation. A weak recommendation was suggested, based on the premise that dengue patients may have concurrent or associated peptic diseases which may warrant the use of acid suppressants. In such cases, a weak recommendation may give clinicians more flexibility in deciding whether or not to give PPI / H2RA drugs to dengue patients. On the other hand, a strong recommendation against its use was lobbied primarily due to the lack of evidence of its efficacy and based on the pathophysiology of how abdominal pain precipitates in dengue patients and the possible adverse reactions following omeprazole use. Literature would suggest various gastrointestinal diseases that may exist synchronously with dengue infection[2,4] that leads to abdominal pain, not all of which can/should be treated with acid suppressants. Essentially, the mechanisms that result to these conditions that cause abdominal pain in dengue converge to vascular leakage leading to organ hypoperfusion, fluid retention causing organ congestion, or abnormal hemostasis for the bleeding. Hence, the use of acid suppressants will not directly relieve abdominal pain. Consequently, the use of PPI and H2RAs may provide clinicians a false sense of security in managing the abdominal pain leading to laxity in disease monitoring. Moreover, adverse events like hypersensitivity, anaphylaxis, and bacterial translocation are seen in critically ill patients with acid suppressant use. All these, on top of additional expenses and potential drug interactions, convinced the panel to give a strong recommendation against their use.

BACKGROUND

As many as 55-100% of patients with dengue fever develop abdominal disturbances throughout the disease, with nausea and pain identified as the most common abdominal symptoms reported.[1,2] The incidence of abdominal pain and upper gastrointestinal bleeding vary across different studies, with reports of 25-100% and 1-40%, respectively.[1,3] Although the most common endoscopic findings in dengue patients were hemorrhagic gastritis, gastric ulcer, and duodenal ulcer4,other etiologies for the abdominal symptoms in dengue were also attributed to several diseases associated with this virus, such as acute hepatitis, acute acalculous cholecystitis, enteritis, acute appendicitis, and pancreatitis.[2]

The use of acid suppressants such as proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2-blockers) have been widely used in the management of dengue patients for stress ulcer prophylaxis because of the thrombocytopenia brought about by the disease.[5-7] H2-blockers inhibit the histamine type-2 receptors on the stomach's acid-producing cells or parietal cells. The more effective gastroprotective drug, proton pump inhibitors, suppress acid production by interfering with the enzymes responsible for producing acid, the H+-K+-ATPase enzymes.[8] Determining the efficacy and safety of acid suppressants in dengue patients is needed, especially since dengue fever has been cited in literature as the most common diagnosis for inappropriate use of proton pump inhibitors.[6]

BENEFITS AND HARMS

No randomized controlled trials or observational studies have investigated the efficacy of acid suppressants in preventing abdominal pain or gastrointestinal bleeding in confirmed or probable dengue patients.

The incidence of diarrhea among dengue patients with omeprazole was 7.4%. Two of the 42 patients (4.8%) with a platelet count of >50,000/mm^3 reported diarrhea, which was lower than those who had a platelet count of <50,000/mm^3 (4/39 or 10.3%), although the difference was not significant (RR 0.46, 95% CI 0.09 to 2.39, p =.36) as shown in Table 5.1.

Table 5.1. Incidence of diarrhea with omeprazole as intervention among dengue patients.

Outcomes	Basis	Effect Estimate	95% Confidence Interval	Interpretation	Certainty of Evidence
Diarrhea	1 observational (81 patients)	0.46	(0.09 – 2.39)	Inconclusive	Very Low ⊕◯◯◯

RECOMMENDATIONS FROM OTHER GROUPS

No other groups or agencies have recommended the use of proton pump inhibitors or H2-blockers specifically for the prevention of abdominal pain and gastrointestinal bleeding in patients with dengue. The Royal College Physician of Thailand recommended against the use of H2-blockers in dengue fever.[10]

CERTAINTY OF EVIDENCE

The included study had high risk for selection bias, as the inclusion and exclusion criteria were not clear. There was no mention of the dose, frequency, and duration of omeprazole and the components of the total cost of hospitalization. There was data regarding the follow-up period for observation of diarrhea, there was a high possibility of confounding because other variables that could affect the incidence of diarrhea were also not controlled.

Overall certainty of evidence was downgraded to very low because of indirectness, risk of bias, and imprecision, however, it was the best available evidence during the search. The study did not have a control group that did not receive omeprazole prophylaxis, but rather two groups of dengue patients with different platelet counts.

ONGOING STUDIES AND RESEARCH GAPS

There are no ongoing clinical trials or observational studies regarding PPIs and H2-blockers on patients with probable or confirmed dengue fever. The use of proton pump inhibitors in dengue fever has been cited in literature as one of the most common reasons for inappropriate PPI use.[6] Studies on the efficacy, safety, cost-effectiveness of these acid suppressants on dengue patients are needed.

COST IMPLICATION

The study by Marvel, et al. (2019) in Indonesia evaluated the difference in the cost of treatment between two groups of dengue patients who were prescribed omeprazole as prophylaxis.[9] The patients in the first group (noncriteria group) had a platelet count of >50,000/mm^3 and the second group (criteria group) had a platelet count of <50,000/mm^3. The median total maintenance cost is Indonesian rupiah (IDR) 1,109,195 (PHP 4,017.27) and 1,261,958 (PHP 4568.84) for the two groups, respectively. The total cost of omeprazole for all patients was IDR 13,072,446 (PHP 47,345.68) for the noncriteria group and IDR 12,247,686 (PHP 44,358.57) for the criteria group. Platelet count did not have a significant effect on the total cost (OR 1.19 [95% CI 0.45 to 3.15), and cost of omeprazole (OR 1.18 [95%CI 0.47 to 2.99]).

There are no local studies done on the cost-effectiveness of omeprazole. The table below summarizes the cost of acid suppressants available in the Philippine National Formulary (PNF) and corresponding drug price index as of 2022.

Table 5.2. Acid Suppressant costs in the Philippines.

Drug	Price Range	2022 DPRI, DOH[11]
H2-Blockers		
Famotidine 20mg powder for injection vial	121.78 - 134.03	133.96
Ranitidine 150mg tab	2.50 - 3.00	3.30
Ranitidine 25mg/mL 2ml solution for injection	1.20 -23.78	23.78
Ranitidine 300mg tablet	2.47 - 3.00	3.15
Proton Pump Inhibitors		
Lansoprazole 30mg/cap	7.00 - 10.00	7.70
Omeprazole 20mg cap	0.66-19.19	19.10
Omeprazole 40mg Cap	2.80 - 87.37	87.30
Omeprazole 40mg Powder for injection	19.39 - 335	335
Pantoprazole 20mg enteric coated tab	20-22.00	22.00
Pantoprazole 40mg tab	8.00 - 20.00	20.00

ETHICAL, SOCIAL AND HEALTH SYSTEMS IMPACT

No studies were found regarding patients' values and preferences regarding the use of acid suppressants in the prevention of abdominal pain or gastrointestinal bleeding specifically on confirmed or probable dengue cases.

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QUESTION 6: Should acid suppressants be used to treat abdominal pain or gastrointestinal bleeding among probable or confirmed dengue patients?

Recommendation:
Among patients with dengue fever, we recommend against the use of acid suppressants for the treatment of gastrointestinal bleeding or pain.
(Very low certainty of evidence, Strong recommendation)

KEY FINDINGS

No published randomized controlled trials or observational studies evaluating the efficacy of acid suppressants in treating gastrointestinal pain or bleeding among patients with confirmed dengue was found. Findings from an observational study investigating factors related to increased risk of mortality among dengue patients showed that patients who were given acid suppressants had the same mortality odds as those who were not (OR 0.98, 95% CI 0.52 to 1.85). Significant harm in terms of thrombocytopenia or platelet count of <50,000 $\times 10^9$/dL was observed for both proton pump inhibitors (OR 1.78, 95% CI 1.54 to 2.06) and H2 receptor antagonists (OR 1.96, 95% CI 1.60 to 2.39). The overall certainty of evidence for these effects was rated very low due to serious risk of bias, indirectness, and imprecision.

CONSIDERATIONS DURING THE CONSENSUS PANEL MEETING

Despite the very low certainty of evidence, a strong recommendation was made by the panel against the use of acid suppressants because of the incompatibility of mechanism of action of the drugs with the pathophysiology of abdominal pain in dengue infection, i.e. vasculitis and gastrointestinal bleeding, lack of evidence of efficacy and significant harm associated with the intervention. Similar reasons as stated in the previous recommendation on the preventive use of acid suppressants for dengue infections were mentioned.

BACKGROUND

Dengue patients have an increased risk of gastrointestinal bleeding within 30 days of disease onset,[2] with 11.8% presenting as hematemesis and/or melena.[1] A local study among 517 hospitalized dengue patients showed that gastrointestinal bleeding occurred in about 12.5% of patients.[5] Endoscopically, hemorrhagic gastritis, gastric and duodenal ulcers, and esophageal ulcers are among the common manifestations.[4] Aside from bleeding and ulcerations, abdominal pain from underlying causes such

acute hepatitis, and acute acalculous cholecystitis accounts for 40% of dengue patients.[3]

Due to these clinical presentations, the use of acid suppressant therapy using proton pump inhibitors and H2 receptor blockers or antagonists have been used as treatment regimens for these dengue complications. PPIs block gastric acid secretion by irreversibly binding to and inhibiting the H^+-K^+ ATPase pump.[6] Meanwhile, H2RAs decrease acid secretion by binding reversibly to histamine H2 receptors in the gastric parietal cells[7], consequently making these acid suppression therapy effective against acid-related gastrointestinal bleeding.

Hence, it has been common practice to use acid suppression therapy among dengue patients with GI bleeding[8] with about 11.7% to 95% of patients receiving PPI or H2RA ranitidine during the course of treatment.[10,11,12] However, in contrast to this practice, an Indian study has cited dengue fever as the most common condition for inappropriate use of proton pump inhibitors, therefore it is important to determine the evidence-based efficacy and safety of using acid suppressants as treatment for dengue patients.[9]

BENEFITS AND HARMS

None of the studies measured efficacy outcomes such as resolution of abdominal pain or cessation of gastrointestinal bleeding.

Similar mortality rates were observed among patients given PPI versus those who were not (24.1% vs. 24.5%; OR 0.98, 95% CI 0.52 to 1.85, N=206).[13] The odds of thrombocytopenia was higher among dengue patients given PPI (50.8% vs. 36.7%, OR 1.78, 95% CI 1.54 to 2.06 for platelet count <50,000/mm^3; OR 1.83, 95% CI 1.53 to 2.19 for platelet count <100,000/mm^3).[14]

Among patients given H2RAs, increased odds of thrombocytopenia were also found (OR 1.96, 95% CI 1.60 to 2.39 for platelet count <50,000/mm^3; OR 1.91, 95% CI 1.47 to 2.49 for platelet count <100,000/mm^3). Outcomes of proton pump inhibitor and H2RA as compared to no intervention are shown in Table 6.1.

Table 6.1. PPI vs no PPI and H2RA vs no H2RA in treatment of dengue fever.

Critical Outcomes	Basis *(No. and type of studies, total participants)*	Effect Size	95% Confidence Interval	Interpretation	Certainty of Evidence
Mortality (PPI vs no PPI)	1 observational	OR 0.98	0.52 to 1.85	Inconclusive	⊕◯◯◯ Very low

	study (n=206)				
Thrombocytopenia platelet count <50,000 (PPI vs no PPI)	1 observational study (n=4005)	OR 1.78	1.54 to 2.06	Harm	⊕◯◯◯ Very low
Thrombocytopenia platelet count <50,000 (H2RA vs no H2RA)	1 observational study (n=4005)	OR 1.96	1.60 to 2.39	Harm	⊕◯◯◯ Very low
Thrombocytopenia platelet count <100,000 (PPI vs no PPI)	1 observational study (n=4005)	OR 1.83	1.53 to 2.19	Harm	⊕◯◯◯ Very low
Thrombocytopenia platelet count <100,000 (H2RA vs no H2RA)	1 observational study (n=4005)	OR 1.91	1.47 to 2.49	Harm	⊕◯◯◯ Very low

RECOMMENDATIONS FROM OTHER GROUPS

Table 6.2. Summary of recommendations from other groups.

Group or Agency	Recommendation	Strength of Recommendation/ Certainty of Evidence
Ministry of Health Malaysia 2009	Other supportive/symptomatic treatments: Upper Gastrointestinal Bleeding: Ranitidine IV 1mg/kg/8hourly (50mg IV TID in adults) or Pantoprazole.	Not stated
Ministry of Health Sri Lanka 2012	Tranexamic acid can also be used together with proton pump inhibitors in gastric bleeding in DHF	Not stated
Royal College Physician of Thailand 2015	Avoid use of H2 blockers	Not stated
WHO Handbook for Clinical Management of Dengue 2012	In gastrointestinal bleeding, H-2 antagonist and proton pump inhibitors have been used, but their efficacy has not been studied.	Not stated

CERTAINTY OF EVIDENCE

The overall certainty of evidence on the efficacy and safety of acid suppressants was very low due to serious risk of bias, indirectness, and imprecision. For both studies, the estimated adverse effects may not be attributed solely to the use of acid suppressants as statistical adjustments for other confounding factors were not performed. In addition, no standard follow-up duration for measuring thrombocytopenia was specified in the study by Adrizain at al.[14] Efficacy could not be determined as the two studies did not report on the number of patients with abdominal pain or gastrointestinal bleeding.

ONGOING STUDIES AND RESEARCH GAPS

There are no ongoing clinical trials on acid suppressants for treating gastrointestinal bleeding or abdominal pain specifically in patients diagnosed with dengue fever. Further research is needed to evaluate its efficacy and safety to make more evidence-based recommendations.

COST IMPLICATION

Acid suppressants are widely available in all pharmacies and drugstores nationwide. According to the 2022 Philippine Drug Price Reference Index (DPRI)[19], the cost of oral PPIs range from PHP 0.66 to 87.30 (omeprazole 20mg and 40mg tablets), while for H2RA, it ranges from PHP 2.47 to 3.00 (150mg and 300mg tablets of ranitidine). For the intravenous preparations, cost estimates range from PHP 19.39 to 335.00 for omeprazole (40mg/vial) and PHP 23.78 to 134.00 for H2RA (ranitidine 25mg/2ml ampule and famotidine 20mg/vial).

ETHICAL, SOCIAL AND HEALTH SYSTEMS IMPACT

No studies were found on the cost-effectiveness, patients values and preference, equity, acceptability, and feasibility of recommending acid suppressants as treatment for dengue patients.

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QUESTION 7: Should herbal medicines available locally be used to treat probable or confirmed dengue patients?

Recommendations:

- Among patients with confirmed dengue infection, we **suggest giving** papaya (*Carica papaya*) leaf extract or juice preparations as a supplement to standard therapy. **(*Very low certainty of evidence, Weak recommendation)***

- Among patients with confirmed dengue infection, we **suggest against** giving tawa-tawa (*Euphorbia hirta*) preparations as a supplement to standard therapy due to insufficient evidence. **(*Very low certainty of evidence, Weak recommendation)***

- Among patients with confirmed dengue infection, we **recommend against** giving guava (*Psidium guajava*) preparations as a supplement to standard therapy due to insufficient evidence (lack of clinical trials in humans). **(*No evidence, Strong recommendation)***

KEY FINDINGS

There were 11 RCTs that investigated the effect of papaya leaf extract compared to standard therapy or placebo as treatment for patients with dengue fever. Papaya leaf extracts show benefit in terms of (a) preventing severe dengue by increasing platelet counts by day 5 of treatment; (b) decreasing duration of illness; (c) decreasing fever duration; (d) decreasing length of hospital stay; and (e) reducing the risk of requiring platelet transfusion.

In contrast, four RCTs showed that there were no significant differences found between papaya leaf extracts and controls on the hematocrit levels of dengue patients, while one RCT showed only inconclusive results regarding risk reduction of pleural effusion versus controls. Moreover, aside from gastrointestinal disturbances such as nausea and vomiting, there were no serious adverse events associated with use of papaya leaf extracts.

The largest trial among the included studies had a high risk of bias in the randomization process, and another trial had a high risk of bias in the deviation from intended interventions. Most studies had some concerns over outcome measurements and selection of reported results. Subgroup analysis results were unlikely to explain the significant statistical heterogeneity of the results, although the general direction of effect estimates remained positive. These issues contributed to the downgrading of the certainty of evidence to very low.

Only one observational study was found that investigated tawa-tawa, and it showed no difference in platelet counts from day 2 to day 10 of illness between dengue fever patients who used tawa-tawa versus those who did not. No other outcomes were reported. Imprecision and serious risk of bias issues contributed to the downgrading of evidence to Very Low certainty of evidence.

Meanwhile, only pre-clinical studies were found for the use of guava in dengue fever.

CONSIDERATIONS DURING THE CONSENSUS PANEL MEETING

Issues were raised regarding the standardization of the herbal medicine preparations – dosage formulations, capsule versus tea preparations, and frequency and duration of use. There are no known standard formulations available commercially aside from a mixed formulation of papaya with other herbal medicines that are not specifically intended for use against dengue infections. Nevertheless, there are suggested dosage formulations of papaya cited in the systematic reviews. The consensus panel noted the use and availability of tea preparations of tawa-tawa among their patients.

Although evidences from RCTs for *Carica papaya* had been downgraded to a very low certainty because of issues of bias and heterogeneity, there is still suggested net benefit. Hence the consensus panel decided that it is worth recommending to patients to prevent severe dengue, particularly in patients presenting with thrombocytopenia. Nonetheless, a weak recommendation was given, since it could be overcome by other results of similar studies in the future.

As opposed to the use of papaya, the use of tawa-tawa has a weak recommendation against its use because of the very low certainty of evidence owing to the lone study used in the review which yielded inconclusive results.

Similarly, the panel unanimously decided to recommend against the use of guava as herbal medicine for treating dengue infection due to insufficient evidence, specifically the lack of human clinical trials. However, since available pre-clinical trials are suggesting potential benefit and shows no evidence regarding its harm, some of the consensus panel members gave a weak recommendation. Meanwhile, some suggested a strong recommendation against its use on account of the absence of objective evidence of its benefit. A consensus was reached to give a weak strength of recommendation to reflect a temporary recommendation until new evidence becomes available.

BACKGROUND

Since dengue has no specific drug available for treatment, patients often ask clinicians whether they can take traditional medicines to prevent worsening of dengue infection. In literature, available herbal medications in the Philippines include tawa-tawa, papaya, and guava.

There are several studies looking into the potential therapeutic effect, biological safety, and herb-drug interactions of papaya (*Carica papaya*) leaf juice or extract, which attracted widespread interest from researchers.[1-6] Similarly, tawa-tawa (*Euphorbia hirta*), a slender-stemmed annual pantropical plant, has had folkloric and anecdotal uses for dengue documented throughout the Philippines.[7] Various studies have been conducted, mostly involving ethnopharmacological and ethnobotanical surveys, in vitro assays, and animal (in vivo) studies.[8] The potential use of guava (*Psidium guajava*) for dengue may be illustrated by in vitro and in silico studies involving the anti-DENV effects of guava compounds[9] and guava nectars for mosquito baiting.[10] As such, there is a growing need to review evidence of the treatment effects of these herbal medications in the management of dengue fever.

BENEFITS AND HARMS

Papaya (*Carica papaya*)

Platelet count increase (Day 5 of treatment)

Based on eight RCTs (n=640), participants who were supplemented with *Carica papaya* showed a statistically significant increase in platelet counts on Day 5 of treatment compared to standard care or placebo (MD 45.81 × 10^9/L, 95% 14.42 to 77.20, p=0.004). However, the clinical significance of a 45.81 × 10^9/L platelet count increase may still be subject to a physician's judgment depending on the dengue patient's case.

To explore the significant heterogeneity of results (Tau^2=1965.67, I^2=99%) discovered during this review, planned subgroup analysis by participant age was done. Based on adult studies (7 out of 8; n=991), increase in platelet counts on Day 5 of treatment with *Carica papaya* versus control remained statistically significant (MD 43.15 × 10^9/L, 95% 7.96 to 78.33, p=0.02), but still with significant heterogeneity (Tau^2=2161.85, I^2=99%). Similarly, the sole pediatric study (n=285) still showed a statistically significant mean difference between intervention and control (MD 63.87 × 10^9/L, 95% 51.80 to 75.94, p<0.001).

It was unlikely that other subgroup analysis results can explain the significant statistical heterogeneity of results (*i.e.*, whether subgrouping by study location, RCT type, population age, dengue status, intervention type and duration, and control), although the general direction of effect estimates remain positive.

Subgroup analysis by risk of bias assessments revealed that pooling studies (n=816) excluding those with high risk of bias, the mean difference in platelet counts were less deflated (MD 54.72 × 10^9/L, 95% 30.37 to 79.07, p<0.001), but still with significant heterogeneity (Tau^2=923.71, I^2=94%). Analyzing studies with high risk of bias (n=460) show inconclusive results (MD 21.59 × 10^9/L, 95% -3.04 to 46.23, p=0.09) with significant heterogeneity (Tau^2=291.81, I^2=92%).

Effect on hemoconcentration (hematocrit changes)

Although specific hematocrit values were not completely reported in most of these studies, based on four RCTs (n=530), there was no significant difference in hematocrit values observed between those given *Carica papaya* versus control.

Recovery time of dengue fever

Only one RCT (n=119) reported on the outcome of improved recovery time of dengue fever, in which those given *Carica papaya* had a shorter mean duration of illness compared to standard therapy alone (MD -0.45 days, 95% -0.88 to -0.02, p=0.04).

Duration of fever

Similarly, the same RCT (n=119) reported on the outcome of improved duration of symptoms, in which those in the intervention group had a shorter duration of fever compared to controls (MD -1.13 days, 95% -1.70 to -0.56, p<0.001).

Length of hospitalization

Five RCTs on adults (n=749) reported on length of hospital stay (n=359), demonstrating a significant difference in reducing length of hospitalization among those supplemented with *Carica papaya* compared to controls (MD -1.50 days, 95% CI -2.23 to -0.77, p<0.001), but with significant heterogeneity (Tau^2=0.66, I^2=96%). No pediatric studies reported this outcome.

Subgroup analysis by risk of bias assessments revealed that pooling studies (n=349) excluding those with high risk of bias, the length of hospitalization was minimally less inflated (MD -1.42 days, 95% -2.55 to -0.28, p=0.01), but still with significant heterogeneity (Tau^2=1.30, I^2=97%). Analyzing the study with high risk of bias (n=400) show slightly inflated results (MD -1.77 days, 95% -1.96 to -1.58, p<0.001).

Risk of developing pleural effusion

Only one RCT (n=119) reported on the prevention of dengue complications among adults initially presenting with dengue fever. Two out of 43 patients (4.65%) in the *Carica papaya* group while 12 out of 76 patients (15.79%) in the control group

developed pleural effusion. There was no statistically significant difference in the risk of developing pleural effusion between these groups (RR 0.29, 95% CI 0.07 to 1.26, p=0.10).

Risk of requiring platelet transfusions

Four RCTs (n=850) reported on the risk of requiring platelet transfusions for severe forms of dengue. It was found that those who received *Carica papaya* would be 36% less likely to require platelet transfusions for severe forms of dengue based on pooled estimates (RR 0.64, 95% CI 0.41 to 0.99, p=0.04), with moderate heterogeneity (Tau^2=0.08, I^2=45%).

Safety outcomes

Only seven RCTs (n=893) reported adverse events within each patient admission (from admission until discharge; mean: 5 days). No serious adverse events were reported throughout these studies.

Two of these studies (n=130) only provided a descriptive narration of adverse events, in which nausea and vomiting were seen in both intervention and control groups. Although no specific distribution was mentioned, one (1) large adult study (n=300) reported 26 cases of nausea and 17 cases of vomiting. The study stated that these cases were similarly distributed in both intervention and control groups, deemed by the investigators as unrelated to the intervention. One (1) large pediatric study (n=294) noted only 2 cases of nausea in those who received *Carica papaya* syrup. Three (3) RCTs (n=169) reported no adverse events for either intervention or control groups. Data could not be pooled due to inadequate data provided.

Table 7.1. Benefits and harms of *Carica papaya* vs placebo/standard therapy for patients with probable or confirmed dengue fever.

Critical Outcomes	**Basis** *(No. and type of studies, total participants)*	**Effect Size**	**95% Confidence Interval**	**Interpretation**	**Certainty of Evidence**
Prevention of severe dengue (platelet count increase on Day 5 of treatment)	8 RCTs (n = 1,276)	MD 45.81	14.42, 77.20	Benefit	⊕◯◯◯ Very low
Prevention of severe dengue (effect on hemoconcentration)	4 RCTs (n = 530)	There was no significant difference in hematocrit values observed between those given *Carica*		Inconclusive	⊕⊕◯◯ Low

		papaya versus control.			
Recovery time of dengue (mean duration of illness)	1 RCT (n = 119)	MD -0.45	-0.88, -0.02	Benefit	⊕⊕◯◯ Low
Duration of symptoms (mean duration of fever in the hospital)	1 RCT (n = 119)	MD -1.13	-1.70, -0.56	Benefit	⊕⊕◯◯ Low
Length of hospitalization	5 RCTs (n = 749)	MD -1.50	-2.23, -0.77	Benefit	⊕◯◯◯ Very low
Preventing complications (incidence of pleural effusion)	1 RCT (n = 119)	RR 0.29	0.07, 1.26	Inconclusive	⊕◯◯◯ Very low
Preventing complications (risk of requiring platelet transfusions)	4 RCTs (n = 850)	RR 0.64	0.41, 0.99	Benefit	⊕⊕◯◯ Low
Adverse events	7 RCTs (n = 893)	No serious adverse events were reported throughout the studies. Only adverse effects such as nausea and vomiting were observed, similarly distributed in both intervention and control groups.		Inconclusive	⊕⊕◯◯ Low

Tawa-tawa (*Euphorbia hirta*)

Only one study (n=93) reported on the comparison of mean platelet counts between patients who took tawa-tawa versus those who did not. Mean platelet counts from Day 2 of illness (tawa-tawa: 125.12 × 109/L vs. control: 189.75 × 109/L) up to Day 10 of illness (tawa-tawa: 113.23 × 109/L vs. control: 131.60 × 109/L) were not significantly different between the two groups by independent t-test (see Appendix 5.7.2 for complete trends). There were no other outcomes reported in this study. No safety outcomes were reported in the included observational study.

Table 7.2. Benefits and harms of *Euphorbia hirta* vs placebo/standard therapy for probable or confirmed patients with dengue fever.

Critical Outcomes	Basis *(No. and type of studies, total participants)*	Impact	Interpretation	Certainty of Evidence
Prevention of severe dengue (platelet count increase on Day 2-10 of illness*)	1 observational study (n = 93)	Mean platelet counts from Day 2 to Day 10 of illness were **not significantly different** between those who took tawa-tawa anytime during the illness and those who did not by independent t-test.	Inconclusive	⊕◯◯◯ Very low

**Tawa-tawa intake by the intervention group varied in the preparation, dosage, frequency, timing, and duration*

Guava (*Psidium guajava*)

There were no published human trials for the use of guava in dengue fever. Search results yielded pre-clinical studies only.

RECOMMENDATIONS FROM OTHER GROUPS

The guideline from the Ministry of Health in Malaysia gave no recommendations on the use of herbal medicine for dengue fever because of insufficient evidence on safety and efficacy (Table 7.3).

Table 7.3. Summary of recommendations from other groups.

Group or Agency	Recommendation	Strength of Recommendation/ Certainty of Evidence
Ministry of Health Malaysia[26] (2020)	There is no evidence on the safety and efficacy of traditional and complementary medicine (*e.g.*, papaya leaf extracts and crab soup) to support its use in the treatment of dengue in children.	Not indicated

CERTAINTY OF EVIDENCE

The overall certainty of evidence ranged from low to very low across the different efficacy outcomes and low for safety outcomes.

For the outcome of prevention of severe dengue (platelet count increase by Day 5 of treatment), the largest trial among the included studies had a high risk of bias in the randomization process,[18] and one trial had a high risk of bias in deviation from intended interventions.[15] There were also some concerns over outcome measurements and reported result selection for some of the studies. Considerable heterogeneity of results was also observed for this outcome. Similar concerns were found for the outcome on the length of hospital stay (except for the deviation from intended interventions as that study[15] did not reflect this outcome). Certainty of evidence was then downgraded to very low due to these issues.

For the included study[25] under the outcomes of dengue recovery time and symptom duration, there were some concerns over missing data due to dropouts in the study as well as not meeting the optimal information size. These concerns led to the downgrading of the certainty of evidence to low. Similar issues were found for the outcome on prevention of pleural effusion as a complication, with the addition that the confidence interval around the effect estimate was wide. This added issue further led to the downgrading of the certainty of evidence to very low.

For the outcome on the risk of requiring platelet transfusion, similar issues on the high risk of randomization bias[18] and some concerns over the measurement of outcomes and reported result selection were found. This led to the downgrading of the certainty of evidence to low. Serious concerns over risks of bias and imprecision for the effect on hemoconcentration and adverse events outcomes led to the downgrading of the certainty of evidence to low.

ONGOING STUDIES AND RESEARCH GAPS

There are trials reported in registers that have yet to recruit participants, exploring the effect of *Carica papaya* leaf extracts on dengue fever versus standard therapy[29,30] or versus placebo.[31,32] Outcomes mainly focus on improvements on platelet counts and hematocrit. Several similar trials are also open to recruitment, exploring CPLE benefits versus standard therapy[33] or versus placebo[34] on dengue fever outcomes.

Areas of interest that may be explored are the standardization of tawa-tawa (*Euphorbia hirta*) herbal preparations for research purposes, and the conduction of further tawa-tawa clinical trials, preferably those with standard therapy or placebo as control. Clinical trials will still be needed to illustrate the usefulness of guava (*Psidium guajava*) in dengue fever.

COST IMPLICATION

There are no published herbal medicine (papaya, tawa-tawa, guava) cost-effectiveness studies found in the Philippine setting and in other countries. It is common in the Philippines to gather these medicinal plants (if available) and manually

transform them to herbal concoctions, while some medicinal plants are processed into food supplement preparations by manufacturing companies. The table below shows the estimated cost of herbal medicine products as registered in the Philippine Food and Drug Administration:

Table 7.4. Registered herbal medicine products in the Philippine FDA[35] and their unit cost estimates

Generic Name	Brand Name	Manufacturer	Unit Cost Estimates*
Carica papaya (papain) 10mg + *Anethum graveolens* L. (dill oil fruit) 2mg + *Pimpinella anisum* L. (anise oil fruit) 2mg + *Carum carvi* L. (caraway oil fruit) 2mg + Alpha amylase 20mg per 1 mL syrup	Neopeptine (marketed as a supplement that aids in digestion)	Raptakos Brett & Co. Ltd. (India)	PHP 93.00 per 100mL bottle
Euphorbia hirta L. (tawa-tawa leaf) 450mg/capsule	Tawa2 Plus	Lejal Laboratories, Inc. (Philippines)	PHP 480.00 per 24 pc-pack (PHP 20.00 per capsule)

ETHICAL, SOCIAL AND HEALTH SYSTEMS IMPACT

There is no published local data yet on the impact of herbal medicines on dengue infection management in terms of health equity and feasibility. There were no studies found on the acceptability of papaya and guava for its use on dengue fever in the Philippines.

