Philippine Guidelines for Periodic Health Examination: Pediatric Immunization

Marimel R. Pagcatipunan, MD,[1] Natasha Ann R. Esteban-Ipac, MD[2] and Korina Ada D. Tanyu, MD[3]
for the Philippine Periodic Health Examination Task Force on Pediatric Immunization 2023

[1]*Division of Infectious and Tropical Diseases, Department of Pediatrics, College of Medicine and Philippine General Hospital, University of the Philippines, Manila, Manila, Philippines*
[2]*St. Luke's Medical Center-Global City, Taguig, Philippines*
[3]*Chinese General Hospital and Medical Center, Manila, Philippines*

ABSTRACT

Background. Immunization is one of the most important public health achievements of the 20th century, second only to clean water. Increased life expectancy from past decades, largely attributed to improved child survival rates and reduced child mortality from vaccine-preventable diseases, has shown that vaccines underpin disease prevention and control programs and are essential for global health security.

Objective. This clinical practice guideline (CPG) provides evidence-based recommendations and best practices on immunization for the prevention of vaccine-preventable diseases, including those outside and within the scope of routine infant immunization provided by the National Immunization Program (NIP).

Methods. We followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to CPG development recommended by the Department of Health Manual, including GRADE Adolopment and the GRADE Evidence to Decision or EtD framework. This CPG contains the systematic synthesis of scientific evidence on immunization for the pre-exposure prophylaxis of rabies infection, *Haemophilus influenzae* B booster, rotavirus, measles, mumps, varicella, BCG, tetanus booster, hepatitis B booster, pneumococcal conjugate vaccine (PCV), and pertussis booster in the pediatric population.

Results. The CPG provides twelve (12) recommendations on prioritized questions regarding the relevant vaccines for preventing these eleven (11) disease conditions. Recommendations for rabies pre-exposure prophylaxis, *Haemophilus influenzae* B booster, rotavirus, measles, mumps, varicella, BCG, tetanus booster, Hepatitis B booster, pneumococcal conjugate vaccine, and pertussis booster vaccination were made.

Conclusion. This CPG can be used to assess each vaccine's eligibility for inclusion in the NIP (rotavirus and varicella), support their continued use in existing immunization programs (*Haemophilus influenzae* B booster, measles, mumps, tetanus booster, PCV, and pertussis booster), and/or address controversy surrounding their use (pre-exposure prophylaxis for rabies and hepatitis B booster).

Poster presented during DOH Evidence Summit, 24th October 2023 Eastwood Richmonde Hotel, Metro Manila, Philippines

Paper presentation – DOH Disease Prevention and Control Bureau - Evidence Generation and Management Division (DPCB-EGMD) Awarding and Presentation of CPGs 2023, October 24, 2023, Richmonde Hotel Eastwood, Quezon City, Philippines.

Full copy of the Philippine Clinical Practice Guidelines for Periodic Health Examination: Pediatric Immunization can be found at this link – https://drive.google.com/file/d/1Uo243yuMiGsj4KmEGocUID2_kAiqz-Lg/view

eISSN 2094-9278 (Online)
Published: May 30, 2026
https://doi.org/10.47895/amp.v60i10.11356

Corresponding author: Marimel R. Pagcatipunan, MD
Division of Infectious and Tropical Diseases
Department of Pediatrics
Philippine General Hospital
University of the Philippines Manila
Taft Avenue, Ermita, Manila 1000, Philippines
Email: mrpagcatipunan@yahoo.com
ORCiD: https://orcid.org/0009-0007-0985-0721

Relevant stakeholders can use these recommendations to continuously improve the performance, reach, and efficacy of the National Immunization Program. 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.

Keywords: vaccines, pediatric, PHEX, immunization, CPG

INTRODUCTION

Immunization is one of the most important public health achievements of the 20th century, second only to clean water.[1] Increased life expectancy from past decades, largely attributed to improved child survival rates and reduced child mortality from vaccine-preventable diseases, has shown that vaccines underpin disease prevention and control programs and are essential for global health security.[1,2] Furthermore, the current COVID-19 pandemic has demonstrated that vaccines are vital for controlling emerging infectious diseases, and that without them, the threat of future pandemics can and will continue to strain even the most resilient health systems.[2]

Immunization is an essential component of primary health care as it has been shown to benefit the individual, the community, and the world.[3] Vaccines protect vulnerable populations from disability and death, prevent the spread of disease, promote socio-economic growth and development, and help ensure a healthier, safer world.[3,4]

This is the first clinical practice guideline (CPG) in pediatric immunization since the establishment of the Expanded Program on Immunization in 1976.[1] The main objective of this CPG is to provide evidence-based recommendations and best practices on immunization for the prevention of vaccine-preventable diseases, including those outside and within the scope of routine infant immunization provided by the National Immunization Program (NIP).[1]

Eleven (11) vaccines indicated for the pediatric population were prioritized for review, namely, vaccines for pre-exposure prophylaxis of rabies infection, *Haemophilus influenzae* B booster, rotavirus, measles, mumps, varicella, BCG, tetanus booster, hepatitis B booster, pneumococcal conjugate vaccine (PCV), and pertussis booster.

