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University of the Philippines
Evidence to Decision Framework Evidence Summary
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PHILIPPINE GUIDELINES on PERIODIC HEALTH EXAMINATION

Pediatric Immunization

PERIODIC HEALTH EXAMINATION TASK FORCE 2023



Disclaimer

This guideline is intended to be used by specialists, general practitioners, allied health professionals who are primary care providers. Although adherence to this guideline is encouraged, it should **not** restrict the healthcare providers in using their sound clinical judgment in handling individual cases.

Payors 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 this guideline should not also be treated as strict rules on which to base legal action.

Contact Us

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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.

The NIH-ICE undertook extensive technical work in: (1) searching and synthesizing the evidence while ensuring objectivity in each stage of the process, and (2) presenting the evidence in the panel discussion and documenting and writing the final report. They were also indispensable in carrying out the legwork, coordinating among various individuals, groups, and committees, and facilitating the *en banc* meeting. The CPG Central Steering Committee and the Task Forces Steering Committee were responsible for overall organization and management and are accountable for the quality of the CPG.

We would like to thank the support given by Dr. Rose Capeding, President of PFV, and Dr. Carmen Nievera, Secretary of PIDSP, for their review of the manuscript.

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.

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

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List of Abbreviations

AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians and Gynecologists
AGE	Acute gastroenteritis
AE	Adverse event
AMSTAR	Assessing the Methodologic Quality of Systematic Reviews
Anti-PRP	Antibody to Polyribosyrlribitol phosphate
AREB	Asian Rabies Expert Bureau
ACWY	Meningococcal Conjugate vaccine
BCG	Bacille Calmette-Guérin
bOPV	Bivalent oral polio vaccine
CDC	Centers for Disease Control
CEA	Cost-effectiveness analysis
CI	Confidence interval
CPG	Clinical practice guideline
DALY	Disability-adjusted life year
DOH	Department of Health
DTaP	Diphtheria, tetanus, acellular pertussis
DTP	Diphtheria, tetanus, (whole cell) pertussis
EPI	Expanded Program on Immunization
ERE	Evidence review expert
EtD	Evidence to decision
ELISA	Enzyme-linked immunosorbent assay
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titer
GRADE	Grading of Recommendations, Assessment, Development and Evaluation



HAV	Hepatitis A virus
HBsAg	Hepatitis B serum Antigen
HBV	Hepatitis B virus
HCW	Healthcare worker
HepB	Hepatitis B
HCC	Hepatocellular carcinoma
Hib	Haemophilus influenza B
HIV	Human immunodeficiency virus
HTAC	Health Technology Assessment Council
ICER	Incremental cost-effectiveness ratio
IGRA	Interferon γ release assay
IIV	Inactivated influenza vaccine
ILI	Influenza-like illness
IM	Intramuscular
IMD	Invasive Meningococcal disease
IPD	Invasive Pneumococcal disease
IPV	Inactivated polio vaccine
IV	Intravenous
LAIV	Live attenuated influenza vaccine
LMIC	Low- and middle-income country
LTBI	Latent Tuberculosis Infection
MCC	Meningococcal conjugate C vaccine
MR	Measles and Rubella
MMR	Measles, Mumps and Rubella
MMRV	Measles, Mumps, Rubella and Varicella
NICE	National Institute for Health and Care Excellence
NIP	National immunization program
NNV	Number needed to vaccinate



OMV	Outer membrane vesicle
OPV	Oral polio vaccine
OR	Odds ratio
PCV	Pneumococcal conjugate vaccine
PEP	Post-exposure prophylaxis (Rabies)
PFV	Philippine Foundation for Vaccination
PHIC	Philippine Health Insurance Corporation
PHP	Philippine peso
PICO	Population, Intervention, Comparator, Outcome
PIDSP	Pediatric Infectious Disease Society of the Philippines
PPS	Philippine Pediatric Society, Inc.
PrEP	Pre-exposure prophylaxis (Rabies)
PSMID	Philippine Society for Microbiology and Infectious Diseases
PT	Pertussis toxoid
QALY	Quality-adjusted life-years
RCT	Randomized controlled trial
RD	Risk difference
RR	Relative risk
RV	Rotavirus
RVGE	Rotavirus gastroenteritis
SAE	Serious adverse event
SIA	Supplemental immunization activities
SMD	Standard mean difference
TB	Tuberculosis
Td	Tetanus and diphtheria
Tdap	Tetanus, diphtheria, acellular pertussis
TST	Tuberculin Skin Test
TTCV	Tetanus toxoid containing vaccine



USD U.S. Dollars

VE Vaccine effectiveness

WHO World Health Organization

WPV Wild poliovirus

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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 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. The CPG provides twelve (12) recommendations on prioritized questions regarding the relevant vaccines for preventing these eleven (11) disease conditions.

Recommendations are based on the appraisal of the best available evidence on each of the eleven 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 or EtD framework.^{1,2} It included: (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 arises.

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1. Schünemann HJ, Wiercioch W, Brozek J, Etxeandia-Ikobaltzeta I, Mustafa RA, Manja V, et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLPMENT. *J Clin Epidemiol.* 2017 Jan;81:101–10.
2. Schünemann HJ, Mustafa R, Brozek J, Santesso N, Alonso-Coello P, Guyatt G, et al. GRADE Guidelines: 16. GRADE evidence to decision frameworks for tests in clinical practice and public health. *J Clin Epidemiol.* 2016 Aug;76:89–98.

Summary of Recommendations

Table 1. Recommendations on pediatric immunization

Recommendation	Certainty of Evidence	Strength of Panel Recommendation
We recommend giving rotavirus vaccination among apparently healthy infants starting at 6 weeks old.	Moderate	STRONG
We recommend giving varicella vaccination among healthy children and adolescents 12 months to 18 years old.	Moderate	STRONG
We recommend giving measles-containing vaccines among apparently healthy children starting at 9 months of age.	Low	STRONG
We suggest giving mumps-containing vaccines among apparently healthy children starting at 12 months of age.	Low	WEAK
We suggest giving two (2) doses of varicella vaccine among healthy children and adolescents 12 months to 18 years old.	Low	WEAK
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
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	WEAK

*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.

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

Among healthy infants, we **suggest routine BCG vaccination** at birth for the prevention of tuberculosis.

Very low

WEAK

We suggest giving 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

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; Very low WEAK
 - PCV13 and PCV15 may be interchanged for the primary and booster doses;
 - PCV10-SII may be used as booster dose in PCV13-primed children.

We suggest giving 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



1. Introduction

The Philippine Guidelines on Periodic Health Examination (PHEX) was first published in 2004. 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 2023 PHEX on pediatric immunization supports 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, has 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. Without vaccines, 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

Eleven 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.

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). These recommendations can be used by relevant stakeholders to continuously improve the performance, reach and efficacy of the NIP.

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 were 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. 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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2. Objective, Scope, Target Population, and Target Users

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).

This clinical practice guideline is a 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. The CPG provides twelve (12) recommendations on prioritized questions regarding the relevant vaccines for preventing these eleven (11) disease conditions.

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. This CPG provides target users on the different evidence-based recommendations and how they can incorporate these vaccines in their practices.

3. Guideline Development Methodology

3.1. Organization of the Process

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. They also finalized the recommendations for each clinical question included.

The technical working group, composed of evidence review experts (EREs), was tasked to review existing CPGs, 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.

The 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.

3.2. Creation of the Evidence Summaries

The clinical questions were developed using the PICO (population, intervention, comparator, and outcome) format. The EREs 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 EREs 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. RevMan, STATA, and GRADEPro were used for the quantitative synthesis of important clinical outcomes for each question. The EREs generated evidence summaries for each of the eleven (11) 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 the decision (i.e., cost of vaccination, cost-effectiveness studies, qualitative studies) were also included in the evidence summaries. The Certainty of Evidence was assessed using the GRADE approach.² See Table 2.

Table 2. Basis for Assessing the Certainty 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:	
<ul style="list-style-type: none"> • Risk of bias • Important inconsistency of results • Some uncertainty about directness • High probability of reporting bias • Sparse data/Imprecision • Publication bias 	
Additional factors that may increase quality are:	
<ul style="list-style-type: none"> • All plausible residual confounding, if present, would reduce the observed effect • Evidence of a dose-response gradient • Large effect 	

3.3. Composition of the CPG Panel

The Steering Committee including the Evidence Review Experts had their conflict of interest declarations and then 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 All key stakeholders were invited to join the CP through their respective societies/organizations. They are all board-certified in their respective fields with practices in their subspecialties or have academic, and clinical experience in both the public and private setting. The key stakeholders included policymakers, patient advocates, allied medical practitioners, and physicians from different specialties (e.g., academic training institutions, subspecialty societies, private foundations, public primary care settings, private practice). In finalizing CP composition, the task force made sure that all stakeholders were part of the target population.

3.4. 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 3. These recommendations, together with the evidence summaries, were presented during the *en banc* meeting.

Table 3. Detailed considerations based on the Evidence-to-Decision framework³

- | |
|---|
| <ol style="list-style-type: none"> 1. Is the problem a priority? 2. How substantial are the benefits of the vaccine? 3. How substantial are the harms of the vaccine? 4. What is the overall certainty of the evidence? 5. Does the balance between benefit and harm favor vaccination or no vaccination? 6. How large are the resource requirements (costs)? 7. What is the certainty of the evidence of resource requirements (costs)? 8. Does the cost-effectiveness of the vaccine favor vaccination or no vaccination? 9. What would be the impact on health equity? 10. Is the vaccine acceptable to key stakeholders? 11. Is the vaccine feasible to implement? 12. 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 the abovementioned factors. Strong recommendation means that the panel is “confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects.” 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.

3.5. Managing Conflicts of Interest

The Central Executive Committee convened an Oversight Committee (OC) whose task was to thoroughly review the declaration of conflict of interest (DCOI) of each of the Task Force members, particularly the Consensus Panel (CP) members, and make recommendations on how to manage the COI. For TF members with potential significant COIs, a member of the OC conducted additional investigations with due diligence to ensure the integrity of the CPG process and the final recommendations.

All task force members submitted a DCOI and their curriculum vitae (CV) prior to the initiation of the guideline development process. The disclosure included a 4-year period of personal potential intellectual and/or financial conflicts of interest (COI).

Management of the COI of the Consensus Panel, Technical Coordinators, and Task Force Steering Committees were deliberated and decided by the OC, using the pre-agreed criteria. A full description of the methods can be found in the [Final Technical Report](#).

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.

3.6. External Review Process

The CPGs were reviewed by independent stakeholders, who were not members of the Task Force. They were also presented in conferences and to relevant societies for their comments and suggestions. The external reviewers are pediatric infectious diseases specialists who are vaccinology experts and clinical vaccine trialists. They appraised the CPG and concurred with the findings from the evidence review presented.

3.7. Planning for Dissemination and Implementation

All recommendations will be incorporated in a web-based and mobile application accessible to the public. The evidence summaries and the full CPG manuscript will be posted online in the DOH website and in <https://phex.ph>. An abridged manuscript of the CPG will be published in the Acta Medica Philippina. This will also be published in the official websites of the participating organizations. The CPG will undergo quality screening by the DOH Evidence Generation and Management Division for recognition and implementation as a National Practice Guideline by DOH and the Philippine Health Insurance Corporation (PHIC).

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4. Recommendation and Evidence Summaries

4.1. Should rabies pre-exposure prophylaxis (PrEP) be given as routine vaccination for prevention of rabies infection in children and adolescents?

RECOMMENDATION

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.*

(weak recommendation, very low certainty evidence)

Consensus Issues

The panel considers rabies 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 outweigh the risk of harm. However, the panel recognizes that pre-exposure rabies vaccination is not cost-effective to low-risk groups. Since there are other more cost-effective ways to curb rabies incidence (including animal vaccination), the specification of the recommendation is limited to individuals belonging to high-risk populations.

Key Findings

A total of four studies were included in this evidence summary. Two randomized controlled trials (RCT) evaluated immunogenicity and one RCT evaluated geometric mean titer (GMT) and safety. Two cost-effectiveness analysis (CEA) studies investigated the costs of universal PrEP + PEP against PEP (post-exposure prophylaxis) alone.

Rabies PrEP significantly induces immunogenic responses in children compared to the control group. Subgroup analysis shows that protective titers wane over time. Participants who received rabies PrEP had significantly higher GMT post-vaccination compared to those who received placebo. Local and systemic adverse events were similar between those who receive the rabies PrEP and the control group. No serious adverse effects were reported. The overall certainty of evidence was rated very low due to significant risk of bias and inconsistency in one of the critical outcomes (immunogenicity).

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 cost of quality vaccines; however, the more recent 2020 CEA done in the Philippines showed that universal school-based PrEP program would be cost-effective in the Philippines when compared with the current recommended PEP only regimen.



Introduction

The global burden of rabies is associated with a loss of 3.7 million DALY (disability-adjusted life year) and results to 59,000 mortalities annually from dog-mediated bites, with majority of deaths estimated to occur in Asia and Africa.¹ In the Philippines in 2018, there was a total of 276 human rabies cases over the estimated population of 107,587,132 with an average of 2.57 rabies incidence per million population.² Regions 3, 4-A, 5, and 12 reported the greatest number of cases from 2008 to 2018. The confirmed number of positive human rabies cases increased by 13.5% in the last 9 years, from the 243 cases reported in 2009 to 276 in 2018.³ According to the recent surveillance report of the Department of Health Epidemiology Bureau, a total of 291 rabies cases were reported from January 1 to October 8, 2022, which is 31% higher than the 222 rabies cases reported in the same period last year. Likewise, 14 regions reported an increase in reported cases with regions 3, 4-A, 11, and 12 contributing majority of the cases.⁴

Rabies remains the most acutely fatal infectious disease claiming 250 to 300 Filipino lives every year, and about one-third of these deaths occur among children less than 15 years of age.² The recent 2022 surveillance report of DOH shows a case fatality rate of 100% with pediatric patients comprising 30% of the total reported cases.⁴ Children are at increased risk for rabies exposure due to their attraction to animals, inability to read their behavioral cues and fend off an attack, the possibility that they may not report an animal bite. Their short stature makes them vulnerable to severe bite to high-risk areas such as the face, head, and neck.⁵

The Republic Act No. 9842 or the Anti-Rabies Act of 2007 paved the way for the development of the National Rabies Prevention and Control Program (NRPCP), a multi-agency effort with the goal of ending human deaths from dog-mediated rabies by 2027 and a rabies free Philippines by 2030. One of the key components of the program is provision of PrEP for high-risk individuals and PEP after an exposure from potentially rabid animals. The NRPCP has identified children 5 to 14 years old living in areas where there is high incidence of rabies as target population to be included for provision of PrEP.² The advantages of receiving PrEP among high-risk individuals is that in cases of suspected exposure to rabies, treatment is simplified by eliminating the need for rabies immune globulin and decreasing the number of doses of vaccine required from a 4-dose PEP regimen to only 2 doses.⁵

Review Methods

A systematic search was undertaken in MEDLINE, Cochrane Library, and Google Scholar from their inception to 09 November 2022. The search strategy includes combined MeSH and free text search using the terms: “rabies, rabies vaccine, pre-exposure prophylaxis, cost-effectiveness analysis.” The reference lists of included studies were hand searched for additional relevant studies.

Only randomized controlled trials that compared rabies pre-exposure prophylaxis against placebo or non-rabies vaccine were included in this review. Outcomes of interest included rabies infection, immunogenicity, adverse events, and cost-effectiveness analysis. Exclusions were animal studies, adult population (≥ 19 years old), and immunocompromised participants. No limits were placed on the type of rabies vaccine, route of administration, or dosing schedule. Subgrouping according to highly prevalent areas was planned.

Results

Characteristics of Included Studies

Two (2) RCTs with a total of 158 participants were included. These RCTs recruited 2-months-old healthy Vietnamese infants and randomly assigned them to the intervention group or control group. Both groups received a single intramuscular injection of combined DTP-IPV (diphtheria, tetanus, whole-cell pertussis, and inactivated poliomyelitis vaccine) at ages 2, 3, and 4 months. A contralateral intramuscular injection of PVRV (Verorab) was given at ages 2 and 4 months for the interventional group. Serum titers for rabies neutralizing antibodies (RVNA) were assayed at 1 and 17 months after the last rabies vaccine dose. Seroconversion was defined at an RVNA titer of ≥ 0.5 IU/ml following the WHO recommendation. Outcome measures during the follow-up period included immunogenicity or the number of participants who seroconverted, geometric mean titer, and local and systemic adverse events.^{6,7}

Efficacy Outcomes

Pooled analysis of 2 RCTs showed that a 2-dose intramuscular (IM) PrEP regimen significantly induces immunogenic response (RR 0.13, 95% CI 0.07 to 0.23, $I^2=89\%$) compared to the control group, with significant heterogeneity. Subgroup analysis showed that the protection wanes over time, with RR 0.01 95% CI 0.00 to 0.19 at 1-month post vaccination and RR 0.26 95% CI 0.15 to 0.45 at 17-months post vaccination.^{6,7} Participants who received rabies PrEP had significantly higher geometric mean titers (GMT) post vaccination compared to those who received placebo (mean difference (MD) 20.07, 95% CI 12.01 to 28.12, 1 study, n=84).⁶

Safety Outcomes

Only one RCT reported on safety, which showed inconclusive results for local reaction adverse events (RR 0.29, 95% CI 0.02 to 5.47) and systemic reaction adverse events (RR 0.52, 95% CI 0.14 to 1.96) among those who received the rabies PrEP compared to those who received control. No serious adverse effects were reported.⁶

Table 4. Summary of findings for rabies PrEP vs. placebo/non-rabies vaccine

Critical Outcomes	Basis (No. and Type of Studies, Total Participants)	Effect Size	95% CI	Interpretation	Certainty of Evidence
Immunogenicity	2 RCTs (n=158)	RR 0.13	[0.07, 0.23]	Benefit	Very Low
Geometric mean titer	1 RCT (n=84)	MD 20.07	[12.01, 28.12]	Benefit	Low
Adverse event (local)	1 RCT (n=125)	RR 0.29	[0.02, 5.47]	Inconclusive	Low
Adverse event (systemic)	1 RCT (n=84)	RR 0.52	[0.14, 1.96]	Inconclusive	Low

CI confidence interval; MD mean difference; PrEP pre-exposure prophylaxis; RCT randomized controlled trial; RR relative risk

Certainty of Evidence

All studies have risk of bias as there were concerns in allocation concealment, and the study design precludes blinding of the participants and study personnel. The risk of bias, inconsistency, and low sample size contributed to downgrading of evidence to very low certainty for the immunogenicity outcome. The outcome geometric mean titer (GMT), as well

as local and systemic adverse events were rated with low certainty due to risk of bias and imprecision.^{6,7}

Recommendations from Other Groups

Table 5. Summary of other groups' recommendations for rabies PrEP

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
WHO Expert Consultation on Rabies (2018)	Recommends PrEP for individuals who are at high risk of exposure to rabies because of their occupation, travel or residence in an endemic setting with limited access to timely and adequate PEP. WHO recommended PrEP regimens include a two-site intradermal regimen given on D0 and D7, or an intramuscular regimen given on D0 and D7. Widescale PrEP should be considered in remote settings with limited access to PEP if the annual dog bite incidence is >5% or if exposure to vampire bats is prevalent. The decision should be based on strong epidemiological evidence and the local context. ¹	Not indicated
Advisory Committee on Immunization Practices (2022)	Recommends a 2-dose (D0 and D7) intramuscular rabies vaccine series in immunocompetent persons <18 years of age for whom rabies vaccine pre-exposure prophylaxis (PrEP) is indicated. An intramuscular booster dose of rabies vaccine administered no sooner than day 21 but no later than 3 years after the 2-dose PrEP series can be given as an alternative to a titer check, for immunocompetent persons <18 years of age who have sustained an elevated risk for only recognized rabies exposures. ⁵	Not indicated
Indian Academy of Pediatrics (2021)	Rabies vaccine PrEP is recommended among high-risk children which includes children having pets at home or children perceived with higher threat of being bitten by dogs such as hostellers, and those with risk of stray dog bite while going outdoors. Three doses are recommended to be given intramuscularly on days 0, 7 and 28. ^{8,9}	Not indicated
Pediatric Infectious Disease Society of the Philippines (2021)	The recommended regimens for PrEP include the use of WHO prequalified vaccines (Verorab or Rabipur). Intramuscular regimen using PVRV 0.5 mL or PCECV 1 mL given on days 0 and 7 or intradermal regimen: PVRV or PCECV 0.1 mL given on days 0 and 7. For immunocompromised individuals or those given non-WHO prequalified vaccines, 3 doses on days 0, 7, 21 or 28 is recommended. ¹⁰	Not indicated

PCECV purified chick embryo cell vaccine; PrEP pre-exposure prophylaxis; PVRV purified Vero cell rabies vaccine; WHO world health organization

Ongoing Studies and Research Gaps

No relevant ongoing studies were found.