Some studies have been published that illustrated the acceptability of tawa-tawa as an additional treatment for dengue fever. A descriptive cross-sectional study on the level of knowledge, practices, and attitudes of a total of 216 Filipinos on the use of tawa-tawa for dengue was published in 2013. It showed that the majority of the participants had inadequate knowledge and poor practice in the use of the herbal plant itself, but most had shown a positive attitude towards its utilization.[36] Similarly, a documentation of a focused group discussion done in the Philippines involving patients who had dengue fever and had taken tawa-tawa as a supplement was published in 2014. It showed that a significant source of information on the use of tawa-tawa for dengue is through word-of-mouth endorsements, which may reflect the community's awareness and acceptance of the use of the herbal plant. However, there seemed to be no uniformity in the preparation of tawa-tawa, and the timing and duration of the intervention is highly variable. The respondents claimed that tawa-tawa aided in the general well-being of their patients and were willing to recommend its use.[37]

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QUESTION 8: Should non-DEET-based mosquito repellents be used for individuals at risk for dengue to prevent infection?

Recommendation: Among individuals at risk for dengue infection, we suggest against the use of plant-based non-DEET extracts over DEET repellents for the prevention of dengue. **(*Low certainty of evidence, Weak recommendation)***

Recommendation: Among individuals at risk for dengue infection, we suggest against the use of IR3535 over DEET repellents for the prevention of dengue. **(*Very low certainty of evidence, Weak recommendation)***

Recommendation: Among individuals at risk for dengue infection, we suggest against the use of Citronella over DEET repellents for the prevention of dengue. (***Very low certainty of evidence, Weak recommendation)***

KEY FINDINGS

A total of 15 RCTs that compared non-DEET repellents to DEET-based repellents used for the prevention of dengue infection were found. No direct clinical outcomes were measured, hence critical surrogate outcomes including mean repellent activity, complete protection time, and adverse events were used.

Pooled estimates of 12 RCTs comparing various plant-based non-DEET repellents did not show significant difference in terms of mean repellent activity and complete protection time.

Six RCTs comparing mean repellent activity and complete protection time of commercially available and FDA-approved repellent, IR3535 to DEET showed no significant difference in mean repellent activity but provided 1.5 hours less complete protection time based on very low quality of evidence. Similarly, citronella repellents versus DEET showed almost 3 hours less complete protection time but had no significant difference in mean repellent activity.

Four RCTs included adverse events in their outcomes but none of the studies recorded any incidence of the events.

The overall certainty of evidence is very low because of some serious risks of bias due to issues in the randomization process, allocation concealment and blinding of assessors, as well as inconsistency and imprecision due to small sample sizes and differences in the interventions of the studies, and indirectness.

CONSIDERATIONS DURING THE CONSENSUS PANEL MEETING

There is consensus among the panel members to suggest against the use of non-DEET repellents – plant-based, IR3535-based, and citronella-based – because evidence, while it has very low to low certainty, suggests that their efficacies are inferior against DEET repellents.

Nevertheless, despite DEET repellents being commercially used as mosquito repellents, some panel members are not supportive of its use, and so concerns that clinicians may perceive this recommendation as promoting the use of DEET-based repellents are raised. Because of this, a weak recommendation was given primarily to relay to clinicians and users to not depend on repellents alone for dengue prevention, and instead utilize behavioral interventions such as removal of mosquito source.

BACKGROUND

Dengue is an acute mosquito-borne viral illness that causes flu-like symptoms and even death in both pediatric and adult populations, with 70% of its global burden located in Asia.[1] To limit transmission, comprehensive mosquito control measures are paramount to the prevention of infection. Even with vector control measures in place, personal protective measures such as the application of topical insect repellents contribute to disease prevention by reducing human contact with its vectors.[2]

One of the most effective broad spectrum topical repellents is N,N-diethyl-m-toluamide (DEET) and remains widely used in the US since the year 2000.[3] Moreover, a global online survey done by Moore in 2018 with over 5,000 responses showed that DEET is still the most widely used repellent. However, the survey also showed a significant portion of the population preferring the use of natural or plant-based repellents following safety concerns due to reports of encephalopathy in children related to the use of DEET.[4]

Six reported cases of encephalopathy in girls aged 1-8 years old after the use of DEET-based repellents [1,3] showed true hypersensitivity reaction to DEET that caused rashes and seizures. An analysis of over 9,000 calls made to American Poison Control Centers from 1985-1989 in reference to DEET exposures showed that the severity of symptoms was related more to misapplication (inhalation, ingestion, contact with eyes) than DEET concentration or patient age.[3] In 2015, Diaz reported six deaths attributed to DEET poisoning between 1956 to 2008 – three from intentional ingestions, two from repeated overapplications, and one was in a child with ornithine transcarbamylase deficiency.[5]

Nevertheless, the fear of side effects from DEET contributed to the market for natural or DEET-free repellents such as IR3535 and plant-based repellents like citronella. IR3535 or ethyl butylacetylaminoproprionate is also a synthetic repellent like DEET,

initially marketed as a skin moisturizer, that quickly adapted as a repellent due to its efficiency in warding off blackflies and sandflies. However, there are no available recommendations for or against its use, especially in children and pregnant women.[5] On the other hand, citronella is a natural plant oil obtained from lemongrass that is an FDA-approved natural repellent and is widely available, even in the Philippines.[5] Even without the aversion to DEET, many populations already use home remedies or plant-based repellents for a variety of reasons such as cost, lack of access, or traditional practices.[4]

Because of its use, expert opinion recommends the use of repellent against mosquitoes[6], however the scarcity of studies comparing the efficacy of non-DEET repellents to DEET led to a lack of strong recommendations for or against the use of specific repellents. Hence, this study attempts to examine available evidence between non-DEET and DEET repellents.

Ideally, clinical outcomes such as prevention of dengue infection, toxicity or hypersensitivity reactions would be best to measure the efficacy and safety of a repellent. However, no studies were found with these outcomes; hence, surrogate markers for efficacy and safety such as mean repellent activity, complete protection time, and adverse events were used. Mean repellent activity estimates how effective a substance is at warding off mosquitoes by counting the number of bites or landings on a predetermined area of a participant's forearm measured over a period of time, while complete protection time is intended to measure how long the repellent activity of a substance is in effect and is estimated by recording the time between the first and second landing or biting of a mosquito. Complete protection time provides an approximation of how often an individual must reapply a repellent to continue experiencing its effect. Meanwhile, adverse events focused on signs of skin irritation or allergic responses.

BENEFITS AND HARMS

Efficacy outcomes

Pooled estimates of 8 RCTs (n= 27) comparing various plant-based non-DEET repellents showed no significant difference in terms of mean repellent activity (RR -1.29, 95% CI -3.79 to 1.21).[7,10,14–19] Subgroup analysis on the effect of the plant-based non-DEET repellents on *Aedes aegypti* compared to other vectors (e.g. *Aedes albopticus*) also did not show significant difference in mean repellent activity. There was also no significant difference in complete protection time found in 5 RCTs comparing plant-based non-DEET and DEET repellents (RR 0.51, 95% CI -0.62 to 1.65).[11–14,20] However, one of the 5 studies showed a lower complete protection time for both intervention and control compared to the other studies.[20] This apparent lowered effect is probably due to the difference in the volume of the cage used – 5.5 L cage versus a 27 L (30x30x30 cm) cage used by the 4 studies.

Six RCTs also compared the commercially available and FDA-approved repellent IR3535 to DEET. Two studies (n= 7) showed that there was no significant difference in mean repellent activity (RR -36.00, 95% CI -95.03 to 23.04).[7,21] However, based on 5 RCTs (n= 36) IR3535 provided about 1.5 hours less complete protection time (RR -1.55, 95% CI -2.16 to -0.95) based on very low quality of evidence.[8,9,13,14,21]

Similarly, 4 RCTs (n= 28) using citronella repellents showed almost 3 hours less complete protection time (RR -2.84, 95% CI -3.91 to -1.77) compared to DEET[9,13,14,21] while 3 RCTs (n=11) showed no significant difference in mean repellent activity (RR -30.05, 95% CI -62.6 to 2.5).[7,10, 21]

The equivalent results for mean repellent activity and complete protection time between plant-based non-DEET repellents and DEET repellents could be due to the allowance of using high concentrations in laboratory settings without having to undergo stability or consumer testing. Whereas studies using commercially-available non-DEET repellents show an overall poorer performance to DEET, especially in longevity and need for reapplication.

Safety outcomes

Four RCTs included adverse events in their outcomes but none of the studies reported any outcome. Three studies defined adverse events as any rash, irritation, dermatitis, swelling or other allergic responses.[11,14,16] None of the studies recorded any such events in the participants, both for the interventions and control (DEET) repellents. One study conducted patch-testing on 27 human volunteers using 25% Apium graveolens hexane extract (AHE) prior to comparison testing for complete protection time.[13] A 4-point scale was used to evaluate skin irritation with 0 indicating no reaction and (+++) signifying a strongly positive reaction (i.e. strong redness or edema). None of the 27 participants indicated a positive skin irritant reaction. The study used this data to infer that the AHE product could be an acceptable alternative to conventional synthetic chemicals (DEET).[13]

Table 8.1. Plant-based non-DEET extracts vs DEET repellents for the prevention of dengue.

Critical Outcomes	Basis *(No. and type of studies, total participants)*	Effect Estimate (RR) 95% Confidence Interval	Interpretation	Certainty of Evidence
Mean Repellent Activity	8 RCTs (82 participants)	MD **1.29 percent lower** (3.79 lower to 1.21 higher)	Equivalent	⊕⊕◯◯ Low
Complete Protection Time	5 RCTs (48 participants)	MD **0.51 hours higher** (0.62 lower to 1.64 higher)	Equivalent	⊕◯◯◯ Very low

Adverse Events	4 RCTs (39 participants)	No adverse events for intervention and control	Equivalent	⊕⊕◯◯ Low

Table 8.2. IR3535 vs DEET repellents for the prevention of dengue.

Critical Outcomes	Basis *(No. and type of studies, total participants)*	Effect Estimate (RR) 95% Confidence Interval	Interpretation	Certainty of Evidence
Mean Repellent Activity	2 RCTs (14 participants)	MD **36 percent lower** (95.03 lower to 23.04 higher)	Equivalent	⊕◯◯◯ Very low
Complete Protection Time	5 RCTs (72 participants)	MD **1.55 Hours lower** (2.16 lower to 0.95 lower)	Harm	⊕◯◯◯ Very low
Adverse Events	4 RCTs (31 participants)	No adverse events for intervention and control	Equivalent	⊕⊕◯◯ Low

Table 8.3. Citronella vs DEET repellents for the prevention of dengue.

Critical Outcomes	Basis *(No. and type of studies, total participants)*	Effect Estimate (RR) 95% Confidence Interval	Interpretation	Certainty of Evidence
Mean Repellent Activity	3 RCTs (22 participants)	MD **30.05 Percent lower** (62.6 lower to 2.5 higher)	Equivalent	⊕◯◯◯ Very low
Complete Protection Time	4 RCTs (56 participants)	MD **2.84 Hours lower** (3.91 lower to 1.77 lower)	Harm	⊕◯◯◯ Very low
Adverse Events	4 RCTs (31 participants)	No adverse events for intervention and control	Equivalent	⊕⊕◯◯ Low

RECOMMENDATIONS FROM OTHER GROUPS

Recent dengue management guidelines from other groups all recommend the use of personal repellents, whether applied on the skin or on clothing, for the prevention of infection based on indirect evidence and expert opinion. The guidelines from PPS-PIDSP attempted to compare the efficacy of citronella-based repellents to DEET-based repellents but could not find sufficient evidence to recommend one over the other.

Table 8.4. Summary recommendations from other groups.

Group or Agency	Recommendation	Strength of Recommendation/ Certainty of Evidence
Philippine Pediatric Society and Pediatric Infectious Disease Society of the Philippines Clinical Practice Guidelines on Dengue in Children (2017)[22]	Insufficient evidence to say that use of citronella-based repellents is more effective than DEET-based repellents in reducing dengue transmission. Focus on vector control and community education rather than making recommendations on using any type of insect repellant.	Strong Recommendation Based on Very Low Quality of Evidence
Ministry of Health and Academy of Health Malaysia Clinical Practice Guidelines on the Management of Dengue in Children (2020)[6]	Although no evidence could be found to support the efficacy of repellent in reducing dengue incidence, experts advocate the use of repellent.	Level III (Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees)

CERTAINTY OF EVIDENCE

The overall certainty of evidence has been downgraded to very low because of issues of bias, inconsistency, imprecision, and indirectness. Five studies showed an overall serious risk for bias, mostly due to lack of clarity in the randomization process, allocation concealment or blinding of assessors. Small sample sizes of the studies and the differences in the interventions contribute to serious inconsistency and imprecision. Since the outcomes were only surrogate for clinical outcomes and all the studies were done in the adult population, the certainty of evidence was also affected by serious indirectness.

ONGOING STUDIES AND RESEARCH GAPS

As of the date of systematic search, there are no ongoing studies evaluating non-DEET repellents and their role in the prevention of dengue infection. More local studies regarding the effect, cost-effectiveness, and safety of insect repellents are needed, especially similar to studies done on the prevention of malaria infection and parasitemia.

COST IMPLICATION

There are no published cost-effectiveness studies for topical mosquito repellents locally or internationally. The table below shows the prices for some of the different FDA-approved DEET and non-DEET repellents in the Philippines. The cost of DEET and non-DEET repellents fall within a similar range. However, local studies should be done to determine the impact on the prevention of dengue infection, and the burden on a Filipino household budget.

Table 8.5. Cost of FDA-approved repellents in the Philippines.

Brand	Active ingredient	Cost
Off! Kids Insect Repellent Spray	DEET	PHP 100.00 – 310.00
Off! Clean Feel Insect Repellent Lotion	Icaridin	PHP 120.00 – 199.00
Moskishield Mosquito Repellent Spray	Eucalyptus Oil	PHP 133.00 – 193.00
DirtBugSun Total Protection Mosquito Repellent Lotion	IR3535	PHP 163.00
Bite Block Naturals Citronella Spray	*Cymbopogon nardus* oil 2% + Citrus lemon oil 0.40% + *Eucalyptus globus* oil 0.2% + *Carapa guaianensis* seed oil 0.2%	PHP 209.00 - 275.00

ETHICAL, SOCIAL AND HEALTH SYSTEMS IMPACT

There are no published local data on the impact on health equity of using topical repellents, whether on plant-based repellents nor DEET repellents. There were also no studies done internationally which assessed the feasibility of using plant-based repellents versus DEET repellents for the prevention of dengue infection. One study done by Das in 2020 was conducted in Bangladesh after a dengue outbreak in 2019 that affected close to 82,000 people. The cross-sectional study assessed the knowledge, attitude, and practices (KAP) of garment factory workers related to dengue. The personal protective measure used by most of the participants was mosquito nets (97.25%). Only three of 400 respondents mentioned using topical repellent and they used coconut oil or neem plant leaf extract.[1]

There were also several studies done on other mosquito-borne diseases such as malaria and Zika virus. A feasibility study done by Sangoro in 2014 assessed the KAP of residents in rural Tanzania to topical repellents for the prevention of outdoor transmission of malaria. The participants were provided topical repellents and placebo

lotion for 14 months. Afterwards, surveys and focused group discussions were done. Important findings relevant to this recommendation include the following: 1) DEET repellents were perceived as having an “irritating odor” which reduced its use in the community, 2) majority of the participants were willing to pay for topical repellents but only up to $0.30/tube (~Php 16.50) whereas a 150 ml bottle of 15% DEET cost $1.00 at the time of the study, and 3) longer lasting repellents are essential to compliance as frequent reapplication was found to be off-putting.[23] Two KAP studies were also done in Colombia and Brazil following Zika virus outbreaks in the area in 2015 and 2017, respectively. Both studies found that the participants did not see the long-term, regular use of topical repellents as financially sustainable.[24,25] In 2019, the study by Mendoza also found that the participants perceived plant-based repellents as inherently less toxic than synthetic repellents.

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Applicability Issues

ORGANIZATIONAL CONSIDERATIONS TO IMPLEMENTATION

The diagnosis of dengue is clinical; however, the use of rapid antigen tests have been widely used locally to allow early diagnosis and intervention of patients with suspected, probable, and confirmed dengue infections. The abundance of different RDTs in the market allow the feasibility of its implementation. However, there are no official list of validated dengue RDTs in the Philippines, and so government and private heath institutions utilize different RDTs based on availability and accessibility regardless of accuracy and cost. Therefore, consolidation of a list of research-proven RDTs for general use can be considered to improve diagnostic accuracy across the nation.

Considering the widespread use of conventional treatment options in the community, promotion and compliance against the use of acid suppressants and some herbal medicines may prove difficult and challenging, especially since there are no alternative interventions proposed to replace it. The accessibility of these interventions will also contribute to the persistence of these practices.

For herbal medicines, the use papaya extract in preventing poor outcomes should be maximized by standardizing available formulations for public use.

RESOURCE IMPLICATIONS

Cost-effectiveness of dengue management is not yet thoroughly studied. Locally, there are no available studies, but international studies showing economic burden of dengue management were identified and used to assess cost-effectiveness. Additionally, costs of available interventions were summarized and alternatively used a basis for resource implications.

The availability and accessibility of the diagnostic tests and treatments included in the development of this CPG were considered. Inquiries from healthcare facilities, diagnostic centers, manufacturing companies and practicing physicians were made to ensure that interventions reviewed were generally available locally, being offered in in government and private hospitals and laboratories, local drug stores, and online or other local sources.

Research Implications/Gaps

Despite the long history of dengue endemicity in the Philippines, most of the recommendations in this clinical practice guideline have very low to low certainty of evidence, if not none. Evidences reviewed and gathered are indirect, and surrogate markers are used to assess outcomes.

There are no ongoing researches on dengue diagnosis, prevention and treatment, which creates a research gap, but also opportunities to improve the management of dengue. For most of the clinical practice, the physician's judgement of the overall clinical presentation, disease severity, and other patient-related factors are the basis for decision making on management. Consequently, further studies on how we can maximize and improve reliability of laboratory parameters and discovery of new biomarkers can be done.

Treatment options for dengue are symptom-based and are inappropriately misused, while herbal medicines are widely used in the community. Although there are ongoing studies exploring the use of papaya extract, there is little known about tawa-tawa and guava. These interventions will greatly benefit if more studies on efficacy of acid suppressant use, rehydration options and herbal medicines are accomplished. Disease prevention which is the center for dengue management requires community engagement. Hence, more studies on the combined utilization of personal, home, community, and hospital interventions should be initiated.

Appendices

Appendix 1. Summary of COI Declarations

Name	Role	Affiliation	Summary of Declared Conflicts of Interest	Assessment
Arthur Dessi E. Roman, MD, MTM, FPCP, FPSMID	Steering Committee	RITM, PSMID, PCP	Secondary Non-Financial Conflict - Alpha tryptase allele of Tryptase 1 (TPSAB1) gene associated with Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) in Vietnam and Philippines	Manageable with minor constraints*
Maria Tricia D. Subido-Cariño, MD, FPPS, FPIDSP	Steering Committee	RITM, PIDSP, PPS	Secondary Non-Financial Conflict – Medical Specialist III – Research Institute for Tropical Medicine	Manageable with minor constraints*
Mayan Uy-Lumandas, MD, FPPS, FPIDSP	Steering Committee	RITM, PIDSP, PPS	Secondary Non-Financial Conflict – Medical Specialist III – Research Institute for Tropical Medicine	Manageable with minor constraints*
John Andrew T. Camposano, MD, FPPS, DPISDP	Steering Committee	PIDSP, PPS	Secondary Non-Financial Conflict - Medical Specialist II (Western Visayas Medical Center, tertiary referral center of the region which caters to dengue patients)	Manageable with minor constraints*
Dolores Rommela Tiples-Ruiz, MD, FPCP, FPSMID	Steering Committee	PSMID	Primary Financial and Non-Financial Conflict - Shareholder in several Bacolod hospitals	Manageable with minor constraints*
Mark Joseph S. Castellano, LPT, MD, DPPS, DPIDSP	Consensus Panel	PIDSP	Secondary Non-Financial Conflict - Medical Specialist III (RITM) - May 2019 to present	Manageable with minor constraints*
Jardine Santiago S. Santa Ana, MD, FPAFP	Consensus Panel	PAFP	None	Participation with no constraints
Paula Pilar G. Evangelista, MD, FPPS, DSPPCMP, FPSCCM	Consensus Panel	PPS	Secondary Non-Financial Conflict - Involved in Dengue Caravan of the Lungsod ng Kabataan	Manageable with minor constraints*
Marilou A. Abiera, MD, FPPS, FPSPH	Consensus Panel	PSPH	None	Participation with no constraints

Florentina U. Ty, MD, FPPS, FPSCCM	Consensus Panel	PPS	Primary Financial and Non-Financial Conflict – Stocks at Diliman Doctor's Hospital; Involved in Dengue Integrated Program 2022 – November 2022 to present; Invited speaker by different institutions on Dengue	Manageable with minor constraints*
Sheila C. Faciol, MD	Consensus Panel	AMHOP	None	Participation with no constraints
Atty. Ma. Louella Martinez-Aranas	Consensus Panel	The Sandy Project	None	Participation with no constraints
Raffy A. Deray, MD, MPH	Consensus Panel	DOH-DPCB	None	Participation with no constraints
John Louie O. Manalili, MD, DPCP, DPSMID	Evidence Review Expert	-	Primary Financial and Non-Financial Conflict - Pampanga Metroeast Medical Center Shareholder; Infectious Disease Specialist	Manageable with minor constraints*
Jose Eladio G. Planta, MD, DPCP, DPSMID	Evidence Review Expert	-	Secondary Non-Financial Conflict - Infectious Disease Specialist	Manageable with minor constraints*
Therese Anne M. Suñe, MD, FPCP, DPSMID	Evidence Review Expert	-	Secondary Non-Financial Conflict - Infectious Disease Specialist	Manageable with minor constraints*
Lorrie Suzette J. Urbano, MD, FPCP, DPSMID	Evidence Review Expert	-	Secondary Non-Financial Conflict - Infectious Disease Specialist	Manageable with minor constraints*
Patricia Castillo Orduña, MD, DPPS, FPNA, FCNS	Evidence Review Expert	-	None	Participation with no constraints
Korina Ada D. Tanyu, MD, DPPS	Evidence Review Expert	-	Secondary Non-Financial Conflict – General Pediatrician	Manageable with minor constraints*
Paul Sherwin O. Tarnate, MD, DPPS, DPIDSP	Evidence Review Expert	-	Secondary Non-Financial Conflict – Pediatric Infectious Disease Specialist	Manageable with minor constraints*
Patricia Marie D. Isada, MD, DPPS	Evidence Review Expert	-	Primary Financial and Non-Financial Conflict - - Stocks in ARDI Health Services Inc	Manageable with minor constraints*

Gianna Kristin M. Santos, MD	Evidence Review Expert	-	None	Participation with no constraints
Cristina D. Tan, MD, FPCP, DPSMID	Evidence Review Expert	-	Secondary Non-Financial Conflict – Infectious Disease Specialist	Manageable with minor constraints*
Rosally P. Zamora, MD, FPCP, FPSMID	Technical Coordinator	-	Secondary Non-Financial Conflict - Infectious Disease Specialist	Manageable with minor constraints*
Howell Henrian G. Bayona, MSc	Technical Coordinator	-	None	Participation with no constraints
Mary Ann R. Abacan, MD, MSc, FPPS	Technical Facilitator	-	Secondary Financial COI - Co-investigator, Registry of Lysosomal Storage Disorders - Sanofi Genzyme (2014 to present); Co- investigator, SHP-ELA-401 - A Long-Term, Open-Label, Multicenter, Phase IV Study to Assess Longitudinal Changes on Height and Weight in Patients with MPS II Who Are Receiving Elaprase and Started Treatment With Elaprase at <6 Years of Age - Shire (2015-present)	Manageable with minor constraints*
Ruth Hechanova, MD, MBA	Admin Officer	-	Secondary Non-Financial Conflict - Medical Officer IV - Research Institute for Tropical Medicine (2021-2022)	Manageable with minor constraints*
Morel Dominic D. Umipon, MD	Technical Writer	-	None	Participation with no constraints

*COIs were managed by disclosure or broadcast of COIs during consensus panel meetings

Appendix 2. Search Strategy

Appendix 2.1. Search strategy and yield for Question 1A.

Database	Search Strategy	Date and Time Search	Results	
			Yield	Eligible
MEDLINE	("Dengue" [MeSH Terms] OR "Dengue" OR "dengue infect") AND ("diagnos*" OR "test*") AND ("NS1 antigen" OR "NS1" OR "NS1 protein" OR ("IgM antibod*" OR "IgM" OR "Immunoglobulin M") OR ("IgG antibod*" OR "IgG" OR "Immunoglobulin G")) AND ("rapid test" OR "RDT" OR "rapid" OR "rapid kit" OR "immunochromatography*" OR "ICT" OR ("enzyme-linked immunosorbent assay" OR "ELISA" OR "enzyme-linked immunosorbent assay"))	Feb 17, 2023 08:10	1508 4 SR	11 9 CS 2 Cohort
CENTRAL	MeSH descriptor: [Dengue] explode all trees OR (Dengue) AND (("rapid diagnostic" OR "rapid antigen" OR radt OR radts OR rdt OR rdts) OR ("immunochromatographic" or "immunochromatography") OR (Enzyme-Linked Immunosorbent Assay) or (ELISA)) AND ((NS1" or "Nonstructural protein" or "non-structural protein") OR ("IgM" or "IgG" or "Antibody") AND ("test*" OR "detect*" OR "diagnos*"OR "assay*" OR "kit" OR "kits"))	Feb 17, 2023, 02:13:59	44	0
HERDIN (herdin.ph)	Dengue Test (Title)	January 25, 2023 21:00	6	0
ClinicalTrials.gov	Dengue RDT	February 2, 2023 19:07	3 2 recruiting 1 unknown	0

Appendix 2.2. Search strategy and yield for Question 1B.

Search Number	Query	Sort By	Filters	Search Details	Results
10	#3 AND #7			("Dengue"[MeSH Terms] OR "Dengue"[Text Word] OR "dengue infect*"[Text Word]) AND ("diagnos*"[Text Word] OR "test*"[Text Word]) AND (("NS1 antigen"[Text Word] OR "NS1"[Text Word] OR "NS1 protein"[Text Word]) AND ("igm antibod*"[Text Word] OR "IgM"[Text Word] OR "Immunoglobulin M"[Text Word]) AND ("igg antibod*"[Text Word] OR "IgG"[All Fields] OR "Immunoglobulin G"[All Fields]))	274
9	#3 AND #8			("Dengue"[MeSH Terms] OR "Dengue"[Text Word] OR "dengue infect*"[Text Word]) AND ("diagnos*"[Text Word] OR "test*"[Text Word]) AND ("NS1 antigen"[Text Word] OR "NS1"[Text Word] OR "NS1 protein"[Text Word] OR ("igm antibod*"[Text Word] OR "IgM"[Text Word] OR "Immunoglobulin M"[Text Word]) OR ("igg antibod*"[Text Word] OR "IgG"[All Fields] OR "Immunoglobulin G"[All Fields]))	2,706
8	#4 OR #5 OR #6			"NS1 antigen"[Text Word] OR "NS1"[Text Word] OR "NS1 protein"[Text Word] OR "igm antibod*"[Text Word] OR "IgM"[Text Word] OR "Immunoglobulin M"[Text Word] OR "igg antibod*"[Text Word] OR "IgG"[All Fields] OR "Immunoglobulin G"[All Fields]	276,412
7	#4 AND #5 AND #6			("NS1 antigen"[Text Word] OR "NS1"[Text Word] OR "NS1 protein"[Text Word]) AND ("igm antibod*"[Text Word] OR "IgM"[Text Word] OR "Immunoglobulin M"[Text Word]) AND ("igg antibod*"[Text Word] OR "IgG"[All Fields] OR "Immunoglobulin G"[All Fields])	387
6	"IgG antibod*"[tw] OR "IgG" OR "Immunoglobulin G"			"igg antibod*"[Text Word] OR "IgG"[All Fields] OR "Immunoglobulin G"[All Fields]	234,972
5	"IgM antibod*"[tw] OR "IgM"[tw] OR "Immunoglobulin M"[tw]			"igm antibod*"[Text Word] OR "IgM"[Text Word] OR "Immunoglobulin M"[Text Word]	96,316
4	"NS1 antigen"[tw] OR "NS1"[tw] OR "NS1 protein"[tw]			"NS1 antigen"[Text Word] OR "NS1"[Text Word] OR "NS1 protein"[Text Word]	5,579
3	#1 AND #2			("Dengue"[MeSH Terms] OR "Dengue"[Text Word] OR "dengue infect*"[Text Word]) AND ("diagnos*"[Text Word] OR "test*"[Text Word])	10,669
2	"diagnos*"[tw] OR "test*"[tw]			"diagnos*"[Text Word] OR "test*"[Text Word]	
1	"Dengue"[Mesh] OR dengue[tw] OR "dengue infect*"[tw]				

Appendix 2.3. Search strategy and yield for Question 2.

Database	Search Strategy	Date and Time Search	Results	
			Yield	Eligible
Medline	(("dengue"[MeSH Terms] OR "dengue"[All Fields] OR "dengues"[All Fields] OR "dengue"[MeSH Terms]) AND ("prognosis"[MeSH Terms] OR "risk factors"[MeSH Terms]) AND "severe dengue"[MeSH Terms]) AND (y_5[Filter]) Metanalysis and Systematic Review	January 25, 2023	16	6
CENTRAL	Dengue OR Severe Dengue and MeSH descriptor: [Prognosis] OR MeSH descriptor [Risk factors]	January 25, 2023	7	0
HERDIN	Dengue Fever and Prognosis or Risk Factors	January 25, 2023	548	16
ClinicalTrials.gov	Dengue Fever Completed Studies	January 25, 2023	155	0
EU Clinical Trials Register	Dengue	January 25, 2023	30	0
Republic of Korea - Clinical Research Information Service	Dengue	January 25, 2023	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Dengue	January 25, 2023	6	0
Medrxiv.org	Dengue title “Dengue”	January 25, 2023	245	1
Biorxiv.org	Dengue title “Dengue”	January 25, 2023	107	0

Appendix 2.4. Search strategy and yield for Question 3.

