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EDITORIAL

THE GENIUS BEHIND GUIDELINES

Armina A. Delos Reyes, MD
Editor-in-Chief, PIDSP Journal

Medical guidelines are documents containing recommendations which can be used in clinical practice. They are intended to help physicians make informed decisions on diagnostic or treatment dilemmas and help achieve the best outcomes for patients.

Medical guidelines are not made overnight. Members of the guidelines development committee, composed of a multidisciplinary panel of experts from key groups, are carefully chosen to produce a high quality scientific document. This is achieved through a transparent, evidence-based decision-making process that is labor intensive and rigorous. This ensures that guidelines are sound, credible and at par with international standards.

The process starts by defining the topic and scope for guideline development. Key issues and questions regarding the topic are drafted. Review of questions, literature search, evidence reviews, and committee discussions are done. Available medical evidence are summarized, and grading of evidence is made, until a draft recommendation is developed. Draft guidelines are then reviewed by stakeholders until a final guideline is produced and published.

In this special issue, we bring you outputs from this guideline development process - four relevant documents on COVID-19, Pediatric Community Acquired Pneumonia (in collaboration with the Philippine Academy of Pediatric Pulmonologists), Leptospirosis, and Pediatric Immunization (prepared by the National Institutes of Health-Institute of Clinical Epidemiology and funded by the Department of Health).

The guideline development process is imperfect. Some shortcomings include paucity of evidence on certain questions, presence of potential conflicts of interest among members of the committee, limitations in funding, and even time. The major advantage is access to a summarized wealth of evidence on a specific topic to enhance physician expertise, improve healthcare quality, and reduce healthcare cost. Guidelines can also influence health policies so that underrecognized health concerns and services can be made available to the majority.

Guidelines should be used with the best interest of the individual patient in mind. They help to improve patient care quality. The complex medical decision making process done by the physician however, should not be limited by simplistic algorithms suggested by guidelines.

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CLINICAL PRACTICE GUIDELINES

CLINICAL PRACTICE GUIDELINES ON LEPTOSPIROSIS IN CHILDREN 2019

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

EXECUTIVE SUMMARY

Leptospirosis is a disease prevalent mostly in tropical and subtropical countries. Its potential to be a concerning problem emerges with the onset of the rainy season, as flooding and heavy rainfall facilitate disease epidemics. Among those at risk of contracting the disease are field workers, veterinarians, sewer workers, military personnel and those who swim or wade in contaminated waters.

In the absence of an existing evidence-based guideline for the pediatric age group, this first edition hopes to standardize approach to diagnosis, antibiotic management, and prevention of leptospirosis. The intended users are primary care physicians, family medicine physicians, pediatricians, and other healthcare workers involved in the management of leptospirosis in children.

Ten priority questions were identified by a group of experts composed of an oversight committee, a guideline writing panel, and a technical review committee. The GRADE methodology was used to determine the quality of evidence of each recommendation. The draft recommendations (summarized below) were finalized after these were presented to and voted on by a panel of stakeholders.

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SUMMARY OF RECOMMENDATIONS

No.	Recommendation	Strength of Recommendation	Quality of Evidence
1	***Clinical manifestations suggestive of leptospirosis in children with acute fever and possible exposure***		
	Recommendation 1: Among children with acute fever and possible exposure, the presence of any or all of the following clinical manifestations should make one highly suspect leptospirosis: • Renal syndrome (defined as any sign or symptom pointing to a possible kidney damage) • Chest pain • Cardiac syndrome (defined as any sign or symptom pointing to a possible cardiac involvement) AND/OR • Conjunctival suffusion/red eye	Strong	Very low
	Recommendation 2: Among children with acute fever and possible exposure, the presence of any or all of the following clinical manifestations may make one highly suspect leptospirosis: • Arthralgia • Myalgia • Muscle tenderness	Strong	Very low
2	***Clinical findings associated with increased risk of mortality***		
	Recommendation 1: In children with leptospirosis, the presence of any one of the following signs and symptoms increases the risk of mortality: • Pallor • Loss of consciousness • Murmur • Meningism • Irregular rhythm • Dyspnea • Pulmonary hemorrhage • Convulsions/seizure • Crackles/rales on lung auscultation • Hemoptysis • Anuria • Disorientation • Jaundice • Tachycardia	Strong	Very low

3	***Laboratory findings associated with severe leptospirosis*** ***Recommendation 1***: The following laboratory parameters are ~~a~~associated with severe leptospirosis: • Deranged prothrombin time (prothrombin time greater than or equal to 15 seconds; prothrombin time less than 68%) • Elevated AST/ALT ratio (greater than or equal to 2) • Elevated LDH (greater than or equal to 390 IU/L) • Elevated CRP (greater than 282 mg/L) • Elevated creatine phosphokinase (greater than 443 U/L) ***Recommendation 2***: There is insufficient evidence to suggest that the following laboratory tests are associated with severe leptospirosis: • Elevated blirubin (greater than 49 µmol/L; total bilirubin greater than or equal to 35 µmol/L) • Thrombocytopenia (less than 92 x 10^9/L) • Elevated creatinine (greater than 154 µmol/L) • Elevated BUN (greater than 9.3 mmol/L) • Hematuria • Decrease in hemoglobin (less than 12.2 g/dL)	Strong Strong	Very low Very low
4	***Use of IgM Immunochromatography Test (ICT) as a rapid test in the diagnosis of leptospirosis in children*** ***Recommendation 1***: IgM ICT may be used as a rapid test in the diagnosis of leptospirosis in children.	Strong	Moderate
5	***Use of IgM ELISA as a rapid test in the diagnosis of leptospirosis in children*** ***Recommendation 1***: IgM ELISA may be used as a rapid test in the diagnosis of leptospirosis in children.	Weak	Low
6	***Use of PCR in the diagnosis of leptospirosis in children*** ***Recommendation 1***: PCR may be used in the diagnosis of leptospirosis in children.	Strong	Low
7	***Effectiveness of antibiotics in the treatment of children with leptospirosis*** ***Recommendation 1:*** The use of antibiotics may be considered in the treatment of children with leptospirosis, but there is no evidence to suggest that this may decrease mortality, duration of fever, renal complications, and the need for dialysis.	Strong	Very low

8	***Doxycycline as pre-exposure prophylaxis in the prevention of leptospirosis in children*** ***Recommendation 1:*** Doxycycline as pre-exposure prophylaxis may be used to prevent both asymptomatic laboratory-identified leptospiral infection and symptomatic leptospirosis in those who live in and intend to visit highly endemic areas.	Strong	Very low
9	***Doxycycline as post-exposure prophylaxis in the prevention of leptospirosis in children*** ***Recommendation 1:*** The use of doxycycline may be considered as post-exposure prophylaxis but there is no evidence in children to suggest that it can prevent symptomatic leptospirosis.	Strong	Very low
10	***Use of antibiotics other than doxycycline as post-exposure prophylaxis for leptospirosis in children*** ***Recommendation 1:*** Oral penicillin may be used for post-exposure prophylaxis to prevent symptomatic leptospirosis in high transmission areas but there are no studies in children.	Strong	Very low

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CHAPTER 1: INTRODUCTION

Leptospirosis, caused by a bacteria belonging to the genus *Leptospira sp.*, is a zoonotic disease that is transmissible to humans commonly thru exposure to vehicles (water, food, or soil) contaminated by urine from infected animals. Main reservoirs of the causative agent are rodents, livestock and dogs. Although leptospirosis occurs worldwide, it is most prevalent in the tropical and subtropical areas. The disease is also common in urban slum areas with inadequate water treatment and improper waste disposal. Leptospirosis can be both an occupational and recreational hazard. Among the groups at risk for the disease are field workers such as farmers and sugar cane workers, veterinarians, sewer workers, military personnel, and those who wade or swim in contaminated waters. Flooding after typhoons, excessive rainfall and other effects of extreme weather conditions propagate disease epidemics (WHO, 2010; WHO, 2017).

A systematic review on the global burden of leptospirosis that utilized morbidity and mortality studies and databases determined an overall estimate of 1.03 million cases of disease occurring annually worldwide. This resulted to about 2.9 million Disability Adjusted Life Years (DALYs). Countries in South and Southeast Asia are among the areas identified to have high disease morbidity (Torgerson, 2015).

Data from the Epidemiology Bureau of the Department of Health (DOH) show that from January 1, 2017 to December 2, 2017, there were a total of 2,495 leptospirosis cases nationwide. This is 49.1% higher than the reported cases from the previous year. Majority of the reported cases belonged to the 15 to 19 year old age group. There were 261 deaths, giving a case fatality rate (CFR) of 10.46%, and the age group with the highest CFR was the 45 to 49 year old age group (DOH, 2017). The year 2018 saw an even greater number of affected individuals, with 5,232 leptospirosis cases reported from January to December 31, 2018. This figure is 71% higher than in 2017. The 20 to 24 year old age group had the highest number of cases. There were 505 deaths (CFR 9.65%) (DOH, 2018). In July 2018, the DOH declared a leptospirosis outbreak in the National Capital Region (Philippine News Agency, 2018).

I. RATIONALE FOR THE GUIDELINE

The CPG, in the absence of an existing evidence-based guideline for the pediatric age group, hopes to standardize approach to diagnosis and antibiotic management of leptospirosis and answer concerns on the use of agents for the prevention of leptospirosis in exposed populations.

II. BACKGROUND

Typhoon “Ondoy” was one of the most destructive calamities that ravaged the country in September 2009, submerging many cities in NCR after its wake. An outbreak of leptospirosis occurred soon after. A report from the National Disaster Coordinating Council (NDCC) showed that there were 2,299 hospital admissions from October 1 to November 19, 2009 in 15 Sentinel Hospitals in Metro Manila due to leptospirosis, with 178 deaths recorded (NDCC, 2009). At this time, the Philippine Society for Microbiology and Infectious Diseases (PSMID), the Philippine Society of Nephrology (PSN) and the Council for Critical Care and Vascular Pulmonary Diseases of the Philippine College of Chest Physicians (PCCP) drafted interim guidelines on the diagnosis, management and prevention of leptospirosis to guide health workers handling diseased patients in affected areas. The interim guidelines were later finalized and updated as “Philippine Clinical Practice Guidelines (CPG) on the Diagnosis, Management and Prevention of Leptospirosis in Adults 2010” by the Leptospirosis Task Force composed of members of the PSMID, PSN and PCCP (PSMID, 2010).

In August 2012, the Pediatric Infectious Disease Society of the Philippines (PIDSP) released a “Post Disaster Interim Advice on the Prevention of Leptospirosis in Children” to guide physicians and parents on the prevention of leptospirosis (PIDSP, 2012).

In 2014, under the leadership of Dr. Salvacion Gatchalian, PIDSP formed CPG committees. Leptospirosis was one of the priority diseases identified that needed a guideline. Dr. Gyneth Bibera headed the initial Leptospirosis CPG group. There was an initial draft developed, but it did not utilize the GRADE method. There was likewise an initial attempt to incorporate the management of renal complications in children, with the help of then president of the Philippine Nephrology Society of the Philippines (PNSP), Dr. Norma Zamora. It was subsequently decided that a separate working group will be formed to address renal issues in leptospirosis.

Using the GRADE approach, this current guideline was created to address issues on recognition, diagnosis, antibiotic management and prevention of leptospirosis in children.

III. GUIDELINE OBJECTIVES:

1. To provide an evidence-based guideline in the diagnosis, antibiotic management, and prevention of leptospirosis in children.
2. To improve patient outcome through early identification of disease and timely intervention of cases for the prevention of complications.
3. To provide recommendations on pre- and post-exposure prophylaxis of leptospirosis in children.

IV. TARGET USERS

These guidelines are intended for primary care physicians, family medicine physicians, pediatricians, and other healthcare workers involved in caring for children with leptospirosis.

V. ORGANIZATION OF THE CLINICAL PRACTICE GUIDELINE ON LEPTOSPIROSIS:

A. Oversight (Steering) Committee (OC)

The Oversight Committee is composed of PIDSP members responsible for formulating the CPG's objectives and determining the intended users of the guideline.

The OC was tasked to schedule activities, coordinate with members of the Technical Review Committee (TRC) and organize the multisectoral stakeholders panel in charge of the final recommendations.

B. Guideline Writing Panel (GWP)

The GWP is composed of specialists in the field of infectious disease and epidemiology. They are responsible for the content of the summary of evidence and the draft recommendations.

C. Technical Review Committee (TRC)

Literature search, tracking and retrieving the journals, appraisal and summary of evidence were done by epidemiologists from the University of the East Ramon Magsaysay Memorial Medical Center and St. Luke's Medical Center.

D. Stakeholders Panel (Voting Consensus Panel)

This panel is composed of stakeholders including heads of societies, representatives from academic institutions, and representatives from government and non-government health agencies. The members are responsible for reviewing the draft recommendation statements and evidence, and will participate in panel deliberation through discussion and voting.

VI. DECLARATION OF CONFLICTS OF INTEREST

Members of the oversight committee, guideline writing panel, and the technical review committee declared potential conflicts of interest prior to the start of activities pertinent to the development of this guideline.

VII. METHODOLOGY

A. Identifying the Guideline Questions

Ten (10) questions were chosen by the Oversight Committee (OC) and the Guideline Panel (GWP) based on the following: (1) relevance, (2) priority and perceived urgency, (3) inconsistency of evidence, and (4) controversies.

The following are the clinical questions contained in this guideline:

Question 1: Among children with acute fever and possible exposure, what clinical manifestations should make one suspect leptospirosis?
Question 2: Among children with leptospirosis, what are the signs and symptoms associated with an increased risk of mortality?
Question 3: What laboratory findings are associated with severe leptospirosis?
Question 4: Can IgM Immunochromatography Test (ICT) be used as a rapid test in the diagnosis of leptospirosis in children?
Question 5: Can IgM Enzyme-linked Immunosorbent Assay (ELISA) be used as a rapid test in the diagnosis of leptospirosis in children?
Question 6: Can Polymerase Chain Reaction (PCR) be used in the diagnosis of leptospirosis in children?
Question 7: How effective is the use of antibiotics in the treatment of children with leptospirosis?
Question 8: How effective is doxycycline as pre-exposure prophylaxis in the prevention of leptospirosis in children?
Question 9: How effective is doxycycline as post-exposure prophylaxis in the prevention of leptospirosis in children?
Question 10: Is there evidence to recommend the use of antibiotics other than doxycycline as post-exposure prophylaxis for leptospirosis in children?

The issues on the management of renal complications, such as IV hydration and the need for dialysis, were not included as it was agreed upon with the Pediatric Nephrology Society of the Philippines (PNSP) that a separate guideline on these will be developed.

B. Search and Retrieval of Relevant Articles

A systematic search of literature was conducted by the TRC using electronic databases and other conventional methods. Medline was searched for relevant articles indexed from 1966 to 2017 using the terms derived from each of the questions. MeSH terms were often used because of their ability to explode. In addition, a local database called Herdin was searched, but since the search engine was not as sophisticated, manual searching was conducted upon obtaining abstracts from a broad topic search. There were no restrictions placed on language, age, or year of publication. Meta-analyses or systematic reviews were retrieved and used when available.

Aside from searching electronic databases, local experts from the Philippine Pediatric Society and the Pediatric Infectious Disease Society of the Philippines were asked for articles that they were aware of, whether published or unpublished. Manual searching of bibliographies from eligible articles was also conducted to identify references missed during the initial search.

C. Grading the Quality of Evidence and Preparation of Evidence Summaries

The quality of evidence and strength of recommendation was rated using the GRADE methodology (GRADE Working Group, 2004) by the TRC (see Table 1).

The quality of evidence is defined as the confidence that the reported estimates of effect are adequate to support a specific recommendation. The GRADE system classifies the quality of evidence as high, moderate, low, and very low. Randomized controlled trials are initially rated as high-quality evidence but may be downgraded for several reasons, including risk of bias, inconsistency of results, indirectness of evidence, imprecision, and publication bias. Observational studies are initially rated as low-quality evidence but may be upgraded if the magnitude of the treatment effect is very large, if evidence indicates a dose-response relationship, or if all plausible biases would underestimate the effect.

Table 1. Quality of evidence rating using the GRADE methodology

Quality	Definition
High	Further research is unlikely to change confidence in the estimates of the effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of the effect and may change the estimate.
Low	Further research is very likely to have an important impact on the confidence of the effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Additional categories considered when grading quality of evidence: (1) risk of bias (study limitations); (2) indirectness; (3) inconsistency; (4) imprecision; and (5) publication bias.

Deciding whether an outcome is critical, important but not critical, or not important, is a value judgment that should take into account the value of those who will be affected by adherence to subsequent recommendations. The outcome is considered as critical for a judgment if the risk of the adverse effect is serious and could result in mortality or a life-threatening condition. Other outcomes that are important but not critical are those that are significant but may not necessarily increase the risk for mortality.

D. Preparation of the Draft Recommendations

The GWP was tasked with reviewing and evaluating the quality of evidence and the draft recommendations submitted by the TRC. They were also responsible for revising and finalizing the guideline recommendations.

E. Consensus Development Process

1. Panel's Declaration of Conflict of Interest (COI) and Management of the Identified COI

Members of the panel were made to accomplish a Declaration of Conflict of Interest Form prior to the presentation of the evidence-based draft. There were two members identified with connections to a pharmaceutical company manufacturing antibiotics. One of them is the spouse of a company executive and the other is the head of the CME arm of the company. These panel members were excluded from the voting process on the clinical questions that addressed antibiotic and prophylactic management of leptospirosis

2. Panel of Stakeholders

The first evidence-based draft was circulated to the panelists one week prior to the scheduled en-banc meeting to allow review of the recommendation statements. During the meeting, the members of the GWP presented each recommendation with the supporting evidence. Using the nominal group technique, each recommendation was discussed, taking into account not only supporting evidence but also consideration of other criteria.

Table 2. Criteria for consideration in recommendation development

Domain	Rationale
Quality of evidence	Assessment of the degree of confidence in the estimate of the effect
Benefits and harms (Risks)	Desirable effects (benefits) need to be weighed against harmful or undesirable effects (risks), considering any previous recommendation or another alternative. The larger the gap or gradient in favor of the benefits over the risks, the more likely that a strong recommendation will be made.
Values and preferences	Judgment of how much the people affected by the intervention or option value each of the outcomes.
Acceptability	How much an intervention or recommendation is accepted by the people who are affected by it or by those who are implementing it. If the recommendation is likely to be widely accepted or valued highly, it is likely that a strong recommendation will be made. If there is a great deal of variability or strong reasons that a recommendation is unlikely to be accepted, it is more likely that a weak recommendation will be made.
Feasibility (including resources use consideration)	Whether an intervention is achievable and sustainable in a setting where the greatest impact is expected.

Assessment for each recommendation as “strong recommendation”, “weak recommendation” or “no recommendation” was determined by the panel based on the criteria provided. A preliminary vote on every item was obtained. A consensus was arrived at when 75% or more of the votes was obtained from any recommendation.

Table 3. Assessment criteria for the strength of recommendations

Strength of recommendations	Rationale
Strong	The Panel is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects.
Weak	The Panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects. However, the recommendation is only applicable to a specific group, population or setting; OR where new evidence may result in changing the balance of risk to benefit; OR where the benefits may not warrant the cost or resource requirements in all settings.
No recommendation	Further research is required before any recommendation can be made.

Comments, feedback, and discussions that resulted from the stakeholders meeting were noted by the GWP and incorporated into the second draft. All issues that were brought up during the stakeholders meeting were resolved. The second draft was circulated to the stakeholders panel for further comments and revisions.

F. Public Forum

The revised draft was presented during the 58th Philippine Pediatric Society (PPS) Annual Convention. Minor corrections noted were incorporated into the final draft.

G. Guideline Dissemination

The final version of the guideline will be accessible through the PIDSP website.

VIII. DISCLAIMER

Recommendations are a guide and may not be appropriate for use in all situations. Healthcare providers need to use clinical judgment, knowledge, expertise, and available resources when deciding whether it is appropriate to apply the recommendations in the guideline.

CHAPTER 2: CLINICAL AND LABORATORY FEATURES OF LEPTOSPIROSIS

Clinical Manifestations of Leptospirosis

Humans become infected through direct contact with the urine of infected animals, or indirectly with exposure to urine-contaminated environment (soil or water). The most common route is via exposure through water contaminated by urine from infected animals, usually rodents, as what happens during flooding. The bacteria enter the body through cuts or abrasions on the skin, or through the mucous membranes of the mouth, nose and eyes. Person-to-person transmission is rare (WHO, 2017). The incubation period is usually 7 to 12 days, but can range from 2 to 20 days (WHO, 2017; Nieves, 2019).

In humans, most cases are asymptomatic or mild and self-limited, but may be severe and potentially fatal (Day, 2018). The clinical course is variable and described as biphasic (Nieves, 2019; Dele Davies, 2016).

The first stage, or septicemic phase, is characterized by systemic signs, such as abrupt onset of fever, chills, headache, myalgia, conjunctival suffusion (red eyes), abdominal pain, vomiting, and/or diarrhea. The septicemic phase lasts for about 4-7 days. Clinical improvement and defervescence coincide with disappearance of leptospires from the blood, CSF, and all other tissues, except from the aqueous humor and kidneys. The second stage, or immune phase, is characterized by rapid antibody formation and lasts from 4-30 days (Nieves, 2019; Dele Davies, 2016).

Leptospirosis may present as an anicteric or icteric disease, with ninety percent or more presenting as an anicteric disease. The signs and symptoms in the septicemic phase are similar for both the anicteric and icteric disease. However, the hallmark of the immune phase of anicteric leptospirosis is meningitis, while the hallmark of the immune phase of icteric disease is characterized by impaired hepatic and renal functions (Nieves, 2019; Dele Davies, 2016). Weil syndrome, a rare (<10% of cases) severe form of leptospirosis, is characterized by impaired hepatic and renal function, vascular collapse, hemorrhage, severe alterations in consciousness, and is associated with a high mortality rate (Nieves, 2019; Dele Davies, 2016).

Laboratory Findings in Leptospirosis

Results of laboratory tests in leptospirosis are non-specific.

Although WBC counts may range from 3,000 to 26,000/microL, it is generally less than 10,000/microL and a left shift may be seen (Day, 2018). Thrombocytopenia (Chierakul, 2008) and pancytopenia (Stefos, 2005) have been noted in case series and case reports.

Proteinuria, pyuria, granular casts, and microscopic hematuria are possible findings on urinalysis (Berman, 1973). Elevated creatine kinase, indicative of renal failure characteristic of severe leptospirosis, has been observed in approximately 50% of affected patients (Johnson, 1975).

Derangements in sodium and potassium levels are seen in leptospirosis. It has been suggested that inhibition of Na^+-K^+-Cl^- co-transporter activity in the thick ascending limb of Henle by the outer membrane protein of the *Leptospira sp.* organism results in sodium wasting and hypokalemia (Wu, 2004; Krishnan, 2003).

Elevation of liver transaminases (<200 IU/L), seen in about 40% of patients, and high bilirubin concentrations (60-80 mg/dl) are the GI abnormalities particularly noted in severe disease (Day, 2018). In Chang's evaluation of 11 patients with sporadic leptospirosis in Taiwan, it was determined that progressive elevation of AST without concomitant change in ALT was indicative of an acute disease course with ensuring death. An AST/ALT Ratio (AAR) of greater than 3 means a grave prognosis (Chang, 2005).

CSF abnormalities in leptospirosis include neutrophilic pleocytosis and elevated protein concentrations. Hypoglycorrachia is rare but has been reported (Helmer, 1973).

Oliguria and WBC count above 12,900/mm^3 were among the mentioned findings associated with adverse outcomes among infected patients (Day, 2018).

Question 1: Among children with acute fever and possible exposure, what clinical manifestations should make one suspect leptospirosis?

Recommendation 1: Among children with acute fever and possible exposure, the presence of any or all of the following clinical manifestations should make one highly suspect leptospirosis:

- Renal syndrome (defined as any sign or symptom pointing to a possible kidney damage)
- Chest pain
- Cardiac syndrome (defined as any sign or symptom pointing to a possible cardiac involvement)

AND/OR

- Conjunctival suffusion/red eye

Quality of evidence: Very low
Strength of recommendation: Strong

Recommendation 2: Among children with acute fever and possible exposure, the presence of any or all of the following clinical manifestations may make one highly suspect leptospirosis:

- Arthralgia
- Myalgia
- Muscle tenderness

Quality of evidence: Very low
Strength of recommendation: Strong

Summary of Evidence

A total of seven studies evaluating signs and symptoms that may make one suspect leptospirosis in children with acute fever and possible exposure to leptospirosis were reviewed. All were cross-sectional studies (Agampodi, 2016; Ellis, 2008; Goarant, 2009; Karande, 2003; Kendall, 2010; Libraty, 2007; Morgan, 2002).

All seven studies were done in hospitals in different countries: Thailand (Libraty, 2007), India (Karande, 2003), Bangladesh (Kendall, 2010), Sri Lanka (Agampodi, 2016), Hawaii (Ellis, 2008), United States (Morgan, 2002), and New Caledonia (Goarant, 2009).

Studies were included if they had children as participants and if comparison was made between those with leptospirosis and without leptospirosis. Two studies had only children as their participants (Karande, 2003; Libraty, 2007) while five studies had both children and adults as participants (Agampodi, 2016; Ellis, 2008; Goarant, 2009; Kendall, 2010; Morgan, 2002).

Table 4. Summary of studies on clinical manifestations of leptospirosis

Study *(Study Design)*	Study Period	Patients (N)	Location	Outcome determined	Remarks
Agampodi 2016 *Cross-sectional*	Feb to May 2011	Sri Lankan children and adults 13 years old and above (mean age= 41) 48 patients were confirmed either by detection of Leptospira DNA in blood (N=26), positive MAT test (N=16), or both (N=6) and 28 who were clinically suspected case of leptospirosis (with negative or unconfirmed laboratory test) (N=76)	Teaching Hospital Anuradhapura (THA), Sri Lanka	Demographic and clinical characteristics for patients who were clinically suspected to have leptospirosis *(conjunctival suffusion (red eyes), anuria, proteinuria, oliguria and hematuria, myalgia, arthralgia, muscle tenderness, prostration, headache, positive Kernig's sign, icterus/jaundice, abdominal pain, anorexia, diarrhea, skin rash)*	There were more adults in the population studied.
Ellis 2008 *Cross-sectional*	Sep 12, 2001 to Apr 30, 2002	Hawaiian children and adults 10-67 years old 53 patients were IgM (ELISA) positive and 1106 who were negative for leptospirosis and dengue infection (N=1159)	All acute care hospitals and major clinics throughout the state of Hawaii	Demographic and clinical characteristics for patients who tested positive for leptospirosis *(Eye pain, myalgia, headache, skin rash)*	There were more adults in the population studied.
Goarant 2009 *Cross-sectional*	Jan to Jun 2008	Children and adults from New Caledonia 4-84 years old 98 cases of confirmed leptospirosis and 410 negative cases diagnosed using qPCR detection and MAT (N=508)	Health center, standard unit or ICU was obtained from the health centers and hospitals in New Caledonia	Symptoms reported from lab-confirmed leptospirosis and negative cases, risk factors *(cardiac syndrome, conjunctival suffusion/red eyes, renal syndrome, myalgia, headache, meningeal syndrome or meningismus, icterus/jaundice, hemorrhage)*	There were more adults in the population studied.

Study ***(Study Design)***	**Study Period**	**Patients (N)**	**Location**	**Outcome determined**	**Remarks**
Karande 2003 *Cross-sectional*	Jul 24, 2000-Sep 14, 2000	Indian children 1 month-12 years old 18 children were confirmed to have leptospirosis by blood dark field microscopy and/or IgM-ELISA and 35 children with no leptospirosis children (N=53)	Outpatient or emergency care department and admitted at the Lokmanya Tilak Municipal Medical College and General Hospital, Sion, Mumbai, India	Commonest complaints, final diagnosis of cases *(conjunctival suffusion/red eyes myalgia, headache, meningeal syndrome or meningismus, icterus/jaundice, abdominal pain, skin rash)*	Only hospitalized patients recruited.
Kendall 2010 *Cross-sectional*	Jan-Dec 2001	Bangladesh children, less than 5 years old and older with fever. There were 49 cases of probable or definite Leptospirosis by MAT and IgM ELISA and 500 controls with undiagnosed fever. Febrile patients were additionally evaluated for dengue, enteric fever and bloodstream infection. No overlap between the diagnoses of dengue, enteric fever and leptospirosis (N=549)	Kamalapur, a low-income neighborhood in Dhaka, Bangladesh, and referred to a field clinic	Demographic and clinical features of patients with leptospirosis and with undiagnosed fever *(chest pain, eye pain, myalgia, headache, abdominal pain, hemorrhage, skin rash)*	Only tested paired sera from febrile persons in a low-income urban community in Bangladesh. Probable cases of leptospirosis were included.
Libraty 2007 *Cross-sectional*	1994-1997	Thai children 6 months-14 years old 18 leptospirosis cases (14 definite and 4 probable) confirmed by ELISA and MAT (cases) and 214 with dengue as control (N=232)	Queen Sirikit Institute of Child Health in Bangkok, Thailand, Kamphaeng Phet Provincial Hospital, Kamphaeng Phet, Thailand	Presenting symptoms and signs between children with leptospirosis and dengue *(headache, abdominal pain, hemorrhage, skin rash)*	There were probable cases included.

Study *(Study Design)*	Study Period	Patients (N)	Location	Outcome determined	Remarks
Morgan 2002 *Cross-sectional*	mid-July 1998	245 triathlon participants and community residents 15–52 years old 52 participants had a laboratory-confirmed case of leptospirosis by 1 or more positive results using ELISA, MAT, culture or immunohistochemical staining and 193 participants with no infection who had two negative ELISA results (N=245)	Springfield, Illinois	Most common symptoms associated with fever, risk factors *(conjunctival suffusion/red eyes, eye pain, myalgia, headache)*	Cases from hospital, controls from community

The clinical manifestations that were evaluated were the following:

Cardiac Symptoms

Chest pain: One study evaluated chest pain (Kendall, 2010). Those who had leptospirosis were almost nineteen times more likely to have chest pain as compared to those without leptospirosis (OR: 18.8; 95% CI: 4.4 to 81.4). There is serious risk of bias inherent in an observational study design. There is also indirectness since there were more adults included in the study. The confidence interval is wide which is suggestive of imprecision. Even after taking into consideration the magnitude of the effect which has a very strong association (Converted RR: 15.96), the evidence is graded as very low.

Cardiac Syndrome: One study evaluated this parameter and, per personal communication, it was defined by the author as any sign or symptom pointing to a possible cardiac involvement, e.g., arrhythmias (Goarant, 2009). Those who had leptospirosis were almost seven times more likely to have cardiac syndrome as compared to those without leptospirosis (OR: 6.7; 95% CI: 2.3 to 19.2). There is serious risk of bias inherent in an observational study design. There is also indirectness since there were more adults included in the study. The confidence interval is wide which suggests imprecision. Even after taking into consideration the magnitude of the effect which has a very strong association (Converted RR: 6.33), the evidence is graded as very low.

Eye Symptoms

Conjunctival suffusion/red eyes: Four studies evaluated this parameter (Agampodi, 2016; Goarant, 2009; Karande, 2003; Morgan, 2002). Pooled analysis showed that those who had leptospirosis were almost six times more likely to have conjunctival suffusion or red eyes as compared to those without leptospirosis (OR: 5.64; 95% CI: 2.46 to 12.91). There is a very serious risk of bias inherent in an observational study design and inclusion of few probable cases. There is inconsistency due to heterogeneity or wide variance of point estimates across studies. There is imprecision as suggested by the wide confidence interval. There is also indirectness since there were more adults included in the studies. Even after taking into consideration the magnitude of the effect which has a strong association (Converted RR: 3.85), the evidence is graded as very low (Figure 1).

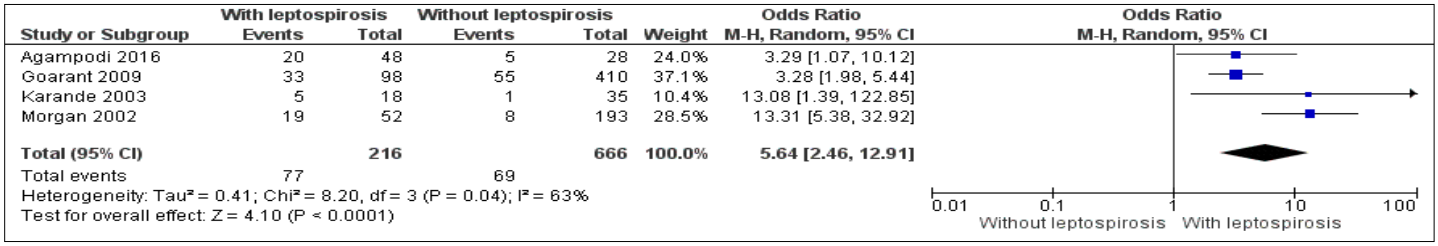

Figure 1. Forest plot of meta-analysis of data for the presence of conjunctival suffusion/red eyes comparing those with and without leptospirosis in admitted patients

Eye pain: Three studies evaluated this parameter (Ellis, 2008; Kendall, 2010; Morgan, 2002). Pooled analysis showed that those who had leptospirosis were almost three times more likely to have eye pain as compared to those without leptospirosis, but this did not reach statistical significance (OR: 2.95; 95% CI: 0.38 to 23.00). There is serious risk of bias inherent in an observational study design. There is inconsistency due to heterogeneity or wide variance of point estimates across studies. The wide confidence interval is suggestive of imprecision. There is also indirectness as there were more adults included in the studies; hence, this evidence is graded as very low (Figure 2).

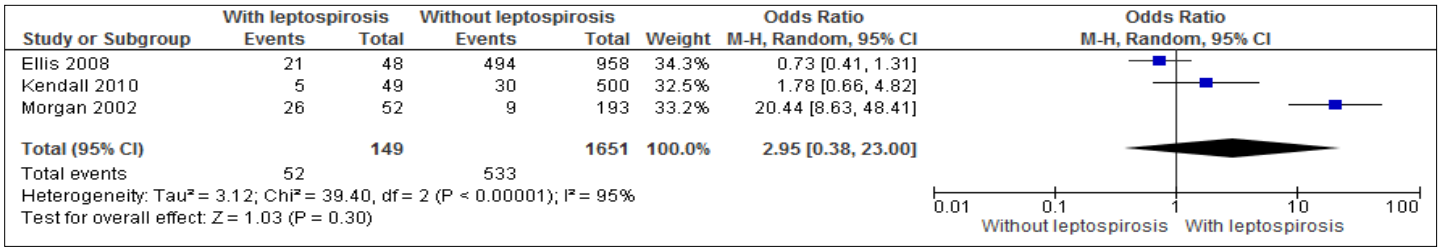

Figure 2. Forest plot of meta-analysis of data for the presence of eye pain comparing those with and without leptospirosis in admitted patients

Renal Symptoms

Renal syndrome: One study evaluated this parameter and, per personal communication, was defined by the author as any sign or symptom pointing to possible kidney damage (e.g., oliguria, anuria) (Goarant, 2009). Those who had leptospirosis were six times more likely to have renal syndrome as compared to those without leptospirosis (OR: 6.3; 95% CI: 3.3 to 12.2). There is serious risk of bias inherent in an observational study design. There is also indirectness since there were more adults included in the study. The wide confidence interval is suggestive of imprecision. After taking into consideration the magnitude of the effect which has a very strong association (Converted RR: 5.00), the evidence is graded as very low.

Anuria: One study evaluated this parameter (Agampodi, 2016). Those who had leptospirosis were three times more likely to have anuria as compared to those without leptospirosis, but this did not reach statistical significance (OR: 3.06; 95% CI: 0.14 to 66.15). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is also indirectness since there were more adults included in the study. There is also serious imprecision since there was an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low.

Proteinuria: One study evaluated this parameter (Agampodi, 2016). Those who had leptospirosis were almost two times more likely to have proteinuria as compared to those without leptospirosis, but this did not reach statistical significance (OR: 1.8; 95% CI: 0.18 to 18.19). There is very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is also indirectness since there were more adults included in the study. There is also serious imprecision since there was an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low.

Oliguria: One study evaluated this parameter (Agampodi, 2016). Those who had leptospirosis were more likely to have oliguria as compared to those without leptospirosis, but this did not reach statistical significance (OR: 1.14; 95% CI: 0.41 to 3.16). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is also indirectness since there were more adults included in the study. There is also serious imprecision since there was an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low.

Hematuria: One study evaluated this parameter (Agampodi, 2016). Those who had leptospirosis were more likely to have hematuria as compared to those without leptospirosis, but this did not reach statistical significance (OR: 1.14; 95% CI: 0.41 to 3.16). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is also indirectness since there were more adults included in the study. There is also serious imprecision since there is an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low.

Constitutional Symptoms

Myalgia: Six studies evaluated this parameter (Agampodi, 2016; Ellis, 2008; Goarant, 2009; Karande, 2003; Kendall, 2010; Morgan, 2002). The site of myalgia was not indicated except for Karande who described myalgia as generalized (Karande, 2003). Pooled analysis showed that those who had leptospirosis were almost three times more likely to have myalgia as compared to those without leptospirosis, but this did not reach statistical significance (OR: 2.81; 95% CI: 0.92 to 8.60). There is serious risk of bias inherent in an observational study design and inclusion of few probable cases. There is inconsistency due to heterogeneity and wide variance of point estimates across studies. The wide confidence interval is suggestive of imprecision. There is also indirectness since there were more adults included in the studies; hence, this evidence is graded as very low (Figure 3).

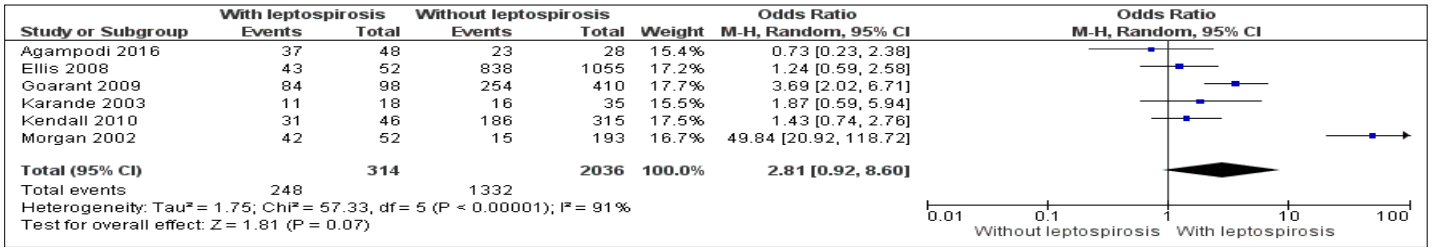

Figure 3. Forest plot of meta-analysis of data for the presence of myalgia comparing those with and without leptospirosis in admitted patients

Arthralgia: One study evaluated this parameter (Agampodi, 2016). Those who had leptospirosis were three times more likely to have arthralgia as compared to those without leptospirosis (OR: 3.4; 95% CI: 1.0 to 11.85). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is also indirectness since there were more adults included in the study, and there is imprecision as suggested by the wide confidence interval. The evidence for arthralgia is graded as very low.

Muscle tenderness: One study evaluated this parameter (Agampodi, 2016). Those who had leptospirosis were two times more likely to have muscle tenderness as compared to those without leptospirosis, but this did not reach statistical significance (OR: 2.11; 95% CI: 0.75 to 6.00). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is also indirectness since there were more adults included in the study. There is also serious imprecision since there is an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low.

Prostration: One study evaluated this parameter (Agampodi, 2016). Those who had leptospirosis were two times more likely to have prostration as compared to those without leptospirosis, but this did not reach statistical significance (OR: 2.01; 95% CI: 0.68 to 5.92). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is also indirectness since there were more adults included in the study. There is also serious imprecision since there is an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low.

Neurological Symptoms

Headache: Seven studies evaluated this parameter (Agampodi, 2016; Ellis, 2008; Goarant, 2009; Karande, 2003; Kendall, 2010; Libraty, 2007; Morgan, 2002). Pooled analysis showed that those who had leptospirosis were almost three times more likely to have headache as compared to those without leptospirosis, but this did not reach statistical significance (OR: 2.45; 95% CI: 0.80 to 7.51). There is a very serious risk of bias inherent in an observational study design and inclusion of few probable cases. There is inconsistency due to heterogeneity or wide variance of point estimates across studies. There is indirectness as there were more adults included in the studies. There is also serious imprecision since there is an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low (Figure 4).

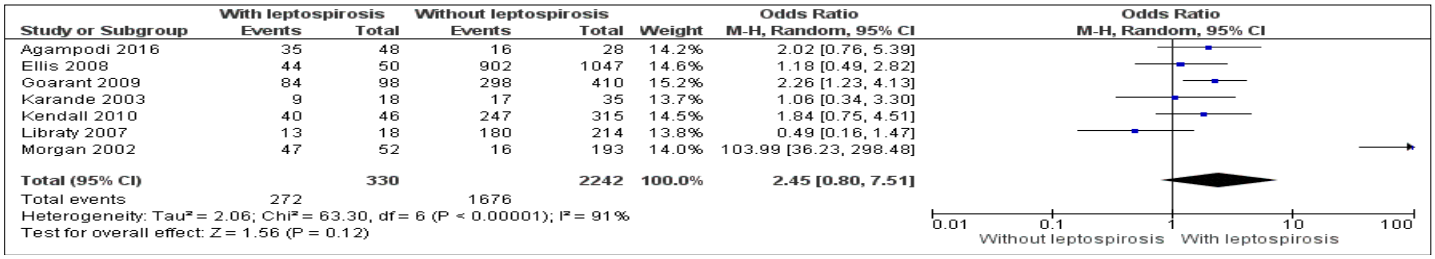

Figure 4. Forest plot of meta-analysis of data for the presence of headache comparing those with and without leptospirosis in admitted patients

Meningeal syndrome/meningismus: Two studies evaluated this parameter (Goarant, 2009; Karande, 2003). Goarant, per personal communication, defined meningeal syndrome as any sign pointing to a possible meningeal involvement such as headache, photophobia, and nuchal rigidity (Goarant, 2009). Meningismus is a constellation of signs and symptoms (e.g., headache, neck stiffness) characterized by meningeal irritation without objective findings. Pooled analysis showed that those who had leptospirosis were two times more likely to have meningeal syndrome as compared to those without leptospirosis, but this did not reach statistical significance (OR: 2.06; 95% CI: 0.40 to 10.56). There is serious risk of bias inherent in an observational study design. There is inconsistency due to heterogeneity or wide variance of point estimates across studies. There is indirectness since there were more adults included in the studies. There is also serious imprecision since there is an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low (Figure 5).

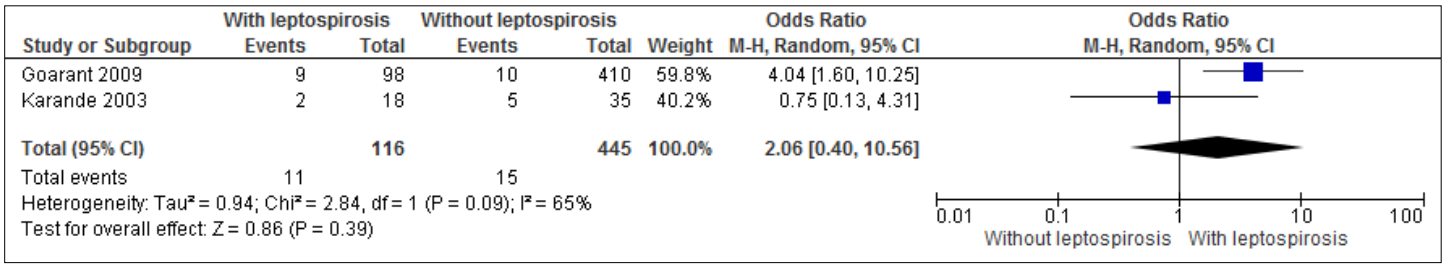

Figure 5. Forest plot of meta-analysis of data for the presence of meningeal syndrome comparing those with and without leptospirosis in admitted patients

Positive Kernig's sign: Only one study evaluated this parameter (Agampodi, 2016). Those who had leptospirosis were likely to have positive Kernig's sign as compared to those without leptospirosis, but this did not reach statistical significance (OR: 1.37; 95% CI: 0.42 to 4.44). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is indirectness since there were more adults included in the study. There is also serious imprecision since there is an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low.

Gastrointestinal Symptoms

Icterus/jaundice: Three studies evaluated this parameter (Agampodi, 2016; Goarant, 2009; Karande, 2003). Pooled analysis showed that those who had leptospirosis were two times more likely to have icterus or jaundice as compared to those without leptospirosis, but this did not reach statistical significance (OR: 2.31; 95% CI: 0.46 to 11.50). There is a very serious risk of bias inherent in an observational study design and inclusion of few probable cases. There is inconsistency due to heterogeneity or wide variance of point estimates across studies. There is indirectness since there were more adults included in the studies. There is also serious imprecision since there is an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low (Figure 6).

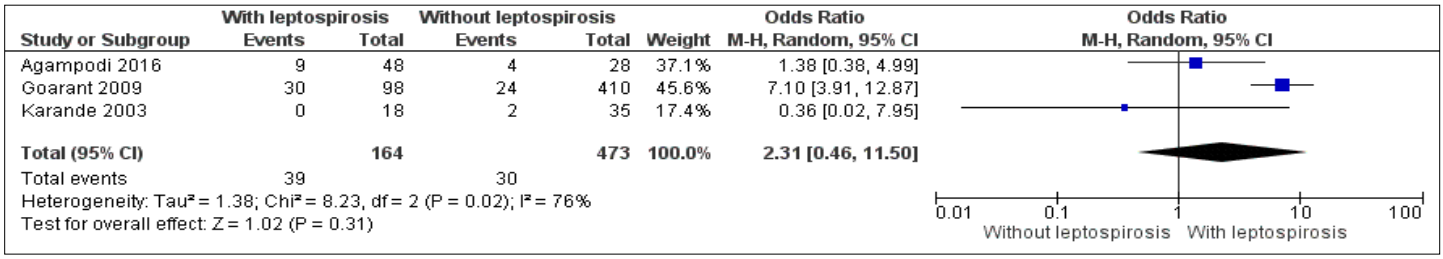

Figure 6. Forest plot of meta-analysis of data for the presence of icterus/jaundice comparing those with and without leptospirosis in admitted patients

Abdominal pain: Four studies evaluated this parameter (Agampodi, 2016; Karande, 2003; Kendall, 2010; Libraty, 2007). Pooled analysis showed that those who had leptospirosis were two times more likely to have abdominal pain as compared to those without leptospirosis, but this did not reach statistical significance (OR: 2.15; 95% CI: 0.96 to 4.85). There is a very serious risk of bias inherent in an observational study design and inclusion of few probable cases. There is inconsistency due to heterogeneity or wide variance of point estimates across studies. There is indirectness since there were more adults included in the studies. There is also serious imprecision since there is an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low (Figure 7).

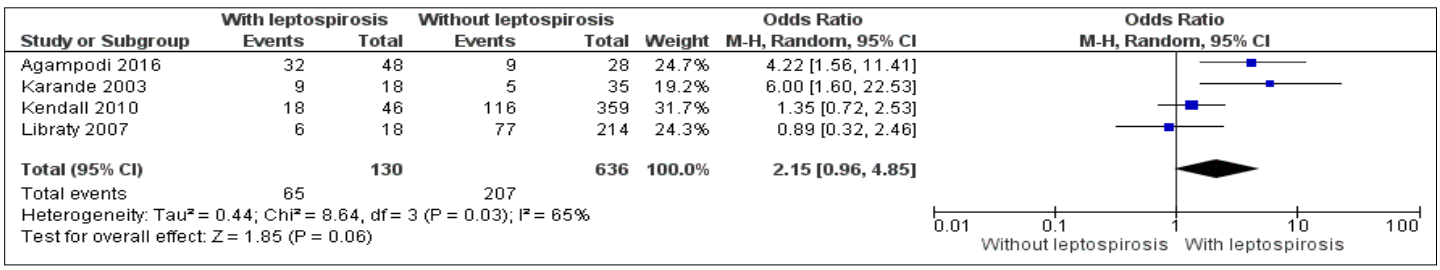

Figure 7. Forest plot of meta-analysis of data for the presence of abdominal pain comparing those with and without leptospirosis in admitted patients

Anorexia: One study evaluated this parameter (Agampodi, 2016). Those who had leptospirosis were almost two times more likely to have anorexia as compared to those without leptospirosis, but this did not reach statistical significance (OR: 1.87; 95% CI: 0.49 to 7.13). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is also indirectness since there were more adults included in the study. There is also serious imprecision since there is an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low.

Diarrhea: One study evaluated this parameter (Agampodi, 2016). Those who had leptospirosis were likely to have diarrhea as compared to those without leptospirosis, but this did not reach statistical significance (OR: 1.37; 95% CI: 0.42 to 4.44). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is also indirectness since there were more adults included in the study. There is also serious imprecision since there is an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low.

Bleeding Symptoms

Hemorrhage: Three studies evaluated this parameter (Goarant, 2009; Kendall, 2010; Libraty, 2007). However, the sites of the bleeding were not indicated. Pooled analysis showed that those who had leptospirosis were two times more likely to have hemorrhage or bleeding as compared to those without leptospirosis, but this did not reach statistical significance (OR: 2.11; 95% CI: 0.68 to 6.61). There is serious risk of bias inherent in an observational study design. There is inconsistency due to heterogeneity or wide variance of point estimates across studies. There is indirectness since there were more adults included in the studies. There is also serious imprecision since there is an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low (Figure 8).

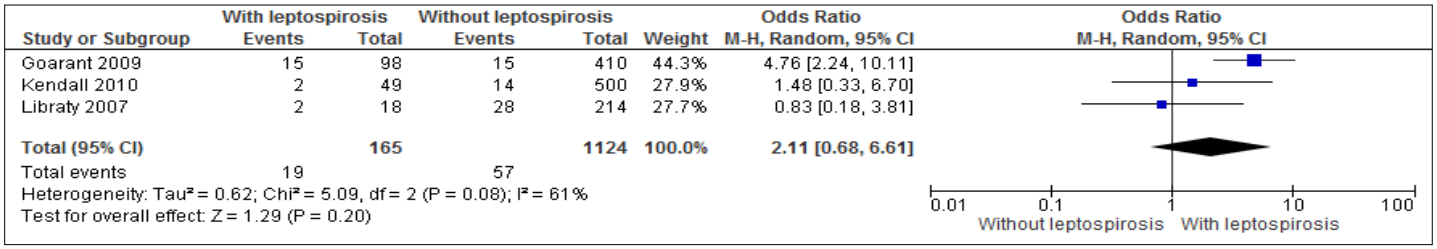

Figure 8. Forest plot of meta-analysis of data for the presence of hemorrhage/bleeding comparing those with and without leptospirosis in admitted patients

Skin rash: Five studies evaluated this parameter (Agampodi, 2016; Ellis, 2008; Karande, 2002; Kendall, 2010; Libraty, 2007). Pooled analysis showed that those who had leptospirosis were almost two times more likely to have skin rash as compared to those without leptospirosis, but this did not reach statistical significance (OR: 1.70; 95% CI: 0.59 to 4.84). There is serious risk of bias due to observational study design and inclusion of few probable cases. There is inconsistency due to heterogeneity or wide variance of point estimates across studies. There is serious imprecision as evidenced by the overlapping confidence interval with the null value. There is indirectness since there were more adults included in the studies; hence, this evidence is graded as very low (Figure 9).

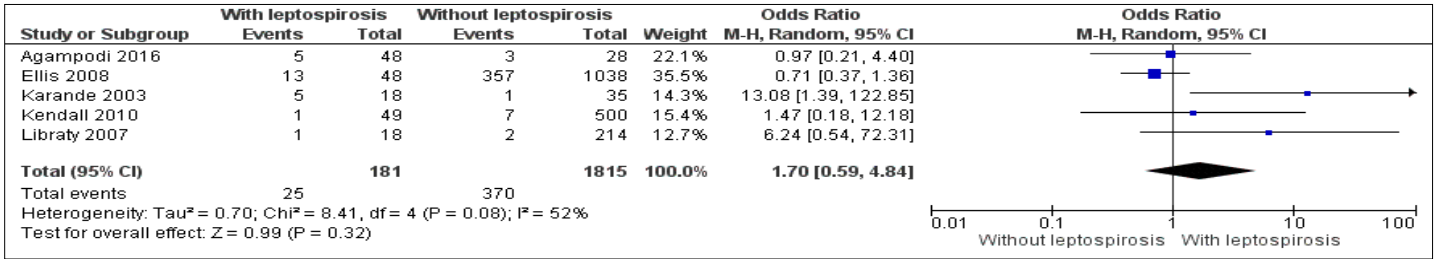

Figure 9. Forest plot of meta-analysis of data for the presence of skin rash comparing those with and without leptospirosis in admitted patients

Considerations for Recommendation Development during the Stakeholders Panel (SP) Meeting:

- The consensus panel had a long discussion on this question that even led to a postponement of the votation. The votation was subsequently done by the Delphi Method.
- The seven studies that evaluated for signs and symptoms that may make one suspect leptospirosis in children with acute fever and possible exposure suffered from risk of bias – all being observational (cross-sectional) studies, with imprecision and indirectness. Hence, the quality of evidence is graded very low.
- Despite the very low quality of evidence, a consensus was made via the Delphi Method for a strong recommendation because renal syndrome and conjunctival suffusion turned out to be statistically significant. These two manifestations, especially the renal manifestations, are what clinicians usually look for when considering the possibility of leptospirosis. According to the representative from PSN, renal syndrome is a more encompassing term, defined by the author as ANY sign or symptom of renal damage.
- Chest pain and cardiac syndrome were likewise voted for a strong recommendation, even if not commonly seen in children with leptospirosis. These were the two significant parameters from a single study that had more adult participants.
- For the second recommendation, the SP also voted on a strong recommendation for arthralgia, myalgia, and muscle tenderness despite very low quality of evidence (not statistically significant) as these are also usually seen in clinical practice among children with leptospirosis.
- A limitation of the guideline was the use of studies involving admitted patients only. There were no studies on patients seen on an outpatient basis.

Question 2: Among children with leptospirosis, what are the signs and symptoms associated with an increased risk of mortality?

Recommendation 1: In children with leptospirosis, the presence of any one of the following signs and symptoms increases the risk of mortality:

- Pallor
- Loss of consciousness
- Murmur
- Meningism
- Irregular rhythm
- Dyspnea
- Pulmonary hemorrhage
- Convulsions/seizure
- Crackles/rales on lung auscultation
- Hemoptysis
- Anuria
- Disorientation
- Jaundice
- Tachycardia

Quality of evidence: Very low
Strength of recommendation: Strong

Summary of Evidence

A total of six studies evaluated signs and symptoms that may predict disease mortality in children and adults with leptospirosis. Five studies were cross-sectional studies (Amilasan, 2012; Daher, 2010; Lopes, 2010; Mendoza, 2013; Pappachan, 2004), while the remaining study was case-control in design (Bonus, 2016). One of the studies involved adults only, but was nonetheless included because it was a local study (Mendoza, 2013).

All the studies classified their data into two categories: those who have leptospirosis and survived, and those who have leptospirosis and died.

All studies included patients who were admitted in the hospital. Three studies were done locally (Amilasan, 2012; Bonus, 2016; Mendoza, 2013), two studies were done in Brazil (Daher, 2010; Lopes, 2004), and one was done in India (Pappachan, 2004).

Table 5. Summary of studies evaluating signs and symptoms that increase the risk of mortality

Study (*Study Design)*	Study Period	Patients (N)	Location	Outcome determined	Remarks
Amilasan 2012 *Cross-sectional*	Oct 11-31, 2009	Filipino children and adult patients There were 34 who were aged <15 years old and 12 who were aged <10 years old 51 died and 420 survived (N=471)	San Lazaro Hospital (SLH)	Clinical manifestations associated with mortality	There were more adults included in the study.
Bonus 2016 *Case-control*	Jan 2008 - Dec 2012	Filipino pediatric patients ≤18 years old 14 died and 390 survived (N=404)	Philippine General Hospital (PGH), Research Institute for Tropical Medicine (RITM) and San Lazaro Hospital (SLH)	Clinical manifestations associated with mortality	There were probable cases of leptospirosis included.
Daher 2010 *Cross-sectional*	May 1985–Dec 2006	Brazilian children and adult patients 8-84 years old 31 patients died and 180 survived (N=201)	Walter Cantídio University Hospital and São José Infectious Diseases Hospital, in Fortaleza City, Northeast Brazil	Clinical manifestations associated with mortality	There were more adults included in the study.
Lopes 2010 *Cross-sectional*	1993-1997	Brazilian children and adult patients 100 pediatric and 740 adult patients 121 died and 719 survived (N=840)	Couto Maia Hospital, Salvador, BA, Brazil	Clinical manifestations associated with mortality	There were more adults included in the study.

Study (*Study Design)*	Study Period	Patients (N)	Location	Outcome determined	Remarks
Mendoza 2013 *Cross-sectional*	Sept 28 - Nov 30, 2009	Adult patients Mean age was 38.9 years old 14 died and 245 survived (N=259)	University of the Philippines-Philippine General Hospital (UP-PGH), National Kidney and Transplant Institute (NKTI), The Medical City (TMC), University of Santo Tomas Hospital (USTH), Manila Doctors Hospital (MDH), Ospital ng Maynila Medical Center (OMMC), Cardinal Santos Medical Center (CSMC), East Avenue Medical Center (EAMC), and Makati Medical Center (MMC)	Clinical manifestations associated with mortality	There were only adults included in the study.
Pappachan 2004 *Cross-sectional*	2002	Indian children and adults 12-75 years old 17 died and 265 survived (N=282)	General medicine wards of Calicut Medical College in Northern Kerala, India	Clinical manifestations associated with mortality	There were more adults included in the study.

The clinical signs and symptoms that were evaluated were the following:

Respiratory Symptoms

Pulmonary hemorrhage: Only one study evaluated this parameter (Mendoza, 2013). Those who died were almost forty-nine times more likely to have pulmonary hemorrhage as compared to those who survived (OR: 48.54; 95% CI: 13.27 to 177.51). There is serious risk of bias due to observational study design. There is also indirectness since only adults were included in the study. The wide confidence interval is suggestive of serious imprecision. Even after taking into consideration the magnitude of the effect which has a very strong association (Converted RR: 14.58), the evidence is graded as very low.

Dyspnea: Two studies evaluated this parameter (Bonus, 2016; Pappachan, 2004). Pooled analysis showed that those who died were nine times more likely to have dyspnea as compared to those who survived (OR: 9.13; 95% CI: 4.20 to 19.88). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is also indirectness since there were more adults included in the study. The wide confidence interval is suggestive of serious imprecision. Even after taking into consideration the magnitude of the effect which has a very strong association (Converted RR: 5.50), the evidence is graded as very low (Figure 10).

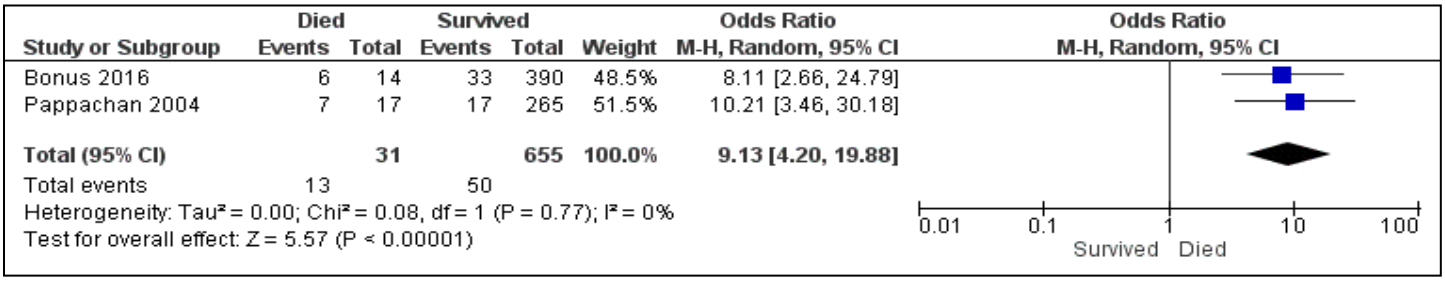

Figure 10. Forest plot of pooling of data for the presence of dyspnea comparing those with leptospirosis who died and survived

Crackles/rales on lung auscultation: Two studies evaluated this parameter (Bonus, 2016; Daher, 2010). Pooled analysis showed that those who died were seven times more likely to have crackles/rales as compared to those who survived (OR: 7.12; 95% CI: 3.28 to 15.44). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is also indirectness since there were more adults included in the study. The wide confidence interval is suggestive of serious imprecision. Even after taking into consideration the magnitude of the effect which has a very strong association (Converted RR: 5.20), the evidence is graded as very low (Figure 11).