Additional Considerations for Evidence-to-Decision (EtD) Phase

Cost

Table 6 shows the cost of different rabies vaccines available in the Philippines. Table 7 shows the cost of post-exposure prophylaxis (PEP) with the corresponding savings among patients

who received and did not receive rabies PrEP. Rabies PrEP with

3 doses of either purified Vero cell rabies vaccine (PVRV) or purified chick embryo cell vaccine (PCECV) was estimated to cost USD 4.77 (PHP 278.32) per patient. For patients who weigh between 26 to 50 kg, rabies PrEP reduced the cost of PEP by up to 38% following category II and by up to 85% following category III exposure after the cost of PrEP was taken into account.¹¹

Table 6. Cost of rabies vaccine in the Philippines (as of 2022)

Rabies Vaccine	Cost (PHP)
WHO Pre-Qualified Rabies Vaccine Verorab (Sanofi) PVRV Rabipur (GSK) PCECV	1,488/vial 1,960/vial
Non-WHO Pre-Qualified Rabies Vaccine Speeda (Liaoning Chengda Biotechnology) PVRV Vaxirab N (Cadila Healthcare) PCECV Abhayrab (Human Biologicals Institute) PVRV	980/vial - 1200/vial
Rabies Immunoglobulin Equirab (BSV Bioscience Phils) ERIG 200 IU/ml x 5ml	1,800/vial

PCECV purified chick embryo cell vaccine; PVRV purified Vero cell rabies vaccine

Table 7. Cost of post-exposure rabies prophylaxis in the Philippines (as of 2022)

Exposure category	Cost per patient (USD)		Savings per patient with PrEP (weight range 26-50 kg)	
	Patients with PrEP	Patients without PrEP (weight range 26-50 kg)	Amount	Percentage savings
Category II	3.19 or PHP 184.98 (2-ID doses of PCECV or PVRV at USD 1.59 per dose; no RIG)	12.76 or PHP 739.94 (8-ID doses of PCECV or PVRV at US\$1.59 per dose; no RIG)	USD 4.80 or PHP 278.32	38%
Category III	3.19 or PHP 184.98 (2-ID doses of PCECV or PVRV at USD 1.59 per dose; no RIG)	51.76 or 3,001.31 PHP (8-ID doses PCECV or PVRV at USD 1.59 per dose; 2 vials of ERIG at USD 19.52 per vial)	USD 43.80 or PHP 2,540.06	85%

ERIG equine rabies immunoglobulin; ID intradermal; PCECV purified chick egg cell embryo vaccine; PVRV purified Vero cell rabies vaccine; PHP Philippine pesos; PrEP pre-exposure prophylaxis; RIG rabies immunoglobulin; USD US Dollars

Two cost-effectiveness analysis (CEA) studies investigated the costs of universal PrEP+PEP against PEP (post-exposure prophylaxis) alone. Their economic evaluations showed contrasting results. An earlier CEA was done in 2006 among Thai children. The lowest price for PrEP regimen using the Thai Red Cross (TRC) intradermal regimen costs USD 2.00-3.75 (PHP 115.99-217.49), and the additional cost of two rabies post-exposure boosters is USD 18.00-21.75 (PHP 1,043.91-1,261.39). The lowest price for PEP regimen using intradermal TRC regimen costs USD 28.75-37.25 (PHP 1,667.08-2,159.89) with the additional costs of USD 27.50 or USD 75.00 (PHP 1,594.54-4,348.77) using ERIG or HRIG, respectively, among severely exposed patients (WHO Category III). Results of the study showed that the costs of

both strategies, PrEP of children or PEP of exposed, becomes equal when the dog bite incidence is 2–30% and depending on the PEP regimen used. They concluded that large scale rabies PrEP of children is not cost effective with current vaccination schedules and cost of quality vaccines.¹²

A CEA done in the Philippines in 2020 using Philippines-specific data from the Research Institute for Tropical Medicine was used in a static decision-tree model to assess cost-effectiveness of a PrEP+PEP program vs. PEP alone. From both payer and societal perspectives, the resulting incremental cost-effectiveness ratios were PHP 36,035 (USD 759; 2016 USD conversion) and PHP 18,663 (USD393)—quality-adjusted life-years gained—respectively, which are both below the willingness-to-pay threshold of PHP 140,255 (USD 2,953). These data suggest that a universal PrEP program targeting 5-year-olds would be cost-effective in the Philippines.¹³

Patient's Values and Preference, Equity, Acceptability, and Feasibility

The WHO/Bill and Melinda Gates foundation consultation in 2009 took note of the many pros and cons of incorporating PrEP in the expanded program of immunization (EPI). However, the consultation could not issue a consensual statement. Further studies and deliberations were deemed needed.

The WHO Secretariat encourages further studies on the feasibility, cost-effectiveness, and long-term impact of incorporating rabies PrEP in the early immunization programs of infants and children in communities where rabies remains to be a major problem. The rabies PrEP regimen, if intended for infants or young children, should be easily adapted to the schedules and timing of national childhood immunization programs. It should not interfere with the immune response to other vaccines given simultaneously. It should be formulated to meet common technical limitations, specifically refrigeration and storage capacity, and it has to be appropriately priced for different markets.¹⁴

During the 6th annual meeting of the Asian Rabies Expert Bureau (AREB), the Philippines was highlighted at the forefront for the fight against rabies. A rabies PrEP pilot program in Cabusao, Camarines Sur was carried out among 188 school children. Cabusao is a municipality where canine rabies is endemic and the incidence of dog bites and rabies deaths in children is particularly high. Aside from the administration of PrEP among school children, the program implemented integration of education on rabies prevention in the school curriculum, increased dog vaccination coverage, and improved access to PEP. Three years after its implementation, the success of the project was evidenced by 77% dog vaccination coverage, and no human rabies deaths have been recorded in Cabusao for the last two years.^{11,15} A similar rabies PrEP study was conducted in Kananga, Leyte among 150 school aged children. This is an unpublished phase IV, prospective, open-label, randomized, single center study. Results showed that intradermal rabies PrEP is highly immunogenic among children 5-9 years old.¹⁶ These pilot projects and studies demonstrated that administration of PrEP in school children is a safe and feasible strategy, which brings significant benefit to the community by preventing deaths in children. Integration of rabies vaccine into the EPI would facilitate access to the targeted population and minimize operational costs. AREB members recommended that demonstration projects should be conducted to evaluate the feasibility of introducing rabies vaccination into the EPI in countries where the risk of rabies is high.¹⁵

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4.2. Among healthy children who completed the primary series of *Haemophilus influenzae B* (Hib) vaccination, is a booster dose of Hib vaccine needed?

RECOMMENDATION

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.
(weak recommendation, very low certainty evidence)

Consensus Issues

The consensus panel considers *Haemophilus influenzae B* to be a burden; it causes life-threatening diseases. The lack of or limited testing capacity for this organism contributes to inadequate data on bacteriologically-confirmed cases.

The benefits of a Hib booster outweigh the risk of harm based on clinical experience. However, the panelists believe that there is a need for more high-quality evidence on disease burden, cost-effectiveness, and prevention to make a strong recommendation.

Key Findings

Results for this evidence review came from two RCTs that were identified from one meta-analysis comparing the different schedules of Hib vaccination. An updated search did not yield any additional studies to answer the clinical question.

There were no direct clinical studies that demonstrated the effect of a Hib booster dose to clinically significant outcomes. Narrative reports, however, described the decrease in Hib-related infection and mortality after booster campaigns in some countries. As a surrogate for vaccine efficacy, one study described the geometric mean concentration (GMC) to antibody to the polyribosylribitol phosphate (anti-PRP) to be higher one month after the booster dose of Hib was given, as compared to those that did not receive one (29.92 ug/mL vs. 0.32 ug/mL). Another study showed that those receiving the booster dose had higher percentage of people reaching the 1.0 ug/mL (RD 0.59, 95% CI 0.52 to 0.67) and 0.15 ug/mL (RD 0.16, 95% CI 0.11 to 0.22) thresholds which represent long term and short-term protection, respectively. Occurrence of adverse events were identical across different preparations of Hib vaccines, with common adverse events of fever, pain, and irritability.

Both studies had issues with risk of bias due to unclear allocation concealment and blinding. Aside from this, there is indirectness in the designs because only data relevant to answer the evidence was extrapolated from the studies. Other factors included in the original design were not included in the assessment. There is also a risk of publication bias as the majority of studies are already comparing different Hib-containing vaccines against each other; hence, the limited evidence gathered. All these factors contributed to downgrading of the certainty of evidence to very low.

Introduction

Haemophilus influenzae serotype B (Hib) is the most predominant form of the *Haemophilus* bacteria, which commonly infects younger children and immunocompromised people. It is known to cause life-threatening diseases such as meningitis, pneumonia, epiglottitis, and sepsis, as well as debilitating diseases such as cellulitis, osteomyelitis, and septic arthritis.^{1,2} Incidence of Hib is highest among children aged 4 months to 48 months old and rarer among older children and adults. Children aged 3 to 5 years are generally thought to be important transmitters of the disease due to nasopharyngeal carriage.^{3,4} With the introduction of the Hib conjugate vaccine, the global burden of diseases caused by this bacteria has significantly decreased.⁵ In the Philippines, the Hib conjugate vaccine was included in the National Immunization Program (NIP) in 2010 as part of a pentavalent vaccine (DTaP-Hep B-Hib vaccine) in selected regions of the country. It was eventually rolled out to the national level in 2012.⁶

Data from the Philippine Pediatric Society disease registry, which started recording reportable cases in 2006, has shown a cumulative decrease in the number of cases of *H. influenzae* infections after the vaccine was introduced. Before 2013, cases of pneumonia, meningitis, and epiglottitis numbered 199, 145, and 48, respectively. Reported cases from 2013 to the present are 172, 37, and 33, respectively.⁷ Despite this, lack of testing (e.g., identification of causative agents) in resource-limited settings lead to underreporting of Hib infections. Pneumonia remains to be the top diagnosis of admitted patients in PPS-accredited hospitals each month of this year, while septicemia continues to be among the top 10 diagnosis of hospital admissions.⁷ Overall incidence of influenza-like illness (not only attributed to Hib) this year has also been reported to have increased by 25% compared to the past year.⁸

Review Methods

A systematic search was done on 15 October 2022 using MEDLINE, Cochrane Library, and Google Scholar with a combined MeSH and free text search using the terms: "*Haemophilus influenzae*, Hib, immunization, vaccination, booster." A filter was applied to initially isolate meta-analyses and systematic reviews. From this, one meta-analysis was identified. Using the last search date of the aforementioned meta-analysis and its search strategy, an updated search was done on 17 October 2022. Clinical practice guideline websites such as the US Preventive Task Force, Canadian Task Force, and UK screening committee were also searched for their resources and recommendations.

Only randomized clinical trials that compared children who received booster dose versus those that did not receive a booster dose at the same age/timepoint was included in the review. Outcomes of interest included clinical outcomes such as mortality, incidence of infection and transmission, vaccine effectiveness, adverse events, and cost-effectiveness. Studies that used the pre-booster immunologic level as comparator to the post-booster levels of patients were excluded.

Risk of bias was assessed using the Painless Evidence-Based Medicine checklist. Grading of certainty of evidence was done using GRADEpro. No pooling of results was done because of the limited number of studies and difference in outcome measures.

Results

Characteristics of Included Studies

Two RCTs that came from one meta-analysis were used as primary evidence for vaccine efficacy. Both made use of polyribosylphosphate antigen conjugated to tetanus toxoid (PRP-T) formulations of the Hib vaccine in combination with other vaccines (manufactured as ActHib by Sanofi and Infanrix by GSK). Infants >1 year old were included in the study as long as they completed their primary series of Hib-containing vaccine with the last dose given at least 6 months before in one study⁹ and 7 months in the other.¹⁰ Anti-PRP levels were determined at least one month after the booster dose was given and compared to a population in the control group that has yet to receive their booster dose. One study reported this outcome as geometric mean concentration.¹⁰ The other reported the number of subjects that reached the threshold for long- and short-term protection.⁹

Vaccine Efficacy

Effect on Prevention of Disease

There are no available direct clinical studies that demonstrate the effect of the booster dose of a Hib-containing vaccine on clinical or carriage outcomes.

Support for the use of a booster dose comes from narrative reviews of nationwide policies of countries like the UK, Republic of Ireland, the Gambia, and the Netherlands which reported populations that had an increase in Hib infection years after the initial vaccination of a primary infant series for Hib disease. The reported effectiveness of the primary series decreased from 61% two years following the last vaccine dose and further decreasing to 27% thereafter.⁴ In the UK, the roll-out of a booster dose campaign for children 6 to 12 months old and 13 to 48 months old led to an immediate decrease of Hib cases across all age groups, even among the adult population, despite the coverage for the two age groups only reaching 71% and 63% respectively.¹¹ Invasive Hib disease after the UK booster roll-out was still reported but was more common among the population that was not given a booster dose because their individual ages were not included in the eligible population. This percentage increased as time progressed further suggesting the waning immunity of the primary series and importance of the booster dose.¹²

Immunogenicity

Measures of immune response as correlates of clinical protection and vaccine efficacy are usually reported in vaccine studies. Such measures include geometric mean concentration and mean antibody titer. For Hib-containing vaccines, the antibody to the polyribosyribitol phosphate (anti-PRP) contributes majority of serum bactericidal activity, and an increasing concentration is associated with a decreased risk of invasive Hib disease.^{13,14} In clinical studies for Hib vaccines, anti-PRP concentrations of more than or equal to 0.15ug/mL and >/1.0ug/mL correspond to short-term and long-term protection, respectively.¹⁵

The meta-analysis cited two studies that reported immunological response from Hib-conjugate vaccines. One study done in Canada showed that, at 16 months, those that received a booster dose of DTaP-IPV/PRP-T vaccine one month prior had a geometric mean concentration (GMC) of 29.92 ug/mL (95%CI, 24.58 to 36.43) which is more than 90% higher compared to those that did not receive a booster who had a GMC of 0.32 ug/mL (95% CI, 0.25 to 0.41).¹⁰

Another study done across multiple countries in Europe assessed immunologic response of a meningococcal conjugate vaccine (ACWY) after coadministration with a DTaP-HBV-IPV/Hib

(hexa) vaccine. One month following receipt of a booster dose of the hexa group, seropositivity compared to the group that received ACWY only showed a higher seropositivity rate for anti-PRP with a risk difference (RD) of 0.59 (95% CI 0.52 to 0.67) at 1.0 ug/mL and 0.16 (95% CI 0.11 to 0.22) at 0.15 ug/mL thresholds.⁹

Vaccine Safety

No RCT directly assessed the safety of Hib-conjugate vaccine given alone as a booster. Commercially available Hib-containing vaccines (Hiberix, Infanrix, Pentacel) report the same incidence for the most common SAEs post-vaccination which include injection site pain, irritability, and drowsiness.¹⁶ In one RCT, HibMenCY-TT+ DTaP-HepB-IPV primed infants were given a booster dose of Hib-conjugate vaccine in the form of HibMenCY-TT at 12 to 15 months and compared to those who received MenACWY-TT at the same age. No significant differences were noted in solicited symptoms such as pain, redness, swelling, drowsiness, fever, irritability, and loss of appetite (any symptom experienced RR 1.20, 95% CI 0.87 to 1.66), and severe adverse events (RR 0.68, 95% CI 0.33 to 1.38).¹⁷

Infanrix hexa, one of the available Hib-containing combination vaccine in the country, published a post-marketing surveillance study last 2020. In general, the vaccine had an acceptable safety profile with common reactions listed (reporting rate per 100,000 doses) including fever (7.74), crying (2.62), injection site erythema (1.87), swelling (1.28), and pain (0.92). Other systemic reactions were vomiting (0.88), somnolence (0.85), and hypotonia(0.75).¹⁸ One study in India reported reactions to Pentaxim, another Hib-containing vaccine in the Philippines¹⁹ where infants who were given a booster dose at 18-19 months had common local reactions including injection site erythema (8.7% any, 0.5% >5cm), swelling (any 11.1%, none >5cm), pain (any 21.7%, crying when injected limb is moved 1%) while systemic reactions included fever (19.3% for fever < 39°C, 1.4% for above), vomiting (any 7.2%), somnolence (any 8.7%), irritability 12.1%, and loss of appetite 9.7%. In a study investigating two pentavalent vaccines in the Philippines (DTPw-HBV/Hib), pain, irritability, and fever were the most frequently reported symptoms (80%, 70-80%, 50-70%). Incidence of grade 3 pain and fever (>39°C) were higher after the booster dose as compared to after the primary series (20% vs 5-10% for pain, 5% vs <3% for fever). No SAEs were reported during the booster phase.²⁰

Table 8. Summary of reported Hib adverse events

Infanrix hexa ^a (Reporting rate per 100,000 doses)	Pentaxim ^b (n=207)	DTPw-HBV/Hib (n= 175)
Fever: 7.74	Pain Any: 21.7% Severe: 1%	Pain: 80%
Crying: 2.62	Fever Any: 19.3% Severe (>39°C): 1.4%	Irritability: 70-80%
Erythema: 1.87	Irritability Any: 12.1 (8-17.3) Severe: None	Fever: 50-70%
Swelling: 1.28	Swelling Any :11.1 (7.2-16.2) Severe (>5cm): None	Erythema: 45%

Inappropriate schedule of vaccine administration: 0.95	Abnormal crying Any: 10.6 (6.8-15.6) Severe: 0.5 (0-2.7)	Swelling: 40-45%
Pain: 0.92	Decreased appetite Any: 9.7 (6-14.5) Severe: 0.5 (0-2.7)	Drowsiness: 40%
Irritability: 0.90	Erythema Any: 8.7 (5.2-13.4) Severe: (>5cm): 0.5 (0-2.7)	Loss of appetite: 20-40%
Vomiting: 0.88	Somnolence Any: 8.7 (5.2-13.4) Severe: None	-
Somnolence: 0.85	Vomiting Any: 7.2 (4.1-11.7) Severe: 0.5 (0-2.7)	-
Hypotonia: 0.75	-	-

^aPost-marketing surveillance study covering 17 years¹⁸

^bGiven at 18-19 months of age until 8 days after booster (India)¹⁹

Table 9. Summary of outcomes for Hib vaccination booster

Outcomes	Comparative Risks (CI 95%)	No. of Participants	Quality of Evidence (GRADE)
Effect on clinical outcome	No studies Narrative reports of immunization booster programs initiated in countries that observed an increase in incidence of Hib disease leading to decrease in incidence		Very low
Geometric mean concentration (GMC) of anti-PRP	At 16 months of age: - 3p+1 GMC of 29.92ug/mL (95% CI 24.58- 36.43) - 3p GMC of 0.32ug/mL (95% CI 0.25-0.41)	449 (1 study)	Low
Seropositivity	1 month after the booster dose was given (3p+1) - 1.0ug/mL: risk difference 0.59 (95% CI 0.52-0.67) - 0.15ug/mL: risk difference 0.16 (95% CI, 0.11-0.22)	444 (1 study)	Very low

Certainty of Evidence

Both RCTs included were assessed to have a high risk of bias because of unclear description of the allocation process, blinding of outcome assessors, and unclear risk for attrition bias. Indirectness was also an issue for both since the main study design was to compare the effect of different vaccines being given at different time-points (ACWY-Hexa vaccine scheduling, DTaP-IPV/PRP-T scheduling). These factors led to downgrading of evidence to very low.

Recommendations from Other Groups

The US Centers for Disease Control (CDC) recommends a booster dose of Hib vaccine 12 through 15 months, regardless of which vaccine is used for the primary series. If a DTaP-IPV/Hib is given, the recommended age for a booster shot is at 15 to 18 months but may be given as early as 12 months so long as more than 6 months have elapsed since the last dose of the primary series.²² The UK national screening committee also recommends that a booster dose of any Hib-containing vaccine be given starting at 12 months of age and may be given concomitantly with the pneumococcal conjugate and MMR vaccine.¹² These guidelines are also recommended locally. Both the Philippine Pediatric Society and Pediatric Infectious Disease Society of the Philippines recommend a booster dose of the DTaP-IPV-Hib vaccine be given at 12 to 18 months.²³

Ongoing Studies and Research Gaps

Because of real-world experience in the effect of a booster dose in incidence and severity of Hib infection, studies are now past comparing populations that received and did not receive a booster dose. Current studies are now comparing different formulations of Hib-containing vaccines and the different timing of administration. Aside from this, there is a gap in identifying the real incidence of Hib-related infection in the Philippines because of inadequate testing.

Additional Considerations for Evidence-to-Decision (EtD) Phase

Cost

There are no local studies detailing the cost-benefit of a booster dose for the Hib vaccine. Limcangco et al. published a paper in 2001 detailing the benefits for the primary series of Hib vaccines in preventing Hib-meningitis, citing savings (at that time) for the government amounting up to PHP 39 million (USD 1.11 million) and PHP 255 million (USD 7.28 million USD) for the society.²⁴ A budget impact analysis for the Hib vaccine in Thailand in 2017 showed that for the 3+0 schedule, the incremental cost-effectiveness ratio (ICER) value is 1,099.13 baht (PHP 1,637.70) per quality-adjusted life year (QALY) gained. The 3+1 schedule was seen to be more expensive with an ICER of 1,835.53 baht (PHP 2,734) per QALY gained. Both values were still below the cost-effectiveness threshold of the country making Hib vaccination cost-effective. This was despite Hib-disease having a low burden of disease in the country and the vaccines being expensive at the time of the analysis.²⁵ In China, the only country that does not include Hib in the National Immunization Program, a cost-effectiveness study published in 2021 showed that introduction of a 3+1 Hib schedule to their National Immunization Program would be cost-effective with an ICER of USD 8,001 (PHP 394,289.30) per QALY gained compared to the GDP per capita. There was an estimated 92% reduction in Hib infection and 93% reduction in related deaths.²⁶ Available Hib-containing vaccine in the country has a tariff among pediatricians of PHP 4,000 for Pentaxim and PHP 4,500 for Infanrix while direct supplier purchases can be made for PHP 2,400 to 2,500 for the said vaccines.