Database	Search Strategy	Purpose	Results	
			Yield	Eligible
Medline	(("blood cell count"[MeSH Terms] OR "blood cell count"[Title/Abstract] OR "complete blood count"[Title/Abstract] OR "platelet"[Title/Abstract] OR ("hematocrit"[Title/Abstract] OR "haematocrit"[Title/Abstract]) OR "hematocrite"[Title/Abstract] OR ("leukocyt*"[Title/Abstract] OR "leucocyt*"[Title/Abstract])) AND ("dengue"[Title/Abstract] AND "severe"[Title/Abstract])) AND (clinicaltrial[Filter] OR meta-analysis[Filter] OR observationalstudy[Filter] OR randomizedcontrolledtrial[Filter])	February 5, 2023 11:00PM	26	3
CENTRAL	ID Search #1 blood cell count #2 (blood cell count):ti,ab,kw #3 MeSH descriptor: [Blood Cell Count] explode all trees #4 (complete blood count):ti,ab,kw #5 MeSH descriptor: [Blood Platelets] explode all trees #6 MeSH descriptor: [Hematocrit] explode all trees #7 MeSH descriptor: [Dengue] explode all trees #8 MeSH descriptor: [Severe Dengue] explode all trees	February 6, 2023 1:10AM	59	0
HERDIN	dengue AND blood cell count	February 7, 2023 10:130AM	7	0

Appendix 2.5. Search strategy and yield for Question 4 (February 2, 2023).

Search Number	Query	Search Details	Results
1	dengue	"dengue"[MeSH Terms] OR "dengue"[All Fields] OR "dengue s"[All Fields]	28,396
2	dengue fever	"dengue"[MeSH Terms] OR "dengue"[All Fields] OR ("dengue"[All Fields] AND "fever"[All Fields]) OR "dengue fever"[All Fields]	28,396
3	therapy	"therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "therapies"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "therapy s"[All Fields] OR "therapys"[All Fields]	10,982,947
4	#2 and #3	("dengue"[MeSH Terms] OR "dengue"[All Fields] OR ("dengue"[All Fields] AND "fever"[All Fields]) OR "dengue fever"[All Fields]) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "therapies"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "therapy s"[All Fields] OR "therapys"[All Fields])	7,180
5	hydration	"hydratation"[All Fields] OR "hydrate"[All Fields] OR "hydrated"[All Fields] OR "hydrates"[All Fields] OR "hydrating"[All Fields] OR "hydration"[All Fields] OR "hydrational"[All Fields] OR "hydrations"[All Fields]	71,767
6	#4 and #5	("dengue"[MeSH Terms] OR "dengue"[All Fields] OR ("dengue"[All Fields] AND "fever"[All Fields]) OR "dengue fever"[All Fields]) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "therapies"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "therapy s"[All Fields] OR "therapys"[All Fields]) AND ("hydratation"[All Fields] OR "hydrate"[All Fields] OR "hydrated"[All Fields] OR "hydrates"[All Fields] OR "hydrating"[All Fields] OR "hydration"[All Fields] OR "hydrational"[All Fields] OR "hydrations"[All Fields])	20
7	oral	"mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]	1,270,317
8	#6 and #7	("dengue"[MeSH Terms] OR "dengue"[All Fields] OR ("dengue"[All Fields] AND "fever"[All Fields]) OR "dengue fever"[All Fields]) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "therapies"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "therapy s"[All Fields] OR "therapys"[All Fields]) AND ("hydratation"[All Fields] OR "hydrate"[All Fields] OR "hydrated"[All Fields] OR "hydrates"[All Fields] OR "hydrating"[All Fields] OR "hydration"[All Fields] OR "hydrational"[All Fields] OR "hydrations"[All Fields]) AND ("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields])	2
9	fluid therapy	"fluid therapy"[MeSH Terms] OR ("fluid"[All Fields] AND "therapy"[All Fields]) OR "fluid therapy"[All Fields]	124,920
10	#2 and #9	("dengue"[MeSH Terms] OR "dengue"[All Fields] OR ("dengue"[All Fields] AND "fever"[All Fields]) OR "dengue fever"[All Fields]) AND ("fluid therapy"[MeSH Terms] OR ("fluid"[All Fields] AND "therapy"[All Fields]) OR "fluid therapy"[All Fields])	226

11	#7 and #10	("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]) AND (("dengue"[MeSH Terms] OR "dengue"[All Fields] OR ("dengue"[All Fields] AND "fever"[All Fields]) OR "dengue fever"[All Fields]) AND ("fluid therapy"[MeSH Terms] OR ("fluid"[All Fields] AND "therapy"[All Fields]) OR "fluid therapy"[All Fields]))	12
12	ORS	"oralit"[Supplementary Concept] OR "oralit"[All Fields] OR "ors"[All Fields]	37,055
13	#2 and #12	("dengue"[MeSH Terms] OR "dengue"[All Fields] OR ("dengue"[All Fields] AND "fever"[All Fields]) OR "dengue fever"[All Fields]) AND ("oralit"[Supplementary Concept] OR "oralit"[All Fields] OR "ors"[All Fields])	34
14	water	"water"[MeSH Terms] OR "water"[All Fields] OR "watering"[All Fields] OR "water s"[All Fields] OR "watered"[All Fields] OR "waterer"[All Fields] OR "waterers"[All Fields] OR "waterings"[All Fields] OR "waters"[All Fields]	1,206,338
15	#2 and #7 and #14	("dengue"[MeSH Terms] OR "dengue"[All Fields] OR ("dengue"[All Fields] AND "fever"[All Fields]) OR "dengue fever"[All Fields]) AND ("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]) AND ("water"[MeSH Terms] OR "water"[All Fields] OR "watering"[All Fields] OR "water s"[All Fields] OR "watered"[All Fields] OR "waterer"[All Fields] OR "waterers"[All Fields] OR "waterings"[All Fields] OR "waters"[All Fields])	11
16	oral rehydration therapy	"fluid therapy"[MeSH Terms] OR ("fluid"[All Fields] AND "therapy"[All Fields]) OR "fluid therapy"[All Fields] OR ("oral"[All Fields] AND "rehydration"[All Fields] AND "therapy"[All Fields]) OR "oral rehydration therapy"[All Fields]	125,776
17	#2 and #16	("dengue"[MeSH Terms] OR "dengue"[All Fields] OR ("dengue"[All Fields] AND "fever"[All Fields]) OR "dengue fever"[All Fields]) AND ("fluid therapy"[MeSH Terms] OR ("fluid"[All Fields] AND "therapy"[All Fields]) OR "fluid therapy"[All Fields] OR ("oral"[All Fields] AND "rehydration"[All Fields] AND "therapy"[All Fields]) OR "oral rehydration therapy"[All Fields])	230

Appendix 2.6. Search strategy and yield for Question 4 (May 7, 2023).

Search Number	Query	Search Details	Results
1	"dengue fever" and "milk"	"dengue fever"[All Fields] AND "milk"[All Fields]	5
2	"dengue fever" and "water"	"dengue fever"[All Fields] AND "water"[All Fields]	242
3	"dengue fever" coconut	"dengue fever"[All Fields] AND ("cocos"[MeSH Terms] OR "cocos"[All Fields] OR "coconut"[All Fields] OR "coconuts"[All Fields])	1
4	dengue fever pocari sweat - Schema: all	"dengue"[All Fields] AND "fever"[All Fields] AND "pocari"[All Fields] AND "sweat"[All Fields]	0
5	dengue fever pocari sweat	("dengue"[MeSH Terms] OR "dengue"[All Fields] OR ("dengue"[All Fields] AND "fever"[All Fields]) OR "dengue fever"[All Fields]) AND "pocari"[All Fields] AND ("sweat"[MeSH Terms] OR "sweat"[All Fields] OR "sweating"[MeSH Terms] OR "sweating"[All Fields] OR "sweats"[All Fields] OR "sweatings"[All Fields])	0
6	dengue fever fluid	("dengue"[MeSH Terms] OR "dengue"[All Fields] OR ("dengue"[All Fields] AND "fever"[All Fields]) OR "dengue fever"[All Fields]) AND ("fluid"[All Fields] OR "fluid s"[All Fields] OR "fluids"[All Fields])	790
7	dengue fever outpatient	("dengue"[MeSH Terms] OR "dengue"[All Fields] OR ("dengue"[All Fields] AND "fever"[All Fields]) OR "dengue fever"[All Fields]) AND ("outpatient s"[All Fields] OR "outpatients"[MeSH Terms] OR "outpatients"[All Fields] OR "outpatient"[All Fields])	189
8	milk	"milk, human"[MeSH Terms] OR ("milk"[All Fields] AND "human"[All Fields]) OR "human milk"[All Fields] OR "milk"[All Fields] OR "milk"[MeSH Terms]	171,404
9	dengue fever	"dengue"[MeSH Terms] OR "dengue"[All Fields] OR ("dengue"[All Fields] AND "fever"[All Fields]) OR "dengue fever"[All Fields]	28,556
10	#8 and #9	("milk, human"[MeSH Terms] OR ("milk"[All Fields] AND "human"[All Fields]) OR "human milk"[All Fields] OR "milk"[All Fields] OR "milk"[MeSH Terms]) AND ("dengue"[MeSH Terms] OR "dengue"[All Fields] OR ("dengue"[All Fields] AND "fever"[All Fields]) OR "dengue fever"[All Fields])	40
11	coconut	"cocos"[MeSH Terms] OR "cocos"[All Fields] OR "coconut"[All Fields] OR "coconuts"[All Fields]	7,116
12	#9 and #11	("dengue"[MeSH Terms] OR "dengue"[All Fields] OR ("dengue"[All Fields] AND "fever"[All Fields]) OR "dengue fever"[All Fields]) AND ("cocos"[MeSH Terms] OR "cocos"[All Fields] OR "coconut"[All Fields] OR "coconuts"[All Fields])	17
13	juice	"juice"[All Fields] OR "juice s"[All Fields] OR "juiced"[All Fields] OR "juices"[All Fields] OR "juicing"[All Fields]	53,701
14	#9 and #13	("dengue"[MeSH Terms] OR "dengue"[All Fields] OR ("dengue"[All Fields] AND "fever"[All Fields]) OR "dengue	20

		fever"[All Fields]) AND ("juice"[All Fields] OR "juice s"[All Fields] OR "juiced"[All Fields] OR "juices"[All Fields] OR "juicing"[All Fields])	
15	water	"water"[MeSH Terms] OR "water"[All Fields] OR "watering"[All Fields] OR "water s"[All Fields] OR "watered"[All Fields] OR "waterer"[All Fields] OR "waterers"[All Fields] OR "waterings"[All Fields] OR "waters"[All Fields]	1,214,328
16	#9 and #15	("dengue"[MeSH Terms] OR "dengue"[All Fields] OR ("dengue"[All Fields] AND "fever"[All Fields]) OR "dengue fever"[All Fields]) AND ("water"[MeSH Terms] OR "water"[All Fields] OR "watering"[All Fields] OR "water s"[All Fields] OR "watered"[All Fields] OR "waterer"[All Fields] OR "waterers"[All Fields] OR "waterings"[All Fields] OR "waters"[All Fields])	1,182
17	sports drink	("sport s"[All Fields] OR "sports"[MeSH Terms] OR "sports"[All Fields] OR "sport"[All Fields] OR "sporting"[All Fields]) AND ("drink"[All Fields] OR "drinking"[MeSH Terms] OR "drinking"[All Fields] OR "alcohol drinking"[MeSH Terms] OR ("alcohol"[All Fields] AND "drinking"[All Fields]) OR "alcohol drinking"[All Fields] OR "drinkings"[All Fields] OR "drinks"[All Fields])	5,689
18	#9 and #17	("dengue"[MeSH Terms] OR "dengue"[All Fields] OR ("dengue"[All Fields] AND "fever"[All Fields]) OR "dengue fever"[All Fields]) AND (("sport s"[All Fields] OR "sports"[MeSH Terms] OR "sports"[All Fields] OR "sport"[All Fields] OR "sporting"[All Fields]) AND ("drink"[All Fields] OR "drinking"[MeSH Terms] OR "drinking"[All Fields] OR "alcohol drinking"[MeSH Terms] OR ("alcohol"[All Fields] AND "drinking"[All Fields]) OR "alcohol drinking"[All Fields] OR "drinkings"[All Fields] OR "drinks"[All Fields]))	1

Appendix 2.7. Search strategy and yield for Question 5.

Database	Search Strategy	Date and Time Search	Results	
			Yield	Eligible
Pubmed	("dengue"[MeSH Terms] OR "dengue"[All Fields] OR "dengue s"[All Fields] OR ("dengue"[MeSH Terms] OR "dengue"[All Fields] OR ("dengue"[All Fields] AND "fever"[All Fields]) OR "dengue fever"[All Fields]) OR ("dengue haemorrhagic fever"[All Fields] OR "severe dengue"[MeSH Terms] OR ("severe"[All Fields] AND "dengue"[All Fields]) OR "severe dengue"[All Fields] OR ("dengue"[All Fields] AND "hemorrhagic"[All Fields] AND "fever"[All Fields]) OR "dengue hemorrhagic fever"[All Fields]) OR ("severe dengue"[MeSH Terms] OR ("severe"[All Fields] AND "dengue"[All Fields]) OR "severe dengue"[All Fields] OR ("dengue"[All Fields] AND "shock"[All Fields] AND "syndrome"[All Fields]) OR "dengue shock syndrome"[All Fields]) OR (("dengue"[MeSH Terms] OR "dengue"[All Fields] OR "dengue s"[All Fields]) AND ("warned"[All Fields] OR "warning"[All Fields] OR "warnings"[All Fields] OR "warns"[All Fields]) AND ("diagnosis"[MeSH Subheading] OR "diagnosis"[All Fields] OR "signs"[All Fields] OR "diagnosis"[MeSH Terms] OR "signs"[All Fields])) OR ("severe dengue"[MeSH Terms] OR ("severe"[All Fields] AND "dengue"[All Fields]) OR "severe dengue"[All Fields]) OR ("dengue"[MeSH Terms] OR "dengue"[All Fields] OR ("breakbone"[All Fields] AND "fever"[All Fields]) OR "breakbone fever"[All Fields]) OR ("arboviruses"[MeSH Terms] OR "arboviruses"[All Fields] OR "arbovirus"[All Fields]) OR ("dengue"[MeSH Terms] OR "dengue"[All Fields] OR "dengue s"[All Fields])) AND ("proton pump inhibitors"[Pharmacological Action] OR "proton pump inhibitors"[MeSH Terms] OR ("proton"[All Fields] AND "pump"[All Fields] AND "inhibitors"[All Fields]) OR "proton pump inhibitors"[All Fields] OR ("histamine h2 antagonists"[Pharmacological Action] OR "histamine h2 antagonists"[MeSH Terms] OR ("histamine"[All Fields] AND "h2"[All Fields] AND "antagonists"[All Fields]) OR "histamine h2 antagonists"[All Fields] OR ("h2"[All Fields] AND "blockers"[All Fields]) OR "h2 blockers"[All Fields]) OR ("histamine h2 antagonists"[Pharmacological Action] OR "histamine h2 antagonists"[MeSH Terms] OR ("histamine"[All Fields] AND "h2"[All Fields] AND "antagonists"[All Fields]) OR "histamine h2 antagonists"[All Fields] OR ("histamine"[All Fields] AND "h2"[All Fields] AND "receptor"[All Fields] AND "antagonists"[All Fields]) OR "histamine h2 receptor antagonists"[All Fields]) OR "PPI"[All Fields] OR ("lansoprazole"[MeSH Terms] OR "lansoprazole"[All Fields] OR "lansoprazol"[All Fields] OR ("omeprazole"[MeSH Terms] OR "omeprazole"[All Fields] OR "esomeprazole"[MeSH Terms] OR "esomeprazole"[All Fields] OR "omeprazol"[All Fields]) OR ("pantoprazole"[MeSH Terms] OR "pantoprazole"[All Fields] OR	February 21, 2023 1 AM	31	0

	"pantoprazol"[All Fields]) OR ("rabeprazol"[All Fields] OR "rabeprazole"[MeSH Terms] OR "rabeprazole"[All Fields]) OR ("esomeprazole"[MeSH Terms] OR "esomeprazole"[All Fields] OR "esomeprazol"[All Fields])) OR ("cimetidine"[MeSH Terms] OR "cimetidine"[All Fields] OR ("ranitidine"[MeSH Terms] OR "ranitidine"[All Fields] OR "ranitidin"[All Fields] OR "ranitidine s"[All Fields]) OR ("nizatidine"[MeSH Terms] OR "nizatidine"[All Fields]) OR ("famotidin"[All Fields] OR "famotidine"[MeSH Terms] OR "famotidine"[All Fields]))))			
CENTRAL	dengue AND proton pump inhibitor OR h2 blocker	February 21, 2023, 1 AM	1	0
HERDIN	dengue AND proton pump inhibitor OR h2 blocker	February 21, 2023, 1 AM	0	0
Google Scholar	dengue "proton pump inhibitor" OR "h2 blocker"	February 21, 2023 1 AM	548	1
PIDSP	dengue AND proton pump inhibitor OR h2 blocker	February 21, 2023 1:30 AM	0	0
Acta Medica	dengue AND proton pump inhibitor OR h2 blocker	February 21, 2023, 1:30 AM	0	0
AUNILO	dengue AND proton pump inhibitor OR h2 blocker	February 21, 2023 1:30 AM	0	0
ClinicalTrials .gov	dengue, proton pump inhibitor or H2 blocker	February 25, 2023 8 PM	0	0
Chinese Clinical Trial Registry	dengue	February 25, 2023 8 PM	0	0
EU Clinical Trials Register	dengue AND proton pump inhibitor or H2 blocker	February 25, 2023 8 PM	0	0
National Medical Research Register (Malaysia)	dengue	February 25, 2023 8 PM	11	0
Indonesia Registry	dengue	February 25, 2023, 8 PM	1	0
Medrxiv.org	dengue AND proton pump inhibitor or H2-blocker	February 25, 2023, 8 PM	7	0
Biorxiv.org	dengue AND proton pump inhibitor or H2 blocker (clinical trials)	February 25, 2023, 8 PM	0	0

Appendix 2.8. Search strategy and yield for Question 6.

Database	Search Strategy	Date and Time Search	Results	
			Yield	Eligible
CENTRAL	((dengue[MeSH Terms]) OR (dengue fever[MeSH Terms])) OR (dengue hemorrhagic fever[MeSH Terms])) OR (dengue shock syndrome[MeSH Terms])) OR (dengue warning signs)) OR (severe dengue)) OR (breakbone fever virus[MeSH Terms])) OR (arbovirus) AND ((gastrointestinal bleeding) OR (abdominal pain)) OR (gastric bleeding)) OR (upper gastrointestinal bleeding)) OR (upper GI bleeding)] AND [(((((proton pump inhibitors[MeSH Terms]) OR (PPI)) OR (omeprazole)) OR (esomeprazole)) OR (lansoprazole)) OR (pantoprazole)) OR (rabeprazole)) OR (dexlansoprazole))] OR ((histamine h2 blockers[MeSH Terms])) OR (histamine h2 blocker)) OR (histamine 2 receptor antagonist)) OR (h2 antagonist) OR (cimetidine)) OR (famotidine)) OR (hydrochloride, ranitidine[MeSH Terms])) OR (nizatidine))]	January 30	32	0
Medline	((dengue[MeSH Terms]) OR (dengue fever[MeSH Terms])) OR (dengue hemorrhagic fever[MeSH Terms])) OR (dengue shock syndrome[MeSH Terms])) OR (dengue warning signs)) OR (severe dengue)) OR (breakbone fever virus[MeSH Terms])) OR (arbovirus) AND ((gastrointestinal bleeding) OR (abdominal pain)) OR (gastric bleeding)) OR (upper gastrointestinal bleeding)) OR (upper GI bleeding)] AND [(((((proton pump inhibitors[MeSH Terms]) OR (PPI)) OR (omeprazole)) OR (esomeprazole)) OR (lansoprazole)) OR (pantoprazole)) OR (rabeprazole)) OR (dexlansoprazole))] OR ((histamine h2 blockers[MeSH Terms])) OR (histamine h2 blocker)) OR (histamine 2 receptor antagonist)) OR (h2 antagonist) OR (cimetidine)) OR (famotidine)) OR (hydrochloride, ranitidine[MeSH Terms])) OR (nizatidine))]	January 30	31	0
Embase	dengue:ti,ab,kw AND ('proton pump inhibitor':ti,ab,kw OR omeprazole:ti,ab,kw OR esomeprazole:ti,ab,kw OR lansoprazole:ti,ab,kw OR pantoprazole:ti,ab,kw OR rabeprazole:ti,ab,kw OR dexlansoprazole:ti,ab,kw OR 'histamine h2 blocker':ti,ab,kw OR 'histamine 2 receptor antagonist':ti,ab,kw OR 'h2 antagonist':ti,ab,kw OR cimetidine:ti,ab,kw OR famotidine:ti,ab,kw OR ranitidine:ti,ab,kw OR nizatidine:ti,ab,kw)	January 31	12	2
Google Scholar	[(dengue) OR (dengue fever) OR (dengue hemorrhagic fever) OR (classical dengue) OR	January 29	422	2

	(severe dengue) OR (dengue shock syndrome) OR (arbovirus) OR (breakbone fever)] **AND** [(proton pump inhibitor) OR (rabeprazole OR lansoprazole OR pantoprazole OR omeprazole OR esomeprazole)] AND [(upper gastrointestinal bleeding) OR (gastrointestinal bleeding) OR (abdominal pain) OR epigastric pain)] (dengue) OR (dengue fever) OR (dengue hemorrhagic fever) OR (classical dengue) OR (severe dengue) OR (dengue shock syndrome) OR (arbovirus) OR (breakbone fever)) **AND** ((histamine h2 blockers) OR (h2 blockers) OR (histamine h2 antagonist) OR (histamine 2 receptor blocker) OR ranitidine OR famotidine OR cimetidine OR nizatidine))		35	1
Herdin	Dengue and proton pump inhibitors Dengue and omeprazole Dengue and esomeprazole Dengue and pantoprazole Dengue and lansoprazole Dengue and rabeprazole Dengue and h2 blocker Dengue and histamine h2 receptor antagonist Dengue and ranitidine Dengue and famotidine Dengue and cimetidine Dengue and nizatidine	January 30	0 0 0 0 0 0 0 0 0 0 0 0	-
Aunilo	Dengue and proton pump inhibitors Dengue and omeprazole Dengue and esomeprazole Dengue and pantoprazole Dengue and lansoprazole Dengue and rabeprazole Dengue and h2 blocker Dengue and histamine h2 receptor antagonist Dengue and ranitidine Dengue and famotidine Dengue and cimetidine Dengue and nizatidine	February 7	0 0 0 0 0 0 0 0 0 0 0 0	
ClinicalTrials.gov	Dengue and proton pump inhibitors Dengue and omeprazole Dengue and esomeprazole Dengue and pantoprazole Dengue and lansoprazole Dengue and rabeprazole Dengue and h2 blocker Dengue and histamine h2 receptor antagonist Dengue and ranitidine Dengue and famotidine Dengue and cimetidine Dengue and nizatidine	January 29	0 0 0 0 0 0 0 0 0 0 0 0	-

Appendix 2.9. Search strategy and yield for Question 7.

Database	Search Strategy	Purpose	Yield
Medline	("dengue"[MeSH Terms] OR "dengue fever"[All Fields] OR "dengue hemorrhagic fever"[All Fields] OR "dengue shock syndrome"[All Fields] OR "dengue warning signs"[All Fields] OR "severe dengue"[All Fields]) AND (("tawa-tawa"[All Fields] OR "*Euphorbia hirta*"[All Fields]) OR ("papaya"[All Fields] OR "*Carica papaya*"[All Fields]) OR ("guava"[All Fields] OR "*Psidium guajava*"[All Fields]))	RCTs (2) Observational studies (4) Reviews (9) Systematic reviews (2) Meta-analysis (2) Economic evaluation (0)	26
CENTRAL	[(MeSH descriptor: [Dengue] explode all trees) OR (dengue) OR (dengue fever) OR (dengue hemorrhagic fever) OR (dengue shock syndrome) OR (dengue warning signs) OR (severe dengue)] AND [((tawa-tawa) OR (Euphorbia hirta)) OR ((papaya) OR (Carica papaya)) OR ((guava) OR (Psidium guajava))]	Trials (28)	28
NHS EED and HTA	MeSH DESCRIPTOR Dengue EXPLODE ALL TREES IN DARE, NHSEED, HTA FROM 01/01/1973 TO 16/11/2023	Systematic reviews (0) Economic evaluation (0) HTA (0)	22
HERDIN	Dengue AND (tawa-tawa OR papaya OR guava)	Local studies (Completed studies: 12)	12

Appendix 2.10. Search strategy and yield for Question 8.

Database	Search Strategy	Date and Time Search	Results	
			Yield	Eligible
Medline	("Insect Repellents"[MeSH Terms] OR "picaridin"[All Fields] OR "citronella"[All Fields] OR "citronella oil"[All Fields] OR ("DEET"[MeSH Terms] OR "DEET"[Text Word] OR "N,N-diethyl-m-toluamide"[All Fields] OR "deet mosquito repel*"[All Fields] OR "deet insect repel*"[All Fields])) AND ("Dengue"[MeSH Terms] OR "Dengue"[Text Word] OR "dengue infect*"[All Fields] OR "dengue infection rate"[All Fields] OR "dengue prevent*"[All Fields])	31 January 2023 4:14 PM	165	18
CENTRAL	#1 MeSH descriptor: [Insect Repellents] explode all trees 60 #2 "picaridin" OR "citronella" OR "citronella oil" OR "non-DEET repellent" OR "non-DEET" OR "non DEET" 23 #3 MeSH descriptor: [DEET] explode all trees 22 #4 “DEET” OR “N,N-diethyl-m-toluamide” OR “DEET mosquito repel*” OR “DEET insect repel*” 58 #5 MeSH descriptor: [Dengue] explode all trees 396 #6 “dengue” OR “dengue infect*” OR “dengue infection rate” OR “dengue prevent*” 873 #7 (#6 OR #5) AND ((#4 OR #3) OR (#2 AND #1)) 4	31 January 2023 1:48 PM	4	1
Herdin.ph	(insect repellent OR citronella OR picaridin OR non-DEET) OR (DEET) AND Dengue	31 January 2023 10:00 AM	9	1

Appendix 3. Identification of Studies

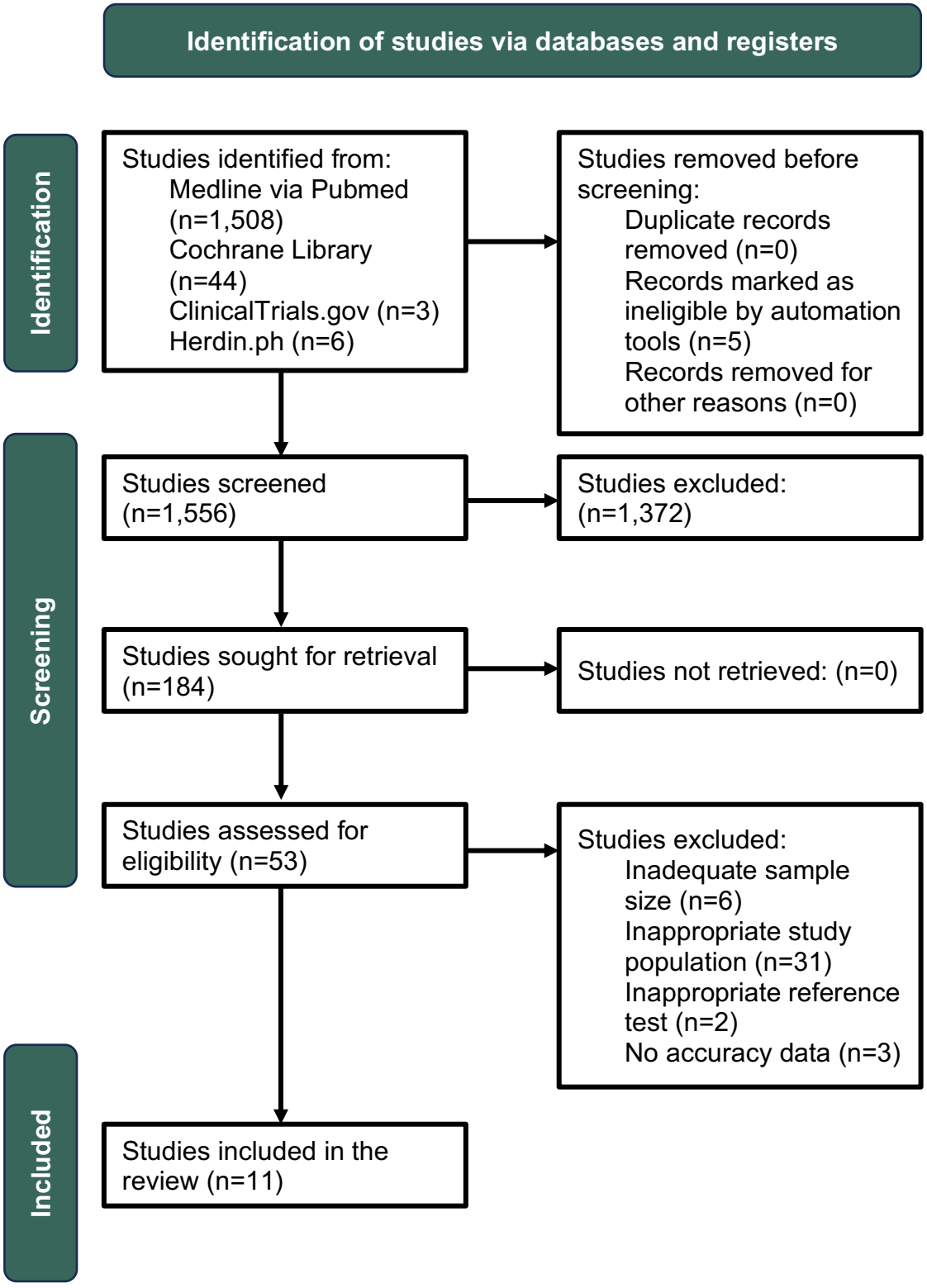


Figure 2. PRISMA Flow Diagram for Question 1A.