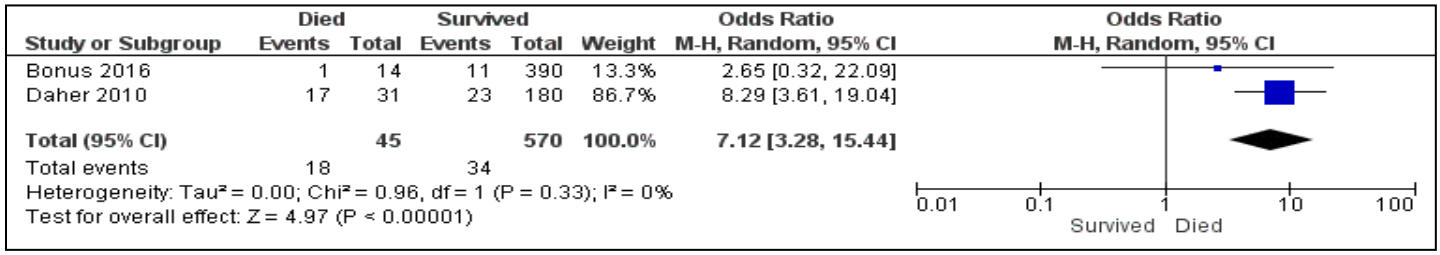

Figure 11. Forest plot of pooling of data for the presence of crackles/rales on auscultation comparing those with leptospirosis who died and survived

Hemoptysis: Three studies evaluated this parameter (Amilasan, 2012; Bonus, 2016; Pappachan, 2004). Pooled analysis showed that those who died were almost seven times more likely to have hemoptysis as compared to those who survived (OR: 6.93; 95% CI: 3.07 to 15.66). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is also indirectness since there were more adults included in the study. The wide confidence interval is suggestive of serious imprecision. Even after taking into consideration the magnitude of the effect which has a very strong association (Converted RR: 6.24), the evidence is graded as very low (Figure 12).

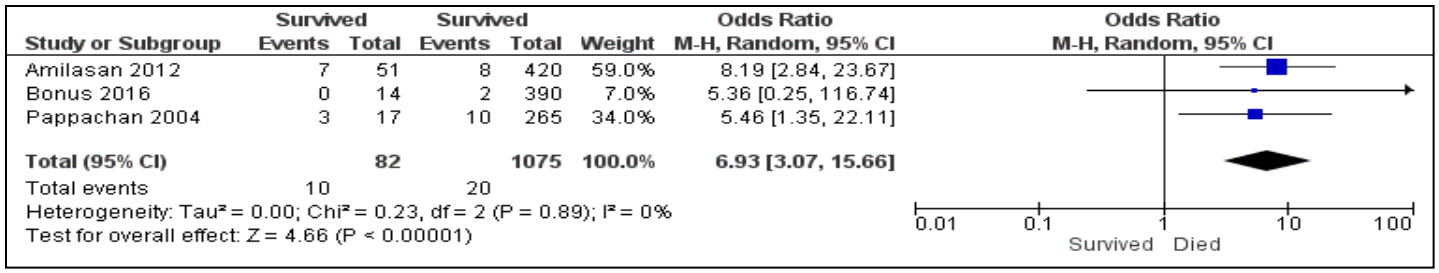

Figure 12. Forest plot of pooling of data for the presence of hemoptysis comparing those with leptospirosis who died and survived

Decreased breath sounds: Only one study evaluated this parameter (Bonus, 2016). Those who died were four times more likely to have decreased breath sounds as compared to those who survived, but this did not reach statistical significance (OR: 4.2; 95% CI: 0.5 to 36.8). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is also serious imprecision since there is an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low.

Constitutional Symptoms

Pallor: Only one study evaluated this parameter (Bonus, 2016). Those who died were almost thirty times more likely to have pallor as compared to those who survived (OR: 29.9; 95% CI: 1.8 to 505.2). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. The wide confidence interval almost inclusive of the null value is suggestive of serious imprecision. Even after taking into consideration the magnitude of the effect which has a very strong association (Converted RR: 27.50), the evidence is graded as very low.

Malaise: Two studies evaluated this parameter (Amilasan, 2012; Bonus, 2016). Pooled analysis showed that those who died were almost two times more likely to have malaise as compared to those who survived, but this did not reach statistical significance (OR: 1.98; 95% CI: 0.46 to 8.54). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is indirectness since there were more adults included in the study. There is inconsistency due to heterogeneity or wide variance of point estimates across studies. There is also serious imprecision since there is an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low (Figure 13).

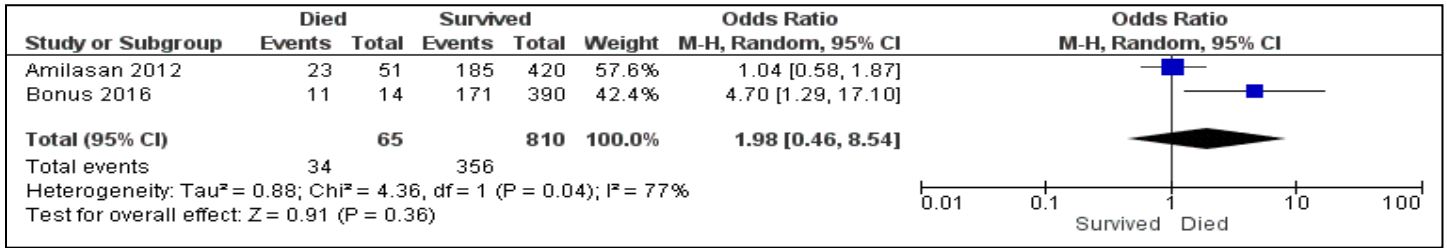

Figure 13. Forest plot of pooling of data for the presence of malaise comparing those with leptospirosis who died and survived

Chills/rigor: Two studies evaluated this parameter (Bonus, 2016; Pappachan, 2004). Pooled analysis showed that those who died were almost two times more likely to have chills or rigor as compared to those who survived, but this did not reach statistical significance (OR: 1.73; 95% CI: 0.73 to 4.13). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is indirectness since there were more adults included in the study. There is also serious imprecision since there is an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low (Figure 14).

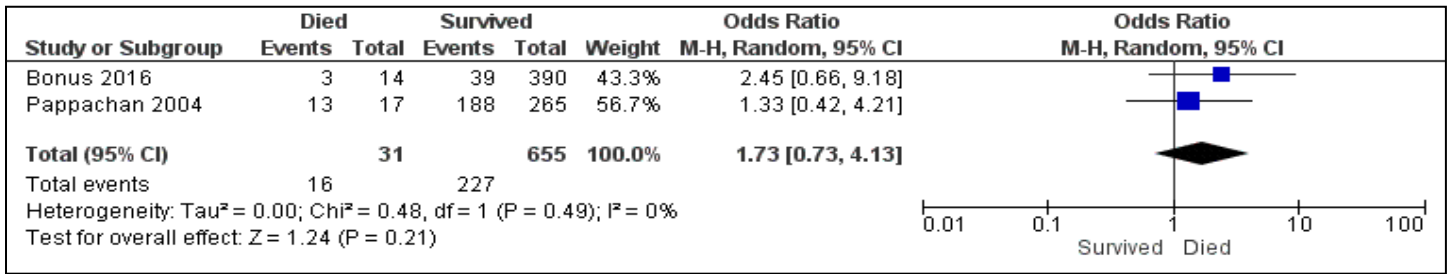

Figure 14. Forest plot of pooling of data for the presence of chills/rigor comparing those with leptospirosis who died and survived

Signs of dehydration: Only one study evaluated this parameter (Bonus, 2016). Those who died were almost three times more likely to have signs of dehydration as compared to those who survived, but this did not reach statistical significance (OR: 2.8; 95% CI: 0.7 to 10.4). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is also serious imprecision since there is an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low.

Anorexia: Only one study evaluated this parameter (Bonus, 2016). Those who died were almost two times more likely to be anorexic as compared to those who survived, but this did not reach statistical significance (OR: 1.7; 95% CI: 0.5 to 6.4). There is a very serious risk of bias inherent in observational study design and inclusion of probable cases. There is also serious imprecision since there is an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low.

Neurological Symptoms

Loss of consciousness: Only one study evaluated this parameter (Bonus, 2016). Those who died were almost thirty times more likely to have loss of consciousness as compared to those who survived (OR: 29.9; 95% CI: 1.8 to 505.2). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. The wide confidence interval is suggestive of serious imprecision. Even after taking into consideration the magnitude of the effect which has a very strong association (Converted RR: 27.50), the evidence is graded as very low.

Meningism: Only one study evaluated this parameter (Pappachan, 2004). Those who died were almost eleven times more likely to have meningism as compared to those who survived (OR: 10.6; 95% CI: 2.3 to 48). There is serious risk of bias inherent in an observational study design. There is also indirectness since there were more adults included in the study. The wide confidence interval is suggestive of serious imprecision. Even after taking into consideration the magnitude of the effect which has a very strong association (Converted RR: 8.23), the evidence is graded as very low.

Convulsion/seizure: Two studies evaluated this parameter (Amilasan, 2012; Bonus 2016). Pooled analysis showed that those who died were almost eight times more likely to have convulsion or seizure as compared to those who survived (OR: 7.81; 95% CI: 1.39 to 43.84). There is a very serious risk of bias inherent in an observational study and inclusion of probable cases. There is also indirectness since there were more adults included in the study. The wide confidence interval is suggestive of serious imprecision. Even after taking into consideration the magnitude of the effect which has a very strong association (Converted RR: 7.55), the evidence is graded as very low (Figure 15).

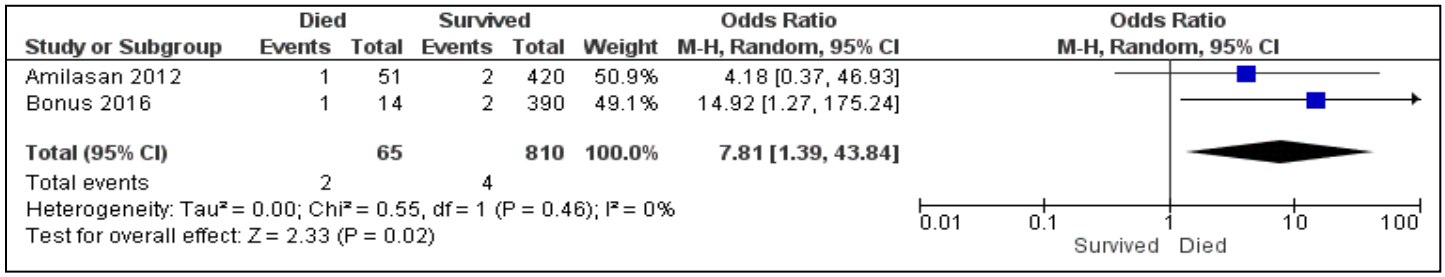

Figure 15. Forest plot of pooling of data for the presence of convulsion/seizure comparing those with leptospirosis who died and survived

Disorientation: Only one study evaluated this parameter (Pappachan, 2004). Those who died were five times more likely to have disorientation as compared to those who survived (OR: 5; 95% CI: 1.3 to 17.6). There is serious risk of bias inherent in an observational study design. There is also indirectness since there were more adults included in the study. Even after taking into consideration the magnitude of the effect which has a strong association (Converted RR: 3.75), the evidence is graded as very low.

Cardiac Symptoms

Murmur: Only one study evaluated this parameter (Bonus, 2016). Those who died were almost fifteen times more likely to have murmurs as compared to those who survived (OR: 14.9; 95% CI: 1.3 to 175.2). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. The wide confidence interval almost inclusive of the null value is suggestive of serious imprecision. After taking into consideration the magnitude of the effect which has a very strong association (Converted RR: 13.95), the evidence is graded as very low.

Irregular rhythm: Only one study evaluated this parameter (Bonus, 2016). Those who died were almost ten times more likely to have irregular rhythm as compared to those who survived (OR: 9.9; 95% CI: 1 to 102). There is a very serious risk

of bias inherent in an observational study design and inclusion of probable cases. There is also serious imprecision since there is an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low.
Tachycardia: Only one study evaluated this parameter (Pappachan, 2004). Those who died were four times more likely to be tachycardic as compared to those who survived (OR: 4.1; 95% CI: 1.2 to 13.1). There is serious risk of bias inherent in an observational study design. There is also indirectness since there were more adults included in the study. The wide confidence interval almost inclusive of the null value is suggestive of serious imprecision. The evidence for tachycardia is graded as very low.

Hypotension: Only one study evaluated this parameter (Bonus, 2016). Those who died were two times more likely to be hypotensive as compared to those who survived, but this did not reach statistical significance (OR: 2.3; 95% CI: 0.6 to 8.7). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is also serious imprecision since there is an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low.

Renal Symptoms

Anuria: Two studies evaluated this parameter (Amilasan, 2012; Bonus, 2016). Pooled analysis showed that those who died were almost seven times more likely to be anuric as compared to those who survived (OR: 6.52; 95% CI: 2.93 to 14.51). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is also indirectness since there were more adults included. The wide confidence interval is suggestive of serious imprecision. After taking into consideration the magnitude of the effect which has a very strong association (Converted RR: 5.77), the evidence is graded as very low (Figure 16).

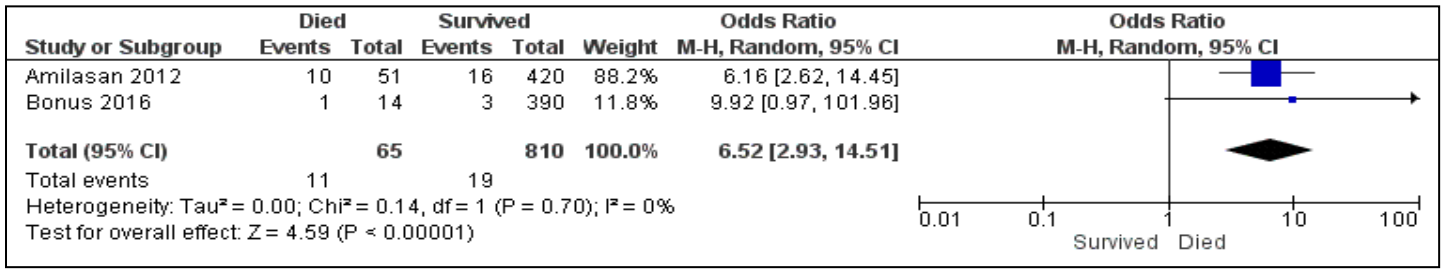

Figure 16. Forest plot of pooling of data for the presence of anuria comparing those with leptospirosis who died and survived

Oliguria: Four studies evaluated this parameter (Amilasan, 2012; Bonus, 2016; Daher, 2010; Pappachan, 2004). Pooled analysis showed that those who died were almost three times more likely to be oliguric as compared to those who survived, but this did not reach statistical significance (OR: 2.66; 95% CI: 0.68 to 10.41). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is indirectness since there were more adults included in the study. There is inconsistency due to heterogeneity or wide variance of point estimates across studies. There is also serious imprecision since there is overlapping of confidence interval with the null value; hence, this evidence is graded as very low (Figure 17).

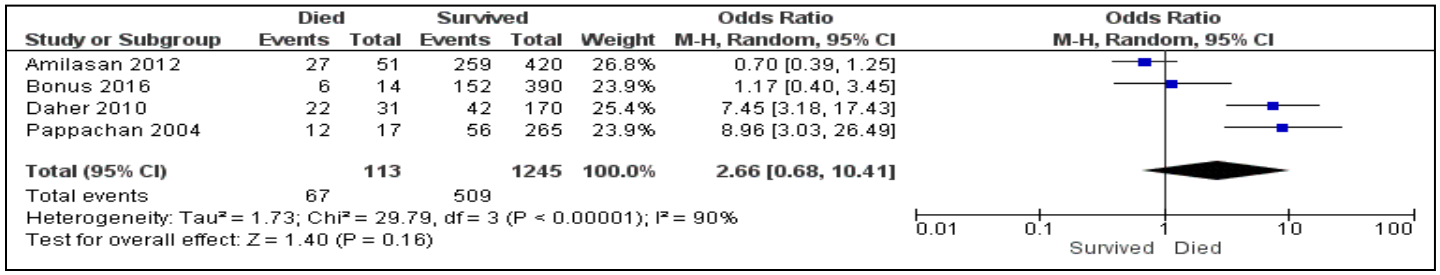

Figure 17. Forest plot of pooling of data for the presence of oliguria comparing those with leptospirosis who died and survived

Edema: Only one study evaluated this parameter (Bonus, 2016). Those who died were two times more likely to have edema as compared to those who survived, but this did not reach statistical significance (OR: 2.1; 95% CI: 0.3 to 16.9). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is also serious imprecision since there is an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low.

Dysuria: Only one study evaluated this parameter (Bonus, 2016). Those who died were almost two times more likely to be dysuric as compared to those who survived, but this did not reach statistical significance (OR: 1.6; 95% CI: 0.09 to 28.2). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is also serious imprecision since there is an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low.

Gastrointestinal Symptoms

Jaundice: Four studies evaluated this parameter (Amilasan, 2012; Bonus, 2016; Lopes, 2010; Pappachan, 2004). Pooled analysis showed that those who died were almost five times more likely to have jaundice as compared to those who survived (OR: 4.76; 95% CI: 2.99 to 7.59). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is also indirectness since there were more adults included in the studies. After taking into consideration the magnitude of the effect which showed weak association (Converted RR: 1.54), this evidence is graded as very low (Figure 18).

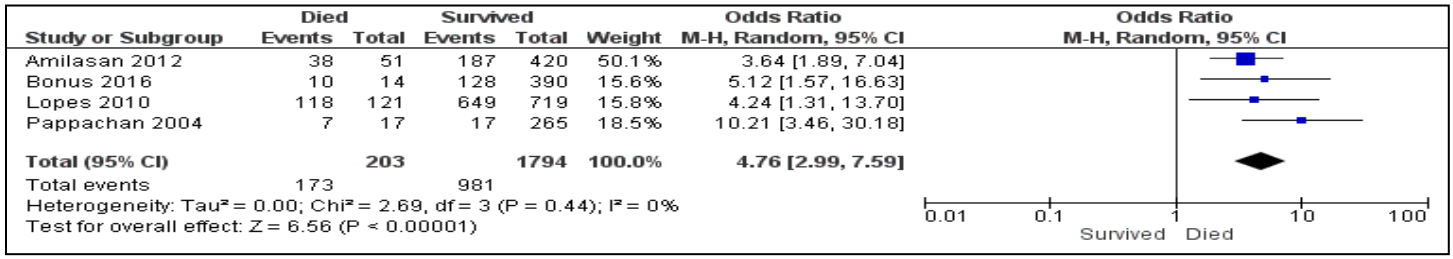

Figure 18. Forest plot of pooling of data for the presence of jaundice comparing those with leptospirosis who died and survived

Abdominal pain: Three studies evaluated this parameter (Amilasan, 2012; Bonus, 2016; Pappachan, 2004). Pooled analysis showed that those who died were likely to have abdominal pain as compared to those who survived, but this did not reach statistical significance (OR: 1.31; 95% CI: 0.53 to 3.26). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is indirectness since there were more adults included in the study. There is inconsistency due to heterogeneity or wide variance of point estimates across studies. There is also serious imprecision due to an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low (Figure 19).

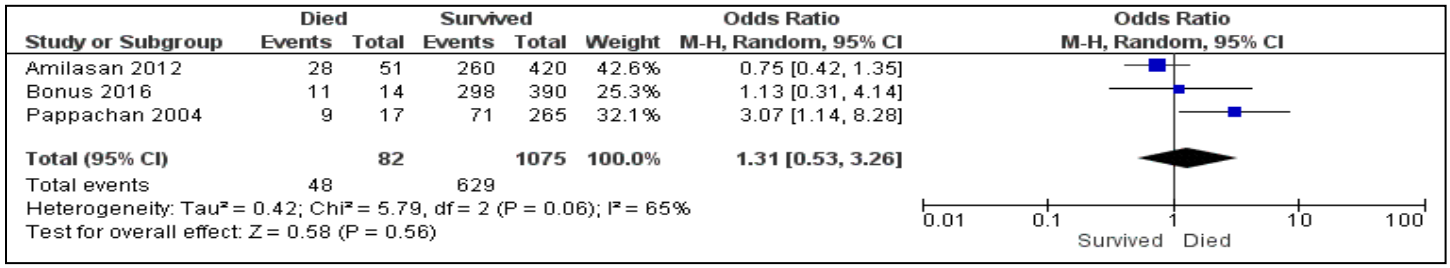

Figure 19. Forest plot of pooling of data for the presence of abdominal pain comparing those with leptospirosis who died and survived

Diarrhea: Two studies evaluated this parameter (Amilasan, 2012; Bonus, 2016). Pooled analysis showed that those who died were likely to have diarrhea as compared to those who survived, but this did not reach statistical significance (OR: 1.40; 95% CI: 0.83 to 2.34). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is indirectness since there were more adults included in the study. There is also serious imprecision since there is an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low (Figure 20).

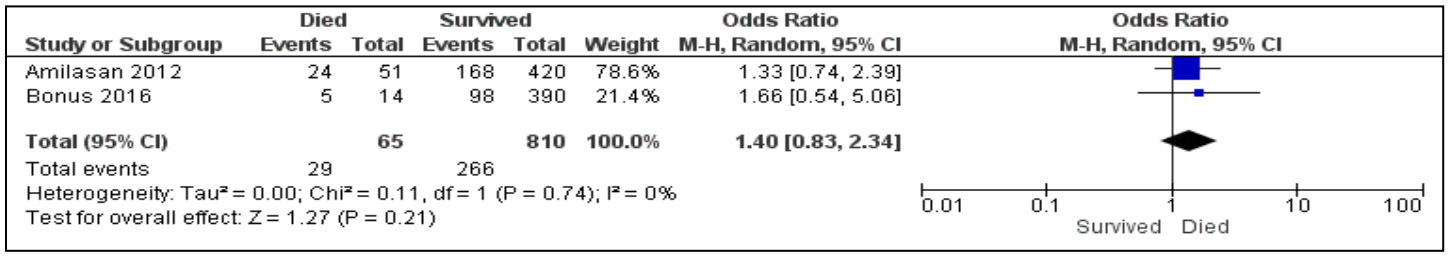

Figure 20. Forest plot of pooling of data for the presence of diarrhea comparing those with leptospirosis who died and survived

Eye Symptoms

Retro-orbital pain: One study evaluated this parameter (Bonus, 2016). Those who died were almost four times more likely to have retro-orbital pain as compared to those who survived, but this did not reach statistical significance (OR: 3.8; 95% CI: 0.2 to 77.4). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is also serious imprecision since there is an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low.

Conjunctival suffusion: Three studies evaluated this parameter (Amilasan, 2012; Bonus, 2016; Pappachan, 2004). Pooled analysis showed that those who died were likely to have conjunctival suffusion as compared to those who survived, but this did not reach statistical significance (OR: 1.40; 95% CI: 0.77 to 2.57). There is a very serious risk of bias inherent in an observational study design and inclusion of probable cases. There is indirectness since there were more adults included in the study. There is also serious imprecision since there was an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low (Figure 21).

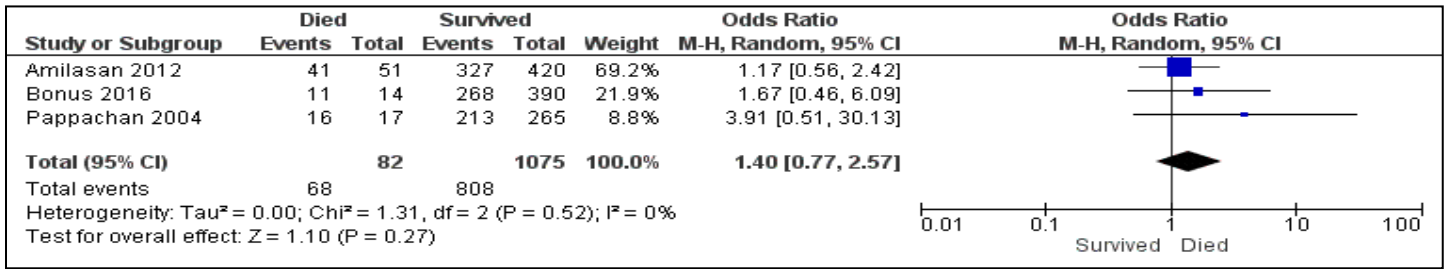

Figure 21. Forest plot of pooling of data for the presence of conjunctival suffusion comparing those with leptospirosis who died and survived

Bleeding Symptoms

Hematemesis: Only one study evaluated this parameter (Bonus, 2016). Those who died were five times more likely to have hematemesis as compared to those who survived, but this did not reach statistical significance (OR: 5.4; 95% CI: 0.2 to 116.8). There is a very serious risk of bias inherent of observational study design and inclusion of probable cases. There is also serious imprecision since there was an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low.

Epistaxis: Only one study evaluated this parameter (Bonus, 2016). Those who died were almost three times more likely to have epistaxis as compared to those who survived, but this did not reach statistical significance (OR: 2.7; 95% CI: 0.3 to 22.1). There is a very serious risk of bias inherent of observational study design and inclusion of probable cases. There is also serious imprecision since there was an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low.

Melena: Only one study evaluated this parameter (Bonus, 2016). Those who died were two times more likely to have melena as compared to those who survived, but this did not reach statistical significance (OR: 2.1; 95% CI: 0.3 to 16.9). There is a very serious risk of bias inherent of observational study design and inclusion of probable cases. There is also serious imprecision since there is an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low.

Gum bleeding: Only one study evaluated this parameter (Bonus, 2016). Those who died were two times more likely to have gum bleeding as compared to those who survived, but this evidence did not reach statistical significance (OR: 2; 95% CI: 0.1 to 38). There is a very serious risk of bias inherent of observational study design and inclusion of probable cases. There is also serious imprecision since there is an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low.

Skin hemorrhage: Only one study evaluated this parameter (Amilasan, 2012). Those who died were almost two times more likely to have skin hemorrhage as compared to those who survived, but this did not reach statistical significance (OR: 1.8; 95% CI: 0.1 to 38.5). There is serious risk of bias inherent of observational study design. There is indirectness as there more adults included in the study. There is also serious imprecision since there is an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low.

Other Symptoms

Presence of wound lesions: Only one study evaluated this parameter (Bonus, 2016). Those who died were almost two times more likely to have wound lesions as compared to those who survived, but this did not reach statistical significance (OR: 1.8; 95% CI: 0.1 to 38.5). There is a very serious risk of bias inherent of observational study design and inclusion of probable cases. There is also serious imprecision since there is an overlapping of the confidence interval with the null value; hence, this evidence is graded as very low.

Considerations for Recommendation Development during the Stakeholders Panel (SP) Meeting:

- All the six studies that were used to evaluate the signs and symptoms associated with an increased risk of mortality suffered from risk of bias because of their study design and serious imprecision. Also, five of the studies had indirectness. Hence, the quality of evidence is graded as very low.

- The SP however voted for a strong recommendation despite very low quality of evidence as all of these sign/symptoms turned out to be statistically significant. Any of these signs/symptoms is noted in actual practice among children with severe leptospirosis who die, reflective of leptospirosis' capability for multi-organ involvement with the potential for severity and even death.
- The representative from PAFP preferred data on clinical signs and symptoms that warrant admission. The GWP will consider including a question on admission criteria in the next edition.

Question 3: What laboratory findings are associated with severe leptospirosis?

Recommendation 1: The following laboratory parameters are ~~a~~ssociated with severe leptospirosis:

- Deranged prothrombin time (prothrombin time greater than or equal to 15 seconds; prothrombin time less than 68%)
- Elevated AST/ALT ratio (greater than or equal to 2)
- Elevated LDH (greater than or equal to 390 IU/L)
- Elevated CRP (greater than 282 mg/L)
- Elevated creatine phosphokinase (greater than 443 U/L)

Quality of evidence: Very low
Strength of recommendation: Strong

Recommendation 2: There is insufficient evidence to suggest that the following laboratory tests are associated with severe leptospirosis:

- Elevated bilirubin (greater than 49 µmol/L; total bilirubin greater than or equal to 35 µmol/L)
- Thrombocytopenia (less than 92 x 10^9/L)
- Elevated creatinine (greater than 154 µmol/L)
- Elevated BUN (greater than 9.3 mmol/L)
- Hematuria
- Decrease in hemoglobin (less than 12.2 g/dL)

Quality of evidence: Very low
Strength of recommendation: Strong

Summary of Evidence

Three studies evaluating abnormal laboratory findings in patients with severe leptospirosis were reviewed: one cross-sectional, one prospective cohort, and one retrospective case-control. One study included pediatric patients while the remaining two involved adult patients only.

Bonus conducted a case control study involving 404 patients aged 0-18 years old with probable or laboratory-confirmed leptospirosis admitted in three tertiary government hospitals in the Philippines. Patients who died were identified as the cases (non-survivor group, n=14), while those who survived (survivor group, n=390) served as the control (Bonus, 2016).

Mikulski focused on 47 adult patients with severe leptospirosis admitted at a hospital in New Caledonia, France between March 2009 and February 2011. In this study, patients were classified as having severe leptospirosis (n=22) if they developed either a fatal outcome or a need for mechanical ventilation or dialysis at any time during hospitalization. Patients without these factors were classified as the non-severe group (n=22) (Mikulski, 2015).

Hochedez included 102 adults with quantitative PCR-confirmed leptospirosis from December 2010 through February 2013 in Martinique, France. Severe leptospirosis was defined as having the presence of more than one of the following: shock treated with vasoactive drugs, acute renal failure requiring dialysis, internal bleeding requiring blood transfusion, respiratory insufficiency requiring mechanical ventilation, or death. In this study, there were no deaths. The patients being compared were those with severe disease (n=12) and those with non-severe disease (n=90) (Hochedez, 2015).

Table 6. Summary of studies evaluating laboratory findings associated with severe leptospirosis

Author *(Study Design)*	Study Period	Patients (N)	Location	Outcome determined	Remarks
Bonus 2016 *Retrospective case control study*	Jan 2008-Dec 2012	Filipino children 0-18 years old with probable or laboratory-confirmed leptospirosis (N=404)	3 tertiary hospitals (PGH, SLH, RITM) in the Philippines	Clinical profile, outcome and risk factors of leptospirosis in children	There were probable cases included in the study.
Mikulski 2015 *Prospective cohort study*	Mar 2009-Feb 2011	Adult patients with (+) PCR or serologic evidence of disease (N=47)	Nouméa Central Hospital in New Caledonia, France	Laboratory findings of severe and non-severe leptospirosis	There were only adults included in the study.
Hochedez 2015 *Cross-sectional study*	Dec 2010-Feb 2013	Adult patients 37-57 years old (N=102)	University Hospital of Martinique, France	Laboratory findings of severe and non-severe leptospirosis	There were only adults included in the study.

The following laboratory parameters are likely to be associated with severe leptospirosis:

Deranged Prothrombin Time (PT): Two studies evaluated derangement in prothrombin time values (Bonus, 2016; Hochedez, 2015). In the study of Bonus, non-survivors were twenty three times more likely to have PT greater than or equal to 15 seconds (OR: 23; 95% CI: 2.8 to189.7), while Hochedez' study showed that severe leptospirosis were almost six times more likely to have a PT value of <68% (OR 5.5; 95% CI: 1.5 to 20.1). Bonus' study is graded as very low because of serious risk of bias inherent to the study design and because of inclusion of probable cases. Both studies had wide confidence intervals suggestive of imprecision. Hochedez' study is graded as very low due to serious risk of bias inherent to the study design, and because of indirectness as only adult subjects were included.

Elevated AST/ALT Ratio: Only one study evaluated this parameter (Mikulski, 2015). Those with severe leptospirosis were seven times more likely to have an AST/ALT ratio greater than or equal to 2 (OR: 7.1; 95% CI: 1.8 to 28.1). The wide confidence interval almost inclusive of the null value is suggestive of serious imprecision. There is very low quality of evidence because of the observational study design and indirectness as only adult subjects were included.

Elevated LDH: Only one study evaluated this parameter (Mikulski, 2015). Patients with severe leptospirosis were almost six times more likely to have an LDH value greater than or equal to 390 IU/L (OR: 5.8; 95% CI: 1.3 to 25.6). There is indirectness as only adult subjects were included and serious risk of bias inherent to the study design.

The wide confidence interval almost inclusive of the null value is suggestive of serious imprecision. The quality of evidence is very low.

Elevated C-Reactive Protein (CRP): Only one study evaluated this parameter (Hochedez, 2015). Those with severe leptospirosis were five times more likely to have an elevated CRP greater than 282 mg/L (OR: 5.2; 95% CI: 1.5 to 18.3). The study included adult subjects only. The wide confidence interval almost inclusive of the null value is suggestive of serious imprecision. The quality of evidence is very low due to indirectness and serious risk of bias inherent to the study design.

Elevated Creatine Phosphokinase: Only one study evaluated this parameter (Hochedez, 2015). Those with severe leptospirosis were almost five times more likely to have a creatine phosphokinase greater than 443 U/L (OR: 4.6; 95% CI: 1.1 to 19.6). The wide confidence interval almost inclusive of the null value is suggestive of serious imprecision. Quality of evidence is very low because of indirectness and risk of bias inherent to the study design.

There is insufficient evidence to say that the following laboratory parameters are associated with severe leptospirosis:

Elevated Bilirubin: Three studies evaluated this parameter (Bonus, 2016; Hochedez, 2015; Mikulski, 2015). Two studies showed that severe leptospirosis was five times more likely to have elevated bilirubin levels, with bilirubin values of greater than 49 µmol/L in Hochedez' study (OR: 5.4; 95% CI: 1.5 to 18.9), and total bilirubin greater than or equal to 35 µmol/L in Mikulski's study (OR: 5; 95% CI: 1.3 to 20.0). Both studies had very low quality of evidence due to indirectness as only adult subjects were included and due to serious risk of bias inherent to the study design. Both studies had wide confidence intervals that overlap with or almost inclusive of the null value is suggestive of serious imprecision. The study of Bonus showed that non-survivors were almost four times more likely to have total bilirubin levels of >20 umol/L (OR: 3.72; 95% CI 0.19 to 74.49); however, results did not reach statistical significance. This study has very low level of evidence due to serious risk of bias inherent to the study design, inclusion of probable cases, and imprecision.

Thrombocytopenia: Two studies evaluated this parameter (Bonus, 2016; Hochedez 2015). Hochedez' study showed that patients with severe leptospirosis were five times more likely to have a platelet count of less than 92 x 10^9/L (OR: 5.2; 95% CI: 1.5 to 18.1). There is very low quality of evidence due to serious risk of bias inherent to the study design and due to indirectness. In Bonus' study, non-survivors were twice more likely to have a platelet count of less than 150 x 10^3/mm^3, but this did not reach statistical significance (OR: 2.3; 95% CI: 0.7 to 7.6). Both studies had wide confidence interval that overlaps with or almost inclusive of the null value is suggestive of serious imprecision. The quality of evidence is graded as very low due to serious risk of bias inherent to the study design, inclusion of probable cases, and imprecision.

Elevated Creatinine: Two studies evaluated this parameter (Bonus, 2016; Hochedez, 2015). Patients with severe leptospirosis in Hochedez' study were five times more likely to have creatinine greater than 154 µmol/L (OR: 5.2; 95% CI: 1.5 to 18.1). The quality of evidence is very low due to serious risk of bias inherent to the study design and due to indirectness. The confidence interval was almost inclusive of the null value which is suggestive of imprecision. In Bonus' study, non-survivors were almost three times more likely to have an elevated creatinine for age, but this did not reach statistical significance (OR: 2.6; 95% CI: 0.3 to 21.1). The quality of evidence is very low due serious risk of bias inherent to the study design, inclusion of probable cases, and serious imprecision.
Hematuria: Only one study evaluated this parameter (Bonus, 2016). Non-survivors were five times more likely to have red blood cells greater than 5 per high power field (HPF) in the urine, but this finding did not reach statistical significance (OR: 5.4; 95% CI: 1 to 30.2). The quality of evidence is very low due to serious imprecision and serious risk of bias inherent to the study design and for inclusion of probable cases.

Decrease in Hemoglobin: Two studies evaluated this parameter (Bonus, 2016; Hochedez, 2015). Severe leptospirosis was almost four times more likely to have hemoglobin less than 12.2 g/dL in Hochedez' study, but this finding did not reach statistical significance (OR: 3.5; 95% CI: 1 to 12). The quality of evidence is very low due to serious imprecision, indirectness, and serious risk of bias inherent to the study design. In Bonus' study, hemoglobin of less than 130 mg/dl was not statistically different between non-survivors and survivors (OR: 1.2; 95% CI: 0.3 to 4.4). The quality of evidence is very low due to serious imprecision, serious risk of bias inherent to the study design, and for inclusion of probable cases.

Elevated Blood Urea Nitrogen (BUN): Two studies evaluated this parameter (Bonus, 2016; Hochedez 2015). Non-survivors were six times more likely to have elevated BUN for age in Bonus' study, but it did not reach statistical significance (OR: 6.2; 95% CI: 0.4 to 107.1). The quality of evidence is very low due to serious imprecision, serious risk of bias inherent to the study design, and for inclusion of probable cases. Patients with severe leptospirosis in Hochedez' study were almost four times more likely to have a BUN greater than 9.3 mmol/L, but this did not reach statistical significance (OR: 3.5; 95% CI: 0.8 to 15.4). The quality of evidence is very low due to serious risk of bias inherent to the study design, indirectness, and serious imprecision.

Considerations for Recommendation Development during the Stakeholders Panel (SP) Meeting:

- The quality of evidence for the 3 studies that looked into laboratory parameters suggestive of severe leptospirosis is very low due to serious risk of bias, serious imprecision and indirectness.
- The SP voted for a strong recommendation for deranged PT, elevated AST/ALT ratio, LDH, CRP, and CPK as laboratory findings associated with severe leptospirosis. These parameters were statistically significant and are actual laboratory findings seen in clinical practice that are reflective of multi-organ dysfunction in severe leptospirosis. Deranged PT and elevated AST/ALT are suggestive of hepatic dysfunction, elevated LDH is suggestive of tissue injury, and elevated creatinine phosphokinase is suggestive of muscle damage.
- For the second recommendation, the SP voted for a strong recommendation that elevated bilirubin, thrombocytopenia, elevated creatinine and BUN, hematuria, and decrease in hemoglobin are associated with severe leptospirosis despite the insufficient evidence. These are the other important parameters for multi-organ dysfunction.
- The representative of DOH prefers to indicate cut-off levels in the pediatric age group. Laboratory values indicated in the recommendation statement were the actual levels mentioned in the studies, majority of which included more of adult subjects. Only Bonus' study was done in the pediatric age group.
- Electrolyte determination was emphasized by the representative of PNSP as an important parameter in the evaluation of patients with leptospirosis because the disease involves the tubules which regulate electrolyte levels.
- The studies that evaluated laboratory findings in severe leptospirosis were limited to hospitalized patients; there were no studies that specifically looked at OPD patients with leptospirosis.

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CHAPTER 3: LABORATORY DIAGNOSIS OF LEPTOSPIROSIS

Leptospirosis presents similarly to other febrile infectious disease conditions. Confirmatory testing is usually carried out in those with a history of exposure coupled with symptoms suggestive of the disease. Direct detection via culture or the use of serology are the methods employed to establish evidence of infection (Lane, 2016).

Culture of appropriate clinical specimens done prior to antibiotic therapy can confirm leptospirosis (Day, 2018). This method, however, is fraught with challenges as it entails the use of special media and the organism takes 1-2 weeks (or may extend to over a month) to grow (Lane, 2016). While highly specific, culture has low sensitivity (5-50%) (Haake, 2015). During the leptospiremic phase, blood and CSF cultures are useful. However, as the immune phase begins, yield from blood culture decreases (Shreier, 2013; WHO, 2003). Urine cultures are most likely to give positive results after the second week of illness (Lane, 2016).

While isolation of leptospires is the only direct and definitive proof of infection, serological data forms an important part of diagnostic investigation, and it must be used in association with clinical presentation and epidemiologic data (WHO, 2003). Antibodies usually become detectable in the blood 5 to 10 days after symptom onset (Levett, 2001).

Microscopic Agglutination Test (MAT), considered as the cornerstone or the "gold standard" of leptospirosis serodiagnosis (WHO, 2003), is used as the reference test for the development of other assays (Day, 2018). ELISA and other rapid screening tests for leptospiral antibodies have also been developed. MAT is carried out by mixing the patient's serum with live antigen suspensions of leptospiral serovars. This mixture is then examined microscopically for agglutination and the titers are determined (Haake, 2015). MAT is usually positive 10-12 days after symptom onset, but seroconversion may sometimes occur as early as 5-7 days after onset of the disease. Antibiotic therapy may cause delay in antibody response. MAT may give an indication of the serogroup to which the infective serovar belongs to, but only rarely identifies it. Both IgM- and IgG-class antibodies are detected. MAT cannot differentiate between agglutinating antibodies due to current, recent or past infections. Paired sera are ideally used and examined for seroconversion or a four-fold or greater rise in titer (WHO, 2003). The appropriate interval between sample collections depends on the onset of symptoms and the presentation of the patient. An interval of 3-5 days may detect rising titers if the characteristic symptoms are present. Longer intervals, i.e., 10-14 days, would be needed for patients that present earlier in the course of illness or if the onset of symptoms cannot be determined (Haake, 2015). The "*WHO Recommended Standards And Strategies For Surveillance, Prevention And Control Of Communicable Diseases*" cites that confirmatory diagnosis of leptospirosis using MAT entails seroconversion or a fourfold or greater rise in titers on paired sera taken at least 2 weeks apart (WHO, 2018). The cut-off titer of a single specimen should be determined in the light of seroprevalence of persistent antibodies due to past infections in the general population, and in relation to the presence of antibodies to other diseases that may cause cross-reactions (e.g., hepatitis, autoimmune diseases, legionellosis) (WHO, 2003).

Although specific, MAT has several limitations that include the following: (1) it needs to maintain panels for live leptospires, hence it is usually carried out in reference laboratories; (2) it cannot be standardized; (3) it is time-consuming; (4) it is technically demanding; and (5) it may pose a potential hazard to the laboratory personnel (WHO, 2003; Nieves, 2019). When the causative strain is not represented in the panel used, antibodies may not be detected or only a low titer is found with a serovar antigenically resembling the absent causative strain. Results reporting "no titer" or "low titer" do not exclude the disease (WHO, 2003).

Other serodiagnostic and rapid screening antibody tests have been developed. Several assays of Enzyme-Linked Immunosorbent Assay (ELISA) are available and it can be performed with commercial kits or with an antigen produced "in house". It uses a broadly reactive genus-specific antigen to detect IgM, and sometimes also IgG, antibodies (WHO, 2003). ELISA is carried out with relative simplicity, and it can be standardized as it does not use a panel of live antigens. It gives a positive response (usually 6-8 days from the appearance of the first clinical signs) a little earlier than MAT because it is more sensitive to IgM antibodies. It can help differentiate between current and previous infection since the antibodies from the past infection may not be detectable. Some test systems, however, are less specific than MAT and weak cross-reactions due to the presence of other diseases is possible. As such, ELISA results should still be confirmed by MAT. ELISA cannot identify the infecting serovar since it is a genus-specific test (WHO, 2003). IgM ELISA is shown to be a sensitive screening test for leptospirosis in one systematic review done in Brazil (Rosa, 2017). Currently, this test is not locally available.

Most local laboratories offer IgM Immunochromatography Test (ICT). ICT has been developed as an alternative rapid screening test for leptospirosis. Some studies show IgM ICT as an acceptable early screening test, but they recommended that a follow-up confirmatory test such as MAT be done (Amran, 2018; Goris, 2013; Iwasaki, 2016;Podgorsek, 2015). One study recommended its use in resource-limited setting (Niloofa, 2015), but other studies found ICT to have limited value in the diagnosis of leptospirosis (Blacksell, 2006; Wagenaar, 2004). Performance of the test was only moderate for samples collected within the first week of illness which is the period crucial for therapeutic intervention (Rao, 2019). In a prospective cohort evaluation of rapid diagnostic tests (that included ICTs), there was low sensitivity of the test in the early acute phase of illness (until 4 days post onset of symptoms) (Goris, 2013), as antibodies are not yet at detectable levels in the early stage of the disease (Goris, 2011). Dengue, syphilis, and scrub typhus can have cross reactivity with rapid tests performed for leptospirosis (Amran, 2018).

In recent years, molecular tests such as the Polymerase Chain Reaction (PCR) are increasingly utilized in the diagnosis of infectious diseases. PCR detects the causative agent's DNA in clinical samples. Short DNA sequences specific for the organism are used as primers and, in combination with DNA polymerase, are subjected to temperature cycles that amplifies the organism's DNA (WHO, 2003). Leptospiral DNA has been detected in the blood during the first 7 days of illness (highest sensitivity between days 1 and 4), and in the urine after day 7 of illness (AAP, 2018). Aside from this, the CSF, aqueous humor, and organs post-mortem are reported sites where leptospiral DNA have been amplified (Levett, 2004). Assays designed for diagnostic purposes target either housekeeping genes such as *rrs, gyrB, or secY*, or pathogen-specific genes such as *lipL32, lig, or lfb1* (Haake, 2015). Conventional PCR for the detection of leptospiral DNA was introduced in 1989 (Ahmed, 2012), using urine samples from cattle (Van Eys, 1989). Studies on the use of conventional PCR in human leptospirosis showed that its value as a diagnostic method is not clear (Ahmed, 2012), detecting only 44% of MAT positive cases in one study (Yersin, 1999) and only in 14 cases of 200 subjects in another (Merien, 1995). A disadvantage of conventional PCR is that it is prone to contamination, and thus may give false positive results (Ahmed, 2009; Jouglard, 2006). Real-Time (RT) PCR, on the other hand, is a PCR-based amplification of DNA that is monitored during the amplification process utilizing several types of dyes and probes. TaqMan probes, Molecular Beacons, Scorpions, Light Upon eXtension technology (LUX), and SYBR Green 1 dye are among the most available formats that detect PCR products by generation of a fluorescent signal. RT PCR has been shown to have a high degree of accuracy on blood samples during the early phase of the disease (Ahmed, 2012). In general, PCR require special equipment, a dedicated laboratory space and highly skilled personnel. In addition to its propensity for contamination giving false positive results, it may also give false negative results in the presence of inhibitors in the sample submitted (WHO, 2003).

The Research Institute for Tropical Medicine (RITM) offers the following diagnostic tests for leptospirosis:

Table 7. Diagnostic tests for Leptospirosis at the Research Institute for Tropical Medicine

Test	Specimen and Collection time	Turnaround time
Culture	Whole blood - Within 10 days after symptom onset CSF - 5-10 days after symptom onset Urine - 2nd week to 30 days after symptom onset	12 weeks
qPCR	Whole blood, CSF, Serum: within 10 days after symptom onset Urine: 2nd week up to 30 days after symptom onset	3-5 days
MAT	Serum: Acute phase: 5-10 days after onset of symptoms Convalescent phase: 5 to 20 days after acute phase of the disease	7 working days

(National Reference Laboratory for Emerging/Re-emerging Bacterial Diseases Leptospirosis Unit, RITM)
*Coordination with RITM for specimen handling (needed volume, storage and transport) is recommended.

Question 4: Can IgM Immunochromatography Test (ICT) be used as a rapid test in the diagnosis of leptospirosis in children?

Recommendation 1: IgM ICT may be used as a rapid test in the diagnosis of leptospirosis in children.
Quality of evidence: Moderate
Strength of recommendation: Strong

Summary of Evidence

Two studies included the evaluation of IgM ICT compared with MAT as a rapid test in the diagnosis of leptospirosis (Iwasaki, 2016; Niloofa, 2015). Subjects included were hospitalized patients. One was done in Manila and the other was done in Sri Lanka.

Iwasaki investigated 113 clinically-diagnosed leptospirosis patients at San Lazaro Hospital who were enrolled in the study after the August 2012 flood. Seventy seven (77) MAT-positive and 36 MAT-negative patients, age-stratified into four groups (<20, 20-40, 41-64, and >64 years old) were included. It was not clearly stated, however, how many patients were less than 20 years old and what the youngest age of the included subjects were (Iwasaki, 2016).

Niloofa included a total of 888 patients, aged 13-80 years old, with 354 MAT-positive cases and 534 controls. The patients were recruited from three hospitals in the Western Province of Sri Lanka from June 2012 to December 2013 (Niloofa, 2015).

For the evaluation of IgM ICT, forest plots were constructed to graphically assess the variability of the estimates of the tests. A random-effects meta-analysis was performed using MetaDisc software version 1.4. Inconsistency (statistical heterogeneity) among studies was assessed by the conventional Chi-squared test for heterogeneity and by calculating the I^2 statistic to highlight the effect of true variability rather than sampling error on the overall variation in diagnostic estimates.

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Table 8. Summary of Sensitivity, Specificity, PPV, and NPV values of studies evaluating IgM Immunochromatographic Test (ICT)

Study	True Positive	False Positive	True Negative	False Negative	PPV	NPV	Sensitivity	Specificity	No. of participants
Iwasaki 2016	61	7	29	16	89.7	64.4	79.2 (68.5 - 87.63)	80.56 (63.98 - 91.81)	113
Niloofa 2015	248	159	436	45	60.9	90.6	84.6 (80.0 - 88.6)	73.3 (69.5 - 76.8)	888

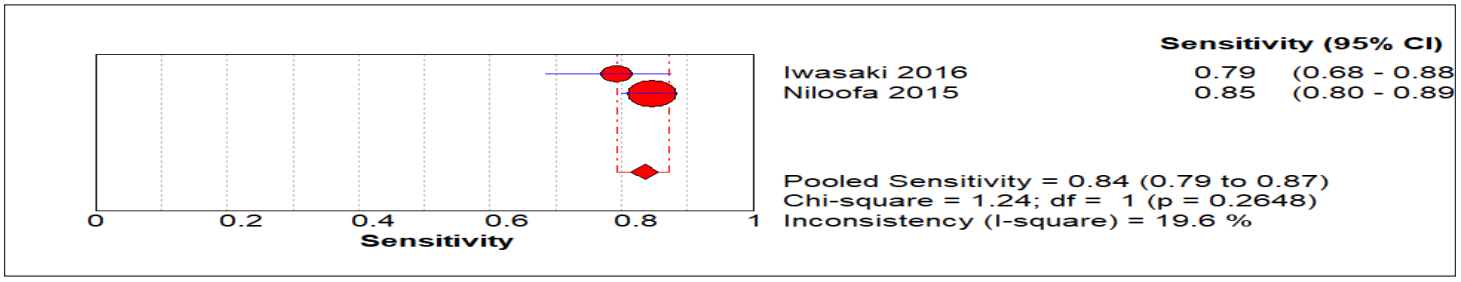

Figure 22. Forest plot of meta-analysis of data of pooled sensitivities of IgM ICT compared with MAT

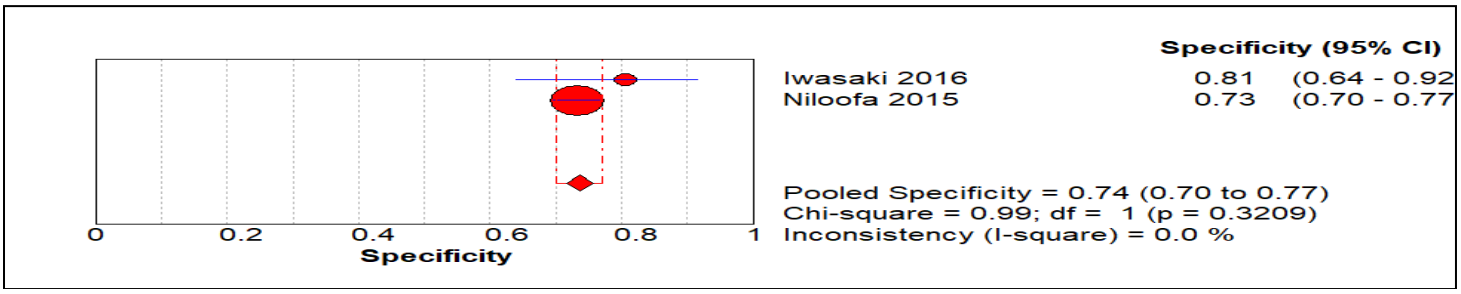

Figure 23. Forest plot of meta-analysis of data of pooled specificities of IgM ICT compared with MAT

Pooled sensitivity of IgM ICT is 84% (95% CI: 79% to 87%; I^2 = 19.6%) for all patients with leptospirosis (confirmed by MAT), while pooled specificity is 74% (95% CI: 70% to 77%; I^2 = 0%) (Figures 22-23). There is indirectness due to inclusion of more adults subjects; thus, the quality of evidence is graded as moderate.

The above data showed variable results. MAT or culture remains to be the gold standard for the diagnosis of leptospirosis.

Table 9. Summary of studies evaluating ICT as a rapid diagnostic test that can be used for the diagnosis of leptospirosis in children

Study *(Study Design)*	Patient characteristics	Location	Tests evaluated in the study	Reference standard	Remarks
Iwasaki 2016 *Cross-sectional*	Individuals, <20 to >64 years old, with clinically-diagnosed leptospirosis (N=113)	San Lazaro Hospital, Manila	*ICT, MAT, ELISA, LAMP, real time PCR	MAT[a]	Most of the subjects belong to the 20-64 year old age group

Study *(Study Design)*	Patient characteristics	Location	Tests evaluated in the study	Reference standard	Remarks
Niloofa 2015 *Cross-sectional*	Hospitalized Sri-Lankan patients, 13-80 years old, with suspected leptospirosis (based on WHO-CLERG epidemiologic criteria) (N=888)	National Hospital of Sri Lanka (NHSL), Colombo North Teaching Hospital (CNTH) and Base Hospital Homagama (BHH)	MAT, IgM-ELISA, IgM ICT** (Leptocheck-WB)	MAT[b]	More adult patients included

a: In Iwasaki's study, sensitivity and specificity of ICT and ELISA were defined with respect to MAT
b: in Niloofa's study, data analysis was performed using MAT as reference standard and using Bayesian Latent Class Model analysis
*Only results of the ICT compared to MAT were evaluated
**Only the results of IgM ICT compared to MAT were evaluated

Considerations for Recommendation Development during the Stakeholders Panel (SP) Meeting:
There was moderate quality of evidence for the use of IgM ICT as a rapid test for leptospirosis diagnosis. Leptospirosis IgM ICT is readily available in most local hospitals. For this, the consensus panel voted for a strong recommendation.

Question 5: Can IgM Enzyme-linked Immunosorbent Assay (ELISA) be used as a rapid test in the diagnosis of leptospirosis in children?

Recommendation 1: IgM ELISA may be used as a rapid test in the diagnosis of leptospirosis in children.
Quality of evidence: Low
Strength of recommendation: Weak

Summary of Evidence

Four studies included IgM ELISA as a rapid diagnostic test in the evaluation of leptospirosis. Three were cross-sectional studies and one was a case-control study.

All studies were done in hospitals. One study was done in the Philippines (Iwasaki, 2016), one in Thailand (Desakorn, 2012), one in Sri Lanka (Niloofa, 2015), and one in mainland France and French overseas territories (Bourhy, 2013). The specific IgM ELISA evaluated in the included studies are summarized below.

Table 10. IgM ELISA used In the Included Studies(as Rapid Test in the Diagnosis of Leptospirosis in Children)

Study	IgM ELISA evaluated
Iwasaki (2016)	ELISA (Diagnostic Automation, Calabasas, CA, USA)
Niloofa (2015)	IgM-ELISA (Institut Virion\Serion GmbH, Warburg, Germany)
Desakorn (2012)	*Leptospira sp.* IgM ELISA (Panbio Pty., Ltd.,Queensland, Australia)
Bourhy (2013)	In-house IgM ELISA – developed an ELISA based on a whole-cell antigen extract obtained from *L. faineiserovar Hurstbridge*

The above studies evaluated IgM ELISA compared with MAT in the rapid diagnosis of leptospirosis.

Desakorn conducted a retrospective case-control study of 218 patients aged 15 years and older. One hundred nine (109) patients with laboratory-confirmed leptospirosis (using *Leptospira sp.* culture and/or Microscopic Agglutination Test [MAT]) were designated as cases, and 109 patients without leptospirosis served as controls. The patients were identified from a prospective cohort study of consecutive patients presenting to Udon Thani Hospital, Northeast Thailand with an acute febrile illness between 2001 and 2002. Sera on admission of two leptospirosis cases and two controls were not available to test by the IgM ELISA (Desakorn, 2012)

Bourhy tested an in-house ELISA using a total of 819 serum samples from patients originating from mainland France, Martinique, Guadeloupe and other French territories. MAT was used as the reference test. Samples were grouped into four panels consisting of confirmed cases with clinical suspicion of leptospirosis and seroconversion between paired sera, probable cases with clinical suspicion of leptospirosis and a single MAT of ≥ 400, confirmed negative cases (healthy donors and patients with infection other than leptospirosis) who were all MAT negative, and probable negative cases with clinical suspicion of leptospirosis and MAT titers of <50 on paired sera. In the analysis, samples from confirmed cases and probable cases (202 MAT-negative and 317 MAT-positive samples, N=519) were evaluated (Bourhy, 2013).

Iwasaki and Niloofa also included IgM ELISA in the evaluation of tests for the diagnosis of leptospirosis among hospitalized patients. Most of the included subjects were adults (Iwasaki, 2016; Niloofa, 2015). Description of their studies were discussed in the previous question (refer to Question No. 3).

Indirectness is rated as serious since adults were included in all the studies reviewed. Imprecision is rated as serious if there was overlapping of confidence interval with the null value.

Similar to the evaluation done for IgM ICT, forest plots were constructed to graphically assess the variability of the estimates of the tests for IgM ELISA. A random-effects meta-analysis was performed using MetaDisc software version 1.4. Inconsistency (statistical heterogeneity) among studies was assessed by the conventional Chi-squared test for heterogeneity and by calculating the I^2 statistic to highlight the effect of true variability rather than sampling error on the overall variation in diagnostic estimates.

Table 11. Summary of the results of studies that included the evaluation of IgM ELISA in the diagnosis of leptospirosis

Study	True Positive	False Positive	True Negative	False Negative	PPV	NPV	Sensitivity (CI)	Specificity (CI)	No. of participants
Desakorn 2012	56	36	71	51	60.9	58.2	52.3 (42.5-62.1)	66.4 (56.6-75.2)	214
Bourhy 2013	298	3	199	19	99	91	94.0 (90.8-96.4)	98.5 (95.7-99.7)	519
Iwasaki 2016	67	19	17	10	77.9	63.0	87.0 (77.4-93.6)	47.2 (30.4-64.5)	113
Niloofa 2015	252	92	503	41	73.3	92.5	86.0 81.5-89.8)	84.5 (81.4-87.3)	888

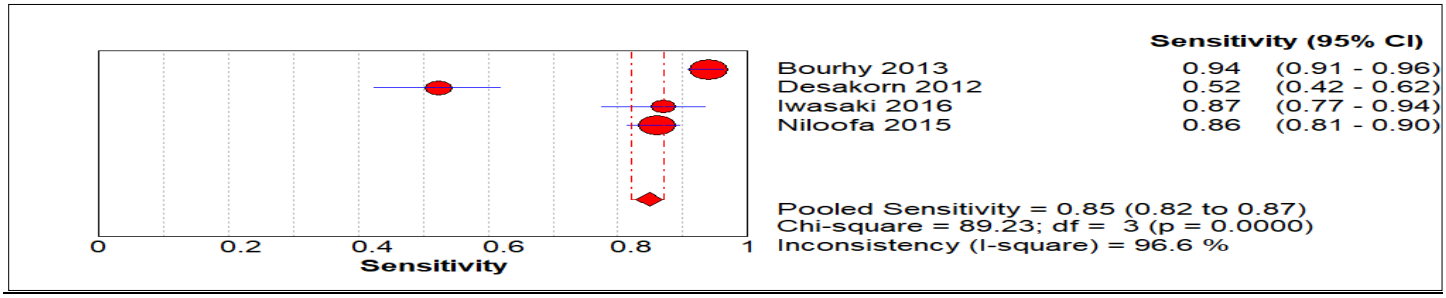

Figure 24. Forest plot of meta-analysis of data of pooled sensitivities of IgM ELISA compared with MAT

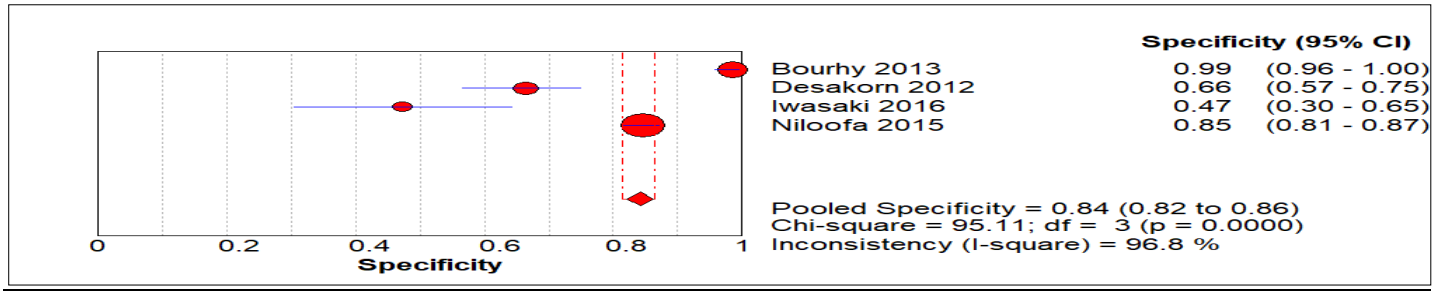

Figure 25. Forest plot of meta-analysis of data of pooled specificities of IgM ELISA compared with MAT

The pooled sensitivity of ELISA was 85% (95% CI: 82% to 87%; I^2 = 96.6%) for all patients with leptospirosis (confirmed by MAT), while the pooled specificity was 84% (95% CI: 82% to 86%; I^2 = 96.8%) (Figures 24-25). The evidence was graded as low due to inconsistency and indirectness.