The expenses of hospital admission due to diseases that may be caused by *Haemophilus influenzae* based on 2022 PhilHealth's case rate are as follows (in PHP): pneumonia PHP 10,500 to 32,000 (moderate and severe, respectively), septicemia PHP 32,000 (whether unknown cause or identified to be due to Hib), meningitis PHP 25,700, and PHP epiglottitis at 9,700.²⁷

Patient's Values and Preference, Equity, Acceptability, and Feasibility

Overall, the rate of immunization in the Philippines dropped due to the pandemic, with the Department of Health reporting a decrease from 69.08% in 2019 to 65.18% in 2020.²⁸ Based on the national statistics office, in 2017, only 79.8% received the primary series of the Hib vaccine, a statistic not taking into account the effect of the pandemic.²⁹

Aside from the problem of adequate coverage in the country, one study also highlighted that the timing of the vaccines is usually not followed in the Philippines, with only 39.1% receiving their 3rd dose of pentavalent vaccine within 4 weeks of the prescribed schedule.³⁰ Although this issue does not directly tackle the issue of a Hib booster dose, it needs to be addressed appropriately as the timing of the booster dose will depend on the completion and timeliness of the last dose of the Hib-containing vaccine. A modeling study has demonstrated that assuming a 90% coverage for the primary series of Hib, a booster dose given within 2 years of the last dose of the vaccine substantially reduces the incidence of carriage and symptomatic disease of Hib infection and maintains herd immunity among the population.³¹

Booster doses are not recommended after 5 years old as pre-vaccination data report that natural immunity to Hib infection is usually attained by 5-6 years old probably due to asymptomatic nasopharyngeal carriage.³² Online databases that show the national coverage of Hib booster in the country are also not available. Aside from this, there may be issues in adequate reporting of Hib-infection as there are a lot of health facilities not capable of isolating and testing the organisms that cause pneumonia, sepsis, or meningitis.

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4.3. Should the Rotavirus vaccine be routinely given to infants for the prevention of Rotavirus gastroenteritis and its complications?

RECOMMENDATION

We recommend giving rotavirus vaccination among apparently healthy infants starting at 6 weeks old.
(strong recommendation, moderate certainty evidence)

Consensus Issues

The consensus panel unanimously recommended giving the rotavirus vaccine. There is significant evidence of its effectiveness in preventing rotavirus gastroenteritis (RVGE), hospitalization from RVGE, and severe all-cause acute gastroenteritis among apparently healthy infants. Despite the absence of local studies on the adverse and serious effects of the rotavirus vaccine, the evidence showed that the benefit of giving the vaccine far outweighs the serious and adverse effects, including the risk of intussusception.

Key Findings

Sixty randomized controlled trials (RCTs) investigated the efficacy and safety of rotavirus vaccine compared with placebo. Rotavirus vaccine did not reduce all-cause mortality compared with the control group. However, regardless of brand, the rotavirus vaccine significantly reduced the risk of severe rotavirus gastroenteritis (RVGE), hospitalizations from RVGE, and severe all-cause acute gastroenteritis among apparently healthy infants and children up to 2 years. There was also no significant difference in the risk of serious adverse events, including intussusception, and reactogenicity manifesting as fever, diarrhea, or vomiting.

Introduction

Despite being a preventable and treatable condition, diarrhea has caused approximately 500,000 deaths worldwide in children less than 5 years old in 2019. In the same year, diarrhea ranked as the 6th leading cause of death among Filipino children less than 5 years old. Diarrheal diseases accounted for 5% or 2,925 deaths under 5 years old, which was equivalent to 295,074.86 disability-adjusted life years (DALY). Although the incidence of diarrhea in children <5 years old steadily decreased over the last few decades, from 233,000 per 100,000 in 1990, 210,000 per 100,000 in 2000, 164,000 per 100,000 in 2010, and 156,000 per 100,000 in 2019, diarrhea continues to cause significant morbidity and mortality particularly in the younger age groups.¹ Most cases of diarrhea have infectious causes, with Rotavirus causing 31-69% of cases among hospitalized Filipino children.²⁻⁴ Rotavirus gastroenteritis (RVGE) occurs throughout life, but severe RVGE is largely limited to children aged 6-24 months.⁵

In 2012, the Philippines was the first country in Asia to introduce the monovalent rotavirus vaccine (Rotarix) in its routine immunization program. However, challenges in implementation such as unequal distribution of families belonging to the lowest economic quintile throughout the country and limited eligibility due to age-related restrictions of the vaccine led to low vaccine coverage.⁶ At present, four oral, live, attenuated rotavirus vaccines are prequalified

by the World Health Organization (WHO): Rotarix, Rotateq, Rotasiil, and Rotavac. WHO prequalification allows United Nation agencies to procure certain products including vaccines. The characteristics of these vaccines are summarized in Table 10.

Table 10. Rotavirus vaccines prequalified by the WHO⁷⁻¹⁰

	Rotarix	Rotateq	Rotasiil	Rotavac
Manufacturer	GlaxoSmithKline Biologicals	Merck & Co, Inc	Serum Institute of India Pvt., Ltd	Bharat Biotech Ltd
Type	Oral, live-attenuated	Oral, live attenuated	Oral, live attenuated	Oral, live attenuated
Strains contained in the vaccine	Monovalent G1P[8]	Pentavalent G1, G2, G3, G4 and P1A[8]	Pentavalent G1, G2, G3, G4 and G9	Monovalent G9P[11]
Source of rotavirus strain(s)	Human strain	Human-bovine reassortant strains	Human-bovine reassortant strains	Human strain
Number of doses	2 doses	3 doses	3 doses	3 doses
Interval between doses	At least 4 weeks	4-10 weeks	4 weeks	4 weeks
First dose	6 weeks	6-12 weeks	6 weeks	6 weeks
Last dose	Before 24 weeks	Before 32 weeks	Not specified	Before 34 weeks
Storage	2-8°C	2-8°C	2-8°C	2-8°C

Review Methods

A systematic search was done until 02 February 2023 using MEDLINE, Cochrane Library, and Google Scholar utilizing combined MeSH and free text search with the terms: “rotavirus, vaccine, children.” Other sources were searched, such as WHO ICTRP, ClinicalTrials.gov, and reference lists of included studies and relevant systematic reviews. Preprints were also searched using medrxiv, chinaxiv, and biorxiv. As appropriate, authors of potentially eligible studies for this review were contacted via email to obtain additional data.

Only randomized controlled trials that compared WHO prequalified rotavirus vaccines against placebo or standard childhood vaccines were included in this review. Studies that evaluated rotavirus vaccines not licensed by the FDA or prequalified by WHO were excluded. Outcomes of interest included: rotavirus gastroenteritis (RVGE) of any severity during first 2 years of life, acute gastroenteritis (AGE) with moderate-severe dehydration, AGE-related ER visit and/or hospitalization, all-cause mortality, adverse events, serious adverse events, immunogenicity,

and cost-effectiveness. Subgroup analysis by brand of vaccine and country-based under-five mortality level was done. Sensitivity analysis was done to assess the robustness of the results when studies with serious risk of bias concerns were excluded.

Results

Rotavirus vaccine, regardless of brand, significantly reduced the risk of severe rotavirus gastroenteritis (RVGE), hospitalizations from RVGE, and severe all-cause acute gastroenteritis among apparently healthy infants and children up to 2 years, without significantly increasing risk of serious adverse events, including intussusception, and reactogenicity manifesting as fever, diarrhea, or vomiting. Rotavirus vaccine did not reduce all-cause mortality compared with the control group.

Characteristics of Included Studies

A Cochrane systematic review published in 2021 synthesized the available evidence on the efficacy and safety of the four WHO-prequalified rotavirus vaccines in children. This review was appraised to be of high quality using AMSTAR2. In this systematic review, PubMed, the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (published in the Cochrane Library), Embase, LILACS, Science Citation Index Expanded, Social Sciences Citation Index, Conference Proceedings Citation Index-Science, and Conference Proceedings Citation Index-Social Science & Humanities were searched until 30 November 2020. A total of 60 RCTs (n=228,233) were included, all of which contributed data in the meta-analysis. Searches of literature from 30 November 2020 until 02 February 2023 did not yield additional RCTs.

36 trials (n=119,114) assessed Rotarix, 15 trials RotaTeq (n=88,934), 5 trials Rotasiil (n=11,753), and 4 trials Rotavac (n=8,432). Majority of the studies included apparently healthy infants who were 6 to 12 weeks old at the time of the first dose of rotavirus vaccine. One RCT on Rotarix and one RCT on RotaTeq included children 2-6 years old and were given 1 dose of vaccine only. Two RCTs included preterm infants and five RCTs included HIV infected or exposed infants. Rotavirus vaccine was given for 3 doses at least 4 weeks apart, except for Rotarix which was given for 2 doses at 6-10 week intervals. Except for one open-label RCT, the rest of the studies were placebo-controlled. Outcomes measured included outcomes on efficacy (rotavirus gastroenteritis (RVGE)-severe or any severity, all-cause severe AGE, RVGE-related hospitalization, all-cause mortality) and safety (reactogenicity, intussusception, serious adverse events, and adverse events leading to discontinuation of intervention). The studies varied in the length of follow-up. In general, safety trials had shorter follow-up as compared to trials which assessed efficacy. The review focused on outcomes that were rated as critical and important outcomes, and measured after 2 years of follow-up.

Efficacy Outcomes

All-cause mortality

Based on 48 RCTs (n=209,967), rotavirus vaccination did not reduce all-cause mortality (RR 1.02, 95% CI 0.88 to 1.18; I² 0%) compared with placebo, regardless of vaccine brand (Table 11) and country-based under-five mortality rate (Table 12). Sensitivity analysis excluding studies which enrolled patients with HIV infection or exposure showed similar results (RR 1.07, 95% CI 0.90 to 1.27).

Rotavirus gastroenteritis (RVGE)

Severe RVGE was significantly reduced among patients given rotavirus vaccine who were followed up for up to 2 years or 2 rotavirus seasons (RR 0.30, 95% CI 0.22 to 0.40; I^2 87%; 23 RCTs, n=82,690), regardless of brand of vaccine, but with significant heterogeneity. Severe RVGE was significantly reduced among participants given any brand of vaccine, however, still with significant heterogeneity. Heterogeneity improved on subgroup analysis according to the country-based level of under-five mortality rate. Rotavirus vaccination significantly reduced severe RVGE in countries with high (RR 0.57, 95% CI 0.49 to 0.66, I^2 35%; 11 RCTs, n=31,406), medium (RR 0.22, 95% CI 0.18 to 0.28, I^2 0% ; 4 RCTs, n=27,697), and low under-five mortality rate (RR 0.09, 95% CI 0.06 to 0.12, I^2 0%; 8 RCTs, n=23,587).

Rotavirus gastroenteritis of any severity was likewise significantly reduced with rotavirus vaccination (RR 0.46, 95% CI 0.37 to 0.57; I^2 92%; 18 RCTs, n=49,523), however, with significant heterogeneity. Subgroup analysis based on brand of vaccine and country-based level of under-five mortality rate was done. Results showed that rotavirus vaccine significantly

reduced rotavirus gastroenteritis of any severity regardless of brand or country-level of mortality rate.

Pooling 7 RCTs on Rotarix (n=35,331) and 1 RCT on Rotasiil (n=7,500), analysis showed that hospitalizations from RVGE were reduced among participants given these vaccines for up to 2 years or 2 rotavirus seasons (RR 0.20, 95% CI 0.08 to 0.48; I^2 86%; 8 RCTs, n=42,831) compared with placebo, with significant heterogeneity. Regardless of vaccine brand, rotavirus vaccine reduced hospitalizations from RVGE but the degree of heterogeneity improved with subgroup analysis according to brand of vaccine—Rotarix (RR 0.15, 95% CI 0.15 to 0.22; I^2 0%) and Rotasiil (RR 0.66, 95% CI 0.52 to 0.85). Another subgroup analysis done showed that the degree of reduction was inversely proportional to level of under-five mortality rate, such that low mortality countries had the greatest reduction in hospitalizations from RVGE (RR 0.10, 95% CI 0.04 to 0.23, I^2 =4%), followed by medium mortality countries (RR 0.17, 95% CI 0.11 to 0.26, I^2 =0%), and lastly by high mortality country (RR 0.66, 95% CI 0.52 to 0.85).

All-cause acute gastroenteritis (AGE)

All-cause AGE was reduced among patients given rotavirus vaccines for up to 2 years or 2 rotavirus seasons (RR 0.78, 95% CI 0.68 to 0.90; I^2 = 84%; 12 RCTs; n=49,335), still with significant heterogeneity. Subgroup analysis based on vaccine brand show that Rotarix reduced all-cause AGE with RR 0.69, 95% CI 0.55 to 0.85, I^2 =83% still with significant heterogeneity, while RotaTeq (RR 0.85, 95% CI 0.74 to 0.99, I^2 =14%) and Rotasiil (RR 0.94, 95% CI 0.88 to 1.01, I^2 =0%) had trends toward benefit. Another subgroup analysis, according to country-based level of under-five mortality rate showed benefit for high mortality (RR 0.90, 95% CI 0.85 to 0.96; I^2 =7%) and low mortality countries (RR 0.49, 95% CI 0.40 to 0.60: I^2 =0%), but not for medium mortality countries (RR 0.74, 95% CI 0.50 to 1.09, I^2 =92%). Results for medium mortality countries show significant heterogeneity.

2 RCTs on Rotarix (n=14,367) reported all-cause AGE requiring hospitalization. Analysis of these 2 RCTs showed that rotavirus vaccination reduced hospitalizations from all-cause AGE for up to 2 years (RR 0.52, 95% CI 0.27 to 0.99; I^2 77%); however, with significant heterogeneity.

Table 11. Summary of efficacy outcomes sub-grouped according to brand of vaccine

Outcomes	Rotarix	RotaTeq	Rotasilo	Rotavac
All-cause mortality	1.02 [0.81, 1.30]	0.97 [0.74, 1.26]	1.14 [0.82, 1.59]	0.88 [0.50, 1.56]
Severe RVGE	0.22 [0.13, 0.38]	0.30 [0.17, 0.55]	0.56 [0.42, 0.74]	0.46 [0.35, 0.60]
RVGE of any severity	0.37 [0.25, 0.54]	0.44 [0.30, 0.65]	0.77 [0.71, 0.84]	0.66 [0.57, 0.76]
RVGE requiring hospitalization	0.15 [0.11, 0.22]		0.66 [0.52, 0.85]	
Severe all-cause AGE	0.69 [0.55, 0.85]	0.85 [0.74, 0.99]	0.94 [0.88, 1.01]	
All-cause AGE requiring hospitalization	0.52 [0.27, 0.99]			

AGE acute gastroenteritis; RVGE rotavirus gastroenteritis

Table 12. Summary of efficacy outcomes sub-grouped according to country-based level of under-five mortality rate

Outcomes	High Mortality	Medium Mortality	Low Mortality
All-cause mortality	0.96 [0.80, 1.14]	1.25 [0.88, 1.77]	1.14 [0.66, 1.95]
Severe RVGE	0.57 [0.49, 0.66]	0.22 [0.18, 0.28]	0.09 [0.06, 0.12]
RVGE of any severity	0.67 [0.59, 0.76]	0.41 [0.31, 0.55]	0.26 [0.22, 0.31]
RVGE requiring hospitalization	0.66 [0.52, 0.85]	0.17 [0.11, 0.26]	0.10 [0.04, 0.23]
Severe all-cause AGE	0.90 [0.85, 0.96]	0.74 [0.50, 1.09]	0.49 [0.40, 0.60]
All-cause AGE requiring hospitalization			0.52 [0.27, 0.99]

AGE acute gastroenteritis; RVGE rotavirus gastroenteritis

Safety Outcomes

There was decreased risk of serious adverse events (SAEs) detected with any of the 4 WHO prequalified vaccines (RR 0.92, 95% CI 0.88 to 0.96; I² 11%; 43 RCTs, n=212,636). On subgroup analysis (Table 13), there was decreased risk of SAEs among infants given Rotarix (RR 0.87, 95% CI 0.81 to 0.95) compared with placebo. Risk of SAEs were equivalent with placebo for infants given RotaTeq (RR 0.93, 95% CI 0.86 to 1.01), Rotasilo (RR 0.98, 95% CI 0.92 to 1.04) or Rotavac (RR 0.93, 95% CI 0.85 to 1.02). The risk of intussusception was not significantly different among infants given any brand of rotavirus vaccine (RR 0.87, 95% CI 0.61 to 1.25; I² = 0%; 43 RCTs, n=212,636) compared with the control group. Of the 43 studies which looked into intussusception, 27 RCTs (n=20,808) did not report intussusception in both rotavirus vaccine (n=11,925) and placebo (n=8,883) groups.

Rotavirus vaccination, regardless of brand, did not increase reactogenicity manifesting as fever (RR 1.03, 95% CI 0.92 to 1.14; I² 73%; 35 RCTs, n=23,786), diarrhea (RR 1.02, 95% CI

0.93 to 1.13; I² 0%; 33 RCTs, n=29,121), or vomiting (RR 1.00, 95% CI 0.93 to 1.08; I² = 0%; 33 RCTs, n=29,121).

Table 13. Summary of safety outcomes sub-grouped according to brand of vaccine

Outcomes	Rotarix	RotaTeq	Rotavac	Rotasiil
Serious adverse events	0.87 [0.81, 0.95]	0.93 [0.86, 1.01]	0.98 [0.92, 1.04]	0.93 [0.85, 1.02]
Intussusception	0.87 [0.52, 1.46]	0.74 [0.38, 1.42]	0.98 [0.35, 2.74]	1.33 [0.35, 5.02]
Reactogenicity: fever	1.06 [0.97, 1.17]	1.15 [0.91, 1.45]	0.99 [0.93, 1.05]	0.26 [0.00, 31.46]
Reactogenicity: diarrhea	1.01 [0.88, 1.17]	1.12 [0.95, 1.31]	0.82 [0.58, 1.16]	0.90 [0.61, 1.30]
Reactogenicity: vomiting	1.03 [0.94, 1.12]	0.85 [0.64, 1.12]	0.93 [0.76, 1.13]	1.34 [0.70, 2.55]

Table 14. Summary of findings for rotavirus vaccine

Critical Outcomes	Basis (No. and Type of Studies, Total Participants)	Effect Size	95% CI	Interpretation	Certainty of Evidence
All-cause mortality	48 (n=209,967)	1.02	0.88 to 1.18	Inconclusive	Moderate
Severe RVGE	23 (n=82,690)	0.30	0.22 to 0.40	Benefit	Moderate
RVGE of any severity	18 (n=49,523)	0.46	0.37 to 0.57	Benefit	Moderate
Severe all-cause AGE	12 (n=49,335)	0.78	0.68 to 0.90	Benefit	Moderate
Serious adverse events	51 (n=206,072)	0.92	0.88 to 0.96	Benefit	High
Serious adverse event: Intussusception	43 (n=212,636)	0.87	0.61 to 1.25	Inconclusive	Moderate

AGE acute gastroenteritis; CI confidence interval; RVGE rotavirus gastroenteritis

Certainty of Evidence

Overall certainty of evidence was downgraded to moderate either due to issues in imprecision (i.e., wide confidence interval in all-cause mortality and intussusception) or inconsistency (i.e., I² was more than 50% in severe RVGE, RVGE of any severity, and severe all-cause AGE).

Recommendations from Other Groups

Rotavirus vaccination is recommended by the WHO and medical societies with no specific preference on the brand of the vaccine.

