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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.

[1] Schunemann H, Wiercioch W, Brozek J, Etxeandia-Ikobaltzeta I, Mustafa R, Manja V. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. J Clin Epidemiol. 2017;81:101-10.

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This project would not have been possible without the initiative and financial support from the DOH. The DOH neither imposed any condition nor exerted any influence on the operations and the final output formulation.

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

**Consensus Panel**
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Rosemarie T. Santana-Arciaga, MD, FPPS, FPIDSP, MSc
Cerelyn E. Dacula, MD, DPPS, MSc
Teri-Marie Laude, MD, MsCM-FM
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Marysia Stella P. Tiongco-Recto, MD, FPPS, FPSAAI
Philline Aurea Grace S. Salvador, MD
Kim Patrick S. Tejano, MD
Expedito T. Yala, MD, FPPS, FPIDSP

**Consensus Panel Meeting Facilitator**
Mayan Uy-Lumandas, MD, FPPS, FPIDSP

**Administrative Officers**
Cynthia C. Lati
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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
- **Teri-Marie Laude, MD, MsCM-FM** – Assistant Professor, UP Los Baños; Advocacy, Madre de Dios - NGO for hospice care; stocks in Healthserve Los Baños and Global Care Medical Center
- **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
- **Philline Aura Grace S. Salvador, MD** – Consultant, KMI & Innovations for Community Health Inc.
- **Kim Patrick S. Tejano, MD** - Medical Officer IV, Department of Health-Disease Prevention and Control Bureau; Program Manager on National Immunization
- **Expedito T. Yala, MD** – Chair, Antimicrobial Committee – Tarlac Provincial Hospital

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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?**<br><br>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?**<br><br>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?**<br><br>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?**<br><br>***Recommendation 1***: Among at-risk children and adolescents, we suggest immunization with meningococcal vaccine.<br><br>***Recommendation 2:*** Among healthy children and adolescents, we suggest immunization with meningococcal vaccine during outbreak situations. | Very Low<br><br>Very Low | Weak<br><br>Weak |
| 5 | **Should Japanese encephalitis vaccine be given to apparently healthy children aged 18 years and below?**<br><br>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?**<br><br>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?**<br><br>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?**<br><br>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:**<br>Risk of bias<br>Important inconsistency of results<br>Some uncertainty about directness<br>High probability of reporting bias<br>Sparse data/Imprecision<br>Publication bias<br><br>**Additional factors that may increase quality are:**<br>All plausible residual confounding, if present, would reduce the observed effect<br>Evidence of a dose-response gradient<br>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).

Pediatric Infectious Disease Society of the Philippines Journal
Vol 24 No 1, pp. 176-244 January-June 2023
*Reyes-Pagcatipunan, MG, Madrid, MAC, Borja-Tabora, CFCC, Tan-Lim, CSC, Cabaluna, IATG, Balmeo, RB, et al.* Philippine Guidelines on Periodic Health Examination: Pediatric Immunization.
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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.

Pediatric Infectious Disease Society of the Philippines Journal
Vol 24 No 1, pp. 176-244 January-June 2023
*Reyes-Pagcatipunan, MG, Madrid, MAC, Borja-Tabora, CFCC, Tan-Lim, CSC, Cabaluna, IATG, Balmeo, RB, et al.* Philippine Guidelines on Periodic Health Examination: Pediatric Immunization.
https://doi.org/10.56964/pidspj20232401005

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 |

Pediatric Infectious Disease Society of the Philippines Journal
Vol 24 No 1, pp. 176-244 January-June 2023
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https://doi.org/10.56964/pidspj20232401005

### 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<br>(Php 315-1,935)<br>(Up to Php2,000+ in private market) | Php 730<br>(562.50-843.50)<br>(Up to Php 4,800+ in private market) | Php 8,437.50<br>(Php 6,750-10,125) |

Pediatric Infectious Disease Society of the Philippines Journal
Vol 24 No 1, pp. 176-244 January-June 2023
*Reyes-Pagcatipunan, MG, Madrid, MAC, Borja-Tabora, CFCC, Tan-Lim, CSC, Cabaluna, IATG, Balmeo, RB, et al.* Philippine Guidelines on Periodic Health Examination: Pediatric Immunization.
https://doi.org/10.56964/pidspj20232401005

### 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.<br><br>First dose: Age 9 and 10 years old<br>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<br><br>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.<br><br>If the interval between the first and second dose is less than 6 months, a third dose is needed.<br><br>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<br><br>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.<br><br>The bivalent and quadrivalent HPV vaccines are not interchangeable to complete the three doses. | Strong recommendation; high quality of evidence |

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Pediatric Infectious Disease Society of the Philippines Journal
Vol 24 No 1, pp. 176-244 January-June 2023
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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]<br>**Private:** Php 700.00 per dose[38]<br>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.<br>▪ Any licensed influenza vaccine appropriate for age and health status (IIV and LAIV) can be used.<br>▪ 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]**<br><br>(Updated: October 2020) | appropriate for age and health status is available.<br>▪ Children 6-35 months of age may receive any licensed, age-appropriate inactivated vaccine, at the dose indicated for the vaccine.<br>▪ Children ≥36 months (≥3 years) should receive a 0.5-mL dose of any available, licensed, age-appropriate inactivated vaccine.<br>▪ 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.<br>▪ 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]**<br><br>(Updated: October 2020) | ▪ Children 6 months to <2 years NOT IN clinical risk groups - vaccination is not recommended.<br>▪ Children 6 months to <2 years and IN clinical risk groups<br>- Children should be offered the recommended inactivated quadrivalent influenza vaccine.<br>- Those who have not received influenza vaccine previously should be offered a second dose at least four weeks later.<br>▪ Children aged 2 to <17 years old and NOT IN clinical risk groups<br>- A single dose of LAIV should be offered per season, unless contraindicated, irrespective of whether influenza vaccine has been received previously.<br>▪ Children aged two to <18 years of age and IN clinical risk groups<br>- These children should be offered LAIV unless it is medically contraindicated or otherwise unsuitable.<br>- 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]**<br><br>(Updated: 2021) | ▪ TIV (IM or SC) or QIV (IM) given at a minimum age of 6 months<br>▪ For pediatric dose, follow the manufacturer's recommendations<br>▪ Children 6 months to 8 years receiving flu vaccine for the 1st time should receive 2 doses separated by at least 4 weeks<br>▪ If only one dose was given during the previous season, give 2 doses of the vaccine then one dose yearly thereafter<br>▪ Children aged 9 to 18 years should receive one dose of the vaccine yearly<br>▪ 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.<br><br>**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<br><br>**Live attenuated vaccine**: Single dose administered at ≥8 months of age<br><br>**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:<br><br>For 2 months-2 years old, 0.25m<br>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.<br><br>Booster dose for 9 months to 18 years old, should be given 12-24months after the primary dose.<br><br>Individuals 18 years and older should receive a single dose only.<br><br>(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.<br><br>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*<br>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)<br><br>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.<br><br>The primary series consists of 3 doses.<br><br>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.