The above figures show variable results. MAT or culture remains to be the gold standard for the diagnosis of leptospirosis. Furthermore, IgM ELISA is not locally available.

Table 12. Summary of studies for IgM ELISA as a rapid diagnostic test for the diagnosis of leptospirosis in children

Author *(Study Design)*	Patient Characteristics	Location	Test Evaluated*	Reference test or Gold standard used	Remarks
Iwasaki 2016 *Cross-sectional*	Individuals (<20 to > 64 yrs. old) with clinically-diagnosed leptospirosis (N=113)	San Lazaro Hospital, Manila	MAT, ELISA*, ICT, LAMP, and real time-PCR	MAT	Most of the subjects belong to the 20-64 years old age group
Niloofa 2015 *Cross- sectional*	Hospitalized Sri-Lankan patients, 13-80 years old, with suspected leptospirosis (based on WHO-CLERG epidemiologic criteria) (N=888)	National Hospital of Sri Lanka, Colombo North Teaching Hospital, and Base Hospital Homagama	MAT, IgM-ELISA* and Leptocheck-WB (ICT)	MAT	More adult patients included
Desakorn 2012 *Retrospective case-control*	Thai individuals 15 years old and above with fever of unknown cause (N=218 with 109 cases and 109 controls; sera from 2 cases and 2 controls were not available to evaluate by ELISA)	Udon Thani Hospital, Thailand	IgM ELISA* (Panbio)	*Leptospira sp.* culture and/or MAT	Included adult patients

Author *(Study Design)*	Patient Characteristics	Location	Test Evaluated*	Reference test or Gold standard used	Remarks
Bourhy 2013 *Cross-sectional*	Human sera (of patients aged 9-89 yrs. old) were tested at National Reference Center for Leptospirosis were used (N=819 sera; in the analysis, 202 MAT-negative samples and 317 MAT-positive samples were evaluated)	Patients were from Mainland France, Martinique, Guadeloupe, and other French territories	in-house ELISA*	MAT	Sera from adults were included

* Only the results of ELISA were included in the evaluation

Considerations for Recommendation Development during the Stakeholders Panel (SP) Meeting:

- An issue that came up during the discussion was the availability of IgM ELISA. Currently, this test is not locally available.
- The representative from the PNSP asked why MAT was not evaluated. It was explained that MAT was used as the reference test or gold standard test in studies that evaluated IgM ELISA.
- Majority of the SP voted for a weak recommendation because IgM ELISA is not yet locally available.

Question 6: Can polymerase chain reaction (PCR) be used in the diagnosis of leptospirosis in children?

Recommendation 1: PCR may be used in the diagnosis of leptospirosis in children.
Quality of evidence: Low
Strength of recommendation: Strong

Summary of Evidence

There were two case-control studies that included the evaluation of PCR as a diagnostic test for leptospirosis (Narayanan, 2016; Thaipadunpanit, 2011). Both studies were conducted in hospitals. Although both studies involved pediatric patients, there were more adult subjects included.

The study of Narayanan identified 134 children and 443 adults with clinically suspected leptospirosis. Subjects were age-stratified into the pediatric group (ages 0-17 years old) and adult group (ages ≥18 years old). Controls consisted of age- and sex-matched healthy subjects. Sensitivity, specificity and predictive values of IgM ELISA, microscopic slide agglutination test and PCR were compared with MAT (Narayanan, 2016).

Thaipadunpanit evaluated two real-time PCR assays targeting *rrs* or *lipL32* in 266 patients (133 cases of leptospirosis and 133 controls). The diagnostic sensitivity and specificity of both assays were determined using positive culture and/or MAT as the gold standard (Thaipadunpanit, 2011).

Studies were included if they had children as participants and if the diagnostic reference standard used included MAT.

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Table 13. Summary of Sensitivity, Specificity, PPV, and NPV valuesof studies that evaluated PCR

Study	TP	FP	FN	TN	PPV	NPV	Sensitivity	Specificity	No. of participants
Narayanan 2016	147	18	5	408	89	99	97 (85 - 100)	96 (91 - 99)	577
Thaipadunpanit 2011 rt PCR assay	74	14	59	119	84	67	56 (47 - 64)	90 (83 - 94)	266

TP - True Positive; FP - False Positive; FN - False Negative; TN- True Negative

For the evaluation of PCR, forest plots were constructed to graphically assess the variability of the estimates of the tests. A random-effects meta-analysis was performed using MetaDisc software version 1.4. Inconsistency (statistical heterogeneity) among studies was assessed by the conventional Chi-squared test for heterogeneity and by calculating the I^2 statistic to highlight the effect of true variability rather than sampling error on the overall variation in diagnostic estimates.

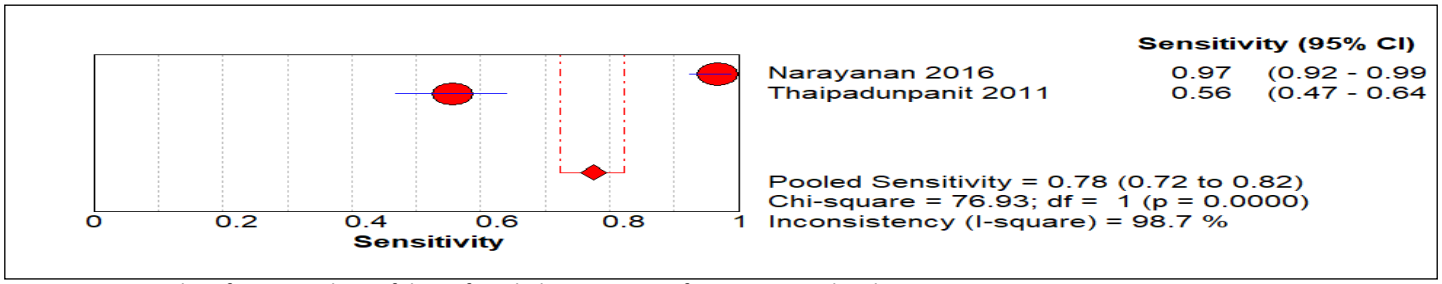

Figure 26. Forest plot of meta-analysis of data of pooled sensitivities of PCR compared with MAT

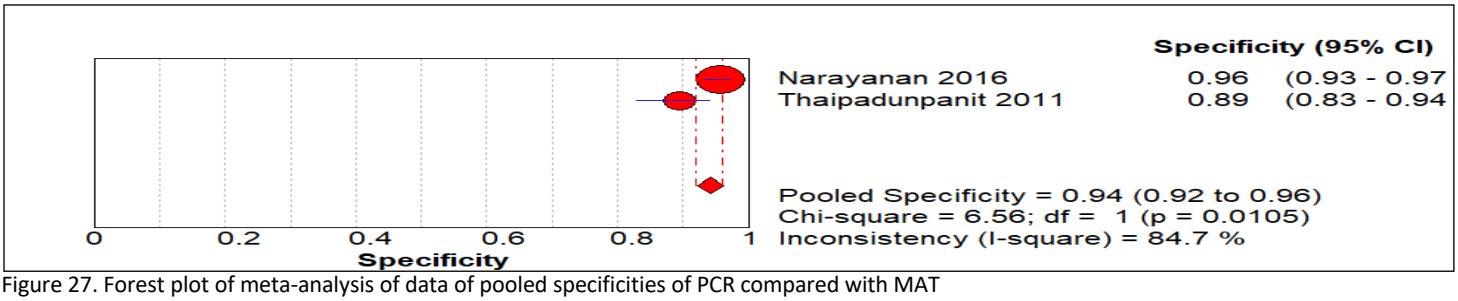

Figure 27. Forest plot of meta-analysis of data of pooled specificities of PCR compared with MAT

Pooled sensitivity of the two studies is 78% (95% CI: 72% to 82%; I^2 = 98.7%) for all patients with leptospirosis (confirmed by MAT), while pooled specificity is 94% (95% CI: 92% to 96%; I^2 = 84.7%) (Figures 26-27). There is indirectness due to inclusion of more adults and heterogeneity is significant. The quality of evidence is graded as low.

The above results show that while PCR's pooled specificity is >90%, pooled sensitivity is only 78%. In the local setting, PCR is not widely available. It is likewise technically demanding, thus limiting its accessibility only in reference laboratories.

Table 14. Summary of studies that included the evaluation of PCR as a diagnostic test for leptospirosis

Author *(Study Design)*	Patients (N)	Location	Tests evaluated	Reference standard used	Remarks
Narayanan 2016 *Case-control*	Hospitalized Indian patients 134 children aged 0-17 years old and 443 adults patients aged ≥18 years old with suspected leptospirosis (N=577)	Government Hospital, Municipality of Chennai, India	MAT, IgM-ELISA, MSAT, PCR	MAT	More adult patients included
Thaipadunpanit 2011 *Case-control*	Patients 15-79 yrs old 133 cases of leptospirosis and 133 controls (N=266)	Udon Thani Hospital, Thailand (2001-2002)	PCR assays (*rrs* and *lipL32*)	Culture and/or MAT	More adult patients included

Considerations for Recommendation Development during the Stakeholders Panel (SP) Meeting:

- The two studies that evaluated PCR as a diagnostic test for leptospirosis show low quality of evidence due to indirectness and significant inconsistency. Pooled analysis showed a higher specificity (>90%) compared to IgM ICT (74%) and IgM ELISA (84%). PCR gives positive results earlier (first 7 days from onset of illness) compared to MAT (10-12 days from onset) and ELISA/ICT (6-8 days from onset). Turnaround time is shorter for PCR (3-5 days) as compared to culture (12 weeks) and MAT (7 days). For these, the SP voted for a strong recommendation.
- A member of the GWP mentioned that PCR is available at RITM, but not readily available in other institutions. The representative from DOH mentioned that PCR for leptospirosis is also available at San Lazaro Hospital, but only for in-patients.

CHAPTER 4: ANTIBIOTIC THERAPY FOR LEPTOSPIROSIS

The role of antibiotics in the treatment of leptospirosis based on current literature remains unclear. Available data generally reflect use of antibiotics in clinical practice.

In children and adults, severity of illness is classified as mild, moderate or severe. Based on the Department of Health National Antibiotic Guidelines of 2018, mild illness is managed with amoxicillin at 30-50 mg/kg/day divided into every 8 hours for 7 days (Max 500 mg q8) or doxycycline 2 mg/kg/day divided into 12 hours for 7 days. Azithromycin at 10 mg/kg/day PO (Max 500 mg/day) for 1 day followed by 5 mg/kg/day (Max 250 mg/day) for 2 days may be used as a second line antibiotic (DOH, 2018).

For moderate and severe disease, penicillin at 250,000-400,000 units/kg/day divided into every 4-6 hours (Max 1.5 MU q6-q8) is recommended as first line. Cefotaxime 100-150 mg/kg/day IV/IM divided every 6-8 hours (Max 1g q6), or ceftriaxone 80-100mg/kg/day IV/IM q24 (Max: 2 g/day), or azithromycin 10 mg/kg/day IV q24 (Max: 500 mg/day) followed by 5 mg/kg/day IV q24h (Max: 250 mg/day) are recommended as second line therapeutics. The antibiotic treatment in severe disease is usually 7 days (DOH, 2018).

There are two published meta-analysis by Brett-Major and Charan which provided evidence on the effectiveness of antibiotic treatment based on its ability to reduce the duration of clinical illness, reduction in complications, and prevention of mortality (Brett-Major, 2012; Charan, 2013).

The GWP decided to solely use duration of fever to evaluate the effect of antibiotics on clinical illness as it was the only measurable parameter that was consistent across all studies.

Question 7: How effective is the use of antibiotics in the treatment of children with leptospirosis?

Recommendation: The use of antibiotics may be considered in the treatment of children with leptospirosis, but there is no evidence to suggest that this may decrease mortality, duration of fever, renal complications, and the need for dialysis.
Quality of evidence: Very low
Strength of recommendation: Strong

Summary of Evidence

A systematic search of the literature did not yield studies that directly answered the clinical question - all studies on the effectiveness of antibiotics as treatment for severe leptospirosis were done on adults, with some studies including adolescents ≥16 years old. Also, the criteria used for severe leptospirosis varied among the different studies, and many studies included both severe and non-severe cases in the analysis.

Seven studies, which evaluated the use of antibiotics in different clinical outcomes, were found in the literature:

A meta-analysis by Brett-Major included randomized controlled trials on infected patients regardless of severity of illness. Seven trials (Costa, 2003; Edwards, 1988; McClain, 1984; Panaphut, 2003; Phimda, 2007; Suppitamongkol, 2004; Watt, 1988) were included in the study after a comprehensive systematic search, three of which were from the 1980s. Four studies assessed antibiotic treatment in severe leptospirosis, however, the criteria for severity were varying.

There were varying antibiotics used: four trials with 403 subjects compared an antibiotic with placebo or no intervention; three trials compared at least one antibiotic regimen with another antibiotic. The trials all had a high risk of bias and the ability to group data for meta-analysis was limited. Although the authors' planned subgroup categorization for severe versus non-severe leptospirosis, these subgroups "did not overlap substantively providing data (events) to inform trial objectives". Pooling of results in the meta-analysis was possible only for death, days of clinical illness, and dialysis employed because the trial outcomes were varying and had limited reporting of data. Forest plots of these pooled data were not shown in the article, which raised concern on reporting bias. The quality of evidence for this meta-analysis was low because of inconsistency of results, indirectness, imprecision and possible reporting bias (Brett-Major, 2012).

Another meta-analysis by Charan evaluated the role of antibiotics in leptospirosis which included five studies: 4 RCTs (Costa, 2003; Edward, 1988; Fairburn, 1956; Watt, 1988) and 1 cohort study (Daher, 2000). All studies looked into the endemic population, except for Fairburn which studied British military men with leptospirosis, mostly non-severe, in the jungles of Malaya (Fairburn, 1956). All studies compared penicillin with no treatment, except for Watt who used a placebo (Watt, 1988). Outcomes were varying among studies. All studies had a high risk for bias and the ability to group the data for meta-analysis was limited. The quality of evidence for this meta-analysis was very low because of inconsistency and imprecision of results. There was indirectness as most studies were on adults (Charan, 2013).

The study by Watt was a randomized controlled trial on penicillin compared to placebo conducted in a national infectious disease hospital in the Philippines. Subjects were 16 years old and older with severe and late leptospirosis (i.e., with symptoms for >4 days) confirmed by antibody titer or isolation of the organism from blood or urine. Criteria for severity were elevated creatinine (>177 umol/L) and/or jaundice present on admission, however, the most severe cases were excluded from the study (i.e., those with anuria, confusion, stupor, coma). Sample size was relatively small (N=42). Intravenous penicillin g at 6 million units per day for 7 days was compared with placebo. The primary outcomes were deaths, duration of fever after treatment, duration of increased serum creatinine, hematologic and biochemical variables, and duration of hospitalization. This study was included in the pooled analysis of death in the meta-analyses of both Brett-Major and Charan (Brett-Major, 2012; Charan, 2013). The quality of evidence for this study was very low. There was a serious risk of bias since randomization procedure and concealment were not described, and most severe cases were excluded from the study. There was not enough information on other forms of management concomitant with the experimental intervention that was done on the patients (Watt, 1998).

Another RCT conducted by Costa assessed the efficacy of Penicillin in 253 patients who were >15 years old with late stage leptospirosis (i.e., >4 days of symptoms) in an infectious disease hospital in Brazil. Cases that reached at least 26 points in a WHO probability score for leptospirosis and without a history of nephropathy, cardiomyopathy or diabetes mellitus were included. Almost all patients (91.6%) were in renal failure, with a creatinine of >1.5 mg/dL and had jaundice (94%) on admission, which suggested that patients in the trial had severe leptospirosis. All but one patient were confirmed leptospirosis by Microscopic Agglutination Test (MAT) and blood cultures. Intravenous penicillin (6 million units per day for 7 days) was compared with no treatment. The main outcome evaluated was mortality, however, the use of peritoneal dialysis and hospitalization were also reported. This study was included in the pooled analysis of death in the meta-analysis by Brett-Major who pooled the data to determine effectiveness of an antibiotic (penicillin or doxycycline) versus no treatment or placebo (Brett-Major, 2012). The quality of evidence of this study was very low. The risk for bias was high since randomization technique and allocation concealment were not mentioned in the study. Subjects in the two groups were not comparable at baseline, however, logistic regression was used to adjust for the differences. There is indirectness of the results because subjects were predominantly men in the 3rd to 5th decade of life and because of the use of the WHO criteria to define late stage leptospirosis (Costa, 2003).

Panaphut conducted an open-label RCT in a tertiary hospital in Thailand comparing ceftriaxone with penicillin g on 173 patients >16 years old with severe leptospirosis (presence of jaundice or serum creatinine >180umol/L, or mean arterial pressure <70 mmHg). Those who had experienced CPR before admission or were comatose or stuporous were excluded. Of the 173 patients who screened positive for leptospirosis using the IgM specific assay (LEPTO dipstick), only 72% were confirmed by MAT; no blood or urine cultures were done. Penicillin g was given at 1.5 million units every 6 hours and ceftriaxone was given at 1 gram per day. Gentamicin was also administered for patients in group P for whom septicemia to gram-negative organism could not initially be excluded, but was terminated if blood and urine cultures were negative. The primary outcome was the time to resolution of fever after treatment. Other outcomes were mortality and time to resolution of organ dysfunction. For those who did not return for follow up consult after discharge, local health care personnel were contacted to obtain the patient's physical condition. The quality of evidence of this study is low. There was no blinding of the patient, caregiver and outcome assessors. Subjects who were most severe were excluded from the study (i.e., those who were stuporous, comatose or had received CPR). Use of gentamicin for patients on penicillin increased variability. Patients were adults and not all were confirmed leptospirosis which could lead to indirectness (Panaphut, 2003).

Suputtamongkol conducted an open label RCT in 4 hospitals in Thailand comparing penicillin with doxycycline and cefotaxime on 256 adult patients with severe leptospirosis (i.e., acute fever <15 days) in the absence of an obvious focus of infection. Excluded were those with diabetes and those with treatment for >48 hours against leptospirosis. Leptospirosis was confirmed for all patients by serologic testing or culture. Some patients had coincident rickettsioses (similar in the 3 groups) or gram-negative bacteremia. Patients received either penicillin g at 1.5 million units every 6 hours, cefotaxime at 1 gram IV every 6 hours, or doxycycline at 200 mg infused for 30 minutes then 100 mg every 12 hours. Treatment was switched to oral amoxicillin or oral doxycycline if the patient was well enough. Gentamicin was administered, at the discretion of individual investigators, when gram-negative sepsis could not be excluded (Group P=8, Group D=4, Group C=3, p=0.34). Outcomes included mortality, time to defervescence, reason for subsequent antimicrobial treatment, duration of renal and/or hepatic dysfunction, and duration of hospitalization. Those who died within 48 hours after admission were excluded from all analysis of clearance of fever. Twenty patients were excluded from subsequent efficacy analysis (no explanation given). The quality of evidence of this study is very low. There was no blinding of the patient, caregiver and outcome assessors. Subjects who were most severe were excluded from the analysis (i.e., those who died within 48 hours of treatment). Use of gentamicin for patients in the three groups, presence of coincident rickettsioses, and gram-negative bacteremia, increased variability of the study. Definition of severe illness was different from other studies as it was based on the number of days of fever. It is noted that not all enrolled patients had renal dysfunction or jaundice. Patients were adults which could also lead to indirectness (Suputtamongkol, 2004).

Phimda conducted a randomized controlled trial on doxycycline versus azithromycin in 4 hospitals in Thailand. Of the 296 patients enrolled, median age was 36 years old (range: 15 to 88 years old). Only 23.3% had leptospirosis, 4.1% had leptospirosis-rickettsia co-infection. Diagnosis was confirmed by isolation from blood or by MAT, although paired sera were not obtained in some patients. Sixty nine (69) cases of non-severe leptospirosis were randomly assigned either to a 7-day course of doxycycline or a 3-day course of azithromycin. There was a high drop-out rate of 30.1% (42 in doxycycline and 47 in azithromycin). Outcomes assessed were cure rate, time to defervescence, and adverse events. The quality of evidence of this study is very low. There was no blinding of the patient, caregiver and outcome assessor, and there was a high drop-out rate. Confirmation of leptospirosis using convalescent sera was not possible in some patients. Indirectness, imprecision and reporting bias were noted (Phimda, 2007).

The effectiveness of antibiotics in children with leptospirosis on the following outcomes was studied: 1) mortality, 2) duration of fever, and 3) renal complications and/or the need for dialysis.

EFFECT ON MORTALITY

Table 15. Summary of studies on the use of antibiotics in preventing mortality in children with leptospirosis

Study *(Study Design)*	Study Period	Patients (N)	Location	Outcome determined	Remarks	Quality
Brett-Major 2012 *Meta-analysis (RCTs only)*		All infected patients, both severe and non-severe. Majority or all subjects in the studies reviewed were adults. (N=403)		Primary: Mortality, hospitalization, ventilator requirement, dialysis requirement Secondary: No. of days on mechanical ventilator, no. of days on dialysis, adverse events that resulted in dose decrease or discontinuation of treatment or registration as an AE	Four out of seven studies purported to assess treatment in severe leptospirosis. However, in most cases clear definition of severity were not given and criteria were varying. The most severe patients were excluded in some of these 4 studies.	Low
Charan 2013 *Meta-analysis (RCT & Cohort)*		All leptospirosis patients, both severe and non-severe. Majority or all subjects in the studies reviewed were adults. (N=409)		Among the predetermined outcomes availability of data, those that could be compared were mortality, fever days, oliguria, number of dialysis, number of patients needing dialysis	Five studies assessed penicillin with no treatment or placebo. All studies looked into leptospirosis in the endemic population except Fairburn 1956 who studied military men.	Very low
Panaphut 2003 *RCT, open*	Jul 2000 to Dec 2001	Patient $\geq$ 16 years old with severe leptospirosis. Of those screened positive using IgM specific LEPTO dipstick assay, 72% were confirmed by MAT. (N=173)	Tertiary hospital in Thailand	Primary: time to resolution of fever after treatment. Secondary: mortality and time to resolution of organ dysfunction	All patients were adults. Severe leptospirosis was based on presence of jaundice, raised creatinine or MAP <70 mmHg. Gentamicin was administered in Group P with gram negative sepsis.	Low

Study *(Study Design)*	Study Period	Patients (N)	Location	Outcome determined	Remarks	Quality
Suputtamongkol 2004 *RCT, open*	Jul 2001 to Dec 2002	Adult patients with suspected severe leptospirosis. Diagnosis was confirmed by serologic testing and blood culture of serologic test (MAT, IFAT or MCAT). (N=256)	4 hospitals in Thailand	Mortality (at > 48 hours after treatment), clinical treatment failure, duration of fever, hospitalization and organ dysfunction after treatment	Gentamicin was administered when gram negative sepsis could not be excluded. When well enough, medication was shifted to oral amoxicillin (PCN group) or oral doxycycline (Doxycycline group). Patients who died within the first 48 hours of admission were excluded from analyses of fever clearance. Some patients had coincident rickettsioses.	Very Low

Antibiotic treatment

The effectiveness of an antibiotic (doxycycline or penicillin) compared to placebo or no intervention was presented in the meta-analysis by Brett-Major (Brett-Major, 2012). Of the four included studies that had mortality as an outcome of interest, death among patients occurred in only two studies (Costa, 2003; Edwards, 1988). Treatment with an antibiotic (doxycycline or penicillin) did not prevent death (OR: 1.16; 95% CI: 0.23 to 5.95; random effects model, I^2=50%).

Penicillin

Mortality was reported in the meta-analysis of Charan which compared penicillin with no treatment or placebo (Charan, 2013). Penicillin showed no protection for death as compared with control (OR: 1.70; 95% CI: 0.75 to 3.82, fixed effect model with p=0.19) on pooled analysis of three studies (Costa, 2003; Daher, 2000; Edwards, 1988).

Ceftriaxone

Comparison of ceftriaxone as compared to penicillin on 173 patients (Panaphut, 2003) showed no advantage on mortality (RR: 1.0; 95% CI: 0.3 to 3.3).

Cefotaxime

Comparison of cefotaxime with penicillin by Supputamongkol showed that although cefotaxime appeared to protect from death, this was not statistically significant (RR: 0.3; 95% CI: 0.0 to 3.1) (Supputamongkol, 2004).

The meta-analysis by Brett-Major pooling two studies on cephalosporins (Panaphut, 2003; Supputamongkol, 2004) reported no significant difference in mortality rates with the controls (OR: 0.65; 95% CI: -23 to 1.87; fixed model) (Brett-Major, 2012).

Doxycycline

Comparison of doxycycline with penicillin in the study by Supputamongkol showed no protection against mortality (RR: 1.1; 95% CI: 0.2 to 7.4) (Supputamongkol, 2004).

Azithromycin

No study compared azithromycin with other treatment on the mortality of patients with leptospirosis.

EFFECT ON THE DURATION OF FEVER

Table 16. Summary of studies on the effect of antibiotics in the duration of fever in children with leptospirosis

Study (Study Design)	Study Period	Patients (N)	Location	Outcome determined	Remarks	Quality
Brett-Major 2012 *Meta-analysis (RCTs only)*		All infected patients, both severe and non-severe. Majority or all subjects in the studies reviewed were adults. (N=403)		Primary: Mortality, hospitalization, ventilator requirement, dialysis requirement Secondary: No. of days on mechanical ventilator, no. of days on dialysis, adverse events that resulted in dose decrease or discontinuation of treatment or registration as an AE	Four out of seven studies purported to assess treatment in severe leptospirosis however, in most cases clear definition of severity were not given and criteria were varying. The most severe patients were excluded in some of these 4 studies.	Low
Charan 2013 *Meta-analysis (RCT & Cohort)*		All leptospirosis patients, both severe and non-severe. Majority or all subjects in the studies reviewed were adults. (N=409)		Among the predetermined outcomes availability of data, those that could be compared were mortality, fever days, oliguria, number of dialysis, number of patients needing dialysis	Five studies assessed penicillin with no treatment or placebo. All studies looked into leptospirosis in the endemic population except Fairburn 1956 who studied military men.	Very Low
Watt 1988 *RCT, placebo*	Sep-Nov,1985 and July-Oct 1986	Patients 16 years old and older with severe and late leptospirosis. Leptospirosis was confirmed by antibody titer or isolation of the organism from blood or urine. (N=42)	A national infectious disease hospital in the Philippines	Duration of fever after start of treatment, duration of increased serum creatinine, hematologic and biochemical variables, hospital duration and leptospiruria after treatment	The most severe cases: anuria, presence of confusion, stupor or coma, or a second illness were excluded.	Very Low

Study (Study Design)	Study Period	Patients (N)	Location	Outcome determined	Remarks	Quality
Panaphut 2003 *RCT, open*	Jul 2000 to Dec 2001	Patient ≥16 years old with severe leptospirosis. Of those screened positive using IgM specific LEPTO dipstick assay, 72% were confirmed by MAT. (N=173)	Tertiary hospital in Thailand	Primary: time to resolution of fever after treatment. Secondary: mortality and time to resolution of organ dysfunction	All patients were adults. Severe leptospirosis was based on presence of jaundice, raised creatinine or MAP <70 mmHg. Gentamicin was administered in Group P with gram negative sepsis.	Low
Suputtamongkol 2004 *RCT, open*	July 2001 to Dec 2002	Adult patients with suspected severe leptospirosis. Diagnosis was confirmed by serologic testing and blood culture of serologic test (MAT, IFAT or MCAT). (N=256)	4 hospitals in Thailand	Mortality (at > 48 hours after treatment), clinical treatment failure, duration of fever, hospitalization and organ dysfunction after treatment	Gentamicin was administered when gram negative sepsis could not be excluded. When well enough, medication was shifted to oral amoxicillin (PCN group) or oral doxycycline (Doxycycline group). Patients who died within the first 48 hours of admission were excluded from analyses of fever clearance. Some patients had coincident rickettsioses.	Very Low
Phimda 2007 *RCT, open*	Jul 2003 to Jan 2005	Patients suspected to have leptospirosis, non-severe between 15-88 years old. Diagnosis was confirmed by isolation from blood or MAT. (N=296)	4 hospitals in Thailand	Cure rate, time to defervescence, and adverse events	Of 296 enrolled subjects, only 23.3% had leptospirosis, and 4.1% were co-infected with rickettsia. Confirmation using convalescent sera was not possible in some patients. High drop out rate was noted.	Very Low

Antibiotic treatment

Meta-analysis of two studies by Brett-Major showed a trend for shorter duration of clinical illness by 4 days (MD: -4.04, 95% CI: -8.66 to 0.58; I^2=81%) among those given antibiotics (doxycycline or penicillin), but this was not significant (Brett-Major, 2012).

Penicillin

Watt reported an advantage with the use of penicillin showing a significantly shorter duration of fever (MD: -6.9 days; 95% CI: -2.65 to -11.15) and a greater proportion of patients who were afebrile on day 4 of Penicillin (RR: 10.4; 95% CI: 0.64 to 73.41) (Watt, 1988). However, in a meta-analysis of Charan (Charan, 2013), it was reported that fever days were similar between penicillin and controls after pooling results of three studies (MD: -0.15; 95% CI: 0.47 to 0.17; p=0.358) (Daher, 2000; Edward, 1988; Watt, 1988).

Ceftriaxone

Panaphut showed no advantage on duration of fever (MD: 0;95% CI: -0.2 to 0.2) on giving ceftriaxone as compared to penicillin (Panaphut, 2003).

Cefotaxime

Supputamongkol compared cefotaxime with penicillin and showed no advantage on time to defervescence (Median of 60 hours vs 72 hours, p=0.42) (Supputamongkol, 2004).

Meta-analysis by Brett-Major pooling studies on cephalosporins (Panaphut, 2003; Supputamongkol, 2004) reported no significant difference in fever days (MD: -0.03; 95% CI: -0.09 to 0.03, fixed model, I^2=94%) (Brett-Major, 2012).

Doxycycline

Comparison of doxycycline with penicillin in the study by Supputamongkol showed no advantage on time to defervescence (Median of 72 hours for both, p=0.42). Supputamongkol used multivariate analyses and showed that dysfunction of >2 organ systems at admission resulted in significantly longer duration of fever after treatment (p<0.001). Antimicrobial therapy (penicillin, doxycycline or cefotaxime) and onset of disease (early onset of <5 days versus late onset) were not associated with the duration of fever after treatment (p=0.56 and p=0.83, respectively) (Supputamongkol, 2004).

Azithromycin

Only one study (Phimda, 2007) compared doxycycline with azithromycin in non-severe leptospirosis. The primary outcome, cure rate, was defined as defervescence within 5 days of treatment (RR: 1.0; 95% CI: 1.0 to 1.1), and time to defervescence were comparable (Median= 45 hours vs 40 hours, p=0.45) in both groups.

EFFECT ON RENAL OUTCOMES

Table 17. Summary of studies on the use of antibiotics in reducing renal complications or the need for dialysis in children with leptospirosis

Study (Study Design)	Study Period	Patients (N)	Location	Outcome Determined	Remarks	Quality
Brett-Major 2012 *Meta-analysis (RCTs only)*		All infected patients, both severe and non-severe. Majority or all subjects in the studies reviewed were adults. (N=403)		Primary: Mortality, hospitalization, ventilator requirement, dialysis requirement Secondary: No. of days on mechanical ventilator, no. of days on dialysis, adverse events that resulted in dose decrease or discontinuation of treatment or registration as an AE	Four out of seven studies purported to assess treatment in severe leptospirosis however, in most cases clear definition of severity were not given and criteria were varying. The most severe patients were excluded in some of these 4 studies.	Low
Charan 2013 *Meta-analysis (RCT & Cohort)*		All leptospirosis patients, both severe and non-severe. Majority or all subjects in the studies reviewed were adults. (N=409)		Among the predetermined outcomes availability of data, those that could be compared were mortality, fever days, oliguria, number of dialysis, number of patients needing dialysis	Five studies assessed penicillin with no treatment or placebo. All studies looked into leptospirosis in the endemic population except Fairburn 1956 who studied military men.	Very Low
Watt 1988 *RCT, placebo*	Sept-Nov, 1985 and July-Oct. 1986	Patients 16 years old and older with severe and late leptospirosis. Leptospirosis was confirmed by antibody titer or isolation of the organism from blood or urine. (N=42)	A national infectious disease hospital in the Philippines	Duration of fever after start of treatment, duration of increased serum creatinine, hematologic and biochemical variables, hospital duration and leptospiruria after treatment	The most severe cases: anuria, presence of confusion, stupor or coma, or a second illness were excluded.	Very Low
Daher 2000 *Cohort, prospective*	May 1996 to June 1998	Patients admitted with confirmed leptospirosis by antibody titers. All patients were on ARF (pl creatinine >1.5 mg/dl) and jaundice on admission. (N=35)	Nephrology service of a university hospital in Brazil	Mortality, oliguria, dialysis, days of hospitalization, days of fever, days required for serum creatinine, bilirubin, platelet count to reach normal	Most cases were males and ≥18 years old. Four patients who died within the first 48 hours of admission were excluded from the study.	Very Low

Study (Study Design)	Study Period	Patients (N)	Location	Outcome Determined	Remarks	Quality
Panaphut 2003 *RCT, open*	Jul 2000 to Dec 2001	Patient ≥16 years old with severe leptospirosis. Of those screened positive using IgM specific LEPTO dipstick assay, 72% were confirmed by MAT. (N=173)	Tertiary hospital in Thailand	Primary: time to resolution of fever after treatment. Secondary: mortality and time to resolution of organ dysfunction	All patients were adults. Severe leptospirosis was based on presence of jaundice, raised creatinine or MAP <70 mmHg. Gentamicin was administered in Group P with gram negative sepsis.	Low

Antibiotic treatment

Pooling of two studies by Brett-Major showed that the rate of dialysis was comparable with no treatment or placebo, with a trend towards increased dialysis requirement noted when given antibiotics (OR: 1.54; 95% CI: 0.91 to 2.60; Fixed Effect) (Brett-Major, 2012).

Penicillin

The study of Watt showed that penicillin significantly shortened the duration of rise in creatinine by 5.6 days (MD: 5.6; 95% CI: 1.9 to 9.2) (Watt, 1988). However, those given penicillin had comparable risk for dialysis (OR: 1.59; 95% CI: 0.92 to 2.73) and oliguria (OR: 1.79; 95% CI: 0.32 to 9.93) as the no treatment or placebo group in the meta-analysis of Charan (Charan, 2013). Daher demonstrated that the days to normalization of creatinine was likewise comparable between penicillin and no antibiotic (MD: -1.0; 95% CI: -3.1 to 5.1) (Daher, 2000).

Ceftriaxone

Comparison of ceftriaxone with penicillin showed no advantage on renal failure rate (RR: 1.0; 95% CI: 0.7 to 1.4) (Panaphut, 2003).

Cefotaxime, doxycycline, and azithromycin

No studies reported the effectiveness of cefotaxime, doxycycline and azithromycin on renal outcomes of the patients with leptospirosis.

Considerations for Recommendation Development during the Stakeholders Panel (SP) Meeting:

- The strong recommendation from the stakeholders panel for the use of antibiotics despite the very low quality of evidence was based on the possibility of leptospirosis having serious complications being of a bacterial etiology.
- The availability of inexpensive antibiotics, absence of evidence to suggest harm, and bacterial etiology lend strength to the recommendation.

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CHAPTER 5: PREVENTION OF LEPTOSPIROSIS

Prevention of leptospirosis remains the priority since eradication is not a realistic goal (Illangasekera, 2008). Control strategies can target any of the nodal points in the transmission cycle: the animal carriers, the environment or the host (Sehgal, 2000). For resource-limited developing counties where the disease exists, the use of protective clothing, safe animal husbandry and immunization are financially not sustainable. Controlling rat populations is practically impossible (Illangasekera, 2008).

Vaccination against leptospirosis in humans does not seem possible due to the existence of more than 200 serovars of leptospires and due to the difference in geographical locations with different circulating serovars (Sehgal, 2000).

Currently, chemoprophylaxis is the only practical preventive measure against leptospirosis. However, the efficacy of chemoprophylaxis has not been sufficiently established because of few clinical trials. Limited studies have shown that chemoprophylaxis with doxycycline at 200 mg weekly, to start 1-2 days before and continuing through the period of exposure, might be effective in preventing clinical disease in adults and could be considered for those at high risk and with short-term exposures. In this chapter, we attempted to determine the usefulness of doxycycline as pre-exposure prophylaxis (Sehgal, 2000; Takafugi, 1984) and as post-exposure prophylaxis (Chusri, 2014; Gonsalez, 1998) for conferring protection against laboratory-identified leptospiral infection and symptomatic leptospirosis. Unfortunately, there are no published studies on the use of doxycycline as prophylaxis for leptospirosis in pediatric patients.

Definition of Terms:

Asymptomatic (laboratory-identified) leptospiral infection: presence of at least a four-fold seroconversion to a leptospiral serovar on the Microscopic Agglutination Test, or a positive culture, or both (Gonsalez, 1998; Takafuji, 1984).

Symptomatic leptospirosis: if the criteria for asymptomatic (laboratory-identified) leptospirosis infection is met and had symptoms of fever, chills, myalgia, headache conjunctival suffusion, meningitis, jaundice, or renal insufficiency (Gonsalez, 1998; Takafuji, 1984).

Question 8: How effective is doxycycline as pre-exposure prophylaxis in the prevention of leptospirosis in children?

Recommendation 1: Doxycycline as pre-exposure prophylaxis may be used to prevent both asymptomatic laboratory-identified leptospiral infection and symptomatic leptospirosis in those who live in, and intend to visit, highly endemic areas.
Quality of evidence: Very low
Strength of recommendation: Strong

Summary of Evidence

There were only two studies (Sehgal, 2000; Takafuji, 1984) that assessed the efficacy of pre-exposure prophylaxis with doxycycline. One study was among an indigenous population during an outbreak period (Sehgal, 2000), and the other study was among deployed soldiers for military training in the jungles (Takafuji, 1984).

Table 18. Summary of studies evaluating doxycycline as pre-exposure prophylaxis in the prevention of leptospirosis in children

Study *(Study Design)*	Study Period	Patients (N)	Location	Intervention	Outcome determined	Remarks
Sehgal 2000 *Single site prospective randomized placebo-controlled trial*	Sept-Dec 1998	Mix of residents including agricultural workers and adolescent school children from ages10 years old and above (N=782)	Diglipur town and adjoining villages in North Andaman, India	386 received doxycycline at 200 mg/week 396 received placebo (Vitamin B complex) Duration: started 2 weeks before the outbreak and continued for 12 weeks	Asymptomatic laboratory-identified leptospiral Infection Symptomatic leptospirosis Mortality Adverse Event	Diglipur is highly endemic for leptospirosis which might be the reason for the lack of impact of the drug regimen on the infection rates.
Takafuji 1984 *Single site prospective double-blind placebo-controlled randomized trial*	Fall of 1982	Active duty army soldiers deployed, younger and healthier population (N=940)	Fort Sherman training area in Panama	469 received doxycycline at 200 mg/week 471 received placebo Duration: 2-3 weeks from start of training to completion of military exercises	Asymptomatic laboratory-identified leptospiral infection Symptomatic leptospirosis Adverse Event	Only adults were included in this study.

Sehgal randomized all healthy persons aged 10 years old and above into two groups from North Andaman, India where leptospirosis was highly endemic. Group A was given doxycycline 200 mg/week (N=386) and Group B was given Vitamin B complex as placebo (N=396). The difference in the laboratory-identified leptospiral infection rates detected by Microscopic Agglutination Test between the two groups was not statistically significant (RR: 1.14; 95% CI: 0.90 to 1.43). However, the proportion of symptomatic leptospirosis was statistically significant between the two groups. There was a lower incidence of symptomatic leptospirosis among those given doxycycline (12, 3.11%) compared to placebo (27, 6.82%) ($p<0.05$). The ones given doxycycline had 54% reduction in the risk of developing symptomatic leptospirosis compared to those given placebo (RR: 0.46; 95% CI: 0.23 to 0.89). In addition, none from the doxycycline group developed complications, as compared with three patients from the placebo group who developed severe pulmonary complications and died (RR: 0.15; 95% CI: 0.0076 to 2.83). The results of the study showed that use of doxycycline as a pre-exposure prophylaxis did not reduce the incidence of asymptomatic laboratory-identified leptospiral infection in an endemic area, but had beneficial effect in reducing symptomatic leptospirosis and mortality (Sehgal, 2000).

Takafuji studied military personnel who were training in the jungles of the Republic of Panama for three weeks and were randomly assigned into two groups: doxycycline group and placebo group. Among the 469 participants from the doxycycline group, only one developed symptomatic leptospirosis. Among the 471 participants from the placebo group, there were 20 people with leptospiral infections who developed symptomatic leptospirosis. There was 95% protective efficacy ($p<0.001$) with doxycycline for both asymptomatic laboratory-identified leptospiral infection and symptomatic leptospirosis (RR: 0.05; 95% CI: 0.01 to 0.37) (Takafuji, 1984).

Pooled results from the two trials (Sehgal, 2000; Takafuji, 1984) show that as pre-exposure prophylaxis, doxycycline reduced the risk of developing asymptomatic laboratory-identified infection by 72% compared to placebo, but did not reach statistical significance (RR: 0.28; 95% CI: 0.01 to 7.16) (Figure 28).

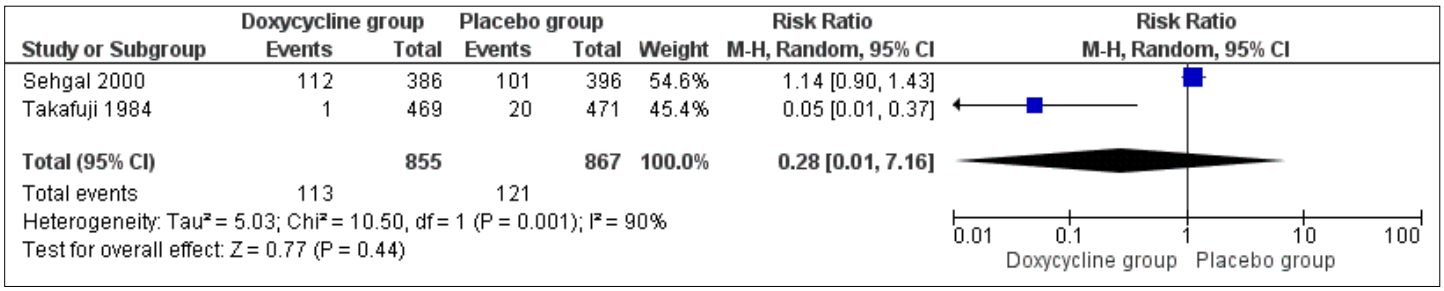

Figure 28. Forest plot of meta-analysis of data for the presence of asymptomatic laboratory-identified infection comparing those who were given pre-exposure doxycycline and those who were given placebo

Pooled data from the two trials (Sehgal 2000; Takafuji 1984) show protective efficacy of 82% in the prevention of symptomatic leptospirosis, but this did not reach statistical significance (RR: 0.18; 95% CI: 0.02 to 1.80). However, this result is non-inferior with a trend of benefit for doxycycline as pre-exposure prophylaxis to prevent symptomatic leptospirosis (Figure 29).

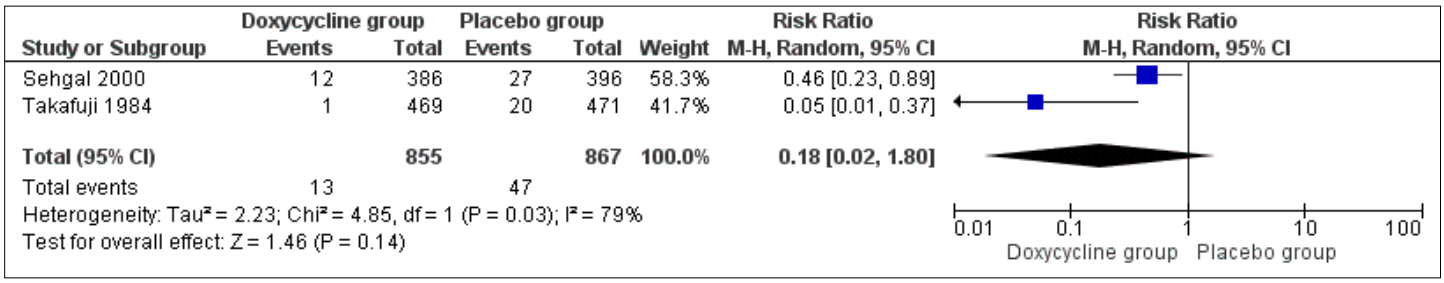

Figure 29. Forest plot of meta-analysis of data for the presence of symptomatic leptospirosis comparing those who were given pre-exposure doxycycline and those who were given placebo

In Takafuji's study, those in the doxycycline group were thirteen times more likely to experience nausea and vomiting, while only 1 had vomiting in the placebo group ($p<0.01$) (Takafuji, 1984). In Sehgal's study, adverse events could not be evaluated because there was no specific number of participants mentioned who experienced adverse events in both groups (Sehgal, 2000). Therefore, pooled data analysis for adverse events is not feasible.

It is important to note that the studies evaluated by the technical working group for leptospirosis pre-exposure prophylaxis involved children ≥10 years of age and adults. There were no published studies that looked into the benefits of pre-exposure prophylaxis with doxycycline for leptospirosis in pediatric patients, even in the local setting.

The quality of evidence for these two trials is very low because of inconsistency of results, indirectness as studies were on adults, and imprecision.

Considerations for Recommendation Development during the Stakeholders Panel (SP) Meeting:

- There is insufficient evidence to recommend the use of doxycycline as pre-exposure prophylaxis in children. However, the SP voted for a strong recommendation as the two studies done mostly in adults showed a trend of benefit towards the use of doxycycline as pre-exposure prophylaxis, even if the results were not statistically significant.

- Nausea and vomiting are strongly associated with the use of doxycycline, but are considered as non-serious side effects.

Question 9: How effective is doxycycline as post-exposure prophylaxis in preventing leptospirosis in children?

Recommendation 1: The use of doxycycline may be considered as post-exposure prophylaxis but there is no evidence in children to suggest that it can prevent symptomatic leptospirosis.
Quality of evidence: Very low
Strength of recommendation: Strong

Summary of Evidence

There were only two studies that evaluated patients aged 18 years old and above that were given doxycycline and placebo as post-exposure prophylaxis for leptospirosis (Chusri, 2014; Gonsalez, 1998). One is a randomized, double-blinded, placebo-controlled trial (Gonsalez, 1998) and the other is a non-randomized controlled trial (Chusri, 2014).

Table 19. Summary of studies on doxycycline as post-exposure prophylaxis in the prevention of leptospirosis in children

Study (Study Design)	Study Period	Patients (N)	Location	Intervention	Outcome determined	Remarks
Gonzalez 1998 *Double-blinded place randomized placebo-controlled trial*	After the Mar 29, 1992 flood	Among residents aged 18-74 years old after exposure to flooding, (N=82)	Cabucu District, Sao Paolo, Brazil	40 received doxycycline 200 mg as a single dose 42 received placebo as a single dose Given until 48 hours of exposure	Asymptomatic laboratory- identified leptospiral infection Symptomatic leptospirosis	Cabucu District is endemic for leptospirosis which might be the reason for the lack of impact of the drug regimen on the infection rates. Only adults were included in this study.
Chusri 2014 *Non-randomized controlled trial*	Oct 8 - 10, 2010	All residents 18 years old and above exposed to flood water since Oct 3,2010 (N=641)	Hat Yai City, Southern Thailand	600 received doxycycline 200 mg as a single dose 41 did not receive doxycycline Given 5-7 days from exposure	Asymptomatic laboratory-identified leptospiral infection Symptomatic leptospirosis Adverse Event	Hat Yai City is endemic for leptospirosis which might be the reason for the lack of impact of the drug regimen on the infection rates. Only adults were included in this study.

Chusri investigated the efficacy of a single dosage of 200 mg doxycycline against leptospirosis in residents aged 18 years old and above who were exposed to flooding in Southern Thailand. As post-exposure prophylaxis, doxycycline reduced the risk of developing asymptomatic laboratory-identified leptospiral infection by 77% compared to placebo (RR: 0.23; 95% CI: 0.08 to 0.66), while the risk for developing symptomatic leptospirosis was reduced by 86% (RR: 0.14; 95% CI: 0.2 to 1.1) (Chusri, 2014).

In addition, the study by Chusri found that having a lacerated wound was associated significantly with asymptomatic laboratory-identified leptospiral infection (OR: 37.20; P<0.001) and symptomatic leptospirosis (OR: 18.24; P=0.003). Those who had ≤3 hours exposure to flood per day was also associated with asymptomatic laboratory-identified leptospiral infection (OR: 3.70; P=0.038). The use of doxycycline as prophylaxis, even among those with lacerated wound, showed a protective efficacy of 92% (95% CI: 81.2% to 96.6.%) for asymptomatic laboratory-identified leptospiral infection, and 95.6% (95% CI: 78.2% to 99.3%) for symptomatic leptospirosis.

The use of doxycycline among those with exposure to flood waters of ≤3 hours, showed a protective efficacy of 89.2% (95% CI: 63.6% to 96.67%) against asymptomatic laboratory-identified leptospiral infection but, there was no mention of protection against symptomatic leptospirosis. Twelve participants in the doxycycline group developed gastrointestinal symptoms, ten of whom developed nausea without vomiting. However, none of these twelve patients developed symptomatic leptospirosis or asymptomatic laboratory-identified leptospiral infection. One participant had skin rash involving the anterior chest wall and neck, which resolved spontaneously. The proportion of gastrointestinal and skin problems was not significantly different between the two groups (P=0.54 and P=0.33, respectively) (Chusri, 2014).

Gonsalez, on the other hand, conducted a trial to determine the effectiveness of single dose of doxycycline among participants 18-74 years old in preventing leptospirosis after high-exposure to flooding of potentially contaminated water in Sao Paulo, Brazil. Among those who were given doxycycline (40 subjects), eleven (11) had asymptomatic laboratory-identified leptospiral infection, while two had symptomatic leptospirosis. In the placebo group (42 subjects), six (6) had asymptomatic laboratory-identified leptospiral infection while five had symptomatic leptospirosis. The risk of having asymptomatic laboratory-identified leptospiral infection among those who were given doxycycline was almost twice as compared to placebo (RR: 1.92; 95% CI: 0.79 to 4.71). The risk of developing symptomatic leptospirosis after being given doxycycline was reduced by 58% as compared to those given placebo (RR: 0.42; 95% CI: 0.86 to 2.04). However, the association was not statistically significant, and the study did not have statistical power to determine more accurate estimates of the magnitude of the potential protection (Gonsalez, 1998).

Pooled analysis of the two trials (Chusri, 2014; Gonsalez, 1998) showed that as post-exposure prophylaxis, doxycycline had no effect in reducing the risk of developing asymptomatic laboratory-identified leptospiral infection compared to placebo (RR: 0.67; 95% CI: 0.08 to 5.59) (Figure 30).

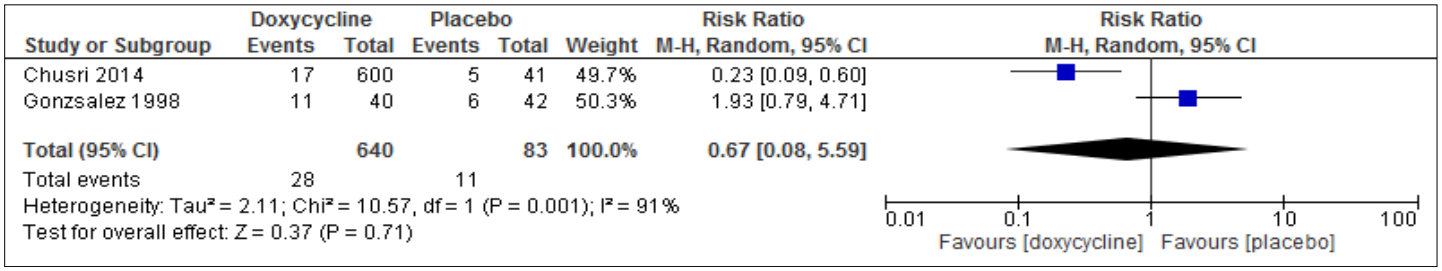

Figure 30. Forest plot of meta-analysis of data for the presence of asymptomatic laboratory-identified leptospiral infection comparing those who were given post-exposure doxycycline and those who were given placebo

The protective efficacy of doxycycline against symptomatic leptospirosis on pooled data was 75%, and statistically significant (RR: 0.25; 95% CI: 0.08 to 0.78) (Figure 31).

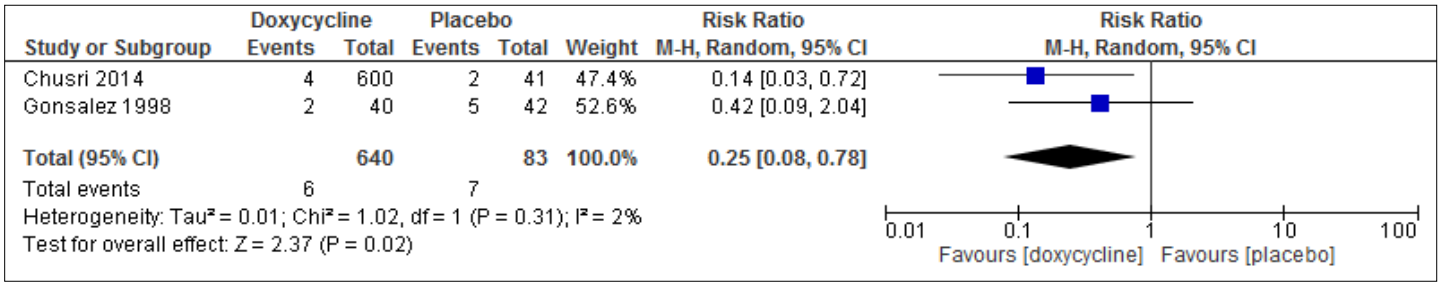

Figure 31. Forest plot of meta-analysis of data for the presence of symptomatic leptospirosis comparing those who were given post-exposure doxycycline and those who were given placebo

In Chusri's study, the use of doxycycline was associated with an increased risk of gastrointestinal adverse events. Minor adverse events occurred twice as more in those given doxycycline (12 had nausea and/or vomiting) (RR: 1.75; 95% CI: 0.11 to 29). There was no increased risk of rash among those given doxycycline (RR: 0.21; 95% CI: 0.01 to 5.07) (Chusri, 2014).

The quality of evidence for these two trials is very low because of risk of bias, inconsistency of results, indirectness as studies were on adults, and imprecision.

Considerations for Recommendation Development during the Stakeholders Panel (SP) Meeting:

- There is insufficient evidence to recommend the use of doxycycline as post-exposure prophylaxis in children as the studies evaluated included mostly adults. However, the SP voted for a strong recommendation since the studies showed protective efficacy of doxycycline against symptomatic leptospirosis and the results were statistically significant.
- Despite adverse events associated with doxycycline and its contraindication for use in children <8 years of age, it may still be used as prophylaxis considering that the dose (4 mg/kg) and duration (single dose) for this indication is unlikely to cause dental staining.

Question 10: Is there evidence to recommend the use of antibiotics other than doxycycline as post-exposure prophylaxis for leptospirosis in children?

Recommendation 1: Oral penicillin may be used for post-exposure prophylaxis to prevent symptomatic leptospirosis in high transmission areas but there are no studies in children.
Quality of evidence: Very low
Strength of recommendation: Strong

Summary of Evidence

There was only one study that used another antibiotic other than doxycycline as post-exposure prophylaxis (Illangasekera, 2008). This study evaluated whether oral penicillin can be used as chemoprophylaxis against leptospirosis in high transmission areas in central Sri Lanka in October 2005. The study recruited full-time farmers, ages 20 to 80 years old, who engaged in active farming on most days during the study period. Subjects were randomly assigned to take either oral penicillin 500 mg twice daily or placebo over a month during the active farming season. There were 152 farmers given penicillin and 167 farmers given placebo. In the treatment group, none developed symptomatic leptospirosis. In the placebo group, three had symptomatic leptospirosis. Since there was a small number of patients included, statistical analysis was not achievable (Illangasekera, 2008).

Penicillin, as post-exposure prophylaxis, reduced the risk of developing symptomatic leptospirosis by 85%, but this did not reach statistical significance (RR: 0.15; 95% CI: 0.01 to 2.92). There was no mention of asymptomatic laboratory-identified leptospiral infection in both study groups.

The quality of evidence for this study is very low due to indirectness as the study involved adults, and due to imprecision.

There were no clinical studies on the use of azithromycin, amoxicillin, ampicillin, ciprofloxacin, erythromycin, clarithromycin, streptomycin, ceftriaxone, cefotaxime, cefepime, imipenem-cilastatin, moxifloxacin, and levofloxacin as post-exposure prophylaxis.

Table 20. Summary of the study on penicillin as post-exposure prophylaxis for leptospirosis

Study *(Study Design)*	Study Period	Patients (N)	Location	Intervention	Outcome determined	Remarks
Illangasekera 2008 *Randomized double blinded placebo-controlled trial*	Oct 2005	Full-time farmers who engaged in active farming on most days, ages 20-80 years old (N=602)	High transmission area in the Medical Officer of Health (MOH) division of Yatinuwara and Udunuwara in the Central Province, Sri Lanka	Oral penicillin 500 mg twice daily or placebo beginning the day before farming 292 on oral penicillin, 143 with poor compliance 310 on placebo,143 with poor compliance Duration: beginning the day before farming and continued over a month during active farming season	Symptomatic leptospirosis	There were only adults in this study.

Considerations for Recommendation Development during the Stakeholders Panel (SP) Meeting:

- There is insufficient evidence to recommend the use of penicillin as post-exposure prophylaxis in children as the only study available was on adults. However, the SP voted for a strong recommendation despite insufficient evidence since the study showed a trend of benefit towards the use of penicillin as post-exposure prophylaxis against symptomatic leptospirosis, even if the results were not statistically significant.

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CLINICAL PRACTICE GUIDELINES

PHILIPPINE PEDIATRIC COVID-19 LIVING CLINICAL PRACTICE GUIDELINES as of March 2022

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

EXECUTIVE SUMMARY

The Coronavirus disease 2019 (COVID-19) pandemic has triggered a global crisis and has affected millions of people worldwide. With the evolution of the different variants of concern, the incidence of COVID-19 in the pediatric population has risen. The Surveillance and Analysis of COVID-19 in Children Nationwide (SALVACION) Registry, developed by the Pediatric Infectious Disease Society of the Philippines (PIDSP) and the Philippine Pediatric Society (PPS), has reported 3,221 cases as of March 31, 2022, with 90.4% requiring hospitalization and 36.2% with moderate to critical disease severity. Given the magnitude of the impact of COVID-19, with most of the clinical recommendations available designed towards adult patients, there was an urgent need for clinicians, public health officials and the government to also prioritize evidence-based clinical practice guidelines for the pediatric population. Hence, the development of the Philippine Pediatric COVID-19 Living Clinical Practice Guidelines was conceptualized. This independent project, funded and supported by the PPS and PIDSP, aimed to formulate up-to-date, evidence-based recommendations on the treatment, diagnosis, infection prevention and control of COVID-19 in children.

Following the standard CPG development process outlined in the DOH Manual for CPG Development and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology, 15 evidence summaries and 24 recommendations were generated by 12 consensus panelists representing their specific health organizations and institutions.