Table 15. Summary of other groups' recommendations for rotavirus vaccines

Group or Agency	Recommendation	Strength of Recommendation/ Certainty of Evidence
World Health Organization ¹⁴ (2021)	<p>Recommends that rotavirus vaccines should be included in all national immunization programs and considered a priority particularly in countries in South and Southeast Asia and sub-Saharan Africa.</p> <p>Recommends that the first dose of rotavirus vaccine be administered as soon as possible after 6 weeks of age, along with DTP vaccination.</p>	Not indicated
Centers for Disease Control and Prevention ¹² (2021)	<p>Recommends that infants receive rotavirus vaccine (either RotaTeq or Rotarix) to protect against rotavirus disease.</p> <p>The first dose of either vaccine should be given before a child is 15 weeks of age.</p> <p>Children should receive all doses of rotavirus vaccine before they turn 8 months old.</p>	Not indicated
Public Health England ¹³ (2021)	<p>All children should be offered vaccines to protect against rotavirus with their primary vaccines scheduled at 8 weeks and 12 weeks of age.</p> <p>Children should receive 2 doses of Rotarix vaccine, which is the vaccine offered as part of the UK national childhood vaccination programme, with an interval of at least 4 weeks between doses.</p> <p>Infants who have received their first dose of vaccine before 15 weeks of age (14 weeks and 6 days) can receive their second dose of Rotarix vaccine as long as it is given before 24 weeks of age (23 weeks and 6 days).</p> <p>It is preferable that the full course of 2 doses of Rotarix be completed before 16 weeks of age, but it must be completed by 24 weeks of age.</p>	Not indicated
Indian Academy of Pediatrics (IAP) Advisory Committee on Vaccines and Immunization Practices (ACVIP) ¹⁵ (2020)	<p>Any of the available rotavirus vaccines may be routinely administered as per the manufacturer's recommendations. All the available vaccines have been demonstrated to be safe and immunogenic.</p> <p>Minimum age: 6 weeks for all available brands</p> <p>Only two doses of RV-1 are recommended at 6 and 10 weeks</p> <p>If any dose in series was RV-5 or RV-116E or vaccine product is unknown for any dose in the series, a total of three doses of RV vaccine should be administered.</p> <p>Recommendations on the age limit for the first dose and the last dose (16 and 32 weeks) should</p>	Not indicated



	continue in spite of recommendation for increase in the age limit as per recent NIP guidelines.	
Pediatric Infectious Disease Society of the Philippines (PIDSP)/Philippine Pediatric Society (PPS) ¹⁶ (2023)	<p>Human (RV1)</p> <ul style="list-style-type: none">Given per orem (PO) as oral liquid formulationGiven as a 2-dose seriesGiven at a minimum age of 6 weeks with a minimum interval of 4 weeks between doses.The last dose should be administered not later than 24 weeks of age. <p>Human-Bovine live-attenuated reassortant (RV5) (oral liquid formulation)</p> <ul style="list-style-type: none">Given as a 3-dose seriesFirst dose is given at age 6-12 weeks, with a minimum interval of 4-10 weeks between doses.The last dose should not be administered beyond 32 weeks of age. <p>Human-Bovine live-attenuated reassortant (RV5) (oral freeze-dried formulation)</p> <ul style="list-style-type: none">Given as a 3-dose series, recommended at 2, 4 and 6 monthsGiven at minimum age 6 weeks with a minimum interval of 4 weeks between dosesThe last dose should not be administered beyond 12 months of age.	Not indicated
Department of Health (DOH)/Philippines Society for Microbiology and Infectious Diseases (PSMID) ¹⁷ (2019)	<p>Universal immunization of infants against rotavirus is recommended.</p> <p>Rotavirus vaccines are effective in preventing rotavirus diarrhea and rotavirus diarrhea-associated hospitalization.</p>	Strong recommendation, moderate quality of evidence

Ongoing Studies and Research Gaps

There are 17 ongoing trials on rotavirus vaccination registered in various clinical trial registry platforms. One trial is on Rotavac, one on Rotasil, and the rest are on rotavirus vaccines which are not prequalified by WHO at present.

Additional Considerations for Evidence-to-Decision (EtD) Phase

Cost

Three local studies on cost-effectiveness of universal rotavirus vaccination programs have been published. In 2014, Lee et al. reported that from a societal perspective, Rotarix would be cost-effective at PHP 12,835/quality adjusted life year (QALY) gained or USD 371/QALY (using 2012 exchange rate of PHP 34.60 per USD), equivalent to only 12% of the 2012 national GDP per capita.¹⁸

In 2015, Lam et al. found conflicting results and reported that Rotarix and RotaTeq would not be cost-effective at a cost of USD 13,184 and USD 11,836 per disability-adjusted life year (DALY) averted, respectively. The cost per DALY averted was four times the national GDP per capita. The authors concluded that for both vaccines to be cost-effective, they need to be

priced below USD 6 per fully immunized child (FIC) to generate a cost per DALY averted below the government cost-effectiveness threshold equal to the national GDP per capita.¹⁹

In 2021, Villanueva-Uy et al. reported that introducing any of the four WHO-prequalified rotavirus vaccines would avert around 40% of RVGE visits, hospitalization, and deaths over the period of 2021-2031. The cost-effectiveness of the least costly product (Rotavac) was USD 1,148 from a government perspective and USD 646 from a societal perspective. Rotasiil, Rotarix, and RotaTeq offered similar benefits but at higher costs from a government perspective of USD 1,162, USD 2,594 and USD 3,066 per DALY averted. All 4 vaccines' incremental cost-effectiveness ratio (ICER) were below the threshold of national GDP per capita of USD 3,485. The authors concluded that both Rotavac and Rotasiil would be cost-effective at a willingness-to-pay threshold set at 0.5 times the national GDP per capita. Rotarix and RotaTeq would need to be priced far more competitively to be considered for introduction, at around USD 2.50 and USD 1.12, respectively.²⁰

Table 16. Cost-effectiveness analysis of universal rotavirus vaccination program in the Philippines

	Incremental cost-effectiveness ratio (ICER)			
	Rotarix	RotaTeq	Rotasiil	Rotavac
Lee 2014 ¹⁸ Societal perspective Threshold: USD 2989	US \$371/QALY			
Lam 2015 ¹⁹ Societal perspective Threshold: USD 3134	USD 13,184/DALY	USD 11,836/DALY		
Villanueva-Uy 2021 ²⁰ Societal perspective Government perspective Threshold: USD 3485	USD 2,091/DALY USD 2,594/DALY	USD 2,563/DALY USD 3,066/DALY	USD 659/DALY USD 1,162/DALY	USD 646/DALY USD 1,148/DALY

DALY disability-adjusted life year; ICER incremental cost-effectiveness ratio; QALY quality adjusted life year; USD US dollar

Patient's Values and Preference, Equity, Acceptability, and Feasibility

Access to routine childhood vaccination will likely be unequally distributed, due to the country's archipelagic geography. The initial roll out of rotavirus vaccination in 2012 was limited to families who belonged to the lowest economic quintile and who received conditional cash transfer (CCT) from the government. Implementation proved to be difficult due to unequal distribution of these families throughout the country.

A local cross-sectional study evaluated the knowledge, attitude, and practices of mothers from a rural community in Pampanga toward childhood immunization from February-May 2019 (n=240). Results of the study showed that 67.50% of the mothers had a high level of knowledge and a positive attitude toward vaccination especially on the importance (96.30%), benefits (92.10%), and safety (95.30%) of immunization. Majority of the mothers also have good practices showing that 90.40% of them have children who are completely immunized, and 91.70% of them complied with the vaccination schedule. It is important to note that

majority (91.30%) availed of immunization services in their respective rural health units because of free vaccines and easy accessibility.²¹

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4.4. Should measles containing vaccines be given to apparently healthy children?

RECOMMENDATION

We recommend giving measles-containing vaccines among apparently healthy children starting at 9 months of age.
(strong recommendation, low certainty evidence)

Consensus Issues

The panel highly considered the significant effect of the measles vaccine in preventing the incidence of measles and its complications. Current evidence on the effectiveness of the vaccine, with moderate certainty of evidence, showed that the benefit outweighs the risk of harm. They also considered that measles outbreaks occur due to low measles vaccination uptake. The panel unanimously voted on a strong recommendation for the vaccine despite the overall low certainty of evidence.

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

Key Findings

A total of 8 cohort studies evaluated the effectiveness of measles-containing vaccines. A single dose resulted in an RR of 0.05 [95% CI 0.02 to 0.13]; 2 doses resulted in an RR of 0.04 [95% CI 0.01 to 0.28]. This translates to vaccine effectiveness of 95% and 96% for 1 dose and 2 doses, respectively.

Among the adverse events, patients given measles vaccine had significantly more incidence of rash (RR of 2.05, 95% CI 1.21 to 3.48) and elevated temperature taken either via axillary site (RR of 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). The results for the occurrence of other adverse events were inconclusive. The overall certainty of evidence was low due to high risk of bias (for attrition and reporting bias) and imprecision in critical outcomes.

Introduction

Measles is a highly contagious viral disease with a high burden of morbidity and mortality, particularly in children in low-income countries.¹ Before the introduction of the measles vaccine, measles infected over 90% of children by age 15, and led to over two million deaths annually.² In January and February 2022, almost 17,338 measles cases were reported worldwide, compared to 9,665 cases during the first two months of 2021.³ In the Philippines, a total of 425 cases have been reported from January 1 to September 24, 2022 with an incidence rate of 0.04 per 10,000. This is 185% increase compared to the same monitoring period in 2021 which reported 149 cases and had an incidence rate of 0.02 per 10,000 population.⁴

The severity of measles varies greatly depending on both host and environmental factors. Approximately one third of patients with measles have at least one immediate or delayed complication.⁵ Relatively common complications of measles include otitis media, croup, diarrhea, and pneumonia. The risk of developing severe or fatal measles increases for children aged <5 years, for persons living in overcrowded conditions, for the malnourished, especially those with vitamin A deficiency, and for those with immunological disorders, such as AIDS. Severe complications of measles include acute progressive encephalitis and a characteristic giant cell pneumonia.⁶

There is no specific treatment for measles. Case management of measles focuses on supportive care as well as the prevention and treatment of measles complications and secondary infections.^{6,7} With the introduction of the vaccine, measles endemicity has decreased.² From 2000 to 2018, measles vaccination prevented an estimated 23.2 million deaths. Global measles deaths have decreased by 73% from an estimated 536,000 in 2000 to 142,000 in 2018.⁸

Review Methods

A systematic search was done from 01 October 2022 until 21 December 2022 using MEDLINE, Cochrane Library, and Google Scholar with a combined MeSH and free text search using the terms: "measles vaccine, measles containing vaccine, children, randomized control trials." Cochrane risk of bias assessment criteria was used in evaluating the studies.

Only trials that compared measles vaccine against placebo were included in this review. Outcomes of interest included vaccine efficacy, adverse events, and cost effectiveness.

Results

Characteristics of Included Studies

The best available data evaluating vaccine efficacy came from 8 cohorts (n=12,039 for 1 dose and n=21,604 for 2 doses), which included healthy children vaccinated between the ages of 9 months and 21 years. Measles was given as an MMR vaccine in majority of the studies. One study included those that received MR vaccine,⁹ and two other studies had undeclared vaccine type of measles-containing vaccine.^{10,11}

Outcomes on efficacy were measured through clinical and/or laboratory confirmation of measles infection. There was no available data on mortality rates, immunogenicity, or complications of the disease in participants given the vaccine compared to those without vaccination.

There were 3 RCTs (n=2,265) used to evaluate short-term side effects or adverse events. These studies were done among children 11 months to 15 years old who received MMR vaccines. Adverse events were observed between 4 days to 6 weeks post vaccination.

Efficacy Outcomes

In a systematic review done by Di Pietrantonj in 2021,¹² a total of 8 cohort studies were used to assess vaccine effectiveness. Seven observational studies evaluated effectiveness after one dose of a measles containing vaccine resulting in an RR of 0.05 [95% CI 0.02 to 0.13] while 5 observational studies evaluated vaccine effectiveness of 2 doses resulting in an RR

of 0.04 [95% CI 0.01 to 0.28]. This translates to vaccine effectiveness of 95% and 96% for 1 dose and 2 doses, respectively.¹³

Table 17. Summary of findings for effectiveness of measles-containing vaccines

Critical Outcomes	Basis (No. and Type of Studies, Total Participants)	Effect Size	95% CI	Interpretation	Certainty of Evidence
Effectiveness against measles (Vaccinated vs. unvaccinated)	For 1 dose 7 observational studies (n=12,039)	RR 0.05	0.02 to 0.13	Benefit	Moderate
	For 2 doses 5 observational studies (n=21,604)	RR 0.04	0.01 to 0.28	Benefit	Moderate

CI confidence interval; RR relative risk

Safety Outcomes

In terms of vaccine safety, the best available evidence found were 3 randomized controlled trials from the systematic review evaluating short-term side effects, which included local or systemic reactions. Among the adverse events, patients given measles vaccine had significantly more incidence of rash (RR of 2.05, 95% CI 1.21 to 3.48) and elevated temperature taken either via axillary site (RR of 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). Other adverse events such as lymphadenopathy, coryza, URTI, and cough had inconclusive results.

Table 18. Summary of safety outcomes for measles-containing vaccines

Critical Outcomes	Basis (No. and Type of Studies, Total Participants)	Effect Size	95% CI	Interpretation	Certainty of Evidence
Rash	3 (n=1,156)	RR 2.05	1.21-3.48	Harm	High
Lymphadenopathy	3 (n=1,156)	RR 1.32	0.52-3.33	Inconclusive	Low
Coryza	2 (n=831)	RR 0.45	0.12-1.63	Inconclusive	Moderate
URTI	2 (n=831)	RR 0.31	0.06-1.56	Inconclusive	Moderate
Cough	2 (n=831)	RR 1.99	0.45-8.81	Inconclusive	Low
Temperature (fever)-Axillary	1 (n=420)	RR 2.04	1.09-3.83	Harm	Moderate
Temperature (fever)-Rectal	1 (n=170)	RR 0.84	0.67-1.06	Inconclusive	Moderate
Temperature (fever)-Site of measurement not reported	2 (n=520)	RR 1.36	1.04-1.81	Harm	Moderate

CI confidence interval; RR relative risk; URTI upper respiratory tract infection



Certainty of Evidence

Although cohort studies were used, the certainty of evidence for vaccine effectiveness was upgraded to moderate due to a large effect. However, the overall certainty of evidence was still rated as low due to high risk of bias (due to attrition and reporting bias) and imprecision in critical outcome of adverse events, specifically that of cough and lymphadenopathy.

Recommendations from Other Groups

Table 19. Summary of other groups' recommendations for measles-containing vaccines

Group	Recommendation	Strength of Recommendation/Quality of Evidence
World Health Organization ⁶ (2017)	<p>Recommended for all susceptible children and adults.</p> <p>Two (2) doses of measles vaccine should be the standard for all national immunization programs.</p> <p>Countries with ongoing transmission (high risk of mortality among infants):</p> <ul style="list-style-type: none"> ● MCV1 at 9 months of age. ● MCV2 at age 15-18 months. ● Minimum interval between MCV1 and MCV2 is 4 weeks. <p>Supplementary dose at 6 months:</p> <ol style="list-style-type: none"> 1. During measles outbreak 2. Endemic countries experiencing regular outbreaks 3. Internally displaced population and refugees, conflict zones 4. Infants at high risk of contracting measles (known contacts, increased exposure during outbreaks) 5. Infants traveling to countries experiencing outbreaks 6. HIV-exposed or HIV-infected infants 	Not indicated
Centers for Disease Control ¹⁶ (2021)	<p>Children should get 2 doses of measles, mumps, and rubella (MMR) vaccine:</p> <ul style="list-style-type: none"> ● 1st dose: 12-15 months ● 2nd dose: 4-6 years but can be given earlier as long as there is at least a 28-day interval from the 1st dose <p>For International travelers:</p> <ul style="list-style-type: none"> ● Infants 6-11 months: 1 dose should be given then 2 more doses, 1 dose at 12-15 months and the next dose at least 28 days after 	Not indicated
Green Book of Immunization, UK ¹⁴ (2019)	<p>As MMR vaccine (2 doses):</p> <ul style="list-style-type: none"> ● 1st dose: 12-13 months ● 2nd dose: from 18 months <p>If a dose of MMR is given prior to the 1st birthday, this dose should be ignored, and two further doses given at the recommended schedule between 12 and 13 months of age and at 3 years, 4 months to 5 years of age.</p> <p>Where protection against measles is urgently required, a second dose can be given from one month after the first. If the child is given the second dose at less than 15 months of age, a 3rd dose should be given after 18 months in order to ensure full protection</p>	Not indicated

Pediatric Infectious Disease Society of the Philippines ¹⁵ (2023)	<p>Measles-containing Vaccine:</p> <ul style="list-style-type: none"> Given at 9 months but can be given as early as 6 months in cases of outbreaks <p>MMR (2 doses):</p> <ul style="list-style-type: none"> 1st dose: Given at a minimum age of 12 months 2nd dose: Usually given at 4-6 years but may be given at an earlier age provided that the minimum interval from 1st dose is 4 weeks 	Not indicated
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HIV human immunodeficiency virus; MCV measles-containing vaccine; MMR measles, mumps, and rubella

Ongoing Studies and Research Gaps

Currently, there are no ongoing studies investigating the research question.

Additional Considerations for Evidence-to-Decision (EtD) Phase

Due to the controversies over the link between measles vaccine and other disease entities, other related adverse events were also evaluated. Unfortunately, studies involving these side effects were limited to cohorts or case control study designs.¹² While most of the adverse events (including autism, encephalitis and leukemia) had inconclusive results, patients given measles vaccine were found to have more incidence of purpura (idiopathic thrombocytopenic purpura and Henoch-Schoenlein purpura) and seizures.

Table 20. Summary of adverse events for measles-containing vaccines

Outcomes	Basis (Studies and Population)	Effect Estimate (95% CI)	Interpretation
Idiopathic thrombocytopenic purpura	2 case control/case cross over case control, 410 cases, 2040 control	OR 2.8 (1.5-5.23)	Harm
Henoch-Schoenlein purpura,	1 case control, 288 cases, 617 control	OR 3.4 (1.18-9.81)	Harm
Seizures within 1 week of MMR vaccine	2 cohort studies, 1,451,990	Rate Ratio 2.45 (2.21-2.71)	Harm
Seizures 1-2 week of MMR vaccine	2 cohort studies, 2,147,638	Rate Ratio 3.16 (2.89-3.46)	Harm
Encephalitis/encephalopathy	1 case control study, 452 cases, 1280 controls	OR 0.98 (0.64-1.5)	Inconclusive
Autism spectrum disorders	2 cohort studies, 1,194,764	Rate Ratio 0.93 (0.85-1.01)	Inconclusive
Inflammatory bowel disease	3 case control, 409 cases, 1416 control	OR 1.42 (0.93-2.16)	Inconclusive
Cognitive/developmental delay	1 cohort study at 24 th month, 337	OR 1.35 (0.15-1207)	Inconclusive
Asthma	3 cohort studies, 886	RR 0.63 (0.24-1.63)	Inconclusive

Dermatitis/eczema	1 cohort study, 555	RR 0.75 (0.29-1.94)	Inconclusive
Leukemia	2 case controls, 941 cases, 1667 controls	OR 0.97 (0.76-1.24)	Inconclusive
Demyelinating disease	1 case control, 272 cases, 1096 controls	OR 1.03 (0.44-2.42)	Inconclusive
Multiple sclerosis	1 case control, 206 cases, 888 controls	OR 1.13 (0.62-2.05)	Inconclusive

CI confidence interval; MMR measles, mumps, and rubella; OR odds ratio

Cost

No local study on the cost-effectiveness of measles vaccination is available. However, there exists a systematic review on cost-effectiveness and economic benefits of vaccines in low- and middle-income countries.¹⁷ Costs per disability-adjusted life year (DALY) averted for

measles vaccine ranged from USD 1.5/DALY to USD 240/DALY (PHP 82-13,128), with the highest cost reported in the Southeast Asian region.

The prices of the available measles-containing vaccines in the Philippines as of 2022 (ranging from PHP 430 to PHP 2,980) were also seen to be lower compared to the expenses incurred if a patient contracts measles and is admitted for complications associated with the disease such as pneumonia or meningitis (ranging from PHP 7,700 to PHP 25,700).¹⁸

Table 21. Price of measles-containing vaccine in the Philippines in 2022^a

	Monovalent Vaccine	MMR Vaccine	MMRV Vaccine
Unit Cost	PHP 430-440	PHP 670-1,350	PHP 2,900-2,980
No. of Doses Given	1 dose (given before 12 months)	2 doses	2 doses

MMR measles, mumps, and rubella; MMRV measles, mumps, rubella, and varicella

^aPrivate clinics/private companies as supplier

Table 22. 2022 PhilHealth coverage for measles¹⁸

Description	Medical Case Rate (in PHP)
Measles without complications	7,700.00
Measles with pneumonia	15,000.00
Measles with meningitis	25,700.00

Patient's Values and Preference, Equity, Acceptability, and Feasibility

The Philippine Expanded Program on Immunization (EPI) is one of the major programs of the Department of Health. It aims to provide Filipino children access to safe and effective vaccines that will protect them from common but deadly diseases like measles, diphtheria, tetanus, and pertussis. Though it has been in existence for over 40 years, the program has never achieved its target to fully immunize at least 95% of children. Based on a discussion paper¹⁹ assessing the status of EPI in the Philippines, several factors affect the immunization coverage in our country. This includes supply and demand factors, distribution, socio-economic factors, and even vaccine confidence. Routine immunization was primarily delivered by the public sector,

with 95% of the children receiving it in a public facility while more affluent households were more likely to get immunized in the private sector, especially for the later doses in a series. Children of mothers without education and with limited access to maternal healthcare services were also more likely to miss later doses in the vaccination series.

Vaccine coverage was improving after 2014, but vaccine confidence in the safety of vaccines plummeted to 66% in 2018 following the Dengvaxia controversy. While demand factors like vaccine confidence have contributed to the weak performance of the program, the sharp decline in immunization coverage is largely a result of deep-seated supply-side systems issues—ones related to leadership, planning, and the supply chain, which led to recurring vaccine stock outs in the past decade. Some solutions proposed to increase immunization coverage and timeliness include: (1) expanding private sector delivery channels, (2) improving planning of vaccine requirements (i.e., using actual headcounts and electronic immunization registries in estimating the actual need and monitoring coverage and timeliness of vaccination—instead of utilizing aggregate census), and (3) addressing supply-side constraints, particularly stock outs (e.g., doing a multi-year planning and procurement with local manufacturers; carefully interfacing with outside suppliers like UNICEF).

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4.5. Should mumps containing vaccines be given to apparently healthy children?

RECOMMENDATION

We suggest giving mumps-containing vaccines among apparently healthy children starting at 12 months of age.
(weak recommendation, low certainty evidence)

Consensus Issues

The panel incorporated mumps-containing vaccine in the recommendation since mumps is part of the measles, mumps, and rubella (MMR) vaccine. The burden of mumps infection is significant and the benefits of vaccination outweigh the risk of harm. However, some panelists believe that more high-quality studies on safety and cost-effectiveness are needed to make a strong recommendation.