METHODS

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to CPG development recommended in the Department of Health (DOH) Manual on Practice Guideline Development was followed.[5-7] The GRADE Adolopment and Evidence-to-Decision (EtD) framework was utilized in finalizing the recommendations.[8,9]

Table 1. Clinical Questions

1.	Should rabies pre-exposure prophylaxis (PrEP) be given as routine vaccination for prevention of rabies infection in children and adolescents?
2.	Among healthy children who completed the primary series of *Haemophilus influenzae* B (Hib) vaccination, is a booster dose of Hib vaccine needed?
3.	Should the Rotavirus vaccine be routinely given to infants for the prevention of Rotavirus gastroenteritis and its complications?
4.	Should measles-containing vaccines be given to apparently healthy children?
5.	Should mumps-containing vaccines be given to apparently healthy children?
6.	Should the varicella vaccine be recommended to apparently healthy children and adolescents?
7.	Should the BCG vaccine be routinely given at birth to healthy infants for the prevention of tuberculosis?
8.	Among children and adolescents who received complete Diphtheria, Pertussis, and Tetanus (DPT) primary immunizations, should tetanus toxoid-containing vaccines be given as a booster?
9.	Should a Hepatitis B vaccine booster dose be given among children and adolescents who completed a 3-dose primary vaccination series during infancy?
10.	Can Pneumococcal Conjugate Vaccine brands be interchanged to complete the primary series? Can Pneumococcal Conjugate Vaccine brands be interchanged as a booster dose?

Preparation

The Task Force Steering Committee set the CPG objectives, scope, target audience, and clinical questions (Table 1). The Task Force Steering Committee convened the technical working group involved in creating the evidence base, and the consensus panel (CP) involved in formulating the recommendations for each clinical question. Questions were prioritized using the criteria set by DOH.

Management of Conflicts of Interest

All task force members submitted their declaration of conflict of interest (COI) and curriculum vitae. A COI committee reviewed and evaluated the potential conflicts of interest and gave its recommendation on how to manage them. In general, those with financial COI were not allowed to vote on questions related to the COI**.** Those with non-financial COIs (such as authorship related to the CPG topic) were allowed to participate, but COIs were declared during the panel meeting and the final manuscript.

Evidence Synthesis

The evidence review questions were developed using the PICO (population, intervention, comparator, and outcome) format. The evidence review experts (ERE) searched and appraised international practice guidelines related to periodic health screening, including but not limited to those of the Canadian Task Force on Preventive Health Care, U.S. Preventive Services Task Force, and National Institute for Health and Care Excellence. If the CPG were of good

Table 2. GRADE Table of Strength of Recommendation and Certainty of Evidence

Certainty of Evidence	Description
High	We are very confident that the true effect lies close to that of the estimated 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 maybe 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
Strength of Recommendation	**Description**
Strong	Advantages of the intervention significantly outweigh disadvantages or disadvantage of the intervention significantly outweigh advantages
Weak	Advantages of the intervention may outweigh disadvantages, disadvantages of the intervention may outweigh advantages, or the relationship between advantages and disadvantages is not clear

quality and done within 5 years, the evidence summaries of the CPG were adopted.

If no updated, relevant, and trustworthy CPG was found, we performed a systematic medical literature search of MEDLINE (via PubMed), The Cochrane Library, and other databases such as Google Scholar. Systematic reviews that met our inclusion criteria to answer the evidence review questions were used directly to identify relevant articles and a summary of findings. If no related systematic reviews were found, we conducted *de novo* systematic reviews. We critically appraised the methodological quality of the included studies using the standard tools, such as the Cochrane Risk of Bias tool (ROB 1.0) for randomized controlled trials (RCTs), Painless EBM appraisal criteria, the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) for diagnostic accuracy studies, and the Newcastle–Ottawa Scale (NOS) for observational studies. We used the GRADE approach to rate the certainty of evidence and the strength of recommendations (Table 2).

Evidence to Decision Consensus Approach

The multisectoral CP was tasked to review the evidence summaries and develop recommendations during the *en banc* meeting. Prior to the meeting, the CP prioritized critical and important outcomes (Appendix).

The CP was provided with the evidence base for all guideline questions, a draft recommendation solely based on the trade-offs between benefit and harm, and the certainty of evidence. Each CP member was then asked to complete an EtD questionnaire. The purpose of this questionnaire survey is for each CP member to explicitly incorporate other important factors, such as cost-effectiveness, patient values and preferences, applicability, feasibility, appropriateness, equity, and resources in their decision-making.

The direction and strength of each recommendation were determined by a formal consensus method. Recommendations were adopted when 75% or more of the voters agreed on the proposed recommendation. If a consensus was not reached initially, two further rounds of voting were allowed. A modified Delphi methodology was planned in case no consensus was reached during the *en banc* meetings. On the rare occasion that no consensus is reached, no recommendation would be indicated in the final CPG manuscript.

In general, a strong recommendation means that the panel is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, while a weak recommendation means that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but the panel is not confident. Include all the steps (preparation, evidence synthesis, EtD), including the COI management.