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CONFLICT OF INTEREST DECLARATION

- **Jeriel R. de Silos -** Consultant, COVID-19 Response to NCR, World Health Organization Philippine Country Office (2020); Evidence Review Expert, Philippine COVID-19 Living Clinical Practice Guidelines (Cloth mask vs. medical mask use)
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- **Juliet O. Sio-Aguilar -** Secretary-General, Asian Pan-Pacific Society for Pediatric Gastroenterology, Hepatology and Nutrition; Guest Editor and Reviewer, Acta Medica Philippina
- **Frances M. Tan -** Speakers bureau of Pediatrica and Menarini; Editorial Board, A Review of Immunomodulators as Therapeutic Interventions for Moderate to Severe COVID-19 Infections; Secretary, PSAAI; Stocks in Marikina Valley Medical Center
- **Maria Esterlita V. Uy -** Co-investigator, Risk factors, clinical characteristic and transmission of COVID in non-pregnant and pregnant women in the Philippines; Director, Institute of Child Health and Human Development, NIH-UP Manila; Vice President, Philippine Society of Newborn Medicine

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SUMMARY OF RECOMMENDATIONS

	Recommendation	Strength of Recommendation	Certainty of Evidence
1	As an alternative specimen to nasopharyngeal swab, we recommend the use of saliva specimen for RT-PCR* among non-hospitalized children suspected of COVID-19 infection. **The use of three specific saliva RT-PCR assays is recommended: Allplex 2019-nCOV assay, Cobas 6800, QuantStudio 7 system.*	Strong	Moderate
2	As an alternate specimen to nasopharyngeal swab, we suggest the use of mid-turbinate swab for RT-PCR* among non-hospitalized children suspected of COVID-19 infection. **The use of two specific mid-turbinate RT-PCR assays is recommended: RealStar SARS-CoV-2 RT-PCR kit or Aptima SAR-CoV-2 Assay.*	Weak	Moderate
3	We suggest against the use of nasopharyngeal aspirate as an alternative clinical specimen among non-hospitalized children suspected of COVID-19 infection.	Weak	Moderate
4	We suggest the against routine use of intravenous immunoglobulin for children with COVID-19 infection.	Weak	Very low
5	We suggest the use of systemic corticosteroids (dexamethasone) among children with severe and critical COVID-19 infection.	Weak	Very low
6	We suggest the addition of tocilizumab to systemic steroids in patients with moderate to severe COVID-19 infection, particularly where there is evidence of systemic inflammation.	Weak	Very low
7	We suggest the use of remdesivir in hospitalized children with severe COVID-19 infection.	Weak	Very low
8	We suggest the use of remdesivir in non-hospitalized children with COVID-19 infection with at least one (1) risk factor* for disease progression. **The risk factors for disease progression are hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity, immune compromise, chronic mild or moderate kidney disease, chronic liver disease, chronic lung disease, current cancer or sickle cell disease.*	Weak	Low
9	We suggest against the routine use of anticoagulation in children with COVID-19 infection or MIS-C.	Weak	Very low
10	There is insufficient evidence to recommend the use of casirivimab plus imdevimab as treatment of non-hospitalized children with COVID-19 infection with ≥1 risk factor* for severe COVID-19. **The risk factors are obesity, cardiovascular disease (including hypertension), chronic lung disease (including asthma), chronic metabolic disease (including diabetes), chronic kidney disease (including receipt of dialysis), chronic liver disease, and immunocompromised conditions.*	--	Low

	Recommendation	Strength of Recommendation	Certainty of Evidence
11	There is insufficient evidence to recommend the use of casirivimab plus imdevimab as treatment of hospitalized children with COVID-19 infection with ≥1 risk factor* for severe COVID-19. **The risk factors are obesity, cardiovascular disease (including hypertension), chronic lung disease (including asthma), chronic metabolic disease (including diabetes), chronic kidney disease (including receipt of dialysis), chronic liver disease, and immunocompromised conditions.*	--	Very low
12	There is insufficient evidence to recommend the use of bamlanivimab plus etesevimab as treatment of non-hospitalized children with COVID-19 infection with ≥1 risk factor* for severe COVID-19. **The risk factors are obesity, cardiovascular disease (including hypertension), chronic lung disease (including asthma), chronic metabolic disease (including diabetes), chronic kidney disease (including receipt of dialysis), chronic liver disease, and immunocompromised conditions.*	--	Low
13	There is insufficient evidence to recommend the use of sotrovimab as treatment of non-hospitalized children with COVID-19 infection.	--	Low
14	We suggest against the use of sotrovimab as treatment of hospitalized children with COVID-19 infection.	Weak	Low
15	We suggest against the use of amubarvimab plus romlusevimab as treatment of children with COVID-19 infection.	Weak	Low
16	We suggest against the use of regdanvimab as treatment of children with COVID-19 infection.	Weak	Low
17	We suggest against the routine use of vitamin D for the prevention of COVID-19 infection in children.	Weak	Very low
18	We suggest against the routine use of vitamin C for the prevention of COVID-19 infection in children.	Weak	Very low
19	We suggest against the routine use of zinc for the prevention of COVID-19 infection in children.	Weak	Low
20	We suggest against the use of vitamin D as adjunctive treatment for COVID-19 infection in children.	Weak	Very low
21	We suggest against the use of vitamin C as adjunctive treatment for COVID-19 infection in children.	Weak	Very low
22	We suggest against the use of zinc as adjunctive treatment for COVID-19 in children.	Weak	Low
23	We recommend the implementation of supportive strategies* to optimize mental health among children and adolescents during the COVID-19 pandemic. **Supportive strategies for mental health during the COVID-19 pandemic include psychological counseling, physical and leisure activities (outdoor and online exercise platforms, art and dance), mindfulness meditation training, personal and spiritual coping, strengthening social support and connecting online with*	Strong	Low

	peers, and health-promoting activities.		
	Recommendation	**Strength of Recommendation**	**Certainty of Evidence**
24	We recommend a multi-layer approach using multiple non-pharmacologic interventions* in school settings to limit transmission of COVID-19 in schools. **The non-pharmacologic interventions are wearing of masks of students, physical distancing, engineering controls (ventilation, personal hygiene and handwashing, disinfection of surfaces), administrative controls (blended learning, phased reopening, no/reduced mixing of classes, restriction of class size, minimized or staggered breaks, symptom monitoring, self-quarantine, contact tracing, and early testing).*	Strong	Very low

The Philippine Pediatric COVID-19 Living CPG used the following definitions for the spectrum of severity of COVID-19 based on the Interim Guidelines on the Screening, Classification and Management of Pediatric Patients with Suspected or Confirmed COVID-19 of PIDSP (as of January 8, 2022):

Mild COVID-19 – no pneumonia or hypoxia/desaturation, acute onset of fever and cough or any three (3) or more of the following: fever, cough, coryza, sore throat, diarrhea, anorexia/nausea/vomiting, loss of sense of smell or taste, general weakness/body malaise/fatigue, headache, myalgia

Moderate COVID-19 – with clinical signs of non-severe pneumonia (cough or difficulty of breathing + fast breathing and/or chest indrawing) and no signs of severe pneumonia, including $SpO_2 \geq 95\%$ on room air; while the diagnosis can be made on clinical grounds, chest imaging may assist in diagnosis and identify or exclude pulmonary complications

Severe COVID-19 – with clinical signs of pneumonia (cough or difficulty in breathing) + at least one of the following:

- Central cyanosis or SpO_2 <95%; severe respiratory distress (e.g. fast breathing, grunting, very severe chest indrawing); general danger signs: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions
- Tachypnea (in breaths/min):
    - 3 months old to 12 months old: ≥50 breaths per minute
    - 1 year old to 5 years old: ≥40 breaths per minute
    - 5 to 12 years old: ≥30 breaths per minute
    - ≥12 years old: ≥20 breaths per minute

Critical COVID-19 – with any one of the following:

- Acute respiratory distress syndrome (ARDS)
- Sepsis
- Septic shock
- Acute thrombosis
- MIS-C

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CHAPTER 1: INTRODUCTION

Coronavirus disease 2019 (COVID-19) has grown into a pandemic and global crisis affecting multiple sectors of society. As of December 27, 2021, over 279 million confirmed COVID-19 cases have been reported globally. In the Philippines, as of December 15, 2021, the number of cases in the Philippines has reached more than 2.8 million with 50,449 COVID-19 related deaths. The national strategy towards the new normal is prevention, detection, isolation, treatment, and reintegration (PDITR). The PDITR strategy has been expanded to include vaccination, with the arrival of COVID-19 vaccines from donor countries and international organizations. Since the launch of the national vaccination campaign against COVID-19 in March 2021, the Philippines had 47 million fully vaccinated individuals as of December 26, 2021. Notwithstanding these strategies, none of the epidemiologic projections on COVID-19 in the Philippines point to a foreseeable end of the pandemic, especially with the rise of variants with increased transmissibility.

Given the magnitude of the impact of COVID-19 in the country, in addition to the concurrent infodemic potentially causing misinformation and disinformation among clinicians, public health officials, and policy makers, there is a need for evidence-based guidelines for the effective management and control of the spread of this disease. Existing international guidelines and living systematic reviews on COVID-19 need to be contextualized for the recommendations to be applicable to local end-users and other stakeholders.

Objectives

The Philippine Pediatric COVID-19 Living CPG aimed to provide up-to-date, evidence-based recommendations on the treatment, diagnosis, infection prevention and control of COVID-19 among children with, or at risk for COVID-19 using the GRADE methodology. Specifically, this project:

1. Identified priority questions related to COVID-19 management, infection prevention and control in children
2. Summarized available literature on each priority question related to COVID-19 management, infection prevention and control in children
3. Formulated recommendations on COVID-19 management, infection prevention and control in children based on the evidence summaries presented

Target Population

This CPG was intended to apply primarily for Filipino children aged 0 to 18 years old diagnosed with, or at risk of COVID-19. The severity of COVID-19 was indicated in several recommendations if it is severity-specific. Other clinical characteristics, such as comorbidities, that would affect the recommendations were indicated clearly in the wording, as appropriate.

Intended Users

The following groups are the expected target users of this Living CPG:

1. Public health professionals, such as provincial/city/municipal health officers, program managers, public health nurses, etc., to inform their localized decisions in implementing national policies on COVID-19, such as on public health standards, management, and preventive interventions
2. Clinicians in the hospitals, quarantine centers, and other treatment facilities handling COVID-19 patients, such as generalist physicians, pediatricians, infectious disease specialists, pulmonologists, other specialist physicians, staff nurses, hospital administrators, etc., to inform their individual clinical decisions from diagnosis to treatment and prevention
3. Academicians and researchers, especially those working on related COVID-19 topics, to guide their research initiatives in addressing the identified gaps during the evidence synthesis of this CPG
4. Policymakers and local government officials, such as the Department of Health, Philippine Health Insurance Corporation, Inter-agency Task Force for the Management of Emerging Infectious Diseases, Food and Drug Administration, Health Technology Assessment Council, etc., to inform their national policies on COVID-19, including standards of care in outpatient and in-patient settings

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CHAPTER 2: GUIDELINE DEVELOPMENT METHODOLOGY

The development process of the Philippine Pediatric COVID-19 Living CPG followed the Philippine Department of Health's Manual for Clinical Practice Guideline Development [5], the Philippine COVID-19 Living CPG [6] and the Grading of Recommendations, Assessment, Development and Evaluation or GRADE Approach [7]. The reporting of this CPG manuscript was based on the AGREE Reporting Checklist [8].

2.1 Guideline Preparation

Composition of The Guideline Task Force

The Steering Committee were composed of members representing one or more of the following expertise: CPG methodology, clinical epidemiology, pediatrics, infectious diseases, pulmonology, infection control, and public health. All members have technical knowledge and expertise on clinical management and policy development related to COVID-19 in children.

The Evidence Review Experts (ERE) were composed of members with one or more of the following expertise: methodologists, clinical epidemiologists, evidence-based medical practitioners. They preferably had previous training and experience in CPG development and evidence synthesis.

The Consensus Panel was composed of multi-sectoral representatives such as health practitioners, both specialists and non-specialists, and patient advocates. Aside from clinicians, there was also a representative from the DOH. All panel members were the designated representatives of the relevant professional groups and stakeholder organizations and were selected based on their content expertise and experience, and potential conflicts of interest. The panelists, being involved directly in COVID-19 patient care and some having children who were infected themselves, acted also as patient advocates to reflect patients' and public's views and preferences.

Key Clinical Issues and Questions

The Philippine Pediatric COVID-19 Living CPG tackled five central themes in COVID-19: Screening and Diagnosis, Treatment, Prophylactic Interventions, Adjunct Interventions, and Non-Pharmacologic Interventions.

Table 1 below summarizes the topics covered. The Steering Committee, together with the TWG and other key stakeholders, finalized the health questions to be addressed in the CPG. The detailed population, interventions/tests, and outcomes were presented in the appropriate sections for each theme.

Table 1. Topics covered in the Philippine Pediatric COVID-19 Living CPG.

Screening and Diagnosis	Treatment
• Alternative clinical specimens to nasopharyngeal swab for RT-PCR	• Intravenous immunoglobulin (IVIG) • Corticosteroids • Tocilizumab • Remdesivir • Anticoagulation • Monoclonal antibodies
Prophylactic Interventions	**Adjunct Interventions**
• Vitamin D • Vitamin C • Zinc	• Vitamin D • Vitamin C • Zinc
Non-Pharmacologic Interventions	
• Supportive strategies to optimize mental health • Preventive interventions used in school settings to reduce transmission	

2.2 Evidence Synthesis

The general approach for the evidence reviews for this CPG was the identification of existing systematic reviews and CPGs on COVID-19. Reference lists were checked vis-a-vis the search yield of the evidence reviewers. If there were none found, or the systematic reviews and CPGs were not high-quality nor updated, a *de novo* systematic review was done. Otherwise, high-quality and up-to-date review CPG evidence summaries were used for generating recommendations.

Each clinical question was reviewed by at least two reviewers, with the oversight of an expert technical coordinator. This was done to ensure reproducibility of the following study assessments: Inclusion/exclusion of studies, study quality appraisal, and data extraction.

Search Methods

Primary studies and systematic reviews were searched from inception until February 2022, using the following sources:

- Electronic databases: MEDLINE through PubMed and Cochrane CENTRAL Database
- Pre-print databases: ChinaXiv.org, MedRxiv.org, and BioRxiv.org
- Trial registries: USA ClinicalTrials.gov, China ChiCtr.org, and WHO ICTRP
- Living COVID-19 databases: COVID-19 Open Living Evidence Synthesis (https://covid-nma.com/), COAP Living Evidence on COVID-19 (https://zika.ispm.unibe.ch/assets/data/pub/search_beta/), and L-OVE Database (https://iloveevidence.com)
- COVID-19 Living CPGs: Australia (https://covid19evidence.net.au/), US NIH (https://www.covid19treatmentguidelines.nih.gov/), and WHO (https://www.who.int/publications/i/item/therapeutics-and-covid-19-living-guideline)

Detailed search strategies for each clinical question were presented in the respective full-text evidence summaries.

Inclusion and Exclusion Criteria

As a rule, questions on clinical efficacy and safety of interventions were answered using randomized controlled trials (RCT). If there were limited or no RCTs available, observational studies were included. For questions on diagnostic tests, appropriately designed diagnostic accuracy studies were sought.

The target population depended on the clinical question, whether it was on pediatric patients with COVID-19 or healthy children. Specific details on inclusion and exclusion criteria were presented in the respective full-text evidence summaries.

Study Quality Assessment

Quality appraisal of primary studies and systematic reviews was done by at least two independent reviewers. The Painless EBM questions on validity [9] were prescribed to be used for quality appraisal of therapy, diagnosis, harm, and systematic review questions. Risk of bias assessments were summarized in evidence tables within the respective full-text evidence summaries.

Certainty of evidence for each outcome was determined using the GRADE approach [6]. The overall certainty of evidence was determined by the ERE by considering the lowest certainty across all critical and important outcomes. There were different factors considered by the reviewers in determining the certainty of evidence, as summarized in Table 2.

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Table 2. Factors influencing certainty of evidence [6].

Certainty of Evidence	Study Design – Intervention Questions	Study Design – Diagnosis Questions	Factors that Decrease COE (by 1 to 2 levels)	Factors that Increase COE (by 1 to 2 levels)
High	Randomized controlled trial	Appropriate cross-sectional or cohort studies in patients with diagnostic uncertainty	• Risk of Bias • Inconsistency • Indirectness • Imprecision • Publication Bias	• Large magnitude of effect • Plausible confounding • Dose-response gradient
Moderate				
Low	Observational study			
Very Low				

Data Synthesis

Meta-analysis was done to pool the treatment effects or the diagnostic performance indices, as appropriate to the clinical question. When studies and results cannot be combined, a narrative synthesis was done, and relevant information was summarized in a table.

2.3. Evidence to Decision: Formulating Recommendations

The Consensus Panel evaluated the direction and strength of recommendation using the GRADE approach and the Evidence to Decision Framework, based on the (1) overall quality of evidence for each question, (2) balance between benefits and harms, (3) values, preferences, and burden on patients, (4) cost and resource use, and (5) other considerations such as feasibility, equity and acceptability.

Certainty of Evidence and Strength of Recommendations

The certainty of evidence was one of the bases of the Consensus Panel in making the final recommendation. Table 3 shows the definition and implication of each:

Table 3. Definitions and Implications of each GRADE Certainty of Evidence [6].

GRADE Certainty of Evidence	Definition	Implication
High	We are **very confident** that the true effect lies close to that of the estimate of the effect.	Further research is **very unlikely to change confidence** in the estimate of effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	Further research is **likely to have an important impact on confidence** in the estimate of effect and may change the estimate.
Low	Our **confidence in the effect estimate is limited**: The true effect may be substantially different from the estimate of the effect.	Further research is **very likely to have an important impact on confidence** in the estimate of effect and is likely to change the estimate.
Very Low	We have **very little confidence** in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.	Any estimate of effect is **very uncertain.**

The strength of recommendation could either be strong or weak. A strong recommendation was stated as "We recommend/We recommend against…", while a weak recommendation was worded "We suggest/We suggest against…".

However, there were three reasons if the Consensus Panel was unable to make a recommendation [7]:

1. Confidence in effect estimates is so low that the panel feels a recommendation is too speculative.
2. Trade-offs are so closely balanced, and the values and preferences, and resource implications are not known or too variable.
3. Management options have very different undesirable consequences, and individual patients' reactions to these consequences are likely to be variable.

For these evidence reviews where the panel was unable to make a recommendation, the recommendation was stated as "There is insufficient evidence to recommend the use of…"

The implications of strong and conditional recommendations are enumerated in Table 4 [7].

Table 4. Implications of the Strength of Recommendation to Patients, Clinicians, and Policymakers [7].

	Strong Recommendation	Weak Recommendation
Patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for different patients. Clinicians must help each patient arrive at a management decision consistent with her or his values and preferences.
Policy makers	The recommendation can be adopted as policy in most situations including for the use as performance indicators.	Policy making will require substantial debates and the involvement of many stakeholders. Policies are also more likely to vary between regions.

Patient Views and Preferences

Patient views and preferences were represented by a nurse who had direct patient care encounters, and consensus panel members who were directly involved in various aspects of COVID-19 care: clinician, administrator, researcher. Some of the panelists were COVID-19 patients themselves or had relatives and friends afflicted with COVID-19. This strategy ensured that patient views and preferences were still considered in the rating of the outcomes and formulation of recommendations.

Resource Implications

Since COVID-19 is a relatively new disease that is being studied internationally, and most COVID-19 diagnostics and interventions are still investigational, there were limited economic evaluations available. In the absence of this information, consensus panelists considered the cost and other local resources needed for the recommendations. This discussion could be found in the *Consensus Issues* subsection of each evidence summary, when appropriate.

Rating of Outcomes

The Consensus Panel rated outcomes for each set of clinical questions according to whether they were critical, important but not critical, or of low importance for decision making. Critical outcomes were primary factors that should influence a recommendation, while those with lower importance did not bear on these recommendations. On a scale of

1–9, those rated 7–9 were critical outcomes, 4–6 were important but not critical outcomes, and 1–3 were outcomes of limited importance. Table 5 below shows the result of the ranking of outcomes:

Table 5. Outcome Ratings by the Consensus Panel

	Critical Outcomes	Important but not critical outcomes
Screening and Diagnosis	• Sensitivity and specificity • Positive and negative predictive values • Likelihood ratio	• Adverse events
Treatment	• Mortality • Recovery • Hospitalization • Adverse events • Clinical improvement • Duration of ICU stay • Need for mechanical ventilation • Duration of hospital stay	• Negative viral conversion
Treatment – Anticoagulation	• Mortality • Thrombosis • Bleeding events	
Prophylactic Interventions	• Forward transmission • Adverse events • Incidence of COVID-19 • Viral load	
Non-Pharmacologic Interventions – School Setting	• Transmission rates • Number of outbreaks • Attack rate • Incidence rate • Prevalence rate • Number of cases	
Non-Pharmacologic Interventions – Mental Health	• Depression • Perception of overall well-being • Anxiety • Resilience	• Life satisfaction • Mindfulness

Consensus Process

A skilled facilitator moderated the discussions during the consensus meetings. Each member voted on the draft recommendation as follows: yes, no, or abstain. The consensus was defined as at least 75% agreement among the members for both the direction and strength of recommendation. If consensus was not reached, members discussed the reasons in support of their votes for or against the recommendation. The voting was repeated, up to three rounds, until a consensus was reached. Any issues left unsettled after the *en banc* meeting were finalized through a modified Delphi activity.

There was one recommendation that required a modified Delphi activity. This was the recommendation regarding the preventive interventions to prevent transmission of COVID-19 in the school setting. Although the panel agreed on the recommendation, the panel voted separately for the individual non-pharmacologic interventions (NPIs) to

be included in the recommendation. Only those NPIs that reached a minimum of 75% vote were included. This was settled on March 29, 2022.

2.4. External Review

The CPG webpage served the dual purpose of a dissemination method and a way to collect the external reviews of the CPG processes, evidence summaries, and recommendations. The manuscripts were also distributed to individual PPS members for their inputs and feedback. This website (https://www.psmid.org/philippine-covid-19-living-recommendations-3/) also allowed health professionals and key stakeholders to suggest additional clinical questions that could be included in the scope of this CPG. This was simultaneously linked to the PPS website (https://pps.org.ph/philippine-pediatric-covid-19-living-clinical-practice-guidelines/).

Over the weeks and months, we will gather feedback from users and members of the Living CPG Taskforce to improve the readability of the webpage, such as toggling of topics, recommendations, and evidence summaries, changing from topics to questions in the listing, rearranging various sections into headers (such as CPG methodology, task force members, contact details, etc.), and other formatting changes.

2.5. Guideline Dissemination

Three methods were used in the dissemination of the Philippine Pediatric COVID-19 Living CPG: (1) online webpage, (2) Living Recommendations document, and (3) full-text CPG manuscript.

The recommendation statements and evidence summaries of the Philippine Pediatric COVID-19 Living CPG were uploaded in the online webpage of the Philippine COVID-19 Living CPG hosted on the PSMID website on **April 4, 2022**, in order to maintain a single repository of all local clinical recommendations on COVID-19, for both the adult and pediatric populations. It has undergone improvements from the feedback of CPG users and members of the Living CPG task force.

The short *Living Recommendations document* contained the content in the PSMID website, including the introduction, CPG methodology, members of the living CPG task force, and the actual recommendation statements. The evidence summaries were not included in this document. This shorter format allowed for an easily accessible document for use by practitioners and selected laypersons.

This full-text CPG manuscript, as well as the complete evidence base, will be submitted to the DOH National Clearinghouse for national promotion regarding use and uptake of the recommendations, including activities such as releasing a department memorandum to notify stakeholders, publicizing the CPG through the DOH newsletter and to other appropriate agencies, and issuing press releases, news articles, and social media posts. The final manuscript will be made available as electronic copies through the websites of DOH, PPS and PSMID.

Furthermore, several dissemination fora have already been conducted during relevant meetings of professional societies, where several members of the Steering Committee and Consensus Panel presented. More avenues for dissemination will be undertaken to promote the use and value of this CPG's recommendations.

Real-time updates of living recommendations were published on the CPG webpage and disseminated to various stakeholders. Further updates will be announced during the DOH daily updates on COVID-19, promoted on various social media platforms, and published on the PPS and PSMID websites.

2.6 Guideline Monitoring and Evaluation

Guideline implementation would be assessed through process and impact evaluation. Only a process evaluation was feasible during the project implementation using webpage analytics. Refer to the subsection on *Monitoring* in the *Discussion* section of this manuscript.

Impact evaluation for the Philippine Pediatric COVID-19 Living CPG would include bi-annual surveys of the following (1) clinicians managing pediatric COVID-19 patients, (2) public health practitioners coordinating local PDITR+ strategies in the community, and (3) the public regarding their compliance to non-pharmacologic interventions and any preventive measures.

The quality of care rendered to pediatric COVID-19 patients can be assessed by measuring adherence of healthcare providers and institutions to the recommendations of the Philippine Pediatric COVID-19 Living CPG. Strong

recommendations would be included in a quality-of-care checklist on COVID-19 care for children, while weak recommendations would be relevant if the identified conditions are satisfied.

Finally, a scheduled bi-annual review would be conducted to evaluate the process efficiency and scientific quality of the Philippine Pediatric COVID-19 Living CPG.

2.7. Updating of Guidelines

Due to the rapidly evolving science of COVID-19 treatment and diagnosis, the Philippine Pediatric COVID-19 Living CPG was updated continuously. The Living CPG Development Process is summarized in Figure 1.

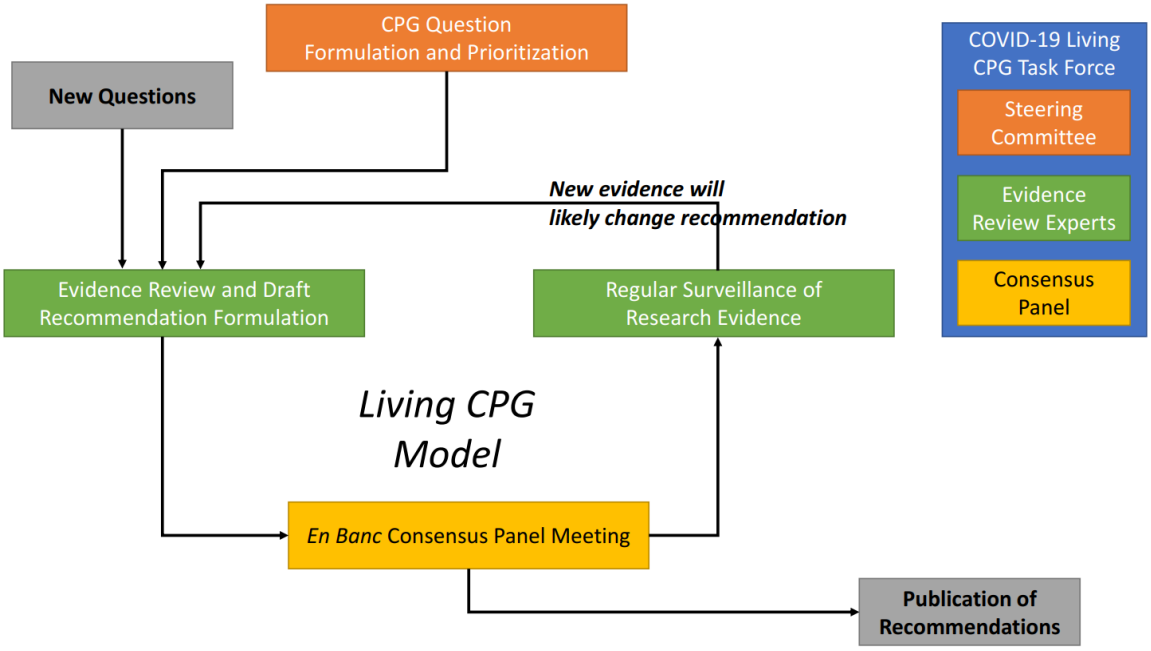

Figure 1. Philippine Pediatric COVID-19 Living CPG Development Process.

After the initial PPS-PIDSP funding for six months, the DOH Disease Prevention and Control Bureau has provided funding support for another six months to continue the surveillance search for the "living recommendations". Further funding will be sought from professional societies and other government agencies to ensure the sustainability of the living CPG throughout the COVID-19 pandemic.

2.8 Editorial Independence

Funding Source

This CPG project was funded by the PPS and PIDSP. Though both organizations were part of the Steering Committee and the Consensus Panel, their influence on the guideline content was limited to the identification of key clinical questions and the discussion of the recommendations. The funding agencies did not have any undue influence on the evidence review conducted, as well as on the interpretation of the research data available.

Management of Conflicts of Interest

All members involved in the creation of this CPG, including the Steering Committee, Technical Working Group, and Consensus Panel, declared any potential conflicts of interest within the last 4 years, using a uniform Declaration of Conflict of Interest (DCOI) form as recommended in the DOH Manual [5]. These were reviewed by an independent

Oversight Committee (OC) and the Steering Committee, to screen and manage the COIs declared. The Oversight Committee was responsible for recommending the extent of participation that can be allowed.

The Oversight Committee has come up with the following guide as bases for their decisions:

a. **Acceptable** – if there are no intellectual nor financial conflicts of interest
b. **Manageable A** – if there are intellectual conflicts of interest only. They can vote but they need to declare their intellectual conflicts (e.g., affiliation with institutions, positions in an organization, authorship in paper or CPG)
c. **Manageable B** – if there are some intellectual and financial conflicts of interest. They cannot vote but they can share their expertise with the group. Examples include panelists from government agencies directly involved in the implementation of the program and panelists from the agency funding the guidelines. The specific terms of management shall be set forth by the OC and shall relate to specific clinical questions.

The declared COIs and decision of the Oversight Committee of members of the Consensus Panel are listed in the beginning of this article. The other members of the Consensus Panel and Evidence Review Experts did not have any conflicts of interest.

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CHAPTER 3:
RECOMMENDATIONS and KEY FINDINGS of the EVIDENCE SUMMARIES

3.1 Screening and Diagnosis of COVID-19 in Children

Which clinical specimen can be used as an alternative to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 infection in children?

	RECOMMENDATIONS	CONSENSUS ISSUES
1	**As an alternative specimen to nasopharyngeal swab, we recommend the use of saliva specimen for RT-PCR* among non-hospitalized children suspected of COVID-19 infection. (Moderate certainty of evidence; Strong recommendation)** **Nasopharyngeal swab is the specimen of choice for RT-PCR for the diagnosis of COVID-19 infection in children. The use of three specific saliva RT-PCR assays is recommended: Allplex 2019-nCOV assay, Cobas 6800, or QuantStudio 7 system.*	There were no consensus issues noted.
2	**As an alternative specimen to nasopharyngeal swab, we suggest the use of mid-turbinate swab for RT-PCR* for among non-hospitalized children suspected of COVID-19 infection. (Moderate certainty of evidence; Strong recommendation)** **Nasopharyngeal swab is the specimen of choice for RT-PCR for the diagnosis of COVID-19 infection in children. The use of two specific mid-turbinate RT-PCR assays is recommended: RealStar SARS-CoV-2 RT-PCR kit or Aptima SAR-CoV-2 Assay.*	There were no consensus issues noted.
3	**We suggest against the use of nasopharyngeal aspirate as an alternative clinical specimen among non-hospitalized children suspected of COVID-19 infection. (Low certainty of evidence; Weak recommendation)**	This recommendation was based on one study performed in children however, due to the low certainty of evidence and issues on availability of the test, the panel voted against the use of nasopharyngeal aspirate in children.

Seven cross-sectional studies on the use of saliva specimen were retrieved however, only three studies were appraised to have no serious risks of bias. Pooled analysis was done for the three studies to check for diagnostic accuracy. Saliva RT-PCR had a sensitivity: 0.87 (95% CI 0.81, 0.91) and specificity: 0.98 (95% CI 0.97, 0.99). Predictive values (PV) ranged from 91.7% - 96.8% and likelihood ratios (LR) for positive result was 45 and 0.13 for a negative result. These accuracy estimates had moderate certainty of evidence. The following assays were used: 1) Allplex 2019-nCoV assay, 2) Cobas 6800, and 3) QuantStudio 7 system.

One study each on using mid-turbinate swab and nasopharyngeal aspirate (NPA) both showed moderate sensitivity but wide confidence interval and high specificity. Other PV and LR accuracy estimates were interpreted moderate to high among non-hospitalized and hospitalized children suspected of COVID-19, respectively. However, while mid-turbinate swab evidence was moderate in certainty of evidence, NPA RT-PCR was based on a study with low certainty of evidence.

No studies in children were seen using the following specimens: oropharyngeal swab, pharyngeal swab, nasal swab, and sputum for RT-PCR.

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3.2 Treatment of COVID-19 in Children

3.2.1. Should intravenous immunoglobulin be used in the treatment of children with COVID-19 infection?

RECOMMENDATION

We suggest against the routine use of intravenous immunoglobulin for children with COVID-19 infection. (Very low certainty of evidence; Weak recommendation)

Consensus Issues
The recommendation was based on the evidence from one retrospective cohort study in children and seven randomized controlled trials in hospitalized adults with moderate to severe COVID-19. Although the evidence in adults showed a significant benefit in reducing clinical deterioration, duration of hospital stay and ICU admission, the evidence was rated as very low due to serious risks of bias, indirectness and imprecision. On the other hand, the evidence in pediatric patients was inconclusive. Coupled with the high cost of the treatment, the panel decided to vote against the routine use of the drug. However, the panel agreed that IVIG may be considered especially when no other treatment option is available. In special circumstances such as MIS-C, expert opinion should be sought.

There were no randomized controlled trials (RCT) found on the use of intravenous immunoglobulin (IVIG) in the treatment of COVID-19 infection in children during the search. However, there was one retrospective cohort study which compared the use of IVIG+CS with CS alone among pediatric patients with Multisystem Inflammatory Syndrome in Children (MIS-C). This showed that addition of IVIG demonstrated tendency towards harm for the composite outcome (use of inotropic support or mechanical ventilation on or after day 2 or death) and inconclusive findings for the other outcomes. When IVIG alone was compared with CS alone (IVIG vs CS) among patients with MIS-C, results were inconclusive for the same composite outcome and for the other outcomes.

Since data in children is limited, indirect evidence was also used through extrapolation of results from the studies included in the Philippine COVID 19 Adult Living Clinical Practice Guideline Phase II as well as from the new adult RCTs found in the search. Pooled results of the seven (7) RCTs on adults showed that the use of IVIG resulted in significant benefit on clinical deterioration, shorter duration of hospital stay and of ICU admission but no significant difference for the rest of the outcomes and adverse events.

The overall certainty of evidence was very low. Thus, there is still insufficient evidence on the use of IVIG for the treatment of COVID-19 in children.

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3.2.2. Should corticosteroids be used in the treatment of children with COVID-19 infection?

RECOMMENDATION

We suggest the use of systemic corticosteroids (dexamethasone) among children with severe and critical COVID-19 infection. (Very low certainty of evidence; Weak recommendation)

Consensus Issues
The recommendation was based on the findings from 20 randomized controlled trials done in hospitalized adult patients with COVID-19. Despite the very low certainty of evidence, the panel agreed that the benefit of significantly reducing all-cause mortality in COVID-19 patients as well as the availability and low cost of dexamethasone is enough to justify its use among pediatric patients with severe and critical COVID-19.

There were no direct studies that enrolled pediatric patients with COVID-19, which compared the use of corticosteroids (CS) with standard care or placebo. Twenty randomized controlled trials (RCTs) on the use of systemic CS as treatment for COVID-19 were included in this review, and all of them included adult COVID-19 patients. These studies used any of the following agents in their experimental arm: Dexamethasone (DEX), Hydrocortisone (HCT), Methylprednisolone (MP), or Prednisolone (PRDL). One study compared inhaled plus intranasal Ciclesonide (CIC) with standard care or placebo.

Pooled estimates for all-cause mortality showed that it was significantly reduced in the systemic CS group; subgroup analysis showed DEX to be the only CS showing significant benefit over standard care or placebo. The results were inconclusive for COVID-19-related mortality. One study showed a significant increase in length of intensive care unit (ICU) stay; another study showed more ventilator-free days in the systemic CS group. However, the studies which used DEX had very low overall certainty of evidence which is partly due to the indirectness caused by the predominantly adult population included.

Comparing MP with DEX, there was a significant decrease in World Health Organization Ordinal Scale (WHO OS) scores and length of hospital stay for the MP group. Mortality and need for mechanical ventilation (MV) were similar for both drugs. For the different doses of DEX, there were conflicting results on mortality rates, length of ICU stay, adverse events (AEs) and other outcomes.

Comparing the systemic CS group and the control group, the results were inconclusive for clinical improvement at 28 days, length of hospital stay, ICU admission rate, intubation rate, extracorporeal membrane oxygenation (ECMO) rate, life support-free days, Sequential Organ Failure Assessment (SOFA) score, and AEs.

Inhaled plus intranasal CIC did not show significantly different results for respiratory symptom resolution, overall symptom resolution, hospital admission rate, mortality, or AEs.

The included RCTs had very low to moderate certainty due to issues with blinding, selective reporting, indirectness, imprecision, and heterogeneity. One cost-effectiveness study showed that the use of 6 mg DEX per day was more cost-effective than standard care for COVID-19.

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3.2.3. Should tocilizumab be used in the treatment of children with COVID-19 infection?

RECOMMENDATION

We suggest the addition of tocilizumab to systemic steroids in patients with moderate to severe COVID-19 infection, particularly where there is evidence of systemic inflammation. (Very low certainty of evidence; Weak recommendation)

Consensus Issues
Although the evidence was based on 17 randomized controlled trials done in hospitalized adult patients with moderate to severe COVID-19, the panel voted for the use of tocilizumab as treatment for COVID-19 in children due to the significant benefit in all-cause mortality and need for mechanical ventilation.

There were no observational or randomized controlled trial (RCT) data on the effectiveness of tocilizumab for the treatment of acute COVID-19 infection in pediatric patients. Taking this into consideration, the review considered the effect of tocilizumab on adults with Covid-19 as indirect evidence for our chosen population basing it primarily on the recently updated Philippine Adult LCPG Phase II.

Pooled results of 17 RCTs (n=9,649) which investigated the efficacy of tocilizumab among hospitalized adult patients with moderate to severe COVID-19 infection comparing to placebo and/or standard of care showed significant benefit in all-cause mortality and need for mechanical ventilation with no significant increase in the risk for adverse events and serious adverse events among those who received tociluzumab. Adverse events reported were neutropenia, leukopenia, anxiety, arrhythmia, insomnia, stroke, constipation, pneumothorax, intracranial bleeding, and pulmonary embolism among others. In addition, co-administration with steroids demonstrated benefit with significant reduction in mortality.

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3.2.4. Should remdesivir be used in the treatment of children with COVID-19 infection?

	RECOMMENDATIONS	CONSENSUS ISSUES
1	**We suggest the use of remdesivir in hospitalized children with severe COVID-19 infection. (Very low certainty of evidence; Weak recommendation)**	Despite the very low certainty of evidence for hospitalized children, the panel voted for the use of remdesivir. This is due to the significant benefit in decreasing the risk for clinical deterioration (based on WHO progression scale) and the risk reduction in mechanical ventilation use, although this was not statistically significant. The panel also agreed that because there are very limited treatment options for pediatric patients with COVID-19, this would give better guidance to clinicians. The panel emphasized though that remdesivir should be used for pediatric patients with severe COVID-19 following the classification of PIDSP and PSMID (on low flow oxygen support).
2	**We suggest the use of remdesivir in non-hospitalized children with COVID-19 infection with at least one (1) risk factor for disease progression. (Low certainty of evidence; Weak recommendation)** **The risk factors for disease progression are hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity, immune compromise, chronic mild or moderate kidney disease, chronic liver disease, chronic lung disease, current cancer or sickle cell disease.*	The panel voted for the use of remdesivir in non-hospitalized children with COVID-19 infection based on the evidence from one double-blind, placebo controlled randomized controlled trial done among patients aged 12 years old and above. This study showed significant benefit in preventing COVID-19 related hospitalization or all-cause mortality. Remdesivir was given to the patients 7 days from symptom onset and to those with at least one of the following risk factors: hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity, immune compromise, chronic mild or moderate kidney disease, chronic liver disease, chronic lung disease, current cancer or sick cell disease.

There are no randomized controlled trials (RCTs) to evaluate the use of remdesivir in the treatment of COVID-19 in the pediatric population. One observational study (n=77) among pediatric patients described the compassionate use of Remdesivir for all 77 patients. It showed 83% of cases recovered after 28 days of follow-up. On subgroup analysis, those on invasive ventilation took a significantly longer time to recover and time to discharge than those without, with 32% of patients presenting at least 1 adverse event. Pooled results of ten RCTs evaluating the use of remdesivir in adults outpatients with mild to moderate COVID-19 with risk factors has shown significant benefit in terms of reducing risk for hospitalizations and death. For hospitalized/in-patients, remdesivir decreased the risk only for clinical deterioration as measured by the WHO progression scale but did not show benefit in other outcomes: all-cause mortality, need for mechanical ventilation and time to clinical improvement. No increased risk of adverse events and serious adverse events

were noted. Overall certainty of evidence was rated low to very low due to serious risk of bias, inconsistency, indirectness and imprecision.

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3.2.5. Should anticoagulation be used in the treatment of children with COVID-19 infection?

RECOMMENDATION

We suggest against the routine use of anticoagulation in children with COVID-19 infection or MIS-C. (Very low certainty of evidence; Weak recommendation)

Consensus Issues
The recommendation was based on the findings from two cohort studies done on pediatric patients with COVID-19 infection and MIS-C. There were no significant benefits noted in both studies. However for those with high risk of thrombotic events, the panel suggested to seek expert opinion.

There was no significant benefit for prophylactic anticoagulation over no anticoagulation in preventing thrombotic events for hospitalized children with COVID-19 or MIS-C in two cohort studies. Risk of bleeding while on prophylactic anticoagulation was inconclusive. In the second study, no deaths and thrombotic events were reported. Overall certainty of evidence was downgraded to very low due to high risk of bias, very small sample size, low event rate and wide confidence intervals.

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3.2.6. Should monoclonal antibodies be used in the treatment of children with COVID-19 infection?

	RECOMMENDATIONS	CONSENSUS ISSUES
1	**There is insufficient evidence to recommend the use of casirivimab plus imdevimab as treatment of non-hospitalized children with COVID-19 infection with ≥1 risk factor* for severe COVID-19. (Low certainty of evidence)**	The recommendation is based on two pre-print studies done on hospitalized patients aged 12 years and above. Although there was a significant decrease in the risk for mechanical ventilation use or death for patients given the intervention, most of these studies were conducted on adults and prior to the emergence of the Omicron variant as the dominant variant of concern.
2	**There is insufficient evidence to recommend the use of casirivimab plus imdevimab as treatment of hospitalized children with COVID-19 infection with ≥1 risk factor* for severe COVID-19. (Very low certainty of evidence)**	The recommendation is based on two pre-print studies and a published one on non-hospitalized patients aged 12 years and above who were both symptomatic and asymptomatic for COVID-19. Although there was a significant decrease in the risk for COVID-19 related hospitalization, ER visit or death and ICU admission, most of these studies were conducted on adults and prior to the emergence of the Omicron variant as the dominant variant of concern.
3	**There is insufficient evidence to recommend the use of bamlanivimab plus etesevimab as treatment of non-hospitalized children with COVID-19 infection with ≥1 risk factor* for severe COVID-19. (Low certainty of evidence)**	The recommendation is based on two published studies done on non-hospitalized patients aged 12 years and above. Although there was a significant decrease in the risk for COVID-19 related hospitalization and death, most of these studies were conducted on adults and prior to the emergence of the Omicron variant as the dominant variant of concern.
4	**There is insufficient evidence to recommend the use of sotrovimab as treatment of non-hospitalized children with COVID-19 infection. (Low certainty of evidence)**	The recommendation is based on one published study done on non-hospitalized patients. Although there was a significant decrease in the risk for COVID-19 related hospitalization and use of supplemental oxygen, the study was conducted on adults and prior to the emergence of the Omicron variant as the dominant variant of concern.
5	**We suggest against the use of sotrovimab as treatment of hospitalized children with COVID-19 infection. (Low certainty of evidence; Weak recommendation)**	The recommendation is based on one published study done on hospitalized adult patients that showed inconclusive results in terms of reducing risk for use of supplemental oxygen, mechanical ventilation and all-cause mortality. The low certainty of evidence with the inconclusive results were the reasons why the panel voted against the use of this drug.
6	**We suggest against the use of amubarvimab plus romlusevimab as treatment of children with COVID-19 infection. (Low certainty of evidence; Weak recommendation)**	The recommendation is based on one published study done on hospitalized adult patients that showed inconclusive results in terms of reducing risk for use of supplemental oxygen, mechanical ventilation and all-cause mortality. The low certainty of evidence with the inconclusive results were the reasons why the panel voted against the use of this drug.
7	**We suggest against the use of regdanvimab as treatment of children with COVID-19 infection. (Low certainty of evidence; Weak recommendation)**	The recommendation is based on one pre-print study done on hospitalized adult patients that showed inconclusive results in terms of reducing risk for use of supplemental oxygen and requirement for rescue therapy. The low certainty of evidence with the inconclusive results were the reasons why the panel voted against the use of this drug.

**The risk factors are obesity, cardiovascular disease (including hypertension), chronic lung disease (including asthma), chronic metabolic disease (including diabetes), chronic kidney disease (including receipt of dialysis), chronic liver disease, and immunocompromised conditions.*

Ten randomized controlled trial (RCTs) evaluated the effect of monoclonal antibodies as treatment for patients with COVID-19. Five RCTs studied casirivimab-imdevimab (REGEN-CoV). Two RCTs studied bamlanivimab-etesevimab. Two RCTs studied sotrovimab, of which one RCT studied both sotrovimab and amubarvimab-romlusevimab. One RCT studied regdanvimab. In all of the RCTs, most of the population studied were adults. Three RCTs included children aged 12 years and above. The overall quality of evidence was very low because of indirectness and imprecision.

There was significantly decreased risk of COVID-19 related hospitalization, ER visit, mechanical ventilation, ICU admission or death for patients given intravenous casirivimab-imdevimab. There was significantly decreased risk of COVID-19 related hospitalization and death for non-hospitalized patients given bamlanivimab-etesevimab. There was significantly decreased risk of hospitalization and supplemental oxygen requirement for non-hospitalized COVID-19 patients given sotrovimab.

For the outcomes assessed, there was inconclusive evidence regarding the benefits of 1) subcutaneous casirivimab-imdevimab on asymptomatic COVID-19 patients, 2) sotrovimab on hospitalized COVID-19 patients, and 3) amubarvimab-romlusevimab and regdanvimab on COVID-19 patients.

Monoclonal antibody therapies were generally safe and well-tolerated by patients. However, the current evidence did not show specific results for children with COVID-19. Further studies are recommended to determine the efficacy of monoclonal antibodies as treatment for children with COVID-19.

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3.3 Prophylactic Interventions of COVID-19 in Children

3.3.1. Should vitamin D be used as a preventive measure for COVID-19 infection in children?

RECOMMENDATION

We suggest against the routine use of vitamin D for the prevention of COVID-19 infection in children. (Very low certainty of evidence, Weak recommendation)

Consensus Issues
Due to the uncertainty of the evidence as well as the cost and availability of the drug for the general population, the panel opted to vote against its use as an adjunctive treatment and preventive measure for COVID-19 in children. They also agreed that this recommendation is subject to change based on the availability of higher certainty of evidence. However, the panel strongly emphasized that vitamin D is necessary for those children with documented vitamin D deficiency.

Eight randomized controlled trials and one observational study, all done in the adult population, served as the evidence for treatment and prevention of COVID-19 in children, respectively. Indirect evidence from one observational study in adults suggests that vitamin D is not associated with reduced risk of SARS-CoV2 infection. Very low quality evidence from eight randomized controlled trials that compared vitamin D versus control in hospitalized adult patients with COVID-19 showed inconclusive results for the outcomes of mortality, ICU admission, need for mechanical ventilation, length of hospital stay, clinical improvement, and virologic clearance. The certainty of evidence was rated very low due to issues on risk of bias, indirectness, inconsistency and imprecision.

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3.3.2. Should vitamin C be used as a preventive measure for COVID-19 infection in children?

RECOMMENDATION

We suggest against the routine use of vitamin C for the prevention of COVID-19 infection in children. (Very low certainty of evidence, Weak recommendation)

Consensus Issues
This recommendation was made based on evidence from two adult observational studies. It revealed that vitamin C did not have significant benefit in preventing COVID-19 infection. Due to the uncertainty of the evidence, the panel opted to vote against the use of the drug specifically for the prevention of COVID-19. However, the panel agreed and strongly emphasized that when consumed within the proper dietary reference intake values, vitamin C is beneficial for the overall health of children. The panel also agreed that this recommendation is subject to change based on the availability of higher certainty of evidence.

We found no published studies done on the role of Vitamin C as preventive measure for COVID-19 in pediatric patients. Indirect evidence from two observational studies in adults showed no significant benefit in using Vitamin C for the prevention of COVID-19 infection. Overall certainty of evidence was very low.

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3.3.3. Should zinc be used as a preventive measure for COVID-19 infection in children?

RECOMMENDATION

We suggest against the routine use of zinc for the prevention of COVID-19 infection in children. (Low certainty of evidence, Weak recommendation)

Consensus Issues
This recommendation is based on the evidence from one randomized controlled trial in adults. The indirectness of the population and the intervention (zinc + vitamin C versus zinc alone) as well as the uncertainty of the evidence led the panel to vote against the use of zinc as a preventive measure for COVID-19 in children and the panel pointed out that this might change until higher certainty of evidence is available. The panel also agreed that the drug may be too costly for those from low- to mid-income families and availability may be an issue in far-flung areas. However, the panel concurred that zinc treatment is important for those with documented zinc deficiency.

We found no direct evidence on the use of zinc for the prevention of COVID-19 in pediatric patients. We found only one randomized controlled trial that enrolled adults, which revealed that compared to control, there was significant benefit of zinc for the outcomes of laboratory-confirmed SARS CoV2 infection (both seropositivity for antibody and positive RT-PCR at Day 42), acute respiratory symptoms, and symptoms of COVID-19. No hospitalization nor death was observed in all treatment arms.

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3.4 Adjunct Interventions for COVID-19 in Children

3.4.1. Should vitamin D be used as an adjunctive treatment for COVID-19 infection in children?

RECOMMENDATION

We suggest against the use of vitamin D as adjunctive treatment for COVID-19 infection in children. (Very low certainty of evidence, Weak recommendation)

Consensus Issues
Due to the uncertainty of the evidence as well as the cost and availability of the drug for the general population, the panel opted to vote against its use as an adjunctive treatment and preventive measure for COVID-19 in children. They also agreed that this recommendation is subject to change based on the availability of higher certainty of evidence. However, the panel strongly emphasized that vitamin D is necessary for those children with documented vitamin D deficiency.

Eight randomized controlled trials and one observational study, all done in the adult population, served as the evidence for treatment and prevention of COVID-19 in children, respectively. Indirect evidence from one observational study in adults suggests that vitamin D is not associated with reduced risk of SARS-CoV2 infection. Very low quality evidence from eight randomized controlled trials that compared vitamin D versus control in hospitalized adult patients with COVID-19 showed inconclusive results for the outcomes of mortality, ICU admission, need for mechanical ventilation, length of hospital stay, clinical improvement, and virologic clearance. The certainty of evidence was rated very low due to issues on risk of bias, indirectness, inconsistency and imprecision.

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3.4.2. Should vitamin C be used as an adjunctive treatment for COVID-19 infection in children?

RECOMMENDATION

We suggest against the use of vitamin C as adjunctive treatment for COVID-19 infection in children. (Very low certainty of evidence, Weak recommendation)

Consensus Issues
The recommendation was based on the evidence from eight (8) adult randomized controlled trials that showed no significant benefit and inconclusive results for length of hospital stay, length of ICU stay and need for mechanical ventilation. Although the panel deemed that the harm from the treatment was small, the benefits were uncertain when used as adjunctive treatment for COVID-19 infection. The uncertainty of the evidence coupled with the cost of the drug led the panel to vote against its use regardless of the route of administration. However, the panel agreed that vitamin C supplementation should still be given for those with low dietary vitamin C intake but not as a adjunctive treatment for COVID-19 infection. They also agreed that this recommendation is subject to change based on the availability of higher certainty of evidence.

We found no published studies on the role of Vitamin C as adjunct treatment in pediatric patients with COVID-19. Indirect evidence from eight (8) adult RCTs included in the Philippine COVID-19 Living Clinical Practice Guidelines [9] was reviewed. For the outcome of mortality, there was only a trend towards benefit with small negligible harm. There was no significant benefit and inconclusive results for length of hospital stay, length of ICU stay and need for mechanical ventilation. One study that used intravenous vitamin C reported no adverse events, while one that used oral preparation noted flushing, headache, vomiting and stomach pain. Overall certainty of evidence was very low because of indirectness, imprecision, and inconsistency.

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3.4.3. Should zinc be used as an adjunctive treatment for COVID-19 infection in children?

RECOMMENDATION

We suggest against the use of zinc as adjunctive treatment for COVID-19 infection in children.
(Low certainty of evidence, Weak recommendation)

Consensus Issues
The panel voted against the use of zinc as adjunctive treatment of COVID-19 in children based on the indirect evidence from six randomized controlled trials done in adults that showed inconclusive results in outcomes of in-hospital mortality, duration of recovery, length of hospital stay and hospitalization among ambulatory patients. The panel also agreed that there is a small to moderate potential for harm with moderate costs. However, the panel concurred that zinc treatment is important for those with documented zinc deficiency. They also agreed that this recommendation is subject to change until higher certainty of evidence is available.

Indirect evidence from 6 RCTs showed inconclusive results on the efficacy of zinc as adjunctive treatment, for the outcomes of in-hospital mortality, duration of recovery, length of hospital stay, and hospitalization among ambulatory patients. Adverse events were significantly higher in the group given zinc, and included local site irritation, metallic taste and GI intolerance.

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3.5 Non-Pharmacologic Interventions of COVID-19 in Children

3.5.1. What are the supportive strategies to optimize mental health among children during the COVID-19 pandemic?

RECOMMENDATION

We recommend the implementation of supportive strategies* to optimize mental health among children and adolescents during the COVID-19 pandemic. (Low certainty of evidence, Strong recommendation)

**Supportive strategies for mental health during the COVID-19 pandemic include psychological counseling, physical and leisure activities (outdoor and online exercise platforms, art and dance), mindfulness medication training, personal and spiritual coping, strengthening social support and connecting online with peers, and health-promoting activities.*

Consensus Issues
There were no consensus panel issues noted.

From the five randomized controlled trials (RCTs) included in this review, supportive strategies/interventions include psychological counseling, outdoor exercises, mindfulness meditation, utilization of online platforms for recreation, art and dance. There was a significantly lower mean level of anxiety in the intervention group across five studies. Two RCTs showed a significantly lower level of depression in the intervention group versus the comparator after instituting psychological counseling, outdoor exercise, and dance therapy. Psychological resilience and life satisfaction levels were shown to be higher in the intervention group after instituting psychological counseling and dance therapy. Mean levels of mindfulness were not significantly different between two types of art therapies (Mandala and emotion-based therapy) but levels were significantly higher post intervention. Overall well-being index is significantly higher in the intervention group after instituting aerobics exercises and mindfulness meditation.

Two qualitative studies elucidated possible effective coping strategies utilized in two countries, namely connecting online, engaging in leisure and health promoting activities, personal and spiritual coping and having social support from family, religious community and school personnel.

The over-all certainty of evidence was low. There was a decrease in anxiety and depression and increase in psychological resilience, life satisfaction, positive emotion score and overall well-being. No net harm was noted in the included RCTs based on the mean levels of measured outcomes after instituting the above interventions.

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3.5.2. What preventive interventions should be used in school settings to reduce transmission of COVID-19?

RECOMMENDATION

We recommend a multi-layer approach using multiple non-pharmacologic interventions* in school settings to limit transmission of COVID-19 in schools. (Very low certainty of evidence, Strong recommendation)

The non-pharmacologic interventions are wearing of masks of students, physical distancing, engineering controls (ventilation, personal hygiene and handwashing, disinfection of surfaces), administrative controls (blended learning, phased reopening, no/reduced mixing of classes, restriction of class size, minimized or staggered breaks, symptom monitoring, self-quarantine, contact tracing, and early testing).

Consensus Issues
The recommendation is based on 17 studies done in first-world countries during the earlier phase of the pandemic. Although the evidence was judged to be very low due to issues on indirectness and risk of bias (descriptive), the consensus panel was unanimous in deciding that the burden of the problem and the equity of the issue deserved a strong recommendation for the use of multi-layer approach coupled with multiple NPIs. The specific NPIs noted above were voted on individually by the consensus panel members and only those that reached a vote of at least 75% were included. The panel noted that these NPIs were the minimum preventive measures for schools to open considering the equity, accessibility and feasibility of the interventions. Despite the low to moderate certainty of evidence favoring the HEPA filters and carbon dioxide monitors respectively, these NPIs did not reach consensus vote due to issues on cost and accessibility especially for public schools in more rural areas. However, the panel noted that these devices are indirect ways to ensure that there is adequate air exchange in enclosed spaces.

Conducted in several countries, 16 cross-sectional and 1 intervention studies on the impact of school re-opening on transmission of COVID-19 were included in this review. All countries put in place multiple-layered prevention strategies–- from community to school to classroom to individual level. Multiple preventive measures were instituted in all the schools with the minimum health protocols of masking, personal hygiene and physical distancing mentioned as NPIs in only 7 studies, which were done in 4 countries (including 2 US counties). Variable combinations of NPIs were used.

Outcomes measured also varied among countries with all studies showing a decrease in transmission in terms of number of cases, transmission rates, number of outbreaks per week, number of cases per outbreak, attack rate, incidence and/or prevalence rates. Two studies found low transmission even in a setting of high community incidence. One study reported a major outbreak due to a breach in the NPI protocols.

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CHAPTER 4: DISCUSSION

4.1 Outputs of the Philippine Pediatric COVID-19 Living CPG Project

Clinical Practice Questions

COVID-19 management issues and questions were collected from the different subspecialty societies of the PPS, the Steering Committee members and Consensus Panelists during the organizational meetings and consensus panel meetings. The topics were reviewed and prioritized. Priority topics were then assigned to the evidence reviewers for evidence reviews. A total of 15 priority topics were identified.

Consensus Meetings, Evidence Summaries, and Recommendations

For the first phase of this project, there were a total of 15 evidence summaries presented and 24 recommendations generated during the consensus panel presentations.

4.2 Applicability Issues

The members of the Consensus Panel provided information on the facilitators, barriers, and resource implications for the implementation of the recommendations. They used their expertise and experience to identify these issues, which were discussed in more detail in the *Consensus Issues* section of each evidence summary. These were considered in the final wording of the recommendations. The following subsections summarize the overall discussion of the panelists.

Organizational Considerations to Implementation

The availability of testing kits and medical equipment for the screening and diagnostic tests for COVID-19 would likely vary at the regional, provincial, or even municipal/city level. These issues were especially relevant to RT-PCR testing, rapid antibody, and antigen testing, chest imaging (X-ray, CT-Scan, and ultrasound), and laboratory parameters (LDH, CRP, Ferritin, D-dimer). Clinical risk assessment and using the 14-day symptom test were useful tools for screening for COVID-19, especially if there was a limitation in the availability of screening tests. Specially trained personnel were needed to do the more specialized tests, such as pooled testing using RT-PCR.

Aside from the availability of various testing modalities, there would be some limitations in the availability of treatment and critical care interventions also, most especially those investigational drugs only being accessible through the public via FDA's emergency use authorization. Medical specialists, especially those from infectious diseases, pulmonary medicine, and critical care medicine, were important to effectively lead in the use of these treatments for the management of COVID-19 patients. These limitations would be further compounded by the limitations in available isolation beds, hospital ward beds, and ICU beds.

For non-pharmacologic and prophylactic interventions for COVID-19, one potentially major barrier was the public's perceptions of these interventions and their actual compliance. This was evident in many instances of violations of the minimum public health standards set by DOH: wearing of face mask, physical distancing, and hand hygiene. In addition to these, there were rising trends in the use of non-proven prophylactic interventions and ineffective medical devices (such as ionizing air filters).

Resource Implications

As a low-middle-income country, our limited resources needed to be allocated and used efficiently. The cost of the tests and interventions being done for COVID-19 management was one important consideration discussed in the panel meetings, especially the investigational drugs (such as remdesivir, tocilizumab and the monoclonal antibodies). Health technology assessment should be a key gatekeeping mechanism to ensure that all payments by the government (through PhilHealth) are cost-effective.

4.3 Monitoring

The recommendations and evidence summaries of the Philippine Pediatric COVID-19 Living Clinical Practice Guidelines were published on the PSMID website last April 4, 2022, in order to maintain a single repository of all local clinical recommendations on COVID-19, both for the adult and pediatric populations. Since the addition of the pediatric recommendations, there were 92,952 views.