Key Findings

There were 11 cohorts that investigated the efficacy of the mumps vaccine: 9 cohorts for the Jeryl Lynn strain (available in the Philippines) and 2 for unspecified or mixed mumps strain. Pooled results show that Jeryl Lynn-containing MMR vaccine significantly decreased the incidence of clinical mumps among children and adolescents by 72% after 1 dose (RR 0.28, 95% CI 0.13 to 0.62) and by 86% after 2 doses (RR 0.14, 95% CI 0.07 to 0.27). MMR vaccines whose strain was not specified or was mixed still significantly reduced mumps by 48% (RR 0.52, 95% CI 0.29 to 0.94).

There were 3 RCTs used to evaluate short-term side effects or adverse events. Among the adverse events, patients given mumps-containing vaccine had significantly more 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). The results for the occurrence of other adverse events were inconclusive.

The overall certainty of evidence was rated low due to serious risk of bias (due to attrition and reporting bias) and imprecision in critical outcomes (vaccine effectiveness and adverse events).



Introduction

Mumps (*parotitis epidemica*) is human viral infection, primarily affecting the salivary glands with peak incidence occurring among those aged 5–9 years.¹ Although the disease commonly presents as a mild infection characterized by pain and swelling of the parotid glands, it can cause serious complications including encephalitis, meningitis, orchitis, myocarditis, pancreatitis, and nephritis. Although mumps is a benign disease, often with complete recovery within a few weeks after being infected, long-term outcomes, such as seizures, cranial nerve palsies, hydrocephalus, and deafness, can occur.²

Worldwide, mumps is not as well-controlled as measles and rubella. From 1999-2019, approximately 500,000 mumps cases were reported to the World Health Organization (WHO) annually. Global mumps incidence is challenging to estimate as mumps is not a notifiable disease in many countries.³ This holds true in the Philippines where the Department of Health does not regularly monitor the statistics for the disease, unlike for measles. The most recent available data was for 2015, with 5 cases reported by the WHO.⁴

In the pre-vaccine era, mumps was a severe contagious disease with a high morbidity of approximately 40 to 726 cases per 100,000 population per year.³ Following mumps vaccine licensure in 1967 and ACIP recommendations for its use, reported cases of mumps steadily decreased from more than 152,000 cases in 1968 to 2,982 in 1985. A resurgence occurred in 1986-1987 with more than 20,000 reported mumps cases caused by low vaccination levels among adolescents and young adults. A second dose of MMR vaccine was recommended in 1989 which subsequently improved control. By the early 2000s, reported mumps cases declined to an average of less than 300 cases annually. Starting in 2006, there has been an increase in the number of mumps cases and outbreaks reported in the United States, mainly driven by outbreaks on college campuses, close-knit communities, and other congregate settings.²

Review Methods

A systematic search was done from 01 October 2022 until 21 December 2022 using MEDLINE, Cochrane Library, and Google Scholar with a combined MeSH and free text search using the terms: “mumps vaccine, children, randomized control trials.” Cochrane risk of bias assessment criteria was used in evaluating the studies. Only trials that compared mumps vaccine against placebo were included in this review. Outcomes of interest included vaccine efficacy, adverse events, and cost effectiveness.

Results

Characteristics of Included Studies

The best available data evaluating mumps vaccine efficacy came from 11 cohorts (n=9,915 for 1 dose, 7,792 for 2 doses, and 2,011 for an unspecified number of doses), which included healthy children vaccinated between the ages of 9 months and 17 years old. All the participants were given at least 1 dose of mumps vaccine in the form of the MMR vaccine. 9 cohorts used vaccines that were specific for the Jeryl Lynn strain while 2 had unspecified

mumps strain. Outcomes of efficacy were measured by either clinical or laboratory confirmed mumps. Most data came from vaccine registry or medical records.

There were 3 RCTs (n=2,265) used to evaluate short-term side effects or adverse events. Studies were composed of subjects vaccinated between 11 months and 15 years of age with a follow-up range of 4 days to 6 weeks post-vaccination.

Efficacy Outcomes

The study by Di Pietrantonj⁵ included evaluation of mumps-containing vaccines of different strains specifically, Jeryl Lynn, Urabe, and Rubini strains. Jeryl Lynn is the only locally available vaccine strain used in the Philippines. Based on 6 studies, Jeryl Lynn-containing MMR vaccine significantly decreased the incidence of clinical mumps among children and adolescents by 72% after 1 dose (6 studies, n=9,915, RR 0.28, 95% CI 0.13 to 0.62) and more

so (by 86%) after 2 doses (5 studies, n=7,792, RR 0.14, 95% CI 0.07 to 0.27). MMR vaccines whose strain was not specified or was mixed (not necessarily Jeryl Lynn-containing MMR vaccine) still significantly reduced mumps (2 studies, n = 769, RR 0.52, 95% CI 0.29 to 0.94) compared to those given placebo. No data on immunogenicity, mortality, or hospitalizations were found in those given the vaccine compared to placebo.

Table 23. Summary of effectiveness of mumps-containing vaccines

Outcomes	No. of Studies (No. of Participants)	RR (95% CI)	Certainty of Evidence
Effectiveness against mumps, Jeryl Lynn Strain	For 1 dose 6 cohort studies (n=9,915)	RR 0.28 (0.13 to 0.62)	Low
	For 2 doses 5 cohort studies (n=7,792)	RR 0.14 (0.07 to 0.27)	Low
	Unspecified number of doses 4 cohort studies (n=2,011)	RR 0.23 (0.14 to 0.35)	Low
Effectiveness against mumps, strain not specified/mixed	2 cohort studies (n=769)	RR 0.52 (0.29 to 0.94)	Very low

CI confidence interval; RR relative risk

Safety Outcomes

Since mumps as a monovalent vaccine is rarely used, the safety profile of the vaccine was assessed as part of the MMR vaccine. The systematic review by Di Pietrantonj⁵ was utilized to assess vaccine safety. Patients given the MMR vaccine had increased incidence of adverse events such as rash, elevated temperature taken either via axillary site and via unspecified site of measurement. Other adverse events such as lymphadenopathy, coryza, URTI and cough had inconclusive results.

Table 24. Summary of safety outcomes for mumps-containing vaccines

Outcomes	No. of Studies (No. of Participants)	RR (95% CI)	Certainty of Evidence

Rash	3 (n=1156)	2.05 (1.21-3.48)	High
Lymphadenopathy	3 (n=1156)	1.32 (0.52-3.33)	Low
Coryza	2 (n=831)	0.45 (0.12-1.63)	Moderate
URTI	2 (n=831)	0.31 (0.06-1.56)	Moderate
Cough	2 (n=831)	1.99(0.45-8.81)	Low
Temperature (fever)-Axillary	1 (n=420)	2.04 (1.09-3.83)	Moderate
Temperature (fever)-Rectal	1 (n=170)	0.84 (0.67-1.06)	Moderate
Temperature (fever)-Site of measurement not reported	2 (n=520)	1.36 (1.04-1.81)	Moderate

CI confidence interval; RR relative risk

Certainty of Evidence

The overall certainty of evidence was rated low due to serious risk of bias (due to attrition and reporting bias) in two critical outcomes (vaccine effectiveness and adverse events) and due to imprecision in one of the critical outcomes (adverse events).

Recommendations from Other Groups

Table 25. Summary of other groups' recommendations for mumps-containing vaccines

Group	Recommendation	Strength of Recommendation/Certainty of Evidence
World Health Organization ¹ (2007)	<p>Routine mumps vaccination is recommended in countries with a well-established, effective childhood vaccination program and the capacity to maintain high levels of vaccination coverage with routine measles and rubella vaccination (coverage >80%) and where the reduction of mumps incidence is a public health priority.</p> <p>Countries still using a 1-dose schedule of MMR are encouraged to add a routine second dose.</p> <ul style="list-style-type: none"> • 1st dose: 12-18 months • Minimum interval between the 1st and 2nd dose is 1 month 	Not indicated
Centers for Disease Control ⁸ (2021)	<p>Children should get 2 doses of MMR vaccine:</p> <ul style="list-style-type: none"> • 1st dose: 12-15 months • 2nd dose: 4-6 years but can be given earlier as long as there is at least a 28-day interval from the 1st dose 	Not indicated

Green Book of Immunization, UK ³ (2013)	<p>First dose of MMR should be given between 12 and 13 months. A second dose is normally given before school entry but can be given routinely at any time from 3 months after the first dose.</p> <ul style="list-style-type: none"> Allowing three months between doses is likely to maximize the response rate, particularly in young children under the age of 18 months where maternal antibodies may reduce the response to vaccination. If a dose of MMR is given before the first birthday, this dose should be ignored, and 2 further doses given at the recommended times between 12 and 13 months and at 3 years 4 months to 5 years of age. If the 2nd dose was given less than 3 months after the first dose and at less than 18 months of age, then the third dose should be given to ensure full protection. 	Not indicated
Pediatric Infectious Disease Society of the Philippines ⁷ (2023)	<p>To be given as part of the MMR vaccine (2 recommended doses):</p> <ul style="list-style-type: none"> 1st dose: Given at a minimum age of 12 months 2nd dose: Usually given at 4-6 years but may be given at an earlier age provided that the minimum interval from 1st dose is 4 weeks 	Not indicated

Ongoing Studies and Research Gaps

There are no current studies discussing the same research question.

Additional Considerations for Evidence-to-Decision (EtD) Phase

Cost

There is no locally available study on the cost-effectiveness of mumps vaccine. However, a recent study in Japan⁹ discussed the cost-effectiveness of the monovalent mumps vaccination program in their country. A monovalent vaccine was evaluated due to the unexpectedly high incidence of aseptic meningitis caused by mumps vaccine associated with the Urabe Am9 strain. This strain led to the discontinuation of the Japanese MMR vaccination program in 1993. This inadvertently resulted in the re-emergence of mumps. Introducing a monovalent mumps vaccine into routine vaccination schedules subsequently became one of the emerging topics in health policy.

Based on the study, cost per shot was ¥6,140 (PHP 2,575.36). This was lower than the estimated cost for mumps seen as outpatient consults at ¥10,187 (PHP 4,272.83) or treating mumps with complications such as meningitis (¥116,494 or PHP 48,862). The incremental cost-effectiveness appears to be below USD 47,170/QALY willingness-to-pay threshold (PHP 257,0977.27). Routine vaccination programs of single- and two-dose programs were also cost-effective from both payers' and societal perspectives. Between the two, the 2-dose vaccination program was observed to be more favorable.

However, monovalent vaccines are not available in the Philippines. The mumps vaccine dose that comes as part of the commercially-available MMR/MMRV vaccine in the Philippines uses

a different strain (Jeryl Lynn). This strain is also different from the one associated with adverse events from the Urabe Am9 strain. Table 26 shows the price of the mumps-containing vaccines available in the Philippines.

Table 26. Price of mumps-containing vaccine in the Philippines in 2022

	MMR Vaccine	MMRV Vaccine
Unit Cost	Php 670-1,350	Php 2,900-2,980
No. of Doses Given	2 doses	

MMR measles, mumps, and rubella; MMRV measles, mumps, rubella, and varicella

^aPrivate clinics/private companies as supplier

Adverse Events

Since mumps vaccine is given as MMR and there are controversies over the link between measles vaccine (one of the components of MMR) and other disease entities, other adverse events related to these were also evaluated. Unfortunately, studies involving these side effects were limited to cohorts or case control study designs.⁹ While most of the adverse events (including autism, encephalitis, and leukemia) had inconclusive results, patients given mumps vaccine (MMR) vaccine were found to have more incidence of purpura (idiopathic thrombocytopenic purpura and Henoch-Schoenlein purpura) and seizures.

Table 27. Summary of adverse events for mumps-containing vaccines

Outcomes	Basis (Studies and Population)	Effect Estimate (95% CI)	Interpretation
Idiopathic thrombocytopenic purpura	2 case control/case cross over case control, 410 cases, 2040 control	OR 2.8 (1.5-5.23)	Harm
Henoch-Schoenlein purpura	1 case control, 288 cases, 617 control	OR 3.4 (1.18-9.81)	Harm
Seizures within 1 week of MMR	2 cohort studies, 1,451,990	Rate Ratio 2.45 (2.21-2.71)	Harm
Seizures 1-2 weeks of MMR	2 cohort studies, 2147,638	Rate Ratio 3.16 (2.89- 3.46)	Harm
Encephalitis/encephalopathy	1 case control study, 452 cases, 1280 controls	OR 0.98 (0.64-1.5)	Inconclusive
Autism spectrum disorders	2 cohort studies, 1,194,764	Rate Ratio 0.93 (0.85-1.01)	Inconclusive
Inflammatory bowel disease	3 case control, 409 cases, 1416 control	OR 1.42 (0.93-2.16)	Inconclusive
Cognitive/developmental delay	1 cohort study at 24 th month, 337	OR 1.35 (0.15-1207)	Inconclusive
Asthma	3 cohort studies, 886	RR 0.63 (0.24-1.63)	Inconclusive
Dermatitis/eczema	1 cohort study, 555	RR 0.75 (0.29-1.94)	Inconclusive

Leukemia	2 case controls, 941 cases, 1667 controls	OR 0.97 (0.76-1.24)	Inconclusive
Demyelinating disease	1 case control, 272 cases, 1096 controls	OR 1.03 (0.44-2.42)	Inconclusive
Multiple sclerosis	1 case control, 206 cases, 888 controls	OR 1.13 (0.62-2.05)	Inconclusive

OR odds ratio; RR relative risk

Patient's Values and Preference, Equity, Acceptability, and Feasibility

The Philippine Expanded Program on Immunization (EPI) is one of the major programs of the Department of Health. It aims to provide Filipino children access to safe and effective vaccines that will protect them from common but deadly diseases like measles, diphtheria, tetanus, and whooping cough. Though it has been in existence for over 40 years, the program has never achieved its target to fully immunize at least 95% of children.

Based on a discussion paper¹⁰ on the assessment of EPI in the Philippines, several factors affect immunization coverage: supply and demand factors, distribution, socio-economic factors, and vaccine confidence. Routine immunization was primarily delivered by the public sector, with 95% of the children receiving it in a public facility. Richer households were more likely to get immunized in the private sector, especially for later doses in a series. Data also showed immunization coverage being slightly higher among the rich. Children of mothers without education and with limited access to maternal healthcare services were also more likely to miss later doses in the vaccination series.

Moving forward, focus should be placed on partnerships between health leaders and the local community, the engagement of multidisciplinary stakeholders, and proper planning in building vaccine infrastructure.¹¹

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4.6. Should varicella vaccine be recommended to apparently healthy children and adolescents?

RECOMMENDATIONS

1. We recommend giving varicella vaccine among healthy children and adolescents 12 months to 18 years old.
(strong recommendation, moderate certainty evidence)

2. We suggest giving two (2) doses of varicella vaccine among healthy children and adolescents 12 months to 18 years old.
(weak recommendation, low certainty evidence)

Consensus Issues

At present, varicella vaccine is not a priority vaccine due to: (1) its low prevalence in the country, (2) self-limiting nature of varicella disease, and (3) less occurrence of complications. However, current evidence shows that the benefits of vaccination far outweigh the risk of harm. The varicella vaccine is effective in decreasing the incidence of varicella—particularly for children who were given one dose of the vaccine.

For the varicella vaccine booster dose, the benefits outweigh the risks of its administration. However, some panelists believe that more high-quality studies on safety and cost-effectiveness are needed to make a strong recommendation.

It was noted that the panelists only considered the monovalent varicella vaccines in their decision-making.

Key Findings

7 RCTs that evaluated one dose of varicella vaccine compared to placebo or non-varicella containing vaccine were included. 4 RCTs were assessed to compare two doses of varicella vaccine to one dose.

In terms of vaccine efficacy, one dose of varicella vaccine significantly prevents the development of varicella disease compared to placebo or non-varicella-containing vaccine with high certainty of evidence. Those who have been vaccinated also mount a significant immune response compared to those who were not—as seen in higher geometric mean titers and rate of seroconversion with moderate certainty. For children and adolescents given two doses of varicella vaccine, there is a significant effect in terms of preventing development of varicella infection and higher immunogenicity (geometric mean titers) compared to those given one dose. Adverse events such as redness, swelling, and fever have been noted to occur more among those who receive the varicella vaccine. However, overall, there is no significant difference in the adverse events between those who were vaccinated and not.

The overall certainty of evidence was rated moderate for one dose of varicella vaccine. It was low for two doses of varicella vaccine due to issues in inconsistency and risk of bias.

Introduction

Primary varicella infection (chickenpox) is caused by the varicella zoster virus. It is considered a highly contagious childhood disease. In the global epidemiology data from 1990-2019,¹ the global incidence of varicella infection is at 83,963,744 with an average of 4 million varicella cases on an annual basis. In a systematic literature review on the burden of varicella disease in the Asia Pacific Region, Goh and colleagues² report that the annual incidence rate of varicella ranges from 17.8 to 2,530 per 100,000 population.

In the Philippines, the Department of Health (DOH) considers varicella infection as one of the notifiable diseases. In 2018,³ chickenpox was top 9 in the leading causes of morbidity in the National Capital Region (4,601 in 100,000 population, 34.2% rate), and top 5 in CALABARZON Region (4,869 in 100,000, 31.6%) and Central Visayas (979 in 100,000, 12.6%). It was also part of the top 10 notifiable diseases in the Ilocos region (1,313 in 100,000 population, 25.4%), Bicol (1,016 in 100,000 population, 16.9%), Davao (379 in 100,000 population, 7.4%) and Northern Mindanao (718 in 100,000 population, 14.7%).

Though there is no local data on varicella-related hospitalizations and mortalities, the global incidence of death cases due to varicella infection is 14,553.¹ The World Health Organization estimates 41-50 hospitalizations and 0.4-0.6 fatalities per million population.⁴

Because of the high burden of disease, the monovalent one dose varicella vaccine has been part of routine childhood immunizations in most countries by 1995. In the United States (US), there was a decrease of >70% in overall disease incidence in communities that had 80% varicella vaccine coverage in children between the ages of 19-35 months in a 5-year span.⁴ Through the disease surveillance system, the Centers for Disease Control and Prevention (CDC) also notes that overall incidence of varicella cases declined an average of 97% from pre-vaccine years among four states in the US.⁵

However, multiple varicella outbreaks—mostly in school-aged children—have been reported in different states despite one dose varicella vaccination. Concerns about breakthrough varicella and waning immunity of the one dose vaccine have paved the way for the booster dose to be added in the national immunization program in the US in 2006.⁵ During the 2-dose era, the National Notifiable Diseases Surveillance System of the US reported an 85% decline in varicella incidence from 2005-2006 to 2013-2014. The greatest declines were seen among children aged 5 to 14 years (85% to 89%).³

In the Asia Pacific, varicella vaccination has been included in publicly-funded childhood immunization programs of middle- to high-income countries such as Taiwan (one dose, January 2004), Australia (one dose, November 2005), Hong Kong (two doses, 2014), South Korea (one dose, January 2005), Japan (two doses, October 2014), and New Zealand (one dose, July 2017).² The commonly used varicella vaccines utilize the Oka strain with licensed brands such as Varivax (live monovalent), Varilrix (live monovalent), ProQuad (combination MMRV), Shingrix (inactivated recombinant varicella-zoster for adults), and Zostavax (live varicella-zoster vaccine for adults).

In the Philippines,⁶ the first dose of the varicella vaccine is recommended for children aged 12-15 months, with the second dose administered at age 4-6 years or at an earlier age provided the interval between the first and the second dose is at least 3 months. However, it is privately funded and not part of the national immunization program. This paper aims to review evidence on: (1) efficacy, immunogenicity, and safety of one dose monovalent varicella

vaccine on healthy children and adolescents, and (2) efficacy, immunogenicity, and safety of two doses monovalent varicella vaccine compared to one dose on healthy children and adolescents.

Review Methods

A systematic search was done from 01 October 2022 to 31 December 2022 using Pubmed Central, Pubmed MEDLINE, Google Scholar, and NIH *clinicaltrials.gov* website. A combined MeSH and free text search was done using the following keywords: “varicella vaccine, varicella immunization, chickenpox vaccine, chickenpox immunization.” The search was limited to children and adolescents (1-18 years old), randomized clinical trials, meta-analysis, and systematic reviews. Only studies using monovalent varicella vaccine and not combined preparations, and with comparators either a placebo or a non-varicella containing vaccine were included in this review. Outcomes of interest include vaccine efficacy, incidence of varicella disease, immunogenicity, rate of seroconversion, geometric mean titers, morbidity, hospitalizations, mortality, adverse events, and cost-effectiveness. The selected studies were assessed using the Cochrane risk of bias assessment criteria.