Planning for Dissemination, Implementation, and Update

The CPG was sent to the DOH for transmittal and publication. The Disease Prevention and Control Bureau will transmit copies of this CPG to the Philippine Health Insurance Corporation (PHIC), health maintenance organizations (HMOs), and NGOs involved in periodic health examination. The recommendations and the evidence summaries were posted in a web-based application (https://phex.ph). These recommendations and evidence summaries were also disseminated by the Task Force to their specific organizations.

The DOH planned to develop a simplified version of this CPG and to make this available in a format that will be ready for reproduction and dissemination to patients in different healthcare settings. It will also be available at the DOH website. The recommendations herein shall hold until new evidence on vaccination emerges, and contingencies dictate updating this Philippine Guidelines on Periodic Health Examination. This guideline will be updated after 3 years.

External Review

Three (3) independent stakeholders, who are all distinguished pediatricians, reviewed the manuscript for completeness and relevance of the evidence, the processes, clarity of the output (the recommendations and the

Table 3. Summary of Recommendations

No.	Recommendations	Certainty of Evidence	Strength of Recommendation
1	Among apparently healthy children and adolescents 5-18 years old with high risk of rabies*, we suggest routine rabies pre-exposure prophylaxis for prevention of rabies infection. * *High risk of rabies includes those: (1) living in areas with high incidence of rabies, (2) with increased exposure to rabies due to their jobs, activities, and travel, and (3) with no or limited access to post-exposure prophylaxis and animal bite centers.*	Very low	Weak
2	Among healthy children who completed the primary series of *Haemophilus influenzae* B (Hib) vaccine, we suggest giving a booster dose of any Hib-containing vaccine starting at 12 months of age, with an interval of at least 6 months from the 3rd dose.	Very low	Weak
3	We recommend rotavirus vaccination among apparently healthy infants starting at 6 weeks old.	Moderate	Strong
4	We recommend giving measles-containing vaccines to apparently healthy children starting at 9 months of age.	Low	Strong
5	We suggest giving mumps-containing vaccines to apparently healthy children starting at 12 months of age.	Low	Weak
6.1	We recommend giving the varicella vaccine to healthy children and adolescents 12 months to 18 years old.	Moderate	Strong
6.2	We suggest giving 2 doses of the varicella vaccine to healthy children and adolescents 12 months to 18 years old.	Low	Weak
7	Among healthy infants, we suggest routine BCG vaccination at birth for the prevention of tuberculosis.	Very Low	Weak
8	We suggest giving a tetanus toxoid-containing vaccine booster dose among healthy infants and children who completed a 3-dose primary series of tetanus toxoid-containing vaccines starting at 12 months of age and following a minimum interval of 6 months after the third dose.	Low	Weak
9	We suggest giving the Hepatitis B vaccine booster to healthy children and adolescents who completed at least a 3-dose primary vaccination series but did not seroconvert.	Very Low	Weak
10	Among apparently healthy children, we suggest that pneumococcal conjugate vaccine brands may be interchanged for the primary series or booster dose if continuing with the same brand is not feasible, specifically: • PHiD-CV and PCV13 may be interchanged for the primary and booster doses; • PCV13 and PCV15 may be interchanged for the primary and booster doses; • PCV10-SII may be used as a booster dose in PCV13-primed children	Very Low	Weak
11	We suggest giving a pertussis-containing vaccine booster dose among children and adolescents who completed the 3-dose primary DPT series starting at 12 months of age and following a minimum interval of 6 months after the 3rd dose.	Very Low	Weak

manuscript), and the planned methods of dissemination of the CPG. Their feedback was considered by the Task Force Steering Committee in finalizing the CPG manuscript.

RESULTS

A total of twelve (12) recommendations were made. The summary of recommendations with certainty of evidence and strength of recommendations is shown below in Table 3.

Recommendation 1. Among apparently healthy children and adolescents 5-18 years old with high risk of rabies*, we suggest routine rabies pre-exposure prophylaxis for prevention of rabies infection. *(Very low certainty of evidence, weak recommendation)*

* *High risk of rabies includes those: (1) living in areas with high incidence of rabies, (2) with increased exposure to rabies due to their jobs, activities, and travel, and (3) with no or limited access to post-exposure prophylaxis and animal bite centers.*

Key findings: Two (2) randomized controlled trials (RCTs) evaluated immunogenicity, and one RCT evaluated geometric mean titer (GMT) and safety. Rabies PrEP significantly induced immunogenic responses in children compared to the placebo, with significantly lower failure of seroconversion in the rabies PrEP compared to placebo (RR 0.13, 95% CI 0.07 to 0.23). Subgroup analysis by time period showed that protective titers wane over time (RR 0.01, 95% CI 0.00 to 0.19 at one month post vaccination; RR 0.26, 95% CI 0.15 to 0.45 at 17 months post vaccination). Participants who received rabies PrEP had significantly higher GMT post-vaccination compared to those who received placebo (MD 20.07 U/L, 95% CI 12.01 to 28.12). Results were inconclusive for the risk of developing local and systemic adverse events between those who received the rabies PrEP and placebo (RR 0.29, 95% CI 0.02, 5.47 for local adverse events; RR 0.52, 95% CI 0.14, 1.96 for systemic events). No serious adverse effects were reported.