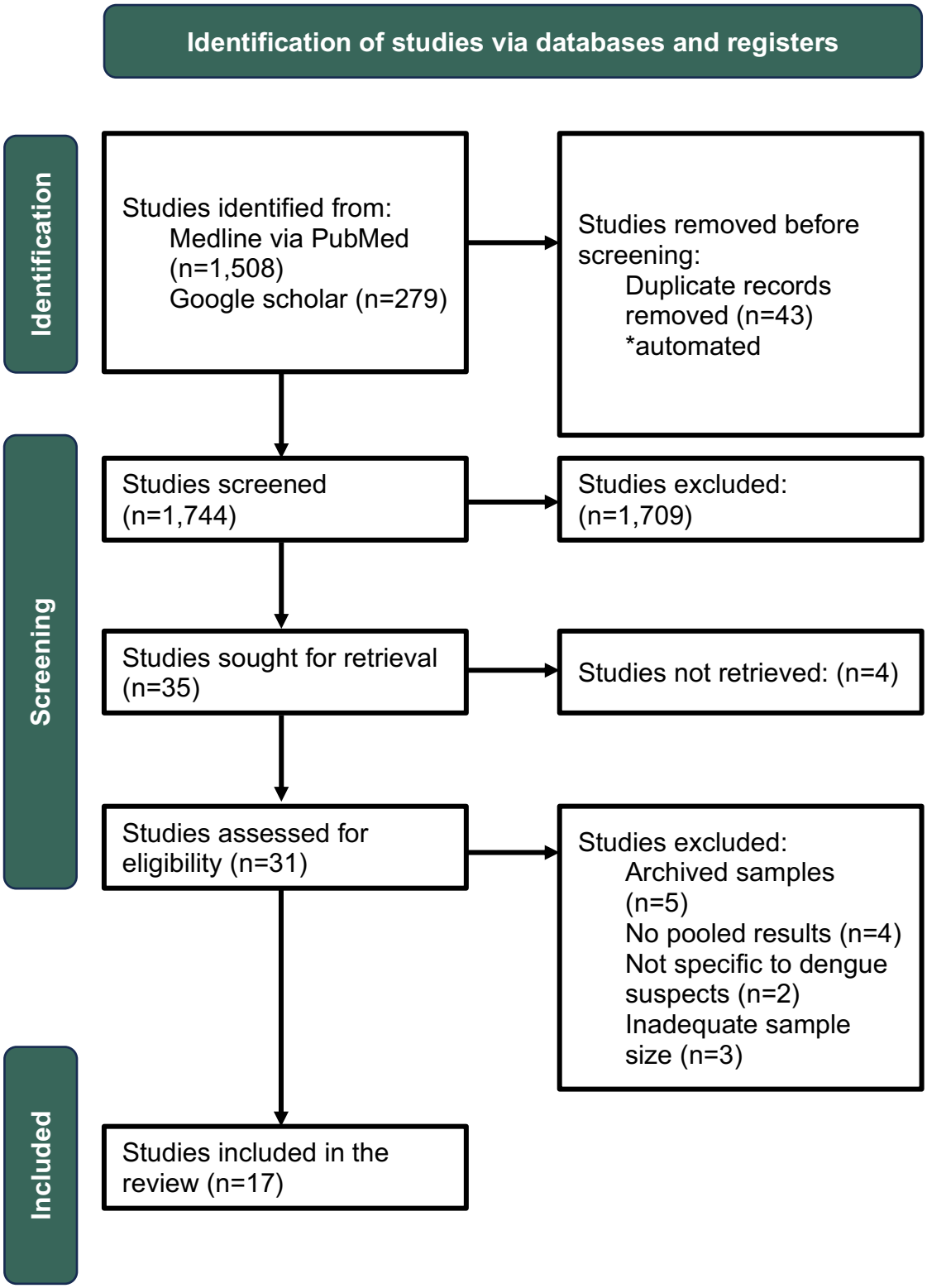
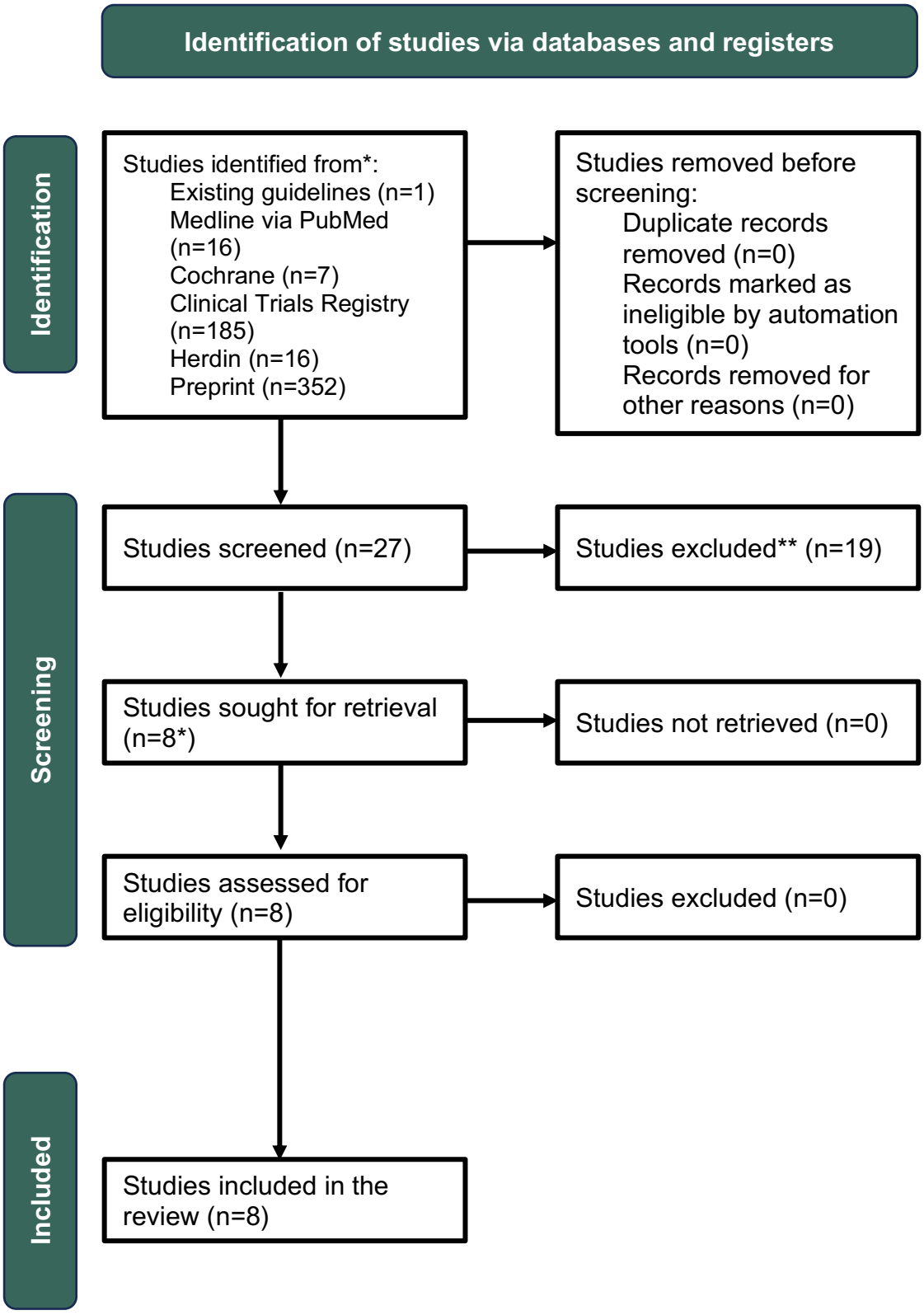


Figure 3. PRISMA Flow Diagram for Question 1B.



* 6 Reviews were included in the MEDLINE search; 1 study from preprint server and 1 study from HERDIN

**studies excluded are not systematic reviews and meta-analysis; most are observational studies pertaining to progression to severe dengue

Figure 4. PRISMA Flow Diagram for Question 2.

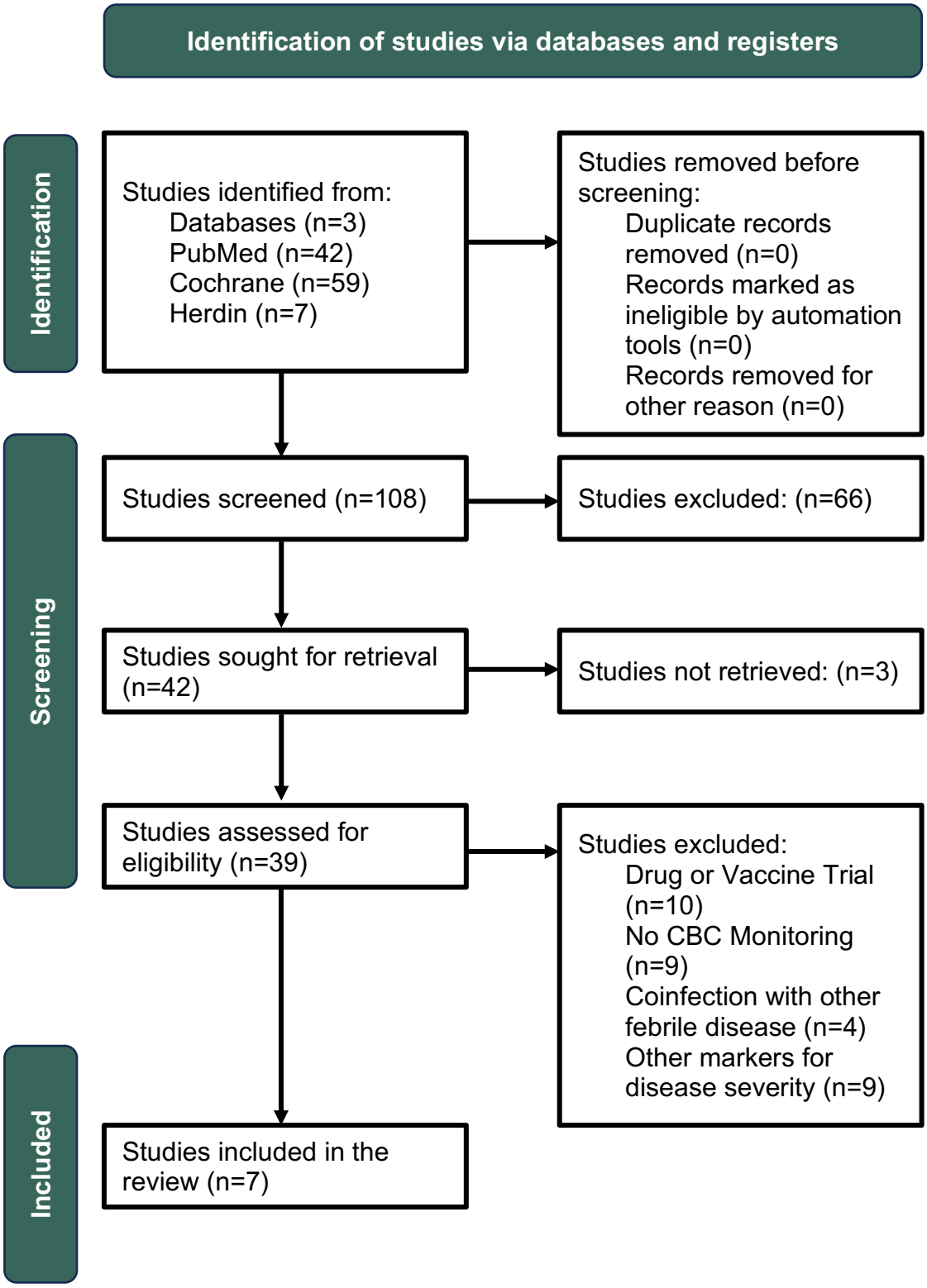
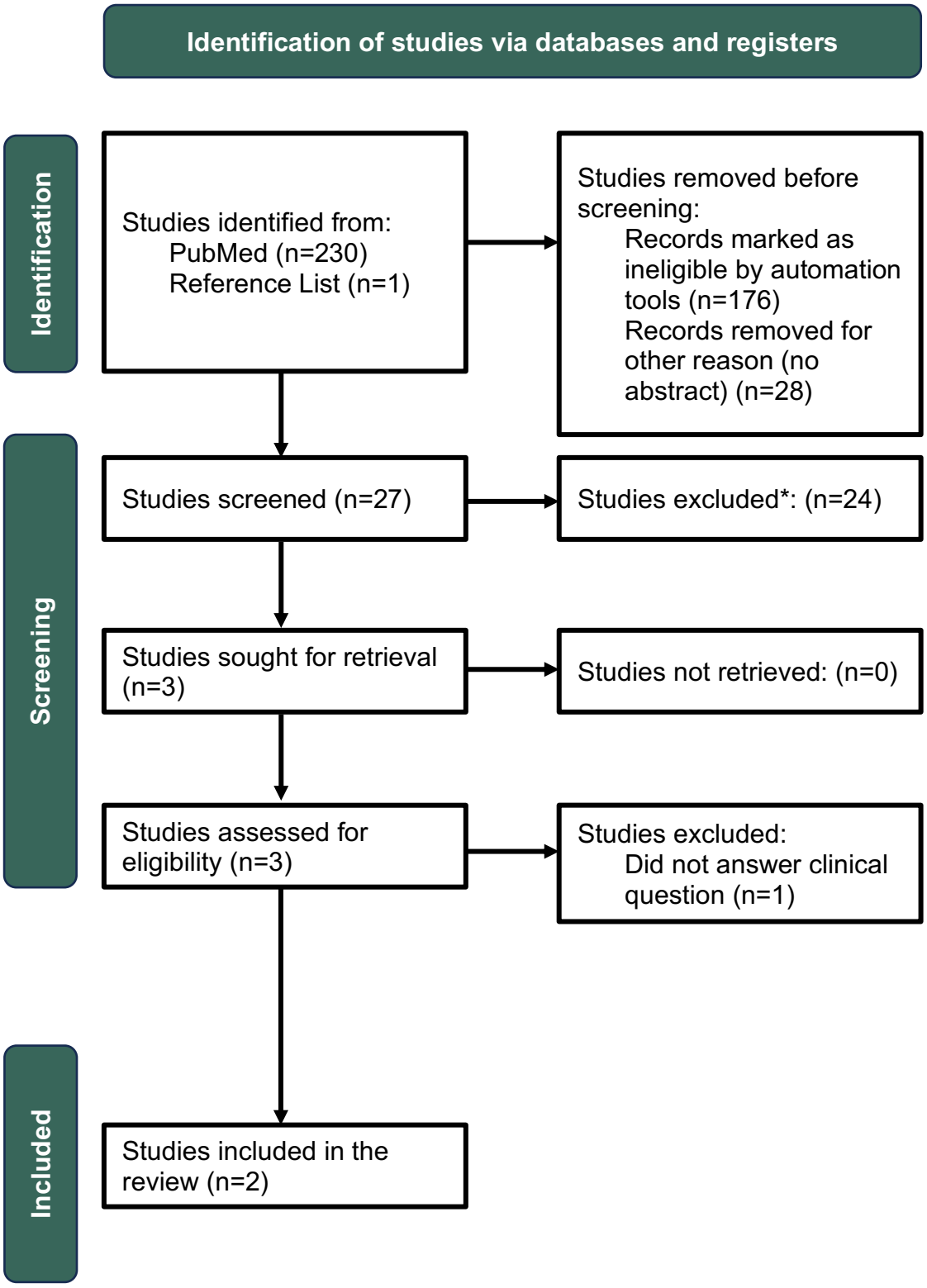


Figure 5. PRISMA Flow Diagram for Question 3.



*Oral therapy was not excluded in the excluded studies

Figure 6. PRISMA Flow Diagram for Question 4.

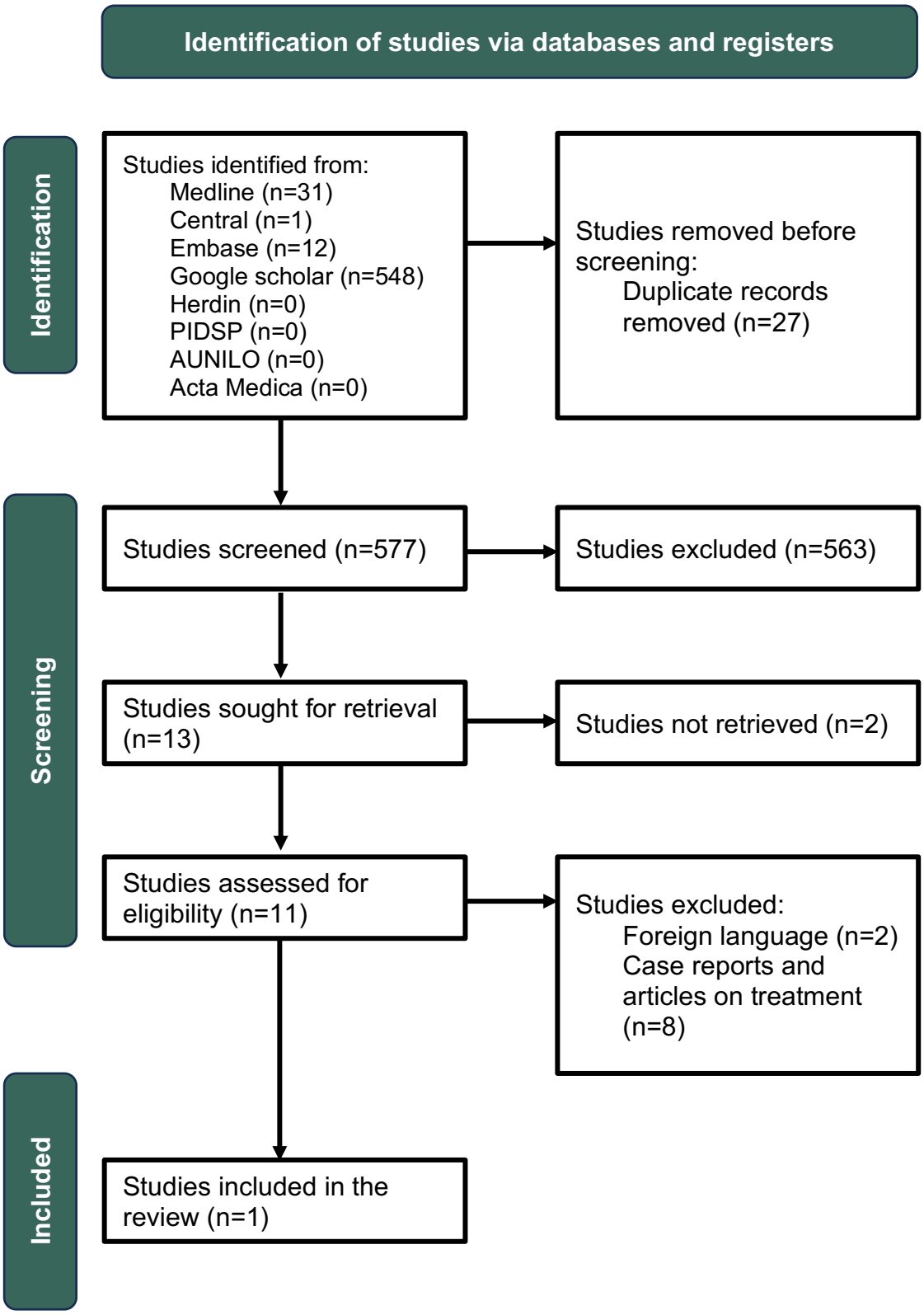


Figure 7. PRISMA Flow Diagram for Question 5.

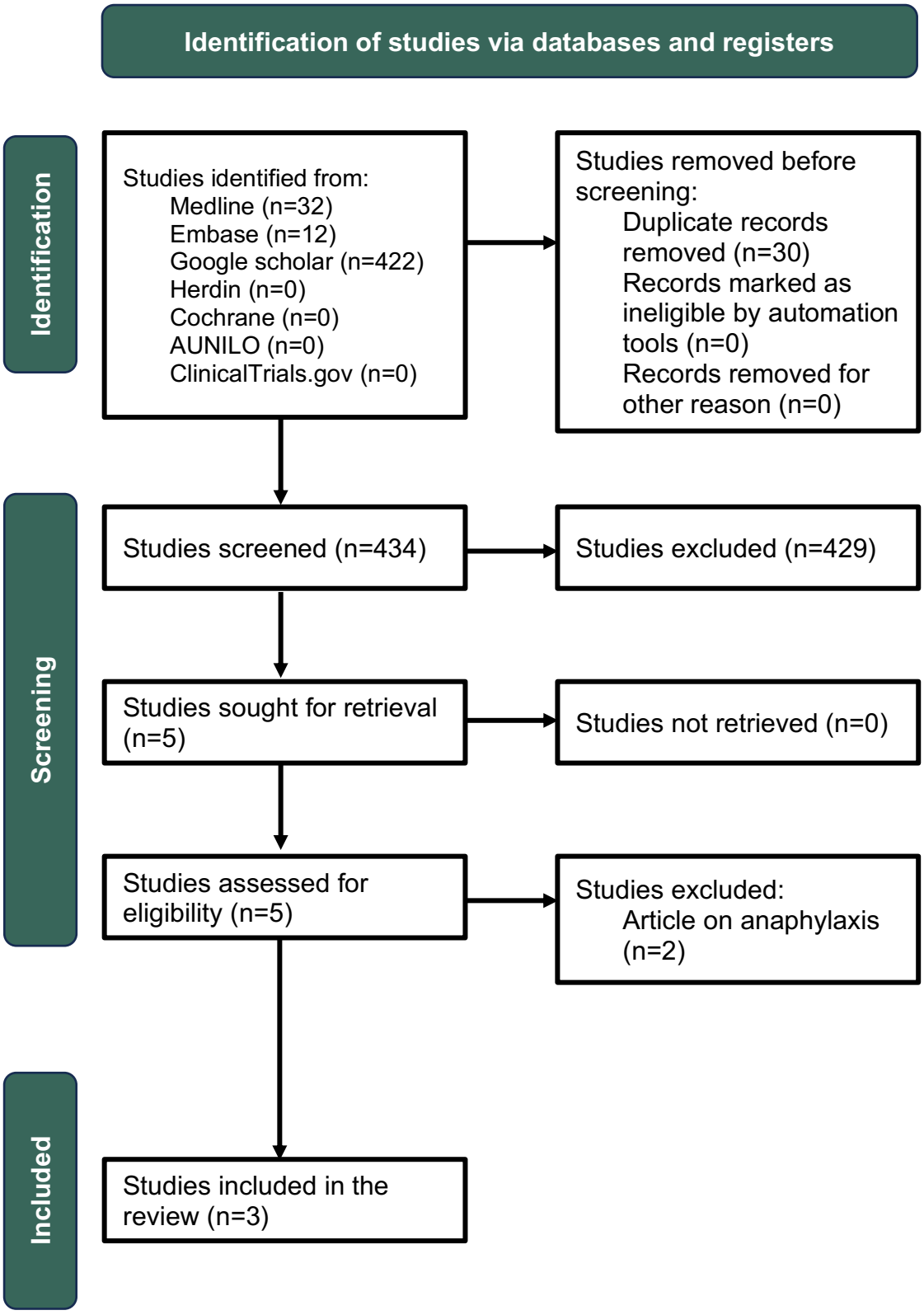


Figure 8. PRISMA Flow Diagram for Question 6.

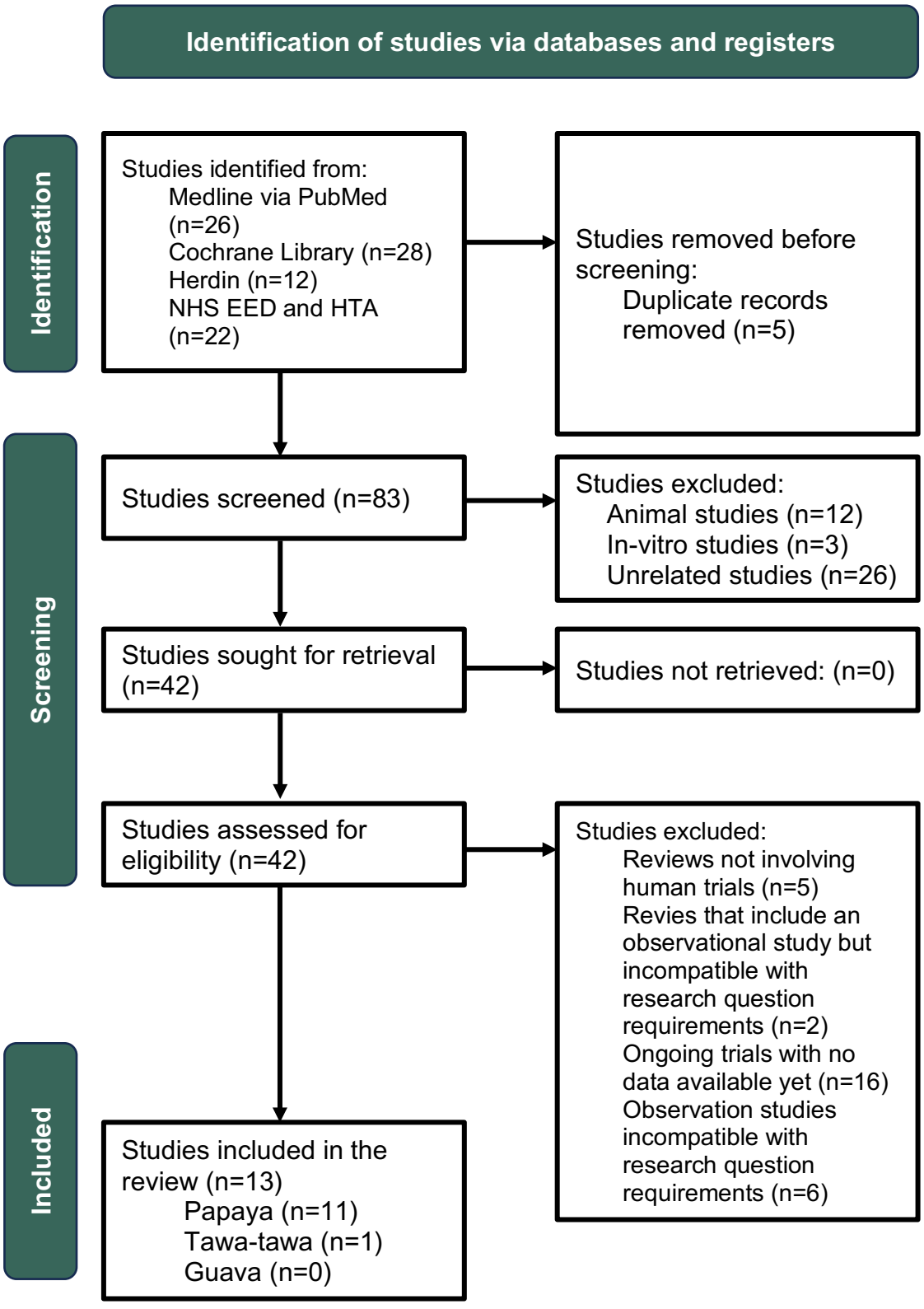


Figure 9. PRISMA Flow Diagram for Question 7.

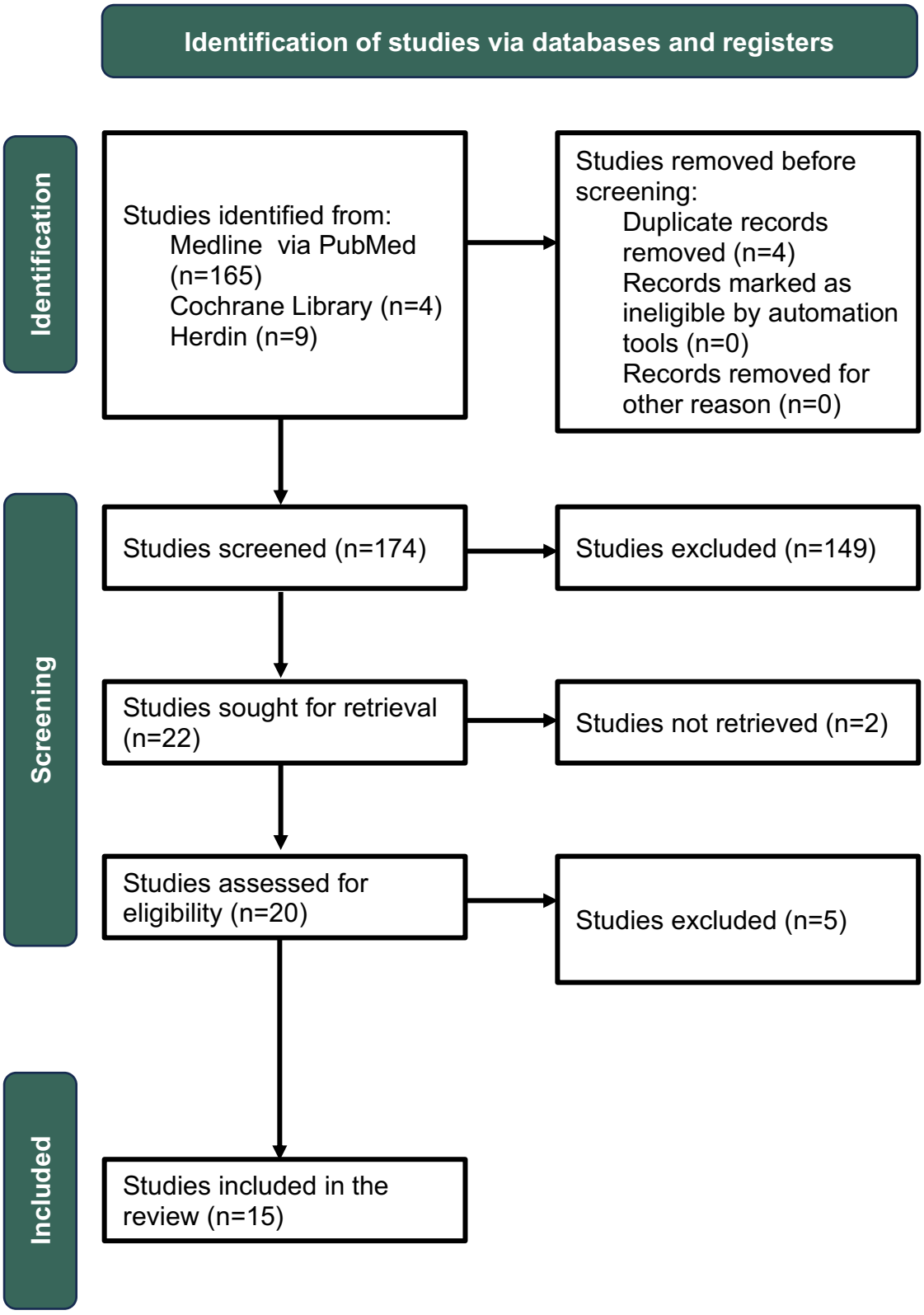


Figure 10. PRISMA Flow Diagram for Question 8.

Appendix 4. Characteristics of Included Studies

Appendix 4.1. Summary of study characteristics of Question 1A.