Results

Characteristics of Included Studies

There were a total of seven RCTs with 1 follow-up study¹⁰ in the evaluation of one dose monovalent varicella vaccine. A total of 9,504 participants were recruited with age groups ranging from 10 months to 14 years old. Four of the included studies compared the varicella vaccine to placebo,⁷⁻¹⁰ while the other three RCTs¹¹⁻¹³ used MMR (a non-varicella-containing vaccine) as a comparator. Two RCTs were conducted in the USA,^{7,10} 1 in Finland,⁸ 1 in Sweden,¹² 1 in France and Italy,¹³ 1 in China,⁹ and 1 is a local study from the Philippines.¹¹

For the two doses of varicella vaccine, there were four RCTs¹⁴⁻¹⁶ with one follow-up study¹⁷ with a total of 2,582 participants. Three studies were conducted in Philadelphia¹⁵⁻¹⁷ while 1 RCT was in Thailand.¹⁴ The age groups recruited in the three studies included children aged 12 months to 12 years old,¹⁵⁻¹⁷ another study¹⁴ consisted of children 13-29 years of age. The Oka vax/Varivax vaccine brand was used in three studies,¹⁵⁻¹⁷ while the Varilrix and Biden brands were used in 1 RCT.¹⁴

Outcomes measured after vaccination during the follow-up period of 30 days to 10 years were incidence of varicella disease (clinical and serologic diagnosis), immunogenicity measured by seroconversion (indirect fluorescent assay vs gpELISA) and geometric mean titers, and local and general adverse events.

Efficacy Outcomes

One dose of monovalent varicella vaccine compared to placebo/non-varicella containing vaccine

One dose monovalent varicella vaccine significantly reduces the risk of developing varicella disease (assessed through clinical and serologic diagnosis) compared to placebo or non-varicella-containing vaccine (RR 0.08, 95% CI 0.05 to 0.15, I²=20%). Three randomized controlled trials (RCT)⁷⁻⁹ and one follow-up¹⁰ study with a total of 7,556 participants were evaluated. All included studies considered the Oka strain varicella vaccine against placebo among participants 10 months old to 14 years old.

For immunogenicity, there was a significant increase in the number of participants who seroconverted among those receiving one dose of monovalent varicella vaccine compared to control (RR 51.68, 95% CI 33.26 to 80.30, $I^2=55\%$). Three of the included RCTs⁷⁻⁹ compared the Oka strain vaccine to placebo, while one local study¹¹ used MMR as the non-varicella-containing vaccine as control. The seroconversion was assessed using antibody measurement through indirect fluorescent assay or glycoprotein ELISA. The magnitude of effect for both outcomes of developing varicella disease and seroconversion across the four randomized controlled trials was noted to be very large with high certainty of evidence.

For the geometric mean titers, there was a significant increase among those receiving one dose of monovalent varicella vaccine compared to control (standard mean difference [SMD] 29.85, 95% CI 24.42 to 35.28, $I^2=92\%$). Two studies^{7,8} showed significant heterogeneity and wide confidence intervals probably due to the difference in baseline titers of the subjects recruited and the difference in duration of follow-up.

Table 28. Vaccine efficacy of one dose monovalent varicella vaccine versus placebo/non-varicella containing vaccine

Outcomes	No. of Studies (No. of Participants)	Effect Estimate (95% CI)	Interpretation	Certainty of Evidence
Incidence of varicella disease	4 RCTs (7,556)	RR 0.08 (95% CI 0.05 to 0.15)	Benefit	High
Immunogenicity				
Seroconversion	4 RCTs (2,113)	RR 51.68 (95% CI 33.26 to 80.3)	Benefit	High
Geometric mean titers	3 RCTs (1,922)	SMD 29.85 (95% CI 24.42 to 35.28)	Benefit	Moderate

CI confidence interval; RCT randomized controlled trial; RR relative risk; SMD standard mean difference

Two doses of monovalent varicella vaccine compared to one dose varicella vaccine

Two doses of monovalent varicella vaccine significantly reduced the risk of developing varicella disease compared to one dose varicella vaccine (RR 0.16, 95% CI 0.03 to 0.79, $I^2=78\%$). Two RCTs^{15,17} with 4,339 participants were evaluated; Oka/Merck strain of varicella vaccine was used.

For immunogenicity, there was a significant increase in the geometric mean titers (SMD 0.83, 95% CI 0.20 to 1.47, $I^2=98\%$) among those who received two doses of varicella vaccine compared to one dose in four RCTs¹⁴⁻¹⁷ including 2,807 participants. It should be noted that there was significant heterogeneity among the studies due to different brands of vaccine used, different scales used in measuring titers, and duration of follow-up.

There was no significant difference in the number of participants who seroconverted among those given two doses of varicella vaccine compared to one dose (RR 1.02, 95% CI 1.00 to 1.03, $I^2=28\%$). Four RCTs¹⁴⁻¹⁷ with 2,429 participants were evaluated.

Among the four studies evaluated, the recommended interval between the two doses was at least 4 weeks to 3 months.¹⁴⁻¹⁷

Table 29. Vaccine efficacy of two doses versus one dose of varicella vaccine

Outcomes	No. of Studies (No. of Participants)	Effect Estimate (95% CI)	Interpretation	Certainty of Evidence
Incidence of varicella disease	2 RCTs (4,339)	RR 0.16 (95% CI 0.03 to 0.79)	Benefit	High
Immunogenicity				
Seroconversion	4 RCTs (2,429)	RR 1.02 (95% CI 1.00 to 1.03)	Inconclusive	Moderate
Geometric mean titers	4 RCTs (2,807)	SMD 0.83 (95% CI 0.20 to 1.47)	Benefit	Low

CI confidence interval; RCT randomized controlled trial; RR relative risk; SMD standard mean difference

Safety Outcomes

One dose of monovalent varicella vaccine compared to placebo/non-varicella containing vaccine

Safety outcomes for one dose varicella vaccine were reported in four RCTs^{7,9,11,12} with a total of 7,446 participants. There was no significant difference in development of adverse events (RR 1.03, 95% CI 0.93 to 1.13, $I^2=58\%$) between those who received one dose varicella vaccine and those who received placebo or non-varicella-containing vaccines. On subgroup analysis, there was no significant increase in generalized symptoms such as fever (RR 0.94, 95% CI 0.83 to 1.05, $I^2=0\%$) among those given the one dose varicella vaccine. There was, however, a significant difference between the two groups in terms of local adverse events which includes local injection symptoms such as pain, swelling, and redness (RR 1.33, 95% CI 1.10 to 1.61, $I^2=23\%$) among those given varicella vaccine. Rash was described as local-site injection rash, varicella-like, and generalized nonspecific rash occurring in 1.2% in one study.¹³ It was generally not considered a significant adverse event associated with varicella vaccination in all included clinical trials.

In one of the clinical trials,⁹ one serious case of allergic purpura in the vaccine group was reported. But generally, no incidence of serious adverse events, such as hospitalization or mortality, was reported in the rest of the included studies.

Table 30. Vaccine safety for one dose monovalent varicella vaccine versus placebo/non-varicella containing vaccine

Outcomes	No. of Studies (No. of Participants)	RR (95% CI)	Interpretation	Certainty of Evidence
Adverse events	4 RCTs (7,446)	1.03 (0.93 to 1.13)	Inconclusive	Moderate
Local (pain and redness)	4 RCTs (7,446)	1.33 (1.10 to 1.61)	Harm	Moderate
General (fever)	3 RCTs (6,490)	0.94 (0.83 to 1.05)	Inconclusive	Moderate

CI confidence interval; RCT randomized controlled trial; RR relative risk

Two doses of monovalent varicella vaccine compared to one dose varicella vaccine

Two RCTs^{14,15} with conflicting results on adverse events of two doses of monovalent varicella vaccines have been reviewed but not pooled. Similar to studies on one dose, the most

common reported local adverse events of two doses varicella vaccination include pain, redness, and swelling of the injection site.¹⁴ For general adverse events, fever and rash have been cited for both studies.

In the RCT of Ngai and colleagues,¹⁵ the incidence of local injection symptoms after being given the second dose of varicella vaccine was significantly increased (n=414, RR 1.2, 95% CI 1.01 to 1.43), while the general symptoms after the booster were significantly decreased (n=3,042, RR 0.71, 95% CI 0.57 to 0.88). On the other hand, Kosuwon¹⁴ reported the opposite: local symptoms decreased (n=189, RR 0.70, 95% CI 0.61 to 0.81) while general symptoms increased (n=124, RR 0.29, 95% CI 0.22 to 0.37) after two doses of varicella vaccine. There were no noted hospitalization, serious adverse events, and mortalities in both studies.

Certainty of Evidence

The certainty of evidence for one dose varicella vaccine has been deemed moderate due to heterogeneity and inconsistency in the critical outcome of immunogenicity. There were noted differences in duration of follow-up (30 days to 6 years) and wide variance of baselines titers recruited.

For the two doses of varicella vaccine, certainty of evidence is low due to issues in heterogeneity from wide duration of follow-up (42 days to 10 years), different duration of spacing in between vaccine doses (6 weeks to 3 months), and high risk of bias in randomization, allocation concealment, and blinding.

Recommendations from Other Groups

Table 31. Summary of other groups' recommendations for varicella vaccines

Group	Recommendation	Strength of Recommendation/Certainty of Evidence
World Health Organization ⁴ (2014)	<p>First dose of varicella vaccine be administered at age 12 to 18 months and that the second dose (for countries with a two-dose schedule) be administered at the recommended minimum interval provided by the vaccine manufacturer (ranging from 4 weeks to 3 months).</p> <p>A 2-dose schedule is recommended for all persons aged \geq13 years.</p>	Strong recommendation
Centers for Disease Control ²⁰ (2021)	Children are routinely recommended to receive the first dose at age 12 through 15 months and the second dose at age 4 through 6 years old (or earlier provided >3 months have elapsed after the first dose).	Not indicated

	Persons aged >13 years should receive 2 doses of vaccine, doses (4--8 weeks apart).	
Philippines Pediatric Society/Pediatric Infectious Disease Society of the Philippines ⁶ (2022)	<p>The first dose of the vaccine is administered from age 12-15 months. The second dose of the varicella vaccine is administered at age 4-6 years or at an earlier age provided the interval between the first and the second dose is at least 3 months.</p> <p>For children \geq 13 years of age, the recommended minimum interval between doses is 4 weeks.</p>	Not indicated

Ongoing Studies and Research Gaps

Most meta-analyses and systematic reviews on varicella vaccines were observational studies (cohort and cross-sectional). RCTs have been dated back to the 1980s with emerging studies investigating new brands of varicella vaccines, ideal dose gradient, and the best spacing of doses. There are also ongoing clinical trials on the efficacy of measles, mumps, rubella, and varicella (MMRV) vaccines compared to monovalent varicella vaccine. This is because MMRV has been becoming a common part of immunization practices in other countries, but is still not part of national immunization programs.

Additional Considerations for Evidence-to-Decision (EtD) Phase

Cost

There are no available cost-effectiveness or cost-benefit studies about varicella vaccination in the country. It is also not included in the National Immunization Program; hence, it is only available through private funding. The range of cost of one dose monovalent varicella vaccine is summarized in Table 32.

Table 32. Price of varicella vaccine in the Philippines in 2022

	Varivax (MSD)	Varilrix (GSK)	VZ-VAX (Vizcarra)
Unit Cost	PHP 1,700-2,000	PHP 1,650-1,700	PHP 1,200-1,380

There was limited data on economic studies about varicella vaccine. However, a systematic review² from neighboring countries in the Asia Pacific region has shown that varicella vaccination programs were associated with an economic benefit per case prevented. Direct medical cost of USD 0.01 to 0.70 (PHP 0.55 to 39.10) was expected to return for every dollar (PHP 50.38) invested in the varicella vaccination program. The real benefit, however, was seen in societal costs with savings of USD 2.91 to 3.42 (PHP 161.87 to 190.56) for every dollar (PHP 50.38) invested.

A systematic review¹⁸ of 23 articles about the cost-effectiveness, cost-benefit, and cost-utility analysis of varicella vaccination has shown that immunization of infants and adolescents with varicella can save the society approximately €637,762 (PHP 35,982,532) to €53 million (PHP 2,992,260,000) annually.

Patient's Values and Preference, Equity, Acceptability, and Feasibility

One of the reasons of why many countries do not include varicella in their routine immunization programs might be due to a high cost of implementation for a perceived mild childhood disease.¹⁹ There is also apprehension that childhood varicella vaccination may increase the development of herpes zoster in the future. Subsequently, the disease incidence may shift to older population where the disease manifests more severely.¹⁹

Goh and colleagues² stated that “a pivotal factor that influences vaccine uptake, whether publicly or privately funded, is the perception of varicella and the need for vaccination.” This is supported by a study in China which claimed participants who had poor knowledge of varicella vaccine resulted in negative attitude and lesser acceptance of the intervention.²¹

A systematic review of Asia Pacific countries, including the Philippines, further shows that poor understanding of disease burden due to poor reporting and lack of awareness of varicella incidence in the country can contribute to the perception that varicella is less important than other diseases. This results in hesitancy of vaccine uptake.² Thus, this highlights the need for adequate monitoring and reporting of the varicella infection in the country to address the importance of varicella vaccination.

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4.7. Should BCG vaccine be routinely given at birth to healthy infants for the prevention of tuberculosis?

RECOMMENDATION

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

Consensus Issues

BCG vaccine is beneficial in decreasing tuberculosis-related mortality and latent tuberculosis infections. It also improves the clinical symptoms of tuberculosis, and is highly effective against meningeal and miliary tuberculosis.

Based on the available evidence, BCG vaccine is not significantly beneficial for pulmonary tuberculosis. However, the panel noted that the pathophysiology of tuberculosis usually starts in the lungs; extrapulmonary tuberculosis (e.g., meningeal and miliary tuberculosis) is a complication of pulmonary tuberculosis.

A universal BCG vaccination program was considered highly cost-effective in high-incidence countries like the Philippines. It is beneficial and outweighs the risk but more high-quality studies on efficacy, safety, and effectiveness are needed to make a strong recommendation.

Key Findings

4 systematic reviews investigated Bacille Calmette-Guérin (BCG) vaccination at birth for the prevention of tuberculosis (TB). From these systematic reviews, a total of 5 randomized controlled trials (RCTs) and 20 observational studies were used. Additional search conducted after the search date of these systematic reviews yielded two observational studies and two RCTs.

BCG vaccination was found to be effective against meningeal and miliary TB. It contributed to reduction of clinical symptoms of pulmonary TB, latent TB infection, TB-related mortality, and all-cause mortality. BCG vaccination, however, was not found to be effective against pulmonary TB—although with a trend towards benefit—and extrapulmonary TB.

The overall certainty of evidence was rated very low due to serious risk of selection, detection, confounding and recall bias, imprecision, and inconsistency.

Introduction

Globally, an estimated 10 million people developed TB in 2020, equivalent to 127 cases per 100,000 population.¹ The Philippines ranked fourth among high TB burden countries in the same year.² The estimated prevalence of TB in adults are as follows: smear-positive

pulmonary TB in ≥15 years: 434 per 100,000 (95% C.I. 350–518),
bacteriologically confirmed pulmonary TB in ≥15 years: 1,159 per 100,000 (95% C.I. 1,016–1,301).³ In children less than

15 years old, the incidence of tuberculosis has remained stable through the years. In 2015, 12.8% of all TB patients were children and adolescents 0 to 14 years.⁴ This has remained at 12.0% in 2019⁵ and 12.4% in 2020⁶, despite programs aimed at improving the diagnosis and treatment of childhood TB and latent TB infection (LTBI).

One strategy for the prevention of tuberculosis is BCG vaccination. The BCG vaccine is a live attenuated vaccine used to protect against disseminated forms of childhood TB, such as miliary TB and TB meningitis. The BCG vaccine was developed by two French scientists named Albert Calmette and Camille Guerin from 1905 to 1921. It was first used in humans in 1921. The BCG vaccine was recognized as safe, and its use was encouraged by health authorities in 1928.⁷ As such, most trials on the efficacy of the BCG vaccine were conducted several decades ago, prior to the development of modern standards for conducting and reporting clinical trials.⁸

Review Methods

A systematic search was done until 13 December 2022 using MEDLINE and Cochrane Library with a combined MeSH and free text search using the terms: “Bacille Calmette Guerin, BCG, tuberculosis, Mycobacterium, TB, child, neonate.”

Only RCTs that compared BCG vaccine against placebo or no vaccination were initially considered for this review. However, systematic reviews recovered also included cohort studies; thus, these were included when RCTs were not available. Outcomes of interest included incidence of TB disease, incidence of severe TB disease, immunogenicity, mortality, adverse events, and cost-effectiveness. For appraising risk of bias, the Cochrane risk of bias assessment criteria was used.

Results

Characteristics of Included Studies

There were 4 systematic reviews included, all of moderate quality using AMSTAR 2. Two systematic reviews included a total of five RCTs from Canada, USA, and India,^{8,9} and 2 systematic reviews included a total of 20 observational studies from Spain, Turkey, Cambodia, Greece, the UK, South Africa, Taiwan, Uganda, and Vietnam.^{10,11}

The RCTs included were conducted from 1938 to 1976, before standard methods for trial conduct and reporting were developed. Some aspects of trial design were not clearly reported, and methods of allocation to BCG or control do not guarantee concealment at recruitment or blinding of participants and trial personnel. In these RCTs, BCG was given at birth mostly via the intradermal route, although some were given BCG orally depending on the practice at the time the studies were conducted; different BCG vaccine strains were used.

The observational studies were retrospective cohort studies that identified BCG-vaccinated individuals through the presence of a BCG scar, medical records, and/or recall of vaccination. Exposure misclassification might occur if a scar did not form after vaccination, and some vaccinated children in various settings do not show a scar years after vaccine administration.¹⁰

Mangtani et al. conducted a systematic review and meta-analysis in 2014 on the efficacy of BCG vaccination against pulmonary and meningeal or miliary TB.⁹ This study included

randomized or quasi-randomized controlled trials that reported pulmonary, meningeal, or miliary TB outcomes. Studies included were conducted from 1933 to 1988. Out of 21 included studies, 5 RCTs analyzed the efficacy of BCG vaccination at birth against pulmonary TB, and 2 RCTs analyzed the efficacy of BCG at birth against meningeal or miliary TB.

Martinez et al. conducted a systematic review and meta-analysis in September 2022 on the effectiveness of BCG vaccination at birth in preventing extrapulmonary TB and all-cause mortality across age groups.¹⁰ This systematic review included published case-contact cohort studies of tuberculosis contacts between 01 January 1998 and 07 April 2018. Out of 26 included cohort studies, 14 studies analyzed the effectiveness of BCG vaccine against extrapulmonary TB, and 4 studies analyzed the effectiveness of BCG vaccine against all-cause mortality.

Roy et al. conducted a systematic review and meta-analysis in 2014 on the effectiveness of BCG vaccine against LTBI.¹¹ TB infection was defined as a positive interferon- γ release assay (IGRA) in close contacts of people with active TB. The literature search was conducted from 1950 to November 2013, and 6 cohort studies analyzed the effectiveness of BCG vaccine against LTBI.

Abubakar et al. conducted a systematic review and meta-analysis in September 2013 on the efficacy of BCG vaccination on mortality from TB⁸. The literature search was conducted from 1950 to May 2009 and included 5 RCTs that analyzed the efficacy of BCG vaccination on TB-related mortality.

A literature search conducted after the search date of these systematic reviews yielded two additional observational studies and two additional RCTs. A retrospective cohort study by Trollfors et al. analyzed the effectiveness of BCG vaccine against LTBI in 1,404 children.¹² A cross-sectional study by Farajnia et al. analyzed the effectiveness of BCG vaccine on pulmonary TB symptoms in 358 patients with pulmonary TB.¹³ The two additional RCTs by Dourado et al.¹⁴ and Richardus et al.¹⁵ assessed adverse events after one or two doses of BCG vaccine.

Outcomes measured include pulmonary TB (5 RCTs), extrapulmonary TB (14 observational studies), meningeal/miliary TB (2 RCTs), clinical symptoms of TB (1 observational study), latent TB infection (7 observational studies), TB-related mortality (5 RCTs), all-cause mortality (4 observational studies), and adverse events (2 RCTs).

Efficacy Outcomes

BCG vaccine against pulmonary TB

Pooled analysis of 5 RCTs (n=40,106) showed BCG vaccination at birth had no significant difference, although there is trend towards benefit, in protecting against pulmonary tuberculosis compared with no BCG vaccination (RR 0.54, 95% CI 0.29 to 1.00, I²=61%). Result shows significant heterogeneity.

It has been recognized that there is an association between geographic location and protective effect of BCG. A subgroup analysis of the 5 RCTs grouped by latitude showed that BCG vaccination significantly protected against pulmonary TB only among those at 40-50° latitude

(RR 0.34, 95% CI 0.21 to 0.54, $I^2=0\%$), but not among those at 10-20° latitude (RR 0.61, 95% CI 0.35 to 1.06) and at >50° latitude (RR 2.65, 95% CI 0.77 to 9.11). The Philippines belongs

to the 10-20° latitude, hence, the result of BCG vaccination against pulmonary disease is not significantly different.

BCG vaccine against extrapulmonary TB

Based on 14 cohort studies (n=56,183), BCG vaccination at birth is not protective against extrapulmonary tuberculosis (OR 1.10, 95% CI 0.76 to 1.59).

BCG vaccine against meningeal/miliary TB

Two RCTs specifically reviewed the effect of BCG vaccine against meningeal and miliary TB. Based on these two RCTs (n=6,653), BCG vaccination at birth significantly decreased meningeal and miliary tuberculosis compared to no BCG vaccine (RR 0.10, 95% CI 0.01 to 0.76, $I^2=0\%$).