Two cost-effectiveness analyses showed contrasting results. An earlier CEA done in 2006 in Thailand concluded

that large-scale rabies PrEP of children is not cost-effective with current vaccination schedules and the cost of quality vaccines; however, the more recent 2020 CEA done in the Philippines showed that a universal school-based PrEP program would be cost-effective in the Philippines when compared with the current recommended PEP-only regimen.

Justification: The panel considered rabies as a highly preventable disease with 100% case fatality rate; hence, the burden of rabies infection is significant. Despite the very low certainty of evidence, the benefits of pre-exposure rabies vaccination were deemed to outweigh the possible harm. However, the panel recognizes that rabies pre-exposure prophylaxis is not cost-effective for low-risk groups, and that there are other, more cost-effective ways to curb rabies incidence, such as animal vaccination. Thus, the CP specified that the recommendation applies only to high-risk populations.

Recommendation 2. Among healthy children who completed the primary series of *Haemophilus influenzae* B (Hib) vaccine, we suggest giving a booster dose of any Hib-containing vaccine starting at 12 months of age, with an interval of at least 6 months from the 3rd dose. *(Very low certainty of evidence, weak recommendation)*

Key findings: There are no direct clinical studies that demonstrate the effect of a Hib booster dose compared to no booster dose on clinical outcomes. Narrative reports, however, describe the decrease in Hib-related infection and mortality after booster campaigns in some countries. One study reported a higher geometric mean concentration (GMC) of anti-polyribosylribitol phosphate (PRP) one month after a Hib booster dose compared to no booster (29.92 ug/mL vs 0.32ug/mL). Another study showed that compared to no booster, those who received a Hib booster dose had a higher percentage of people reaching the 1.0ug/mL (RD 0.59, 95% CI 0.52, 0.67) and 0.15ug/mL (RD 0.16, 95% CI 0.11, 0.22) thresholds, which represent long-term and short-term protection, respectively. The occurrence of adverse events was identical across different preparations of Hib vaccines, with common adverse events cited as fever, pain, and irritability.

Justification: The CP considered *Hemophilus influenzae* B infection to be a burden, causing life-threatening diseases. Due to the lack of or limited testing capacity, there is inadequate data on bacteriologically-confirmed cases in the Philippines. However, the benefits of a Hib booster were deemed to outweigh the possible harm based on clinical experience, but the panelists believe that there is a need for high-quality evidence on disease burden, cost-effectiveness, and prevention to make a strong recommendation.

Recommendation 3. We recommend rotavirus vaccination among apparently healthy infants starting at 6 weeks old. *(Moderate certainty of evidence, strong recommendation)*

Key findings: Sixty randomized trials (RCTs) investigated the efficacy and safety of the rotavirus vaccine compared with placebo. The rotavirus vaccine did not reduce all-cause mortality compared to placebo (RR 1.02, 95% CI 0.88, 1.18). Regardless of brand, the rotavirus vaccine significantly reduced the risk of severe rotavirus gastroenteritis (RVGE) (RR 0.30, 95% CI 0.22, 0.40), hospitalizations from RVGE (RR 0.20, 95% CI 0.08, 0.48), and severe all-cause acute gastro-enteritis (RR 0.78, 95% CI 0.68 to 0.90) among apparently healthy infants and children up to 2 years compared to no rotavirus vaccine. There was no significant difference in the risk of serious adverse events (RR 0.92, 95% CI 0.88, 0.96), including intussusception and reactogenicity manifesting as fever, diarrhea, or vomiting.

Justification: The CP unanimously recommended giving the rotavirus vaccine, taking into consideration its effectiveness in preventing RVGE, hospitalization from RVGE, and severe all-cause acute gastroenteritis among apparently healthy infants. Despite the absence of local studies on the adverse effects of the rotavirus vaccine, the evidence showed that the benefit of giving the vaccine far outweighs the risk of serious adverse effects, such as intussusception

Recommendation 4. We recommend giving measles-containing vaccines to apparently healthy children starting at 9 months of age. *(Low certainty of evidence, strong recommendation)*

Key findings: A total of 8 cohort studies evaluated the effectiveness of measles-containing vaccines. Compared to no measles vaccine, administration of a single dose of measles-containing vaccine resulted in significant benefit in preventing measles infection (RR 0.05, 95% CI 0.02, 0.13). Similarly, administration of 2 doses of measles-containing vaccine resulted in significant benefit in preventing measles infection compared to placebo (RR 0.04, 95% CI 0.01, 0.28).

For adverse events, patients given the measles vaccine had a significantly higher incidence of rash (RR 2.05, 95% CI 1.21 to 3.48) and elevated temperature taken either via axillary site (RR 2.04, 95% CI 1.09 to 3.83) or via unspecified site of measurement (RR 1.36, 95% CI 1.04 to 1.81) compared to those not given the vaccine. The results for the risk of other adverse events, such as lymphadenopathy, coryza, URTI, and cough, were inconclusive.

Justification: The panel considered the effect of the measles vaccine in preventing the incidence of measles and its complications. The benefits of the vaccine were deemed to outweigh the possible harm. The CP also considered that measles outbreaks were occurring due to low measles vaccination uptake. With these considerations, the panel was unanimous in strongly recommending the vaccine despite

the low overall certainty of evidence. Although the vaccine is given starting at 9 months of age, the panel also recognizes that the measles vaccine can be given at an earlier age in situations such as outbreaks and for international travel, as necessary.