Study ID	Setting	Index Test	Population	Sample Size	Reference Standard
Alidjinou CS 2022	New caledonia	Biosynex Dengue NS1 Ag RDT (Biosynex, France)	Patients suspected of dengue infection with symptoms within 7 days of onset, attending a local hospital	471	RT-PCR
Buonora CS 2016	Brazil	Dengue NS1 Bioeasy (SD, South Korea)	Adult patients >18yrs old presenting at an emergency care center within 72 hours of an acute febrile illness without an evident source of infection during the 2013 DENV4 epidemic	325	RT-PCR and ELISA NS1/IgM/IgG
Hang Cohort 2009	Vietnam	NS1-LFRT by BioRad (Biorad, France)	Patients >2 yrs of age admitted to the intensive care units (adult or paediatric) or to one of the general wards with a clinical suspicion of dengue as their primary diagnosis, within 10 days onset of illness	138	RT-PCR and ELISA IgM IgG
Kyaw CS 2019	Myanmar	1 Humasis Dengue Combo Kit (Humasis, Korea) 2 CareUs Dengue Combo Kit (WellsBio, Korea) 3 Wondfo Dengue Combo Kit (Biotech, China)	Pediatric patients admitted at Mandalay Children Hospital clinically diagnosed with Dengue, serum samples were collected within 7 days after onset of fever	202	RT-PCR and ELISA IgM IgG
Liu CS 2018	Solomon Islands	1 SD Bioline Dengue Duo (SD, Korea) 2 CTK Dengue Ag (Biotech, USA)	Acute phase serum samples (between Day 0-6 after onset of fever or symptoms) from patients with Dengue-like illness at the NRH during the 2013 DENV 3 outbreak	412	RT-PCR
Liu CS 2020	Taiwan	1 Dengue NS1 Ag Strip (Bio-Rad, France)	Patients suspected to have Dengue fever during the 2012–2013 dengue outbreak in Kaohsiung City, Taiwan.	173	RT-PCR and ELISA IgM IgG

		2 Dengue Ag Rapid Test-Cassette (CTK Biotech, USA) 3 SD Dengue Duo Bioline - NS1 only (Standard Diagnostics, Korea)	Single acute-phase serum sera were collected between days 0&6 post-symptom onset		
Mata CS 2017	Brazil	Dengue Eden Test NS1 Bioeasy (SD, South Korea)	Patients over 18 years of age with up to 4 days of acute febrile syndrome without an established diagnosis, treated consecutively and by spontaneous demand at an emergency hospital during a DENV 1 epidemic in 2015	144	RT-PCR
Mata CS 2020	Brazil	1 Dengue NS1-Bioeasy (Standard Diagnostic, Korea) 2 Dengue NS1 Ag Strip - BioRad (Bio-Rad Laboratories, France) 3 IVB Dengue Ag NS1 - Orangelife (Orangelife, Brazil) 4 Dengue NS1-K130 Bioclin (Quibasa Brazil)	Adults older than 18 yrs who during the 2013 DENV 4 outbreak, had acute febrile syndrome for up to 72 hours, in the absence of identified focus of infection and at least 2 or more symptoms of suspected Dengue cases according to WHO, who spontaneously sought care at the emergency unit	321	RT-PCR
Najioullah CS 2011	Caribbean	Dengue NS1-Ag STRIP (Bio-Rad Lab, France)	Patients with fever ≥38.4 °C lasting for less than 8 days consulting at a hospital facility, conducted in the context of an DENV 2 outbreak	537	Nested RT-PCR
Pok Cohort 2010	Singapore	BioRad Dengue NS1 Antigen Strip (Bio-Rad Lab, France)	Individuals suspected of having dengue within 8 days after the onset of fever at primary healthcare clinics	321	RT-PCR and ELISA IgM IgG
Shukla CS 2017	India	Dengue Day 1 Test (J. Mitra, India)	Samples from patients in acute phase of illness (0-5 days) having symptoms of DEN	249	RT-PCR

Appendix 4.2. Summary of study characteristics of Question 1B.

Study ID	Setting	Index Test	Population	Sample Size	Reference Standard
Chong, 2022	Malaysia	SD Bioline Dengue Duo (NS1/IgM/IgG)	febrile patients >9 months with symptoms fulfilling WHO 2009 criteria for suspected dengue Age: mean 27.2 yrs (11 mos – 70.7 yrs) Day of illness: mean 4.3 days (1-11 days)	494	RT-PCR NS1, IgM ELISA
Kulkarni, 2022	India	Dengue Day 1 (NS1/IgM/IgG) SD Bioline Dengue Duo (NS1/IgM/IgG)	Patients with suspected dengue presenting within one week of symptom onset	809	RT-PCR NS1, IgM ELISA
Jang, 2019	Myanmar	CareUS (NS1/IgM/IgG) SD Bioline Dengue Duo (NS1/IgM/IgG) Humasis (NS1/IgM/IgG)	Patients with suspected dengue fever Age: mean 7.5 yrs (1-14 yrs) Day of illness: day 3-7 of fever	220	RT-PCR IgM, IgG ELISA
Krishnananthasivam, 2015	Sri Lanka	SD Bioline Dengue Duo (NS1/IgM/IgG)	suspected dengue patients	143	RT-PCR IgM, IgG ELISA
Sanchez Vargas, 2014	Mexico	SD Bioline Dengue Duo (NS1/IgM/IgG)	With febrile illness and other symptoms suggesting dengue infection	310	IgM, IgG ELISA
Gan, 2014	Singapore	SD Bioline Dengue Duo (NS1/IgM/IgG)	Patients age 18 years and above with an acute undifferentiated febrile illness (recorded temperature .37.5uC with no alternative syndromic diagnosis determined by treating clinician). Age: median 34 yrs (18-69 yrs) Day of illness: day 6 (1-14)	246	Viral isolation, RT PCR, NS1-, IgM, IgG ELISA
Blacksell, 2011	Sri Lanka	SD Bioline Dengue Duo (NS1/IgM/IgG) Merlin (IgM/IgG) Biosynex (IgM/IgG)	Adult (16 years) febrile (38°C) patients Age: median 30 yrs (16-86) Day of illness: day 5	259	RT-PCR IgM, IgG ELISA

		Panbio Dengue Duo (IgM/IgG)			
Tricou, 2010	Vietnam	SD Bioline Dengue Duo (NS1/IgM/IgG)	Patients above 6 months of age with clinically suspected dengue and fever for less than 7 days Day of illness: median day 3 (1-6)	292	RT-PCR
Kyaw, 2019	Myanmar	CareUS (NS1/IgM/IgG) Humasis (NS1/IgM/IgG) Wondfo Dengue combo (NS1/IgM/IgG)	Clinically diagnosed DEN patients Age: mean 5.45 yrs ±3	202	RT-PCR IgM, IgG ELISA
Liu, 2018	Solomon Islands	SD Bioline Dengue Duo (NS1/IgM/IgG) CTK (NS1/IgM/IgG)	Patients with dengue-like illness Day of illness: median day 2	412	RT-PCR IgM, IgG ELISA
Liu, 2020	Taiwan	SD Bioline Dengue Duo (NS1/IgM/IgG) CTK (NS1/IgM/IgG)	Dengue fever-suspected patients Age: mean 47 yrs (12-89) Day of illness: mean day 3 (0-7)	173	RT-PCR
Vivek, 2017	India	Dengue Day 1 (NS1/IgM/IgG)	Children with suspected or probable dengue Age: mean 6.8 yrs ± 4.5 Day of illness: mean 4 days ±1.4	211	RT-PCR
Naz, 2014	Pakistan	Panbio Dengue Duo (IgM/IgG)	Patient with presentation of defined clinical symptoms and history of acute febrile illness of 2–7 days with or without hemorrhage Age: mean 28 yrs (2-65) Day of illness: median 5 days (2-17)	184	IgM, IgG ELISA
Nga, 2007	Vietnam	Panbio Dengue Duo (IgM/IgG)	Patients with acute fever without signs of severe systemic or organ specific disease	220	IgM, IgG ELISA
Kumarasamy, 2006	Malaysia	Acon (IgM/IgG)	-	239	IgM ELISA
Pun, 2012	India	SD Bioline (IgM/IgG)	Age: median 35.5 yrs (1-68)	131	IgM ELISA

Appendix 4.3. Summary of study characteristics of Question 2.

Study Parameters			Significant Prognostic Factors
Study ID: Sandinirwan 2023 **No. of Included studies:** 49 **Target Population:** Pediatric dengue (serologically and clinically confirmed), 1997 or 2009 WHO classification (N > 20)	**Exposure:** Clinical or laboratory parameters with severe dengue (i.e. clinical shock state due to plasma leakage, severe bleeding, organ involvement), n > 20 **Outcome:** Summary measure or effect measure for severe dengue thru RR, OR, with CI or P values between	**Overall Risk Bias:** Most studies have low ROB in study participation (~80% of studies), study attrition (~80%), prognostic factor measurement (~70%), outcome measurement (~70%), statistical analysis and reporting (~55%). Moderate ROB for confounding bias (~55% of studies with moderate or high ROB) **Prognostic factors Reviewed:** Abdominal pain, Activated partial thromboplastin time, Age, Clinical fluid accumulation, DENV-2 Serotype Elevated hematocrit, Elevated AST and ALT, Gastrointestinal bleeding Hepatomegaly, Higher WBC Low albumin levels, Low platelet count Male gender, Neurological sign Normal nutrition, Petechiae Primary infection, Positive torniquet test, Rash, Secondary infection Temperature, Vomiting	**IN CHILDREN** **Factors with strong association (OR > 5)** Secondary infection (OR 8.66 [4.99, 15.04]; 3 studies) Low albumin levels (OR 7.34 [3.29, 16.38]; 10 studies) Neurological sign (OR 6.88 [2.91, 16.25]; 7 studies) Gastrointestinal bleeding (OR 5.87 [2.03, 16.98]; 5 studies) **Factors with moderate association (OR 1.6 to 5.0)** Elevated activated PTT (OR 4.59 [2.24, 9.37]; 3 studies) Elevated hematocrit (OR 3.14 [2.03, 4.85]; 16 studies) Elevated aspartate aminotransferase (OR 3.08 [2.18, 4.36]; 10 studies) Clinical fluid accumulation (OR 3.03 [1.28, 7.17]; 14 studies) Hepatomegaly (OR 2.28 [1.54, 3.38]; 16 studies) Vomiting (OR 2.01 [1.54, 2.64]; 14 studies) Elevated alanine aminotransferase (OR 1.98 [1.27, 3.08]; 9 studies) Low platelet count (OR 1.76 [1.50, 2.06]; 20 studies) DENV-2 serotype (OR 1.66 [1.30, 2.13]; 4 studies) Petechiae (OR 1.62 [1.31, 2.02]; 5 studies) **Factors with weak association (OR > 5)** Abdominal pain (OR 1.58 [1.07, 2.35]; 12 studies)
Study ID: PAHO CPG 2022 **No. of Included studies:** 217 **Target Population:** Patients with dengue (all ages)	**Exposure:** Cohort studies that reported the clinical evolution of patients with dengue infection and described different variables considered to be potential prognostic factors **Outcome:** Summary measure of effect in OR (adjusted and unadjusted)	**Overall Risk Bias:** Most of the studies included in the meta-analysis had serious methodological problems for the following outcomes: Acute renal failure, coagulopathy, splenomegaly, high fever, positive torniquet test, rhinorrhea, petechiae, nausea, obesity, malnutrition, headache. A subgroup analysis showed a significantly different estimate for studies that provided adjusted estimates or that had a low risk of bias. All of the studies included in the meta-analysis had serious	**IN ALL AGES** **Factors with strong association (OR > 5)** Narrowing pulse pressure (OR 7.12 [3.02, 16.76]; 6 studies; n=5,096) Acute renal failure (OR 6.73 [1.66, 27.20]; 8 studies; n=4,348) Arterial hypotension (OR 5.38 [3.31, 8.75]; 19 studies; n=7,463) Sensory disorder (OR 5.23 [3.45, 7.93]; 33 studies; n=76,881) Hemorrhages (OR 5.21 [3.53, 7.69]; 59 studies; n=18,469) Fluid accumulation manifesting in edema, ascites, pleural effusion, pericardial effusion (OR 5.04 [3.56, 7.14]; 54 studies; n=26,241) **Factors with moderate association (OR 1.6 to 5.0)** Increased capillary refill time (OR 4.96 [1.72, 14.32]; 3 studies; n=210) 3rd trimester of pregnancy (OR 3.94 [2.10, 5.42]; 1 study; n=99) Difficulty breathing (OR 3.93 [2.40, 6.42]; 12 studies; n=25,771)

		methodological problems for the following outcomes: retro-ocular pain, narrowing pulse pressure, arterial hypotension, increased capillary refill, pregnancy, microscopic hematuria, diarrhea, anorexia/hyporexia, cutaneous eruption, cough. **Prognostic factors Reviewed:** Abdominal pain, Acute renal failure Anorexia or hyporexia, Arterial hypotension, Coagulopathy, Diarrhea, Difficulty breathing, Elevated hematocrit, Elevated transaminases Fluid accumulation, Hemorrhages Hepatomegaly, High fever, Increased capillary refill time, Low platelet count, Malnutrition, Microscopic hematuria Mucosal bleeding, Narrowing pulse pressure, Nausea, Obesity, Petechia or ecchymosis, Positive torniquet test, Pregnancy, Rhinorrhea, Sensory disorder, Splenomegaly Third trimester of pregnancy, Vomiting	Pregnancy (OR 3.38 [2.10, 5.42]; 1 study; n=N/A) Hepatomegaly (OR 3.14 [2.38, 4.15]; 62 studies; n=25,989) Microscopic hematuria (OR 3.12 [1.23, 7.90]; 3 studies; n=1,831) Low platelet count (OR 3.02 [2.45, 3.73]; 62 studies; n=50,586) Coagulopathy assessed by altered hemostasis parameters (OR 2.83 [1.59, 5.04]; 10 studies; n=6,895 studies) Splenomegaly (OR 2.64 [1.31, 5.31]; 10 studies; n=2,367) Elevated transaminases (OR 2.55 [1.78, 3.64]; 39 studies; n=18,579) Elevated hematocrit (OR 2.30 [1.74, 3.05]; 45 studies; n=17,462) Abdominal pain (OR 2.02 [1.74, 2.35]; 87 studies; n=85,769 Mucosal bleeding (OR 1.96 [1.47, 2.69]; 50 studies; n=24,661) Vomiting (OR 1.74 [1.48, 2.05], 56 studies; n=72,312) **<u>Factors with weak association (OR 1.0 to 1.5)</u>**High fever with at least 1 documented temp ≥ 38.5C (OR 1.50 [0.97, 2.32]; 7 studies; n=2,125) Positive torniquet test (OR 1.48 [0.99, 2.20]; 32 studies; n=16,133) Diarrhea (OR 1.33 [1.06, 1.68]; 33 studies; n=9,549) Rhinorrhea (OR 1.24 [0.64, 2.42]; 4 studies; n=2,118) Anorexia or hyporexia (OR 1.21 [0.68, 2.15]; 8 studies; n=2,089) Petechia or ecchymosis (OR 1.21 [0.96, 1.52]; 31 studies; n=9,663)Nausea (OR 1.21 [0.85, 1.71]; 12 studies; n=2,967) Obesity (OR 1.18 [0.92, 1.52]; 17 studies; n=6,776) Malnutrition (OR 1.09 [0.84, 1.42]; 13 studies; n=5,909)Cutaneous eruption (OR 1.04 [0.79, 1.37]; 52 studies; n=71,994) Cough (OR 1.02 [0.62, 1.64]; 14 studies; n=4,314) Leukopenia (OR 0.88 [0.66, 1.17]; 29 studies; n=14,336) Retro-ocular pain (OR 0.88 [0.70, 1.10]; 28 studies; n=58,552) Headache (OR 0.87 [0.76, 0.99]; 46 studies; n=61,520)Myalgias or arthralgias (OR 0.79 [0.66, 0.95]; 43 studies; n=89,323)
Study ID: Yuan 2022 **No. of Included studies:** 87 **Target Population:** Patients with dengue (all ages)	**Exposure:** Dengue infections were confirmed by laboratory tests; severe dengue and dengue fever groups with characteristic data, such as epidemiological factors, clinical signs, and laboratory parameters; studies that provided original data **Outcome:** Summary effect or measure of effect in pooled OR and standardized mean difference (SMD) using fixed or random effect model	**Overall Risk Bias:** 34.5% were high quality; 63.2% were intermediate quality; 2.3% low quality **Prognostic factors Reviewed:** Age Diabetes Secondary Infection DENV Day of illness Lethargy Vomiting Diarrhea Abdominal Pain Hepatomegaly Petechiae Bleeding Pleural Effusion Ascites Hypotension Hematocrit Thrombocytopenia Transaminases (ALT, AST) Creatine Kinase Albumin Total Protein Proteinuria BUN LDHPT APTTIL-10Il-	**<u>IN ALL AGES</u>** **<u>Factors with strong association (OR >5 or SMD > 0.80)</u>** Bleeding (OR 6.586 [4.160, 11.30] 32 studies n=27000)Pleural Effusion (OR 15.836 [6.974, 35.967] 19 studies n=3666)Ascites (OR 24.299 [4.377, 136.138] 12 studies n=2213)High Hematocrit (OR 12.389 [6.091, 25.199] 7 studies n=18180) Thrombocytopenia (OR 8.146 [3.374, 19.665] 12 studies n=1238)ALT (SMD 1.007 [0.386, 1.627] 30 studies n=23694)High ALT (OR 4.030 [2.408, 6.747] 8 studies n=1069)AST (SMD 1.278 [0.640, 1.916] 29 studies n=25527) High AST (OR 4.053 (2.255, 7.287] 4 studies n=366)Creatine Kinase (SMD 2.647 [1.117, 4.177] 4 studies n=404)hypoalbuminemia (OR 20.601 [4.441, 95.562] 2 studies n=161)Low total protein (OR 10.993 [2.949, 40.978] 2 studies n=72) BUN (SMD 1.301 [0.330, 2.273] 4 studies n=2966)LDH (SMD 1.873 [0.494, 3.253] 5 studies n=469)IL-10 (SMD 0.868 [0.197, 1.539] 6 studies n=425) IL-8 (SMD 3.37 [1.059, 5.615] 3 studies n=151)sVCAM-1 (SMD 1.297 [0.856, 1.737] 2 studies n=70)

		8sVCAM-1IP-10GenderFever Headache Weakness Osteodynia Myalgia Retro-orbital Pain Rash Positive Tourniquet Test WBC count Hemoglobin Lymphocyte Count Neutrophil Count Monocyte Count Alkaline Phosphatase Creatinine Total Bilirubin Urine Protein Cholesterol Triglyceride IFN-gamma TNF alpha IL-6 IL-12 P70	**<u>Factors with moderate association (OR 1.6 to 5.0 or SMD 0.50-0.79)</u>** Diabetes (OR 4.418 [2.698, 7.232; 9 studies n=4844) Secondary Infection (OR 2.693 [2.083, 3.481]; 22 studies n=21149) Sero DENV 2 (OR 1.843 [1.269, 2.678] 17 studies n=4814) Day of Illness (SMD 0.614 [0.346, 0.882] 21 studies n=3220) Lethargy (OR 2.563 [1.517, 4.329] 8 studies n=29412)Persistent Vomiting (OR 5.569 (3.041, 10.2) 3 studies n=813) Abdominal pain (OR 1.850 [1.466, 2.335] 33 studies n=27727) Hepatomegaly (OR 4.403 [3.016, 6.430] 17 studies n=20581) Petechiae (OR 2.508 [1.720, 3.655] 19 studies n=3529)Proteinuria (OR 3.681 [2.038, 6.649] 2 studies n=1098) Protime (SMD 0.781 [0.219, 1.343] 6 studies n=2611) APTT (SMD 0.529 [0.046, 1.013] 6 studies n=2089) IP-10 (SMD 0.531 [0.059, 1.004] 2 studies n=86) **<u>Factors with weak association (OR < 1.5 or SMD 0.20 to 0.49)</u>** Age SMD (0.151 [0.027-0.275]; 46 studies n=11000) Sero DENV 1 (OR 0.709 [0.504, 0.997] 15 studies n=4462) Sero DENV 3 (OR 0.694 [0.492, 0.979] 16 studies n=4424) Vomiting (OR 1.533 [1.203, 1.953] 26 studies n=9417)Diarrhea (OR 1.245 [1.008, 1.537] 16 studies n=3750)Hematocrit (SMD 0.327 [0.109, 0.546] 27 studies n=7612) Albumin (SMD -0.767[-0.989, -0.544] 13 studies n=21740)Total Protein (SMD -0.271[-.0.449, -0.093] 5 studies n=3390)
Study ID: Tsheten 2021 **No. of Included studies:** 143 **Target Population:** Patients with dengue (all ages)	**Exposure:** Observational studies conducted in humans; comparing severe and non-severe dengue; reported patient's demographic characteristics, comorbidities and clinical warning signs **Outcome:** Summary eff in pooled OR using Inverse variance	**Overall Risk Bias:** Attrition rate were either below <20% or non-existent in 143 studies; deficient standards across studies were equal prognosis 88.6%; equal implementation 64.6%; and equal retention 59.4%; Temporal precedence 1.5% across studies **Prognostic factors Reviewed:** Ascites Cardiovascular disease Children Diabetes Elevated hematocrit with concurrent decrease in platelet count Epistaxis Female Gastrointestinal bleeding Gum bleeding Hematemesis Hepatomegaly Hypertension Lethargy Melena Obesity Pleural effusion Renal disease Secondary infection Skin bleeding Vomiting	**<u>Factors with strong association (OR >5 or SMD > 0.80)</u>** Increased Hematocrit and decreased platelet count (OR 5.13 [1.61, 16.34]7 studies)Hepatomegaly (OR 5.92 [3.29, 10.65] 47 studies)Ascites (OR 6.30[3.75, 10.6]) 22 studies) Pleural Effusion (OR 5.72 [3.24, 10.10] 25 studies)Hematemesis (OR 12.35 [4.97, 30.72] 5 studies) GI Bleeding (OR 9.49[2.75, 32.70 5 studies) **<u>Factors with moderate association (OR 1.6 to 5.0 or SMD 0.50-0.79)</u>** Children (OR 1.96[1.22, 3.13] 22 studies) Secondary Infection (OR 3.23 [2.28, 4.57] 29 studies)Diabetes (OR 2.88 [1.72, 4.81] 29 studies) Renal Disease (OR 4.54 [1.55, 13.3] 4 studies) Abdominal Pain (OR 2.00 [1.49, 2.68] 55 studies)Vomiting (OR 1.80 [1.43, 2.26] 53 studies) Lethargy (OR 2.73 [1.05, 7.10] 10 studies) Melena (OR 4.05 [1.64, 10.00] 9 studies) **<u>Factors with weak association (OR < 1.5 or SMD 0.20 to 0.49)</u>**

Study ID: Sangkaew 2021 **No. of Included studies:** 150 **Target Population:** Symptomatic infected individuals in the febrile phase and Laboratory confirmed Dengue diagnosis according to WHO Guideline in 1997 and 2009	**Exposure:** Demographic features, clinical manifestations (signs and symptoms), laboratory parameters, or imaging techniques and parameters collected during the febrile phase **Outcome:** Summary effect or measure of effect in pooled OR and standardized mean difference (SMD) using random effect model	**Overall Risk Bias:** High risk of bias in terms of potential confounders not being addressed and adjusted for appropriately. There was also considerable risk of bias in terms of patient participation because some studies recruited patients from the inpatient department, which could have missed some patients presenting with mild symptoms. The risk of bias in terms of study attrition was low. Although the risk of bias in terms of measurement of outcomes and prognostic factors was low because the included studies used definition based on the WHO guidelines, 25% of includes studies were considered to have a moderate risk of bias for outcomes and prognostic factors **Prognostic factors Reviewed:** Age Sex Nutritional Status Weight Mixed Comorbidity Hypertension Diabetes Renal Disease Rash Cardiovascular Disease Vomiting Abdominal Pain and Tenderness Headache Minor Bleeding Positive Tourniquet Test Immune Status Clinical Fluid Accumulation Serotypes Viraemia Levels Platelet Counts Leukocyte Cell Counts Hematocrit AST ALT Serum Albumin	**IN ALL AGES** **Factors with strong association (OR >5 or SMD > 0.80)** AST (SMD 1.06[0.54, 1.57]7 studies) **Factors with moderate association (OR 1.6 to 5.0 or SMD 0.50-0.79)** Diabetes (OR 4.38[2.58, 7.43] 12 studies n=5852) Renal Disease (OR 4.67[2.21, 9.88] 6 studies n=1786)Hypertension (OR 2.19[1.36, 3.53] 9 studies n=4380) Cardiovascular Disease (OR 2.79[1.04, 7.5] 5 studies n=1832)Vomiting (OR 2.25[1.87, 2.71] 9 studies n=6229)Abdominal pain and tenderness (OR 1.92[1.35, 2.74] 9 studies n=7171)Bleeding (OR 1.57[1.13, 2.19]10 studies n=1498)Clinical Fluid Accumulation (OR 4.61[2.29, 9.26] 4 studies n=1520)Secondary Infection (OR 2.26[1.65, 3.09] 32 studies n=23912) ALT (SMD 0.73[0.36, 1.09] 7 studies) DENV 2 vs DENV-1 (OR 1.81[1.24, 2.65] 10 studies) DENV 2 vs DENV 3 (OR 2.24[1.48, 3.38)10 studies) **Factors with weak association (OR < 1.5 or SMD 0.20 to 0.49)** Female (OR 1.13[1.01, 1.26] 78 studies n=45623)Platelet count (SMD -0.34[-0.54, -0.15] 12 studies Serum Albumin (SMD -0.15[-0.86, -0.15] 4 studies) **IN CHILDREN** **Factors with moderate association (OR 1.6 to 5.0 or SMD 0.50-0.79**) DENV 2 vs DENV-1 (OR 1.81[1.24, 2.65] 10 studies)DENV 2 vs DENV 3 (OR 2.24[1.48, 3.38)10 studies)
Study ID: Htun 2021 **No. of Included studies:** 39 **Target Population:** Patients with severe dengue (all ages)	**Exposure:** Any type of studies (retrospective, Prospective or cohort, case-control, cross-sectional studies reporting severe dengue (defined by 2009 WHO diagnosis criteria) compared with dengue fever; studies that distinguished clinical signs and symptoms	**Overall Risk Bias:** Only 12% (5/39) of the studies scored ≥ 7 deemed high quality **Prognostic factors Reviewed:** Nausea Headache Retro-Orbital Pain Arthralgia Myalgia Hematuria Cough Diarrhea Splenomegaly Shock Dyspnea Gallbladder Wall Thickening	**IN ALL AGES** **Factors with strong association (OR >5 or SMD > 0.80)** Pleural Effusion (OR 6.2[3.66, 10.51] 14 studies n=264)Ascites (OR 5.2[3.27, 8.29] 15 studies n=266) Gallbladder wall thickening (OR 5.61[2.73, 11.53] 4 studies n=141)GI bleeding (OR 14.56[5.38, 39.39] 10 studies n=104)Shock (OR 47.51[14.80, 152.5) 6 studies n=235)Dyspnea (OR 11.19[6.91, 18.11] 6 studies n=99)Impaired Consciousness (OR 29.81[4.08, 217.94) 5 studies n=37)

	and/or laboratory features of severe dengue and dengue fever with or without warning signs; studies that published on and after 2009; studies that classified dengue severity according to new 2009 WHO classification; studies that included either children or adults only or both children and adults **Outcome:** Summary of effects as OR using fixed-effect or random-effect model	Gender Comorbidity Fever Vomiting Rash Tourniquet Test (+) Leukopenia Abdominal pain or tenderness Persistent Vomiting Pleural Effusion Ascites Epistaxis Gum bleeding Gastrointestinal Bleeding (hematemesis or melena) Vaginal Bleeding Lethargy or Restlessness Hepatomegaly >2 cm Increased Hematocrit with decreased Platelets skin bleeding (petechiae, purpura, ecchymosis) Impaired consciousness Thrombocytopenia (<150)elevated ALT (>40) elevated AST (>40) hypoalbuminemia primary infection secondary infection	**Factors with moderate association (OR 1.6 to 5.0 or SMD 0.50-0.79)** Comorbidity (OR 2.03[1.09, 3.78] 8 studies n=100) Vomiting (OR 2.18[1.5, 3.16] 19 studies n=849)Abdominal Pain (OR 2.00[1.49, 2.68] 33 studies n=1338) Persistent Vomiting (OR 2.57[1.40, 4.73] 12 studies n=296) Epistaxis (OR 2.23[1.04,4.77] 9 studies n=73) Gum bleeding (OR 3.34[1.6, 6.98] 10 studies n=48) Skin Bleeding (petechiae, purpura, ecchymosis (OR 2.12[[1.53, 3.19] 19 studies n=386) Lethargy or restlessness (OR 4.32[1.86, 10.04] 13 studies n=464)Hepatomegaly >2 cm (OR 3.34[2.38, 4.68] 25 studies n=796) Elevated ALT >40 (OR 3.24[1.87, 5.61] 7 studies n=290) Elevated AST >40 (OR 3.75[2.11, 6.68) 8 studies n=338) Thrombocytopenia <150 (OR 2.7[1.6, 4.55] 18 studies n=893)Secondary Infection (OR 1.93[1.25, 2.97] 5 studies n=96) **Factors with weak association (OR < 1.5 or SMD 0.20 to 0.49)**
Study ID: Zulkipli 2018 **No. of Included studies:** 15 **Target Population:** Pediatric patients with Dengue (0-18 years old)	**Exposure:** Interventional/ observational studies that evaluated obesity and dengue outcomes; studies that have information on body compositions such as weight, height, body mass index, and waist circumference **Outcome:** Severe dengue infection compared to non-severe dengue infection, summary effect measured as OR using random-effects model	**Overall Risk Bias:** 9 studies as good quality studies 6 studies as moderate quality studies **Prognostic factors Reviewed:** Obesity	**IN CHILDREN** **Factors with strong association (OR >5 or SMD > 0.80)** **Factors with moderate association (OR 1.6 to 5.0 or SMD 0.50-0.79)** **Factors with weak association (OR < 1.5 or SMD 0.20 to 0.49)** Obesity (OR 1.38[1.10, 1.73] 15 studies n=579)
Study ID: Domingo, 2021 **No. of Included studies:** 4 **Target Population:** Pediatric patients with Dengue (0-18 years old)	**Exposure:** Serum calcium levels of patients tested and correlated with dengue fever, patients diagnose with dengue through Dengue NS1 and/or Dengue IgG, IgM and /or ELISA RT-PCR, severity of dengue of patients was specified and	**Overall Risk Bias:** All of the included studies had low risk of bias; with one study showed unclear applicability in the patient selection and index test because target population only involved a specific group **Prognostic factors Reviewed:** Serum calcium Levels	**IN CHILDREN** **Factors with strong association (OR >5 or SMD > 0.80)** **Factors with moderate association (OR 1.6 to 5.0 or SMD 0.50-0.79)** **Factors with weak association (OR < 1.5 or SMD 0.20 to 0.49)** Mean Serum total and ionized calcium (Sensitivity 74%[0.58, 0.84] and Specificity 75%[0.67, 0.81]; PPV 67% and NPV 90.7%)

	serum calcium levels of patient were stated. **Outcome:** Summary effect expressed in sensitivity and specificity of the test in predicting dengue; plotting of the sensitivity and specificity of the ROC curve included in the results are the PPV, NPV, Likelihood Ratios and Diagnostic OR		

Appendix 4.4.1. Summary of study characteristics of Question 3 involving pediatric patients.