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CHAPTER 5: RESEARCH IMPLICATIONS

The novel coronavirus, now known as SARS-CoV-2, brought about a disease condition that is new to everyone. Despite the rapidly evolving evidence on COVID-19, many research gaps need to be filled in the management, prevention, and control of this disease. These were identified during the evidence reviews done in this CPG and were documented in the evidence summaries. The following discussion presents a synthesis of these research gaps.

As expected in a novel disease condition, many of the recommendations were answered with low to very low certainty of evidence. This emphasized the need for further primary research to be conducted.

While existing studies on investigational treatment interventions identified the subset of patients that would benefit best (such as tocilizumab with dexamethasone for patients with elevated inflammatory biomarkers), many of these studies were performed on adult patients. Studies on treatment for pediatric patients were sorely lacking especially when it comes to dosing frequency of administration, combinations with other drugs, etc.

Diagnosis and treatment were sometimes overemphasized in the management of COVID-19. Equally important were the prophylactic and non-pharmacologic interventions that are more proximal steps in the national strategy of prevention, detection, isolation, treatment, and reintegration. However, these areas were still not very much studied. These studies were also crucial to prove the lack of effectiveness of interventions that many may subscribe to.

Finally, the living CPG methodology used in this project was the second local adoption known to the project team, the first being the Philippine COVID-19 Living CPG for adults. Research into streamlining the living CPG process is important to make it more efficient. The impact measurement of this living CPG, as described in the *Guideline Monitoring and Evaluation Criteria* subsection, would be another study to formally demonstrate the effects of CPG implementation in the country.

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CHAPTER 6: CONCLUSIONS

The Philippine Pediatric COVID-19 Living CPG identified 15 priority questions on COVID-19 management, infection prevention, and control, generated 15 evidence summaries, and came up with 24 recommendations. Thematic areas included in this CPG were screening and diagnosis, treatment, prophylactic interventions, adjunct interventions and non-pharmacologic interventions.

The main challenges in doing a living CPG for a new disease condition in a pandemic setting were the rapidly evolving evidence and the need to come out with point in time recommendations for clinicians and policymakers. Consensus panels needed to balance the quality and totality of the evidence with the net benefit and the contextual factors related to the implementation of the interventions, i.e., cost, equity, acceptability, and feasibility.

Flexibility and adaptability are key in developing a Living CPG, especially in the context of the pandemic. Given this project experience, we recommend the following for the succeeding updating of the Philippine Pediatric COVID-19 Living CPG:

1. Retain consensus panel members who wish to continue contributing their time and expertise to the COVID-19 Living CPG.
2. Continue holding capacity building workshops on CPG development, systematic reviews, and evidence-based medicine to increase the pool of skilled evidence reviewers.
3. As much as possible, allow a longer project cycle for both the implementation of the Living CPG development and capacity building activities. This will ensure that adequate preparation is done by the task forces and consensus panelists prior to the *en banc* meeting.

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CLINICAL PRACTICE GUIDELINES

2021 CLINICAL PRACTICE GUIDELINES IN THE EVALUATION AND MANAGEMENT OF PEDIATRIC COMMUNITY-ACQUIRED PNEUMONIA

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These guidelines are intended for use by health care providers responsible for the management of immunocompetent infants and children aged 3 months to 18 years with uncomplicated community-acquired pneumonia in both ambulatory and hospital settings.

The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

PREFACE

The Clinical Practice Guidelines (CPG) for the Diagnosis and Management of Pediatric Community-Acquired Pneumonia (PCAP) was initiated by the Philippine Academy of Pediatric Pulmonologists, Inc. (PAPP) and the Pediatric Infectious Disease Society of the Philippines (PIDSP), in cooperation with Philippine Pediatric Society, Inc. (PPS) way back in 2004. Several CPG updates were then undertaken by the PAPP PCAP CPG Task Force from 2008 to 2016. Clinically-relevant research questions were answered with recent and current recommendations based on evidence from local and international data.

The 2021 PCAP CPG initiative was envisioned in March 2018 upon the recommendations of the 2018 PAPP Board for the purpose of updating the evidence in the PCAP CPG 2016 clinical questions. This led to the collaboration of PAPP and PIDSP to develop this CPG. Individual members were identified from each society as content experts to form the Steering Committee along with a clinical epidemiologist and technical writer as review experts. The committee identified the scope and target end user of the CPG as well as additional clinical questions to be included in the 2021 update aside from the questions on the previous CPGs. Selected members from the two societies formed the Technical Working Group (TWG) who did the literature search, appraisal of evidences, and formulation of recommendations. These recommendations were then presented to the stakeholders who became part of the consensus panel. There was no identified conflict of interest among the CPG developers, TWG members and stakeholders. A survey to determine potential competing interests were conducted during the development of this CPG. This initiative was fully funded by the PAPP and PIDSP societies.

The 2021 PCAP CPG significantly differs from the previous CPGs in several aspects. First, the current guideline is a consensus between two pediatric societies. Second, much of the literature review has been centered on meta-analyses or systematic reviews instead of individual studies. Finally, appraisal of published literature was based on Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria. Such methodological differences may provide difficulties in defining evolution of care through the years.

As identified in the previous CPG updates, there is lack of local data hence most of the evidences gathered came from international studies. The applicability of such data to the local setting needs to be critically assessed for its value and relevance. Corollary to this, several gaps in knowledge are identified and these may serve as a guide for future research.

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SUMMARY OF RECOMMENDATIONS

	CLINICAL QUESTIONS	RECOMMENDATIONS
1.	Among infants and children aged 3 months to 18 years, what clinical signs and symptoms will accurately diagnose community-acquired pneumonia?	Pediatric community-acquired pneumonia (PCAP) is considered in a patient who presents with cough or fever, PLUS any of the following positive predictors of radiographically-confirmed pneumonia: *(Conditional recommendation, very low-grade evidence)* (1) Tachypnea 3 months to 12 months old: ≥50 breaths per minute >1 year old to 5 years old: ≥40 breaths per minute >5 years to 12 years old: ≥30 breaths per minute >12 years old: ≥20 breaths per minute (2) Retractions or chest indrawing (3) Nasal flaring (4) O2 saturation <95% at room air (5) Grunting
2.	Among infants and children 3 months to 18 years with community-acquired pneumonia, what clinical and ancillary parameters will determine the need for admission?	Patients classified as having severe PCAP or high-risk for pneumonia-related mortality based on the clinical parameters and/or ancillary features are considered for admission. *(Conditional Recommendation, moderate to low-grade evidence)* See Page 135
3.	Among infants and children aged 3 months to 18 years, what diagnostic aids will confirm the presence of non-severe community-acquired pneumonia in an ambulatory setting?	Routine diagnostic aids are NOT considered for non-severe PCAP in an ambulatory setting. *(Conditional recommendation, Expert opinion)*
4.	Among infants and children aged 3 months to 18 years, what diagnostic aids will confirm the presence of severe community-acquired pneumonia in a hospital setting?	(1) Chest X-ray is strongly recommended as an initial diagnostic aid for patients classified as having severe PCAP. *(Strong recommendation, high-grade evidence)* (2) Point-of-care chest ultrasonography (POCUS) performed by a skilled expert is strongly recommended as a diagnostic aid for patients classified as having severe PCAP. *(Strong recommendation, high-grade evidence)* (3) Procalcitonin (PCT) is recommended to be used in conjunction with other factors such as clinical presentation, imaging modalities and other laboratory aids in diagnosing bacterial PCAP. (Conditional recommendation, moderate-grade evidence) (4) Sputum Gram stain and culture are not considered to be done routinely in patients classified as having severe PCAP. *(Conditional recommendation, low-grade evidence)* (5) Complete blood count, arterial blood gas, serum electrolytes and other diagnostic aids are considered to be used as necessary based on the clinician's evaluation. *(Conditional recommendation, Expert opinion)*

	CLINICAL QUESTIONS	RECOMMENDATIONS
5.	Among infants and children aged 3 months to 18 years with community-acquired pneumonia, what clinical and ancillary parameters will determine the need for antibiotic treatment?	Empiric antibiotic therapy is considered to be started in patients with clinical signs and symptoms of PCAP with ANY of the following parameters suggestive of bacterial etiology for both non-severe and severe pneumonia: *(Conditional recommendation, low-grade evidence)* (1) Elevated white blood cell count (WBC) (2) Elevated C-reactive protein (CRP) (3) Elevated procalcitonin (PCT) (4) Imaging findings such as: (5) Alveolar infiltrates in chest radiograph; or (6) Unilateral, solitary lung consolidation and/or air bronchograms and/or pleural effusion in lung ultrasound
6.	A. Among infants and children aged 3 months to 18 years with community-acquired pneumonia, what empiric treatment is effective if a bacterial etiology is considered?	(1) For patients classified as having non-severe PCAP, regardless of immunization status against *Streptococcus pneumoniae* and/or *Haemophilus influenzae type b* (Hib), any of the following is considered: (1.1) start Amoxicillin trihydrate at 40-50mg/kg/day Q8 for 7 days OR at 80-90mg/kg/day Q12 for 5 to 7days. (1.2) start Amoxicillin-clavulanate at 80-90mg/kg/day Q12 (based on Amoxicillin content using a 14:1 amoxicillin:clavulanate formulation) for 5 to 7 days OR Cefuroxime at 20-30mg/kg/day Q12 for 7 days in settings with documented high-level penicillin-resistant pneumococci or beta-lactamase-producing H. influenzae based on local resistance data or hospital antibiogram. *(Conditional recommendation, low-grade evidence)* (2) For patients classified as having severe PCAP, regardless of immunization status against *Streptococcus pneumoniae*, any of the following is considered: (2.1) start Penicillin G at 200,000 units/kg/day Q6 if with complete Haemophilus influenzae type b (Hib) vaccination OR Ampicillin at 200mg/kg/day Q6 if with no or incomplete or unknown Haemophilus influenzae type b (Hib) vaccination (2.2) start Cefuroxime at 100-150mg/kg/day Q8 OR Ceftriaxone at 75-100mg/kg/day Q12 to Q24 OR Ampicillin-sulbactam at 200mg/kg/day Q6 (based on ampicillin content) in settings with documented high-level penicillin-resistant pneumococci or beta-lactamase-producing H. influenzae based on local resistance data or hospital antibiogram (2.3) add Clindamycin at 20-40mg/kg/day Q6 to Q8 when *Staphylococcal* pneumonia is highly suspected based on clinical and chest radiograph features. However, in cases of severe and life-threatening conditions such as sepsis and shock, Vancomycin at 40-60 mg/kg/day Q6 to Q8 is preferred. *(Conditional recommendation, low-grade evidence)*

	CLINICAL QUESTIONS	RECOMMENDATIONS
		(3) For patients with known hypersensitivity to penicillin, classified as (3.1) Non-type 1 hypersensitivity to Penicillin, cephalosporins such as Cefuroxime PO 20-30mg/kg/day Q12 or IV 100-150mg/kg/day Q8 OR Ceftriaxone at 75-100mg/kg/day Q12 to Q24 is considered. (3.2) Type 1 hypersensitivity to Penicillin (immediate, anaphylactic-type), any of the following is considered: (3.2.1) Azithromycin at 10mg/kg/day PO or IV Q24 for 3 days OR 10mg/kg/day on day 1 followed by 5 mg/kg/day Q24 for days 2 to 5 (3.2.2) Clarithromycin at 15mg/kg/day Q12 for 7 days (3.2.3) Clindamycin at 10-40mg/kg/day PO or 20-40mg/kg/day IV Q6 to Q8 for 7 days *(Conditional recommendation, low-grade evidence)* (4) When an atypical pathogen is highly suspected, starting a macrolide is considered as follows: (4.1) Azithromycin at 10mg/kg/day PO or IV Q24 for 5 days, particularly in infants less than 6 months old whom pertussis is entertained, OR 10mg/kg/day Q24 for 3-5 days OR 10mg/kg/day on day 1 followed by 5 mg/kg/day Q24 for days 2 to 5 (4.2) Clarithromycin at 15mg/kg/day Q12 for 7 to 14 days *(Conditional recommendation, low-grade evidence)* (5) When a specific pathogen is identified, modifying the empiric treatment based on the antibiotic susceptibility pattern and/or the drug of choice is recommended. *(Strong recommendation, high-grade evidence)* (6) When treating for uncomplicated bacterial PCAP, 7 to 10 days treatment is considered but a longer duration may be required depending on the patient's clinical response, virulence of the causative organism and eventual development of complications. *(Conditional recommendation, low-grade evidence)*
6.	B. Among infants and children aged 3 months to 18 years with bacterial community-acquired pneumonia, will the addition of a macrolide to standard empiric regimen improve treatment outcome?	The addition of a macrolide to standard beta-lactam antibiotic therapy is not considered in the empiric treatment of bacterial PCAP. *(Conditional recommendation, very low-grade evidence)*
7.	Among infants and children aged 3 months to 18 years with community-acquired pneumonia, what treatment is effective if a viral etiology is considered?	Oseltamivir is strongly recommended to be started immediately within 36 hours of laboratory-confirmed influenza infection. *(Strong recommendation, high-grade evidence)*
8.	Among infants and children aged 3 months to 18 years with community-acquired pneumonia, what clinical and ancillary parameters will determine a good response to current therapeutic management?	(1) For patients classified as having non-severe PCAP, good clinical response to current therapeutic management is considered when clinical stability is sustained for the immediate past 24 hours as evidenced by improvement of cough or normalization of core body temperature in Celsius in the absence of antipyretics within 24-72 hours after initiation of treatment. *(Conditional recommendation, very low-grade evidence)*

	CLINICAL QUESTIONS	RECOMMENDATIONS
		(2) For patients classified as having severe PCAP, good clinical response to current therapeutic management is considered when clinical stability is sustained for the immediate past 24 hours as evidenced by ANY ONE of the following physiologic and ancillary parameters observed within 24-72 hours after initiation of treatment: (2.1) Absence or Resolution of hypoxia (2.2) Absence or Resolution of danger signs (2.3) Absence or Resolution of tachypnea[1] (2.4) Absence or Resolution of fever[2] (2.5) Absence or Resolution of tachycardia[3] (2.6) Resolving or Improving radiologic pneumonia (2.7) Resolving or Absent chest ultrasound findings (2.8) Normal or Decreasing CRP (2.9) Normal or Decreasing PCT *(Conditional recommendation, very low-grade evidence)*
9.	Among infants and children aged 3 months to 18 years with community-acquired pneumonia, what can be done if the patient is not responding to current therapeutic management?	(1) For patients classified as having non-severe PCAP and are not improving or clinically worsening within 24-72 hours after initiating therapeutic management, diagnostic evaluation is considered to determine if any of the following is present: *(Conditional recommendation, low-grade evidence)* (1.1) Coexisting or other etiologic agents (1.2) Etiologic agent resistant to current antibiotic, if being given (1.3) Other diagnosis (1.3.1) Pneumonia-related complication (1.3.1.1) Pleural effusion (1.3.1.2) Necrotizing pneumonia (1.3.1.3) Lung abscess (1.3.2) Asthma (1.3.3) Pulmonary tuberculosis (2) For patients as having non-severe PCAP and are not improving or clinically worsening within 24-72 hours after initiating a therapeutic management, (2.1) and started on standard dose Amoxicillin at 40-50mg/kg/day, increasing the dose to 80-90mg/kg/day Q12 OR shifting to Amoxicillin-Clavulanate at 80-90mg/kg/day (based on Amoxicillin content using a 14:1 amoxicillin:clavulanate formulation) Q12 OR Cefuroxime at 20-30 mg/kg/day Q12 is considered. (2.2) and started on high-dose Amoxicillin, Amoxicillin-Clavulanate or Cefuroxime, admitting the patient for parenteral antibiotics is considered. (2.3) adding a macrolide is considered when an atypical pathogen is highly suspected: (2.3.1) Azithromycin at 10mg/kg/day PO or IV Q24 for 5 days, particularly in infants less than 6 months old whom pertussis is entertained, OR 10mg/kg/day Q24 for 3-5 days OR 10mg/kg/day on day 1 followed by 5 mg/kg/day Q24 for days 2 to 5 (2.3.2) Clarithromycin at 15mg/kg/day Q12 for 7 to 14 days *(Conditional recommendation, low-grade evidence)*

[1] Respiratory rate taken at full minute based on the WHO-defined, age-specific values for tachypnea.

[2] Fever is defined as having a core body temperature of 38 degrees Celsius and above

[3] Cardiac rate taken at full minute based on Pediatric Advanced Life Support age-based values for tachycardia

	CLINICAL QUESTIONS	RECOMMENDATIONS
		(3) For patients classified as having severe PCAP and are not improving or clinically worsening, within 24-72 hours after initiating a therapeutic management, diagnostic evaluation is considered to determine if any of the following is present: (3.1) Coexisting or other etiologic agents (3.2) Etiologic agent resistant to current antibiotic, if being given (3.3) Other diagnosis (3.3.1) Pneumonia-related complication (3.3.1.1) Pleural effusion (3.3.1.2) Pneumothorax (3.3.1.3) Necrotizing pneumonia (3.3.1.4) Lung abscess (3.3.2) Asthma (3.3.3) Pulmonary tuberculosis (3.3.4) Sepsis *(Conditional recommendation, Expert opinion)* (4) The following diagnostic evaluations are considered in the presence of treatment failure in severe PCAP: (4.1) Cultures (4.2) Nucleic acid amplification test (e.g. PCR) (4.3) Serology (4.4) Imaging modalities: (chest radiography, UTZ or CT scan) (4.5) Biomarkers (e.g. CBC, CRP, PCT) *(Conditional recommendation, Expert opinion)* (5) For patients that are not improving or clinically worsening within 24-72 hours after initiating a therapeutic management, a referral to a specialist is considered. *(Conditional recommendation, Expert opinion)*
10.	Among infants and children aged 3 months to 18 years, what clinical parameters will determine that switch therapy can be considered in the management of severe community-acquired pneumonia?	Switch therapy is considered among patients with bacterial PCAP when **ALL** of the following clinical parameters are present: (1) Current parenteral antibiotic has been given for at least 24 hours (2) Afebrile for at least 8 hours without the use of any antipyretic drug (3) Able to feed and without vomiting or diarrhoea (4) Presence of clinical improvement as defined by **ALL** of the following: (4.1) Absence of hypoxia (4.2) Absence of danger signs (4.3) Absence of tachypnoea (4.4) Absence of fever (4.5) Absence of tachycardia *(Conditional recommendation, low-grade evidence)*
11.	Among infants and children aged 3 months to 18 years, what adjunctive treatment is effective for community-acquired pneumonia?	(1) Vitamins A is strongly recommended as adjunctive treatment for measles pneumonia. *(Strong recommendation, high-grade evidence)* (2) Zinc is not considered as adjunctive treatment for severe PCAP as it does not have any effect in shortening recovery time. *(Conditional recommendation, low-grade evidence)* (3) Vitamin D is not considered as adjunctive treatment for severe PCAP as it does not reduce the length of hospital stay. *(Conditional recommendation, low-grade evidence)*

	CLINICAL QUESTIONS	RECOMMENDATIONS
		(4) Bronchodilators are considered as adjunctive treatment for PCAP in the presence of wheezing. *(Conditional recommendation, expert opinion)* (5) Mucokinetic, secretolytic, and mucolytic agents are not considered as adjunctive treatment for PCAP. *(Conditional recommendation, low-grade evidence)* (6) There is insufficient evidence to recommend the use of the following as adjunctive treatment for PCAP: *(Very low-grade evidence)* (6.1) Oral folate (6.2) Probiotics (6.3) Vitamin C (6.4) Virgin coconut oil (VCO) (6.5) Nebulization with saline solution (6.6) Steam inhalation
12.	Among infants and children aged 3 months to 3 years, what interventions are effective for the prevention of community-acquired pneumonia?	(1) The following strategies are recommended to prevent PCAP: (1.1) Vaccination against Streptococcus pneumoniae (pneumococcus), Haemophilus influenzae type b (Hib), Bordetella pertussis (pertussis), Rubeola virus (measles) and Influenza virus *(Strong recommendation; high-grade evidence)* (1.2) Breastfeeding *(Strong recommendation; high-grade evidence)* (1.3) Avoidance of environmental tobacco smoke or indoor biomass fuel exposure *(Strong recommendation; high-grade evidence)* (1.4) Zinc supplementation *(Strong recommendation; moderate-grade evidence)* (2) There is insufficient evidence to recommend Vitamin A, C or D supplementation for the prevention of PCAP. *(Very low-grade evidence)*

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GUIDELINE DEVELOPMENT

Lead CPG Developers

The lead CPG developer is formed by key members from the Philippine Academy of Pediatric Pulmonologists and the Pediatric Infectious Disease Society of the Philippines. Together with two evidence review experts, they identified the scope and the target end user of the CPG, coordinated meetings during the development of the CPG, and relevant stakeholders who will be part of the consensus panel.

A Technical Working Group composed of PAPP and PIDSP members is likewise formed to conduct literature search, appraisal of evidence, and formulation of recommendations. This organized PCAP CPG team is identified as the 2021 PAPP/PIDSP Joint Task Force on PCAP in this manuscript.

Scope, Objectives, and Target Users of the Clinical Practice Guidelines

The 2021 Clinical Practice Guidelines in the Evaluation and Management of Pediatric Community- Acquired Pneumonia (2021 PCAP CPG) is focused on the recognition of clinical features, appropriate and practical diagnostic procedures, effective therapeutic management and preventive measures in an immunocompetent infant and children aged 3 months to 18 years with uncomplicated community-acquired pneumonia. This does not cover topics on coronavirus disease 2019 (COVID-19) pneumonia as well as recurrent, persistent, complicated, aspiration, and health care-associated pneumonia. Moreover, differentiating the three broad categories namely bacterial, viral and atypical pathogens in terms of their peculiar management approaches were not tackled. Treatment options were directed to the most common causative agents for PCAP but are not organism-specific and did not include pathogens such as *Mycobacterium tuberculosis*, fungi, and viruses other than the Influenza virus. These guidelines are intended for use by health care providers responsible for the management of PCAP in both ambulatory and hospital settings. This CPG is envisioned to guide the clinician and should not supersede sound clinical judgement in the overall care of pediatric patients with community-acquired pneumonia.

Clinical questions pertaining to evaluation, treatment and prevention

The lead CPG developers updated the recommendations to answer the clinical questions formulated in the first Clinical Practice Guideline in the Evaluation and Management of Pediatric Community-acquired Pneumonia (2004) created by the joint efforts of PPS, PIDSP, and PAPP. The clinical questions in 2004 were identified through consensus meetings among the lead CPG developers then and were based on a prospective study on the knowledge, attitude, and practice of pediatricians, family physicians, and general practitioners in the Philippines. The 2008, 2012 and 2016 CPG updates used the same clinical questions.

Literature search, and inclusion and appraisal of evidence

The literature search, and inclusion and appraisal of evidence was made in line with DOH and PhilHealth's Manual for Clinical Practice Guideline Development (2018). Members of the TWG assigned in each clinical question were tasked to search the literature. Local researches submitted to the Philippine Pediatric Society (PPS) and published on the Abstracts of Philippine Pediatric Researches 2012-2015, Philippine Academy of Pediatric Pulmonologists (PAPP), and Pediatric Infectious Disease Society of the Philippines (PIDSP) Journal, Health Research and Development Information Network (HERDIN); and international publications identified using the systematic literature search of PubMed, Cochrane Library, and Google Scholar databases were searched and limited to the following: [1] Existing CPGs, meta-analyses or systematic reviews (individual studies were considered in the absence of the aforementioned study types); [2] source of data from January 1, 2016 to April 31, 2021; [3] 3 months to 18 years of age; and [4] immunocompetent host. Search terms were structured based on the PICO format of each clinical question. Bibliography search within the initially selected articles was also done to expand literature search.

Based on the Manual for Clinical Practice Guideline Development 2018, existing and published CPGs, systematic reviews and meta-analyses can be used as references to answer the PICO questions. In this case, an existing systematic review is

evaluated to determine if it can be used instead of performing a de novo systematic review. Titles and abstracts were screened and those that met the inclusion criteria for each clinical question were retrieved as full-text.

Quality Assessment using GRADE Approach

STUDY DESIGN	QUALITY OF EVIDENCE	DOWNGRADE IN PRESENCE OF	UPGRADE IN PRESENCE OF
Randomized trial	High	**Risk of bias** (-1) Serious (-2) Very serious **Inconsistency** (-1) Serious (-2) Very serious **Indirectness** (-1) Serious (-2) Very serious **Imprecision** (-1) Serious (-2) Very serious **Publication bias** (-1) Serious (-2) Very serious	**Large effect** (+1) Large, no plausible confounders, consistent and direct evidence (+2) Very large, no major threats to validity and direct evidence **Dose response** (+1) Evidence of a gradient **All plausible confounding** (+1) Would reduce a demonstrated effect (+1) Would suggest a spurious effect when results show no effect
	Moderate		
Observational study	Low		
	Very low		

Source: Guyatt G et al. GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. [Adapted Journal of Clinical Epidemiology 64 (2011) 383-394] as cited in the DOH and PhilHealth Manual for CPG Development (2018).

Appraisal of evidence and interpretation of results were done in line with DOH and PhilHealth guidelines. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used in assessing the quality of evidence and strength of recommendations. GRADE was developed by an international panel that considered clinical questions on diagnosis, screening, prevention and therapy, and assessing them based on potential sources of bias.

For existing Clinical Practice Guidelines, the International Appraisal of Guidelines, Research and Evaluation version 2009 (AGREE II) was used. This is also an internationally-recognized assessment tool endorsed by DOH. This tool consists of the following dimensions: Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity of Presentation, Applicability, Editorial Independence, and Overall Guideline Assessment.

Reporting of results of studies in the Summary of Evidence

The results of studies as reported in the Summary of Evidence are summarized to include study design, clinically important end points, and effect measures.

Grade recommendation with description of level of evidence

The 2021 PCAP CPG adopted the following recommendation statement as supported by corresponding levels of evidence:

GRADE	Strength of recommendation	Recommendation Statement	Description of evidence
High	Strong	Should [or should not] be recommended OR Strongly [or strongly not] recommended	Evidence based on an existing high-quality CPG, meta-analysis, or systematic review.
Moderate	Can be strong or conditional	Is [or is not] recommended	Evidence based on an existing moderate quality CPG, meta-analysis, systematic review, or individual studies with definite evidence.
Low or Very Low	Conditional	Is [or is not] suggested/ considered	Evidence based on an existing low-quality CPG, meta-analysis, systematic review, or individual studies with equivocal evidence.
No evidence	Conditional	Expert opinion	The recommendation was based on a consensus among members of the 2021 PAPP/PCAP Joint Task Force on PCAP.

Development of recommendations also accounted for facilitators and barriers to implementation. These include the presence or lack of training and/or access to resources to follow the recommendation. A limitation, however, in the development of recommendations is the lack of economic evaluation of the health interventions mentioned and so the costs of interventions as potential barrier were not presented.

Stakeholder's consultation

Results of questionnaire surveys on PCAP among participants of the PAPP Annual Convention from 2016-2019 were reviewed and considered in this 2021 CPG. In addition, a preliminary draft was sent to selected stakeholders for individual evaluation as to clarity, acceptability, and applicability of the CPG. The preliminary draft was also presented to them by the lead CPG developers through an online teleconference where each stakeholder was given the opportunity to ask clarifications and give comments. Potential facilitators and barriers for the CPG pursual were brought up during the stakeholder's consultation and these were considered when the finalizing the CPG. Opinions expressed by the individual stakeholder did not necessarily reflect the medical society or institution he/she is affiliated with.

The following stakeholders were engaged during the development of this CPG:

1. CLEMENCIA BONDOC M.D. - Association of Municipal Health Officers of the Philippines (AMHOP)
2. ZASHKA ALEXIS GOMEZ, M.D. – DOH - Disease Prevention and Control Bureau (DOH-DPCB)
3. RAZEL NIKKA HAO, M.D.- DOH - Disease Prevention and Control Bureau (DOH-DPCB)
4. JAN DEREK JUNIO, M.D.- DOH - Disease Prevention and Control Bureau (DOH-DPCB)
5. MR. PHILIP BUGAYONG – DOH - National Reference Laboratories (DOH-RITM-NRL) for Microbiology and Virology
6. MAYAN LUMANDAS, M.D. – DOH - National Reference Laboratories (DOH-RITM-NRL) for Microbiology and Virology
7. FERDINAND DE GUZMAN, M.D. - Philippine Academy of Family Physicians (PAFP)
8. RACQUEL LOPEZ, M.D. - Philippine Academy of Family Physicians (PAFP)
9. ENDRIK SY, M.D. - Philippine Academy of Family Physicians (PAFP)
10. DORIS LOUISE OBRA, M.D. - Philippine Academy of Pediatric Pulmonologists (PAPP)
11. RITA MARIE LOURDES VERGARA, M.D. - Philippine Academy of Pediatric Pulmonologists (PAPP)
12. RODOLFO PAGCATIPUNAN, JR., M.D. - Philippine College of Chest Physicians (PCCP)
13. RICHARD HENRY SANTOS, M.D. - Philippine College of Emergency Medicine
14. PATRICK JOSEPH TIGLAO, M.D. - Philippine College of Emergency Medicine

15. MS. CHARISSE BANAAG – Philippine Health Insurance Corporation (PhilHealth)
16. MERCY JEANE UY-ARAGON, M.D. - Pediatric Infectious Disease Society of the Philippines (PIDSP)
17. BELLE RANILE, M.D. - Pediatric Infectious Disease Society of the Philippines (PIDSP)
18. MARGARITA LUISA ALFONSO, M.D. - Philippine Pediatric Society (PPS)
19. EDNA SARAH MORADA, M.D. - Philippine Pediatric Society (PPS)
20. MICHELLE ANNE MANGUBAT, M.D. - Philippine Society of Adolescent Medicine Specialists (PSAMS)
21. OLIVIA CAMILLE REYES, M.D. - Philippine Society of Pediatric Emergency Medicine
22. MA. VICTORIA RIBAYA, MD. - Philippine Society of Pediatric Emergency Medicine
23. ROBERTO PADUA, JR. M.D. - Philippine Society of Pathologists (PSP)
24. MIRIAN VITERBO, M.D. - Philippine Society of Pathologists (PSP)
25. NATHAN DAVID CONCEPCION, M.D. - Philippine Society of Pediatric Radiology
26. JOANNA CHOA-GO, M.D. - Philippine Society of Pediatric Radiology
27. LEONILA DANS, M.D. – Professor, University of the Philippines, Manila

Formulation of the final draft

At least three-fourths of the members of the PAPP and PIDSP lead CPG developers met through teleconferencing and voted to reach consensus for each recommendation. Consensus was defined as more than 75% of the participating members. Stakeholders made up the consensus panel during the finalization of the recommendations and consensus was defined as at least 75% agreement among the members (one organization is equivalent to one participation). As a contingent plan if a consensus is not reached in a clinical question, the members who disagree can present new evidence or perspectives to the lead CPG developers and concur again in a consensus panel meeting through teleconference. A survey will then be done to determine if a consensus can be made. If still a consensus regarding a clinical question is not attained despite the discussions, it will then be declared as undecided. However, for this CPG there was a consensus from the participating members in all the recommendations presented. The final draft was presented to the 2020-2021 PAPP and PIDSP Board Members for approval and official endorsement then forwarded to the stakeholders.

Dissemination and Monitoring Plan

Copies of the 2021 PCAP CPG will be distributed to PAPP, PIDSP, and PPS training institutions, posted on their official websites, and stakeholders' websites. Survey forms will be disseminated during the annual conventions of the PAPP and PIDSP to assess compliance and applicability of the formulated guidelines. This will be done annually for the next 3 years in time for the next CPG update in 2024. Assessing the knowledge, attitude, and practices of physicians on the 2021 PCAP CPG will also be part of the research agenda of PAPP and PIDSP for the succeeding years.

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EVIDENCE SUMMARIES and RECOMMENDATIONS

Clinical Question 1

AMONG INFANTS AND CHILDREN AGED 3 MONTHS TO 18 YEARS, WHAT CLINICAL SIGNS AND SYMPTOMS WILL ACCURATELY DIAGNOSE COMMUNITY-ACQUIRED PNEUMONIA?

KEY RECOMMENDATION

Pediatric community-acquired pneumonia (PCAP) is considered in a patient who presents with cough or fever, PLUS any of the following positive predictors of radiographically-confirmed pneumonia[1]:
(Conditional recommendation, very low-grade evidence)

Tachypnea[2]
- 3 months to 12 months old: ≥50 breaths per minute
- >1 year old to 5 years old: ≥40 breaths per minute
- >5 years to 12 years old: ≥30 breaths per minute
- >12 years old: ≥20 breaths per minute

Retractions or chest indrawing[3]
Nasal flaring
O2 saturation <95% at room air[4]
Grunting

Chest radiograph was the reference standard used in the studies.
[2] The age-specific definition of tachypnea was adopted from the WHO (below 5 years old) and PALS (age 5 years and above). Currently, there is no age-specific criteria of tachypnea in the Filipino population
[3] Chest indrawing was defined by the WHO as *"the inward movement of the lower chest wall when the child breathes in, and is a sign of respiratory distress. It does not refer to the inward movement of the soft tissue between the ribs."*
[4] The oxygen saturation of <95% cut-off was based on expert opinion. No study was found that recommends a specific cut-off value predictive of pneumonia.

SUMMARY OF EVIDENCE

Outcome 1	**Sensitivity, Specificity, +LR, -LR of clinical signs and symptoms in diagnosis of CAP in children**		**Importance: Critical**
# of studies (and list of authors)	**Study Design/s**	**Key findings**	**Grade level of evidence**
17 (Schot, 2018)	Systematic Review	*High prevalence pneumonia (>10%)* Cough: *Sen = 78.5-88* *Sp = 16-30.2* PPV= 36.8-37.2. NPV = 70.6-72.7. LR = 1.3 Fever: *Sen = 47-94.* *Sp = 36-68* PPV= 20-45. NPV = 70-97. LR = 2.9	Very low

23 (Shah 2017)	Meta-analysis of Cohort studies	Cough: *Sen= 88 (80-97)* *Sp= 25(08-42)* +LR= 1.2 (0.98-1.4) -LR= 0.47 (0.24-0.70) Fever: >37.5 °C *Sen= 80-92* *Sp= 47-54* +LR= 1.7-1.8 -LR= 0.17-0.37 Chest pain: *Sen= 22 (5-62)* *Sp= 91 (56-99)* +LR= 1.9 (1.1-3.4) -LR= 0.82 (0.66-1.0) Oxygen saturation ≤96%: *Sen= 64 (49-78)* *Sp= 77 (73-81)* +LR= 2.8 (2.1 -3.6) -LR= 0.47 (0.32-0.67) ≤95%: *Sen= 16 (11-2)* *Sp=96 (93-97)* +LR=3.5(2.0-6.4). -LR=0.88(0.82-0.94) ≤92%: *Sen= 26 (21-32)* *Sp= 88 (82-93)* +LR= 2.2 (1.3-3.8) -LR= 0.84 (0.76-0.94) Grunting: *Sen=13 (5-32)* *Sp=95 (83-99)* +LR=2.7 (1.5-5.1) -LR=0.92 (0.80-0.97) Nasal flaring: *Sen= 36 (17-54)* *Sp= 84 (71-97)* +LR= 2.2 (1.3-3.1). -LR= 0.77 (0.64-0.90) Retractions or indrawing: *Sen= 38 (20-56)* *Sp= 80 (70-90)* +LR= 1.9 (1.2-2.5) -LR= 0.78 (0.61-0.94)	Very low
19 (Rambaud-Althaus 2015)	Meta-analysis of Cohort and Case-control studies	Cough: *Sen=96 (91-98)* *Sp=14 (3-46)* +LR=1.12 (0.90-1.39) -LR=0.30 (0.09-0.96) History of fever: *Sen=94 (88-97).* *Sp=12 (6-23)* +LR=1.06 (1.0-1.12) -LR=0.53 (0.41-0.69) Respiratory rate >50: *Sen=53 (30-74)* *Sp=72 (58-83)* +LR=1.9 (1.5-2.5) -LR=0.6 (0.5-0.9) Nasal flaring: *Sen= 47 (28-66)* *Sp= 73 (52-87)* +LR= 1.75 (1.20-2.56) -LR= 0.73 (0.59-0.89)	Very low

		Grunting: *Sen=24 (10-47)* *Sp=87 (65-96)* +LR=1.8 (1.1-2.9) -LR=0.9 (0.8-1.0) Retractions or indrawing: *Sen= 48 (16-82)* *Sp= 72 (47-89)* +LR= 1.8 (0.9-1.2). -LR= 0.7 (0.4-1.4)	

CONTEXT AND CONSIDERATIONS

The positive predictors of radiographically-confirmed pneumonia were included based on the positive likelihood ratio of ≥2 or sensitivity of ≥80%. If the given criteria are not met but pneumonia is highly considered, further diagnostic work-up is suggested. Auscultatory lung findings such as decreased breath sounds, crackles or rales, wheeze and rhonchi were not included due to their low sensitivity (<80%) or positive likelihood ratio (<2) for diagnosing pneumonia mainly due to interobserver variability. No single clinical feature was found to predict pneumonia accurately. There was no supporting evidence on the predictive accuracy of a combination of signs and/or symptoms in giving a definitive diagnosis of pneumonia.

The 2021 PAPP/PIDSP Joint Task Force on PCAP retained the position statement of the 2012 PAPP 2nd PCAP update that chest radiograph is the reference standard in establishing the presence or absence of pneumonia. The task force similarly acknowledges the limitation of chest radiograph as a diagnostic tool. There is no evidence evaluating the accuracy in comparison with microbiology as the gold standard. In addition, moderate reliability exists due to interobserver variability in radiographic interpretation.

Even in the absence of chest radiograph, pneumonia may be considered using the above clinical predictors. Chest radiograph findings should always be correlated with the patient's clinical findings. A normal chest radiograph does not exclude the presence of pneumonia. Inconsistencies in the chest radiograph and clinical findings warrant re-evaluation or referral to a specialist.

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Clinical Question 2

AMONG INFANTS AND CHILDREN 3 MONTHS TO 18 YEARS WITH COMMUNITY-ACQUIRED PNEUMONIA, WHAT CLINICAL AND ANCILLARY PARAMETERS WILL DETERMINE THE NEED FOR ADMISSION?

KEY RECOMMENDATION

Patients classified as having severe PCAP or high-risk for pneumonia-related mortality based on the following clinical parameters and/or ancillary features are considered for admission: (*Conditional Recommendation, moderate to low-grade evidence)*

PARAMETERS AT SITE-OF-CARE	RISK CLASSIFICATION FOR PNEUMONIA-RELATED MORTALITY			
	Low Risk (Non-Severe PCAP)		High Risk (Severe PCAP)	
Formerly classified as:	*PCAP A*	*PCAP B*	*PCAP C*	*PCAP D*
Clinical Parameters*				
Respiratory signs				
1.1 Cyanosis/ Hypoxemia	None		Present	
1.2 Head bobbing	None		Present	
1.3 Chest indrawing/Retractions	None		Present	
1.4 Apnea	None		Present	
1.5 Grunting	None		Present	
Central nervous system signs				
2.1 Altered sensorium	None or irritable But consolable		Lethargic/stuporous/comatose/ GCS <13	
2.2 Convulsion	None		Present	
Circulatory signs				
3.1 Poor perfusion	None		Capillary refill >3s or in shock	
3.2 Pallor	None		Present	
General considerations				
4.1 Malnutrition**	None or mild		Moderate to severe	
4.2 Refusal OR inability to drink/ feed/ take oral medications	No		Yes	
4.3 Dehydration	None		With some to severe signs	
4.4 Age <6 months	No		Yes	
Ancillary Parameters (desirable variables but not necessary as determinants for admission at site-of-care)				
1. Chest radiograph or ultrasound findings of consolidation, multi-focal disease, moderate to large effusion, abscess, air leak	None		Present	
2. Sustained oxygen saturation at RA using pulse oximetry for 20-30 minutes	>94%		<93%***	

**Each of the clinical parameters and radiographic findings is an independent predictor of pneumonia-related mortality. The presence of any of the above predictors classifies the patient into the high-risk category.*
***Weight for Height [WFH][4]: moderate = SD score < -2; severe = SD score < -3 (WHO Management of severe malnutrition: a manual for physicians and other health workers. Geneva. World Health Organization 1999); Weight for Age (based on 2017 WHO IMCI Update on Assessing and managing children at primary healthcare facilities to prevent overweight and obesity in the context of the double burden of malnutrition): moderate = -2 SD (≥ -2 Z score); severe = -3 SD (≥ -3 Z score)*
****If oxygen saturation is less than 90%, oxygen therapy should be initiated.*

[4] Although body mass index (BMI) was not mentioned in the studies/ reviews used in the development of this CPG, it may be used in the assessment of the nutritional status of children and adolescents. However, the same recommendations for malnutrition status as a parameter for admission cannot be applied since no evidence was gathered as to the level associated with mortality among patients with pneumonia.

SUMMARY OF EVIDENCE

Outcome 1	**Severe Pneumonia and Pneumonia-related Mortality**		**Importance: Critical**
# of studies included in MA or SR (and list of authors)	**Study Design/s**	**Key findings**	**Grade level of evidence**
56 (Dean & Florin,2018)	Meta-analysis of Cohort and Case-control studies	Sustained SPO_2 of <90% at RA – hypoxemia OR = 11; 95% CI = 6.2 – 19.6 Age <6 months associated with treatment failure and mortality OR = 2.2; 95% CI = 1.1 – 4.2 Chest indrawing was associated with severe outcomes OR = 2.12; 95% CI = 1.62 – 2.78 Head bobbing was associated with mortality RR = 8.3; 95% CI = 2.71 – 12.77 and mechanical ventilation RR = 4.7 95% CI = 1.50 – 6.36 Grunting is associated with hypoxemia and suggestive of impending respiratory failure OR = 5.210; 95% CI = 2.287 – 7.482 AMS associated with severe outcomes OR = 11.9; 95% CI = 6.41 – 22.23 AMS – Glasgow Coma Score <13 was the most associated with mortality in children admitted with pneumonia OR = 324; 95% CI = 131 – 805 In children admitted with WHO-defined severe or very severe pneumonia, AMS was associated with mortality RR = 5.44; 95% CI = 1.34–17.56 In children admitted with WHO-defined pneumonia in a developing nation, “alteration of general status” based on clinician impression was also associated with mortality OR = 3.23; 95% CI = 1.17–8.94 Oxygen saturation <90% at RA OR = 20.9; 95%CI = 5.0–87	Low
5 (Deardorff *et al.,*2018)	Systematic review of cohort and case-control studies	Chest indrawing OR = 4.6; 95%CI = 2.2–9.4 Wheezing OR = 0.2; 95% CI = 0.05 – 0.6 Refusing to feed OR = 1.8; 95% CI = 0.9 – 3.8	Moderate

		Unable to drink/ breastfeed OR = 1.8; 95% CI = 1.2 – 2.8 Weight for age: Low (≤ -2 Zscore). OR = 2.5; 95% CI = 1.6 – 3.8 Very low (≤ -3 Zscore). OR = 6; 95% CI = 2.5 – 14.4 Weight for age: Low (≤ -2 Zscore) OR = 2.1; 95% CI = 1.3 – 3.2 Very low (≤ -3 Zscore) OR = 3.8; 95% CI = 2.7 – 5.4 Dehydration OR = 1.9; 95% CI = 1.3 – 2.8 Child not conscious at exam (mRISC) OR = 2.3; 95%CI = 1.6 – 3.4	
56 (Dean & Florin,2018)	Systematic review of cohort and case-control studies	Multifocal disease and fluid bronchograms on transthoracic ultrasound are associated with severity (CHEN) – multifocal involvement was an independent risk factor for a poor outcome including: - ICU admission (OR = 5.38) - longer LOS (>9 days) (OR = 9.75) - tube thoracotomy (OR = 20.12) – fluid bronchogram was an independent predictor of a longer hospital stay (> 9 days) (OR = 5.00) and tube thoracotomy (OR = 13.33) Moderate or large effusions were associated with ICU admission (CHEN) OR = 3.2; 95% CI = 1.1–8.9 and mechanical ventilation OR = 14.8; 95% CI = 9.8–22.4 Impaired perfusion on lung US – lung necrosis — a longer hospital stay would be expected if moderate-to-massive pleural effusion was observed in addition to impaired perfusion in ultrasonography (LAI) OR = 3.08; 95% CI = 1.15–8.29	Low

CONTEXT AND CONSIDERATIONS

The PCAP Guideline development from 2004 through 2016 has been utilizing PCAP A, B, C, and D for its pneumonia risk classification nomenclature. The 2021 CPG lead developers recommend the use of Non-Severe PCAP or Low-Risk for pneumonia-related mortality in lieu of PCAP A and B and Severe PCAP or High Risk for pneumonia-related mortality in lieu of PCAP C and D. This change was done to align with existing international guidelines in classifying PCAP.

The Risk Classification for pneumonia-related mortality should be used when assessing a pediatric patient diagnosed to have community-acquired pneumonia for admission. The presence of one (1) parameter, clinical and/or imaging, in the Severe or High Risk for Mortality category is an indication for admission. This classification is not a pneumonia severity classification, rather it is a categorization of the risk of mortality from pediatric pneumonia. It utilizes clinical and diagnostic parameters to assign the patient to a risk level at point- of- care.

The aforementioned clinical parameters and imaging findings are predictors of high-risk for pneumonia-related mortality. To classify to a higher risk category, at least 1 clinical or ancillary parameter should be present. In the absence of an ancillary parameter, a clinical parameter may suffice.

A patient classified as having non-severe PCAP would have a low risk for pneumonia-related mortality and may be treated in an outpatient basis with the recommended management plan. A caveat to this initial disposition would be a return to the facility for admission if there is no clinical improvement OR with signs of deterioration such as hypoxemia, chest indrawing/ retractions, grunting, altered sensorium, pallor within 48 hours; OR if the patient refuses or is unable to feed, drink or take medications. Patients classified as having non-severe PCAP should also be admitted if they have an underlying medical condition that can aggravate the overall clinical status. Other relative indications for admission of non-severe PCAP patients are absence of a reliable caregiver, inability for close follow-up, and no easily accessible medical facility.

A patient classified as having severe PCAP would have a high risk for pneumonia-related mortality and should be admitted for close observation and immediate institution of the recommended management plan. The indications for admission to a critical care unit should also be noted and close monitoring must be performed as these patients are at greater risk for mortality.

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Clinical Question 3

AMONG INFANTS AND CHILDREN AGED 3 MONTHS TO 18 YEARS, WHAT DIAGNOSTIC AIDS WILL CONFIRM THE PRESENCE OF NON-SEVERE COMMUNITY-ACQUIRED PNEUMONIA IN AN AMBULATORY SETTING?

KEY RECOMMENDATION

Routine diagnostic aids are not considered for non-severe PCAP in an ambulatory setting.
(Conditional recommendation, Expert opinion)

SUMMARY OF EVIDENCE

No evidence was found regarding the use of diagnostic aids in confirming non-severe PCAP. Diagnostic aids are not routinely recommended in children with mild clinical presentation and managed in an ambulatory setting. It is the discretion of the attending physician to request for diagnostic aids based on his initial clinical assessment.

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Clinical Question 4

AMONG INFANTS AND CHILDREN AGED 3 MONTHS TO 18 YEARS, WHAT DIAGNOSTIC AIDS WILL CONFIRM THE PRESENCE OF SEVERE COMMUNITY-ACQUIRED PNEUMONIA IN A HOSPITAL SETTING?

KEY RECOMMENDATIONS

Chest X-ray is strongly recommended as an initial diagnostic aid for patients classified as having severe PCAP. (*Strong recommendation, high-grade evidence)*
Point-of-care chest ultrasonography (POCUS) performed by a skilled expert is strongly recommended as a diagnostic aid for patients classified as having severe PCAP. (*Strong recommendation, high-grade evidence*)
Procalcitonin (PCT) is recommended to be used in conjunction with other factors such as clinical presentation, imaging modalities and other laboratory aids in diagnosing bacterial PCAP. (*Conditional recommendation, moderate-grade evidence*)
Sputum Gram stain and culture are not considered to be done routinely in patients classified as having severe PCAP. (*Conditional recommendation, low-grade evidence*)
Complete blood count, arterial blood gas, serum electrolytes and other diagnostic aids are considered to be used as necessary based on the clinician's evaluation. (*Conditional recommendation, Expert opinion*)

SUMMARY OF EVIDENCE

1. Chest radiography

Outcome	**Positive diagnosis of pneumonia**		**Importance: Critical**
# of studies included in MA or SR (and list of authors)	**Study Design/s**	**Key findings**	**Grade level of evidence**
12 (Balk *et al.,* 2017)	Meta-analysis of Cohort and Case-control studies	Chest X-ray is recommended as an initial test Sn: 86.80%. Sp: 98.20% LR (+): 48.22. LR (-): 0.13	High

2. Chest ultrasonography

Outcome	Positive diagnosis of pneumonia		Importance: Critical
# of studies included in MA or SR (and list of authors)	Study Design/s	Key findings	Grade level of evidence
6 (Wang *et al*., 2019)	Meta-analysis of Cohort and Case-control studies	CUS[5] as a diagnostic aid Sn: 86.80% Sp: 98.20% LR (+): 48.22 LR (-): 0.134	High
22 (Najgrodzka *et al*., 2019)	Meta-analysis of Cohort and Case-control studies	CUS as a diagnostic aid Sn: 96.70%. Sp: 87.39% LR (+): 7.61. LR (-): 0.04	High
12 (Hua Xin *et al*., 2017)	Meta-analysis of Cohort and Case-control studies	CUS as a diagnostic aid Sn: 93.00% Sp: 96.00% LR (+): 23.25. LR (-): 0.07	High
6 (Zar *et al*., 2017)	Meta-analysis of Cohort and Case-control studies	CUS as a diagnostic aid Positive: 0.71 Negative: 0.80	Very low

3. Procalcitonin

Outcome	Positive diagnosis of pneumonia		Importance: Critical
# of studies included in MA or SR (and list of authors)	Study Design/s	Key findings	Grade level of evidence
25 (Tsou *et al*., 2020)	Meta-analysis of Cohort and Case-control studies	PCT for bacterial pneumonia Sn: 64.00% Sp: 72.00% LR (+): 2.29 LR (-): 0.50	Moderate

4. Sputum GS/CS

Outcome	Positive diagnosis of pneumonia		Importance: Critical
# of studies included in MA or SR (and list of authors)	Study Design/s	Key findings	Grade level of evidence
21 (Ogawa *et al.,* 2019)	Meta-analysis of Cohort and Case-control studies	Sputum Gram stain, culture, and sensitivity as a diagnostic aid for bacterial CAP *S. pneumoniae* Sn: 69.00 Sp: 91.00 LR (+): 7.67 LR (-): 0.34 *H. influenzae* Sn: 76.00 Sp: 97.00 LR (+): 25.33 LR (-): 0.25	Low

[5] CUS – chest ultrasound

CONTEXT AND CONSIDERATIONS

Chest radiography remains to be the initial diagnostic aid of choice for severe PCAP. Postero-anterior and lateral (PA-L) views are preferred for children who are able to stand upright, otherwise antero-posterior *and lateral* (AP-L) views are acceptable especially for younger infants. Proper patient positioning is vital to obtain a good quality chest radiograph. As best practice, consider having two (2) radiologists to review the X-ray images to eliminate intra-observer variability and encourage clinicians to review the radiographs for better clinical correlation.

In recent years, robust evidences show the value of chest ultrasonography as an initial tool in the diagnosis of PCAP. Zar *et. al* enumerated the advantages of point-of-care ultrasound (POCUS) in their study, namely: [1] it can be performed at point-of-care; [2] it is feasible and less costly than chest radiography; [3] it is less affected by movement or crying than other imaging modalities; [4] it can be done in sleeping children and [4] it is free of ionizing radiation. Operator dependency is one of the limitations often cited with regard to the ultrasound imaging study (Wang *et al.,* 2019), other limitations include: [1] inability to visualize the whole lung at the same time or to identify consolidation deep within the lung parenchyma;(Zar *et al*., 2017) [2] subscapular or sub-clavicular consolidations that did not reach the pleura are inaccessible to ultrasound imaging and may be missed;(Najgrodzka *et al.*, 2019) [3] the spleen or air in the stomach can be misinterpreted as lung consolidation with air bronchograms (Zar *et al*., 2017).
The meta-analysis of Hua Xin *et al.* highlighted 4 major abnormalities that are frequently observed on CUS: pulmonary consolidation, positive air bronchogram, abnormal pleural line, and pleural effusion. Among these 4, positive air bronchogram and lung consolidation are the most often detected signs on CUS.

There is some evidence that procalcitonin (PCT) can be used to distinguish between bacterial and viral aetiology of pneumonia. PCT, a precursor of the calcitonin hormone, increases after exposure to bacterial endotoxins and inflammatory cytokines (Dandona *et al*. 1994). It is a favourable characteristic in a biomarker for diagnosis of bacterial infections, determination of disease severity, evaluation of patients' response to treatment, and prevention of antibiotic overuse (Shcuetz, McCluskey *et al*., 2017). Current evidence on the other biomarkers such as CRP, plasma interferon-γ protein-10, chitinase 3-like-1, RNA biosignatures remain conflicting and overlapping (Principi *et al*., 2017).

Gram stain of expectorated sputum is an inexpensive, non-invasive, readily available test that can promptly identify causative bacteria if performed by an experienced observer in a qualified laboratory on good-quality specimens (Skerrett *et al.,* 1999). A good-quality specimen is defined as one containing ≥25 leukocytes and <10 squamous epithelial cells per low power field (Ogawa et al., 2020). One meta-analysis was found advocating sputum GS, culture and sensitivity as a diagnostic aid for bacterial CAP. This study, though with modest limitation in terms of methodology, showed that sputum GS was highly specific to diagnose *S. pneumoniae* and *H. influenzae* infections in patients with CAP with values of 91% and 97% respectively. Sensitivity, on the other hand for the two microorganisms were 69% and 76%. Selecting good-quality specimens could increase this yield, although data supporting this are limited (Ogawa *et al*., 2020). There is insufficient evidence to support the routine use of culture and sensitivity of blood, tracheal aspirate, and bronchoalveolar lavage for the diagnosis of severe PCAP.

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Clinical Question 5

AMONG INFANTS AND CHILDREN AGED 3 MONTHS TO 18 YEARS WITH COMMUNITY-ACQUIRED PNEUMONIA, WHAT CLINICAL AND ANCILLARY PARAMETERS WILL DETERMINE THE NEED FOR ANTIBIOTIC TREATMENT?

KEY RECOMMENDATION

Empiric antibiotic therapy is considered to be started in patients with clinical signs and symptoms of PCAP with ANY of the following parameters suggestive of bacterial etiology for both non-severe and severe pneumonia: *(Conditional recommendation, low-grade evidence)*

- Elevated white blood cell count (WBC)[1]
- Elevated C-reactive protein (CRP)
- Elevated procalcitonin (PCT)
- Imaging findings such as:
  - Alveolar infiltrates in chest radiograph; or
  - Unilateral, solitary lung consolidation and/or air bronchograms and/or pleural effusion in lung ultrasound

Age	Mean (x10^3/ml)	Range (x10^3/ml)
1 month	*10.8*	*4.0 – 19.5*
6 mos – 2 years	*10.6*	*6.0 – 17*
2 – 6 years	*8.5*	*5.0 – 15.5*
6 – 12 years	*8.1*	*4.5 – 13.5*
12 – 18 years	*7.8*	*4.5 – 13.5*

Reference: The Harriet Lane Handbook 22nd ed, 2021

SUMMARY OF EVIDENCE

Outcome:	**Differentiating bacterial from viral pneumonia using CBC, CRP, PCT**		**Importance: Critical**
# of studies included in MA or SR (and list of authors)	**Study Design/s**	**Key findings**	**Grade level of evidence**
12 (Thomas *et al.,* 2020)	Meta-analysis of Cohort and Case-control studies	CRP: Sn 63.5 - 75% Sp 53.8 - 90% PCT: Sn 63.8 - 86% Sp 38.9 - 80% WBC: Sn 41.6% Sp 61.3%	Very Low
25 (Po-Yang *et al.,* 2020)	Meta-analysis of Cohort and Case-control studies	Procalcitonin showed moderate diagnostic accuracy for diagnosis of bacterial pneumonia in children, and may be used in conjunction with clinical presentation and laboratory and imaging findings prior to starting of antibiotics. Pooled Sn: 0.64 (95% CI: 0.53–0.74)	Low

		Pooled Sp: 0.72 (95% CI: 0.64–0.79) Pooled +LR 2.3 (95% CI: 1.8–3.0) Pooled -LR: 0.50 (95% CI: 0.38–0.66)	
Zar, *et. al.,* 2020	CPG	General tests for infection, including acute-phase reactants (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white cell count (WCC), neutrophil count and procalcitonin (PCT)) do not reliably differentiate bacterial from viral pneumonia and should not be routinely used. CRP concentrations ≥ 40 mg/L with radiological confirmation of pneumonia suggests bacterial pneumonia.	High
Tapiainen, *et. al.,* 2016	CPG	Elevated C-reactive protein concentrations or leucocyte counts increase the possibility of bacterial pneumonia, but low C-reactive protein concentrations or leucocytes do not exclude bacterial pneumonia.	High

Outcome:	**Differentiating bacterial from viral pneumonia using imaging findings**		**Importance: Critical/ Important**
# of studies included in MA or SR (and list of authors)	**Study Design/s**	**Key findings**	**Grade level of evidence**
Buonsenso *et al*., 2021	individual cohort study	Differentiating bacterial from viral pneumonia: Large-sized consolidation: OR 13.62 (95% CI 1.16-159.88) Air bronchogram: OR 6.58 (95% CI 1.67-25.93) Pleural effusion: OR 1.48 (95% CI 0.42 – 5.16) Deep vertical artifacts: OR 0.27 (95% CI 0.07-1.06)	Very low
Malla *et al.*, 2020	individual cross-sectional analytical study	Sn 91% (95% CI 84-96) Sp 91.3% (95% CI 84-96) PPV 91.9% (95% CI 85-96) NPV 90.3% (95% CI 82-95)	Very low

Berce *et al.,* 2019	Individual cohort study	Differentiating bacterial from viral pneumonia Unilateral consolidation: OR 12.42 (95% CI 4.59-33.62) PPV 65.7 NPV 85.7 Solitary consolidation: OR 9.01 (95% CI 3.94-20.60) PPV 71.3. NPV 78.3 Differentiating bacterial from atypical pneumonia: Unilateral consolidation: OR 9.41 (95% CI 2.80-31.66) PPV 65.7. NPV 85.7 Solitary consolidation: OR 8.86 (95% CI 2.96-26.51) PPV 71.3. NPV 78.3	Very low
Tapiainen, *et al.,* 2016	CPG	Alveolar pneumonia is reliably detected in chest radiography, but interstitial changes are not so reliably diagnosed. Alveolar infiltrates suggest bacterial pneumonia.	High

CONTEXT AND CONSIDERATIONS

There is insufficient evidence to differentiate bacterial from viral pneumonia based on clinical signs and symptoms alone. In the absence of the aforementioned ancillary parameters, the decision to start antibiotics empirically is based on the clinician's assessment and sound judgment. Efforts should be made to obtain evidence of the causative pathogen for PCAP to avoid unnecessary use of antibiotics and to provide optimal pathogen-directed care to patients.

Laboratory tests and chest imaging are not routinely requested prior to starting antibiotic therapy. If these ancillary tests are done, empiric antibiotics may be started in patients with clinical signs and symptoms of PCAP with elevated WBC for age, elevated CRP or elevated procalcitonin. However, a low or normal level of biomarkers does not exclude bacterial pneumonia. Furthermore, no optimal cut-off values for CRP and procalcitonin can be derived from the reviewed literature since different units, cut-off values and laboratory testing systems were used in the clinical setting. In patients with clinical signs and symptoms of PCAP, the presence of alveolar infiltrates, solitary lung consolidation or air bronchogram on chest radiograph and pleural effusion on lung ultrasound are suggestive of a bacterial etiology and warrants antibiotic use.

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Clinical Question 6A

AMONG INFANTS AND CHILDREN AGED 3 MONTHS TO 18 YEARS WITH COMMUNITY-ACQUIRED PNEUMONIA, WHAT EMPIRIC TREATMENT IS EFFECTIVE IF A BACTERIAL ETIOLOGY IS CONSIDERED?