Recommendation 5. We suggest giving mumps-containing vaccines to apparently healthy children starting at 12 months of age. *(Low certainty of evidence, weak recommendation)*

Key findings: There were 11 cohorts that investigated the efficacy of the mumps vaccine, which included 9 cohorts for the Jeryl Lynn strain (strain available in the Philippines) and 2 for unspecified or mixed mumps strains. Pooled results show that Jeryl Lynn-containing MMR vaccine significantly decreased the incidence of clinical mumps among children and adolescents after 1 dose (RR 0.28, 95% CI 0.13 to 0.62) and after 2 doses (RR 0.14, 95% CI 0.07 to 0.27) compared to no MMR vaccine. MMR vaccines whose strain was not specified or was mixed still significantly reduced mumps compared to no MMR vaccine (RR 0.52, 95% CI 0.29 to 0.94).

For the adverse events, patients given the mumps-containing vaccine had a significantly higher incidence of rash (RR 2.05, 95% CI 1.21 to 3.48) and elevated temperature taken either via axillary site (RR 2.04, 95% CI 1.09 to 3.83) or via unspecified site of measurement (RR 1.36, 95% CI 1.04 to 1.81) compared to those not given the vaccine. The results for the risk of other adverse events, such as lymphadenopathy, coryza, URTI, and cough, were inconclusive.

Justification: The panel used the term 'mumps-containing vaccine' in the recommendation statement since mumps is part of the measles-mumps-rubella (MMR) vaccine. The burden of mumps infection was considered significant, and the benefits of vaccination were deemed to outweigh the possible harm. However, some panelists believed that high-quality studies on safety and cost-effectiveness are needed to make a strong recommendation.

Recommendation 6.1. We recommend giving the varicella vaccine to healthy children and adolescents 12 months to 18 years old. *(Moderate certainty of evidence, strong recommendation)*

Recommendation 6.2. We suggest giving two (2) doses of the varicella vaccine to healthy children and adolescents 12 months to 18 years old. *(Low certainty of evidence, weak recommendation)*

Key findings: There were 7 RCTs that evaluated one dose of the varicella vaccine compared to a placebo or a non-varicella-containing vaccine, while 4 RCTs compared two doses of the varicella vaccine to one dose.

One dose of the varicella vaccine significantly reduced the development of varicella disease compared to placebo or non-varicella-containing vaccine (RR 0.08, 95% CI 0.05 to 0.15). There were also significantly higher antibody titers and seroconversion rates among those given one dose of the varicella vaccine compared to no varicella vaccine (RR 51.68, 95% CI 33.26 to 80.30). Children and adolescents given two doses of the varicella vaccine had a significantly lower risk for development of varicella infection (RR 0.16, 95% CI 0.03, 0.79, I^2 = 78%) and higher antibody titers (SMD 0.83, 95% CI 0.20, 1.47) compared to those given one dose. There was no significant difference in the risk for adverse events between those who were vaccinated and not (RR 1.03, 95% CI 0.93 to 1.13).

Justification: Varicella vaccine is not considered a priority vaccine at present due to its low prevalence in the country, the self-limiting nature of the disease, and lower rates of complications. Current evidence shows that the benefits of vaccination far outweigh the possible harm. The panelists considered the effectiveness of the varicella vaccine in decreasing the incidence of varicella, particularly shown in children who were given one dose of the vaccine. For the recommendation on two doses of the varicella vaccine, the benefits were deemed to outweigh the risks in giving a second dose of the varicella vaccine. However, some panelists believe that more high-quality studies on safety and cost-effectiveness are needed to make a strong recommendation. The panelists only considered the monovalent varicella vaccines in their decision-making.

Recommendation 7. Among healthy infants, we suggest routine BCG vaccination at birth for the prevention of tuberculosis. *(Very low certainty of evidence, weak recommendation)*

Key findings: BCG vaccine was found to be effective in reducing the risk for meningeal and miliary tuberculosis (TB) (RR 0.10, 95% CI 0.01, 0.76), reduction of clinical symptoms of pulmonary TB (OR 0.05, 95% CI 0.01, 0.19), latent TB infection (RR 0.50, 95% CI 0.36, 0.70), TB-related mortality (RR 0.34, 95% CI 0.12, 0.92), and all-cause mortality (RR 0.19, 95% CI 0.11, 0.35). BCG vaccine, however, was not found to be effective against pulmonary TB (although with a trend towards benefit) (RR 0.54, 95% CI 0.29 to 1.00, I^2 = 61%) and extrapulmonary TB (OR 1.10, 95% CI 0.76 to 1.59).

Justification: The CP considered that the BCG vaccine showed benefit in decreasing TB-related mortality and latent TB infections, as well as in improving the clinical symptoms of TB. It is also highly effective against meningeal and miliary TB. Based on the available evidence, the BCG vaccine is not significantly beneficial for pulmonary tuberculosis. However, the panel noted that the pathophysiology of tuberculosis usually starts in the lungs, and extrapulmonary TB (e.g., meningeal and miliary TB) is a complication of pulmonary TB. A universal BCG vaccination program was considered highly cost-effective in high-incidence countries

like the Philippines. The CP deemed that it is beneficial and outweighs the possible harm, but high-quality studies on efficacy, safety, and effectiveness are needed to make a strong recommendation.