Author, Year, Study Title	Study design	Country	No. of patients	Population	Frequency of CBC	Intervention Group(s)	Outcomes
Butthep et al. 2006 Elevated soluble thrombomodulin in the febrile stage related to patients at risk for dengue shock syndrome	Retrospective Observational	Thailand	111	Pediatric (4-16 yrs) with suspected dengue; hospitalized No mention of co-infections or comorbidities among the population. All were enrolled during the febrile phase of illness. Warning signs were not specified if present upon start of study. DF: 25 (22.52%) DHF: 64 (57.66%) DSS: 14 (12.61%) OFI: 8 (7.21%)	Once a day	Blood sample collection daily beginning on day of admission	Mean hematocrits of patients were highest at day of defervescence; mean platelet counts of DSS patients were lowest on the 1st 2 days of defervescence.
Wills et al. 2009 Hemostatic changes in Vietnamese children with mild dengue correlate with the severity of vascular leakage rather than bleeding	Prospective Observational	Vietnam	431	Previously healthy children with symptoms of viral syndrome. No mention of co-infections or comorbidities among the population. All were enrolled during the febrile phase of illness. Warning signs were not specified if present upon start of study. Age: 2-15 years old Confirmed dengue: 375 (87%) * 8 with limited clinical and/or laboratory data 33 (8.8%) developed shock OFI: 40 (9.29%) Indeterminate: 16 (3.71%)	Once a day	Once a day CBC monitoring beginning on admission	Thrombocytopenia was noted starting day 2 of illness, and lowest platelet count noted at day 6 of illness.
Butthep et al. 2012 Alteration of cytokines and	Retrospective Observational	Thailand	164	Pediatric patients with Suspected Dengue No mention of co-infections or comorbidities among the population. All were enrolled during the febrile phase of	Once a day	Blood sample collection daily beginning on admission	Platelet count <100,000 were noted 1-2 days before shock or defervescence and will

chemokines during febrile episodes associated with endothelial cell damage and plasma leakage in dengue hemor-rhagic fever.				illness. Warning signs were not specified if present upon start of study. DF: 51 (31.10%) DHF: 79 (48.17%) DSS: 19 (11.58%) OFI: 15 (9.15%)			start to rise on day 1-2 after defervescence.
Sreenivasan et al. 2017 Development of a prognostic prediction model to determine severe dengue in children.	Prospective Analytical	India	359	Pediatric patients with confirmed dengue (based on NS1Ag ELISA or IgM ELISA positivity). Patients with co-morbidities and with probable co-infections were excluded. All were enrolled during the febrile phase of illness; Presence of warning signs on admission: abdominal pain/tenderness (59.05%), lethargy/restlessness (90.81%), vomiting (27.30%), mucosal bleed (15.88%), hepatomegaly (39.83%), clinical fluid accumulation (12.81%), thrombocytopenia (75.21%) Age: 1 month-12 years old Non-severe Dengue: 266 (74.09%) Severe Dengue: 93 (25.91%)	Once a day	Total count, hematocrit and platelet counts were done daily beginning on admission	A rising hematocrit and falling platelet count usually marks the onset of the critical phase.
Lam et al. 2017 The value of daily platelet counts for predicting dengue shock syndrome: Results from a prospective	Prospective Observational	Vietnam	2301	Pediatric patients (5-15 yrs) with laboratory-confirmed dengue; hospitalized. No mention of co-infections or comorbidities among the population. All were enrolled during the febrile phase of illness (days 1-4); Presence of warning signs on admission: vomiting (36%), tiredness (84%), positive tourniquet test	Once a day	Daily platelet monitoring beginning on enrollment (Days 1-4 of illness)	Platelet counts for patients who progressed to DSS were lower than those who did not progress to DSS. The platelet nadir commonly occurred around day 6 of illness. Usually the day before DSS occurred.

observational study of 2301 Vietnamese children with dengue				(29%), abdominal pain (20%), palpable liver (10%), mucosal bleeding (7%) No DSS: 2158 (93.79%) DSS: 143 (6.21%)			As to hematocrit levels, there was no clear difference between those who developed DSS and those who did not develop DSS.

Appendix 4.4.2. Summary of study characteristics of Question 3 involving adult and pediatric patients.

Author, Year, Study Title	Study design	Country	No. of patients	Population	Frequency of CBC	Intervention Group(s)	Outcomes
Ralapanawa et al. 2018 Value of peripheral blood count for dengue severity prediction	Retrospective Observational	Sri Lanka	515	Confirmed Dengue No mention of co-infections or comorbidities among the population. All were enrolled during the febrile phase of illness; Presence of warning signs: thrombocytopenia (96.3%) <u>Age: 14-86 years old</u> DF: 182 (35.34%) DHF: 333 (64.66%)	Days 2, 3 and 5 of illness	Routine blood investigation beginning on Day 2 then on Days 3 and 5 of illness	Leukopenia was observed in days 2 or 3 of illness. Thrombocytopenia was observed during the acute febrile phase.
Chaloemwong et al 2018 Useful clinical features and hematological parameters for the diagnosis of dengue infection in patients with acute febrile illness: a retrospective study	Retrospective Observational	Thailand	300	With symptoms of acute febrile illness (less than 7 days) The dengue infected patients with evidence of co-infection were excluded All were enrolled during the febrile phase of illness. Presence of warning signs: myalgia (48.7%) headache (47.4%), loss of appetite (34.4%), nausea (33.8%), sore throat (9.1%), rash (6.8%), bleeding (5.8%), abdominal pain (5.8%), diarrhea (5.2%)	Frequency depends on physician's decision	Frequency of blood test depend on physician decision as individual case beginning of collection not stated	Hemoglobin and hematocrit higher in dengue group with peak hemoglobin and hematocrit at days 3-10 of illness (highest at day 7); Platelet and WBC were lower in dengue with platelet nadir at days 3-10 (lowest at day 6) and WBC nadir at days 2-10 (lowest at day 4).

				Age: 15 years old and older DF: 154 (51.33%) OFI: 146 (48.67%)			
Rao et al. 2020 Dengue fever: prognostic insights from a complete blood count	Retrospective Observational	India	56	Dengue Confirmed Patients with pancytopenia secondary to other causes, blood component transfusion, chronic liver disease, hematological disease, and administration of immunosuppressive drugs, including steroids were excluded. All were enrolled during the febrile phase of illness. Presence of warning signs: myalgia (70%), headache (50%), vomiting (39%), abdominal pain (14%) Age: 11-63 years old Patients were not classified as to Non-severe and Severe Dengue	Frequency depends on clinician's discretion	Frequency of tests in each case was based on the clinician's discretion in accordance with the patient's condition	Most common hematological feature was thrombocytopenia (90%), followed by leukopenia (76%) and an increase in the hematocrit.

Appendix 4.5. Summary of study characteristics of Question 4.

Primary Author	Study design	No. of patients	Population	Intervention Group(s)	Control	Outcomes
Lee et al. 2010 Comparison of the effects of oral hydration and intravenous fluid replacement in adult patients with non-shock dengue hemorrhagic fever in Taiwan	Observational study	49 (ORS: n=19, IV fluid: n=30)	Adults aged >18 years with clinically suspected DHF grade I or II on arrival and with subsequently serological confirmation via PCR, dengue IgM ELISA, or four-fold increase in dengue-specific hemagglutination inhibition titer	Oral hydration with water or fruit juice (amount depended on their physiological demands or whenever they felt thirsty)	intravenous fluid (0.9% saline, 0.9% saline plus 5% glucose, or Ringer's lactate) infusion at more than 40 ml/kg/day during the first 72h of hospitalization	Laboratory data • Leukopenia • Leukocytosis • Atypical lymphocytosis • Mean peak hematocrit • Mean nadir platelet count • Prolongation of aPTT • Prolongation of PT • Mean AST • Mean ALT Total units of platelets transfused Mean duration of fever (days) Pleural effusion or pulmonary edema Gallbladder swelling Ascites Patients receiving furosemide Mean length of hospital stay (days)
Nainggolan et. al 2018 The Tolerability and Efficacy of Oral Isotonic Solution versus Plain Water in Dengue Patients: A Randomized Clinical Trial	RCT	24	Dengue patients with no warning signs, age >18 years, having fever <48 h, able to tolerate an adequate volume of oral fluids, positive dengue NS 1 antigen test and confirmed by polymerase chain reaction (PCR), and agreed to participate in the study	OIS beverage composed of Na+ 21 mEq/L, K+ 5 mEq/L, Ca2+ 1 mEq/L, Mg2+ 0.5 mEq/L, Cl− 16 mEq/L, citrate3− 10 mEq/L, and lactate 1 mEq/L And 500 ml of maintenance Ringer Lactate intravenously per day until discharge.	Plain water 500 ml of maintenance Ringer Lactate intravenously per day until discharge	Tolerability (observing nausea, vomiting, bloating, and oral fluid intake) Efficacy (body temperature, hematocrit, mean arterial pressure (MAP), fluid balance (oral and parenteral fluid intake minus urine output), Na^+, and K^+ every 24 h)

Appendix 4.6. Summary of study characteristics of Question 5.

Author	Study design	Country	No. of patients	Population	Group A	Group B	Outcomes
Marvel 2019	Retrospective Cohort	Indonesia	81	Patients with dengue fever and dengue hemorrhagic fever	Omeprazole in criteria group (platelet <50,000) n = 42	Omeprazole in noncriteria group (platelet >50,000) n = 39	Total maintenance cost: Group A (Median) IDR 1,109,195 (591,873 - 4,104,192) Php 4,015.77 (2,142.84-14,858.98) Group A (CI 95%) IDR 1,106,679 - 1,496,235 Php 4,006.66 - 5,417.03 Group B (Median) IDR 1,261,958 (664,107-2,750,078) Php 4568.84 (2,404.36 - 9,956.49) Group B (CI 95%) IDR 1,216,891 - 1,597,250 Php 4,405.68 - 5,782.75 Total cost of omeprazole for all patients: Group A:IDR 13,072,446 Php 47,345.68 Group B:IDR 12,247,686 Php 44,358.57 Adverse events (Diarrhea) Group A: 2/42 Group 2: 4/39

Appendix 4.7. Summary of study characteristics of Question 6.

Author/Title	Study design	Country	No. of patients	Population	Exposure	Outcomes
Chang et al. 2017 Differences in Mortality and Clinical Manifestations of Dengue Hemorrhagic Fever in Taiwan in Different Years: A Comparison for Cases in 2014 and 2015 Epidemics	Descriptive	Taiwan	N=206	Adult patients (≥20yo) with dengue hemorrhagic fever	Clinical manifestations and management factors including PPI use	Death/ fatality
Adrizain et al. 2021 Correlation of histamine-2 receptor antagonist (H2RA) and proton pump inhibitor (PPI) to the platelet count in patient with dengue viral infection	Descriptive	Indonesia	N=4005	Adults and children with dengue fever, dengue hemorrhagic fever or dengue shock syndrome	H2RA PPI	Platelet count (thrombo-cytopenia)

Appendix 4.8.1. Summary of study characteristics for Papaya (*Carica papaya*) of Question 7.

<table>
<tr><th>Author</th><th>Study design</th><th>Country</th><th>No. of patients</th><th>Population</th><th>Intervention Group(s)</th><th>Control</th><th>Outcomes</th></tr>
<tr>
<td>Abhishek 2015</td>
<td>RCT, open label</td>
<td>India</td>
<td>n = 60
(I: 30; C: 30)</td>
<td>Age:
18–60 years (hospitalized)
Dengue status:
DF or DHF I, II
Platelet count: 30-100×10^9</td>
<td>Carica papaya leaf extract 1100mg three times a day for five days</td>
<td>Standard therapy</td>
<td>Platelet counts
<table>
<tr><td>mean (SD)</td><td>Int</td><td>Ctrl</td></tr>
<tr><td>Day 5</td><td>110.71 (30.57)</td><td>75.63 (22.49)</td></tr>
<tr><td>Diff D1-D5</td><td>39.89 (38.50)</td><td>0.71 (24.76), p=0.0003</td></tr>
</table>
<u>Adverse events</u>
Not reported</td>
</tr>
<tr>
<td>Adarsh 2017</td>
<td>RCT, double-blinded</td>
<td>India</td>
<td>n = 100
(I: 50; C: 50)</td>
<td>Age:
Adult patients (hospitalized)
Dengue status:
DF
Platelet count:
No limits</td>
<td>Carica papaya leaf extract 500mg capsule three times a day for five days</td>
<td>Placebo capsules in same frequency</td>
<td>Platelet counts
<table>
<tr><td>mean</td><td>Int</td><td>Ctrl</td></tr>
<tr><td>Day 1</td><td>59</td><td>60</td></tr>
<tr><td>Day 2</td><td>55</td><td>56</td></tr>
<tr><td>Day 3</td><td>72</td><td>54, p<0.01</td></tr>
<tr><td>Day 4</td><td>89</td><td>66, p<0.01</td></tr>
<tr><td>Day 5</td><td>98</td><td>75, p<0.01</td></tr>
<tr><td>Day 6</td><td>110</td><td>98</td></tr>
<tr><td>Day 7 / Time of discharge</td><td>140</td><td>132</td></tr>
</table>
<u>Hematocrit</u>
No significant difference in the hematocrit values in both groups

<u>Average duration of hospital stay (days)</u>
Int: 3.45+/-0.98, p<0.01
Ctrl: 6.42+/-0.98, p<0.01

<u>Requirement of platelet transfusion</u>
Int: 14/50 (p<0.01)
Ctrl: 23/50

<u>Adverse events</u>
Nausea, vomiting seen in both groups</td>
</tr>
</table>

<table>
<tr>
<td>Assir 2012</td>
<td>RCT, single-blinded</td>
<td>Pakistan</td>
<td>n = 39
(I: 19; C: 20)</td>
<td>Age:
>14 years (hospitalized)
Dengue status:
DF or DHF
Platelet count:
<50×10^9</td>
<td>Carica papaya leaf extract 5mL syrup twice a day for four days</td>
<td>Placebo solution in same frequency</td>
<td>Platelet counts (in increments)
<table>
<tr><td>mean (SD)</td><td>Int</td><td>Ctrl</td></tr>
<tr><td>Day 1</td><td>36.2</td><td>34.1</td></tr>
<tr><td>Day 2</td><td>23.7</td><td>15.9, p=0.242</td></tr>
<tr><td>Day 3</td><td>42.6</td><td>35.1, p=0.424</td></tr>
<tr><td>Day 4</td><td>71.6</td><td>58.4, p=0.309</td></tr>
<tr><td>Day 5</td><td>106 (69.16)</td><td>82.3 (37.28), p=0.189</td></tr>
<tr><td>Time of discharge</td><td>142.3</td><td>116.5, p=0.182</td></tr>
</table>
<u>Adverse events</u>
Not reported</td>
</tr>
<tr>
<td>Gadhwal 2015</td>
<td>RCT, open label</td>
<td>India</td>
<td>n = 400
(I: 200; C: 200)</td>
<td>Age:
>16 years (hospitalized)
Dengue status:
DF
Platelet count:
<150×10^9</td>
<td>Carica papaya leaf extract
500mg capsule once a day for five days</td>
<td>Standard therapy</td>
<td>Platelet counts
<table>
<tr><td>mean (SD)</td><td>Int</td><td>Ctrl</td></tr>
<tr><td>Day 1</td><td>59.82 (18.63)</td><td>61.06 (20.03), p=0.36</td></tr>
<tr><td>Day 2</td><td>61.67 (19.46)</td><td>59.93 (19.52), p=0.20</td></tr>
<tr><td>Day 3</td><td>82.96 (16.72)</td><td>66.45 (17.36), p<0.01</td></tr>
<tr><td>Day 4</td><td>122.43 (19.36)</td><td>88.75 (21.65), p<0.01</td></tr>
<tr><td>Day 5</td><td>112.47 (17.49)</td><td>102.59 (19.35), p<0.01</td></tr>
<tr><td>Day 7 / Time of discharge</td><td>124.47 (12.35)</td><td>122.46 (19.76), p=0.08</td></tr>
</table>
<u>Average duration of hospital stay (days)</u>
Int: 3.65±0.97, p<0.01
Ctrl: 5.42±0.98 days, p<0.01
<u>Requirement of platelet transfusion</u>
Int: 55/200 (27.5%)
Ctrl: 88/200 (46.5%)</td>
</tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td><u>Adverse events</u>
Not reported</td></tr>
<tr><td>Gowda 2014</td><td>RCT, open label</td><td>India</td><td>n = 30
(I: 14; C: 16)</td><td>Age:
18–60 years (hospitalized)
Dengue status:
DF or DHF I, II
Platelet count:
30-100×10^9</td><td>Carica papaya leaf extract 1100mg tablet three times a day for five days</td><td>Standard therapy</td><td><u>Platelet counts</u><table><tr><td>mean (SD)</td><td>Int</td><td>Ctrl</td></tr><tr><td>Day 1</td><td>64.79 (20.86)</td><td>65.94 (17.79), p=0.956</td></tr><tr><td>Day 2</td><td>51.86 (18.19)</td><td>58.19 (16.19)</td></tr><tr><td>Day 3</td><td>64.14 (16.27)</td><td>53.69 (19.02)</td></tr><tr><td>Day 4</td><td>80.71 (20.12)</td><td>58.69 (19.86)</td></tr><tr><td>Day 5</td><td>104.71 (30.57)</td><td>66.63 (22.49)</td></tr><tr><td>Diff D1-D5</td><td>39.92 (38.51)</td><td>0.69 (24.75), p=0.003</td></tr></table><u>Adverse events</u>
GI disturbance (nausea, vomiting) similar in both groups</td></tr>
<tr><td>Hettige 2020</td><td>RCT, open label</td><td>Sri Lanka</td><td>n = 161
(I: 77; C: 84)</td><td>Age:
18–60 years (hospitalized)
Dengue status:
DF but not DHF
Platelet count:
<150×10^9</td><td>Carica papaya leaf extract 20mL syrup every 12 hours until discharge</td><td>Standard therapy</td><td><u>Platelet counts</u><table><tr><td>mean (SD)</td><td>Int</td><td>Ctrl</td></tr><tr><td>Day 6</td><td>67.47 (33.39)</td><td>60.96 (33.74), p=0.299</td></tr></table><u>Average duration of hospital stay (days)</u>
Int: 3.69 ± 1.08
Ctrl: 4.47 ± 1.40 (p<0.001)

<u>Mean duration of fever in the hospital (days)</u>
Int: 1.67 ± 1.36
Ctrl: 2.8 ± 1.79 (p <0.001)

<u>Mean duration of the illness (days)</u>
Int: 6.51 ± 1.05
Ctrl: 6.96 ± 1.32 (p <0.05)

<u>Clinically evident complications (DHF)</u>
Int: 2/43</td></tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>Ctrl: 12/76 (p<0.05)</td></tr>
<tr><td>Kasture 2016</td><td>RCT, double-blind</td><td>India</td><td>n = 300
(I: 150;
C: 150)</td><td>Age:
18–60 years
(unclear if hospitalized, outpatient, or mixed)
Dengue status:
DF or DHF I, II
Platelet count:
30-100×10^9</td><td>Carica papaya leaf extract 1100mg tablet three times a day for five days</td><td>Placebo tablet in same frequency</td><td><u>Platelet counts</u>
<table><tr><td>median</td><td>Int</td><td>Ctrl</td></tr><tr><td>Baseline</td><td>52.543</td><td>51.850</td></tr><tr><td>Day 1</td><td>48.0</td><td>46.345</td></tr><tr><td>Day 2</td><td>59.5</td><td>49.437</td></tr><tr><td>Day 3</td><td>88.897</td><td>55.633</td></tr><tr><td>Day 4</td><td>102.579</td><td>64.582</td></tr><tr><td>Day 5</td><td>155.886</td><td>70.528</td></tr></table>
<u>Hematocrit</u>
No significant difference in the hematocrit values in both the groups

<u>Requirement of platelet transfusion</u>
Int: 0/150
Ctrl: 12/150

<u>Adverse events</u>
GI disturbance: nausea (26) and vomiting (17) distributed similarly in both groups and not related to drugs
Rash, mild and self-limiting (9) in intervention group</td></tr>
<tr><td>Sathya palan 2020</td><td>RCT, double-blind</td><td>India</td><td>n = 50
(I: 26; C: 24)</td><td>Age:
≥18 years
(hospitalized)
Dengue status:
DF or DHF
Platelet count:
≤30×10^9</td><td>Carica papaya leaf extract 1100mg tablet three times a day for five days</td><td>Placebo tablet in same frequency</td><td><u>Platelet counts (in increments)</u>
<table><tr><td>mean (SD)</td><td>Int</td><td>Ctrl</td></tr><tr><td>Baseline</td><td>19 (6)</td><td>22 (8), p=0.37</td></tr><tr><td>Day 3</td><td>482% (284)</td><td>331% (370), p=0.007</td></tr></table>
<u>Hematocrit</u>
No significant difference observed between the two groups

<u>Average duration of hospital stay (days)</u>
Int: 5.04</td></tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>Ctrl: 5.0

<u>Requirement of platelet transfusion</u>
Int: 8/26
Ctrl: 7/24

<u>Adverse events</u>
No serious adverse events</td></tr>
<tr><td>Srikanth 2019</td><td>RCT, open label</td><td>India</td><td>n = 294
(I: 147; C: 147)</td><td>Age:
1–12 years
(hospitalized)
Dengue status:
DF or DHF I, II
Platelet count:
30-100×10^9</td><td>Carica papaya leaf extract syrup three times a day for five days
1-5y: 275mg
>5y: 550mg</td><td>Standard therapy</td><td><u>Platelet counts</u><table><tr><td>mean (SD)</td><td>Int</td><td>Ctrl</td></tr><tr><td>Day 1</td><td>59.89721</td><td>56.79354</td></tr><tr><td>Day 2</td><td>67.50344</td><td>64.70714</td></tr><tr><td>Day 3</td><td>89.73931 (29.97362)</td><td>71.11428, p=0.030</td></tr><tr><td>Day 4</td><td>120.78896 (36.40403)</td><td>91.12714, p=0.019</td></tr><tr><td>Day 5</td><td>168.92275 (49.70655)</td><td>105.05012, p=0.023</td></tr></table><u>Adverse events</u>
Nausea (2) in intervention group</td></tr>
<tr><td>Subenthiran 2013</td><td>RCT, open label</td><td>Malaysia</td><td>n = 290
(I: 145; C: 145)</td><td>Age:
18–60 years
(hospitalized)
Dengue status:
DF or DHF
Platelet count:
<100×10^9</td><td>Carica papaya leaf fresh juice 50g once a day for three days</td><td>Standard therapy</td><td><u>Platelet counts (mean difference)</u><table><tr><td>MD (CI)</td><td>Int</td><td>Ctrl</td></tr><tr><td>8-16h</td><td>0.933 (-1.660, 3.645), p=0460</td><td>-1.411 (-3.961, 1.140), p=0.276</td></tr><tr><td>8-24h</td><td>-0.432 (-4.422, 3.558), p=0.831</td><td>2.213 (-0.523, 4.948), p=0.112</td></tr><tr><td>8-32h</td><td>-2.716 (-7.540, 2.107), p=0.267</td><td>2.775 (-0.796, 6.347), p=0.127</td></tr><tr><td>8-40h</td><td>-7.890 (-14.472, -1.310), p=0.019</td><td>0.867 (-3.472, 5.207), p=0.693</td></tr></table></td></tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>
<table>
<tr><td>8-48h</td><td>-16.764 (-24.566, -8.964), p<0.001</td><td>-7.703 (-14.055, 1.351), p=0.018</td></tr>
<tr><td>Diff D1-D5</td><td>39.92 (38.51)</td><td>0.69 (24.75), p=0.003</td></tr>
</table>
<u>Adverse events</u>
Not reported
</td>
</tr>
<tr>
<td>Yunita 2012</td>
<td>RCT, open label</td>
<td>Indonesia</td>
<td>n = 80
(I: 40; C: 40)</td>
<td>Age:
15–55 years
(hospitalized)
Dengue status:
DF
Platelet count: <150×10^9</td>
<td>Carica papaya leaf extract 550mg/tab, 2 tablets three times a day for five days</td>
<td>Standard therapy</td>
<td>
<u>Platelet counts (taken twice daily)</u>
<table>
<tr><td>mean (SD)</td><td>Int</td><td>Ctrl</td></tr>
<tr><td>Day 1</td><td>98.33, 94.425</td><td>100.1, 94.3</td></tr>
<tr><td>Day 2</td><td>94.475, 94.475</td><td>94.3, 84.9</td></tr>
<tr><td>Day 3</td><td>106.98, 133.88</td><td>85.1, 86.1</td></tr>
<tr><td>Day 4</td><td>155.76, 168.5</td><td>94.6, 99.8</td></tr>
<tr><td>Day 5</td><td>200.0</td><td>117.48</td></tr>
</table>
<u>Hematocrit</u>
No significant difference observed between the two groups

<u>Average duration of hospital stay (days)</u>
Int: 3.48 +/- 0.60, p<0.05
Ctrl: 5.38 +/-0.67, p<0.05
<u>Adverse events</u>
No adverse events
</td>
</tr>
</table>

Appendix 4.8.2. Summary of study characteristics for Tawa-tawa (*Euphorbia hirta*) of Question 7.

<table>
<tr><th>Author</th><th>Study design</th><th>Country</th><th>No. of patients</th><th>Population</th><th>Intervention Group(s)</th><th>Control</th><th>Outcomes</th></tr>
<tr>
<td>Tungol-Paredes 2014</td>
<td>Non-concurrent cohort study</td>
<td>Philippines</td>
<td>n = 93
(Group A: 46; Group B: 47</td>
<td>Age:
13.5±5.9 years (E. hirta group)
13.9±7.2 years (control group)
Dengue status:
DF or DHF I-IV
Platelet count:
Not indicated

Excluded:
Patients with incomplete data</td>
<td>E. hirta group:
Taken Euphorbia hirta at any time during the course of illness (regardless of preparation, dosage, frequency, and duration of intake)</td>
<td>Control:
No intake of Euphorbia hirta</td>
<td><u>Platelet counts</u>
1. Mean platelet counts were not significantly different between groups
<table>
<tr><th>Mean (SD)</th><th>E. hirta group</th><th>Control group</th></tr>
<tr><td rowspan="2">Day 2</td><td>125.12 (66.3)</td><td>189.75 (30.0)</td></tr><tr><td colspan="2">p=0.277</td></tr>
<tr><td rowspan="2">Day 3</td><td>116.42 (35.2)</td><td>120.05 (44.7)</td></tr><tr><td colspan="2">p=0.546</td></tr>
<tr><td rowspan="2">Day 4</td><td>88.84 (42.0)</td><td>84.94 (38.4)</td></tr><tr><td colspan="2">p=0.768</td></tr>
<tr><td rowspan="2">Day 5</td><td>60.54 (37.7)</td><td>81.91 (49.9)</td></tr><tr><td colspan="2">p=0.070</td></tr>
<tr><td rowspan="2">Day 6</td><td>50.0 (32.8)</td><td>63.34 (43.3)</td></tr><tr><td colspan="2">p=0.296</td></tr>
<tr><td rowspan="2">Day 7</td><td>50.56 (34.0)</td><td>71.56 (51.3)</td></tr><tr><td colspan="2">p=0.056</td></tr>
<tr><td rowspan="2">Day 8</td><td>64.34 (45.1)</td><td>82.96 (49.7)</td></tr><tr><td colspan="2">p=0.147</td></tr>
<tr><td rowspan="2">Day 9</td><td>86.85 (41.7)</td><td>110.21 (62.8)</td></tr><tr><td colspan="2">p=0.125</td></tr>
<tr><td rowspan="2">Day 10</td><td>113.23 (45.1)</td><td>131.6 (73.2)</td></tr><tr><td colspan="2">p=0.440</td></tr>
</table>
2. Percentage increase in E. hirta group was more favorable than control group (within group analysis)
3. Initial drop in platelets during the first 4 days of illness was greater in the control group.
4. The rise in platelet counts beginning day 5 to 6 was twice greater in the E. hirta group compared to the control group.</td>
</tr>
</table>

Appendix 4.9. Summary of study characteristics of Question 8.