BCG vaccine in improving clinical symptoms of PTB

A cross-sectional study done in Iran assessed the effectiveness of BCG vaccination on reducing the clinical symptoms of PTB. BCG vaccine showed a strong protective effect against acute TB based on clinical symptoms with an overall effectiveness of 95.5% (OR 0.045, 95% CI 0.011 to 0.193). This study involved 358 patients with active PTB from 6 months to 96 years old (mean 56.6 years) and evaluated 11 clinical symptoms, including cough, chest pain, dyspnea, sputum production, fever, hemoptysis, weight loss, loss of appetite, wheezing, weakness, and fatigue.

BCG vaccine against latent TB infection

BCG vaccine was found to be effective against LTBI compared to those not given the vaccine (RR 0.50, 95% CI 0.36 to 0.70, $I^2 =58\%$) based on 7 cohort studies (n=3,149). LTBI in these studies was diagnosed by IGRA or tuberculin skin test (TST).

BCG vaccine against TB-related and all-cause mortality

Pooled analysis of five RCTs (n=50,900) showed that BCG vaccination significantly protects against tuberculosis-related mortality (RR 0.34, 95% CI 0.12 to 0.92, $I^2=28\%$). Similarly, BCG vaccination is significantly protective against all-cause mortality for all ages (RR 0.19, 95% CI 0.11 to 0.35) based on 4 cohort studies (n=18,187).

Duration of protection

No RCTs were found that assessed the duration of protection of BCG vaccine.

Safety Outcomes

No studies directly assessed the adverse events and serious adverse events of BCG vaccine compared to placebo or non-BCG vaccine. However, two RCTs reported adverse events among older children given one dose vs. two doses of BCG vaccine, which showed no significant difference between the 2 regimens of BCG vaccination (RR 0.81, 95% CI, 0.48 to 1.37, $I^2=0\%$). The common reported adverse events were large ulcers measuring 10-35mm, axillary lymphadenopathy, and keloids. There were no reported serious adverse events in both studies.

Table 33. Summary of critical outcomes for BCG vaccine

Outcome	Basis (No. and type of studies, total participants)	Effect Size	95% CI	Interpretation	Certainty of Evidence
BCG vaccine against pulmonary TB	5 RCTs (40,106)	RR 0.54	0.29, 1.00	Trend towards benefit	Very low
BCG vaccine against extrapulmonary TB	14 cohort studies (56,183)	OR 1.10	0.76, 1.59	Inconclusive	Very low
BCG vaccine against meningeal/miliary TB	2 RCTs (6,653)	RR 0.10	0.01, 0.76	Benefit	Low
BCG vaccine in improving the clinical symptoms of PTB	1 cross-sectional study (358)	OR 0.045	0.011, 0.193	Benefit	Very low
BCG vaccine against latent TB infection	7 cohort studies (3,149)	OR 0.50	0.36, 0.70	Benefit	Very low
BCG vaccine against TB-related mortality	5 RCTs (56,169)	RR 0.34	0.12, 0.92	Benefit	Very low
BCG vaccine against all-cause mortality	4 cohort studies (18,175)	OR 0.19	0.11, 0.35	Benefit	Very low
Adverse events	2 RCTs (86,157)	RR 0.81	0.48, 1.37	Inconclusive	Very low

BCG Bacille Calmette-Guérin; CI confidence interval; OR odds ratio; PTB pulmonary tuberculosis; RCT randomized controlled trial; RR relative risk; TB tuberculosis

Certainty of Evidence

Of the 33 studies included in this review, 5 RCTs had overall high risk of selection and detection bias due to inadequate generation of randomized sequence and inadequate allocation concealment. Some observational studies had serious risk of selection, confounding, and recall bias.

The overall certainty of evidence was rated very low due to the serious risk of bias, indirectness, inconsistency, and imprecision across the different critical outcomes.

Recommendations from Other Groups

Table 34. Summary of other groups' recommendations for BCG vaccine

Group	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence

World Health Organization (WHO) ¹⁶ (2018)	<p>In countries with a high incidence of TB and/or a high leprosy burden, a single dose of BCG vaccine should be given to all healthy neonates at birth for prevention of TB and leprosy.</p> <p>If BCG vaccine cannot be given at birth, it should be given at the earliest opportunity thereafter, and should not be delayed in order to protect the child before exposure to infection occurs.</p>	Not indicated
US Centers for Disease Control (CDC) ¹⁷ (2011)	<p>BCG vaccination should only be considered for children who have a negative tuberculin skin test and who are continually exposed, and cannot be separated from, adults who are untreated or ineffectively treated for TB disease or have MDR TB.</p> <p>BCG vaccination of healthcare workers should be considered on an individual basis.</p>	Not indicated
European Centre for Disease Prevention and Control (eCDC) ¹⁸ (2014)	<p>Included in national childhood immunization programs in most high-burden countries in Europe, and is also administered to high-risk populations in non-endemic areas.</p> <p>In western Europe and other low-incidence regions, national BCG vaccination has been discontinued.</p>	Not indicated
Department of Health Philippines ¹⁹ (2021)	<p>BCG is given preferably 90 minutes after birth. Areas with high TB infection incidence should routinely immunize infants with a single dose of BCG at birth. If not given at birth, BCG may be given at the infant's first contact with the health system before turning one year old. BCG immunization of infants born of mothers positive for TB should be delayed and should be given one month after a negative PPD Test.</p>	Not indicated
Philippine Pediatric Society (PPS)/Pediatric Infectious Disease Society of the Philippines (PIDSP)/Philippine Foundation for Vaccination (PFV) ²⁰ (2023)	<p>BCG is given at the earliest possible age after birth preferably within the first 2 months of life.</p>	Not indicated

Ongoing Studies and Research Gaps

No other studies with the same clinical question are ongoing. However, clinical trials for new BCG vaccines are currently ongoing. In addition, 14 candidate TB vaccines are currently in different stages of clinical development from phase 1 to phase 3.²¹

Additional Considerations for Evidence-to-Decision (EtD) Phase

Cost

There are no local studies available on the cost-effectiveness of the BCG vaccine, but there are several foreign studies and a recently conducted systematic review which assessed the vaccine's cost-effectiveness.

Machlaurin et al. designed a modeling study in 2017 to assess the cost effectiveness of the BCG vaccination program of Indonesia.²² Comparing relevant parameters between Indonesia and the Philippines in the year 2017, the TB incidence in Indonesia was 319/100,000 while that in the Philippines was 554/100,000. The birth cohort in Indonesia was 4.9 million infants, while the birth cohort in the Philippines was 1.7 million infants. The GDP of Indonesia was USD 3,837.58 (PHP 241,900.00) while that of the Philippines was USD 3,123.25 (PHP 174,900.00).

In this modeling study, incremental cost-effectiveness ratios (ICERs) were evaluated from the healthcare (cost of vaccination and medical treatment) and societal (including loss of productivity) perspectives. A BCG vaccination strategy for the birth cohort costs approximately USD 57 million (PHP 3.2 billion) at an uptake level of 87%. Assuming protection for the first 10 years after birth, the vaccination strategy would yield 488,592 QALYs and would save around USD 55 million (PHP 3.1 billion) and USD 51 million (PHP 2.8 billion) from the

healthcare and societal perspective, respectively. The ICER from the healthcare perspective is USD 112.00 (PHP 6,272.00) per QALY, while the ICER from the societal perspective is USD 104.00 per QALY (PHP 5,824.00).

Machlaurin et al. also conducted a systematic review in 2019 comparing the outcomes of economic evaluation studies involving various BCG vaccination strategies (universal vaccination, selective vaccination, and revaccination) in various regions and target populations (high-, moderate- and low-incidence populations).²³ A universal BCG vaccination program was considered highly cost-effective in high-incidence countries at an ICER of USD 206.00 (PHP 11,536.00) (year 2001) per life-year gained, while ICER values were much higher in low-incidence countries and ranged from USD 36,000 to 175,000 (PHP 2.0M to 9.8M) (year 2002) per life-year gained. This study concluded that universal vaccination is the most cost-effective strategy in high-incidence countries, while in low-incidence countries, universal vaccination was less cost-effective than no vaccination or selective vaccination strategies.

Table 35. Price of BCG vaccine in the Philippines in 2022²⁴

BCG vaccine (20-dose preparation) ^a	Cost (in USD)	Cost (in PHP ^b)
Japan BCG Laboratory (Japan)	0.1870	10.50
Serum Institute of India	0.1205	6.70
AJ Vaccines (Denmark)	0.2825	15.80
BulBio-NCIPD (Bulgaria)	0.1005	5.60
GreenSignal Bio Pharma (India)	0.1050	5.90

BCG Bacille Calmette-Guérin

^a Awarded price per dose (in USD) per product per supplier per calendar year, based on a multi-year supply agreement with UNICEF.

^b Conversion rate: 1 USD = PHP 56.00

Patient's Values and Preference, Equity, Acceptability, and Feasibility

A study on the timeliness of childhood vaccination in the Philippines showed that only 28.1% of infants receive BCG at birth, and the median age of receipt of BCG vaccine is 2.7 weeks. Overall, around 75% of infants are vaccinated within 4 weeks after birth.²⁵

A significant difference in timely vaccination of infants was observed according to the frequency of immunization at the local health center (LHC). LHCs which conduct weekly immunizations had a higher percentage of timely BCG vaccination (69.7%) compared to those that vaccinate 2-3 times a month (6.1%) or once a month (24.3%). In terms of caregiver characteristics, having a female caregiver, a parent (as opposed to other relatives), a caregiver aged 25-34 years old, having 0-2 children, and having attended secondary school, all led to a higher percentage of timely vaccination of infants, but these were all not statistically significant.

One of the most cited reasons in the delay of BCG vaccination is the health worker's decision to open a new vial of BCG vaccine only when a minimum number of vaccinees is reached, due to cost reasons. This is despite national guidelines requiring health workers to open vials and vaccinate infants regardless of whether the minimum number of vaccinees is reached. A BCG multidose vial is only viable for 6 hours after reconstitution, and must be discarded if not used.

A mathematical modeling study conducted in Guinea-Bissau in West Africa assessed the potential effect of disregarding the restrictive vial-opening policy (a local practice of not opening a vial of BCG unless a sufficient number of children are present for vaccination) on TB-related and all-cause mortality in children 0-4 years old, and its cost-effectiveness.²⁶ The study compared the restrictive policy to a non-restrictive policy scenario where all children

were vaccinated in the first health facility contact. Results showed that disregarding the restrictive vial-opening policy was estimated to reduce TB deaths by 11% (95% uncertainty range UR 0.5%-28.8%) which corresponds to 4 (95% UR 0-15%) TB deaths averted per birth cohort. For all-cause mortality, the estimated reduction was 8.1% (95% UR 3.3%-12.7%) corresponding to 392 (95% UR 158-624) fewer deaths from all causes. In terms of cost, disregarding the restrictive vial-opening policy translated to higher BCG vaccination costs but lower household costs. For TB-specific effects, the incremental cost-effectiveness ratio (ICER) is USD 911.00 (PHP 51,016.00) per discounted life-year gained and USD 26,527.00 (PHP 1.5M) per discounted TB death averted. For all-cause effects, the ICER is USD 9.00 (PHP 504.00) per discounted life-year gained and USD 259.00 (PHP 14,504.00) per discounted all-cause mortality averted.

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4.8. Among children and adolescents who received complete Diphtheria, Pertussis, and Tetanus (DPT) primary immunizations, should tetanus toxoid-containing vaccines be given as a booster?

RECOMMENDATION

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.

(weak recommendation, low certainty evidence)

Consensus Issues

Tetanus toxoid-containing vaccine booster shows significant benefits: improved immunogenicity and increased seroprotection.

The need to give booster tetanus vaccination is evident, and benefits outweigh the risk of harm. However, the panelists believe that more high-quality evidence on efficacy, cost-effectiveness, equity, feasibility, and acceptability are needed to make a strong recommendation.

Key Findings

Only one RCT investigated the effect of tetanus toxoid-containing vaccine (TTCV) booster dose compared to placebo for children who already completed the primary immunization series for tetanus. TTCV booster doses show benefits in terms of increasing seroprotection and tetanus antibody mean geometric concentrations against tetanus 1-month post-booster vaccination compared to placebo. There were no serious adverse events that occurred in this study. There was no conclusive difference in terms of generalized adverse events and local adverse events experienced 15 days post-booster by those who received TTCV booster compared to controls. This was due to a wide confidence interval across all parameters.

The RCT had risk of bias (concerns with randomization and allocation concealment) and high risk of imprecision (failure to achieve optimum sample size for the study). This led to downgrading of evidence to low certainty of evidence for the TTCV booster dose seroprotection outcome. Additionally, imprecision and inconclusiveness of the effect estimates on general and local adverse event outcomes contributed to further downgrading the evidence of these safety outcomes to very low certainty of evidence.

Introduction

Non-neonatal tetanus remains the second most common vaccine preventable disease in the Philippines. A total of 583 cases were reported in 2021, with an incidence rate of 5.29 per 100,000, and a case fatality rate of 19%.¹ A five-year retrospective study done in a public tertiary hospital in the Philippines showed that 40% of patients who acquired tetanus belonged to the 6-10-year age group. This was followed by the 11-18-year age group (32%) and 2-5-

year age group (32%), with no reported cases in patients aged 1 month to 1 year old.² Only 22.2-52% of Filipino children with tetanus completed the primary series.^{2,3}

Tetanus is caused by *Clostridium tetani*, an anaerobic bacterium whose spores are found in the environment. It releases tetanospasmin, a neurotoxin which inhibits the release of gamma-aminobutyric acid (GABA) and glycine, causing unregulated excitatory responses in the nervous system. Treatment of tetanus generally involves administration of tetanus antitoxin and intensive care.⁴ Unlike other vaccine preventable diseases, tetanus is not transmitted from person-to-person, and natural immunity after acquiring disease does not occur.

After the implementation of the Expanded Program on Immunization (EPI) by the World Health Organization (WHO), tetanus vaccination became part of the routine immunization program of the Philippines in 1976.⁵ Currently, there are 20 tetanus toxoid-containing vaccines (TTCV) available in the Philippines (see Table 36).

Table 36. Tetanus toxoid-containing vaccines (TTCV) available in the Philippines

Vaccine Components		Brand Name	Manufacturer
Tetanus toxoid	TT (4)	<i>Abhay-TOX</i>	Human Biologicals Institute (A Division of Indian Immunologicals Limited)
		<i>T-Vac</i>	Serum Institute of India Ltd.
		<i>IMATET</i>	Amson Vaccines & Pharma Pvt. Ltd.
		<i>Bio-Tt</i>	P.T. Biofarma
Diphtheria, Tetanus Toxoid	DT (1)	<i>Ditevac</i>	Serum Institute of India Ltd.
	Td (2)	<i>BE Td</i>	Biological E. Limited
		<i>SII TD-VAC</i>	Serum Institute of India Pvt. Ltd.
Diphtheria, Tetanus Toxoid, Pertussis	DTP (1)	<i>Perdinus</i>	Serum Institute of India Private Limited
Diphtheria, Tetanus Toxoid, Acellular Pertussis, Inactivated Poliomyelitis	DTaP-IPV (1)	<i>Tetrarixim</i>	Sanofi Pasteur
Diphtheria, Tetanus, Acellular Pertussis, Inactivated Poliomyelitis, <i>Haemophilus influenzae</i> Type B	DTaP-IPV-Hib (2)	<i>Pentaxim</i>	Sanofi Pasteur
		<i>Infanrix-IPV+Hib</i>	GlaxoSmithKline Biologicals SA
Diphtheria, Tetanus, Whole Cell Pertussis, Recombinant DNA Hepatitis B, <i>Haemophilus influenzae</i> Type B Conjugate	DTwP-HepB-Hib (4)	<i>EUPENTA</i>	LG Chem Limited
		<i>Combe Five</i>	Biological E. Limited
		<i>Shan 5</i>	Shantha Biotechnics Limited
		<i>Easyfive TT</i>	Panacea Biotec Limited (Vaccine Division)

Diphtheria, Tetanus, Whole Cell Pertussis, Recombinant DNA Hepatitis B, Inactivated Poliomyelitis, <i>Haemophilus influenzae</i> Type B Conjugate	DTaP-HepB-IPV-Hib (2)	<i>Infanrix Hexa</i>	GlaxoSmithKline Biologicals SA
		<i>Hexaxim</i>	Sanofi Pasteur
Tetanus Toxoid, Diphtheria, Acellular Pertussis	Tdap (2)	<i>Boostrix</i>	GlaxoSmithKline Biologicals S.A.
		<i>Adacel</i>	Sanofi Pasteur Limited - Ontario, Canada
Tetanus Toxoid, Diphtheria, Acellular Pertussis, Inactivated Poliomyelitis	Tdap-IPV (1)	<i>Boostrix Polio</i>	GlaxoSmithKline Biologicals SA

The accepted seroprotective level of circulating anti-tetanus antibodies is at least 0.1 IU/mL using standard enzyme-linked immunosorbent assays (ELISA) or 0.01 IU/ml using modified ELISAs, in vivo neutralization tests, or bead-based immunofluorescence assays. However, evidence supporting this value is limited, as there have been cases of tetanus occurrence

despite achievement of protective levels in the blood. Hence, the goal of tetanus immunization is to maintain high levels of anti-tetanus antibodies to ensure protection.^{4,6}

Review Methods

A systematic search was initially conducted on 22 October 2022 and updated last 15 February 2023 using MEDLINE, Cochrane Library, and HERDIN with a combined MeSH and free text search using the terms: "tetanus, booster, vaccination." A total of 1,550 unique results was yielded.

Only randomized controlled trials that compared tetanus toxoid-containing vaccine (TTCV) as a booster against placebo or no booster for children and adolescents who received complete DPT primary series were included in this review. Outcomes of interest include vaccine efficacy, immunogenicity, vaccine timing, adverse events, and cost-effectiveness. Cochrane risk of bias assessment criteria were used to appraise all included studies

Results

Characteristics of Included Studies

Only one randomized controlled trial comparing TTCV (intervention) booster with Hepatitis A vaccine (control) was found fulfilling the search criteria. This phase IIIb, partially blind, randomized controlled trial from Australia⁷ recruited forty-eight (n=48) children 18-20 months of age with no comorbidities who had completed primary vaccination with three doses of DTaP (InfanrixTM) at 2, 4, and 6 months.

The study randomized subjects into the intervention group (a booster dose of DTaP or a booster dose of Tdap) or the control group (a booster dose of Hepatitis A vaccine/HAV). The DTaP (InfanrixTM) vaccine and Tdap (BoostrixTM) vaccine contained ≥ 40 IU and ≥ 20 IU

tetanus toxoid, respectively. The HAV (Havrix Junior) contained 720 ELISA units of inactivated hepatitis A antigen. All vaccines were administered intramuscularly into the left deltoid.

Outcome measurements included assessments of immunogenicity via collection of blood samples prior to and 1 month after the booster dose, in which antibody concentrations were measured by standard ELISAs. Protective anti-tetanus antibody levels must be ≥ 0.1 IU/mL. Assessments of reactogenicity (local and generalized adverse events) were assessed using diary cards for 15 days (Day 0-14) after booster vaccination. The characteristics of this included study are summarized in Appendix A.

Efficacy Outcomes

Prevention of morbidity and mortality

There were no randomized controlled trials found comparing the effect of TTCV as boosters versus placebo in the prevention of tetanus morbidity (including hospitalization) and mortality.

Immunogenicity

The included RCT in this review (n=48) showed that all participants given anti-tetanus boosters achieved seroprotective levels ≥ 0.1 IU/mL. The booster vaccine significantly

increased the number of participants who seroconverted compared to those who received placebo (RR 1.46, 95% CI 1.05 to 2.03, p=0.03). Apart from the seroprotection rate, anti-tetanus geometric mean concentrations (GMCs) of the intervention groups also significantly increased compared to controls (MD 4.87, 95% CI 3.77 to 5.97, p<0.001).⁷

Additionally, immunogenicity and seroprotection with a TTCV booster dose after the 3-dose primary series were adequately described in several trials without control groups.⁸⁻¹⁸ Booster schedules vary throughout the studies, with as early as 15 months of age¹³ or as late as 27 months of age.⁹ The usual vaccination age for the rest of the studies was set at 18 months of age. At least 1-month post-booster vaccination, 95.5%¹⁸ to 100%⁹⁻¹⁷ of the infants were found to be seroprotected from a pre-booster rate of as low as 70.9%.¹⁴ All studies that measured anti-tetanus antibody titers in geometric mean concentrations were found to have increased well beyond the 0.1 IU/mL protective cutoff after booster vaccination.^{8,10,13,14,16-18}

Timing of booster vaccination

No randomized controlled trials investigated the timing of tetanus boosters among patients who completed the primary series.