Recommendation 8. We suggest giving a tetanus toxoid-containing vaccine booster dose among healthy infants and children who completed a 3-dose primary series of tetanus toxoid-containing vaccines starting at 12 months of age and following a minimum interval of 6 months after the 3rd dose. *(Low certainty of evidence, weak recommendation)*

Key findings: There was only one RCT that investigated the effect of a tetanus toxoid-containing vaccine (TTCV) booster dose compared to placebo for children who had already completed the primary immunization series for tetanus. TTCV booster doses showed benefit in terms of increasing seroprotection (RR 1.46, 95% CI 1.05, 2.03) and tetanus antibody titers (MD 4.87 U/L, 95% CI 3.77, 5.97) at 1-month post-booster vaccination compared to placebo. There were no serious adverse events that occurred in this study. There were inconclusive results in terms of generalized adverse events (RR 1.75, 95% CI 0.41, 7.48) and local adverse events (RR 3.00, 95% CI 0.39, 22.85) experienced 15 days post-booster by those who received the TTCV booster compared to placebo.

Justification: Tetanus toxoid-containing vaccine booster showed significant benefit in immunogenicity and increased seroprotection. The CP considered that the need to give booster tetanus vaccination is evident, and the benefits outweigh the possible harm. The panelists believed that high-quality evidence on efficacy, cost-effectiveness, equity, feasibility, and acceptability is needed to make a strong recommendation.

Recommendation 9. We suggest giving the Hepatitis B vaccine booster to healthy children and adolescents who completed at least a 3-dose primary vaccination series but did not seroconvert. *(Very low certainty of evidence, weak recommendation)*

Key findings: There were 4 RCTs that studied the effect of administering a hepatitis B booster compared to no booster among children and adolescents who completed a 3-dose primary vaccination series during infancy. Based on one large RCT, the hepatitis B booster had a significant benefit in preventing all-cause mortality (RR 0.31, 95% CI 0.12, 0.78) and primary liver cancer (RR 0.19, 95% CI 0.05, 0.65). Hepatitis B booster also resulted in significantly reduced risk of HBsAg seropositivity (RR 0.30, 95% CI 0.15, 0.61). Pooled analysis of 4 RCTs showed that the hepatitis B booster had an inconclusive effect in HBV seroprotection (RR 1.85, 95% CI 0.97, 3.52) and anti-HBc seropositivity (RR 0.49, 95% CI 0.12, 1.98). There were no adverse events reported in the studies.

Justification: Children and adolescents who complete the 3-dose primary vaccination of hepatitis B generally have acceptable immunogenicity and high efficacy against hepatitis B infection. However, there are some who do not seroconvert despite being given a 3-dose primary series. The CP suggests a hepatitis B vaccine booster for the population of healthy children and adolescents who did not seroconvert. The panelists believe that high-quality evidence on cost-effectiveness, equity, acceptability, and feasibility in the context of giving extra doses of the hepatitis B vaccine is needed to make a strong recommendation.

Recommendation 10. Among apparently healthy children, we suggest that pneumococcal conjugate vaccine brands may be interchanged for the primary series or booster dose if continuing with the same brand is not feasible, specifically:

- **PHiD-CV and PCV13 may be interchanged for the primary and booster doses;**
- **PCV13 and PCV15 may be interchanged for the primary and booster doses; and**
- **PCV10-SII may be used as a booster dose in PCV13-primed children**

(Very low certainty of evidence, weak recommendation)

Key findings: Two observational studies evaluated the vaccine effectiveness (VE) of the pneumococcal conjugate vaccine against invasive pneumococcal diseases (IPD). A study from Canada found similar effect in protecting against IPD among those given 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHID-CV)-only schedule (VE 75%, 95% CI 51, 87%), a 13-valent pneumococcal conjugate vaccine (PCV13)-only schedule (VE 65%, 95% CI 29, 83%), or a mixed PHID-CV+PCV13 schedule (VE 66%, 95% CI 23, 85%). A study from Taiwan found similar VE in PCV13-only schedule (VE 80%, 95% CI 65, 89%) and mixed PCV7/PHID-CV+PCV13 schedule (VE 85%, 95% CI 66, 93%), but a lower VE for PHID-CV-only schedule (VE 50%, 95% CI 51, 87%). For PHiD-CV and PCV13 mixed schedules, two studies evaluated immunogenicity after a primary series and three studies evaluated immunogenicity after a booster dose; no significant difference in the IgG response was seen for the 13 pneumococcal serotypes. There was no significant difference in the 10 common serotypes among those given PCV10-SII and PCV13 boosters. There was no significant difference in IgG response for 13 common serotypes among those given PCV13 and PCV15. There was inconclusive effect in the risk of adverse events between mixed and single-brand schedules (RR 0.76, 95% CI 0.48, 1.21).