KEY RECOMMENDATIONS

For patients classified as having non-severe PCAP, regardless of immunization status against *Streptococcus pneumoniae* and/or *Haemophilus influenzae type* b (Hib), any of the following is considered:

start Amoxicillin trihydrate at 40-50mg/kg/day Q8 for 7 days **OR** at 80-90mg/kg/day Q12 for 5 to 7days.

start Amoxicillin-clavulanate at 80-90mg/kg/day Q12 (based on Amoxicillin content using a 14:1 amoxicillin:clavulanate formulation) for 5 to 7 days **OR** Cefuroxime at 20-30mg/kg/day Q12 for 7 days in settings with documented high-level penicillin-resistant *pneumococci or* beta-lactamase-producing *H. influenzae* based on local resistance data or hospital antibiogram.

(*Conditional recommendation, low-grade evidence)*

For patients classified as having severe PCAP, regardless of immunization status against *Streptococcus pneumoniae*, any of the following is considered:

start Penicillin G at 200,000 units/kg/day Q6 if with complete *Haemophilus influenzae type b (Hib)* vaccination **OR** Ampicillin at 200mg/kg/day Q6 if with no or incomplete or unknown *Haemophilus influenzae type b (Hib)* vaccination

start Cefuroxime at 100-150mg/kg/day Q8 **OR** Ceftriaxone at 75-100mg/kg/day Q12 to Q24 **OR** Ampicillin-sulbactam at 200mg/kg/day Q6 (based on ampicillin content*)* in settings with documented high-level penicillin-resistant *pneumococci* or beta-lactamase-producing *H. influenzae* based on local resistance data or hospital antibiogram

add Clindamycin at 20-40mg/kg/day Q6 to Q8 when *Staphylococcal* pneumonia is highly suspected based on clinical and chest radiograph features. However, in cases of severe and life-threatening conditions such as sepsis and shock, Vancomycin at 40-60 mg/kg/day Q6 to Q8 is preferred.

(Conditional recommendation, low-grade evidence)

For patients with known hypersensitivity to penicillin, classified as

Non-type 1 hypersensitivity to Penicillin, cephalosporins such as Cefuroxime PO 20-30mg/kg/day Q12 or IV 100-150mg/kg/day Q8 **OR** Ceftriaxone at 75-100mg/kg/day Q12 to Q24 is considered.

Type 1 hypersensitivity to Penicillin (immediate, anaphylactic-type), any of the following is considered:

Azithromycin at 10mg/kg/day PO or IV Q24 for 3 days **OR** 10mg/kg/day on day 1 followed by 5 mg/kg/day Q24 for days 2 to 5

Clarithromycin at 15mg/kg/day Q12 for 7 days

Clindamycin at 10-40mg/kg/day PO or 20-40mg/kg/day IV Q6 to Q8 for 7 days

(*Conditional recommendation, low-grade evidence*)

When an atypical pathogen is highly suspected, starting a macrolide is considered as follows:

Azithromycin at 10mg/kg/day PO or IV Q24 for 5 days, particularly in infants less than 6 months old whom pertussis is entertained, **OR** 10mg/kg/day Q24 for 3-5 days **OR** 10mg/kg/day on day 1 followed by 5 mg/kg/day Q24 for days 2 to 5

Clarithromycin at 15mg/kg/day Q12 for 7 to 14 days

(*Conditional recommendation, low-grade evidence*)

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Jalandoni-Cabahug MVS, Capending MRZ, Alvarado-Dela Cruz K, Castellano MJS, De Leon MNA, Padua JRO, et al. 2021
Clinical Practice Guidelines in the Evaluation and Management of Pediatric Community-Acquired Pneumonia
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KEY RECOMMENDATIONS

When a specific pathogen is identified, modifying the empiric treatment based on the antibiotic susceptibility pattern and/or the drug of choice is recommended.
(*Strong recommendation, high-grade evidence*)
When treating for uncomplicated bacterial PCAP, 7 to 10 days treatment is considered but a longer duration may be required depending on the patient's clinical response, virulence of the causative organism and eventual development of complications.
(*Conditional recommendation, low-grade evidence*)

SUMMARY OF EVIDENCE

Antimicrobial Resistance Surveillance Pattern from 2016 to 2020 (https://arsp.com.ph/)

Streptococcus pneumoniae	**ALL ISOLATES** 69% resp.	66% resp.	**RESPIRATORY ISOLATES**		
	2016	**2017**	**2018**	**2019**	**2020**
Penicillin (nm)	6.1%	10%	1%	0.8%	1.1%
Chloramphenicol	3.4%	4.8%	-	-	-
Cotrimoxazole	18.1%	15.1%	18%	13.8%	22.4%
Erythromycin	7%	9.8%	15%	11.3%	12%
Ceftriaxone (nm)	3%	1.2%	3%	0	3.8%
Levofloxacin	1.1%	0.8%	2%	1.7%	0
Clindamycin	-	-	-	-	5.1%

Haemophilus influenzae	**ALL ISOLATES** **94% resp.**	**95% resp.**	**RESPIRATORY ISOLATES**		
	2016	**2017**	**2018**	**2019**	**2020**
Ampicillin	7.8%	14%	10%	10.8%	7.2%
Amoxicillin-clavulanate	5.8%	-	5%	2.6%	2.2%
Ampicillin-sulbactam	-	5%	3%	2.7%	3.5%
Chloramphenicol	5.3%	9%	-	8.2%	-
Cefuroxime	-	-	7%	1.5%	-
Ceftriaxone	-	-	1%	2.9%	2%
Levofloxacin	0	0	0	0.7%	-
Azithromycin	0	0	0	0	0

Staphylococcus aureus	**ALL ISOLATES** resp. 19%	21%	20.5%	21.1%	22.51%
	2016	**2017**	**2018**	**2019**	**2020**
Oxacillin	61.5%	57%	54.2%	52.1%	47.6%
Cotrimoxazole	24.6%	26%	31.8%	35.5%	34.3%
Clindamycin	11.4%	13%	12.4%	10.4%	10.7%
Vancomycin	0.8%	2%	1%	0.8%	1.2%%
Linezolid	1.4%	1%	1%	0.6%	0.7%

SUMMARY OF EVIDENCES			
Outcome	**Etiology**		**Importance: Critical**
# of studies included in SR/MA and authors	**Study Design/s**	**Key Findings**	**Grade level of evidence**
1 Nathan, *et.al*. 2020	Cohort	*H. influenzae, S. aureus* and *S. pneumoniae* were the most commonly detected bacteria	Very low
48 Ning, *et.al.,* 2017	Meta-analysis of Cohort studies	The most frequently detected bacterial pathogens were *K. pneumoniae, S. pneumoniae, H. influenzae* and *S. aureus*	Very low
1 Das, *et.al.* 2016	Cohort	The most common detected bacterial pathogen obtained through nasopharyngeal swab and BAL were *S. pneumoniae* and non-type b *H. influenzae* followed by *K. pneumoniae* and MSSA	Very low
Outcome	**Treatment, Dose and Duration of Therapy**		**Importance: Critical**
South African Thoracic Society Guidelines (Reubenson *et al.*, 2020)	CPG	1. Oral amoxicillin is recommended for children >1 month of age who do not require hospitalization 2. For ambulatory treatment of pneumonia, amoxicillin (45 mg/kg/dose 12-hourly) remains the preferred antibiotic for children >1 month old. 3.Treatment duration should be 5 days, but longer duration may be needed in children with severe or complicated disease. 4.Bacteremic staphylococcal pneumonia should be treated for 14-28 days, dependent on complications and response to treatment while uncomplicated presumed staphylococcal pneumonia (blood culture negative) may be managed with 10-day course of targeted antibiotic therapy, depending on clinical response. 5. If cultures are positive, use targeted therapy according to organism's susceptibility pattern. 6. Macrolide antibiotics should be used if pertussis, Mycoplasma or Chlamydia is suspected (evidence level IVa) such as Azithromycin 10mkd daily for 5 days, or Clarithromycin 15mkd Q12 for 10days	High
Chou et al, 2019	CPG	1. Empiric therapy for outpatient treatment of CAP in children for presumed atypical pneumonia is macrolides, Azithromycin 10mkd daily for 3-5 days and Clarithromycin 15mkd Q12 for 7-14 days. 2. Targeted therapy for treatment of CAP in children with atypical organisms such as Mycoplasma and Chlamydophila are Azithromycin and Clarithromycin with 3 to 7 days treatment duration	High
1 (Mathur *et al.,* 2017)	Evidence review	2014 revision preferred oral amoxicillin to oral cotrimoxazole for the treatment of fast-breathing pneumonia and was equivalent to injectable penicillin/ampicillin in cases of chest-indrawing pneumonia.	Low

1 (Messinger *et al.* 2021)	Evidence review	1. Length of therapy for uncomplicated bacterial CAP should not exceed 7 days 2. similar success rates of 7 days when compared with 10 days and 5 days	Low
1 (Leung, *et.al.,* 2018)	Evidence review	1. In previously healthy children under the age of 5 years, high dose amoxicillin is the treatment of choice. 2. For those with type 1 hypersensitivity to penicillin, clindamycin, azithromycin, clarithromycin, and levofloxacin are reasonable alternatives. 3. For children with a non-type 1 hypersensitivity to penicillin, cephalosporins should be considered.	Low
1 (Dizon and Rivera, 2019)	RCT	Paediatric community-acquired pneumonia A and B can be treated as efficaciously with either high-dose (80mkd in 2 divided doses for 5 days) or standard-dose (40mkd in 3 divided doses for 7 days) Amoxicillin. No significant difference in the clinical course of the 2 groups by days 3 and 7 and frequency of adverse events were also similar.	Low

CONTEXT AND CONSIDERATIONS

The causative agents of community acquired pneumonia vary according to age of the child and the setting in which the infection is acquired. Generally, viruses notably Respiratory Syncytial Virus (RSV), are the most common cause of pneumonia in children younger than 5 years. *Streptococcus pneumoniae* is the most common bacteria across all age groups. Other important bacterial causes in children younger than 5 years include *Hemophilus influenzae*, *Streptococcus pyogenes* and *Moraxella catarrhalis*. In children 5 years and older, other important causes include Mycoplasma and Chlamydophila.

The advent of universal childhood immunization with pneumococcal and Hib conjugate vaccines have resulted in a shift in bacterial etiology, with non-typeable *H. influenzae* and *Staphylococcus aureus* causing a greater proportion of severe pneumonia in hospitalized children worldwide.

With the global emergence of antimicrobial resistance, judicious use of antibiotics cannot be overemphasized. The choice of empiric antibiotics in PCAP should always be guided by the general principles of rational antibiotic use and the most likely pathogen should be considered. Starting with broad spectrum antibiotics to treat uncomplicated PCAP is highly discouraged and such antibiotics should be reserved for more complicated forms of the disease and for drug-resistant pathogens. Amoxicillin is still the treatment of choice because it is effective against the majority of pathogens causing CAP in this age group. High-dose amoxicillin is recommended for treatment of suspected or confirmed penicillin-resistant *S. pneumoniae*; the resistance of which can be overcome at higher drug concentrations. Practitioners commonly presume that oral cephalosporins are superior to amoxicillin for *S. pneumoniae*; this likely stems from the knowledge that some penicillin-resistant pneumococci isolates are susceptible to ceftriaxone hence, oral cephalosporins are assumed superior to amoxicillin. However, oral cephalosporins have short half-lives, highly protein bound and often have long dosing intervals. This results in serum concentrations that do not provide enough bactericidal time. Because the pharmacokinetics of the oral cephalosporins are far inferior to amoxicillin, their use in CAP should be reserved for patients who are allergic to penicillin or patients with isolates known to be resistant to amoxicillin but susceptible to cephalosporins such as *M. catarrhalis* or *beta-lactamase–positive H. influenzae*. When atypical pathogens are highly suspected especially in a child who is not ill-looking despite having clinical pneumonia (“walking pneumonia”), although clinical presentation may be indistinguishable with viral pneumonia, starting a macrolide may be considered.

Staphylococcal pneumonia may present with high fever or hypothermia, cough, respiratory distress, signs of shock, and or with presence of skin lesions (point of bacterial entry). However, skin lesions may also be absent in other instances. Pulmonary auscultation is often normal; sometimes with dullness indicating pleural effusion. Typical chest radiographic findings may show multi-lobar consolidation with cavitation, pneumatoceles and/or spontaneous pneumothorax. Other bacterial agents, however, may have similar imaging findings.

There is no definite recommendation for an acceptable antimicrobial resistance rate, but some literature state that between 10-20% is tolerable. Allowable resistance rate will also depend on certain factors such as local resistance data and hospital antibiograms as this varies from place to place and over time.

Currently, there is no defined optimal duration of antibiotic therapy in PCAP. Most experts and guidelines recommend that 7 to10 days antibiotic treatment is appropriate for most uncomplicated PCAP. However, treatment duration should be extended as necessary depending on the patient's clinical response, virulence of the causative organism and eventual development of complications. Recent studies are now looking into shortening the duration of antibiotic therapy especially in non-severe cases of PCAP.

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Clinical Question 6B

AMONG INFANTS AND CHILDREN AGED 3 MONTHS TO 18 YEARS WITH BACTERIAL COMMUNITY-ACQUIRED PNEUMONIA, WILL THE ADDITION OF A MACROLIDE TO STANDARD EMPIRIC REGIMEN IMPROVE TREATMENT OUTCOME?

KEY RECOMMENDATION

The addition of a macrolide to standard beta-lactam antibiotic therapy is NOT considered in the empiric treatment of bacterial PCAP. *(Conditional recommendation, very low-grade evidence)*

SUMMARY OF EVIDENCE

Outcomes of studies which **did not recommend** the use of macrolides

Outcome 1:	**Macrolide resistance**		**Importance: CRITICAL**
# of studies included in MA or SR (and list of authors)	**Study Design/s**	**Key findings**	**Grade level of evidence**
24 (Chen *et al.*, 2020)	Meta-analysis of Randomized trials	Overall effect of macrolide resistance Pooled OR 4.42, 95%CI = 2.32-8.41)	High

Outcomes of studies which **recommended** the use of macrolides

Outcome 2:	**Length of hospitalization**		**Importance: *NOT CRITICAL***
# of studies included in MA or SR (and list of authors)	**Study Design/s**	**Key findings**	**Grade level of evidence**
8 (Lin *et al.,* 2018)	Meta-analysis of Cohort and Case-control studies	Length of stay (LOS) for macrolide-treated group −0.051 days, range: −0.377 to 0.274 days, $p = 0.756$, $I^2 = 76.8\%$	Very Low
1 (Williams *et al.*, 2017)	Individual cohort study	Time to discharge *(reported in hazard ratio and 95%CI)* HR (Propensity score-matched): 0.92, 95%CI = 0.77-1.08 HR (Propensity score-weighted): 0.92, 95%CI = 0.79-1.07	Low

Outcome 3:	**Treatment failure**		**Importance: *NOT CRITICAL***
# of studies included in MA or SR (and list of authors)	**Study Design/s**	**Key findings**	**Grade level of evidence**
1 (Ambroggio *et al.*, 2016)	Individual cohort study	Treatment failure: 14 Day TF: 1 to <6 years OR 1.34, 95%CI = 0.83-2.18) 6-18 years OR 0.51, 95%CI = 0.28-0.95) 7 Day TF: 1 to <6 years OR 1.33, 95%CI = 0.74-2.39 6-18 years OR 0.33, 95%CI = 0.12-0.91	Very low

CONTEXT AND CONSIDERATIONS

There is some evidence on the empiric use of macrolides as an add-on therapy to beta-lactams for non-severe PCAP in patients >5 years of age to cover for atypical pathogens when suspected**.** However, this practice is not routinely recommended, considering that several studies attest that it is difficult to clinically distinguish signs and symptoms definitive to the diagnosis of atypical pneumonia, and that the inadvertent use of macrolides have the potential to induce macrolide resistance.

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Clinical Question 7

AMONG INFANTS AND CHILDREN AGED 3 MONTHS TO 18 YEARS WITH COMMUNITY-ACQUIRED PNEUMONIA, WHAT TREATMENT IS EFFECTIVE IF A VIRAL ETIOLOGY IS CONSIDERED?

KEY RECOMMENDATION

Oseltamivir is strongly recommended to be started immediately within 36 hours of laboratory-confirmed influenza infection. *(Strong recommendation, high-grade evidence)*

SUMMARY OF EVIDENCE

Outcome	**Reduction in the duration of illness**		**Importance: CRITICAL**
# of studies included in MA or SR (and list of authors)	**Study Design/s**	**Key findings**	**Grade level of evidence**
5 (Malosh *et al.,* 2018)	Meta-analysis of Randomized trials	Significant reduction in the duration of illness among those who received timely oseltamivir treatment (RMST difference -17.6 hours, (95% CI, -34.5 to -0.7 hours) Stratified analysis: Observed larger RMST for individual who received early treatment (<24 hours compared to those who received treatment 24 to 48 hours after the onset (-22 hours, (95% CI, -29.4 to 16.2 hours VS -4.4 hours,95%CI, -15.5 to 6.5 hours	High
20 (Jefferson *et al.,* 2014)	Meta-analysis of Randomized trials	Oseltamivir in healthy children reduced the time to first alleviation of symptoms with mean difference of 29 hours, (95% confidence interval 12 to 72 hours(p=0.001) Hospitalization No significant effect on hospitalization. Risk difference (RD) 0.15%(95% CI -0.78 to 0.9) Pneumonia Oseltamivir significantly reduced self-reported, investigator mediated, unverified pneumonia. No oseltamivir treatment studies reported effects on radiologically confirmed pneumonia Harm of treatment In children, induced vomiting (RD 5.34%, 94% CI 1.75 to 10.29)	High

CONTEXT AND CONSIDERATIONS

Recommendations on the treatment of viral pneumonia are limited by the availability of laboratory confirmation for influenza and the available antiviral treatments accessible to clinicians. As of this writing, only oseltamivir is available locally as treatment for influenza.

Laboratory confirmation for influenza may be costly and is not widely available in all healthcare facilities. These point-of-care tests, when available, are helpful in initiating early therapy and decreasing the use of unnecessary diagnostics and antibiotics. These point of care tests include influenza point of care kits and the multiplex respiratory panel. This respiratory panel uses nasopharyngeal specimens to detect 4 bacteria and 18 respiratory viruses, including SARS-CoV2. It has an overall sensitivity of 97.1% and specificity of 99.3%.

Treatment for suspected or confirmed influenza is recommended in those with severe illness, i.e, those who are admitted in the hospital, have serious complications like myocarditis and encephalitis, or who are clinically deteriorating. While for non-severe illness suspected with viral pneumonia, treatment is indicated in 1) high-risk children such as those less than five years old, especially those under 2 years old, or those with other comorbidities, and 2) children with high-risk contacts to reduce amount of viral shedding and decreasing risk of transmission to high-risk contacts.

Laboratory-confirmed influenza should be treated with oseltamivir. Timing of treatment should be within 48 hours of symptoms. Early antiviral treatment has been shown to provide maximal benefit. Initiating treatment beyond 48 hours of symptom onset may still provide clinical benefit in hospitalized children or those with serious complications or deteriorating disease. Treatment of oseltamivir is given twice a day for 5 days with the following doses: (1) for children younger than 1 year old, 3mg/kg/dose; (2) for 1 year and older, dose varies by child's weight: for 15kg or less, 30mg; for >15 to 23 kg, 45mg; for >23 to 40kg, 60mg; and for >40kg, the dose is 75mg.

Antiviral may be considered in the following circumstances: (1) any previously healthy, symptomatic outpatient not at high-risk for complications in whom influenza is suspected or confirmed if treatment can be given within 48 hours; and (2) children with suspected or confirmed influenza disease whose siblings/household contacts are less than 6 months old or at high risk for influenza complications.

Immunization status for influenza for the year should not influence decision to initiate treatment with oseltamivir if influenza is highly considered.

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Clinical Question 8

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AMONG INFANTS AND CHILDREN AGED 3 MONTHS TO 18 YEARS WITH COMMUNITY-ACQUIRED PNEUMONIA, WHAT CLINICAL AND ANCILLARY PARAMETERS WILL DETERMINE A GOOD RESPONSE TO CURRENT THERAPEUTIC MANAGEMENT?

KEY RECOMMENDATIONS

For patients classified as having non-severe PCAP, good clinical response to current therapeutic management is considered when clinical stability is sustained for the immediate past 24 hours as evidenced by improvement of cough or normalization of core body temperature in Celsius in the absence of antipyretics within 24-72 hours after initiation of treatment. (*Conditional recommendation, very low-grade evidence*)

For patients classified as having severe PCAP, good clinical response to current therapeutic management is considered when clinical stability is sustained for the immediate past 24 hours as evidenced by **ANY ONE** of the following physiologic and ancillary parameters observed within 24-72 hours after initiation of treatment:

- Absence or Resolution of hypoxia
- Absence or Resolution of danger signs[2]
- Absence or Resolution of tachypnea[3]
- Absence or Resolution of fever[4]
- Absence or Resolution of tachycardia[5]
- Resolving or Improving radiologic pneumonia
- Resolving or Absent chest ultrasound findings[6]
- Normal or Decreasing CRP
- Normal or Decreasing PCT

(*Conditional recommendation, very low-grade evidence*)

Hypoxia is defined as having peripheral O2 saturation less than 95% at room air.

[2] Danger signs are nasal flaring, grunting, head bobbing, cyanosis.

[3] Respiratory rate taken at full minute based on the WHO-defined, age-specific values for tachypnea.

[4] Fever is defined as having a core body temperature of 38 degrees Celsius and above

[5] Cardiac rate taken at full minute based on Pediatric Advanced Life Support age-based values for tachycardia

[6] Chest ultrasound findings include fluid bronchogram (presence of fluid in the airways), multifocal involvement, and pleural effusion.

SUMMARY OF EVIDENCE

Outcome 1	**Time to recovery and treatment failure**		**Importance: Critical/ Important**
# of studies included in MA or SR (and list of authors)	**Study Design/s**	**Key findings**	**Grade level of evidence**
1 (Basnet *et al.*, 2015)	Individual cohort study	Absence of hypoxia (SpO2 < 90%) OR 0.52 (1.33, 2.74). p <0.001 Absence of any danger sign (nasal flaring, grunting, head bobbing, cyanosis) OR 0.61 (1.18, 2.32) p = 0.004 Absence of radiologic pneumonia OR 0.45 (1.49, 3.31) p < 0.001	Moderate

Outcome 2	**Disease progression or complicated pneumonia**		**Importance: Critical/ Important**
# of studies included in MA or SR (and list of authors)	**Study Design/s**	**Key findings**	**Grade level of evidence**
1 (Chen *et al.,* 2017)	Individual cohort study	Absent multifocal involvement and ICU admission OR 0.19 p = 0.0027 Absent multifocal involvement and LOS > 9 days OR 0.10 p = 0.02 Absent pleural effusion and LOS > 9 days OR 0.17 p = 0.003 Absent fluid bronchogram and LOS > 9 days OR 0.20 p = 0.006 Absent multifocal involvement and tube thoracotomy OR 0.05 p = 0.0262 Absent fluid bronchogram and tube thoracotomy OR 0.08 p = 0.0262	Low
1 (Erdman *et al.,* 2015)	Individual cohort study	End-point pneumonia vs normal CXR using CRP Sn 80% Sp 78.7% +LR 3.8 -LR 0.25 End-point pneumonia vs normal CXR using PCT Sn 70% Sp 69.2% +LR 2.3 -LR 0.43	Very Low

1 (Wolf *et al.*, 2015)	Individual observational cohort	Median time of normalization of physiologic parameters (in hours, CI 95%) **Age <2years** Fever: 14.5 (4.5-45.3) Tachycardia: 4.5 (0.3-18.4) Tachypnea: 38.6 (18.7-68.9) **Age 2-4 years** Fever: 18.4 (2.8-42.8) Tachycardia: 21.8 (5.7-51.9) Tachypnea: 31.6 (9.5-61.9) **Age 5-17 years** Fever: 10.6 (0.8-34) Tachycardia: 18 (5.8-42.2) Tachypnea: 24.3 (10.8-59.2)	Low

CONTEXT AND CONSIDERATIONS

It is important to define several terms that are used in these recommendations. *Absolute clinical stability* is defined as the resolution of *ALL* pneumonia-associated signs and symptoms AND recovery to pre-pneumonia health status. *Approaching clinical stability* is defined as resolution of *ANY* pneumonia-associated sign or symptom OR delayed recovery to pre-pneumonia health status.

It is also important to note that even if absence of radiographic pneumonia on repeat chest X-ray is one of the ancillary parameters that determines good response to therapeutic management, performing a follow-up chest X-ray is not routinely done as long as there is clinical improvement as evidenced by the physiologic parameters mentioned.

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Clinical Question 9

AMONG INFANTS AND CHILDREN AGED 3 MONTHS TO 18 YEARS WITH COMMUNITY-ACQUIRED PNEUMONIA, WHAT CAN BE DONE IF THE PATIENT IS NOT RESPONDING TO CURRENT THERAPEUTIC MANAGEMENT?

KEY RECOMMENDATIONS

For patients classified as having non-severe PCAP and are not improving or clinically worsening within 24-72 hours after initiating therapeutic management, diagnostic evaluation is considered to determine if any of the following is present: *(Conditional recommendation, low-grade evidence)*

- Coexisting or other etiologic agents
- Etiologic agent resistant to current antibiotic, if being given
- Other diagnosis
  - Pneumonia-related complication
    - Pleural effusion
    - Necrotizing pneumonia
    - Lung abscess
  - Asthma
  - Pulmonary tuberculosis

For patients as having non-severe PCAP and are not improving or clinically worsening within 24-72 hours after initiating a therapeutic management,

and started on standard dose Amoxicillin at 40-50mg/kg/day, increasing the dose to 80-90mg/kg/day Q12 **OR** shifting to Amoxicillin-Clavulanate at 80-90mg/kg/day (based on Amoxicillin content using a 14:1 amoxicillin:clavulanate formulation) Q12 **OR** Cefuroxime at 20-30 mg/kg/day Q12 is considered.

and started on high-dose Amoxicillin, Amoxicillin-Clavulanate or Cefuroxime, admitting the patient for parenteral antibiotics is considered.

adding a macrolide is considered when an atypical pathogen is highly suspected:

Azithromycin at 10mg/kg/day PO or IV Q24 for 5 days, particularly in infants less than 6 months old whom pertussis is entertained, **OR** 10mg/kg/day Q24 for 3-5 days **OR** 10mg/kg/day on day 1 followed by 5 mg/kg/day Q24 for days 2 to 5

Clarithromycin at 15mg/kg/day Q12 for 7 to 14 days

(*Conditional recommendation, low-grade evidence*)

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KEY RECOMMENDATIONS

For patients classified as having severe PCAP and are not improving or clinically worsening, within 24-72 hours after initiating a therapeutic management, diagnostic evaluation is considered to determine if any of the following is present:

- Coexisting or other etiologic agents
- Etiologic agent resistant to current antibiotic, if being given
- Other diagnosis
  - Pneumonia-related complication
    - Pleural effusion
    - Pneumothorax
    - Necrotizing pneumonia
    - Lung abscess
  - Asthma
  - Pulmonary tuberculosis
  - Sepsis

(Conditional recommendation, Expert opinion)

The following diagnostic evaluations are considered in the presence of treatment failure in severe PCAP:

- Cultures
- Nucleic acid amplification test (e.g. PCR)
- Serology
- Imaging modalities: (chest radiography, UTZ or CT scan)
- Biomarkers (e.g. CBC, CRP, PCT)

(Conditional recommendation, Expert opinion)

For patients that are not improving or clinically worsening within 24-72 hours after initiating a therapeutic management, a referral to a specialist is considered. *(Conditional recommendation, Expert opinion)*

CONTEXT AND CONSIDERATIONS

The recommendations as to the clinical approach to take for the different severities of pediatric community-acquired pneumonia are all based on expert opinion and would still warrant validation studies. Each clinical scenario of non-response to treatment may warrant different approaches hence studies designed to individualize the clinical pathways and validate their effectiveness need to be undertaken.

Regarding ancillary work-up, performing a blood culture is not routinely done in pediatric patients with community-acquired pneumonia, especially in non-severe cases, as studies have shown a low positive culture yield of only 0.4% to 2.5% of cases. However, if a patient is classified as having severe pneumonia and is suspected have concomitant septicemia or bacteremia, blood culture and sensitivity is considered. Other appropriate cultures may be included and are not limited to sputum, bronchoalveolar lavage and endotracheal aspirates.

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Clinical Question 10

AMONG INFANTS AND CHILDREN AGED 3 MONTHS TO 18 YEARS, WHAT CLINICAL PARAMETERS WILL DETERMINE THAT SWITCH THERAPY CAN BE CONSIDERED IN THE MANAGEMENT OF SEVERE COMMUNITY-ACQUIRED PNEUMONIA?

KEY RECOMMENDATION

Switch therapy is considered among patients with bacterial PCAP when **ALL** of the following clinical parameters are present: (*Conditional recommendation, low-grade evidence*)

- Current parenteral antibiotic has been given for at least 24 hours
- Afebrile for at least 8 hours without the use of any antipyretic drug
- Able to feed and without vomiting or diarrhoea
- Presence of clinical improvement as defined by **ALL** of the following:
  - Absence of hypoxia
  - Absence of danger signs
  - Absence of tachypnoea
  - Absence of fever
  - Absence of tachycardia

SUMMARY OF EVIDENCE

RECOMMENDATION:

1. Current parenteral antibiotic has been given for at least 24 hours
2. Afebrile for at least 8 hours without the use of any antipyretic drug
3. Able to feed and without vomiting or diarrhea

Outcome 1	**Length of hospital stay and Readmission rate (within 30 days upon discharge)**		**Importance: CRITICAL**
# of studies (and list of authors)	**Study Design/s**	**Key findings**	**Grade level of evidence**
1 (In-iw *et al.* 2015)	Individual randomized trial	Length of hospital stay: Conventional therapy: 4.77+1.5 days Switch therapy: 3.8+1.6 days P value 0.019 Readmission rate: Conventional therapy: 1 (3.8%) Switch therapy: 2 (6.5%) P value 0.66	MODERATE

RECOMMENDATION:
Presence of clinical improvement as defined by ALL of the following:
Absence of hypoxia, danger sign, tachypnoea, fever, tachycardia

Outcome 1	**Time to recovery and treatment failure**		**Importance: CRITICAL**
# of studies (and list of authors)	**Study Design/s**	**Key findings**	**Grade level of evidence**
1 (Basnet *et al.,* 2015)	Cohort	Absence of hypoxia (SpO2 < 90%) OR 0.52 (1.33, 2.74) p <0.001 Absence of any danger sign (nasal flaring, grunting, head bobbing, cyanosis) OR 0.61 (1.18, 2.32) p = 0.004	MODERATE
Outcome 2	**Physiologic Parameters and Time to clinical stability**		**Importance: CRITICAL**
# of studies included in MA or SR (and list of authors)	**Study Design/s**	**Key findings**	**Grade level of evidence**
1 (Wolf *et al.*, 2015)	Individual observational cohort	Median time of normalization of physiologic parameters (in hours, CI 95%) **Age <2years** Fever: 14.5 (4.5-45.3) Tachycardia: 4.5 (0.3-18.4) Tachypnea: 38.6 (18.7-68.9) **Age 2-4 years** Fever: 18.4 (2.8-42.8) Tachycardia: 21.8 (5.7-51.9) Tachypnea: 31.6 (9.5-61.9) **Age 5-17 years** Fever: 10.6 (0.8-34) Tachycardia: 18 (5.8-42.2) Tachypnea: 24.3 (10.8-59.2)	Low

CONTEXT AND CONSIDERATIONS

Switch therapy is an approach in the management involving discontinuation of intravenous (IV) antibiotics and be shifted to oral antibiotics as soon as the patient's condition allows. The choice of antibiotics from intravenous to oral must take into account the appropriate antibacterial spectrum, the pharmacokinetics and pharmacodynamics, and should have proven clinical efficacy in the condition being treated. There is no new evidence found for this clinical question, hence, the TWG decided to carry over the recommendations in the 2016 CPG update. The first three recommendations are taken from the inclusion criteria of the RCT done by In-iw, *et al*., comparing the treatment outcomes of switch therapy and conventional therapy in pediatric patients with community-acquired pneumonia who required hospitalization. The clinical outcomes showed that there was statistically significant reduction in length of hospital stay found in the switch therapy group ($p = 0.019$), whereas the readmission rate for both groups was not significantly different ($p = 0.66$). Furthermore, switch therapy can also be considered in the presence of clinical improvement as defined in the studies of Basnet *et al*. and Wolf *et al.* as absence of danger signs and hypoxia and normalization of fever, tachypnea and tachycardia, respectively. The advantages of switch therapy include reduced length of hospital stay which can lead to lesser risk of infections from infected IV lines and hospital pathogens and reduced cost. In an observational study of Sharma, *et al*., the switch therapy group showed lower number of complications but there was no difference in treatment outcome when compared to the standard treatment group. Restricted and monitored antibiotics should follow the DOH-Antimicrobial Stewardship Manual of Procedures regarding switch therapy.

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Clinical Question 11

AMONG INFANTS AND CHILDREN AGED 3 MONTHS TO 18 YEARS, WHAT ADJUNCTIVE TREATMENT IS EFFECTIVE FOR COMMUNITY-ACQUIRED PNEUMONIA?

KEY RECOMMENDATIONS

Vitamins A is strongly recommended as adjunctive treatment for measles pneumonia. (*Strong recommendation, high-grade evidence*)

Zinc is not considered as adjunctive treatment for severe PCAP as it does not have any effect in shortening recovery time. *(Conditional recommendation, low-grade evidence)*

Vitamin D is not considered as adjunctive treatment for severe PCAP as it does not reduce the length of hospital stay. *(Conditional recommendation, low-grade evidence)*

Bronchodilators are considered as adjunctive treatment for PCAP in the presence of wheezing. *(Conditional recommendation, expert opinion)*

Mucokinetic, secretolytic, and mucolytic agents are not considered as adjunctive treatment for PCAP. *(Conditional recommendation, low-grade evidence)*

There is insufficient evidence to recommend the use of the following as adjunctive treatment for PCAP: (*Very low-grade evidence*)

- Oral folate
- Probiotics
- Vitamin C
- Virgin coconut oil (VCO)
- Nebulization with saline solution
- Steam inhalation

SUMMARY OF EVIDENCE

Outcome	**Treatment success**		**Importance: CRITICAL**
# of studies included in MA or SR (and list of authors)	**Study Design/s**	**Key findings**	**Grade level of evidence**
4 CHANG (2014)	SR	Pediatric - Mucolytics - no significant difference between groups (odds ratio (OR) 0.40, 95% confidence interval (CI) 0.10 to 1.62) In the combined data (adult & pedia) meta-analysis showed no significant difference between groups for the primary outcome of 'not cured or not improved' (OR 0.85, 95% CI 0.40 to 1.80)	LOW

Outcome	**Decreased length of stay, treatment failure, time to recovery**		**Importance: CRITICAL**
# of studies included in MA or SR (and list of authors)	**Study Design/s**	**Key findings**	**Grade level of evidence**
11 (Brown *et al.,* 2020)	SR/MA	There is no evidence that adjunctive zinc treatment improves recovery from pneumonia in children in LMICs. Treatment failure - For all pxs (OR 0.95 (95% CI 0.80 to 1.14) For severe pneumonia (OR 0.93 (95% CI 0.75 to 1.14) Time to recovery - HR 1.01 (95% CI 0.89 to 1.14)	Moderate
7 (Das *et al.,* 2018)	SR/MA	time to resolution of acute illness (hours) (mean difference (MD) -0.95, 95%(CI) -6.14 to 4.24; mortality rate (risk ratio (RR) 0.97, 95% CI 0.06 to 15.28; duration of hospitalisation (MD 0.49, 95% CI -8.41 to 9.4 time to resolution of fever (MD 1.66, 95% CI -2.44 to 5.76)	Low
13 (Yang *et al.,* 2021)	SR/MA	Time to resolution of pneumonia (hours) MD = −1.02; 95% CI, −5.74 to 3.70; P = .67; I^2 = 12%; Duration of hospitalization (hours). MD = −1.40; 95% CI, −9.53 to 6.73; P = .74; I^2 = 12% Recovery rate of pneumonia. recovery rate of pneumonia in the vitamin D group (RR = 1.28; 95% CI, 0.94–1.74; I^2 = 13%) compared with that in the placebo group, which was not statistically different (P = .12)	

CONTEXT AND CONSIDERATIONS

Vitamin A is a necessary substrate for preserving epithelial cell integrity and also plays a role in immune modulation. WHO recommends that all children diagnosed with measles, in communities where vitamin A deficiency is a recognized problem, vitamin A should be administered as follows: 100,000 IU by mouth for infants younger than 12 months of age and 200,000 IU for older children. The dose should be repeated in 24 hours and after 4 weeks in the presence of ophthalmologic signs of vitamin a deficiency such as night blindness, xerophthalmia or Bitot's spots (grayish white deposits on the bulbar conjunctiva adjacent to the cornea).

Mucokinetic agents like short-acting bronchodilators (SABA) and secretolytic or mucolytic agents such as ambroxol, carbocisteine, acetylcysteine, and bromhexine are not suggested to be used as adjunctive treatment during the course of illness of non-severe pneumonia due to the limited studies and conflicting outcomes that were reported in these studies (Chang et al., 2014). Furthermore, this same study also mentioned that there is insufficient evidence to decide whether OTC medications for cough associated with acute pneumonia are beneficial.

Bronchodilators are drugs that relax the airway smooth muscles. Narrowing or obstruction of the bronchial airways which leads to wheezing may occur during an infection, an episode of allergy and/or hyperreactive airway disease. Hence, bronchodilators are considered in PCAP in the presence of wheezing.
Based on the WHO recommendations, zinc can be added to the management of pediatric community acquired pneumonia, however recent evidences show that zinc does not shorten the recovery time of childhood pneumonia.

As part of standard of care in the management of pediatric community-acquired pneumonia, hydration and oxygenation if indicated must be administered.

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Clinical Question 12

AMONG INFANTS AND CHILDREN AGED 3 MONTHS TO 3 YEARS, WHAT INTERVENTIONS ARE EFFECTIVE FOR THE PREVENTION OF COMMUNITY-ACQUIRED PNEUMONIA?

KEY RECOMMENDATIONS

The following strategies are recommended to prevent PCAP:

Vaccination against *Streptococcus pneumoniae* (pneumococcus), *Haemophilus influenzae* type b (Hib), *Bordetella pertussis (pertussis)*, *Rubeola* virus (measles) and *Influenza* virus *(Strong recommendation; high-grade evidence)*

Breastfeeding *(Strong recommendation; high-grade evidence)*

Avoidance of environmental tobacco smoke or indoor biomass fuel exposure *(Strong recommendation; high-grade evidence)*

Zinc supplementation *(Strong recommendation; moderate-grade evidence)*

There is insufficient evidence to recommend Vitamin A, C or D supplementation for the prevention of PCAP. *(Very low-grade evidence)*

SUMMARY OF EVIDENCE

Outcome 1	**Disease prevention and PCV**		**Importance: Critical**
Number of studies (and list of authors)	**Study Design/s**	**Key findings**	**Grade level of evidence**
(Zar et al., 2020)	CPG	In children aged 24–59 months, a reduction of 9% (95%CI: 5–14%, p-value < 0.001) and of 24% (95%CI: 12–33%, p-value < 0.001) in the hospitalization rates for clinically and radiologically confirmed pneumonia, respectively, after the introduction of the novel PCVs.	**High**
12 (Alicino et al., 2017)	Meta-analysis of Cohort and Case-control studies	In children aged < 24mos , a reduction of 17% (95%CI: 11–22%, p-value < 0.001), and of 31% (95%CI: 26–35%, p-value < 0.001) in the hospitalization rates respectively for clinically and radiologically confirmed pneumonia, respectively, after the introduction of the novel PCVs.	**Low**

Outcome 2	**Disease prevention and breastfeeding**		**Importance: Critical**
Number of studies (and list of authors)	**Study Design/s**	**Key findings**	**Grade level of evidence**
(Zar et al., 2020)	CPG	Breastfeeding has been shown to decrease the incidence of pneumonia in young children by up to 32% (Wright et al., 1998) Shorter duration of breastfeeding is associated with pneumonia mortality, particularly among infants 95% confidence interval (CI) 0.67 - 332.74) (Lamberti et al., 2013)	**High**
Outcome 3	**Disease prevention and avoidance of tobacco smoke or indoor biomass fuel exposure**		**Importance: Important**
Number of studies (and list of authors)	**Study Design/s**	**Key findings**	**Grade level of evidence**
(Zar et al., 2020)	CPG	Reduction in tobacco smoke or indoor fuel exposure Active and passive exposure to tobacco should be strongly discouraged in women of child-bearing age, particularly among pregnant women, and more generally in the household. Exposure to fumes from indoor cooking fuels should be limited by opening windows and doors when cooking; the chimney should function well; the stove should be cleaned and maintained; and there should be safe child location practices while fires are burning in the house. The practice of carrying children on caregivers' backs while cooking is an independent risk factor for pneumonia morbidity and mortality. Children should sleep in rooms separate from where food is cooked	**High**
Outcome 4	**Disease prevention and zinc supplementation**		**Importance: Important**
Number of studies (and list of authors)	**Study Design/s**	**Key findings**	**Grade level of evidence**
6 (ZS et al., 2016)	SR/MA RCTs	Analysis showed that zinc supplementation reduced the incidence of pneumonia by 13% (fixed-effect risk ratio (RR) 0.87; 95% confidence interval (CI) 0.81 to 0.94, six studies, low-quality evidence) and prevalence of pneumonia by 41% (random-effects RR 0.59; 95% CI 0.35 to 0.99, one study, n = 609, low-quality evidence). On subgroup analysis, zinc reduced the incidence of pneumonia defined by specific clinical criteria by 21% (i.e. confirmation by chest examination or chest radiograph) (fixed-effect RR 0.79; 95% CI 0.71 to 0.88, four studies, n = 3261), but had no effect on lower specificity pneumonia case definition (i.e.	**Moderate**

		age-specific fast breathing with or without lower chest indrawing) (fixed-effect RR 0.95; 95% CI 0.86 to 1.06, four studies, n = 1932)	
Outcome 5	**Disease prevention and Vitamin C supplementation**		**Importance: Important**
Number of studies (and list of authors)	**Study Design/s**	**Key findings**	**Grade level of evidence**
7 (Padhani et al., 2020)	SR/MA RCTs (5) Quasi-RCT (2)	Due to the small number of included studies and very low quality of the existing evidence, we are uncertain of the effect of vitamin C supplementation for the prevention and treatment of pneumonia	**Very Low**
Outcome 6	**Disease prevention and Vitamin D supplementation**		**Importance: Important**
Number of studies (and list of authors)	**Study Design/s**	**Key findings**	**Grade level of evidence**
4 (MY et al., 2016)	SR/MA RCTs	For pneumonia, episodes of 'radiologically confirmed' first or only episode of pneumonia were little different in the supplemented and un-supplemented group (Rate Ratio: 1.06, 95% confidence interval (CI) 0.89 to 1.26; two trials, 3134 participants, moderate quality evidence), and similarly for children with confirmed or unconfirmed pneumonia (RR 0.95, 95% CI 0.87 to 1.04; one trial, 3046 participants). In the single large trial from Afghanistan, the trial authors reported that vitamin D supplementation was associated with an increase in repeat episodes of pneumonia confirmed by chest radiograph (RR 1.69, 95% CI 1.28 to 2.21; one trial, 3046 participants), but not reflected in the outcome of confirmed or unconfirmed pneumonia (RR 1.06, 95% CI 1.00 to 1.13; one trial, 3046 participants).	**Very Low**

CONTEXT AND CONSIDERATIONS

Advances in the prevention of paediatric pneumonia have led to a reduction in the burden of disease and have lowered the case fatality risk and mortality over the past two decades. The following strategies can prevent community-acquired pneumonia in children:

Vaccination

Pneumonia can be prevented by immunizing against *Haemophilus influenzae* type b (Hib), pneumococcus, measles and pertussis (whooping cough) (WHO 2015). WHO also recommends the inclusion of PCVs in childhood immunization programs worldwide. The use of pneumococcal vaccine should be complementary to other disease prevention and control measures, such as appropriate case management, promotion of exclusive breastfeeding for the first 6 months of life and reducing known risk factors such as indoor air pollution and tobacco smoke. The 23-valent pneumococcal polysaccharide vaccine is not routinely recommended for immunocompetent children and is only given to children >2 years old, who are

at risk of developing invasive pneumococcal disease, including those with chronic diseases, with primary and secondary immune deficiencies and with functional or anatomical asplenia.

Breastfeeding

Nutrition including breastfeeding for the first six months of life plays a major role by boosting immunity against causative organisms of pneumonia (WHO 2015). Breastfeeding has been shown to decrease the incidence of pneumonia in young children by up to 32%. Shorter duration of breastfeeding is associated with pneumonia mortality, particularly among infants < 5 month of age. Mortality among infants who are not breastfed compared with exclusively breastfed infants through 5 months of age is ~15-fold higher (relative risk (RR) 14.97; 95% confidence interval (CI) 0.67 - 332.74). (Zar, 2020)

Avoidance of environmental tobacco smoke or indoor biomass fuel exposure

Pneumonia remains the leading cause of childhood mortality outside the neonatal period, in low- and middle-income countries. Environmental tobacco smoke (ETS) exposure is strongly associated with an increased risk for pneumonia and of severe disease. ETS exposure often begins in utero with maternal smoking or exposure. Antenatal or early-life ETS exposure, from maternal, household, or community contacts, may impact on the susceptibility of the infant to develop respiratory disease and impair lung development. However, the effects of postnatal tobacco smoke exposure may also be substantial, leading to poorer respiratory health. (Vanker, 2017). ETS exposure is reported as an important risk factor for childhood LRTI in several studies. A systematic review found smoking by either parent (OR 1.22, 95% CI 1.10–1.35), both parents (OR 1.62, 95% CI 1.38–1.89), or a household member (OR 1.54, 95% CI 1.40–1.69) significantly increased the risk of LRTI (Vanker, 2017). Exposure to household air pollution almost doubles the risk for childhood pneumonia and is responsible for 45% of all pneumonia deaths in children less than 5 years old. (WHO, Household Air Pollution and Health, 22 September, 2021)

Zinc supplementation

Zinc plays an important role in cell regeneration, immunity and growth. Zinc deficiency decreases T-lymphocytes and T-helper, impairs macrophage function and reduced killer cells, and adversely impacts innate immunity affecting interferon (IFN) gamma production, interleukin-2 (IL-2) and tumor necrosis factor-α (TNF-α)(Lassi, 2016). A local study done by *Goyena et al.* assessed the adequacy of dietary zinc intake and the prevalence and associated factors of serum zinc deficiency among Filipino preschool-age children 6–71 months old. Data from the 8th National Nutrition Survey (NNS) conducted in 2013, involving 2,892 preschool-age children, were analyzed. Almost half (47.2%) of preschool-age children had inadequate zinc intake. The national prevalence of serum zinc deficiency was 17.9%, and it is highest among children 6–23 months old and those from rural, poorest, and food-insecure households relative to other subgroups (Goyena, 2021). Daily supplementation with 10mg of Zinc (as gluconate or sulfate) for at least 4 to 6 months can prevent pneumonia in children aged 2 to 59 months. Zinc supplementation in children increases levels of complement in the blood that modulate the function of T-lymphocytes, T-helper, macrophages and neutrophils and hence improves the ability to fight infection. Zinc supplementation improves circulating levels of T-lymphocytes and other macrophages that enhance ability to fight infection. (Lassi, 2016)

The Technical Working Group did not find robust evidence that supplementation with vitamin A, C or D can prevent pneumonia in children.

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AREAS FOR FUTURE RESEARCH

The 2021 PAPP/PIDSP Joint Task Force on PCAP has identified several gaps in knowledge in the evaluation and management of pediatric community-acquired pneumonia. There is paucity of data in some of the clinical questions due to limited high quality studies, more particularly in the local setting. Objective outcome measures should be established to understand fully the difference in the clinical course between causative agents, across all pediatric age groups and socio-economic strata. Relevant outcomes to be considered include time to resolution of observed abnormalities in the clinical and ancillary parameters, development of pneumonia-associated complications, and mortality. Other outcomes that can be measured to assess the effectiveness of interventions include the requirement for hospitalization, length of hospital stay, readmission after hospital discharge, persistence of clinical and laboratory signs and symptoms, and costs of care. These outcomes should be measured, standardized and compared to guide clinicians in decision-making and ultimately improve patient care. We, therefore, recommend adequately powered, well-designed and well-conducted clinical trials in the following areas to provide more specific, evidence-based guidance in the future:

- Identification of clinical feature/s or oxygen saturation level to accurately predict PCAP
- Evaluation of the accuracy of scoring systems using clinical features and oxygen saturation level in predicting the likelihood of PCAP
- Standard triage criteria for selection of the initial site of care, whether ambulatory or in-hospital settings, and to identify patients at high or low risk of clinical deterioration, pneumonia-associated complications and mortality
- Epidemiology of PCAP caused by specific bacteria, viruses, atypical bacteria, and presence of co-infection, especially in areas with good vaccine coverage against *Streptococcus pneumoniae* and *Hemophilus influenzae* type b
- Use of less or non-invasive diagnostic tests using blood, induced sputum, or other respiratory tract secretions and lung tissues that will reliably/accurately document clinical disease caused by one or more pathogens
- Use of laboratory tests, such as acute-phase reactants like procalcitonin, that to aid in clinical diagnosis, severity classification and assessment of appropriate treatment response in PCAP.
- Clinical, laboratory and epidemiological risk factors for severe PCAP, respiratory failure and hospitalization in the local setting
- Best imaging techniques that provide will high-quality diagnostic information with minimal radiation exposure
- Development and validation of a standard criteria for interpretation of chest radiographs in the diagnosis of PCAP
- Evaluation of the role of point-of-care chest ultrasonography (POCUS) as a diagnostic aid for PCAP in local setting
- Strengthening of antimicrobial resistance surveillance and reporting in the local and national levels and disseminate these data to guide local and institutional policy-makers of antimicrobial stewardship programs.
- Information on the lowest effective antimicrobial dose and shortest optimal duration of therapy to decrease risk of toxicity and development of resistance
- Role of antimicrobial therapy for atypical bacterial pathogens in PCAP particularly children <5 years of age.
- Assessment of the value of combination antimicrobial therapy for severe pneumonia, especially the addition of a macrolide in the regimen
- Impact of viral testing on patient outcomes and antibiotic prescribing behavior to avoid inappropriate use of antibiotic therapy.
- Use of clinical, laboratory, and oximetry parameters that will reliably assess the outcome of interventions for non-severe and severe PCAP
- Cost-effectiveness analysis of each diagnostic and therapeutic intervention for PCAP
- Standard discharge criteria required for children who continue to need antibiotics administered intravenously, intramuscularly, or orally
- Role of parenteral outpatient therapy for severe pneumonia and use oral antibiotics for severe bacterial PCAP in hospitalized patients

- Outcome of switch therapy in the management of severe PCAP
- Role of vitamin C and D in the treatment and prevention of PCAP
- Assessment of the value of adjunctive treatment (such as oral folate, probiotics, virgin coconut oil, steam inhalation, and nebulization with saline solution) in the management of PCAP
- Identification of non-clinical factors including psychosocial or behavioral concerns, socio-economic issues, likelihood of non-adherence to prescribed therapy, and other barriers medical care
- Analysis of medical costs in the management of PCAP, including non-medical costs such as lost parental income and family stress
- Long-term outcomes of children who had one or more episodes of PCAP

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CLINICAL PRACTICE GUIDELINES

PHILIPPINE GUIDELINES ON PERIODIC HEALTH EXAMINATION: PEDIATRIC IMMUNIZATION

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

EXECUTIVE SUMMARY

This Clinical Practice Guideline for the Periodic Health Examination (Pediatric Immunization) is an output from the joint undertaking of the Department of Health and National Institutes of Health-Institute of Clinical Epidemiology.

This clinical practice guideline is a systematic synthesis of scientific evidence on immunization for the prevention of human papilloma virus (HPV) infection, influenza, typhoid fever, Japanese encephalitis, poliomyelitis, meningococcal infection, and Hepatitis A in the pediatric population. The CPG provides nine (9) recommendations on prioritized questions regarding the relevant vaccines for preventing these seven (7) diseases.

Recommendations are based on the appraisal of the best available evidence on each of the eight identified clinical questions. The CPG is intended to be used by general practitioners and specialists in the primary care setting, policy makers, employers and administrators, allied health practitioners and even patients. The guideline development process followed the widely accepted Grading of Recommendations, Assessment, Development, and Evaluation or the GRADE approach including GRADE Adolopment, a systematic process of adapting evidence summaries and the GRADE Evidence to Decision (EtD) framework. [1,2] It includes 1) identification of critical questions and critical outcomes, 2) retrieval of current evidence, 3) assessment and synthesis of the evidence base for these critical questions, 4) formulation of draft recommendations, 5) convening of a multi-sectoral stakeholder panel to discuss values and preferences and assess the strength of the recommendations, and 6) planning for dissemination, implementation, impact evaluation and updating.

The recommendations in this CPG shall hold and will be updated after 3 years or when new evidence arise.

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Lastly, this guideline is invaluable because of the contribution and participation of panelists from different sectors of healthcare who committed their time and effort to share their knowledge, experience, and expertise in analyzing the scientific evidence and their values and preferences in formulating the recommendations with consideration of patients and the current healthcare system in the country.

PERIODIC HEALTH EXAMINATION PHASE 2 TASK FORCE 2021

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PERIODIC HEALTH EXAMINATION TASK FORCE ON PEDIATRIC IMMUNIZATION 2021

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Consensus Panel Meeting Facilitator
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DECLARATION OF CONFLICT OF INTEREST OF CONSENSUS PANELISTS

- **Cynthia Alcantara-Aguirre, MD** – Vice President, Immunization Partners for Asia Pacific; Lecturer for Japanese encephalitis and MCV4
- **Rosemarie T. Santana-Arciaga, MD, MSc** – Chairman, Dept. of Pediatrics, Zamboanga Peninsula Medical Center; Past-President, PPS–Southwestern Mindanao Chapter; stocks in Zamboanga Peninsula Medical Center and Arciaga Pediatric Clinic
- **Cerelyn E. Dacula, MT(ASCPi), MD, MSc** – Research on vaccines; Medical Specialist II, Food and Drug Administration; Member, NAEFIC until 2018; Board Member, FEU Medical Society; FDA representative – Dengue Immunization Technical Working Group
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- **Melissa Joyce Ramboanga, MD** – Medical Specialist II, UP-PGH; Member, Phil. Ambulatory Pediatric Association, stocks in Medical Center Taguig
- **Marysia Stella P. Tiongco-Recto, MD** – Professor, UP College of Medicine; stocks in Makati Medical Center and Asian Hospital Medical Center
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SUMMARY OF RECOMMENDATIONS

No.	Recommendation	Certainty of Evidence	Strength of Panel Recommendation
1	**Should human papilloma virus vaccine be recommended to apparently healthy girls aged 9 to 18 years?** Among apparently healthy girls aged 9 to 18 years old, we suggest HPV vaccination using bivalent or quadrivalent HPV vaccine.	Low	Weak
2	**Should influenza vaccine be recommended to apparently healthy children?** Among healthy children aged 6 months to 18 years, we suggest annual influenza immunization with inactivated influenza vaccine.	Low	Weak
3	**Should typhoid vaccine be recommended to apparently healthy children?** Among apparently healthy children and adolescents, we suggest typhoid vaccination with either typhoid conjugate vaccine for those aged 6 months to 18 years, or typhoid polysaccharide vaccine for those aged 2 to 18 years, in areas of high burden of disease.	Very Low	Weak
4	**Should meningococcal vaccine be recommended in apparently healthy children in the Philippines, a country with low incidence of meningococcal infection?** ***Recommendation 1***: Among at-risk children and adolescents, we suggest immunization with meningococcal vaccine. ***Recommendation 2:*** Among healthy children and adolescents, we suggest immunization with meningococcal vaccine during outbreak situations.	Very Low Very Low	Weak Weak
5	**Should Japanese encephalitis vaccine be given to apparently healthy children aged 18 years and below?** Among apparently healthy children aged 18 years and below from high-risk areas, we suggest immunization with Japanese Encephalitis vaccine.	Very Low	Weak
6	**Should inactivated poliovirus vaccine be given over bivalent oral poliovirus vaccine to healthy children 6 weeks to 5 years of age?** Among healthy infants, we recommend vaccination with bivalent oral poliovirus vaccine (bOPV) plus inactivated poliovirus vaccine (IPV) or IPV alone if bOPV is not available.	Moderate	Strong

7	**Should oral polio vaccine be given in the neonatal period?** Among healthy infants less than 28 days-old, we suggest immunization with oral poliovirus vaccine during outbreak response immunization activities.	Very Low	Weak
8	**Should Hepatitis A vaccine be recommended to apparently healthy children?** Among healthy children, we suggest immunization with hepatitis A vaccine starting at 12 months of age.	Very Low	Weak

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CHAPTER 1: INTRODUCTION

The Philippine Guidelines on Periodic Health Examination (PHEX) was first published in 2004.[1] It was a comprehensive appraisal and synthesis of evidence on screening interventions committed to providing early prevention services among apparently healthy Filipinos. It was a long-awaited publication and the first to offer evidence-based recommendations for screening tests made possible through the concerted effort of various medical and paramedical organizations composed of more than a hundred experts, researchers, and stakeholders.[1] It was inspired by the Canadian and the US Preventive Services Task Forces, but it was tailored to the Philippine setting.

This 2021 Philippine Guidelines support the objectives stated in the Universal Health Care Act which gives all Filipinos access to high-quality and affordable medical services, including primary care benefits.[2] In order to deliver truly comprehensive, holistic, evidence-based preventive health services, there is a pressing need to update the Philippine Guidelines and expand its recommendations to include guidance on immunization in children, the most vulnerable subset of the population.

Immunization is one of the most important public health achievements of the 20th century, second only to clean water.[3] Increased life expectancy from past decades, largely attributed to improved child survival rates and reduced child mortality from vaccine-preventable diseases, have shown that vaccines underpin disease prevention and control programs and are essential for global health security.[3,4] Furthermore, the current COVID-19 pandemic has demonstrated that vaccines are vital for controlling emerging infectious diseases, and that without it, the threat of future pandemics can and will continue to strain even the most resilient health systems.[4]

Immunization is an essential component of primary health care as it has been shown to benefit the individual, the community and the world.[5] Vaccines protect vulnerable populations from disability and death, prevent the spread of disease, promote socioeconomic growth and development and help ensure a healthier, safer world.[5,6]

This is the first clinical practice guideline in pediatric immunization since the establishment of the Expanded Program on Immunization in 1976.[3] The main objective of this CPG is to provide evidence-based recommendations and best practices on immunization for the prevention of vaccine-preventable diseases outside the scope of routine infant immunization provided by the National Immunization Program (NIP).[3]

Seven vaccines indicated for the pediatric population were prioritized for review, namely, vaccines for human papilloma virus (HPV) infection, influenza, typhoid fever, Japanese encephalitis, poliomyelitis , meninigococcal infection and Hepatitis A. While the efficacy, safety and socioeconomic impact of the major components of the NIP like the Hepatitis B, BCG and measles vaccines are already well-established, the effects of these 7 vaccines on critical outcomes such as burden of illness, morbidity and mortality, disease-related hospitalization, immunogenicity, safety and cost-effectiveness in the pediatric population are less defined.

Conclusions from the systematic review of evidence can be used to assess each vaccine's eligibility for inclusion in the NIP (influenza and typhoid vaccine), support their continued use in existing immunization programs (Japanese encephalitis, polio, meningococcal and HPV vaccines), and/or address controversy surrounding their use (OPV). These recommendations can be used by relevant stakeholders to continuously improve the performance, reach and efficacy of the National Immunization Program.

In the guideline development, evidence-based recommendations for pediatric immunization were formulated using the GRADE Evidence-to-Decision (EtD) framework.[7,8] The EtD framework aims to facilitate the adaptation of recommendations and decisions of experts and stakeholders based on specific contexts, essential health outcomes, benefits, and harms while looking through equity, applicability, and feasibility lenses.

The evidence collated to answer the research questions on pediatric immunization are used in formulating the recommendations. While the beneficial effects of vaccines are well-documented and manifold, immunization also carries potential harm in the form of severe or serious adverse events and rare side effects. Because of the probable safety risk, criteria are set to determine if vaccinating healthy children to prevent a particular condition can be beneficial and pragmatic. The voting panel members used these criteria aligned with the EtD framework: (1) the burden of illness must be high, (2) the benefits of vaccination must outweigh the harms, (3) vaccination is equitable, feasible to implement and acceptable to stakeholders, and (4) the costs of vaccination must be proportional with the potential benefit.

These recommendations are intended for use in the Philippines only since vaccine access and epidemiologic conditions might vary in other countries and warrant different recommendations. Aside from the regulatory agencies and policymakers in the national government, the target users of this guideline on screening strategies include primary care providers, general physicians, specialists, academic training institutions, payors, patients, the general public, and industry partners.