Author	Study design	Country	No. of patients	Population	Intervention Group(s)	Control	Outcomes
Benelli 2019	RCT, open label	Madagascar	n=4	Adult, healthy volunteers	0.1 ml *Hazomalania voyronii* essential oil in varying concentrations	Positive control: 10% DEET	Mean repellent activity against *Aedes aegypti*
Bissinger 2014	RCT, not stated	USA	n=4	Adult, healthy volunteers	5% geraniol (TT-4302) 14 commercially available plant-based arthropod repellents	positive control: 15% DEET (OFF! Active)	Mean repellent activity against *Aedes aegypti*
Champakaew 2015	RCT, single-blinded	Thailand	n=4	Adult, healthy volunteers	*Angelica sinensis* extract in varying solutions	25 % DEET	Median Complete Protection Time Adverse events
Cilek 2004	RCT, double-blinded	USA	n=8	Adult, healthy volunteers	10% IR3535 20% IR3535	10%DEET 20% DEET	Median Complete Protection time against *Aedes aegypti*
Fradin 2002	RCT, double-blinded	USA	n=15	Adult, healthy volunteers	10 commercially available non-DEET repellents in various forms (oil, moisturizer, wristbands)	DEET (varying formulations and concentrations)	Median Complete Protection time against *Aedes aegypti* Complete protection time = elapsed time to the first bite
Gou 2020	RCT, open label	China	n=4	Adult, healthy volunteers	*Artemisa indica, Blumea balsamifera, Chromolaena odorata, Nicotiana tabacum, Vitex trifolia* plant extracts	Positive control: DEET	Mean effective dosage per minute Mean repellent activity against *Aedes albopictus*
Hidayatulfathi 2017	RCT, single-blinded	Malaysia	n=8	Adult, healthy volunteers	*Litsea elliptica, Piper aduncum,* and *Piper sarmentosum* essential oil gel	Positive control: 5% DEET	Mean repellent activity against *Aedes aegypti* Mean repellent activity against field mosquito population
Iovinella 2022	RCT, open label	Italy	n=4	Adult, healthy volunteers	Citronella derivatives	DEET	Mean repellent activity against *Aedes aegypti* Mean repellent activity against *Aedes albopictus*

							Mean protection time against *Aedes aegyptis* in a field trial
Kuri-Morales 2017	RCT, open label	Mexico	n=3	Adult, healthy volunteers	16 synthetic-based and 13 natural-based commercial topical insect repellents	none	Mean repellent activity against *Aedes aegypti*
Miot 2005	RCT, open label	Brazil	n=4	Adult, healthy volunteers	100% Andiroba Oil	Positive control: 50% DEET	Mean Complete Protection Time (Distribution of time between 1st and 3rd bites from *Aedes sp*.)
Misni 2009	RCT, single blinded	Malaysia	n=4	Adult, healthy volunteers	*Piper aduncum* essential oil	10% DEET	Mean repellent activity against *Aedes albopictus* Percent reduction of biting/landing of *Aedes albopticus* Adverse events
Sanghong 2015	RCT, Open label	Thailand	n=6	Adult, healthy volunteers	*Ligusticum sinense* (Umbelliferae) Hexane extract (LHE)	DEET	Median complete protection time against *Anopheles minimus* and *Aedes aegypti*
Sta. Ana 2005	RCT, double-blinded	Philippines	n=20	Adult, healthy volunteers	1 ml 50% *Melaleuca alternifolia* (tea tree) oil	Positive control: 1 ml 7% DEET (Standard formulation)	Mean number of bites (Computed Mean Repellent Activity)
Tuetun 2005	RCT, Single-blinded	Thailand	n=4	Adult, healthy volunteers	*A. graveolens* (celery) hexane extract (AHE) + 5% vanillin:	DEET + 5% vanillin:	Median Complete Protection time against *Aedes aegypti* Mean Repellent activity to field population of mosquitoes Adverse Events
Tuetun 2008	RCT, single-blinded	Thailand	n=6 n=27 for skin irritant potential	Adult, healthy volunteers	*A. graveolens* (celery) hexane extract (AHE) formulation in varying solution and gel forms	Positive control: 25% DEET Negative Control: ethanol	Complete protection time against Aedes aegypti Adverse events (skin irritant potential)

Appendix 6. GRADE Profile Evidence Tables

QUESTION 1A: Should NS1 RDT be used to diagnose acute dengue infection in suspected patients?
Patient or Population: Suspected Dengue Patients
Setting: Primary Health Care Centers, Hospitals
Test: Dengue NS1 Ag Rapid Diagnostic Tests (RDT)
Pooled Sensitivity: 0.70 (95% CI: 0.56 to 0.81), I^2 Sn=0.97
Pooled Specificity: 0.96 (95% CI: 0.93 to 0.98), I^2 Sp=0.82
Prevalence: 0.56

Outcome	No. of Studies (No. of patients)	Study Design	Factors					Effect per 1,000 patients tested			Test accuracy CoF
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 25%	Pre-test probability of 50%	Pre-test probability of 75%	
True positives (patients with acute dengue infection)	11 studies (3,296 patients)	cross-sectional (cohort type accuracy study)	serious[a]	not serious	serious[b]	not serious	none	**175** (140 to 203)	**350** (280 to 405)	**525** (420 to 608)	⊕⊕◯◯ Low
False negatives (patients incorrectly classified as not having acute dengue infection)								**75** (47 to 110)	**150** (95 to 220)	**225** (142 to 330)	
True negatives (patients without acute dengue infection)	11 studies (3,296 patients)	cross-sectional (cohort type accuracy study)	serious[a]	not serious	serious[b]	not serious	none	**720** (698 to 735)	**480** (465 to 490)	**240** (233 to 245)	⊕⊕◯◯ Low
False positives (patients incorrectly classified as having acute dengue infection)								**30** (15 to 52)	**20** (10 to 35)	**10** (5 to 17)	

Explanations
a. high risk issues (2/11) and unclear issues (3/11) in flow and timing, unclear issues in patient selection (7/11), unclear issue on reference standard (1/11)
b. significant heterogeneity among included studies (I^2 Sn = 0.97; I^2 Sp = 0.82)

QUESTION 1A: Should NS1 RDT be used to diagnose acute dengue infection in suspected patients?
Subgroup: individuals presenting within 3 days of symptom onset
Pooled Sensitivity: 0.91 (95% CI: 0.85 to 0.95), I^2 = 80

Outcome	No. of Studies (No. of patients)	Study Design	Factors					Effect per 1,000 patients tested			Test accuracy CoF
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 25%	Pre-test probability of 50%	Pre-test probability of 75%	
True positives (patients with acute dengue infection)	4 studies 1044 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	serious[b]	not serious	none	**228** (213 to 238)	**455** (425 to 475)	**683** (638 to 712)	⊕⊕◯◯ Low
False negatives (patients incorrectly classified as not having acute dengue infection)								**22** (12 to 37)	**45** (25 to 75)	**67** (38 to 112)	

Explanations:
b. unclear issues in patient selection (3 of 4) and in flow and timing (1 of 4).
c. significant heterogeneity among included studies. I^2 Sn = 80

QUESTION 1A: Should NS1 RDT be used to diagnose acute dengue infection in suspected patients?
Subgroup: individuals with no previous dengue infections
Pooled Sensitivity: 0.89 (95% CI: 0.85 to 0.92); I^2 = 77
Pooled Specificity: 0.99 (95% CI: 0.84 to 0.99); I^2 = 78

Outcome	No. of Studies (No. of patients)	Study Design	Factors					Effect per 1,000 patients tested			Test accuracy CoF
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 25%	Pre-test probability of 50%	Pre-test probability of 75%	
True positives (patients with acute dengue infection)	4 studies 1155 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	serious[b]	not serious	none	**223** (213 to 230)	**445** (425 to 460)	**668** (638 to 690)	⊕⊕◯◯ Low
False negatives (patients incorrectly classified as not having acute dengue infection)								**27** (20 to 37)	**55** (40 to 75)	**82** (60 to 112)	
True negatives (patients without acute dengue infection)	4 studies 1155 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	serious[b]	not serious	none	**746** (630 to 742)	**498** (420 to 495)	**249** (210 to 248)	⊕⊕◯◯ Low
False positives (patients incorrectly classified as having acute dengue infection)								**4** (8 to 120)	**2** (5 to 80)	**1** (2 to 40)	

Explanations:
a. unclear issues in patient selection (3 of 4) and in flow and timing (1 of 4)
b. significant heterogeneity among included studies. I^2 Sn = 0.77, I^2 Sp = 78

QUESTION 1B: Should dengue NS1/IGM/IGG rapid diagnostic test kits be used to diagnose dengue infection in suspected patients?

Sensitivity: 0.86 (95% CI: 0.80 to 0.91)
Specificity: 0.94 (95% CI: 0.89 to 0.96)
Prevalence: 25% 50% 75%

Outcome	No. of Studies (No. of patients)	Study Design	Factors					Effect per 1,000 patients tested			Test accuracy CoF
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 25%	Pre-test probability of 50%	Pre-test probability of 75%	
True positives (patients with acute dengue infection)	12 studies 5561 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	serious[b]	not serious	none	**216** (201 to 227)	**431** (402 to 453)	**647** (602 to 680)	⊕⊕◯◯ Low
False negatives (patients incorrectly classified as not having acute dengue infection)								**34** (23 to 49)	**69** (47 to 98)	**103** (70 to 148)	
True negatives (patients without acute dengue infection)	12 studies 5561 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	serious[c]	not serious	none	**703** (667 to 724)	**469** (445 to 483)	**234** (222 to 241)	⊕⊕◯◯ Low
False positives (patients incorrectly classified as having acute dengue infection)								**47** (26 to 83)	**31** (17 to 55)	**16** (9 to 28)	

Explanations

a. 50% of the included studies had unclear risk of bias in patient selection
b. I^2 = 94%
c. I^2 = 87%

QUESTION 1B: Should dengue IgM/IgG rapid diagnostic test (RDT) kits be used to diagnose dengue infection in suspected patients?

Sensitivity: 0.60 (95% CI: 0.42 to 0.75)

Specificity: 0.79 (95% CI: 0.65 to 0.88)

Prevalence: 25% 50% 75%

Outcome	No. of Studies (No. of patients)	Study Design	Factors					Effect per 1,000 patients tested			Test accuracy CoF
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 25%	Pre-test probability of 50%	Pre-test probability of 75%	
True positives (patients with acute dengue infection)	5 studies 1771 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	serious[b]	serious[c]	none	216 (201 to 227)	431 (402 to 453)	647 (602 to 680)	⊕⊕◯◯ Low
False negatives (patients incorrectly classified as not having acute dengue infection)								34 (23 to 49)	69 (47 to 98)	103 (70 to 148)	
True negatives (patients without acute dengue infection)	5 studies 1771 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	serious[d]	serious[e]	none	703 (667 to 724)	469 (445 to 483)	234 (222 to 241)	⊕⊕◯◯ Low
False positives (patients incorrectly classified as having acute dengue infection)								47 (26 to 83)	31 (17 to 55)	16 (9 to 28)	

Explanations

a. 25-50% had unclear risk of bias in patient selection
b. i2 = 95%
c. the sensitivity was low to moderate
d. i2 = 90%
e. the specificity was moderate to high

QUESTION 2: What clinical findings and laboratory parameters should be used to identify patients that require in-hospital management?
Population: All age groups

No. of Studies	Study Design	Certainty Assessment					Impact	Certainty	Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations			
Vomiting									
4[a]	observational studies	serious[b]	serious[c]	not serious	not serious	none	All included studies exhibited moderate association in identifying patients at risk for severe dengue ranging from OR 1.53 to OR 2.25 Sangkaew 2021 **OR 2.25[1.87, 2.71]** 9 studies, n=6229 Htun 2021 **OR 2.18[1.5, 3.16]** 19 studies, n=849 PAHO 2022 **OR 1.74[1.48, 2.05]** 56 studies, n=72312 Yuan 2022 **OR 1.533[1.203, 1.953]** 26 studies, n=9417	⊕⊕◯◯ Low	CRITICAL
Persistent vomiting									
2[d]	observational studies	serious[e]	serious[f]	not serious	serious[g]	none	Effect estimates vary across reviews, unclear definition of persistent vomiting. Yuan 2022 **OR 5.569[3.041, 10.2]** 3 studies, n=813 Htun 2021 **OR 2.57[1.40, 4.73]** 12 studies, n=296	⊕◯◯◯ Very low	CRITICAL

Explanations

a. Sangkaew 2021, Htun 2021, PAHO 2022, Yuan 2022

b. Sangkaew 2021, high risk of bias wherein potential confounders were not addressed or adjusted, selection bias as only inpatients were included in the study; Htun 2021, only 5/39 studies were rated as high quality; PAHO 2022, most of the studies had methodological problems although certainty did not change i.e. effect estimates were not significantly different in studies with low risk of bias versus studies that are of high risk of bias; Yuan 2022 almost all of the studies included (~97%) were rated as intermediate to high quality studies

c. Markedly different CIs reported accross reviews.

d. Yuan 2022, Htun 2021

e. Yuan 2022 almost all of the studies included (~97%) were rated as intermediate to high quality studies; Htun 2021, only 5/39 studies were rated as high quality

f. varying effect estimates were reported across studies from strong association OR 5.569[3.041, 10.2] Yuan 2022 to moderate association OR 2.57[1.4, 4.73] Htun 2021; unclear definition of persistent vomiting on both studies included in the reviews

g. CIs on the studies ranged from CI 1.4, 10.2 ranging from low to strong association in identifying severe dengue infection

No. of Studies	Study Design	Certainty Assessment					Impact	Certainty	Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations			
Abdominal pain or tenderness									
5	observational studies	serious[h]	not serious	not serious	serious[i]	none	Abdominal pain or tenderness demonstrated moderate association as a predictor for severe dengue varying from OR 1.85 to OR 2.02 PAHO 2022 **OR 2.02[1.74,2.35]** 87 studies, n=85769 Tsheten 2021 **OR 2.00[1.49, 2.68]** 55 studies	⊕⊕◯◯ Low	CRITICAL
Mucosal bleeding									
5[j]	observational studies	serious[k]	serious[l]	not serious	serious[m]	none	Mucosal bleeding showed a moderate association in identifying patients at risk for severe dengue. Mucosal Bleeding: Melena Tsheten 2021 **OR 4.05[1.64, 10]** 9 studies, n/a Mucosal bleeding: gum bleeding Htun 2021 **OR 3.34[1.6, 6.98]** 10 studies, n=48 Mucosal bleeding: hematuria PAHO 2022 **OR 3.12[1.23,7.9]** 3 studies, n=1831 Mucosal bleeding: epistaxis Htun 2021 **OR 2.23[1.04, 4.77]** 9 studies, n=73 PAHO 2022 **OR 1.96[1.47, 2.69]** 50 studies, n=24661 Sangkaew 2021 **OR 1.87[1.23, 2.84]** 4 studies, n=7057	⊕◯◯◯ Very low	CRITICAL

Explanations

h. Sangkaew 2021, high risk of bias wherein potential confounders were not addressed or adjusted, selection bias as only inpatients were included in the study; Htun 2021, only 5/39 studies were rated as high quality; PAHO 2022, most of the studies had methodological problems although certainty did not change (i.e. effect estimates were not significantly different in studies with low risk of bias versus studies that are of high risk of bias); Yuan 2022 almost all of the studies included (~97%) were rated as intermediate to high quality studies; Tsheten 2021, using the MASTER scale showed high rates of deficient standard on the following domains: equal prognosis, equal implementation, and equal retention

i. confidence intervals across reviews ranged from low to moderate strength of association CI 1.35, 2.74

j. PAHO 2022, Tsheten 2021, Htun 2021, Sangkaew 2021, Yuan 2022

k. Sangkaew 2021, high risk of bias wherein potential confounders were not addressed or adjusted, selection bias as only inpatients were included in the study; Htun 2021, only 5/39 studies were rated as high quality; PAHO 2022, most of the studies had methodological problems although certainty did not change (i.e. effect estimates were not significantly different in studies with low risk of bias versus studies that are of high risk of bias); Yuan 2022 almost all of the studies included (~97%) were rated as intermediate to high quality studies; Tsheten 2021, using the MASTER scale showed high rates of deficient standard on the following domains: equal prognosis, equal implementation, and equal retention

l. Mucosal bleeding definition/inclusion vary across reviews, with some included all manifestation of mucosal bleeding while some reviews had separate subgroup analysis on each different manifestations of mucosal bleeding (e.g. epistaxis, gum bleeding, petechiae)

m. CI vary across studies from 1.03 to 10 from low to strong strength of association in identifying patients at risk for severe dengue

No. of Studies	Study Design	Certainty Assessment					Impact	Certainty	Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations			
Lethargy/restlessness									
3[n]	observational studies	serious[o]	not serious	not serious	serious[p]	none	Effect estimates across reviews showed moderate association in identifying patients at risk for severe dengue infection Htun 2021 **OR 4.32[1.86, 10.04]** 13 studies, n=464 Tsheten 2021 **OR 2.73[1.05, 7.10]** 10 studies Yuan 2022 **OR 2.563[1.517, 4.329]** 8 studies, n=29412	⊕⊕◯◯ Low	CRITICAL
Hepatomegaly (assessed with: >2cms)									
4[q]	observational studies	serious[r]	serious[s]	not serious	serious[t]	none	Hepatomegaly showed a moderate to strong association in identifying patients at risk for the development of severe dengue. Tsheten 2021 **OR 5.92[3.29, 10.65]** 47 studies Yuan 2022 **OR 4.403[3.016, 6.43]** 17 studies, n=20581 Htun 2021 **OR 3.34[2.38, 4.68]** 25 studies, n=796 PAHO 2022 **OR 3.14[2.38, 4.15]** 62 studies, n=25989 Yuan 2022 **OR 2.563[1.517, 4.329]** 8 studies, n=29412	⊕◯◯◯ Very low	CRITICAL

Explanations

n. Htun 2021; Tsheten 2021; Yuan 2022

o. Htun 2021, only 5/39 studies were rated as high quality; Yuan 2022 almost all of the studies included (~97%) were rated as intermediate to high quality studies; Tsheten 2021, using the MASTER scale showed high rates of deficient standard on the following domains: equal prognosis, equal implementation, and equal retention

p. effect estimates ranges from weak to strong association with the outcome ranging from CI 1.05, 10.04 across all reviews

q. Tsheten 2021; Yuan 2022; Htun 2021; PAHO 2022

r. Tsheten 2021, using the MASTER scale showed high rates of deficient standard on the following domains: equal prognosis, equal implementation, and equal retention; Yuan 2022 almost all of the studies included (~97%) were rated as intermediate to high quality studies; Htun 2021, only 5/39 studies were rated as high quality; PAHO 2022, most of the studies had methodological problems although certainty did not change (i.e. effect estimates were not significantly different in studies with low risk of bias versus studies that are of high risk of bias);
s. There is varying effect estimates across studies with three studies and one study showed strong association in predicting patients at risk for severe dengue
t. with range of confidence intervals across studies are reported from CI 2.38, 10.65

No. of Studies	Study Design	Certainty Assessment					Impact	Certainty	Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations			
Increase in hematocrit with or without increase in platelet count									
3[u]	observational studies	serious[v]	serious[w]	not serious	serious[x]	none	Increasing hematocrit with or without concurrent decrease in platelet count showed a moderate to strong association in identifying patients at risk for severe dengue. Yuan 2022 **OR 12.389[6.10, 25.20]** 7 studies, n=18180 Tsheten 2021 **OR 5.14[1.61, 16.34]** 7 studies PAHO 2022 **OR 2.30[1.74,2.35]** 45 studies, n=17462 Showed a moderate to strong association in identifying patients at risk for severe dengue	⊕◯◯◯ Very low	CRITICAL

Explanations

u. Tsheten 2021; PAHO 2022; Yuan 2022
v. Tsheten 2021, using the MASTER scale showed high rates of deficient standard on the following domains: equal prognosis, equal implementation, and equal retention;PAHO 2022, most of the studies had methodological problems although certainty did not change (i.e. effect estimates were not significantly different in studies with low risk of bias versus studies that are of high risk of bias); Yuan 2022 almost all of the studies included (~97%) were rated as intermediate to high quality studies;
w. some studies included a concurrent decrease in platelet counts; effect estimates varies across studies from moderate to strong association in identifying patients at risk for severe dengue
x. effect estimates i.e. wide range of CI ranges from 1.74 to 25.199

No. of Studies	Study Design	Certainty Assessment					Impact	Certainty	Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations			
Elevation of transaminases									
4[y]	observational studies	serious[z]	serious[aa]	not serious	serious[ab]	none	Elevation of transaminases showed moderate to strong association in identifying patients at risk for severe dengue. Elevated AST Yuan 2022 **OR 4.053[2.255,7.287]** 4 studies, n=366 Elevated ALT Yuan 2022 **OR 4.030[2.408,6.747]** 8 studies, n=1069 Elevated AST Htun 2021 **OR 3.75[2.11, 6.68]** 8 studies, n=338 Elevated ALT Htun 2021 **OR 3.24[2.38, 4.68]** 25 studies, n=796 Elevated transaminases PAHO 2022 **OR 2.55[1.78,3.64]** 39 studies, n=18579 Elevated ALT Sangkaew 2021 **SMD 0.73[0.36, 1.09]** 7 studies Elevated AST Sangkaew 2021 **SMD 1.06[0.54, 1.57]** 7 studies	⊕◯◯◯ Very low	CRITICAL

Explanations

y. PAHO 2022; Yuan 2022; Htun 2021; Sangkaew 2021;

z. Sangkaew 2021, high risk of bias wherein potential confounders were not addressed or adjusted, selection bias as only inpatients were included in the study; Htun 2021, only 5/39 studies were rated as high quality; PAHO 2022, most of the studies had methodological problems although certainty did not change (i.e. effect estimates were not significantly different in studies with low risk of bias versus studies that are of high risk of bias); Yuan 2022 almost all of the studies included (~97%) were rated as intermediate to high quality studies

aa. varying inclusion of transaminases (i.e AST or ALT or both) across studies, likewise effect estimates ranges from moderate to strong association in identifying patients at risk for severe dengue

ab. confidence intervals across studies ranges from CI 2.11 to 7.287

No. of Studies	Study Design	Certainty Assessment					Impact	Certainty	Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations			
Impaired consciousness									
2[ac]	observational studies	serious[ad]	serious[ae]	not serious	serious[af]	none	Decreasing levels of consciousness are associated with a strong association in identifyi patients at risk for severe dengue. Htun 2021 **OR 29.81[4.08, 217.94]** 5 studies, n=37 PAHO 2022 **OR 5.23[3.45,7.93]** 33 studies, n=76881	⊕◯◯◯ Very low	CRITICAL
Acute renal failure									
1[ag]	observational studies	serious[ah]	serious[ai]	not serious	serious[aj]	none	Acute renal failure has a strong association in identifying patients at risk for severe dengue. PAHO, 2022 **OR 6.73[1.66,27.20]** 8 studies, n=4348	⊕◯◯◯ Very low	CRITICAL
Coagulopathy (assessed with: PT or APTT or both)									
2[ak]	observational studies	serious[al]	serious[am]	not serious	serious[an]	none	Presence of coagulopathy has a moderated association in identifying patients at risk for severe dengue. Coagulopathy PAHO 2022 **OR 2.83[1.59, 5.04]**10 studies, n=6895 Prothrombin time Yuan 2022 **SMD 0.781[0.219, 1.343]**6 studies,n=2611 APTT Yuan 2022 **SMD 0.529 [0.05, 1.01]**6 studies,n=2089	⊕◯◯◯ Very low	CRITICAL

Explanations

ac. PAHO 2022, Htun 2021

ad. PAHO 2022, most of the studies had methodological problems although certainty did not change (i.e. effect estimates were not significantly different in studies with low risk of bias versus studies that are of high risk of bias); Yuan 2022 almost all of the studies included (~97%) were rated as intermediate to high quality studies

ae. varying definition of impaired consciousness are reported; PAHO 2022 includes all sensory disorder from restlessness to impaired consciousness whereas Htun 2021 based its variables in the 2009 WHO dengue classification wherein lethargy and restlessness are Dengue warning sign classification and Impaired consciousness as severe dengue under the spectrum of organ impairment

af. effect estimates across studies ranges from CI 3.45, 217.94

ag. PAHO 2022

ah. 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. There is significant heterogeneity in the results of the included studies.

ai. significant heterogeneity is reported

aj. confidence intervals are wide, ranging from CI 1.66, 27.2

ak. PAHO 2022; Yuan 2022

al. PAHO 2022: 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.
am. There is significant heterogeneity in the results of the included studies.
an. Standard Mean difference are wide across studies from SMD 0.046, 1.343; effect estimates using ORs are wide from 1.59, 5.04

No. of Studies	Study Design	Certainty Assessment					Impact	Certainty	Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations			
Thrombocytopenia									
4[ao]	observational studies	serious[ap]	serious[aq]	not serious	serious[ar]	none	Effect estimates showed varying strengths of association from low to strong in identifying patients at risk for severe dengue. Yuan 2022 **OR 8.146[3.374,19.665]** 12 studies, n=1238 PAHO 2022 **OR 3.02[2.45,3.73]** 62 studies, n=50586 Htun 2021 **OR 2.7[1.6, 4.55]** 18 studies, n=893 Sangkaew 2021 **SMD -0.15[-0.54, -0.15]** 12 studies	⊕◯◯◯ Very low	CRITICAL
Pregnancy (assessed with: first to third trimester)									
1[as]	observational studies	serious[at]	not serious	not serious	serious[au]	none	Pregnancy has a moderate association in identifying patients at risk for severe dengue. 3rd trimester of pregnancy PAHO 2022 **OR 3.94[2.10,5.42]** 1 study, n=99 pregnancy PAHO 2022 **OR 3.38[2.10,5.42]** 1 study, n=n/a	⊕⊕◯◯ Low	CRITICAL

Explanations

ao. PAHO 2022; Yuan 2022; Htun 2021; Sangkaew 2021
ap. Sangkaew 2021, high risk of bias wherein potential confounders were not addressed or adjusted, selection bias as only inpatients were included in the study; Htun 2021, only 5/39 studies were rated as high quality; PAHO 2022, most of the studies had methodological problems although certainty did not change (i.e. effect estimates were not significantly different in studies with low risk of bias versus studies that are of high risk of bias); Yuan 2022 almost all of the studies included (~97%) were rated as intermediate to high quality studies
aq. some studies assessed coagulopathy using only or all of the parameters for hemostasis e.g. PT, APTT
ar. effect estimates using OR and SMD showed a wide confidence interval ranging from CI OR 2.45, 19.665 or SMD -0.54, -0.15
as. PAHO 2022
at. All of the studies included in the meta-analysis had serious methodological problems.
au. optimal sample size is not reached; wide confidence interval is reported from CI 2.10, 5.4

No. of Studies	Study Design	Certainty Assessment					Impact	Certainty	Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations			
Headache									
2[av]	observational studies	serious[aw]	not serious	not serious	not serious	none	Headache is not a significant predictor of severe dengue PAHO 2022 **OR 0.87[0.76, 0.99]** 46 studies, n=61520 Htun 2021 **OR 0.84[0.70, 1.00]** 18 studies, n=2893	⊕⊕⊕◯ Moderate	IMPORTANT
Myalgia or Arthralgia									
2[ax]	observational studies	not serious	not serious	not serious	serious[ay]	none	The presence of myalgia and arthralgia is a not a significant predictor of severe dengue Myalgia/ Arthralgia PAHO 2022 **OR 0.79[0.66, 0.95]** 43 studies, n=89323 Arthralgia Htun 2021 **OR 1.10[0.89, 1.36]** 16 studies, n=1847 Myalgia Htun 2021 **OR 1.01[0.83, 1.24]** 17 studies, n=2949	⊕⊕⊕◯ Moderate	IMPORTANT
Rash or Cutaneous Eruption									
2[az]	observational studies	serious[ba]	serious[bb]	not serious	serious[bc]	none	The presence of rash or cutaneous eruption are not predictors of severe dengue	⊕◯◯◯ Very low	IMPORTANT

Explanations

av. PAHO 2022, Htun 2021

aw. PAHO 2022: 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. Htun 2021: Htun 2021, only 5/39 studies were rated as high quality

ax. PAHO 2022; Htun 2021

ay. the effect estimate is wide ranging from CI OR 0.66, 1.94

az. PAHO 2022; Htun 2021

ba. The 95% CI includes the possibility and absence of prediction of severe dengue. Htun 2021, only 5/39 studies were rated as high quality

bb. Significant moderate heterogeneity is reported

bc. wide confidence intervals are reported across studies from CI 0.79, 1.52

No. of Studies	Study Design	Certainty Assessment					Impact	Certainty	Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations			
Anorexia									
1[bd]	observational studies	serious[be]	serious[bf]	not serious	serious[bg]	none	Anorexia is not a significant predictor of severe dengue PAHO 2022 **OR 1.21[0.68, 2.15]** 8 studies, n=2089	⊕◯◯◯ Very low	IMPORTANT
Obesity									
4[bh]	observational studies	serious[bi]	serious[bj]	not serious	serious[bk]	none	Obesity is not a significant predictor of severe dengue PAHO 2022 **OR 1.18[0.92, 1.52**] 17 studies, n=6776 Tsheten 2021 **OR 0.76[0.41, 1.40]** 5 studies Htun 2021 **OR 1.06[0.90, 1.24]** 5 studies, n=4839	⊕◯◯◯ Very low	IMPORTANT
Malnutrition									
2[bl]	observational studies	serious[bm]	serious[bn]	not serious	serious[bo]	none	The presence of malnutrition is not a significant predictor of severe dengue PAHO 2022 **OR 1.09[0.84, 1.42]** 13 studies, n=5909 Sangkaew 2021 **OR 0.80[0.63, 1.01]** 4 studies, n=3774	⊕◯◯◯ Very low	IMPORTANT

Explanations

bd. PAHO 2022

be. All of the studies included in the meta-analysis had serious methodological problems.

bf. There is significant heterogeneity in the results of the included studies.

bg. effect estimates are wide ranging from CI 0.68, 2.15

bh. PAHO 2022: Tsheten 2021; Htun 2021; Zulkipli 2018

bi. 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.

bj. varying definitions of obesity of across studies; There is significant heterogeneity in the results of the included studies

bk. effect estimates are wide with CI straddling the line of no effect; CI 0.41, 1.52

bl. PAHO 2022; Sangkaew 2021

bm. PAHO 2022: 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. Sangkaew 2021: Sangkaew 2021, high risk of bias wherein potential confounders were not addressed or adjusted, selection bias as only inpatients were included in the study

bn. There is significant heterogeneity in the results of the included studies

bo. effect estimates are wide with CI ranging from CI 0.80 to 1.42

QUESTION 2: What clinical findings and laboratory parameters should be used to identify patients that require in-hospital management?