Justification: The panelists recognized that the immunogenicity and efficacy of pneumococcal conjugate vaccines remained similar despite interchanging vaccines for the primary series and booster dose. The panel suggests considering the cost of the vaccine, as well as the recommendations from the manufacturers regarding interchangeability of vaccine

doses. The benefits of interchanging vaccines were deemed to outweigh the possible harm. Some panelists believe that high-quality evidence on the cost-effectiveness of giving different vaccine brands, equity, acceptability, and feasibility is needed to make a strong recommendation.

Recommendation 11. We suggest giving a pertussis-containing vaccine booster dose among children and adolescents who completed the 3-dose primary DPT series starting at 12 months of age and following a minimum interval of 6 months after the 3rd dose. *(Very low certainty of evidence, weak recommendation)*

Key findings: Pertussis-containing (DTaP) booster vaccinations during childhood compared to no or under vaccination were found to significantly reduce the risk of pertussis infection (RR 0.09, 95% CI 0.07, 0.11), but protection declines over time. There was an inconclusive effect on the risk of pertussis infection among children with a delay in receiving the recommended number of vaccine doses compared to those without delay (RR 0.8, 95% CI: 0.5-1.4). Pertussis-containing (Tdap) booster vaccination among adolescents decreased the odds of developing pertussis disease (OR 0.42, 95% CI 0.35, 0.52); however, its effectiveness wanes over time. There was a significantly lower risk of convulsions (RR 0.47, 95% CI 0.31, 0.73) and hypotonic hyporesponsive episodes (RR 0.26, 95% CI 0.08, 0.81) for acellular pertussis vaccines compared to whole cell vaccines. There was an inconclusive effect on all-cause mortality (RR 1.08, 95% CI 0.26, 4.42) and deaths due to infection (RR 1.21, 95% CI 0.19, 7.80) between acellular vaccines and placebo. Tdap vaccines have a significantly higher incidence of injection-site pain than non-pertussis vaccines (RR 1.20, 95% CI 1.11, 1.30).

Justification: The CP considered pertussis-containing vaccine booster doses as beneficial. Studies show that the acellular pertussis-containing vaccines have a better safety profile compared to the whole-cell pertussis-containing vaccine. The panel recognizes that both types of pertussis vaccines are effective in reducing the incidence of pertussis in the country. The benefits of vaccination were deemed to outweigh the possible harm. Some panelists believe that high-quality evidence on burden, cost-effectiveness of different pertussis-containing vaccine types, equity, acceptability, and feasibility in the context of a school-based or community-based program is needed to make a strong recommendation. Pertussis booster is usually scheduled to be given at 12-23 months, 4-7 years, and 9-15 years.

DISCUSSION

Eleven (11) vaccines indicated for the pediatric population were prioritized for this review, namely, vaccines for pre-exposure prophylaxis of rabies infection, *Haemophilus influenzae* B booster, rotavirus, measles, mumps, varicella, BCG, tetanus booster, hepatitis B booster, pneumococcal conjugate vaccine (PCV), and pertussis booster.

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 to the potential benefit.

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.

Conclusions from the systematic review of evidence can be used to assess each vaccine's eligibility for inclusion in the NIP (rotavirus and varicella), support their continued use in existing immunization programs (*Haemophilus influenzae* B booster, measles, mumps, tetanus booster, PCV, and pertussis booster), and/or address controversy surrounding their use (pre-exposure prophylaxis for rabies and hepatitis B booster). Relevant stakeholders can use these recommendations to continuously improve the performance, reach, and efficacy of the National Immunization Program.

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.

Strengths and Limitations

Formulating definite recommendations was made challenging by the lack of well-designed vaccine trials in the pediatric population. There were also vaccines in which studies were done prior to the development of proper research ethics and guidelines (e.g., BCG). Issues with risk of bias, heterogeneity, and inconsistency were observed in the reporting of harm data.

Determining the true burden of certain diseases like *Haemophilus influenzae*, mumps, and rotavirus gastroenteritis 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 due to diagnostic laboratories being concentrated in a few institutions or the costly pricing of such diagnostics.

Research Gaps

Research gaps in terms of benefits and harms of vaccination in the pediatric population, cost-effectiveness, equity, applicability, or feasibility were observed for the majority of the vaccines under review. In general, 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 from other countries. 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 very limited 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 local studies are 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. 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 the direct costs 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.

CONCLUSION

This CPG can be used to assess each vaccine's eligibility for inclusion in the NIP (rotavirus and varicella), support their continued use in existing immunization programs (*Haemophilus influenzae* B booster, measles, mumps, tetanus booster, PCV, and pertussis booster), and/or address controversy surrounding their use (pre-exposure prophylaxis for rabies and hepatitis B booster). Relevant stakeholders can use these recommendations to continuously improve the performance, reach, and efficacy of the NIP. 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.

Disclaimer

This guideline is intended to be used by general practitioners, specialists, and health professionals who are primary care providers. Although adherence to this guideline is encouraged, it should not restrict the primary care providers from using their sound clinical judgment in handling individual cases. Payers and policymakers, including hospital administrators and employers, can also utilize this CPG, but this document should not be the sole basis for evaluating insurance claims. Recommendations from the PHEX app and the guidelines therein should also not be treated as strict rules on which to base legal action. Professional Medical Societies and their representatives involved in the technical process have given their consent and approved the publication of the CPG.

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Queries, suggestions, and other concerns regarding this CPG may be directed to the DOH office by email.