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CHAPTER 2: GUIDELINE DEVELOPMENT METHODOLOGY

2.1 Organization of the Process

Following international standards, the DOH outlined the guideline development process into four phases: 1) preparation and prioritization, 2) CPG generation, 3) CPG appraisal, and 4) implementation in the Manual for CPG Development.[1]

In the preparation and prioritization phase, the Steering Committee set the CPG objectives, scope, target audience, and clinical questions. They identified and formed the working groups involved in creating the evidence base and finalizing the recommendations for each clinical question included.

The evidence review experts (ERE) or the technical working group were tasked to review existing CPGs if available, appraise and summarize the evidence, and draft the initial recommendations. The evidence summaries were then presented to the consensus panel members to finalize the recommendations.

A consensus panel comprised of multisectoral representatives was tasked to review the evidence summaries and develop recommendations during the *en banc* meeting. In the meeting, panelists prioritized critical and important outcomes; discussed necessary considerations revolving around the recommendations and voted on each recommendation and its strength. The panel was also instructed to participate in a modified Delphi activity to decide on recommendations that were not resolved during the *en banc* meeting.

2.2 Creation of the Evidence Summaries

The clinical questions were developed using the PICO (population, intervention, comparator and outcome) format. The ERE searched and appraised international practice guidelines related to pediatric immunization, including but not limited to those of the World Health Organization, United States Centers for Disease Control - Advisory Committee on Immunization Practices, and National Institutes for Health and Care Excellence. If the CPG were of good quality and done within 5 years, the evidence summaries of the CPG were adopted.

Formal appraisal of existing CPGs and their evidence summaries determined the need for an updated systematic search of electronic databases (MEDLINE via PubMed, CENTRAL, Google Scholar) and the need for a de-novo systematic review and meta-analysis for each question. Relevant local databases and websites of medical societies were also included in the search. Keywords were based on PICO (MeSH and free text) of each question. The ERE also contacted authors of related articles to verify details and identify other research studies for appraisal, if needed.

At least two reviewers worked on each PICO question. Evidence reviewers appraised the directness, methodological validity, results, and applicability of each relevant article included. Review Manager, STATA, and GRADEPro were used for the quantitative synthesis of important clinical outcomes for each question. The ERE generated evidence summaries for each of the eight (8) questions. Each evidence summary included evidence on the burden of the problem, benefits, harm, and social and economic impact of the intervention. Other evidence or information that will facilitate in the decision (i.e. cost of vaccination, cost-effectiveness studies, qualitative studies) were also included in the evidence summaries. The Quality of Evidence was assessed using the GRADE approach.[2] See table 1.

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Table 1. Basis for Assessing the Quality of the Evidence using GRADE Approach

Certainty of Evidence	Interpretation
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Factors that lower quality of the evidence are: Risk of bias Important inconsistency of results Some uncertainty about directness High probability of reporting bias Sparse data/Imprecision Publication bias **Additional factors that may increase quality are:** All plausible residual confounding, if present, would reduce the observed effect Evidence of a dose-response gradient Large effect	

2.3 Composition of the CPG Panel

The Steering Committee convened the Consensus Panel (CP), considering possible conflicts of interests of each panel member. To ensure fairness and transparency, the composition was guided by the DOH manual.[1] Content experts and other key stakeholders were invited to join the CP. The key stakeholders included policymakers, patient advocates, allied medical practitioners, and physicians from different settings (eg. academic training institutions, subspecialty societies, private foundations, public primary care settings, and private practice)

2.4 Formulation of the Recommendations

Draft recommendations were formulated based on the quality of evidence, trade-offs between benefit and harm, cost-effectiveness, applicability, feasibility, equity, required resources and uncertainty due to research gaps. Prior to the series of online consensus panel meetings, the consensus panel received the draft recommendations together with evidence summaries based on the EtD framework shown in Table 2. These recommendations, together with the evidence summaries, were presented during the *en banc* meeting.

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Table 2.Detailed considerations based on the EtD framework[3]

Is the problem a priority?
How substantial are the benefits of the vaccine?
How substantial are the harms of the vaccine?
What is the overall certainty of the evidence?
Does the balance between benefit and harm favor vaccination or no vaccination?
How large are the resource requirements (costs)?
What is the certainty of the evidence of resource requirements (costs)?
Does the cost-effectiveness of the vaccine favor vaccination or no vaccination?
What would be the impact on health equity?
Is the vaccine acceptable to key stakeholders?
Is the vaccine feasible to implement?
Is there important uncertainty or variability in how much people value the main outcomes, including the adverse effects and burden of vaccination?

The strength of each recommendation (i.e. strong or weak) was determined by the panel considering all the factors mentioned above. Strong recommendation means that the panel is "confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects" while weak recommendation means that the "desirable effects of adherence to a recommendation probably outweigh the undesirable effect but is not confident."[4]

The recommendation for each question and its strength was determined through voting. A consensus decision was reached if 75% of all CP members agreed.[2] If consensus was not reached in the first voting, questions, and discussions were encouraged. Two further rounds of voting on an issue were conducted. Evidence-based draft recommendations were also revised based on input arrived at by consensus in the *en banc* discussions.

2.5 Managing Conflicts of Interest

The Steering Committee facilitated the whole CPG formulation process, but their members had no direct participation in assessing and synthesizing the evidence, generating the evidence summaries and evidence-based draft recommendations of the Evidence Review Experts, and voting on final recommendations during the *en banc* consensus panel review. They invited the relevant organization to nominate individuals who can become part of the consensus panel.

Each nominee was required to fill out and sign a declaration of interest form and submit their curriculum vitae. The SC and the Oversight Committee screened the nominees for any possible conflict of interest that may bias their decisions. Those with significant potential COI based on the decision of the Oversight Committee were not allowed to vote during the en banc meeting but fully participated in the panel discussions.

2.6 Planning for Dissemination and Implementation

The SC discussed with relevant stakeholders such as DOH and PhilHealth to prepare a dissemination plan that will actively promote the adoption of this guideline with strategies for copyrights. Suggestions ranged from making guidelines available on websites, press conferences, social media sites, professional society conventions, and journal publications.

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CHAPTER 3: RECOMMENDATIONS AND PANEL DISCUSSION

3.1 Human Papillomavirus Vaccine

RECOMMENDATION

Among apparently healthy girls aged 9 to 18 years old, we suggest HPV vaccination using bivalent or quadrivalent HPV vaccine. (Weak recommendation, Low certainty of evidence)

Considerations

- The consensus panel considered the following when formulating this recommendation:
- Prevention of HPV infection is a priority.
- The burden of HPV infection is significant and the benefits of HPV vaccination outweigh the risk of harm. However, some panelists believe that more high-quality studies on cervical cancer as the primary endpoint, safety and cost-effectiveness of the different HPV vaccines are needed to make a strong recommendation.
- Furthermore, the cost is prohibitive and there is disparity in HPV awareness across geographical regions and socioeconomic groups, which raises issues regarding acceptability.

3.1.1 Burden of disease

Cervical cancer is the second most frequent cancer among Filipino women, with an age standardized incidence rate of 15.2 per 100,000 women and a mortality rate of 7.9 per 100,000 women.[1] The link between persistent high-risk oncogenic human papillomavirus (HPV) infection in the cervix and the development of cervical cancer, including its precursor lesions, is well-established.[2] Of the 200 HPV types identified, types 16 and 18 are strongly associated with cervical cancer. Other cancer-causing types include HPV types 31, 45, 33, 35, 39, 51, 52, 56, 58, 66, 68, and 70. Meanwhile, non-cancer causing HPV types (types 6 and 11) are associated with the development of genital warts, also known as condyloma acuminata.[3]

It may take 10 to 20 years for HPV infection to transform into invasive carcinoma. While most cervical cancer precursor lesions spontaneously regress over time, it is estimated that 11-18% of cases will eventually progress to invasive cancer if left untreated.[3]

In the Philippines, it is estimated that 2.9% of women in the general population are infected with HPV 16 and/or HPV 18 at any given time.[4] Approximately 3 out of 5 cases (58.6%) of invasive cervical cancers among Filipino women are attributed to high-risk oncogenic HPV types 16 and 18[1] but other HPV types have been isolated in cervical cancer specimens, particularly type 45, 52, and 51.[4]

At present, there are three prophylactic HPV vaccines available and marketed in the Philippines (Table 1). Increasing valency is associated with increasing coverage of HPV types.

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Table 1. HPV vaccines and types covered

HPV vaccine	HPV types covered	Adjuvant Used	Producer cells	Brand name
Bivalent	16 and 18	Aluminum hydroxyphosphate sulfate	*Trichoplusia ni* insect cell line infected with L I recombinant baculovirus	Cervarix
Quadrivalent	6, 11, 16, and 18	Aluminum hydroxide and 3-O-deacylated-4-monophosphoryl lipid A	*Saccharomyces cerevisiae* expressing L I	Gardasil
Nonavalent	6, 11, 16, 18, 31, 33, 45, 52, and 58	Aluminum hydroxyphosphate sulfate	*Saccharomyces cerevisiae* expressing L I	Gardasil-9

To prevent infection of cancer-causing HPV types, the World Health Organization recommends HPV vaccination for all girls, beginning at 9 years old.[5] Since 2015, the Philippine National Immunization Program of the Department of Health (DOH) has implemented a two-dose (0, 6 months) schedule of the quadrivalent vaccine for all females aged 9 to 10 years old.[6,7]

3.1.2 Benefits and Harms of the Vaccine

Vaccine Efficacy (HPV vaccine versus Placebo or Non-HPV vaccine)

HPV vaccination significantly reduces the risk of developing genital warts and cervical pre-cancer lesions. There is no significant difference in all-cause mortality and serious adverse events.

There were no studies found reporting cervical cancer as a study endpoint. Twelve primary randomized controlled trials (RCT) and 3 follow-up studies evaluated the effectiveness and safety of HPV vaccination compared to no vaccination in young girls with respect to the development of cervical cancer precursor lesions, namely high grade cervical intralesional neoplasms (CIN) and adenocarcinoma in situ (AIS). [8-22] CIN is further differentiated to CIN 2 (moderate dysplasia) and CIN 3 (severe pre-cancer dysplasia). One follow-up study evaluated the development of genital warts among those who received the quadrivalent vaccine.[22]

Four large RCTs and 3 follow-up studies reported efficacy data with follow-up periods ranging from 3 to 7.3 years.[8-11,20-22] A total of 23,771 young women from multiple countries were enrolled. One study followed-up the study participants of the FUTURE I and II trials.[20,10-11] Of the 4 primary RCTs, 2 studies evaluated bivalent vaccine (Harper 2004; PATRICIA trial) and 2 studies evaluated quadrivalent vaccine as the intervention (FUTURE I and II). Three RCTs used placebo as control and 1 RCT used hepatitis A vaccine as control. The effect of baseline HPV DNA status (HPV-naïve or non-naïve) on clinical outcome was also investigated in 3 RCTs (PATRICIA, FUTURE I, and FUTURE II). See Appendix C for the characteristics of the included studies.

Development of Cervical Intralesional Neoplasms

Regardless of baseline HPV status, pooled analysis shows that HPV vaccines reduce the risk of developing CIN 2 (RR=0.23, 95% CI 0.03-2.09), CIN 3 (RR=0.67, 95% CI 0.46-1.00), and AIS (RR=0.31, 95% CI 0.15-0.66) compared to control. Among women who are HPV-naïve at baseline, HPV vaccine compared to no HPV vaccine reduces the risk of developing CIN 2 (RR=0.44, 95% CI 0.36-0.54), CIN 3 (RR=0.21, 95% CI 0.02-1.75), and AIS (RR=0.09, 95% CI 0.01-0.71).

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Development of Genital Warts

In terms of preventing genital warts, the follow-up study of two large RCTs observed benefit among those given the quadrivalent vaccine (RR=0.17, 95% CI 0.12-0.26). There were no studies investigating genital warts as an outcome from the pool of bivalent HPV vaccine efficacy trials.

Subgroup analysis by type of HPV vaccine shows significant benefit for bivalent (RR=0.51, 95% CI 0.40-0.64) and quadrivalent (RR=0.57, 95% CI 0.41-0.79) HPV vaccine in reducing CIN2+ regardless of baseline HPV DNA status. Similar benefits are observed with bivalent (RR=0.55, 95% CI 0.42-0.71) and quadrivalent (RR=0.81, 95% CI 0.69-0.96) HPV vaccines in reducing the incidence of CIN 3+. Subgroup analysis also shows significant benefit for both bivalent vaccine (RR=0.23, 95% CI 0.07-0.81) and quadrivalent vaccine (RR=0.38, 95% CI 0.15-0.96) in terms of reducing the risk for AIS.

Among women who were documented to be HPV-naïve at baseline, subgroup analysis showed significant benefit in reducing CIN 2 for bivalent HPV vaccine (RR=0.35, 95% CI 0.26-0.46) and quadrivalent HPV vaccine (RR=0.57, 95% CI 0.57-0.76). Similar benefits were observed for bivalent HPV vaccine (RR=0.07, 95% CI 0.02-0.22) and quadrivalent HPV vaccine (RR=0.54, 95% CI 0.36-0.82) in reducing the risk of developing CIN 3. Significantly reduced risk for AIS among HPV-naïve females is observed only for the quadrivalent vaccine (RR=0.09, 95% CI 0.01-0.71).

In terms of preventing genital warts, one follow-up study of two large RCTs reported benefit among participants who received quadrivalent HPV vaccine (RR=0.17, 95% CI 0.12-0.26).[22] No studies on bivalent HPV vaccine investigated genital warts as an outcome.

The summary of outcomes and the corresponding certainty of evidence is shown below. Please refer to Appendix D and E for the forest plots and GRADE profiles supporting these findings.

Table 2. Summary of outcomes of HPV vaccine compared to no HPV vaccine

Outcomes	No. of Studies	RR (95% CI)	Certainty of Evidence
Development of CIN 2	2 studies	0.23 (0.03-2.09)	Low
Development of CIN 3	2 studies	0.67 (0.46-1.00)	Low
Adenocarcinoma in situ	2 studies	0.31 (0.15-0.66)	Moderate
Development of genital warts	1 study	0.17 (0.12-0.26)	High
Severe Adverse Events	12 studies	0.96 (0.88-1.05)	Moderate
All-Cause Mortality	12 studies	0.85 (0.47-1.53)	Low

Vaccine Efficacy (Nonavalent HPV vaccine vs Quadrivalent or Bivalent HPV vaccine)

Compared to the quadrivalent HPV vaccine, the nonavalent HPV vaccine significantly reduces the risk of developing genital warts and high grade cervical, vulvar or vaginal disease caused by HPV types 31, 33, 45, 52, or 58. There is no significant difference in the development of cervical disease from HPV types 6, 11, 16, and 18.

Two RCTs and 1 follow-up study enrolled 18,959 young and adolescent women (16 to 26 years od) to compare the effectiveness of nonavalent versus quadrivalent HPV vaccines in preventing the development of high grade cervical, vulvar or vaginal disease.[23-25] This outcome broadly includes high-grade cervical epithelial neoplasia, AIS, cervical cancer, high-grade vulvar intraepithelial neoplasia, high-grade vaginal intraepithelial neoplasia, vulvar cancer, and vaginal cancer. One of the RCTs compared the effectiveness of the two vaccines on the development genital warts (condyloma acuminata). Both RCTs assessed the efficacy against HPV types 31, 33, 45, 52 and 58, while the follow-up study assessed efficacy against HPV types 6, 11, 16 and 18.

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Pooled analysis of the 2 RCTs shows that the nonavalent vaccine significantly reduces the risk of developing high grade cervical, vulvar, or vaginal pre-cancer disease caused by HPV types 31, 33, 45, 52, or 58 (RR=0.04, 95% CI 0.01-0.16) compared with the quadrivalent vaccine. The six-year follow-up study reported no significant difference between the two vaccines in the development of cervical, vulvar or vaginal pre-cancer disease caused by HPV types 6, 11, 16 and 18 (RR= 1.0, 95% CI 0.06-16.01). No significant benefit for genital warts was observed among those who received nonavalent vaccines compared to those who received quadrivalent vaccines (RR=0.14, 95% CI 0.01-2.80).

Vaccine Safety

Safety outcomes were reported by 12 primary RCTs enrolling 23,859 young and adolescent women from multiple countries. Seven studies evaluated bivalent HPV vaccines; 5 studies evaluated quadrivalent HPV vaccines. Nine RCTs used placebo as control, 3 RCTs used hepatitis A vaccine as control.[8-19] The characteristics of all included studies are shown in Appendix C.

Pooled analysis showed no significant differences were observed in all-cause mortality (RR=0.85, 95% CI 0.47-1.53) and severe adverse events (RR=0.96, 95% CI 0.88-1.05). Subgroup analysis by type of vaccine showed no significant difference in severe adverse events for both bivalent HPV vaccine (RR=0.97, 95% CI 0.88-1.06) and quadrivalent HPV vaccine (RR=0.93, 95% CI 0.70-1.22) compared to control. Subgroup analysis for all-cause mortality showed no significant difference for bivalent HPV vaccine (RR=0.64, 95% CI 0.29-1.38) and quadrivalent HPV vaccine (RR=1.31, 95% CI 0.51-1.53). Subgroup analysis by type of control showed no significant difference in comparing HPV vaccine against placebo (RR=0.83, 95% CI 0.68-1.01) or against Hepatitis A vaccine (RR=1.00, 95% CI 0.91-1.11).

There was no significant difference between the nonavalent and quadrivalent HPV vaccine in severe adverse events (RR=1.0, 95% CI 0.14-7.10) and death (RR=1.0 95% CI 0.29-3.36). The summary of outcomes and corresponding certainty of evidence is shown below.

Table 3. Summary of outcomes of Nonavalent HPV vaccine compared to Quadrivalent HPV vaccine

Outcomes	**No. of Studies** *(No. of participants)*	**RR (95% CI)**	**Certainty of Evidence**
Development of high grade cervical, vulvar, or vaginal pre-cancer disease caused by HPV types 6, 11, 16 or 18	1 study (11,781)	1.00 (0.06-16.01)	Low
Development of high grade cervical, vulvar, or vaginal pre-cancer disease caused by caused by HPV types 31, 33, 45, 52, or 58	2 studies (18,959)	0.04 (0.01-0.16)	High
Development of genital warts	1 study (4,079)	0.14 (0.01-2.80)	Low
Severe Adverse Events	2 studies (18,875)	1.00 (0.14-7.10)	Low
All-cause Mortality	2 studies (18,875)	1.00 (0.29-3.46)	Low

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3.1.4 Cost Implication

Two local studies evaluated the cost-effectiveness of HPV vaccination in the Philippines. In 2017, Germar et al. projected that the implementation of a two-dose bivalent HPV vaccine was more cost-effective than a two-dose quadrivalent vaccine in terms of total cases, deaths and quality adjusted life-years (QALY).[26] A 2015 study concluded that adding bivalent or quadrivalent HPV vaccination to visual inspection with acetic acid may potentially be cost-effective and may result in reducing cervical cancer burden by two-thirds.[27]

A cost-effectiveness study from 2018 (preprint) assessed the impact of nonavalent HPV vaccination compared to bivalent and quadrivalent HPV vaccination in the Philippine setting using a dynamic transmission model. In this model, the nonavalent vaccine resulted in 339,806 fewer cases of CIN 2/3, 90,357 fewer cases of cervical cancer, and 37,693 fewer cervical cancer deaths compared to both bivalent and quadrivalent HPV vaccine. There were also 16,157,310 fewer cases of genital warts compared to bivalent vaccine. The overall disease cost avoided by nonavalent HPV vaccination was $466,163,869 and $79,241,435 compared with bivalent and quadrivalent vaccine, respectively, which corresponded to an incremental cost-effectiveness ratio (ICER) of $2,046/QALY and $2,496/QALY, respectively.[28]

A 2020 study by Llave et al. (preprint) assessed the cost-effectiveness of different HPV vaccines in the Philippine market versus no vaccination using a proportional outcomes model. The study concluded that the bivalent and quadrivalent HPV vaccines are cost-effective from the government and societal perspective compared to no vaccination and that the bivalent vaccine is superior to the quadrivalent vaccine as it offers the same benefits with smaller costs. Due to its price, the nonvalent vaccine was determined to be not cost-effective.[29]

A 2018 international systematic review on the cost-effectiveness of HPV vaccines (bivalent, quadrivalent, or nonavalent) in low- to middle-income countries (LMIC) included 19 studies from Africa, South America, and Southeast Asia. All studies reported that HPV vaccination was overall cost-effective in reducing cervical cancer cases, particularly in areas where the incidence of the disease is high. However, cost-effectiveness was strongly correlated with vaccine price. Low vaccine prices of less than 25 USD (Php 1,250) were recommended for LMICs.[30]

The cost of HPV vaccination is summarized in the table below. The nonavalent HPV vaccine is not included in the Philippine Drug Formulary and is only available in the private market.

Table 4. Cost of HPV vaccine

	Vaccine Type		
	Bivalent HPV vaccine	**Quadrivalent HPV vaccine**	**Nonavalent HPV vaccine**
Unit cost of single-dose vaccine (range)[31-32]	Php 490 (Php 315-1,935) (Up to Php2,000+ in private market)	Php 730 (562.50-843.50) (Up to Php 4,800+ in private market)	Php 8,437.50 (Php 6,750-10,125)

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3.1.5 Equity, Acceptability, and Feasibility

A 2017 scoping review that included 63 studies from low- to middle-income countries in Southeast Asia and Western Pacific Region (including the Philippines) reported the main factors influencing HPV vaccination acceptability and feasibility among women.[33-34]

The key findings of the studies show that:

- Among Filipino women, the willingness to be vaccinated appears to be contingent on affordable pricing.
- Awareness of HPV infection, vaccines, and cervical cancer were noticeably different among women residing in urban and rural areas, with higher awareness among those in urban areas. However, overall knowledge about HPV and its prevention was lacking in general.
- Women are concerned about the adverse effects of vaccination, which stemmed from doubts regarding its efficacy and safety.
- There is a lack of urgency to be vaccinated because the perception of contracting HPV infection and cervical cancer was low.

- Physician recommendation or discussing the HPV vaccine with a physician, along with familial and social support, were factors associated with vaccine acceptance and initiation.
- Health promotion programs for HPV vaccination conducted in schools improve the health literacy levels of young adolescent girls to make informed decisions.

3.1.6 Recommendations from Other Groups

Several societies strongly recommend routine immunization with HPV vaccines as prophylaxis, with primary doses given as early as 9 years of age. Table 5 shows the specific recommendations of the DOH as well as other medical advisory committees and societies regarding HPV vaccines.

Group	Recommendation	Strength of recommendation and certainty of evidence
Department of Health[7]	All females aged 9-10 years in priority provinces shall be vaccinated with two doses of HPV quadrivalent vaccine, 0.5mL, intramuscular, left deltoid arm. First dose: Age 9 and 10 years old Second dose: 6 months after the first dose	Not indicated
US Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP)[35]	Recommended for 11- to 12-year-olds (girls and boys) to receive two doses of HPV vaccine (bivalent, quadrivalent, or nonavalent vaccines) 6 to 12 months apart The first dose is routinely recommended at age 11–12 years old; the series can be started at age 9 years.	Strong recommendation; high quality of evidence
Philippine Society for Microbiology and Infectious Diseases (PSMID)[36]	Bivalent vaccine: Effective in preventing cervical cancer associated with HPV 16/18 among immunocompetent adult females and can be given until 26 years old	Strong recommendation; high quality of evidence
	Quadrivalent and nonavalent vaccines: Both vaccines are effective in preventing cervical cancer and anogenital	Strong recommendation; high

	warts among immunocompetent adult females and can be given until 26 years old	quality of evidence
	Quadrivalent and nonavalent vaccines: May be given to adult immunocompetent males from ages 16-26 for the prevention of anal cancer and genital warts	Strong recommendation; moderate to high quality of evidence
Pediatric Infectious Disease Society of the Philippines (PIDSP), Philippine Pediatric Society (PPS) & Philippine Foundation for Vaccination (PFV)[37]	For ages 9-14 years, a two-dose series is recommended. Bivalent HPV, quadrivalent or nonavalent should be given at 0 and 6 months. If the interval between the first and second dose is less than 6 months, a third dose is needed. For ages 15 years and older, a three-dose series is recommended. Bivalent, quadrivalent or nonavalent HPV vaccine should be given at 0, 2 and 6 months.	Not indicated
American College of Obstetricians and Gynecologists (ACOG)[38]	Routine HPV vaccination for girls and boys at the target age of 11–12 years (but it may be given from the age of 9 years) as part of the adolescent immunization platform Obstetrician–gynecologists should assess and vaccinate adolescent girls and young women with the HPV vaccine during the catch-up period (ages 13–26 years), regardless of sexual activity, prior exposure to HPV, or sexual orientation, if they were not vaccinated in the target age of 11–12 years.	Strong recommendation; Committee Opinion
Philippine Obstetrical and Gynecological Society (POGS)[39]	The bivalent HPV vaccine (three-dose; 0-1-6 months) can be given to patients aged 10-14 years, while the quadrivalent HPV vaccine (three-dose; 0-2-6 months) can be given to patients aged 9-45 years old. The bivalent and quadrivalent HPV vaccines are not interchangeable to complete the three doses.	Strong recommendation; high quality of evidence

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3.2 Influenza Vaccine

RECOMMENDATION

Among healthy children aged 6 months to 18 years, we suggest annual influenza immunization with inactivated influenza vaccine. (Weak recommendation, Low certainty of evidence)

Considerations

The consensus panel considered the following when formulating this recommendation:

- Prevention of influenza is a priority.
- The burden of influenza is evident, and benefits outweigh the risk of harm but some panelists believe that more high-quality evidence on efficacy, cost-effectiveness, equity, feasibility and acceptability are needed to make a strong recommendation.
- Targeting all pediatric patients for annual immunization has some feasibility and implementation issues especially in the absence of local cost-effectiveness studies. Limiting vaccination to a targeted population may be more cost-effective and should be investigated.

3.2.1 Burden of disease

Influenza is a serious public health problem occurring globally in yearly epidemics with a high risk of morbidity and mortality in the very young and the very old.[1] It is estimated that each year, 870,000 children less than 5 years old are hospitalized worldwide and about 28,000 to 111,500 children below 5 years old die from influenza-related causes, the vast majority of which occur in developing countries.[2,3]

The burden of influenza in the Philippines remains largely unknown, especially in children, because diagnosis is often made clinically, and testing is rarely done.[4] In 2019, DOH surveillance data recorded 55,000 cases of influenza-like-illness (ILI) in the country, approximately 30% of which occurred in children less than 5 years old. Retrospective studies done locally report a mean annual influenza incidence rate of 22.6 per 1,000 and an annual excess influenza mortality rate of 2.14 per 100,000 in Filipino children aged 5 years and below.[5,6]

Influenza is a highly communicable, acute viral illness.[7] For majority of patients, it is a self-limited infection that will resolve within a week. Children, especially those aged <5 years, are at the highest risk of developing serious complications such as acute otitis media, bacterial co-infections, pneumonia, hospitalization, and death.[7,8]

Patients with mild illness who are low risk for complications are prescribed symptomatic treatment.[9] For pediatric high-risk groups (i.e. children <5 years or children with chronic illness), antiviral therapy is recommended regardless of vaccine status because early therapy is proven to reduce the duration of symptoms, hospitalization and death.[10] Oral oseltamivir remains to be the antiviral drug of choice, and is one of two anti-influenza treatments available locally.[10,11] The other is zanamivir, an antiviral drug in nasal spray format.

3.2.2 Benefits and Harms of the Vaccine

Inactivated influenza vaccine (IIV) significantly reduces the risk of laboratory-confirmed illness and influenza-like illness compared to no influenza vaccine in children 6 months to 18 years. There is no significant difference in influenza-related hospitalization and serious adverse events among those who received influenza vaccine compared to control.

These findings are based on an update of a high-quality, 2018 Cochrane systematic review and meta-analysis that assessed the effectiveness and safety of live attenuated and inactivated influenza vaccines for healthy children under 16 years old.[12] Relevant studies from 1966 to December 31, 2016, were identified from multiple databases (CENTRAL, MEDLINE, Embase) and a total of 41 placebo-controlled RCTs (>200,000 children) were included in the meta-analysis. Only studies on trivalent and quadrivalent IIV (8 studies) were retrieved from the original meta-analysis since these are the only vaccine types available in the Philippines. Search of literature since December 31, 2016, yielded an additional 17 RCTs. A total of 25 RCTs are included in this present review.[8,13-36] Of the 25 studies, 10 were placebo-controlled while 15 studies used active controls such as pneumococcal conjugate vaccine, inactivated polio vaccine, meningococcal C conjugate vaccine and vaccines for hepatitis A and B, varicella or tick-borne encephalitis. Nineteen RCTs evaluated trivalent inactivated influenza vaccine (TIV), while 6 RCTs evaluated quadrivalent inactivated influenza vaccine (QIV). The characteristics of included studies are found in Appendix B.

Vaccine Efficacy

Pooled analysis shows that IIV significantly reduces the risk of influenza-like illness (RR 0.70, 95% CI 0.58 to 0.85) in children aged 6 months to 18 years after one or two age-appropriate doses during a given influenza season. Subgroup analysis by type of vaccine shows that both TIV (RR 0.52, 95% CI 0.35 to 0.78) and QIV (RR 0.89, 95% CI 0.81 to 0.98) significantly reduce the risk of influenza-like illness when compared to placebo or active control.

IIV significantly reduces the risk of laboratory-confirmed influenza (RR 0.52, 95% CI 0.45 to 0.61) in children aged 6 months to 18 years after one or two age-appropriate doses during a given influenza season. Subgroup analysis by age also shows that IIV significantly reduces the risk of laboratory-confirmed influenza in children 6 months to <3 years old, (RR 0.61, 95% CI 0.50 to 0.75, number needed to vaccinate [NNV] 33), 3 to <9 years old (RR 0.55, 95% CI 0.43 to 0.70, NNV 33) and ≥9 years old (RR 0.57, 95% CI 0.35, 0.94, NNV 17). Subgroup analysis by vaccine type shows that both TIV (RR 0.54, 95% CI 0.45 to 0.66) and QIV (RR 0.50, 95% CI 0.45 to 0.55) reduce the risk for laboratory-confirmed influenza in children aged 6 months to 18 years.

There is no significant difference between the IIV and control groups with respect to influenza-related hospitalization (RR 0.44, 95% CI, 0.18 to 1.06) in children aged 6 months to 18 years after one or two age-appropriate doses during a given influenza season.

Vaccine Safety

There is also no significant difference in serious adverse events (SAE) between the IIV group and control group (RR 0.90, 95% CI 0.73 to 1.12). Subgroup analysis by type of vaccine showed no significant difference in SAEs in the TIV (RR 0.79, 95% CI 0.60 to 1.04) and QIV (RR 1.06, 95% CI 0.83 to 1.34) groups when compared with placebo or active control.

Meta-analysis of specific adverse event (AE) outcomes was not done due to inconsistencies in study design, definition, assessment, and reporting. A descriptive review of the incidences of systemic and local adverse events is presented in Appendix F. The most common (>20%) local AEs reported after IIV include bruising, pain/tenderness, and erythema. The most common (>20%) systemic AEs reported were myalgia, fever, fatigue, irritability, headache, loss of appetite/decreased feeding, diarrhea, drowsiness, and malaise. Majority of AEs were mild and self-limiting.

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The summary table of outcomes is shown below. Please refer to Appendix C and D for the GRADE evidence profiles and meta-analyses supporting these findings.

Table 1. Summary Table of Influenza Outcomes

Outcomes	No. of Studies (No. of Participants)	RR (95% CI)	Certainty of Evidence
Influenza-like Illness	7 (28,524)	0.70 (0.58, 0.85)	Low
Laboratory-confirmed Influenza	15 (74,730)	0.52 (0.45, 0.61)	Low
Influenza-associated hospitalization	3 (22,361)	0.44 (0.18, 1.06)	Moderate
Serious adverse events	13 (74,279)	0.90 (0.73, 1.12)	Low

3.2.4 Cost Implication

Table 2. Cost of Influenza Vaccine

Parameter	Estimates
Unit cost of vaccine (In Philippine Peso)	**Public:** Php 184.00 – 570.00 per dose[37] **Private:** Php 700.00 per dose[38] Price range: Php 184.00 – 700.00 per dose

Systematic reviews from high-income settings suggest that seasonal influenza vaccination in children is likely to be cost-effective.[39,40] While there are no published influenza vaccine cost-effectiveness studies done in children in the Philippine setting, economic evaluations from other low- and middle-income countries (LMICs) provide some insight.[41-46] Please refer to Appendix G for the characteristics of these studies.

Overall, cost-effectiveness studies from different LMICs (Colombia, Thailand, South Africa, Vietnam, Mexico) show that an influenza vaccination program targeting children is generally cost-effective compared with no vaccination. However, country-specific factors may significantly affect these evaluations, including influenza epidemiology and circulation patterns, vaccine pricing, impact of vaccine costs on the national healthcare budget and the willingness-to-pay threshold definition.[43]

3.2.5 Equity, Acceptability, and Feasibility

A childhood influenza vaccination program will provide the masses a safe and effective vaccine that is presently only available to upper- and middle-class Filipino families from the private health sector. However, its establishment can be challenging in the Philippine setting due to nonconformity of influenza circulation patterns to traditional hemispheric seasons that dictate vaccine formulation as well as important issues relating to vaccine access and acceptability.[29]

A global survey of national health managers from LMICs identified the following barriers to establishing or maintaining an influenza vaccination program: [47]

- Limited access to WHO-prequalified vaccines
- Lack of multi-year government commitments for vaccines
- Limited number of vaccines being registered in the country
- Lack of data on influenza morbidity and mortality
- Competing health priorities

- Limited domestic funding mechanisms
- Absence of information on the cost-effectiveness of a national influenza vaccination program
- Lack of risk awareness for influenza complications
- Perception that influenza is not a serious illness
- Lack of risk communication tools that educate patients about influenza
- Constant exposure to broad misinformation on social media platforms

Across Asia, influenza vaccine uptake in the general population is low (14.3%) while uptake in HCWs is suboptimal (37%).[49] The latter is significant since recommendations from HCWs and public health authorities were found to be influential in vaccine uptake within the general and high-risk populations.[49]

In the Philippines, recent studies suggest that vaccine confidence is in decline (from 93% in 2015 to 32% in 2018) and childhood immunization coverage is dropping (88-93% in 2008 to 65-75% in 2019).[50,51] There is fear and mistrust toward both the state and health institutions,[52] and vaccine hesitancy is reported by one out of three Filipinos living in urbanized communities.[53] The main reasons for refusal were negative information from the media (related to Dengvaxia) and concerns about safety.[53]

A multinational prospective observational study on respiratory illnesses in LMICs conducted from 2015-2017 examined perceived knowledge, attitudes, and practices about influenza illness and vaccination in mothers of infants aged < 1 year, and their willingness to accept influenza vaccination if offered (for infants aged 6–11 months).[54] Of the 624 Filipino mothers interviewed, majority reported no knowledge of influenza illness (74%) nor the influenza vaccine (80%), but were very worried about their children getting sick with influenza (>90%). Of those with eligible children, 65% would accept an influenza vaccination for their infant if offered at no cost. Perceived knowledge of influenza vaccine and perceived vaccine safety and effectiveness were the best predictors of intention to accept pediatric influenza vaccination among the respondents.

These findings show that for influenza vaccination to be accepted by Filipino parents, perceptions that influenza vaccines are safe, well tolerated, and effective need to be reinforced by trusted health authority figures and agencies as well as legitimized media sources.

3.2.6 Recommendations from Other Groups

Since 2012, the WHO Strategic Advisory Group of Experts on Immunization recommended for children aged 6–59 months be included into seasonal influenza vaccination programs in all countries.[55] The United States and United Kingdom (UK) now have universal recommendations for influenza vaccination in all children aged from 6 months (United States) or 2 years (UK).[10,56] Both groups recommend that any licensed influenza vaccine appropriate for age and health status can be used for influenza vaccination in children, with LAIV being preferred over IIV in British children 2 years old and above who do not belong in the high clinical risk group (children with chronic kidney, heart, lung, liver or neurologic disease; diabetes, immunosuppression).[56]

Group	Recommendation*
American Academy of Pediatrics (AAP)/The Centers for Disease Control and Prevention's Advisory Committee	▪ The AAP recommends annual influenza vaccination for children 6 months and older. ▪ Any licensed influenza vaccine appropriate for age and health status (IIV and LAIV) can be used. ▪ There is no preference for any influenza vaccine product over another for children who have no contraindication to vaccination and for whom more than one licensed product

on Immunization Practices (ACIP)[10] (Updated: October 2020)	appropriate for age and health status is available. ▪ Children 6-35 months of age may receive any licensed, age-appropriate inactivated vaccine, at the dose indicated for the vaccine. ▪ Children ≥36 months (≥3 years) should receive a 0.5-mL dose of any available, licensed, age-appropriate inactivated vaccine. ▪ Children 6 month to 8 years of age who are receiving influenza vaccine for the first time or who have received only 1 dose, or whose vaccination status is unknown, should receive 2 doses, ideally by the end of October. ▪ Children needing only 1 dose of influenza vaccine, regardless of age, should also receive vaccination, ideally by the end of October.
Green Book, Public Health England[56] (Updated: October 2020)	▪ Children 6 months to <2 years NOT IN clinical risk groups - vaccination is not recommended. ▪ Children 6 months to <2 years and IN clinical risk groups - Children should be offered the recommended inactivated quadrivalent influenza vaccine. - Those who have not received influenza vaccine previously should be offered a second dose at least four weeks later. ▪ Children aged 2 to <17 years old and NOT IN clinical risk groups - A single dose of LAIV should be offered per season, unless contraindicated, irrespective of whether influenza vaccine has been received previously. ▪ Children aged two to <18 years of age and IN clinical risk groups - These children should be offered LAIV unless it is medically contraindicated or otherwise unsuitable. - Children who have never received influenza vaccine before and are 2 to <9 years should be offered a second dose of LAIV at least 4 weeks later. If LAIV is unavailable or medically contraindicated, a suitable quadrivalent inactivated influenza vaccine should be offered.
Pediatric Infectious Disease Society of the Philippines (PIDSP)/Philippine Pediatric Society (PPS)[57] (Updated: 2021)	▪ TIV (IM or SC) or QIV (IM) given at a minimum age of 6 months ▪ For pediatric dose, follow the manufacturer's recommendations ▪ Children 6 months to 8 years receiving flu vaccine for the 1st time should receive 2 doses separated by at least 4 weeks ▪ If only one dose was given during the previous season, give 2 doses of the vaccine then one dose yearly thereafter ▪ Children aged 9 to 18 years should receive one dose of the vaccine yearly ▪ Annual vaccination should begin in February but may be given throughout the year

*Strength of recommendation/Certainty of evidence for all recommendations were not available in the source material

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3.3 Typhoid Vaccine

RECOMMENDATION

Among apparently healthy children and adolescents, we suggest typhoid vaccine using either typhoid conjugate vaccine for those aged 6 months to 18 years, or typhoid polysaccharide vaccine for those aged 2 to 18 years, in areas of high burden of disease*. (Weak recommendation, Very low certainty of evidence)

**As of 2021, areas of high burden of disease are the following: Region 7, 8, 9 and ARMM*

Considerations

The consensus panel considered the following when formulating this recommendation:

- Prevention of typhoid fever is a priority in areas with high burden of disease.
- The benefits outweigh the risk of harm but some panelists believe that more high-quality evidence on burden, cost-effectiveness of different vaccine types, equity, acceptability and feasibility in the context of a school-based or community-based program are needed to make a strong recommendation.
- The panel anticipates the future availability of typhoid conjugate vaccine, hence its inclusion in this recommendation.

3.3.1 Burden of disease

Typhoid fever ranks as the most common cause of food and waterborne illness in the Philippines. The Department of Health Epidemiology Bureau reported a nationwide total of 10,842 typhoid fever cases from January 1 to June 29, 2019, a 5% increase from the previous year's total.[1] The most affected age group were children aged 5 to 9 years, comprising 17% (1,875) of the total cases, with an associated case mortality rate of 0.23%

A systematic review of 13 studies reported that approximately 1 in 4 children develop complications from typhoid fever and the prevalence of complications is higher in children than in adults (27% vs 17%).[2] The most common complications include encephalopathy, gastrointestinal bleeding, and nephritis and case fatality rates range from 0.5% to 6.7% despite the high occurrence of complications.[2] Among pediatric cases, a delay of more than 10 days in seeking care translates to 3 times greater odds of developing complications.[2] Delay in care is also significantly correlated with increased fatality.[3]

Effective and early treatment with antibiotics shortens the disease course and reduces the risk of typhoid fever complications. However, the emergence of multidrug and extremely drug resistant strains of *Salmonella typhi* have posed a significant challenge in terms of disease management.[4] To address this, the World Health Organization (WHO) recommends typhoid fever vaccination in populations at high risk of infection. Immunization has the manifold potential of preventing typhoid fever infection, decreasing antibiotic use, and limiting the emergence of resistant strains, thus providing an ideal short-to-medium term measure for lowering the disease burden of typhoid fever.[5]

3.3.2 Benefits and Harms of the Vaccine

Typhoid polysaccharide vaccine, typhoid live oral vaccine, and typhoid conjugate vaccine significantly reduce the incidence of typhoid fever compared to no typhoid vaccination. All 3 types of vaccines significantly induce antibody

responses (immunogenicity). In general, no significant increase in the risk of adverse events is associated with typhoid vaccines.

A total of 20 randomized controlled trials (RCTs) representing 3 types of typhoid vaccines (typhoid polysaccharide vaccine or Vi PS, oral typhoid vaccine or Ty21a; and typhoid conjugate vaccine or TCV) were included in this systematic review. Ten studies reported on the incidence of typhoid fever with different vaccine types (Vi PS: 4; Ty21a: 3; and TCV: 3), 12 studies evaluated immunogenicity (Vi PS: 4; Ty21a: 2; TCV: 6), and 10 studies reported on adverse events. The characteristics of included studies are found in Appendix B.

Typhoid Polysaccharide Vaccine (Vi PS vaccine)

Pooled analysis of 4 RCTs shows that a single dose of Vi PS vaccine significantly reduces the 3-year cumulative incidence of typhoid fever (RR 0.44, 95% CI 0.34 to 0.56) compared to no typhoid vaccine.[6-9] Subgroup analysis by year of follow-up shows that Vi PS vaccine significantly reduces the incidence of typhoid fever at year 1 (RR 0.39, 95% CI 0.18 to 0.84), year 2 (RR 0.44, 95% CI 0.33 to 0.57), and year 3 (RR 0.50, 95% CI 0.22 to 1.11). Subgroup analysis by age shows that Vi PS vaccine significantly reduces the incidence of typhoid fever for children less than 5 years old (RR 0.54, 95% CI 0.32 to 0.91) and for children 5 to 16 years of age (RR 0.39, 95% CI 0.27 to 0.56).

The Vi PS vaccine significantly induces an immunogenic response at 3 to 6 weeks post-vaccination, (RR 0.13, 95% CI 0.08 to 0.23) and at 2 years post-vaccination (RR 0.71, 95% CI 0.62 to 0.82) compared to the control group.[6,10-12]

There was no significant difference in adverse events, particularly fever (RR 1.93, 95% CI 0.48 to 7.75) and pain at the injection site (RR 0.92, 95% CI 0.77 to 1.10) between the Vi PS vaccine group and the control group. None of the trials reported any serious adverse events.[6,11]

Typhoid Oral Live Attenuated Vaccine (Ty21a Oral Vaccine)

Pooled analysis of 3 RCTs shows that Ty21a oral vaccine significantly reduces the 3-year cumulative incidence of typhoid fever (RR 0.35, 95% CI 0.18 to 0.67) compared to no typhoid vaccine.[13-15] Subgroup analysis by year of follow-up shows that Ty21a oral vaccine significantly reduces the incidence of typhoid fever at year 1 (RR 0.23, 95% CI 0.11 to 0.52), year 2 (RR 0.29, 95% CI 0.14 to 0.63) and year 3 (RR 0.48, 95% CI 0.39 to 0.61). Subgroup analysis by age shows that Ty21a oral vaccine significantly reduces the incidence of typhoid fever for children 5 to 9 years (RR 0.41, 95% CI 0.20 to 0.85) and for children 10 to 14 years of age (RR 0.33, 95% CI 0.17 to 0.66).

The Ty21a oral vaccine also significantly induces an immunogenic response at 3 to 4 weeks post-vaccination (RR 0.22, 95% CI 0.08 to 0.61) compared to the control group.[16,17]

There was no significant difference in adverse events, particularly fever (RR 1.00, 95% CI 0.33 to 3.01), vomiting (RR 0.83, 95% CI 0.25 to 2.71), diarrhea (RR 2.48, 95% CI 0.42 to 14.55) and rashes (RR 0.28, 95% CI 0.04 to 2.03) between the Ty21a oral vaccine group and the control group. No trials reported on serious adverse events.[16,17]

Typhoid Conjugate Vaccine (TCV)

TCV significantly reduces the 2-year cumulative incidence of typhoid fever (RR 0.12, 95% CI 0.06 to 0.22) compared to no typhoid vaccine.[18-20] Subgroup analysis by year of follow-up shows that TCV significantly reduces the incidence of typhoid fever at year 1 (RR 0.04, 95% CI 0.00 to 0.70) and year 2 (RR 0.13, 95% CI 0.07 to 0.24).

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TCV significantly induces an immunogenic response at 1 and 6 months post-vaccination (RR 0.05, 95% CI 0.01 to 0.16) compared to the control group. [20-25] Subgroup analysis shows that TCV significantly induces an immunogenic response at 1 month post-vaccination (RR 0.03, 95% CI 0.01 to 0.10) and at 6 months post-vaccination (RR 0.37, 95% CI 0.30 to 0.45).

In terms of adverse events, there was no significant difference in fever (RR 1.21, 95% CI 0.83 to 1.77), local adverse effects such as swelling and erythema (RR 1.07, 95% CI 0.59 to 1.93), and diarrhea (RR 0.92, 95% CI 0.75 to 1.11) between the TCV group and the control group. [18,20,21,23-25] There was a significant decrease in vomiting among those given TCV compared to the control group (RR 0.75, 95% CI 0.60 to 0.94). None of the trials reported any serious adverse events.

Table 1. Summary of outcomes of Typhoid vaccine compared to no vaccine

Outcomes	No. of Studies *(No. of participants)*	RR (95% CI)	Certainty of Evidence
Typhoid polysaccharide vaccine (Vi polysaccharide vaccine)			
Cumulative incidence of typhoid fever	4 (169,764)	0.44 (0.34 to 0.56)	High
Immunogenicity (3-6 weeks)	4 (853)	0.13 (0.08 to 0.23)	Low
Immunogenicity (2 years)	2 (230)	0.71 (0.62 to 0.82)	High
Adverse events (fever)	2 (495)	1.93 (0.48 to 7.75)	Very Low
Adverse events (pain)	2 (495)	0.92 (0.77 to 1.10)	Low
Typhoid oral live attenuated vaccine (Ty21a oral vaccine)			
Cumulative incidence of typhoid fever	3 (89,115)	0.35 (0.18 to 0.67)	Moderate
Immunogenicity (3-4 weeks)	2 (619)	0.22 (0.08 to 0.61)	Moderate
Adverse events (fever)	2 (619)	1.00 (0.33 to 3.01)	Very Low
Adverse events (vomiting)	2 (619)	0.83 (0.25 to 2.71)	Very Low
Adverse events (diarrhea)	2 (619)	2.48 (0.42 to 14.55)	Very Low
Adverse events (rashes)	2 (619)	0.28 (0.04 to 2.03)	Very Low
Typhoid conjugate vaccine (TCV)			
Cumulative incidence of typhoid fever	3 (33,882)	0.12 (0.06 to 0.22)	Moderate
Immunogenicity (1 month)	6 (2,075)	0.03 (0.02 to 0.04	Low
Immunogenicity (6 months)	2 (399)	0.37 (0.30 to 0.46)	Moderate
Adverse events (fever)	6 (31,411)	1.21 (0.83 to 1.77)	Low
Local adverse events (combined endpoint)	5 (31,311)	1.07 (0.59 to 1.93)	Very Low
Adverse events (diarrhea)	3 (19,002)	0.92 (0.75 to 1.11)	Moderate
Adverse events (vomiting)	3 (19,002)	0.75 (0.60 to 0.94)	Moderate

3.3.4 Cost Implication

Table 2. Cost of Typhoid Vaccine

Type of Vaccine	Cost
Vi Polysaccharide (Typhim Vi, Sanofi)	Php 730
Typhoid Conjugate Vaccine (Typbar, Bharat Biotech)	Php 850
Ty21 Oral Vaccine (Vivotif, Crucell Switzerland)	Php 4,760.30* ($95.46)

*Not locally available, converted from US dollars

Typhoid fever imposes a substantial economic burden on low- and middle-income countries, with considerable hospitalization costs ($159 to $636) and outpatient costs ($17 to $74) per case.[26] Our review found 1 cost-effectives analysis (CEA) on the use of Vi polysaccharide vaccine against typhoid fever in 4 Asian countries, namely: India, Pakistan, Indonesia and Vietnam.[27] The study reported that a vaccination program targeting children aged 2 to 5 years would be very cost effective as it will prevent 456, 158, and 258 typhoid cases (and 4.6, 1.6, and 2.6 deaths), and avert 126, 44, and 72 disability-adjusted life years (DALYs) over 3 years in India, Indonesia and Pakistan, respectively. The net social costs would be US$160/DALY averted in India and US$549/DALY averted in Indonesia.[27]

Three studies investigated the cost-effectiveness of typhoid conjugate vaccine. Two studies done in 3 typhoid-endemic countries (Kenya, India, Vietnam) found that vaccination is a cost-effective strategy compared to no vaccination when it is administered through routine immunization and incorporated into the national expanded program of immunization (EPI).[28,29] The strategy becomes more cost effective if a catch-up campaign to provide booster doses of typhoid vaccine is instituted thereafter. A third study in India found that the introduction of TCV will reduce the number of typhoid cases and deaths by 17% to 36%, assuming that the protective effect will last for 5, 10 and 15 years. With the exclusion of indirect costs, the incremental cost per QALY gained was $ 2,062.71, $840.91 and $615.77 for scenarios 1, 2 and 3 respectively and all 3 scenarios were deemed cost saving.[30]

3.3.5 Equity, Acceptability, and Feasibility

A 2015 study reviewed the experiences of Chile, China, Indonesia, Nepal, Pakistan, and Vietnam with various vaccination strategies using locally available typhoid vaccines. The authors concluded that all vaccination strategies were found to be acceptable, feasible and effective in endemic and outbreak settings.[31] A combination of community and school-based strategies would be the most useful approach for the protection of both children and adults in high-incidence settings where all ages are at risk. Community-based routine vaccination is likely to be successful in places where immunization infrastructure and service delivery will allow high coverage in a high-risk population. Meanwhile, high rates of school enrolment, sound school-based infrastructure, existing school health programs, and good coordination with school officials will facilitate the success of a school-based immunization program. Advocacy to parents is also important for acceptability, and collaboration with local officials is crucial to the program's success. The vaccine is found to be generally acceptable as parents are willing to pay US$2 to US$16 per child.[31]

It is expected that the development and availability of TCVs in the Philippines in the near future will result in programmatic advantages over the other types of typhoid vaccine since TCV has been shown to be immunogenic in both adults and children as young as 6 months, and is associated with high efficacy, long duration of immunity following a single dose, and good booster response. These characteristics would facilitate the use of TCVs in routine infant immunization programs in endemic areas. Any strategy combining routine vaccination with a catch-up campaign is expected to have the highest impact on disease burden and cost-effectiveness.[31]

Another study reported on the hypothetical implementation of a subnational typhoid vaccination program in low-to-middle-income subtropical countries.[32] Subnational strategies do not introduce the vaccine on a national level but rather recognizes the heterogenous differences in risks within a country and therefore vaccination is geared towards areas identified with the highest risk. Factors that need to be considered for the appropriateness of subnational strategies include disease burden, outbreak potential, treatment availability and costs, cost-effectiveness, and availability of other preventive interventions. Challenges identified in the implementation of subnational immunization strategies are reliability of surveillance and disease-burden data, political challenges of vaccinating only a portion of a population, and higher costs of delivery to reach target populations disadvantaged by geographical and socioeconomic

barriers. Benefits of a subnational strategy include targeted reduction of disease burden, increased equity for marginalized populations, and progress on development goals.

3.3.6 Recommendations from Other Groups

The Pediatric Infectious Disease Society of the Philippines (PIDSP) recommends typhoid vaccination at a minimum age of 2 years.[34] Re-vaccination is done every 2-3 years for those traveling to areas with risk for exposure as well as during periods of outbreak.

Since October 2020, the Department of Health has endorsed the adoption of the 2017 Clinical Practice Guideline for the Diagnosis, Treatment and Prevention of Typhoid Fever in Adults (developed by the Philippine Society for Microbiology and Infectious Diseases) by the National Food and Waterborne Disease Prevention and Control Program.[35] In this CPG, typhoid vaccine is indicated in the following situations: (1) travelers to endemic areas such as Sub-Saharan Africa, Central Asia, Indian Subcontinent, Latin America, Middle East, South and Southeast Asia; (2) persons with intimate exposure to a typhoid fever carrier; and (3) laboratory workers routinely exposed to cultures of Salmonella serotype. The policy is based on a strong recommendation with high quality of evidence.[35] The schedule for typhoid vaccine is as follows: Vi PS is recommended for children at a minimum age of 2 years, given as 1 dose with booster doses every 2 years.[35] The oral vaccine is recommended at a minimum age of 6 years, given as 4 doses (Day 0, 2, 4, 6) with booster doses every 5 years.[35]

The WHO, in its 2018 position statement on typhoid vaccines, re-emphasized programmatic use of typhoid vaccines for the control of typhoid fever.[5] Among the available typhoid vaccines, WHO specified that TCV is preferred for all ages in view of its improved immunological properties, suitability for use in younger children, and expected longer duration of protection. The WHO also recommends the prioritized introduction of TCV in countries with the highest burden of typhoid disease or a high burden of antimicrobial-resistant *Salmonella typhi*.[5] A single dose of TCV is recommended in children as early as 6 months old. The polysaccharide vaccine is recommended from 2 years of age, as a single dose. The oral vaccine is recommended from 6 years of age, given as 3 doses (Day 0, 2, 4). The need for revaccination with TCV is still unclear but it is recommended that revaccination be done every 3 years for the polysaccharide vaccine, and every 3 to 7 years for the oral vaccine.[33]

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3.4 Meningococcal Vaccine

RECOMMENDATIONS

1. **Among at-risk children and adolescents*, we suggest immunization with meningococcal vaccine. (Weak recommendation, Very low certainty evidence)**

2. **Among healthy children and adolescents, we suggest immunization with meningococcal vaccine during outbreak situations. (Weak recommendation, Very low certainty evidence)**

**Risk factors*
- *Residing in high-risk areas (college or military dorms/residency halls, areas where meningococcal disease is hyperendemic or epidemic)*
- *Travellers to or residents of areas where meningococcal disease is hyperendemic or epidemic, or belonging to a defined risk group during a community or institutional meningococcal outbreak*
- *With medical risk factors (complement deficiency, functional or anatomic asplenia, HIV, receiving complement inhibitors)*

Considerations

The consensus panel considered the following when formulating this recommendation:
- Prevention of invasive meningococcal disease is a priority in children and adolescents at high risk of exposure.
- Benefits outweigh the risk of harm and evidence shows that vaccination prevents invasive meningococcal disease and mortality, but some panelists believe more high-quality studies are needed on cost-effectiveness, equity, acceptability and feasibility to make a strong recommendation.
- Some of the panelists believe that the cost of the vaccine is prohibitive for the general population and for inclusion in the national immunization program.

3.4.1 Burden of disease

The incidence of meningococcal disease in the Asia-Pacific region appears to be low. In 2016, the reported annual incidence of meningococcal illness in the Asia-Pacific region was 0.02 to 0.1 per 100,000 population.[1] However, it is likely that incidence rates do not reflect the true burden of meningococcal disease due to underreporting of cases, inconsistent case definitions, weak surveillance systems and lack of guidelines.

The Department of Health reported a total of 130 meningococcal cases from January 1 to June 29, 2019.[2] There were 68 reported deaths, giving a case fatality ratio of 50%. From 1988-2011, seven meningococcal epidemics were reported in the country, the largest of which was documented in 2004−2006 in the Cordillera region with 418 cases. Majority (71.4%) of these epidemics had less than 10 suspected cases. Case fatality rates ranged from 32.0% (Cordilleras) to 100% (Tawi-tawi).

Invasive meningococcal disease (IMD) is a life-threatening disease caused by *Neisseria meningitidis*, and presents most commonly as meningitis and sepsis.[3] Disease incidence is highest during infancy, with a second peak during adolescence. Out of the 12 meningococcal serogroups, serogroups A, B, C, W, X and Y are the most common causes of invasive disease. IMD can be fatal within 24 to 48 hours of symptom onset, with high case fatality ratios of up to 20%. Common long-term complications include hearing loss and neurodevelopmental abnormalities. Persons with anatomic or functional asplenia, persistent complement deficiencies, human immunodeficiency virus (HIV) infection, or those who are receiving complement inhibitors are at increased risk for meningococcal disease.[4] Nasopharyngeal carriage occurs in up to 10% of the population and is commonly seen in the adolescent and adult population.

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Effective antibiotics should be promptly administered to patients suspected of having meningococcal disease. Empirical therapy for suspected cases should include an extended-spectrum cephalosporin, such as cefotaxime or ceftriaxone. Once the microbiologic diagnosis is established, definitive treatment with penicillin G, ampicillin, or an extended-spectrum cephalosporin (cefotaxime or ceftriaxone) is recommended.[5] Meningococcal vaccination is advised to prevent the development of meningococcal disease.

In the Philippines, only the inactivated quadrivalent meningococcal conjugate vaccine MenACWY is available and is thus the focus of this review. Other types of meningococcal vaccines such as the meningococcal polysaccharide vaccine MPSV4, serogroup A meningococcal or MenA vaccine, serogroup B meningococcal or MenB vaccine, and serogroup A and C meningococcal or MenAC vaccine, are not available in the Philippines.[6]

3.4.2 Benefits and Harms of the Vaccine

Meningococcal vaccination leads to a significant reduction in invasive meningococcal disease and elicits a robust immune response compared to no meningococcal vaccination. There is no significant benefit for nasopharyngeal carriage of *Neisseria meningitidis*. No significant differences in serious adverse effects and systemic adverse effects were noted, but there were significantly less local adverse effects observed among those given meningococcal vaccination compared to those given control.

Incidence of Invasive Meningococcal Disease

A 2021 systematic review by McMillan et al. synthesized all available evidence on the effectiveness of meningococcal vaccines in reducing invasive meningococcal disease and pharyngeal carriage of *Neisseria meningitidis*.[7] The review, which included randomized controlled trials (RCTs), non-RCTs, observational cohort studies, case-control studies, and analytical cross-sectional studies, was appraised to be of moderate quality using AMSTAR 2. A systematic search of Pubmed, Scopus, Embase, ClinicalTrials.gov, International Pathogenic Neisseria Conference abstracts, and the World Health Organization International Clinical Trials Registry Platform was originally performed on 13 December 2017, which was updated in November 2019 and February 2020. A total of 27 studies were included in the review.

Thirteen studies investigated the impact of meningococcal vaccines on invasive meningococcal disease. Of these, 4 studies reported on meningococcal conjugate C (MCC) vaccine, 7 studies reported on meningococcal B outer membrane vesicle (OMV) vaccines, 1 study on recombinant multicomponent meningococcal B (4CMenB) vaccine. Only 1 case control study investigated the MenACWY vaccine.[8]

An update of this systematic review yielded no randomized controlled trials but found 1 new observational, retrospective cohort study that reported the effect of MenACWY on IMD.[9] Both the retrospective cohort and case control studies involved adolescents and compared MenACWY to no meningococcal vaccine. Pooled analysis of the 2 observational studies shows that meningococcal vaccination with MenACWY lowers the odds of IMD compared to no vaccination (OR 0.11, 95% CI 0.04 to 0.30).

Meningococcal Carriage

The systematic review by McMillan et al. also reported on the effectiveness of meningococcal vaccines at reducing pharyngeal carriage of *Neisseria meningitidis*. Fourteen studies investigated this outcome, including 8 studies on MenACWY vaccine, 3 studies on meningococcal B OMV vaccine, 3 studies on 4CMenB vaccine, 2 studies on

recombinant bivalent factor H-binding protein meningococcal B vaccine (MenB-FHbp), and 2 studies on MCC vaccine. The 8 studies on MenACWY included 6 cross-sectional studies, 1 cohort study, and only 1 RCT, only the latter will be included in this present review.[10]

Update of this systematic review yielded 1 additional RCT.[11] The two RCTs analyzed the effect of meningococcal vaccination on nasopharyngeal carriage of *Neisseria meningitidis*.[10,11] Both studies compared MenACWY to control (Japanese encephalitis vaccine) in adolescents and adults 18 to 24 years old. Pooled analysis shows no significant difference in the nasopharyngeal carriage of *Neisseria meningitidis* between the meningococcal vaccination group and the control group (RR 1.06, 95% CI 0.76 to 1.47).