Population: Pediatric patients

No. of Studies	Study Design	Certainty Assessment					Impact	Certainty	Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations			
Vomiting									
2[bp]	observational studies	serious[bq]	not serious	not serious	serious[br]	none	Vomiting has a **moderate** strength of association with progression to severe dengue, with reported ORs ranging from 2.01 to 2.37. Sangkaew 2021 **OR 2.37[1.89, 2.97]** 4 studies Sandinirwan, 2023 **OR 2.01[1.54, 2.64]** 14 studies	⊕⊕◯◯ Low	CRITICAL
Abdominal pain									
2[bs]	observational studies	serious[bt]	not serious	not serious	serious[bu]	none	Abdominal pain or tenderness has moderate strength of association with progression to severe dengue. Sangkaew 2021 **OR 1.61[1.31, 1.99]** 5 studies Sandinirwan 2023 **OR 1.58 [1.07, 2.35]** 15 studies	⊕⊕◯◯ Low	CRITICAL
Petechiae									
1[bv]	observational studies	serious[bw]	not serious	not serious	serious[bx]	none	The presence of petechiae is weak to moderate with progression to severe dengue. Sandinirwan, 2023 **OR 1.62[1.31,2.02]** 5 studies Sangkaew, 2021 **OR 1.57[1.10, 2.25]** 4 studies	⊕⊕◯◯ Low	CRITICAL

Explanations

bp. Sandinirwan 2023; Sangkaew 2021

bq. moderate risk for confounding bias is reported; rest of the domains are rated low risk of bias

br. effect estimate is wide with CI ranging 1.54, 2.64

bs. Sandinirwan 2023; Sangkaew 2021

bt. moderate risk for confounding bias is reported; rest of the domains are rated low risk of bias; Sangkaew 2021, high risk of bias wherein potential confounders were not addressed or adjusted, selection bias as only inpatients were included in the study

bu. effect estimate are with CI ranges from weak to moderate strength of association to severe dengue

bv. Sandinirwan 2023

bw. Sandinirwan 2023: moderate risk for confounding bias is reported; rest of the domains are rated low risk of bias

bx. effect estimates are wide ranging from CI 1.31, 2.02

No. of Studies	Study Design	Certainty Assessment					Impact	Certainty	Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations			
Hepatomegaly									
1[by]	observational studies	serious[bz]	serious[ca]	not serious	not serious	none	Hepatomegaly has a moderate association with progression to severe dengue. Sandinirwan 2023 **OR 2.28[1.54,2.64]** 16 studies	⊕⊕◯◯ Low	CRITICAL
Increase in Hematocrit									
1[cb]	observational studies	serious[cc]	serious[cd]	not serious	not serious	none	Elevation of hematocrit has a moderate association in identifying patients at risk for severe dengue. Sandinirwan, 2023 **OR 3.14[2.03,4.85]** 16 studies	⊕⊕◯◯ Low	CRITICAL
Thrombocytopenia									
2[ce]	observational studies	serious[cf]	serious[cg]	not serious	not serious	none	The presence of thrombocytopenia has a weak to moderate strength of association in identfying pediatric patients at risk for severe dengue Sandinirwan 2023 **OR 1.76[1.50,2.06]** 20 studies	⊕⊕◯◯ Low	CRITICAL

Explanations

by. Sandinirwan 2023
bz. moderate risk for confounding bias is reported; rest of the domains are rated low risk of bias;
ca. Significant heterogeneity is reported
cb. Sandinirwan 2023
cc. moderate risk for confounding bias is reported; rest of the domains are rated low risk of bias
cd. Significant hetergeniety is reported in the review
ce. Sandinirwan 2023; Sangkaew 2021
cf. moderate risk for confounding bias is reported; rest of the domains are rated low risk of bias; Sangkaew 2021, high risk of bias wherein potential confounders were not addressed or adjusted, selection bias as only inpatients were included in the study
cg. effect estimate with OR or SMD showed weak to moderate strength of association

No. of Studies	Study Design	Certainty Assessment					Impact	Certainty	Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations			
Elevated transaminase									
1[ch]	observational studies	serious[ci]	serious[cj]	not serious	not serious	none	Elevation of Transaminases either AST or ALT has a moderate association in identifying pediatric patients at risk for severe dengue. AST: Sandinirwan 2023 **OR 3.08[2.18,4.36]** 14 studies ALT: Sandinirwan 2023 **OR 1.98[1.27,3.09]** 9 studies	⊕⊕◯◯ Low	CRITICAL
Impaired consciousness									
1[ck]	observational studies	serious[cl]	serious[cm]	not serious	serious[cn]	none	The presence of impaired consciousness has a strong association in identifying patients at risk for severe dengue Sandinirwan 2023 **OR 6.88[2.91,16.25]** 7 studies	⊕◯◯◯ Very low	CRITICAL
Coagulopathy									
1[co]	observational studies	serious[cp]	serious[cq]	not serious	serious[cr]	none	The presence of coagulopathy has a moderate association in identifying patients at risk for dengue Sandinirwan 2023 **OR 4.59[2.24, 9.37]** 3 studies	⊕◯◯◯ Very low	CRITICAL
Obesity									
1[cs]	observational studies	serious[ct]	not serious	serious[cu]	not serious	none	The presence of obesity has a weak association in identfying patients at risk for severe dengue Zulkipli 2018 **OR 1.38[1.10, 1.73]** 15 studies, n=579	⊕⊕◯◯ Low	CRITICAL

Explanation

ch. Sandinirwan 2023
ci. moderate risk for confounding bias is reported; rest of the domains are rated low risk of bias
cj. There is significant heterogeneity reported across studies
ck. Sandinirwan 2023
cl. moderate risk for confounding bias is reported; rest of the domains are rated low risk of bias
cm. There is significant heterogeneity reported across studies
cn. effect estimate are wide ranging from CI of 2.34, 17.13
co. Sandinirwan 2023
cp. moderate risk for confounding bias is reported; rest of the domains are rated low risk of bias
cq. There is significant hetergeneity reported across studies
cr. effect estimate is wide ranging from CI 4.79. 15.95
cs. Zulkipli 2018
ct. 9 studies as good quality studies 6 studies as moderate quality studies (n=15) using NOS score; varying definition of obesity across studies
cu. varying definition of obesity across studies

QUESTION 4: Should ORS be given to patients with mild dengue or dengue without warning signs to prevent disease progression?
Setting: Chang Gung Memorial Hospital- Kaohsiung (CGMH-KS), a 2500-bed medical facility serving as a primary care and tertiary referral center in southern Taiwan
Intervention: Oral rehydration therapy compared to intravenous therapy for patients with non-shock dengue fever

No. of Studies	Study Design	Certainty Assessment					No. of patients		Effect		Certainty	Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Oral rehydration therapy	Intravenous therapy	Relative (95% CI)	Absolute (95% CI)		
Leukopenia												
1	observational studies	serious[a]	not serious	not serious	not serious	none	13/19 (68.4%)	17/30 (56.7%)	not estimable		⊕◯◯◯ Very low	LIMITED
Leukocytosis												
1	observational studies	serious[a]	not serious	not serious	not serious	none	1/19 (5.3%)	7/30 (23.3%)	not estimable		⊕◯◯◯ Very low	LIMITED
Atypical lymphocytosis												
1	observational studies	serious[a]	not serious	not serious	not serious	none	32/19 (168.4%)	15/30 (50.0%)			⊕◯◯◯ Very low	LIMITED
Hematocrit levels												
1	observational studies	serious[a]	not serious	not serious	not serious	none	19	30	-	MD 0.7 lower (3.66 lower to 2.26 higher)	⊕◯◯◯ Very low	LIMITED
Platelet Count												
1	observational studies	serious[a]	not serious	not serious	not serious	none	19	30	-	MD 31.6 higher (21.39 higher to 41.81 higher)	⊕◯◯◯ Very low	LIMITED

No. of Studies	Study Design	Certainty Assessment					No. of patients		Effect		Certainty	Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Oral rehydration therapy	Intravenous therapy	Relative (95% CI)	Absolute (95% CI)		
Prolongation of APTT												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	5/19 (26.3%)	14/30 (46.7%)	not estimable		⊕◯◯◯ Very low	LIMITED
Prolongation of PT												
1	observational studies	serious[a]	not serious	not serious	serious[c]	none	1/19 (5.3%)	0/30 (0.0%)	not estimable		⊕◯◯◯ Very low	LIMITED
AST Levels												
1	observational studies	serious[a]	not serious	not serious	not serious	none	17	23	-	MD **307.2 lower** (641.08 lower to 26.68 higher)	⊕◯◯◯ Very low	LIMITED
ALT Levels												
1	observational studies	serious[a]	not serious	not serious	not serious	none	16	27	-	MD **137.5 lower** (268.2 lower to 6.8 lower)	⊕◯◯◯ Very low	LIMITED
Platelets Transfused												
1	observational studies	serious[a]	not serious	not serious	not serious	none	A total of 240 units of platelets were transfused in the ORS group and 756 units of platelets were transfused to the intravenous fluid therapy group				⊕◯◯◯ Very low	LIMITED
Pleural effusion and/or pulmonary edema												
1	observational studies	serious[a]	not serious	not serious	serious[d]	none	3/19 (15.8%)	14/30 (46.7%)	not estimable		⊕◯◯◯ Very low	IMPORTANT

No. of Studies	Study Design	Certainty Assessment					No. of patients		Effect		Certainty	Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Oral rehydration therapy	Intravenous therapy	Relative (95% CI)	Absolute (95% CI)		
Gallbladder swelling												
1	observational studies	serious[a]	not serious	not serious	serious[e]	none	7/19 (36.8%)	15/30 (50.0%)	not estimable		⊕◯◯◯ Very low	LIMITED
Ascites												
1	observational studies	serious[a]	not serious	not serious	not serious[e]	none	1/19 (5.3%)	3/30 (10.0%)	not estimable		⊕◯◯◯ Very low	LIMITED
Patients receiving furosemide for symptomatic fluid overload												
1	observational studies	serious[a]	not serious	not serious	not serious	none	1/19 (5.3%)	5/30 (16.7%)	not estimable		⊕◯◯◯ Very low	LIMITED
Duration of fever												
1	observational studies	serious[a]	not serious	not serious	not serious	none	19	30	-	MD **0.2 lower** (1.27 lower to 0.87 higher)	⊕◯◯◯ Very low	LIMITED
Length of hospital stay												
1	observational studies	serious[a]	not serious	not serious	not serious	none	19	30	-	MD **2.1 lower** (3.48 lower to 0.72 lower)	⊕◯◯◯ Very low	CRITICAL

Explanations

a. Non-randomized design, unclear assessor blinding, unclear amount of fluids taken by the oral hydration group
b. Only 28 patients had available data for this (10 in the intervention group and 28 for the control group)
c. Only 27 patients had available data for this (10 in the intervention group and 17 for the control group)
d. Only 16 patients for the intervention group had data whether they developed pulmonary edema/pleural effusion
e. Only 43 patients had available data for this (16 in the intervention group and 27 for the control group)

QUESTION 4: Should ORS be given to patients with mild dengue or dengue without warning signs to prevent disease progression?
Setting: Cipto Mangunkusumo Hospital
Intervention: Oral isotonic solution compared to water for patients with dengue fever

No. of Studies	Study Design	Certainty Assessment					No. of patients		Effect		Certainty	Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Oral rehydration therapy	Intravenous therapy	Relative (95% CI)	Absolute (95% CI)		
Adverse events												
1	randomized trials	serious[a]	not serious	serious[b]	not serious	none	There are 12 patients for the intervention and 12 for the control group. The intervention group (OIS) experienced less nausea, less vomiting, had positive fluid balance and higher MAP, and became afebrile faster compared to the control group (plain water). But the OIS group had a higher incidence of abdominal distention.				⊕⊕◯◯ Low	CRITICAL
Laboratory parameters												
1	randomized trials	serious[a]	not serious	serious[b]	not serious	none	There were no significant differences in the hematocrit levels (P = 0.60) as well as the sodium (P = 0.707) and potassium levels (P = 0.581) for both groups. All patients were treated with parenteral hydration. In this study, the OIS group received fewer intravenous fluids and a higher oral fluid intake compared to the control group.				⊕⊕◯◯ Low	LIMITED

Explanations
a. Lack of blinding or significant loss of information or both
b. The study does not directly answer the research question.

QUESTION 5: Should acid suppressants be used among probable or confirmed dengue patients to prevent abdominal pain or gastrointestinal bleeding?
Patient or population: Confirmed or probable dengue patients
Setting: In-patient or outpatient
Intervention: Acid suppressants
Comparison: None

No. of Studies (No. of patients)	Study Design	Certainty Assessment					Summary of findings					Certainty	Importance
							Study event rates (%)		Anticipated absolute effects				
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Platelet count of <50,000/ mm3	Platelet count of >50,000/ mm3	Risk with none	Risk difference with acid suppressants	Relative effect (95% CI)		
Diarrhea													
1 (81 patients)	observational studies	serious[a]	not serious	very serious[b]	serious[c]	All plausible residual confounding would suggest spurious effect, while no effect was observed	4/39 (10.3%)	2/42 (4.8%)	103 per 1,000	55 fewer per 1,000 (From 93 fewer to 143 more)	**RR 0.46** (0.09 to 2.39	⊕◯◯◯ Very low	IMPORTANT

QUESTION 6: Should acid suppressants be used to treat abdominal pain or gastrointestinal bleeding among probable or confirmed dengue patients?

Intervention: PPI compared to no PPI for the treatment of abdominal pain or gastrointestinal bleeding among probable or confirmed dengue patients

Setting: Hospitalized dengue patients (adult and pediatric)

No. of Studies	Study Design	Certainty Assessment					No. of patients		Effect		Certainty	Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	PPI	No PPI	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	observational studies	serious[a]	not serious	serious[b]	serious[c]	none	26/108 (24.1%)	24/98 (24.5%)	**OR 0.98** (0.52 to 1.85)	**4 fewer per 1,000** (from 101 fewer to 130 more)	⊕◯◯◯ Very low	IMPORTANT
Thrombocytopenia platelet count <50,000												
1	observational studies	very serious[d]	not serious	serious[b]	not serious	none	510/1004 (50.8%)	1102/3001 (36.7%)	**OR 1.78** (1.54 to 2.06)	**141 more per 1,000** (from 105 more to 177 more)	⊕◯◯◯ Very low	IMPORTANT
Thrombocytopenia platelet count <100,000												
1	observational studies	very serious[d]	not serious	serious[b]	not serious	none	826/1004 (82.3%)	2153/3001 (71.7%)	**OR 1.83** (1.53 to 2.19)	**105 more per 1,000** (from 78 more to 130 more)	⊕◯◯◯ Very low	IMPORTANT

Explanations

a. Effect on outcome cannot be isolated to intervention used, since mulitiple factors that could affect outcome were included

b. No mention of patients treating for GI bleeding or pain

c. Wide confidence interval

d. Point or time of outcome measurement not standard (obtained lowest platelet count at any time during course of illness)

QUESTION 6: Should acid suppressants be used to treat abdominal pain or gastrointestinal bleeding among probable or confirmed dengue patients?
Intervention: H2RA compared to no H2RA for the treatment of abdominal pain or gastrointestinal bleeding among probable or confirmed dengue patients
Setting: Hospitalized dengue patients (adult and pediatric)

No. of Studies	Study Design	Certainty Assessment					No. of patients		Effect		Certainty	Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	H2RA	No H2RA	Relative (95% CI)	Absolute (95% CI)		
Thrombocytopenia platelet count <50,000												
1	observational studies	very serious[a]	not serious	serious[b]	not serious	none	243/442 (55.0%)	1369/3563 (38.4%)	**OR 1.96** (1.60 to 2.39)	**166 more per 1,000** (from 115 more to 214 more)	⊕◯◯◯ Very low	IMPORTANT
Thrombocytopenia platelet count <100,000												
1	observational studies	very serious[a]	not serious	serious[b]	not serious	none	371/442 (83.9%)	2608/3563 (73.2%)	**OR 1.91** (1.47 to 2.49)	**107 more per 1,000** (from 69 more to 140 more)	⊕◯◯◯ Very low	IMPORTANT

Explanations
a. Point or time of outcome measurement not standard (obtained lowest platelet count at any time during course of illness)
b. No mention of patients treating for gastrointestinal bleeding or pain

QUESTION 7: Should herbal medicines available locally be used to treat probable or confirmed dengue patients?
Intervention: *Carica papaya* compared to placebo/standard treatment for dengue fever
Setting: Inpatient

No. of Studies	Study Design	Certainty Assessment					No. of patients		Effect		Certainty	Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	*Carica papaya*	Placebo/ Standard	Relative (95% CI)	Absolute (95% CI)		
Prevention of severe dengue (platelet count increase on Day 5 of treatment); (in: counts ×109/L; follow-up: until day 5 of treatment)												
8	randomized trials	very serious[a,b,c]	serious[d]	not serious	not serious	none	640	636	-	MD **45.81 higher** (14.42 higher to 77.2 higher)	⊕◯◯◯ Very low	IMPORTANT
Prevention of severe dengue (effect on hematocrit / hemoconcentration); (follow-up: until hospital discharge, mean of 5 days)												
4	randomized trials	serious[e,f]	not serious	not serious	serious[g]	none	Although specific hematocrit values were not completely reported in most of these studies, all have stated that there were no significant difference in hematocrit values observed between those given CPLE versus controls. This may indicate CPLE treatment may not significantly influence hematocrit values in patients.				⊕◯◯◯ Very low	IMPORTANT
Recovery time of dengue (mean duration of illness); (*in*: days; *follow-up*: until hospital discharge, mean of 5 days)												
1	randomized trials	serious[h]	not serious	not serious	serious[i]	none	43	76	-	MD **0.45 lower** (0.88 lower to 0.02 lower)	⊕⊕◯◯ Low	IMPORTANT
Duration of symptoms (mean duration of fever in the hospital); (*in*: days; *follow-up*: until hospital discharge, mean of 5 days)												
1	randomized trials	serious[h]	not serious	not serious	serious[i]	none	43	76	-	MD **1.13 lower** (1.7 lower to 0.56 lower)	⊕⊕◯◯ Low	IMPORTANT

No. of Studies	Study Design	Certainty Assessment					No. of patients		Effect		Certainty	Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	*Carica papaya*	Placebo/ Standard	Relative (95% CI)	Absolute (95% CI)		
Length of hospitalization (*in*: days; *follow-up*: until hospital discharge, mean of 5 days)												
5	randomized trials	very serious[a,c]	serious[d]	not serious	not serious	none	359	390	-	MD **1.5 lower** (2.23 lower to 0.77 lower)	⊕◯◯◯ Very low	IMPORTANT
Preventing complications (incidence of pleural effusion); (*follow-up*: until hospital discharge, mean of 5 days)												
1	randomized trials	serious[h]	not serious	not serious	very serious[i,j]	none	2/43 (4.7%)	12/76 (15.8%)	**RR 0.29** (0.07 to 1.26)	**112 fewer per 1,000** (from 147 fewer to 41 more)	⊕◯◯◯ Very low	IMPORTANT
Preventing complications (risk of requiring platelet transfusion); (*follow-up*: until hospital discharge, mean of 5 days)												
4	randomized trials	very serious[a,c]	not serious[k]	not serious	not serious	none	77/426 (18.1%)	130/424 (30.7%)	**RR 0.64** (0.41 to 0.99)	**110 fewer per 1,000** (from 181 fewer to 3 fewer)	⊕⊕◯◯ Low	IMPORTANT
Adverse events (*follow-up*: until hospital discharge, mean of 5 days)												
7	randomized trials	serious[c,e]	not serious	not serious	serious[g]	none	No serious adverse events were reported throughout the studies. Only adverse effects such as nausea and vomiting were observed, similarly distributed in both intervention and control groups.				⊕⊕◯◯ Low	IMPORTANT

Explanations

a. largest trial had a high risk of bias in the randomization process (Gadhwal 2015)
b. one trial had a high risk of bias in deviating from the intended interventions (Abhishek 2015)
c. some concerns over measurement of outcomes and selection of the reported results
d. considerable heterogeneity of results
e. some concerns over the randomization process
f. some concerns over the selection of the reported results
g. narrative synthesis conducted; effect estimates not precise
h. some concerns over missing data due to dropouts
i. optimal information size not met
j. confidence interval crosses the clinical decision threshold between recommending and not recommending treatment
k. moderate heterogeneity of results

QUESTION 7: Should herbal medicines available locally be used to treat probable or confirmed dengue patients?
Intervention: *Euphorbia hirta* compared to placebo/standard treatment for dengue fever
Setting: Inpatient

No. of Studies	Study Design	Certainty Assessment					No. of patients		Effect		Certainty	Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	*Carica papaya*	Placebo/ Standard	Relative (95% CI)	Absolute (95% CI)		
Prevention of severe dengue (platelet count increase on Day 2-10 of illness); (*in:* counts ×10^9/L; *follow-up*: 10 days)												
1	observational study	very serious[a]	not serious	not serious	serious[b]	none	This non-concurrent cohort study (n=93) done in the Philippines involved patients with dengue fever who took tawa-tawa at any time during the illness regardless of preparation, dosage, frequency, and duration of intake. Patients who did not take the herbal preparation served as the control group. Mean platelet counts from Day 2 to Day 10 of illness were **not significantly different** between the two groups by independent t-test.				⨁◯◯◯ Very low	IMPORTANT

Explanations
a. some concerns with (1) baseline confounding bias, as there were no adjustments for key prognostic variables; (2) selection bias, as records with incomplete data were excluded
b. no significant difference between groups

QUESTION 8: Should non-DEET-based mosquito repellents be used for individuals at risk for dengue to prevent infection?
Intervention: Plant-based Non-DEET Extract compared to DEET repellents for individuals at risk for dengue to prevent infection
Setting: Outpatient

No. of Studies	Study Design	Certainty Assessment					No. of patients		Effect		Certainty	Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	*Carica papaya*	Placebo/ Standard	Relative (95% CI)	Absolute (95% CI)		
Mean Repellent Activity (Plant-based Non-DEET Extract vs DEET) (assessed with: Percent; Scale from: 0 to 100 (better))												
8	randomised trials	not serious	serious[a]	serious[b,c,d]	not serious	none	41	41	-	MD **1.29 Percent lower** (3.79 lower to 1.21 higher)	⊕⊕◯◯ Low	CRITICAL
Complete Protection Time (Plant-based Non-DEET Extract vs DEET) (assessed with: Hours; Scale from: 0 to 10)												
5	randomised trials	serious[e]	serious[a]	serious[b,c,d]	not serious	none	24	24	-	MD **0.51 Hours higher** (0.62 lower to 1.64 higher)	⊕◯◯◯ Very low	CRITICAL
Adverse Events												
4	randomised trials	not serious	not serious[f]	serious[b,d]	serious[g]	none	The studies defined adverse events as any rash, irritation, dermatitis, swelling or other allergic responses. None of the studies recorded any such events in the participants, both for the interventions and control (DEET) repellents.				⊕⊕◯◯ Low	CRITICAL

Explanations
[a]Considerable heterogeneity between studies (p-value is <0.00001 and I2 is 95%). Inconsistency can come from difference in intervention and concentration of control (DEET) used. I2 between subgroups is 0%.
[b]Intervention (plant-based extracts) are not available for use commercially.
[c]Outcome is a surrogate for dengue infection.
[d]No studies were done in the pediatric population.
[e]All studies have an overall some risk of bias (failed to mention blinding of outcome assessor)
[f]Interventions (concentration and formulation) were different across the studies which could contribute to inconsistency. However, outcomes were similarly defined & conduct of studies was similar in quality.
[g]Sample size was small for all studies included (<10 participants each for intervention and control).

QUESTION 8: Should non-DEET-based mosquito repellents be used for individuals at risk for dengue to prevent infection?
Intervention: IR3535 compared to DEET repellents for individuals at risk for dengue to prevent infection
Setting: Outpatient

No. of Studies	Study Design	Certainty Assessment					No. of patients		Effect		Certainty	Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	*Carica papaya*	Placebo/ Standard	Relative (95% CI)	Absolute (95% CI)		
Mean Repellent Activity (IR3535vs DEET) (Scale from: 0 to 100 (better))												
2	randomised trials	serious[a]	serious[b]	serious[c,d,e]	serious[f,g]	none	7	7	-	MD **36 percent lower** (95.03 lower to 23.04 higher)	⨁◯◯◯ Very low	CRITICAL
Complete Protection Time (Plant-based Non-DEET Extract vs DEET) (assessed with: Hours; Scale from: 0 to 10)												
5	randomised trials	serious[a]	serious[h]	serious[c,d,e]	not serious	none	36	36	-	MD **1.55 Hours lower** (2.16 lower to 0.95 lower)	⨁◯◯◯ Very low	CRITICAL
Adverse Events												
2	randomised trials	not serious	not serious	serious[d,e]	serious[f]	none	The studies defined adverse events as any rash, irritation, dermatitis, swelling or other allergic responses. None of the studies recorded any such events in the participants, both for the interventions and control (DEET) repellents.				⨁⨁◯◯ Low	CRITICAL

Explanations
[a]One of the studies had an overall high risk of bias
[b]Confidence intervals do not overlap. Considerable heterogeneity (I2 is large).
[c]Outcome is a surrogate for dengue infection.
[d]No studies were done in the pediatric population.
[e]Commercial preparations are unavailable or are not similar to locally available products.
[f]Sample size extremely small.
[g]Confidence intervals are wide.
[h]Considerable heterogeneity between studies (p-value is <0.00001 and I2 is 95%). Inconsistency can come from difference in intervention and concentration of control (DEET) used. I2 between subgroups is 0%.

QUESTION 8: Should non-DEET-based mosquito repellents be used for individuals at risk for dengue to prevent infection?
Intervention: Citronella compared to DEET repellents for individuals at risk for dengue to prevent infection
Setting: Outpatient

No. of Studies	Study Design	Certainty Assessment					No. of patients		Effect		Certainty	Importance
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	*Carica papaya*	Placebo/ Standard	Relative (95% CI)	Absolute (95% CI)		
Mean Repellent Activity (Citronella vs DEET) (Scale from: 0 to 100 (better))												
3	randomised trials	serious[a]	serious[b]	serious[c,d,e]	serious[f]	none	11	11	-	MD **30.05 Percent lower** (62.6 lower to 2.5 higher)	⊕◯◯◯ Very low	CRITICAL
Complete Protection Time (Citronella vs DEET) (assessed with: Hours; Scale from: 0 to 10 (better))												
4	randomised trials	serious[a]	serious[g]	serious[c,d,e]	serious[h]	none	28	28	-	MD **2.84 Hours lower** (3.91 lower to 1.77 lower)	⊕◯◯◯ Very low	CRITICAL
Adverse Events												
2	randomised trials	not serious	not serious	serious[d,e]	serious[h]	none	The studies defined adverse events as any rash, irritation, dermatitis, swelling or other allergic responses. None of the studies recorded any such events in the participants, both for the interventions and control (DEET) repellents.				⊕⊕◯◯ Low	CRITICAL

Explanations
[a]One of the studies had an overall high risk of bias
[b]Confidence intervals do not overlap. Considerable heterogeneity (I2 is large).
[c]Outcome is a surrogate for dengue infection.
[d]No studies were done in the pediatric population.
[e]Commercial preparations are unavailable or are not similar to locally available products.
[f]Confidence intervals are wide.
[g]Considerable heterogeneity between studies (p-value is <0.00001 and I2 is >90%). Inconsistency can come from difference in intervention and concentration of control (DEET) used.
[h]Sample size extremely small.

Appendix 7. AGREE II Reporting Checklist (Self Evaluation)

This checklist is intended to guide the reporting of clinical practice guidelines.

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
DOMAIN 1: SCOPE AND PURPOSE		
1. OBJECTIVES *Report the overall objective(s) of the guideline. The expected health benefits from the guideline are to be specific to the clinical problem or health topic.*	☒ Health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) ☒ Expected benefit(s) or outcome(s) ☒ Target(s) (e.g., patient population, society)	5
2. QUESTIONS *Report the health question(s) covered by the guideline, particularly for the key recommendations.*	☒ Target population ☒ Intervention(s) or exposure(s) ☒ Comparisons (if appropriate) ☒ Outcome(s) ☒ Health care setting or context	6-10
3. POPULATION *Describe the population (i.e., patients, public, etc.) to whom the guideline is meant to apply.*	☒ Target population, sex and age ☒ Clinical condition (if relevant) ☒ Severity/stage of disease (if relevant) ☒ Comorbidities (if relevant) ☐ Excluded populations (if relevant)	6
DOMAIN 2: STAKEHOLDER INVOLVEMENT		
4. GROUP MEMBERSHIP *Report all individuals who were involved in the development process. This may include members of the steering group, the research team involved in selecting and reviewing/rating the evidence and individuals involved in formulating the final recommendations.*	☒ Name of participant ☒ Discipline/content expertise (e.g., neurosurgeon, methodologist) ☒ Institution (e.g., St. Peter's hospital) ☐ Geographical location (e.g., Seattle, WA) ☒ A description of the member's role in the guideline development group	11
5. TARGET POPULATION PREFERENCES AND VIEWS *Report how the views and preferences of the target population were sought/considered and what the resulting outcomes were.*	☒ Statement of type of strategy used to capture patients'/publics' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences) ☒ Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups) ☐ Outcomes/information gathered on patient/public information ☒ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	21-22
6. TARGET USERS *Report the target (or intended) users of the guideline.*	☒ The intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/ administrators) ☒ How the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)	6

DOMAIN 3: RIGOUR OF DEVELOPMENT		
7. SEARCH METHODS *Report details of the strategy used to search for evidence.*	☒ Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL) ☒ Time periods searched (e.g., January 1, 2004 to March 31, 2008) ☒ Search terms used (e.g., text words, indexing terms, subheadings) ☒ Full search strategy included (e.g., possibly located in appendix)	109-122
8. EVIDENCE SELECTION CRITERIA *Report the criteria used to select (i.e., include and exclude) the evidence. Provide rationale, where appropriate.*	☒ Target population (patient, public, etc.) characteristics ☒ Study design ☒ Comparisons (if relevant) ☒ Outcomes ☒ Language (if relevant) ☐ Context (if relevant)	132-159
9. STRENGTHS & LIMITATIONS OF THE EVIDENCE *Describe the strengths and limitations of the evidence. Consider from the perspective of the individual studies and the body of evidence aggregated across all the studies. Tools exist that can facilitate the reporting of this concept.*	☒ Study design(s) included in body of evidence ☒ Study methodology limitations (sampling, blinding, allocation concealment, analytical methods) ☒ Appropriateness/relevance of primary and secondary outcomes considered ☒ Consistency of results across studies ☒ Direction of results across studies ☒ Magnitude of benefit versus magnitude of harm ☒ Applicability to practice context	160-189
10. FORMULATION OF RECOMMENDATIONS *Describe the methods used to formulate the recommendations and how final decisions were reached. Specify any areas of disagreement and the methods used to resolve them.*	☒ Recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered) ☒ Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures) ☒ How the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote)	14-15
11. CONSIDERATION OF BENEFITS AND HARMS *Report the health benefits, side effects, and risks that were considered when formulating the recommendations.*	☒ Supporting data and report of benefits ☒ Supporting data and report of harms/side effects/risks ☒ Reporting of the balance/trade-off between benefits and harms/side effects/risks ☒ Recommendations reflect considerations of both benefits and harms/side effects/risks	See relevant sections

12. LINK BETWEEN RECOMMENDATIONS AND EVIDENCE *Describe the explicit link between the recommendations and the evidence on which they are based.*	☒ How the guideline development group linked and used the evidence to inform recommendations ☒ Link between each recommendation and key evidence (text description and/or reference list) ☒ Link between recommendations and evidence summaries and/or evidence tables in the results section of the guideline	See relevant sections
13. EXTERNAL REVIEW *Report the methodology used to conduct the external review.*	☒ Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence) ☒ Methods taken to undertake the external review (e.g., rating scale, open-ended questions) ☒ Description of the external reviewers (e.g., number, type of reviewers, affiliations) ☒ Outcomes/information gathered from the external review (e.g., summary of key findings) ☒ How the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations)	16
14. UPDATING PROCEDURE *Describe the procedure for updating the guideline.*	☒ A statement that the guideline will be updated ☒ Explicit time interval or explicit criteria to guide decisions about when an update will occur ☒ Methodology for the updating procedure	16
DOMAIN 4: CLARITY OF PRESENTATION		
15. SPECIFIC AND UNAMBIGUOUS RECOMMENDATIONS *Describe which options are appropriate in which situations and in which population groups, as informed by the body of evidence.*	☒ A statement of the recommended action ☒ Intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) ☒ Relevant population (e.g., patients, public) ☒ Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply) ☒ If there is uncertainty about the best care option(s), the uncertainty should be stated in the guideline	See relevant sections
16. MANAGEMENT OPTIONS *Describe the different options for managing the condition or health issue.*	☒ Description of management options ☒ Population or clinical situation most appropriate to each option	See relevant sections
17. IDENTIFIABLE KEY RECOMMENDATIONS	☒ Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms	See relevant sections

Present the key recommendations so that they are easy to identify.	☒ Specific recommendations grouped together in one section	and Page 2
DOMAIN 5: APPLICABILITY		
18. FACILITATORS AND BARRIERS TO APPLICATION *Describe the facilitators and barriers to the guideline's application.*	☒ Types of facilitators and barriers that were considered ☒ Methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation) ☒ Information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography) ☒ How the information influenced the guideline development process and/or formation of the recommendations	103
19. IMPLEMENTATION ADVICE/TOOLS *Provide advice and/or tools on how the recommendations can be applied in practice.*	☒ Additional materials to support the implementation of the guideline in practice. For example: ○ Guideline summary documents ○ Links to check lists, algorithms ○ Links to how-to manuals ○ Solutions linked to barrier analysis (see Item 18) ○ Tools to capitalize on guideline facilitators (see Item 18) ○ Outcome of pilot test and lessons learned	103-104
20. RESOURCE IMPLICATIONS *Describe any potential resource implications of applying the recommendations.*	☒ Types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) ☒ Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.) ☒ Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course) ☒ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	103 and other relevant sections
21. MONITORING/ AUDITING CRITERIA	☒ Criteria to assess guideline implementation or adherence to recommendations	15, 103

Provide monitoring and/or auditing criteria to measure the application of guideline recommendations.	☒ Criteria for assessing impact of implementing the recommendations ☒ Advice on the frequency and interval of measurement ☒ Operational definitions of how the criteria should be measured	
DOMAIN 6: EDITORIAL INDEPENDENCE		
22. FUNDING BODY *Report the funding body's influence on the content of the guideline.*	☒ The name of the funding body or source of funding (or explicit statement of no funding) ☒ A statement that the funding body did not influence the content of the guideline	16
23. COMPETING INTERESTS *Provide an explicit statement that all group members have declared whether they have any competing interests.*	☒ Types of competing interests considered ☒ Methods by which potential competing interests were sought ☒ A description of the competing interests ☒ How the competing interests influenced the guideline process and development of recommendations	16-17, 107