Acknowledgments

The authors gratefully acknowledge the invaluable contributions of the members of the Task Force Steering Committee (led by Chair Marimel G. Reyes-Pagcatipunan, MD, FPPS, FPIDSP, and Co-Chair Carmina A. Delos Reyes, MD, FPPS, FPIDSP), together with members Mary Antonette C. Madrid, MD, FPPS, FPIDSP; Charissa Fay Corazon C. Borja-Tabora, MD, FPPS, FPIDSP; and Melody Kiat Tolentino, MD, DPPS, DPIDSP, whose leadership and guidance were instrumental in the development of this work.

The authors likewise extend their sincere appreciation to the Technical Working Group (under the coordination of Natasha Ann R. Esteban-Ipac, MD, FPPS, DPSAMS), and to—Evidence Review Experts—Kia S. Anarna, MD; Reginald B. Balmeo, MD; John Andrew T. Camposano, MD; Fides Roxanne M. Castor-Racelis, MD; Patricia Marie D. Isada, MD; Michelle Cristine B. Miranda, MD; April P. Padua-Zamora, MD; Francesca Mae T. Pantig, MD; Frangelo Conrad P. Tampus, MD; and Paul Sherwin O. Tarnate, MD—for their rigorous review and critical appraisal of the evidence.

We are also grateful to Mary Ann Abacan, MD, FPPS, for facilitating the consensus panel meeting, and to Jonalyn N. Nuqui for her dedicated administrative support, which ensured the smooth coordination of all activities related to this project.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

Funding Source

This is a joint undertaking of the Department of Health and the National Institutes of Health - Institute of Clinical Epidemiology.

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TASK FORCE MEMBERS

Task Force Steering Committee

Chair: Marimel G. Reyes-Pagcatipunan, MD, FPPS, FPIDSP
Co-chair: Carmina A. Delos Reyes, MD, FPPS, FPIDSP
Members:
Mary Antonette C. Madrid, MD, FPPS, FPIDSP
Charissa Fay Corazon C. Borja-Tabora, MD, FPPS, FPIDSP
Melody Kiat Tolentino. MD, DPPS, DPIDSP

Technical Working Group

Technical Coordinator:
Natasha Ann R. Esteban-Ipac, MD, FPPS, DPSAMS

Evidence Review Experts:
Kia S. Anarna, MD
Reginald B. Balmeo, MD
John Andrew T. Camposano, MD
Fides Roxanne M. Castor-Racelis, MD
Patricia Marie D. Isada, MD
Michelle Cristine B. Miranda, MD
April P. Padua-Zamora, MD
Francesca Mae T. Pantig, MD
Frangelo Conrad P. Tampus, MD
Paul Sherwin O. Tarnate, MD

Consensus Panel

Cynthia Alcantara-Aguirre, MD, FPPS, FPIDSP, PFV
Rosemarie T. Santana-Arciaga, MD, FPPS, FPIDSP, PIDSP
Mary Ann Bunyi, MD, FPPS, FPIDSP, PIDSP
Teri-Marie Laude, MD, MsCM-FM, PAFP
Melissa Joyce Ramboanga, MD, PAPA
Marysia Stella P. Tiongco-Recto, MD, PSAAI
Maria Teresa D. Villanueva, MD, FPPS, PPS
Maria Lourdes Bernadeth V. Manipon, RN, PHICNA
Bryan S. Posadas, RPh, PPAI

Panel Meeting Facilitator: Mary Ann Abacan, MD, FPPS
Technical Writer: Korina Ada D. Tanyu, MD, FPPS
Administrative Officer: Jonalyn N. Nuqui

APPENDIX

Critical Outcomes

The following table lists the critical and important outcomes that were asked of the consensus panelists. These were asked before the *en banc* meeting:

Vaccine	Critical Outcome	Important Outcome
Pre-exposure Rabies	• Incidence of rabies • Immunogenicity • Serious adverse events	• Adverse events
Hib booster	• Incidence of Hib • Serious adverse events	• Immunogenicity • Adverse events
Rotavirus	• All-cause mortality • Severe RVGE • RVGE of any severity • Severe all-cause AGE • Serious adverse events	• Adverse events
Measles	• Incidence of measles • Adverse events – fever, rash, coryza, URTI • Adverse events – cough, lymphadenopathy	
Mumps	• Incidence of mumps (Philippines) • Adverse events – cough, lymphadenopathy	• Incidence of mumps (strain not specified) • Adverse events – fever, rash, coryza, URTI
Varicella	• Incidence of varicella • Immunogenicity • Adverse events • Serious adverse events	
BCG	• Incidence of pulmonary TB • Incidence of EPTB • Incidence of LTBI • Mortality • Clinical symptoms • Adverse events	
Tetanus	• Incidence of tetanus • Immunogenicity • Serious adverse events	• Adverse events
Hepatitis B	• All-cause mortality • Primary liver CA • Chronic liver failure • HBsAg seropositivity • HBV seroprotection • Adverse events	• Anti-HBC
Pneumococcal	• Incidence of IPD • Immunogenicity • Adverse events	• Nasopharyngeal colonization • Otitis media
Pertussis	• Incidence of pertussis • Immunogenicity • Serious adverse events	• Adverse events