Immunogenicity of MenACWY vaccine

Immunogenicity of the MenACWY vaccine is determined by measuring the human complement serum bactericidal assay (hSBA). An hSBA ≥ 8 is an accepted correlate of protection against IMD.[12]

There were no systematic reviews analyzing the immunogenicity of MenACWY. Four RCTs investigated the immunogenicity of MenACWY vaccine.[12–15] All four RCTs enrolled infants aged 2 to 15 months old and used routine childhood vaccines as control. Pooled analysis shows that MenACWY is significantly associated with achievement of the immunogenicity criteria of hSBA ≥ 8 (RR 27.67, 95% CI 15.05 to 50.85) compared to no meningococcal vaccine. Subgroup analysis by serogroup showed significant immunogenicity for serogroup A (RR 67.40, 95% CI 13.04 to 348.36), serogroup C (RR 30.41, 95% CI 8.00 to 115.56), serogroup W (RR 19.94, 95% CI 3.82 to 104.03) and serogroup Y (RR 18.75, 95% CI 10.76 to 32.70).

Vaccine Safety

There are 10 RCTs on local adverse events (AE),[12,14,16–23] 12 RCTs on systemic AEs,[12–18,20–22,24,25] and 6 RCTs on serious AEs following meningococcal vaccination.[12,15,18,19,22,23] All of the RCTs evaluated MenACWY.

Of the 10 RCTs on local AEs, 6 RCTs involved infants 1.5 to 23 months old, and 4 RCTs involved adolescents. Of the 12 RCTs on systemic AEs, 9 RCTs involved infants 1.5 to 23 months old, and 3 RCTs involved adolescents. Of the 6 RCTs on serious AEs, 4 RCTs involved infants 2 to 23 months, and 2 RCTs involved adolescents 10 to 17 years old. All RCTs reporting safety data used non-meningococcal vaccines as controls, including PCV 13, DTaP-IPV-HepB-Hib, MMRV, Tdap+HPV, hepatitis A and B vaccine, and Tdap.

Pooled analysis shows that meningococcal vaccination is associated with significantly less local AEs (RR 0.80, 95% CI 0.67 to 0.95) compared to control. Subgroup analysis by age showed no significant difference in the risk of local AEs among children aged 1.5 to 23 months (RR 0.88, 95% CI 0.76 to 1.01), while the risk of local AEs was significantly reduced among adolescents (RR 0.70, 95% CI 0.56-0.86). The most common local AE in the infant and adolescent age groups is injection site tenderness, as reported in 8 RCTs.

There was no significant difference in the risk of systemic AEs among those given meningococcal vaccine compared to placebo (RR 1.00, 95% CI 0.85 to 1.19). Subgroup analysis by age showed no significant difference in the risk of systemic AEs among children aged 1.5 to 23 months (RR 1.12, 95% CI 0.94 to 1.34) while risk was significantly reduced among adolescents (RR 0.74, 95% CI 0.60 to 0.92). The most common systemic AEs reported in infants are irritability and somnolence, as reported in 7 RCTs. Headache is the most common systemic AE in adolescents, as reported in 3 RCTs.

There was no significant difference in the risk of serious AEs among those given meningococcal vaccine compared to no meningococcal vaccine (RR=1.32, 95% CI: 0.87-2.00). Subgroup analysis by age showed no significant difference in the risk of serious AEs among children aged 2 to 23 months (RR 1.51, 95% CI 0.96 to 2.39) and among adolescents (RR 0.54, 95% CI 0.18 to 1.64). The most common serious AE reported is febrile seizure, as reported in 2 studies.

Immunogenicity and Safety of Meningococcal Vaccines in High-risk Populations

One non-randomized controlled study evaluated the immunogenicity and safety of MenACWY among children and adolescents with anatomic and functional asplenia (sickle cell anemia, histiocytosis X, celiac disease).[26] Results showed that both the high-risk group and the age-matched, healthy control group had high responses following a 2-dose MenACWY regimen, as measured by hSBA vaccine response rate, with no significant difference in immunogenicity response between the two groups (RR 1.09, 95% CI 0.97 to 1.22). There was no significant difference in the risk of local AEs in the high-risk population compared to the control population (RR 1.22, 95% CI 0.97 to 1.53). The risk of systemic AEs is significantly increased in the high-risk population compared to the control population (RR 1.58, 95% CI: 1.01-2.48). The summary table of all outcomes is shown below.

Table 1. Summary of Outcomes for Meningococcal Vaccine versus Control

Outcomes	**No. of Studies** *(no. of participants)*	**Effect estimate (95% CI)**	**Certainty of Evidence**
Effect of meningococcal vaccination on invasive meningococcal disease	2 observational studies (38,776)	OR=0.11 (0.04 to 0.30)	Very low
Effect of meningococcal vaccination on nasopharyngeal carriage	2 RCTs (2,236)	RR=1.06 (0.76 to 1.47)	Low
Immunogenicity of MenACWY vaccine	4 RCTs (7,629)	RR= 27.67 (15.05 to 50.85)	Low
Effect of meningococcal vaccination on local adverse effects	10 RCTs (8,593)	RR=0.80 (0.67 to 0.95)	Low
Effect of meningococcal vaccination on systemic adverse effects	12 RCTs (16,343)	RR=1.00 (0.85 to 1.19)	Low
Effect of meningococcal vaccination on serious adverse effects	6 RCTs (3,337)	RR=1.32 (0.87 to 2.00)	Low

The forest plots are shown in Appendix C. The summary of findings table and reasons for downgrading are found in Appendix D.

3.4.4 Cost Implication

There are no local cost-effectiveness studies available on meningococcal vaccines. Several foreign studies on cost-effectiveness of meningococcal vaccination programs have conflicting results.

A study done in the USA reported that a MenACWY vaccination program in 1 year old children and in 11 year old adolescents was cost-effective, but not in infants aged 2, 4 and 6 months old.[27] In contrast, another study done in the Netherlands evaluated the cost-effectiveness of meningococcal vaccination at 14 months and a booster dose at 12 years, and reported that routine vaccination in infants with MenACWY is cost-saving, but a booster dose during adolescence is not likely to be cost-effective.[28] Two other studies on adolescent meningococcal vaccination reported the

program to be cost-effective [29,30] while 1 study on adolescent MenACWY vaccination reported that the program was not cost-effective.[31] The cost-effectiveness studies are summarized in appendix E.

Table 2: Estimated cost of one dose of meningococcal vaccination

Vaccine	Cost
Quadrivalent meningococcal vaccine (MenACWY-TT in pre-filled syringe, MenACWY-D in vial)	Php 2,250.00 to 2,500.00*

*Cost obtained from local vaccine suppliers

3.4.5 Equity, Acceptability, and Feasibility

There are no local studies on the feasibility and acceptability of meningococcal vaccination. A study from the Netherlands looked into the decision-making process within households regarding MenACWY vaccination after its introduction into the National Immunization Program and catch-up campaign for adolescents.[32] Eighteen parent-adolescent dyads and 2 parents (adolescent opted out) were interviewed. Parents reported that previously developed ideas about vaccinations, either in favor or against, played an important role in their decision about the MenACWY vaccination. Lasting impressions surrounding previous experience with meningococcal disease also greatly influenced their decision. Severity of disease was also frequently mentioned as a motivation to get vaccinated. In contrast, some parents and adolescents chose not to get vaccinated after learning that the risk of disease in their country is low. In decision-making, parents frequently involved the adolescent, but only rarely did the adolescent have an actual influence on the outcome, despite the adolescents being of an age at which they can self-consent to getting vaccinated or not.

3.4.6 Recommendations from Other Groups

The US CDC Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination with a quadrivalent meningococcal conjugate vaccine (MenACWY) for adolescents aged 11 or 12 years, followed by a booster dose at age 16 years.[33] ACIP also recommends routine vaccination with MenACWY for persons aged ≥2 months at increased risk for meningococcal disease (i.e., persons with persistent complement component deficiencies, anatomic or functional asplenia, or HIV infection; receiving a complement inhibitor; microbiologists routinely exposed to isolates of *Neisseria meningitidis*; persons identified to be at increased risk because of a meningococcal disease outbreak caused by serogroups A, C, W, or Y; people who travel to or live in areas where meningococcal disease is hyperendemic or epidemic; unvaccinated or incompletely vaccinated first-year college students living in residence halls; military recruits). ACIP recommends MenACWY booster doses for previously vaccinated persons who become or remain at increased risk.

The Philippine Pediatric Society (PPS) and the Pediatric Infectious Disease Society of the Philippines (PIDSP) recommends the meningococcal vaccine for those at high risk of invasive disease, which includes persons with persistent complement component deficiencies, anatomic/functional asplenia, HIV infection; travelers to or residents of areas where meningococcal disease is hyperendemic or epidemic; and belonging to a defined risk group during a community or institutional meningococcal outbreak.[34]

At present, the meningococcal vaccine is not part of the Department of Health National Immunization Program.[35]

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3.5 Japanese Encephalitis Vaccine

RECOMMENDATION

Among apparently healthy children aged 18 years and below from high-risk areas*, we suggest Japanese Encephalitis vaccine (Weak recommendation, Very low certainty of evidence)

**High-risk areas*
- *Luzon: Nueva Ecija, Tarlac, Metro Manila, Bulacan, Laguna, Mindoro Pampanga*
- *Visayas: Camarines Norte, Camarines Sur, Northern Samar, Iloilo, Negros Oriental*
- *Mindanao: North Cotabato*

Considerations

The consensus panel considered the following when formulating this recommendation:
- Prevention of Japanese encephalitis is a priority in children and adolescents living in high-risk geographical regions of the country.
- Benefits outweigh the risk of harm and evidence shows that vaccination prevents encephalitis, but some panelists believe more high-quality evidence are needed on burden of disease, cost-effectiveness, equity, acceptability and feasibility to make a strong recommendation.
- There is a pressing need to strengthen surveillance and identify high-risk areas of disease.

3.5.1 Burden of disease

Japanese encephalitis virus (JEV) infection, the most important cause of viral encephalitis in Asia, primarily affects children.[1–3] JEV is the leading cause of acute encephalitis in the Philippines with a high proportion of cases seen among children aged <15 years and occurring with a slightly male predominance (78% of confirmed cases).[4] The annual national incidence of Japanese encephalitis (JE) is estimated at 8.6/100,000 and higher rates are observed in the northern regions during rainy seasons.[5,6]

From 2012 to 2018, greater than 60% seroprevalence for JEV was recorded in the adolescent populations of Manila, Muntinlupa, and Laguna.[6] Furthermore, the surveillance for acute encephalitis syndrome, a proxy for JE cases, recorded a three-fold increase of suspected and confirmed cases from 2014 (448 suspected cases and 49 confirmed) to 2017 (2159 suspected cases and 313 confirmed). These data prompted the Department of Health to launch a one-time subnational immunization campaign in April 2019, administering Japanese encephalitis vaccine in the northern regions of the country.[6]

Japanese encephalitis (JE) initially presents with non-specific, mild systemic symptoms but can develop fatal neurologic manifestations. Mortality rate is increased at 20-30% of cases.[7,8] Local studies have shown that 30-50% of survivors have moderate to severe neurological, behavioral and cognitive deficits.[4,5]

There is no proven treatment for JEV infection. Vaccination has been shown to be the most effective measure for disease prevention.[7,9] The incidence of JE has significantly declined in countries that have incorporated JE vaccination in their national immunization program (NIP). Previously high-incidence countries such as China, Japan and Republic of Korea have achieved JE incidence rates as low as 0.0039/100,000. In contrast, high-incidence countries without JE vaccination programs such as the Philippines and Myanmar have incidence rates of roughly 10/100,000 or greater.[10,11] In 2016, 12 out of 24 JE-endemic countries in Asia and the Western Pacific Region incorporated JE vaccination into their NIP.[8]

The JE vaccine is currently not included in our NIP and JE prevention efforts are still underway. The live, attenuated, Japanese encephalitis chimeric virus vaccine (JE-CV) is the only vaccine available and approved for use in children in the country.[8,12,13]

3.5.2 Benefits and Harms of the Vaccine

Japanese Encephalitis vaccine is associated with a significantly reduced risk of developing encephalitis from JEV. There is no significant effect on immunogenicity at Day 28, serious adverse events, systemic adverse events and local adverse events.

Four primary randomized controlled trials (RCT) and 2 follow-up studies evaluated the effectiveness and safety of JE vaccine in healthy children.[14–19] Of the 4 primary RCTs, 2 evaluated live-attenuated JE vaccine while 2 evaluated inactivated JE vaccine. JE vaccine was compared against active controls (hepatitis A vaccine, pneumonia vaccine) in 2 RCTs, placebo in 1 RCT, and no JE vaccination in 1 RCT.

Encephalitis from JEV

Only 1 RCT reported the effect of JE vaccine in the development of encephalitis from JEV. This study involved 65,224 children aged 1-14 years old who were given monovalent or inactivated JE vaccine. Findings from this study showed that the JE vaccine significantly reduced the risk of developing encephalitis from JEV compared to placebo (RR 0.09, 95% CI 0.02-0.40).[1]

There were no RCTs comparing the effect of live-attenuated JE vaccine versus no vaccine or inactivated JE vaccine on encephalitis from JEV.

Immunogenicity

One RCT assessed the development of antibodies against the JE live attenuated chimeric vaccine using plaque reduction neutralization test (PRNT50).[3] There was no significant difference in the anti-JE PRNT antibody responses at Day 28 between the JE vaccine group and the control group (Hepatitis A; RR 0.90, 95% CI 0.28-2.90). The authors reported that 3 of the study participants in the control group and 24 of the study participants in the JE vaccine group were already positive for JE already at screening. A sensitivity analysis excluding these 27 participants showed a trend towards benefit for JE vaccine in PRNT antibody response, but the results were not statistically significant (RR 1.24, 95% CI 0.07-22.32).[3]

Long term immunogenicity data was reported by 1 study which was a follow-up of the Feroldi 2012 study.[20,21] Three years after receiving the JE-CV vaccine, 93.1% (95% CI 90.5-95.1) of participants demonstrated persistence of seroprotection. At 5 years, 85.4% (95% CI 81.9-88.4%) remained seroprotected. However, results of the control group were not reported, hence relative risk cannot be computed. Another follow-up study reported that after 1 year, 99.4% of children aged 36-42 months who received 2 doses of JE-CV vaccine (1 primary dose and 1 booster dose) remained seroprotected.[5,6]

Vaccine Safety

Serious adverse event outcomes were pooled from 3 studies that evaluated JE vaccines in comparison with non-JE vaccines.[15,17,19] Two RCTs used live-attenuated JE vaccine while 1 RCT used inactivated vaccine. There was no significant difference in serious adverse events (RR 0.73, 95% CI 0.35-1.50). In all studies, no severe adverse events were reported among the vaccinees within 30 minutes post-vaccination. One study using inactivated JE vaccine reported 1 death (disseminated intravascular coagulation in a 12-year-old male, 4 months after the 2nd dose) which was deemed unrelated to the vaccine. Other serious adverse events included mild to moderate febrile convulsions.

Pooled analysis of 2 RCTs also showed no significant difference in local adverse events (RR 0.95, 95% CI 0.79-1.14).[17,19] The most common local adverse events were post-injection site pain and tenderness. There was also no significant difference in systemic adverse events (RR 0.84, 95% CI 0.45-1.55). The most common systemic adverse events were mild to moderate fever.

Table 1. Summary of Outcomes for JE vaccine vs Control

Outcomes	**No. of Studies** *(No. of participants)*	**RR (95% CI)**	**Certainty of Evidence**
Encephalitis from JEV	1 study (65,224)	0.09 (0.02-0.40)	High
Immunogenicity at Day 28	1 study (1,200)	0.90 (0.28-2.90)	Very low
Serious adverse events	3 studies (29,601)	0.73 (0.35-1.50)	Low
Local Adverse Effects	2 studies (3,069)	0.95 (0.79-1.14)	Low
Systemic Adverse Effects	2 studies (3,069)	0.84 (0.45-1.55)	Low

3.5.4 Cost Implication

One study evaluated the cost-effectiveness of three JE vaccination strategies in the Philippines, with the aim of supporting the integration of JE vaccine into the national immunization program.[22] The study reported that a one-time national campaign followed by national routine immunization was the most cost-effective strategy. Based on their model, this strategy is projected to prevent 27,856-37,277 cases, 5571-7455 deaths, and 173,233-230,704 disability adjusted life years in children <5 years old. Authors conclude that JE vaccination will be cost-effective, reduce long-term cost associated with JE illness, and promote better health outcomes compared to no vaccination.

Three other cost-effectiveness studies in Asia report that JE vaccination is cost-effective. In Thailand, routine immunization with JE vaccine at 18 months (at a cost of US$ 2.28/child) would prevent 124 cases per 100,000 and lead to savings of US$72,922 for each prevented case (i.e., treatment costs, disability care, and loss of future earnings).[23] In China, JE vaccination using inactivated and live-attenuated JE vaccine would result in cost savings compared with no vaccination, with the live vaccine resulting in greater cost savings because it requires fewer doses (US$512,456 per 100,000 people for live-attenuated vaccine versus US$348,246 for inactivated vaccine).[24] In Indonesia, a 2-dose regimen of the live-attenuated JE vaccine will prevent 54 JE cases and 5 deaths, and save 1224 disability adjusted life years compared with no vaccination, at a cost of US$700 per JE case averted and US$31 per DALY saved.[25]

Table 2. Cost of Japanese Encephalitis Vaccine

	Live attenuated JE vaccine*
Cost in Php	PHP1800 per dose (private sector)

*IMOJEV, the only locally available JE vaccine, is not included in the Philippine Drug Formulary and is only available in the private market**.**

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3.5.5 Equity, Acceptability, and Feasibility

The Philippines has recognized JE infection as a public health priority; in 2019, a one-time campaign of JE vaccination was implemented in 4 northern regions of the country due to increasing number of cases. Without a high-quality surveillance system and in the presence of underreporting of cases, the true burden of JE is likely underestimated and expansion of the NIP to include JE vaccination should be considered.[1,12]

JE imposes a significant burden to society and the health care system. Aside from the high cost and unavailability of the JE vaccine in other regions of the country, costs of testing, treatment and permanent neurologic complications can place a heavy burden on family resources.[26]

There are no published local or international studies on patient values and preferences, equity, acceptability, or feasibility with respect to implementing JE vaccination in children.

3.5.6 Recommendations from Other Groups

The World Health Organization recommends that JE vaccination be integrated into the national immunization program of endemic countries, including the Philippines. The US Centers for Disease Control recommends 2 doses of inactivated JE vaccine for children 2 months to 17 years old while our Pediatric Infectious Disease Society of the Philippines recommends 2 doses of live attenuated JE vaccine for children 9 months to 17 years old.

Group	Recommendation	Strength of recommendation and certainty of evidence
World Health Organization[1]	JE-endemic countries to conduct a one-time JE vaccination campaign in the primary target population then integrate into the national immunization (NIP) as a routine immunization. **Inactivated Vero cell-derived vaccine**: Primary series according to manufacturer's recommendations, generally 2 doses at 4-week intervals starting the primary series at ≥6 months of age in endemic settings **Live attenuated vaccine**: Single dose administered at ≥8 months of age **Live recombinant vaccine:** Single dose administered at ≥9 months of age	**Strong recommendation; high quality of evidence**
Centers for Disease Control and Prevention[26]	**JE inactivated** primary series for children aged 2 months through 17 years old, given intramuscularly for 2 doses administered 28 days apart: For 2 months-2 years old, 0.25m For 3 years17 years old, 0.5mL	**Strong recommendation; high quality of evidence**

Pediatric Infectious Disease Society of the Philippines (PIDSP) and Philippine Pediatric Society (PPS)[27,28]	**Live attenuated recombinant vaccine:** Recommended for minimum age of 9 months old, primary dose of 0.5ml, subcutaneously. Booster dose for 9 months to 18 years old, should be given 12-24months after the primary dose. Individuals 18 years and older should receive a single dose only. (In times of scarce supply, priority should be given to <15 years old living in the high risk areas.)	**Not indicated**
Department of Health/ National Immunization Program[29]	**Live attenuated**: Single dose of 0.5ml administered for children <8 months of age, upper arm, subcutaneously. A one-time national campaign vaccination in the high-risk areas of Region I, II, III and Cordillera Administrative Region (CAR) were implemented last March 2019 followed by integration to national immunization program.	**Not indicated**

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3.6 Inactivated Polio Vaccine

RECOMMENDATION

Among apparently healthy infants, we recommend vaccination with bivalent Oral Poliovirus Vaccine (bOPV) plus Inactivated Poliovirus Vaccine (IPV) or IPV alone if bOPV is not available. (Strong recommendation, Moderate certainty of evidence)

Considerations

The consensus panel considered the following when formulating this recommendation:

- Prevention of poliomyelitis must continue to be a health priority in order to maintain the polio eradication status of the Philippines.
- While there are no studies assessing the direct efficacy or effectiveness of vaccination on poliomyelitis incidence, current evidence shows that the benefits of vaccination outweigh the risk of harm. The national health system response to previous polio outbreaks also shows that vaccination is a successful, cost-effective, feasible and acceptable strategy for polio prevention in the country.
- The panel is aligned with the WHO and Global Polio Eradication Initiative for the eventual withdrawal OPV and transition to pure IPV vaccination. However, vaccination with OPV is still recommended for the mucosal protection it provides since the Philippines remains vulnerable to outbreaks.
- Practitioners who cannot access OPV from their Rural Health Units or City Health Office have the option to give an IPV only regimen.

3.6.1 Burden of disease

Poliomyelitis is an infectious neurologic disease predominantly affecting children less than 5 years old. The causative agent is poliovirus, an enteric pathogen with distinct serotypes 1, 2, and 3, which is frequently transmitted via the fecal-oral route. There is no cure for polio.[1] It is estimated that 1 in 200 children infected with poliovirus develop irreversible paralysis with some cases leading to death.[1]

The Philippines has been certified free of circulating wild poliovirus (WPV) in 2000. However, in September 2019, an outbreak of circulating vaccine-derived poliovirus type 2 (cVDPV2) was declared when a polio case was detected in Lanao del Sur and two environmental samples from Manila and Davao were found to have cVDPV2.[2] The Philippines has since been found to have a high risk for outbreaks due to many factors, with low vaccination coverage as a primary factor.

Eventual discontinuation of OPV use worldwide is one of the goals of the Global Polio Eradication Initiative as OPV is the major source of cVDPVs. In 2016, the World Health Organization (WHO) implemented a global switch from trivalent oral poliovirus vaccine (tOPV) to bivalent OPV (bOPV) containing only types 1 and 3, with the aim of decreasing the incidence of polio secondary to cVDPV2, the most common causative agent of vaccine-derived polio in the world. The risk of paralytic polio associated with continued routine use of OPV is deemed greater than the risk of imported wild virus. To provide the necessary immunity to poliovirus type 2, the inactivated poliovirus vaccine (IPV) containing all three types is being given concomitantly as part of the National Immunization Program (NIP). In countries that are polio-free,

IPV is the vaccine of choice. The current NIP schedule in the country is bOPV at 6, 10, and 14 weeks, plus one dose of IPV administered at 14 weeks.

In the Philippines, bOPV is available only in the NIP. Patients who avail of vaccinations in the private sector are given IPV, usually as part of a combination vaccine that includes DTP, Hepatitis B, and Hib antigens, using a 6, 10, 14 weeks primary schedule. Since tOPV has been phased out, this review will only include relevant studies evaluating bOPV.

3.6.2 Benefits and Harms of the Vaccine

IPV versus Bivalent OPV

IPV has significantly lower seroconversion rates than bOPV for poliovirus type 1, higher seroconversion rates for poliovirus type 2, and no significant difference for poliovirus type 3. IPV has significantly higher fecal viral shedding compared to bOPV for poliovirus type 1 and 3, and no significant difference in fecal viral shedding in poliovirus type 2.

Prevention of Disease

There were no randomized controlled trials (RCTs) or observational studies comparing the efficacy of IPV and bOPV in the prevention of poliomyelitis.

Immunogenicity

Effect on Seroconversion

Two RCTs compared primary vaccination schedules containing IPV alone and bOPV alone[3,4]. Both studies were done on healthy newborns and had multiple trial arms that evaluated different schedules of IPV and OPV. Outcomes reported in both studies include seroconversion to each poliovirus type and fecal viral shedding after tOPV challenge. The characteristics of included studies are in Appendix B.

Pooled analysis of seroconversion to each poliovirus type after completion of the series show that the IPV regimen has significantly lower seroconversion rates than the bOPV regimen for poliovirus type 1 (RR = 0.88, 95%CI 0.79-0.99). As expected, the IPV regimen has significantly higher seroconversion rates than the bOPV regimen for type 2 (RR = 5.15, 95% CI 3.62-7.32). There was no significant difference between IPV and bOPV regimens in seroconversion rates for poliovirus type 3 (RR = 0.99, 95% CI 0.96-1.03).

Effect on Fecal Viral Shedding after Oral Challenge

Pooled analysis showed that after an oral polio vaccine challenge, there are significantly more subjects in the IPV regimen with fecal viral shedding compared to bOPV both for poliovirus type 1 (RR=14.13, 95%CI 6.93-28.81) and type 3 (RR=2.91, 95% CI 1.73-4.90). There is no significant difference between IPV and bOPV regimens in fecal viral shedding for poliovirus type 2 (RR=1.02, 95%CI 0.89-1.17).

Vaccine Safety

There were no observational population-based studies that compared adverse events (i.e. vaccine-associated paralytic polio and vaccine-derived poliovirus prevalence) between IPV and bOPV. Of the 2 RCTs, one did not report adverse events while safety data from the other was not available.

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Table 1. Summary of outcomes for IPV vs bOPV

Outcomes	Effect estimate (95% CI)	No. of Studies *(no. of participants)*	Certainty of Evidence
Seroconversion to Poliovirus Type 1	RR = 0.88, 95%CI 0.79-0.99	2 RCTs (790)	Moderate
Seroconversion to Poliovirus Type 2	RR = 5.15, 95% CI 3.62-7.32	2 RCTs (790)	Moderate
Seroconversion to Poliovirus Type 3	RR = 0.99, 95% CI 0.96-1.03	2 RCTs (790)	Moderate
Fecal Viral Shedding Poliovirus Type 1	RR = 14.13, 95%CI 6.93-28.81	2 RCTs (661)	High
Fecal Viral Shedding Poliovirus Type 2	RR = 1.02, 95%CI 0.89-1.17	2 RCTs (661)	High
Fecal Viral Shedding Poliovirus Type 3	RR = 2.91, 95% CI 1.73-4.90	2 RCTs (661)	High

IPV with bOPV versus IPV alone

IPV with bOPV significantly lower seroconversion rates to poliovirus type 2 compared to IPV-only regimens. There was no significant difference in seroconversion rates to poliovirus types 1 and 3. There was significantly lower fecal viral shedding with all poliovirus types with IPV+bOPV compared to IPV alone. There was no significant difference in serious adverse events.

Effect on Prevention of Disease

There were no RCTs or observational studies comparing the efficacy of immunization schedules containing IPV and bOPV with those containing IPV alone in the prevention of poliomyelitis.

Immunogenicity

Effect on Seroconversion

Seven RCTs evaluated IPV+bOPV and IPV-only primary immunization schedules for seroconversion to poliovirus[3-9]. All were done on healthy infants; the IPV+bOPV regimens were given as follows: fractional IPV + bOPV, 4bOPV+IPV (mixed schedule), and sequential schedules of IPV (using Salk or Sabin strains) followed by 1 or 2 bOPV while the IPV-only regimens were given as 2, 3, or 4 doses. Study details are presented in Appendix B.

There was no significant difference between the IPV+bOPV and IPV-only regimens in seroconversion rates to poliovirus type 1 (RR=1.03, 95% CI 1.00-1.06) and poliovirus type 3 (RR = 1.01, 95% CI 0.99-1.02). IPV+bOPV regimens were associated with significantly lower seroconversion rates to poliovirus type 2 compared with IPV-only regimens (RR=0.83, 95% CI 0.74 - 0.92) but there was significant heterogeneity (I^2=97%), likely due to the different schedules used for IPV+bOPV administration. Subgroups using 2 IPV doses with bOPV showed no significant difference to IPV-only regimens for seroconversion to poliovirus type 2 (low certainty of evidence); subgroups with 1 IPV dose plus bOPV showed significantly lower seroconversion compared to IPV-only regimens for seroconversion to poliovirus type 2 (moderate certainty of evidence).

Effect on Fecal Viral Shedding after Oral Challenge

Two RCTs evaluated viral shedding among IPV+bOPV and IPV-only regimens after a tOPV challenge,[3,4] while one RCT studied poliovirus type 2 shedding after a monovalent OPV2 (mOPV2) challenge.[6] Pooled analysis of the first two RCTs showed that those given bOPV+IPV regimen had significantly less viral shedding compared to the IPV-only regimen with poliovirus type 1 (RR=0.26, 95% CI 0.18 - 0.37) and poliovirus type 3 (RR = 0.35, 95% CI 0.24 - 0.5). Pooled analysis of the 3 RCTs showed significantly less subjects in the IPV+bOPV regimen with viral shedding of poliovirus type 2 (RR = 0.82 [95%CI 0.69-0.99) compared to IPV-only regimens.

Vaccine Safety

There were no observational population-based studies that compared adverse events (i.e. vaccine-associated paralytic polio and vaccine-derived poliovirus prevalence) between IPV+bOPV and IPV-only regimens. Pooled data of severe adverse events from 4 RCTs did not have significant difference between IPV+bOPV and IPV-only regimens (RR=0.95, 95%CI 0.64-1.43). O'Ryan et al. in 2015 reported one serious adverse event as vaccine-related (a child admitted for surgery for intussusception 4 days after receiving the mOPV2 challenge at age 7 months); the case was subsequently judged as indeterminate.

Table 2. Summary of outcomes for IPV with bOPV versus IPV alone

Outcomes	**RR (95% CI)**	**No. of Studies** *(no. of participants)*	**Certainty of Evidence**
Seroconversion			
Poliovirus Type 1	1.03 (1.00-1.06)	7 RCTs (3290)	Moderate
Poliovirus Type 2	0.83 (0.74-0.92)	7 RCTs (3286)	Moderate
Poliovirus Type 3	1.01 (0.99-1.02)	7 RCTs (3277)	High
Fecal viral shedding			
Poliovirus Type 1	0.26 (0.18-0.37)	2 RCTs (733)	High
Poliovirus Type 2	0.82 (0.69-0.99)	3 RCTs (1262)	Moderate
Poliovirus Type 3	0.35 (0.24-0.5)	2 RCTs (733)	High
Adverse events	0.95 (0.64-1.43)	4 RCTs (1970)	Moderate

Forest plots supporting these findings are shown in Appendix C. The summary of findings table and reasons for downgrading are found in Appendix D.

3.6.4 Cost Implication

There are no local cost-effectiveness studies comparing vaccination with IPV+bOPV versus IPV alone. A cost-effectiveness study from Shanghai, China compared the cost-effectiveness of a schedule of 2IPV+2bOPV and 4IPV compared to 4tOPV.[10] The incremental cost-effectiveness ratio (ICER) was substantially high for both two-IPV-two-bOPV and four-IPV vaccination regimens compared to 4 doses of tOPV in averting Vaccine-Associated Paralytic Polio-induced disability-adjusted life years. The authors concluded that IPV-containing schedules are currently cost-ineffective in Shanghai. Meanwhile, a cost-minimization analysis study from Chile compared the cost of pentavalent vaccine plus IPV/OPV vaccines to hexavalent vaccine with IPV (Hexaxim).[11] The authors concluded that the cost of switching to the hexavalent vaccine would incur an additional cost of US$ 6.45 million.

The 2016 WHO Position Paper on Polio Vaccines has stated that incremental net benefits of polio eradication between 1988 and 2035 were estimated at US$ 40–50 billion with the lower value corresponding to increased adoption of IPV.[12] However, delays in achieving polio eradication and increased costs were considered in an updated economic analysis where the authors estimated the incremental net benefits of the Global Polio Eradication Initiative to be 28 billion (US$2019), falling below the prior estimate.[13]

A recent study estimated the costs (in US$ 2019) of administering different poliovirus regimens to a child by routine immunization.[14] The projected costs per regimen for lower-middle income countries are as follows: 3OPV + 1 IPV full dose = $7.72; 3OPV + 2 IPV full dose = $12.61; 3OPV + 2 IPV fractional dose = $7.82; 3 IPV = $14.68; 4 IPV = $21.18.[14]

Table 3. Cost of Polio Vaccine

Parameter	Estimates
Unit cost of vaccine (in Philippine Peso)	IPV alone or in combination – Php 805-2350* OPV – Php 5.85 - 9.45**

*Cost obtained from local vaccine suppliers; **UNICEF estimates

The Philippine Health Technology Assessment Council (HTAC) published an evidence summary on two-dose versus one-dose IPV for the prevention of poliomyelitis, including a cost-effectiveness analysis.[21] The HTAC stated: "Despite the costly implementation of two-dose IPV due to expected suboptimal coverage in the early years of implementation, the DOH-NIP aims to achieve high coverage in later years. This will result in savings to the healthcare system because of the averted costs of outbreak response. However, the program should consistently achieve at least 95% vaccination coverage to reach the elimination or eradication target." There was no comparison on the cost-effectiveness of IPV-only regimens compared to IPV+bOPV or bOPV-only regimens in the HTAC analysis.

The 2016 WHO Position Paper states that intradermal IPV administration with fractional doses of IPV (0.1mL or 1/5 of a full dose) is a potential strategy for cost reduction and would allow immunization of a larger number of persons.[12] An IPV based on the attenuated Sabin virus strains (sIPV) was developed and licensed in 2012 and its use is also being studied; sIPV offers the advantage of less stringent biocontainment requirements in its manufacture.[12] The Sabin IPV is not yet licensed for use in the Philippines but is WHO-prequalified. These approaches may help address global supply of IPV.

3.6.5 Equity, Acceptability, and Feasibility

A study on the acceptability of an additional parenteral poliovirus vaccine (IPV dose at 14 weeks) in the Philippine NIP was done in 2015-2016.[15] Results showed that 87% of healthcare providers that had administered three or more injectable vaccines post-introduction reported being comfortable or very comfortable with the number of vaccines they had administered. The study mentioned anecdotal reports of some public health centers deliberately spreading out the scheduled vaccines over multiple visits to avoid administering 3 parenteral vaccines at one visit.

A study that included reach, timeliness, equity, public expenditure, and supply side assessment of the expanded program on immunization in the Philippines using various methodologies showed that the coverage of basic vaccines has only hovered between 70 and 80 percent in the last 30 years.[16] Demand factors like vaccine confidence have contributed to the weak performance of the program but the assessment concluded that the sharp decline in immunization coverage is largely a result of deep-seated supply-side systemic issues related to leadership, planning, and the supply chain, which led to recurring vaccine stock-outs in the past decade.

3.6.6 Recommendations from Other Groups

Polio immunization schedules vary per country, with some developed countries using IPV-only schemes given alone or in combination with other antigens, or a sequential schedule of IPV followed by bOPV. Other countries, including the Philippines, use mixed schedules of OPV+IPV. The schedule of OPV and IPV per country is available at: https://apps.who.int/immunization_monitoring/globalsummary/schedules.

Group	Recommendations
World Health Organization[17]	Two doses of IPV at ages 14 weeks and 9 months or 6 weeks and 14 weeks in addition to the bOPV series (mixed schedule) or at 2 and 4 months followed by bOPV (sequential schedule) This strategy is part of the global effort on OPV withdrawal, one of the goals necessary for complete eradication of polioviruses.
US Centers for Disease Control and Prevention[18]	IPV 4-dose series at ages 2, 4, 6–18 months, 4–6 years
Philippine Pediatric Society - Pediatric Infectious Disease Society of the Philippines[19]	Polio, usually administered in combination with DTaP and Hib, with or without Hep B, is given at a minimum age of 6 weeks with a minimum interval of 4 weeks. The primary series consists of 3 doses. A booster dose of IPV-containing vaccine should be given on or after the 4th birthday.
Department of Health - National Immunization Program[20,21]	bOPV at 6,10,14 weeks plus IPV at 14 weeks and 9 months (to be implemented starting calendar year 2022)

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3.7 Oral Polio Vaccine

RECOMMENDATION

Among healthy infants less than 28 days-old, we suggest immunization with oral poliovirus vaccine during outbreak response immunization activities. (Weak recommendation, Very Low certainty of evidence)

Considerations

The consensus panel considered the following when formulating this recommendation:

- Prevention of poliomyelitis in neonates is a priority.
- Current evidence shows that the benefits of vaccination outweigh the risk of harm but some panelists believe that more high-quality evidence are needed on efficacy, cost-effectiveness, equity, acceptability and feasibility to make a strong recommendation.
- An OPV birth dose in not part of routine immunization but neonates may receive an OPV dose during outbreak response immunization activities.

3.7.1 Burden of disease

The Philippines has been certified free of circulating wild poliovirus (WPV) since 2000 but the country has been found to have a high risk for polio outbreaks due to many factors, including persistently low routine immunization coverage as well as poor sanitation and hygiene.[1] In September 2019, an outbreak of circulating vaccine-derived poliovirus type 2 (cVDPV2) was declared when a polio case was detected in Lanao del Sur and two environmental samples from Manila and Davao were found to have cVDPV2.[2] In response to the outbreak, the Department of Health (DOH) implemented supplemental immunization activities (SIA) nationwide by administering oral polio vaccines (OPV) in the form of bivalent oral polio vaccines (bOPV) and monovalent oral polio vaccines containing poliovirus type 2 (mOPV2) to children 0-59 months old.[3,4]

Since 1985, the World Health Organization has recommended OPV administration at birth and at 6, 10, and 14 weeks - a safe and effective means of protection against poliomyelitis in resource-poor regions. The OPV birth dose is especially important because this dose can provide early protection to newborns in polio-endemic settings. The birth dose was initially referred to as “zero-dose OPV” and is not typically counted as part of the three-dose routine OPV schedule in developing countries.[5] In polio-endemic countries and in countries at high risk for importation and subsequent spread, the WHO recommends an OPV birth dose followed by a primary series of 3 OPV and 2 IPV doses based on its latest recommendation.[6] The cVDPV2 outbreak in the Philippines ended on June 2021 but the country is still considered vulnerable to re-infection by WPV or cVDPV. Although the Philippine National Immunization Program provides the first OPV dose at 6 weeks of age as part of routine immunization, infants younger than 6 weeks may encounter being offered OPV during SIAs, raising the need for this review.

3.7.2 Benefits and Harms of the Vaccine

Immunization with a birth dose of tOPV is associated with significant seroconversion (measured after the birth dose) to all poliovirus serotypes compared to no birth dose. There is no significant difference in seropositivity (measured after the birth dose) for serotypes 1 and 3 among those with or without a birth dose of bOPV. Among infants completing a primary series with or without an OPV birth dose, there is no significant difference for final seroconversion and seropositivity to all poliovirus serotypes. There is no significant difference in mortality at 12 months among those with an OPV birth dose and those without.

Effect on the Incidence of Poliomyelitis

This review found no randomized controlled trials (RCTs) or observational studies investigating the effect of adding an OPV birth-dose to a polio vaccination schedule on the incidence of poliomyelitis.

Immunogenicity of OPV Birth Dose

Six RCTs on healthy term infants compared the immunogenicity of an OPV birth dose compared to no birth dose. Of these, 5 evaluated trivalent OPV (tOPV),[7-11] and one evaluated bivalent OPV (bOPV).[12] In the RCTs using tOPV, routine OPV vaccination followed a Week 6, 10, 14 schedule in 3 studies; Month 2, 3, 4 schedule in 1 study; and Month 2, 4, 6 schedule in 1 study. Seroconversion was measured after the birth dose in 2 RCTs and upon completion of the immunization schedule in 5 studies. In the bOPV study, seropositivity was measured after the birth dose and at 6 months of age. Characteristics of included studies are presented in Appendix B.

Two RCTs assessed seroconversion after a birth dose of tOPV versus no birth dose. Blood samples were taken before patients received their regular vaccination series (age 6 weeks in 1 RCT, age 2 months in 1 RCT). Pooled analysis shows a significant difference in seroconversion for poliovirus type 1 (RR=3.66, 95% CI 1.58-8.47), type 2 (RR=3.96, 95% 1.00-15.68) and type 3 (RR=4.59, 95% CI 2.32-9.06) among those given birth dose tOPV compared to no birth dose.

One RCT studied seropositivity after a bOPV birth dose versus no birth dose. There was no significant difference for poliovirus type 1 (RR=0.95, 95% CI 0.84–1.08) and type 3 (RR=0.85, 95%CI 0.67–1.09).

Five RCTs studied seroconversion upon completion of the immunization schedule, all of which used tOPV. Pooled analysis shows no significant difference in final seroconversion for poliovirus type 1 (RR=1.08, 95% CI 0.94-1.24), poliovirus type 2 (RR=1.04, 95% CI 0.97-1.12) and poliovirus type 3 (RR=1.12, 95% CI 0.97-1.30). One RCT studied final seropositivity at 6 months of age where there was no significant difference between the birth dose and no birth dose group for poliovirus type 1 (RR=0.94, 95%CI 0.87–1.02) and type 3 (RR=0.93, 95% CI 0.84–1.04).

Preterm Infants

There are no RCTs comparing a birth dose OPV versus no birth dose among preterm infants. One RCT compared seroconversion among apparently healthy preterm babies who were given OPV 'early' at 34 to 35 weeks, versus a control group of term babies vaccinated in the first week of life.[12]
The mean chronological age of babies in the ‘early’ group was 1.5 weeks.[12] Poliovirus antibodies were measured immediately before and 6-8 weeks after vaccination to assess seroconversion. Between the preterm babies and control group, there were no significant differences between seroconversion rates to the 3 poliovirus serotypes (poliovirus type 1 RR=1.01, 95% CI 0.61-1.67, poliovirus type 2 RR=1.17, 95% CI 0.26-5.25, poliovirus type 3 RR=1.17, 95% CI 0.26-5.25; very low certainty of evidence).

Effect on Intestinal Immunity to Poliovirus

No RCTs studied the effect of OPV birth dose on viral shedding after a vaccine challenge.

Vaccine Safety

Only 2 tOPV RCTs reported adverse events. In Dong et al., "slight diarrhea occurred in a few, but cleared in 1-2 days without treatment".[7] Meanwhile, Osei-Kwasi et al. noted no adverse reactions in any of the infants up to 4 weeks after the last dose; 24 cases of diarrhea (watery stools >3 times within 24 hours) were reported but resolved within 1-3 days after treatment with oral rehydration. The number of adverse events in the treatment group and control group was not reported.

The RCT on bOPV was part of a larger trial studying the effect of an OPV birth dose on infant mortality.[13] Results showed no significant difference in mortality at 12 months (HR=0.83, 95% CI 0.61–1.13).

The summary of outcomes is presented in the table below. Forest plots and GRADE evidence profiles in support of these findings are detailed in Appendix C and D.

Table 1. Summary of outcomes for OPV birth dose versus no birth dose

Outcomes		**No. of Studies** *(no. of participants)*	**Effect estimate (95% CI)**	**Certainty of Evidence**
Seroconversion after birth dose vs no birth dose	Poliovirus type 1	2 RCTs (269)	RR 3.66 (1.58-8.47)	Very Low
	Poliovirus type 2	2 RCTs (269)	RR 3.96 (1.00-15.68)	Very Low
	Poliovirus type 3	2 RCTs (269)	RR 4.59 (2.32-9.06)	Very Low
Seropositivity after birth dose vs no birth dose	Poliovirus type 1	1 RCT (173)	RR 0.95 (0.84-1.08)	Moderate
	Poliovirus type 3	1 RCT (151)	RR 0.85 (0.67-1.09)	Low
Final seroconversion after completion of immunization schedule	Poliovirus type 1	5 RCTs (790)	RR 1.08 (0.94-1.24)	Low
	Poliovirus type 2	5 RCTs (790)	RR 1.04 (0.97-1.12)	Low
	Poliovirus type 3	5 RCTs (790)	RR 1.12 (0.97-1.30)	Low
Seropositivity at 6 months	Poliovirus type 1	1 RCT (521)	RR 0.94 (0.87-1.02)	Moderate
	Poliovirus type 3	1 RCT (498)	RR 0.93 (0.84-1.04)	Moderate
Mortality; birth dose vs no birth dose		1 RCT	HR 0.83 (0.61-1.13)	Low

3.7.4 Cost Implication

There are no cost-effectiveness studies evaluating a birth dose of oral polio vaccine. The table below shows price per dose of OPV for calendar year 2021 based on a multi-year supply agreement between vaccine manufacturers and UNICEF (United Nations Children's Fund).[14] Oral polio vaccine is not available for purchase in the private market.

Table 2. Cost of OPV vaccine

Vaccine Type	**Manufacturers**	**Price per dose (US$)**	**Price per dose in Php (US$1=Php50)**
Bivalent OPV vaccine	Bharat Biotech (India), Bio Farma (Indonesia), GlaxoSmithKline Biologicals (Belgium), Beijing Bio-Institute Biological (China), Sanofi Pasteur (France)	$ 0.117 - 0.189	Php 5.85 - 9.45

*Source: UNICEF[14]

3.7.5 Equity, Acceptability, and Feasibility

There are no studies on the feasibility and acceptability of administering a birth dose of OPV. No studies were found on acceptability of supplemental polio immunization activities in the Philippines.

One study conducted in the Philippines assessed the timeliness of infant vaccinations and reported that only 28.1% and 62.5% of infants received BCG and Hepatitis B birth doses, with a median age of receipt of 2.7 and 0 weeks, respectively.[15] Infants who were enrolled at local health centers and offered a monthly immunization schedule were 40% and 50% less likely to receive BCG and Hepatitis B birth doses, respectively, compared to infants with more frequent immunization schedules.

3.7.6 Recommendations from Other Groups

The WHO recommends a birth dose of OPV in polio-endemic countries and in countries at high risk for importation and subsequent spread of disease. The list of countries where the OPV birth dose is given can be accessed at https://apps.who.int/immunization_monitoring/globalsummary/schedules. The 2016 WHO Position Paper on Polio Vaccines states that there is "high scientific evidence that OPV schedules starting with a birth dose are at least as immunogenic as otherwise comparable OPV schedules starting at 6-8 weeks of age".[16] It further states that "theoretically, giving the first OPV dose at a time when the infant is still protected by maternally-derived antibodies may also prevent VAPP" but there are no studies yet to support this. To date, there are no recommendations for a birth dose of OPV from the Philippine Department of Health, Pediatric Infectious Disease Society of the Philippines, and the US Centers for Disease Control.

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3.8 Hepatitis A Vaccine

RECOMMENDATION

Among apparently healthy children, we suggest immunization with hepatitis A vaccine starting at 12 months of age. (Weak recommendation, Very low certainty of evidence)

Considerations

The consensus panel considered the following when formulating this recommendation:

- Hepatitis A is not a health priority at present due to its low prevalence in the country, self-limiting nature of disease and rare occurrence of complications.
- Current evidence shows that the benefits of vaccination outweigh the risk of harm but the panel believes that more high-quality evidence are needed on the true burden of the disease, efficacy, cost-effectiveness, equity, acceptability and feasibility to make a strong recommendation.
- While the panelists agree that all children should be immunized before they are exposed, some panelists believe that vaccination efforts should be focused on geographical areas with high burden of disease, once "high disease burden" is defined and these areas are identified.
- The recommendation to vaccinate starting at 12 months of age includes both inactivated and live-attenuated Hepatitis A vaccine.

3.8.1 Burden of disease

Hepatitis A virus (HAV) is transmitted via the fecal-oral route or through contaminated water and food. Hepatitis A infection is included in the surveillance of the Department of Health's Food and Waterborne Diseases Prevention and Control Program. In 2015, 830 Hepatitis A cases were reported from the DOH surveillance sentinel sites. Majority of Hepatitis patients come from the 15-39 years age group, as well as the 5-14 years age group.[1]

Hepatitis A is a self-limiting disease that may last for 1-2 weeks. Symptoms may range from mild to severe and may include fever, malaise, loss of appetite, diarrhea, nausea, jaundice and abdominal discomfort.[2] Treatment is mainly supportive.[3] Complications of Hepatitis A are rare and may include immunologic, neurologic, hematologic, pancreatic, and renal manifestations. Fulminant hepatitis, the most severe complication, is rare and carries an estimated mortality rate of 80%.[4]

In the Philippines, there are 3 locally available Hepatitis A vaccines. Two are inactivated Hepatitis A vaccines, marketed under the brand names Avaxim (Sanofi-Pasteur) and Havrix (GSK).[5,6] Both are administered intramuscularly. The third available brand is Mevac A (Biogenetech) is a live attenuated Hepatitis A vaccine.[7] It is administered subcutaneously.

3.8.2 Benefits and Harms of the Vaccine

Hepatitis A vaccination has significantly reduced the annual incidence of Hepatitis A infection and hospitalization rate in countries implementing universal vaccination programs. Compared with control, hepatitis A vaccine shows no significant difference in terms of local and systemic adverse events.

A systematic review involving 31 studies evaluated the impact of two-dose and one-dose universal vaccination programs on non-live hepatitis A vaccines in children on the incidence and burden of hepatitis A and persistence of immune responses.[8] The review included national and regional vaccination programs done in the United States, Israel, Panama, China, Kingdom of Saudi Arabia, Uruguay and Belarus.[9-23]

Effectiveness of Universal Hepatitis A Vaccination in the Incidence of Hepatitis A

Fifteen before and after studies compared the effectiveness of a two-dose universal Hepatitis A vaccination on the incidence of Hepatitis A. Pooled estimate showed a decrease in the annual incidence of Hepatitis A by 98% (Rate Ratio = 0.02, 95%CI: 0.01 to 0.04) after introducing the vaccination programs. Vaccine coverage for the studies ranges from 40% to >= 99%.[9-23]

Vaccine Efficacy

Incidence of Hepatitis A among vaccinated children were compared to unvaccinated children using inactivated HAV. Two studies done in US and Belarus showed a significant decrease in the incidence of Hepatitis A (OR 0.06, 95% CI: 0.04 to 0.11, I2= 92%). [16,17]

Hepatitis A-related Hospitalization and Mortality

Studies in the United States and Greece showed a decline in Hepatitis A-related hospitalization rate by 72% in the post-vaccination period (OR = 0.28, 95% CI 0.25 to 0.30). [24,25] Hepatitis A-related mortality had a non-significant decline by 32% from 0.038/100,000 to 0.026/100,000 in the United States after vaccination (OR =0.68, 95%CI: 0.4111, 1.125).[24]

Immunogenicity

Six studies reported on the long-term protective effects of inactivated hepatitis A vaccines.[26-31] Patients were followed up across different time frames, ranging from 3.5-15.1 years. Seropositivity tests ranged from 67.4%-100%, while geometric mean concentrations ranged from 21 to 712.5mIU/ml.

In a systematic review by Ott et al. in 2019, five observational studies assessed the long-term protective effects of live attenuated hepatitis A vaccines.[32] Follow up was done across different time frames as well, with a range of 7 to 15 years. Seropositivity tests ranged from 71%-100%, and geometric mean concentrations ranged from 80-145 mIU/ml.[33-37]

Vaccine Safety

The systematic review done by Bravo[38] also looked at adverse events. There were no reported immediate reactions related to the vaccination across the studies. There was also noted decreased reactogenicity post-dose 2 compared with post-dose 1. [38]

Local Adverse Events

Pooled data from 19 studies[39-50] (12 published, 7 unpublished) showed that 29% (1551/5353) of participants experienced a local reaction post-dose 1, compared to 17% (822/4762) of participants post-dose 2. The most common complaint was injection site tenderness or pain at 18.1%. Other reported local reactions include injection site redness, swelling, or hematoma.[38]

Systemic Adverse Events

Pooled data from 19 studies[39-50] (12 published, 7 unpublished) showed that post-dose 1, 22% (993/4598) of participants experienced a systemic reaction versus 11% (447/4002) of participants post-dose 2. The most common complaint was gastrointestinal disturbance at 16.9%. Other frequently reported systemic reactions included malaise, abnormal crying, headache, loss of appetite and fever.[38]

3.8.4 Cost Implication

There were no Philippine cost-effectiveness studies, cost-utility studies or cost-benefit studies found during this review.

Search yielded two studies that assessed the cost-effectiveness of hepatitis A vaccination in children.[51,52] The study by Jacobs et al looked at regional variation in the cost effectiveness of childhood hepatitis A immunization. He concluded that childhood hepatitis A vaccination is most cost-effective in areas with the highest incidence rates.[51] A 2014 study by Suwantika et al assessed the cost-effectiveness of Hepatitis A immunization in Indonesia. From a societal perspective, hepatitis A vaccination would save the country US$ 3,795,148 and US$ 2,892,920 in healthcare costs (i.e. hepatitis A treatment) for the two-dose and one-dose vaccine schedules, respectively; also saving 8917 and 6614 discounted quality-adjusted-life-years (QALYs), respectively. At a price of US$ 3.21 per dose, a single-dose regimen would yield an incremental cost-effectiveness ratio (ICER) of US$4933/QALY gained versus no vaccination, whereas the two-dose versus one-dose schedule would cost US$14,568/QALY gained. Their study concluded that the implementation of hepatitis A vaccination in Indonesia would be a cost-effective health intervention.[52]

3.8.5 Equity, Acceptability, and Feasibility

Hepatitis A vaccination is included in the recommended vaccines in the Philippine Childhood Immunization Calendar but is not included in the National Immunization Program of the Philippines.[53] Hence, those who would want to avail of it will have to shoulder the cost for the vaccine. Presently, vaccine prices range from P1500-P3000 per unit in the private market.

There were two studies found on acceptance and willingness for Hepatitis A vaccination.[54,55] In 2003, Bardenheier et. al looked at the parental knowledge, attitudes, and practices associated with not receiving Hepatitis A vaccine in Butte County, California. Their survey results showed that the factor most strongly associated with not receiving the vaccine was not having received a healthcare provider's recommendation for it. Other factors that were associated with not receiving at least one dose of the Hepatitis A vaccine also included mother's education, family income, not having heard of the vaccine and the perception that the child is not likely to get hepatitis A disease.[54]

Another study on the public acceptance and willingness to hepatitis A vaccination reported that the mothers' willingness to vaccinate their children was associated with the family's income, family member's travel overseas and plan to send the child overseas.[55]

3.8.6 Recommendations from Other Groups

In 2007, the American Academy of Pediatrics issued a Policy Statement regarding their recommendations on the use of Hepatitis A Vaccines.[56] In the statement, they recommended that all children who live in the United States should receive the hepatitis A vaccine at 12-23 months of age as a 2-dose regimen, with preference for the use of the same brand of hepatitis A vaccine for both doses. States, counties and communities with existing Hepatitis A immunization programs for children 2-18 years of age are encouraged to maintain such programs and to expand coverage to include children aged 12-23 months. In areas where there are no immunization programs in place, catch-up immunization of children 2-18 years old may be considered. [56]

The Advisory Committee on Immunization Practices recommends vaccination of all children aged 2-18 years who have not previously received Hepatitis A vaccine. [57] They also recommended vaccination of all persons aged ≥1 year infected with Human Immunodeficiency virus (HIV). Likewise, vaccination with Hepatitis A vaccine is recommended for persons with chronic liver diseases.[57]

The Philippine Pediatric Society (PPS), in collaboration with the Pediatric Infectious Disease Society of the Philippines (PIDSP) and the Philippine Foundation for Vaccination (PFV) recommend Hepatitis A vaccine to be given at a minimum age of 12months as a 2-dose series with a minimum interval of 6 months if using inactivated vaccine. For live attenuated vaccine, the recommendation is to give it at a minimum age of 18 months and as a single dose.[53]

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RESEARCH IMPLICATIONS

Many research questions from the identified clinical questions in this CPG were unanswered due to lack of evidence. Research gaps in terms of benefits and harms of vaccination in the pediatric population, cost-effectiveness, equity, applicability, or feasibility were observed for majority of the vaccines under review.

Formulating definite recommendations was made challenging by the lack of well-designed vaccine trials in the pediatric population (eg. influenza and meningococcal vaccines). Meta-analysis of RCTs indicated a tendency for risk of bias, heterogeneity and inconsistency in the assessment and reporting of harms data.

Determining the true burden of certain diseases like influenza, typhoid fever, Japanese encephalitis and hepatitis A was difficult due to outdated or nonexistent local epidemiologic data in the pediatric population. Surveillance information, when available, is limited to adults or to certain regions or sentinel sites only. Diagnostic confirmation is infrequently done, with diagnostic laboratories being concentrated in a few institutions.

There is a lack of direct evidence on vaccine efficacy or effectiveness such as reduction in cervical cancer incidence for HPV vaccine and poliomyelitis incidence for IPV and OPV. Studies relied on indirect or surrogate outcomes (pre-cancerous lesions for HPV or immunogenicity for IPV/OPV) which were considered to be of less clinical importance than direct outcomes.

Excluding HPV and Japanese encephalitis, there was a lack of local studies assessing the cost-effectiveness of these vaccines, a requisite for any successful immunization program. Cost analyses for decision-making were extrapolated from data on Western countries or LMICs. Even with the latter, conclusions are not always generalizable to the Philippine setting.

Social science research also plays a vital role in examining the potential impact of immunization but there were hardly any studies that investigated psychosocial and cultural determinants of vaccine acceptability and uptake or patient values and preferences regarding immunization. Perspectives and experiences of clinical practitioners and other stakeholders directly involved in immunization programs are rarely reported in studies.

Further research to generate real-world evidence from local studies is recommended to address these research gaps. Implementation of mechanisms for active and passive surveillance and establishment of both national and regional reference laboratories are two strategies to address weak surveillance systems should be investigated. To ensure high-quality and robust data, regulatory agencies should provide specific guidance on the conduct of pediatric vaccine trials while vaccine developers need to conduct more pharmacovigilance studies in the pediatric population. Local economic evaluation studies need to determine not just cost-effectiveness of an immunization program but also overall costs (i.e. supply, logistics, human healthcare resources) in order to facilitate any decision-making. More qualitative studies should investigate relevant topics such as disease awareness and health literacy as they pertain to patients and immunization.

For now, only 7 vaccines indicated for use in healthy children are discussed in this CPG.

Other pediatric vaccines as well as other aspects of pediatric immunization including vaccination of children with comorbidities, booster doses and catch-up immunization, would need to undergo similar rigorous appraisal in future editions of this CPG. For now, the Central Panel voted by consensus that users of this guideline may refer to the PIDSP/PPS/PFV Annual Childhood Immunization Schedule for guidance on topics outside the scope of the CPG until the publication of succeeding guidelines.

Many research questions emerged from collating the evidence for this CPG and can be explored further. Filling in these gaps can provide a clearer picture of the impact of immunization of Filipino children and may influence the recommendations for updating this guideline.

DISSEMINATION AND IMPLEMENTATION

A full copy of this document will be sent to the Department of Health for transmittal and publication. The Disease Prevention and Control Bureau will transmit copies of this CPG to the Philippine Health Insurance Corporation (PHIC) and health maintenance organizations (HMOs) and NGOs involved in a periodic health examination. The recommendations and the evidence summaries will be posted in the PHEX web based application.

The DOH planned to develop a simplified version of this CPG and made it available in the format that will be ready for reproduction and dissemination to the patients in different health care settings. It will also be available for interested parties who might visit the DOH website.

The Taskforce proposes to submit the CPG for presentation in professional society conventions such as the annual symposia of the Philippine Pediatric Society and the Pediatric Infectious Disease Society of the Philippines as well as submit abridged and full-text copies to relevant journals under the auspices of PPS and PIDSP for possible publication.

APPLICABILITY ISSUES

The PHEX Task Force accentuates some caveats of this CPG using equity and applicability lenses. Comprehensive history taking, physical examination, and regular follow-up are essential parts of evaluating risk factors and the probability of developing vaccine-preventable diseases in children. This CPG does not necessarily supersede the consumers' (i.e., health professionals, hospital administrators, employers, payors, patients) values, settings, and circumstances.

Although this CPG intends to influence the direction of health policies for the general population, it should not be the sole basis for recreating or abolishing practices that aim to improve the health conditions of all Filipino children.

UPDATING OF THE GUIDELINES

The recommendations herein shall hold until such time that new evidence on screening, diagnosing or managing various risk factors and diseases emerges and contingencies dictate updating this Philippine Guidelines on Periodic Health Examination. This guideline will be updated after 3 years.