Safety Outcomes

Only one RCT (n=48) reported safety outcomes and no serious adverse events occurred in all the groups (DTaP, Tdap, HAV). For the adverse events, the results were inconclusive in terms of general (RR 1.75, 95% CI 0.41 to 7.48, p=0.45) and local adverse events (RR 3.00, 95% CI 0.39 to 22.85, p=0.29) compared to placebo.⁷

General symptoms reported in the intervention group compared to control group from day 0-14 post-booster were drowsiness (RR 1.83, 95% CI 0.59 to 5.66, p=0.29), irritability (RR 1.25, 95% CI 0.71 to 2.19, p=0.43), loss of appetite (RR 1.00, 95% CI 0.46 to 2.17, p=1.00), and fever (RR 0.63, 95% CI 0.19 to 2.01, p=0.43).⁷

All participants reported local symptoms from day 0-14 post-booster, and those who received tetanus boosters were not significantly different from those who received placebo. Symptoms reported included redness (RR 1.56, 95% CI 0.93 to 2.64, p=0.09), swelling (RR 1.67, 95% CI 0.84 to 3.31, p = 0.15) and pain (RR 1.25, 95% CI 0.60 to 2.60, p = 0.55).⁷

Table 37. Benefits and harms of tetanus toxoid-containing vaccine booster vs. placebo for infants who completed a 3-dose primary series

Critical Outcomes	Basis (No. and type of studies, total participants)	Effect Size	95% CI	Interpretation	Certainty of Evidence
Seroprotection/Immunogenicity	1 RCT (n = 48)	RR 1.46	1.05, 2.03	Benefit	Low
Serious Adverse Events	1 RCT (n = 48)		There were no serious adverse events noted for all participants in this study.		Low

CI confidence interval; RCT randomized controlled trial; RR relative risk

Certainty of Evidence

The included study in this review had some concerns in biases arising from the randomization process due to insufficient details regarding the study randomization and allocation concealment. The optimal sample size for this study was not met because of the premature discontinuation of the study due to local policy changes in vaccination. Hence, this RCT was deemed to have a serious risk of bias and imprecision, thereby downgrading the certainty of evidence for the critical outcomes of immunogenicity and serious adverse events to low.

Recommendations from Other Groups

A clinical practice guideline for the prevention of pertussis, tetanus, and diphtheria with vaccines was published by the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP) in 2018.¹⁹ This was updated in 2020 to include the ACIP's recommendations on the use of Tdap as booster in adolescents and adults.²⁰ Likewise, the WHO released a position paper on the use of tetanus vaccines in 2017.²¹ All groups recommend a three-dose primary series during infancy, followed by periodic booster doses as early as 12 months old. In the Philippines, a fully immunized child is considered to have 5 doses of DTP, or 4 doses of DTP if the 4th dose was given on or after the 4th birthday.

Table 38. Summary of other groups' recommendations for tetanus toxoid-containing vaccine booster dose

Group	Recommendations	Strength of Recommendation/Certainty of Evidence
World Health Organization ²¹	<p>Primary series: 3 doses of TTCV</p> <ul style="list-style-type: none"> • First dose is administered from 6 weeks of age, with a minimum interval of 4 weeks for the succeeding 2 doses <p>Booster doses:</p>	Not indicated

	Given at 12-23 months of age, 4-7 years of age, and 9-15 of age, with at least 4 years between booster doses	
Centers for Disease Control and Prevention ²⁰	<p>Primary series: 3 doses given at ages 2, 4, and 6 months</p> <p>Booster doses: Given at 15-18 months, 4-6 years, and 11-12 years, then 1 booster dose of either Td or Tdap every 10 years throughout life</p>	Not indicated
Canadian Immunization Guide ²²	<p>Primary series: 3 doses given at 2, 4, and 6 months old</p> <p>Booster doses: Given at 12-23 months, 4-6 years old, and 14-16 years old</p>	Not indicated
Pediatric Infectious Diseases Society of the Philippines ²³	<p>Primary series: 3 doses given at 6-10-14 weeks old</p> <p>Booster doses: Given at 12-18 months, 4-6 years, and 7-10 years, then every 10 years (Td/Tdap)</p>	Not indicated

Ongoing Studies and Research Gaps

No ongoing studies are investigating the effects of TTV booster dose in comparison with placebo or no booster vaccination. More local studies that investigate the efficacy, timing, cost-effectiveness, and harms of administering booster doses are needed.

The rationale for timing the tetanus booster vaccination is to maintain the seroprotective status of the child during school age, adolescence, and throughout adulthood. The goal of protecting women through their childbearing years is key to supporting maternal and neonatal tetanus

elimination (MNTE).⁴ Research gaps include the determination of the duration of immunity following tetanus booster vaccination to properly guide policy on booster dose timing. Additionally, data involving the duration of immunity following the Expanded Program of Immunization (EPI) schedule are difficult to interpret, especially since limitations involve study designs (cross-sectional), type of assay performed, appropriateness of data analyses, and documentation of ages at vaccination or duration since last vaccination.⁴

Another area of contention is the uncertainty regarding the need for routine tetanus booster doses every 10 years due to the lack of appropriate evidence to base policy. Modeling studies have determined that there is a constant decline in the anti-tetanus antibody levels over time.²⁴⁻²⁶ Compared to other vaccines such as measles, diphtheria, rubella, mumps and varicella, the level of protection from tetanus in the absence of boosting declines the fastest at a rate of 6.2% per year.²⁴ Based on modeling studies, the duration of immunity from primary vaccination is 5 years. Administering a booster at 5 years old after primary vaccination results in protective anti-tetanus levels that last for 21 years.²⁵ In another study that compared the

duration of immunity of Td5ap-IPV, Td5ap-OPV, and DT2aP-IPV, 69-86% of children maintain protective levels of anti-tetanus antibody levels 9 years after the administration pre-school tetanus booster.²⁶ Although studies illustrate the behavior of tetanus antibody titers and immune persistence, further research is needed to determine if clinical implications will become evident if the titers decline.⁴

Additional Considerations for Evidence-to-Decision (EtD) Phase

Cost

There were no local studies done on the cost-effectiveness of tetanus boosters. In the United States, a study done in 2009 illustrated the economic impact of five doses of DTaP in a hypothetical cohort of 4,261,494 children. With the assumption that there was a 100% probability of hospitalization in non-neonatal tetanus, an average hospital stay will be 16.7 days, with the cost of each hospitalization estimated to be at USD 90,635 (approximately PHP 4.1 million). Through vaccinating one cohort with 5 doses of DTaP, 169 cases and 25 deaths from tetanus could be prevented. From an economic standpoint, direct costs of USD 12 million (approximately PHP 556 million) and societal costs of USD 45 million (approximately PHP 2.1 billion) could be saved.²⁷ An unpublished study done in a public tertiary hospital evaluated the cost of tetanus admission in the Philippines from 2019 to 2021. The total cost of tetanus management for 9 pediatric patients amounted to PHP 3,229,337, for which medications comprised the bulk of the treatment cost.³ Tetanus immunoglobulin, the mainstay of treatment, retails for PHP 768.9 per 250 IU/ml vial. The recommended treatment dose for tetanus of 500-3000 IU would amount to an additional PHP 1,537.8-4,613.4 in the management of tetanus.²⁸

Table 39. Price of tetanus toxoid-containing vaccines in the Philippines in 2022

	Vaccine Type					
	DTP-HepB-Hib	DTaP-IPV	DTaP-IPV-HepB-Hib	DTaP	Tdap	Tetanus toxoid
Unit Cost	PHP 59.4 – 2,300 per dose	PHP 1,650	PHP 2,200 – 2,300	PHP 1,200	PHP 1,200	PHP 29.22 – 90 per dose

Patient's Values and Preference, Equity, Acceptability, and Feasibility

There are no studies on the acceptability, values, and preference of tetanus booster vaccination in the Philippines. For the primary series, the World Health Organization estimated

the vaccine coverage of the 3rd dose of DTP-containing vaccine at 57% in 2021. The immunization coverage for this vaccine has declined over the years since 2017, during which immunization coverage of 80% was already achieved. Reasons for decreasing immunization coverage included limitations in financial and human resources, lower demand for routine immunization, and vaccine hesitancy brought about by the dengue vaccine issue.²⁹

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4.9. Should Hepatitis B vaccine booster dose be given among children and adolescents who completed a 3-dose primary vaccination series during infancy?

RECOMMENDATION

We suggest giving Hepatitis B vaccine booster to healthy children and adolescents who completed at least a 3-dose primary vaccination series but did not seroconvert.

(weak recommendation, very low certainty evidence)

Consensus Issues:

Children and adolescents who completed the 3-dose primary vaccination of hepatitis B generally have acceptable immunogenicity and high efficacy against infection. However, there are some who do not seroconvert despite being given a 3-dose primary series. Hepatitis B vaccine booster is thus suggested among the population of healthy children and adolescents who did not seroconvert.

The panelists believe that more high-quality evidence on cost-effectiveness, equity, acceptability, and feasibility in the context of giving extra doses of hepatitis B vaccine are needed to make a strong recommendation.

Key Findings

There were 4 RCTs that studied the effect of administering 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, hepatitis B booster had a significant effect in preventing all-cause mortality and primary liver cancer. Hepatitis B booster also showed a significant conversion to HBsAg seropositivity. Pooled analysis of 4 RCTs showed that the hepatitis B booster had no conclusive benefit in increasing HBV seroprotection and anti-HBc seropositivity. There were no adverse events reported.

The overall certainty of evidence is very low because of serious risks of bias due to issues in the randomization process, allocation concealment, and missing outcome data. Inconsistency and imprecision were also noted in one critical outcome (HBV seroprotection).

Introduction

Hepatitis B virus (HBV) infection affects 350 million people globally and contributes to an estimated 780,000 deaths worldwide each year.^{1,2} Over the last five decades, it has shown high endemicity in low-income countries such as the Philippines.³ An estimated 7.3 million Filipinos (16.7% HBsAg seroprevalence) are chronically infected by the Hepatitis B virus, making the country hyperendemic to HBV.⁴ In a local cross-sectional study published in 2014, adult hepatocellular carcinoma cases (HCC) from a liver tumor registry in a general hospital in the Philippines were found to have a prevalence rate of 7.8%. The most common risk factor for HCC development was chronic hepatitis B infection, and the overall mortality rate for this

study was marked at 25%.⁵ The Department of Health noted that there was a 58.3% increase in viral hepatitis cases in the first three quarters of 2022 compared to 2021.⁶

Children in all phases of HBV infection should undergo regular monitoring to monitor for disease progression and hepatic decompensation. In view of chronic infection, development of liver cirrhosis and hepatocellular carcinoma should be of key concern in HBV surveillance.⁷ Acute HBV infection in children is generally managed supportively, with increases in severity requiring appropriate antiviral therapy. In terms of prevention, hepatitis B vaccination has been integrated into the routine childhood immunization program of the Philippines since 1992. A dose is given upon birth, followed by a vaccination series at 6 weeks, 10 weeks, and 14 weeks of age.⁸⁻⁹

Although hepatitis B vaccination provides high protective efficacy against infection, determining the duration of its protection remains elusive. Previously published studies state that protection against breakthrough HBV infection and chronic carriage can be achieved for as long as 15 years,¹⁰⁻¹¹ but some studies show that immune memory may wane by this time.¹²⁻¹⁵

Review Methods

A systematic search was done on 30 September 2022 and repeated on 18 February 2023, where relevant studies starting from 1972 were identified from multiple databases (MEDLINE, Cochrane Library) using the terms: “Hepatitis B vaccines, booster, immunogenicity, seropositivity, cost-benefit analysis, cost utility, cost effectiveness.”

Only randomized controlled trials that compared giving a booster dose of hepatitis B versus placebo or non-hepatitis B containing vaccines were included. Outcomes of interest were immunogenicity (Anti-HBs titers at least 10mIU/mL), HBV DNA seropositivity, anti-HBc seropositivity, HBsAg seropositivity, incidence of adverse events related to vaccination, incidence of primary liver cancers, incidence of liver failure, all-cause mortality, and cost-effectiveness of hepatitis B vaccine booster dose. Risk of bias was appraised using the Cochrane risk-of-bias tool for randomized trials (RoB 2), and data was pooled using Review Manager 5 (RevMan).

Results

Characteristics of Included Studies

Four (4) RCTs with a total of 64,301 patients were included in the meta-analysis.¹⁶⁻¹⁹ Three RCTs gave boosters to adolescents 10-15 years old^{17, 18, 19} and one RCT gave boosters to children at 5 years old¹⁶. These patients received only three doses of Hepatitis B vaccine prior to the booster dose. Two RCTs were done in China, and one RCT each from Thailand and Gambia—countries which are hyperendemic for hepatitis B. All RCTs involved participants who received their primary hepatitis B vaccinations as children or adolescents. The study from Gambia used plasma-derived hepatitis B vaccine as the booster dose intervention, while the other three used recombinant hepatitis B vaccines. Time to booster vaccination varied across studies with a range of 5 years to 15 years. Likewise, post-booster assessments varied across studies with a range of 12 months to 12 years.

Outcome measures in these studies were HBV seroprotection,¹⁶⁻¹⁹ HBsAg seropositivity,¹⁷ anti-HBc seropositivity,¹⁹ primary liver cancer,¹⁷ acute-on-chronic liver failure,¹⁷ mortality,¹⁷ and adverse events after immunization.¹⁸

Efficacy Outcomes

Only one (1) RCT (n=63,615) reported on all-cause mortality, primary liver cancer, and acute-on-chronic liver failure.¹⁷ HBV vaccine booster dose significantly decreased all-cause mortality (RR 0.31, 95% CI 0.12 to 0.78) and significantly prevented the development of primary liver cancer (RR 0.19, 95% CI 0.05 to 0.65) among individuals who have previously received a 3-dose primary series compared to those not given hepatitis B booster. However, there is inconclusive result noted in the development of acute-on-chronic liver failure (RR 0.44, 95% CI 0.11 to 1.75).

Seroprotection after the primary Hepatitis B series waned over time. In 5-year-old children, only 87.5% retained seroprotective levels from the primary series.¹⁶ In adolescents, the percentage of seroprotected children also declined, ranging from 57-77.6%.¹⁷⁻¹⁸ One (1) large population-based, cluster-randomized, controlled trial¹⁷ and three (3) small RCTs^{16,18-19} reported outcomes on HBV seroprotection after booster dose, which pertained to those individuals who achieved anti-HBs titers $\geq 10\text{mIU/mL}$ after the intervention. Pooled analysis showed that HBV vaccine booster dose had no significant effect on HBV seroprotection (4 studies, n=861; RR 1.85, 95% CI 0.97 to 3.52, $I^2=95\%$) and had significant heterogeneity. This may be due to the variation in time to booster vaccination (which ranges from 5 years to 15 years) as well as the post-booster assessments (which ranges from 12 months to 12 years).

One (1) RCT (n=975)¹⁹ showed that there is a significant reduction in HBsAg seropositivity after booster dose (RR 0.30, 95% CI 0.15 to 0.61). However, there was no significant reduction in anti-HBc seropositivity after booster dose (RR 0.49, 95% CI 0.12 to 1.98). There were no reported outcomes on HBV DNA seropositivity.

Safety Outcomes

Based on one (1) published RCT involving 446 participants, there were no local and systemic adverse events related to HBV booster vaccination.¹⁸ Other RCTs did not report this outcome.

Table 40. Summary of outcomes for hepatitis B vaccine booster dose

Critical Outcomes	Basis (No. of Studies)	Effect Size	95% CI	Interpretation	Certainty of Evidence
All-cause mortality	63,615 (1 RCT)	RR 0.31	(0.12 to 0.78)	Benefit	Moderate
Acute on chronic liver failure	63,615 (1 RCT)	RR 0.44	(0.11 to 1.75)	Inconclusive	Low
Primary liver cancer:	63,615 (1 RCT)	RR 0.19	(0.05 to 0.65)	Benefit	Moderate
HBV seroprotection (Anti-HBs $\geq 10\text{mIU/L}$)	861 (4 RCTs)	RR 1.85	(0.97 to 3.52)	Inconclusive	Very low

HBsAg seropositivity	975 (1 RCT)	RR 0.30	(0.15 to 0.61)	Benefit	Moderate
Anti-HBc seropositivity	140 (1 RCT)	RR 0.49	(0.12 to 1.98)	Inconclusive	Low
Adverse events	446 (1 RCT)	No adverse events reported on all included participants			Moderate

Anti-HBc hepatitis B core antibody; anti-HBs hepatitis B surface antibody; CI confidence interval; HBsAg hepatitis B surface antigen; HBV hepatitis B virus; RCT randomized controlled trial; RR relative risk

Certainty of Evidence

Three studies had an overall low risk of bias. The study by Poovorawan 1997 had some risk of bias due to unclear randomization processes, allocation concealment, and deviations from intended interventions. The study of Qu 2014 had unclear risk of reporting bias. The remaining two studies (Van der Sande 2007 and Wu 2011) had low risk of bias. The overall certainty of evidence has been downgraded to very low because of the serious risk of bias, imprecision, and inconsistency in one critical outcome (HBV seroprotection).

Recommendations from Other Groups

All identified groups who have published guidelines and statements do not recommend the use of booster dose of hepatitis B vaccine after the completion of the primary vaccination series in routine immunization programs. They recommend, however, booster doses for certain subgroups of the population, including immunocompromised individuals.

Table 41. Summary of other groups' recommendations for hepatitis B vaccine booster dose²⁸⁻³⁴

Group	Recommendations	Strength of Recommendation
World Health Organization ²⁸	General population: There is no evidence to support the need for booster dose of hepatitis B vaccine after the completion of the primary vaccination series in routine immunization programs. However, additional longer-term studies on the need for booster doses in different subgroups of the population should be conducted.	Not indicated
US CDC Advisory Committee on Immunization Practices (ACIP) ³³	Children and adolescents aged 18 years or younger: Revaccination (i.e., booster dose, challenge dose, or revaccination with a complete series) is not generally recommended for persons with a normal immune status who were vaccinated as infants, children, or adolescents. Available data do not suggest a maximum number of booster doses. Revaccination when anti-HBs is <10mIU/mL is recommended for the following persons: <ul style="list-style-type: none"> • Infants born to HBSAg-positive mothers* • Healthcare providers • Hemodialysis patients • Other immunocompromised persons (e.g., HIV-infected persons, transplant patients, persons receiving chemotherapy) *For infants born to HBSAg-positive mothers and having received the final dose of the vaccine series, they should be serologically tested for HBV immunity at age 9 to 12 months,	Not indicated

	or 2 months after the final dose if the series is delayed. Revaccination with a single dose of Hepatitis B vaccine is advised for those with antibody levels <10mIU/mL, with retesting 1 to 2 months later.	
National Advisory Committee on Immunization (NACI) ²⁹	Immunocompetent individuals: NACI does not recommend routine booster doses of hepatitis B vaccine for immunocompetent individuals following the completion of a recommended hepatitis B immunization schedule given in infancy.	NACI Grade B (Fair evidence to recommend immunization)
American Association for the Study of Liver Diseases (AASLD) ³⁰	Immunocompetent individuals: Booster doses are not indicated in immunocompetent individuals if the primary vaccination series is completed, as long-term follow-up studies indicate that immune memory persists despite declining anti-HBs levels. Immunocompromised individuals: Booster injection is advised when the anti-HBs titer falls below 10mIU/mL for individuals undergoing postvaccination serologic testing especially immunocompromised patients (such as persons on dialysis or with chronic inflammatory conditions, such as HIV). Non-responders to the initial vaccination series: A second series of 0-, 1-, and 6-month vaccination is recommended.	Not indicated
Canadian Association for the Study of the Liver (CASL) ³¹ Association of Medical Microbiology and Infectious Disease Canada (AMMI) ³¹	General population: Routine booster doses of HBV vaccine are not indicated in average-risk, immune-competent individuals who responded to the primary series of vaccine. Immunocompromised individuals: A repeat series (three doses of vaccine) should be offered to those at high risk of exposure or those who are immunosuppressed and who do not respond to the first series of vaccines.	Strong recommendation
Ministry of Health, Republic of Zambia ³²	Children: Booster vaccination is not recommended for persons who have completed the 3-dose vaccination schedule	Not indicated
Hepatology Society of the Philippines ³⁴	Patients with chronic kidney disease: For known responders to vaccination, annual determination of anti-HBs titer is recommended. If the anti-HBs titer is <10mIU/ml, a booster dose is recommended.	Moderate quality of evidence; strong recommendation

Ongoing Studies and Research Gaps

There are no ongoing studies regarding the effectiveness of hepatitis B booster vaccination. More local studies regarding the effect, cost-effectiveness, and harms of administering this booster are needed.

Additional Considerations for Evidence-to-Decision (EtD) Phase

Cost

There are no published hepatitis B vaccine booster cost-effectiveness studies done in the Philippine setting. However, some economic evaluations from other countries provide some insight. Using hypothetical cohorts and modelling, the use of hepatitis B primary vaccination

series is more cost-effective than no vaccination,²⁰ and choosing 6-component vaccines were likely to be more cost-effective than monovalent hepatitis B vaccines.²¹

A study done in China compared the cost-effectiveness of the country's strategy of no booster and no screening (HBsAg and anti-HBs) with two different strategies: (1) one-dose booster if negative on HBsAg screening, and (2) one-dose booster if negative on HBsAg and anti-HBs screening. It showed that HBV vaccine booster given at 10 years of age was cost-saving, with cost-effectiveness ratios (USD/QALY) at USD 6,961 or PHP 385,117 per QALY gained in Strategy 1 and USD 6,872 or PHP 380,193 per QALY gained in Strategy 2.²² However, a commentary emphasized that due consideration on randomizing individuals to compare booster versus no booster may provide better insight.²³

A recent review of available evidence suggested that HBV booster should be implemented into health programs in India considering that there is low vaccination awareness, small coverage, high disease burden, and high treatment cost.²⁴

Appendix D shows the review of these cost-effectiveness studies and articles.

Table 42. Price of hepatitis B recombinant vaccination in 2022

Hepatitis B Vaccine (Recombinant) Preparation		
10mcg/0.5mL, 5mL vial		20mcg/mL, 1 mL vial
Unit Cost^a	PHP 117.33-165.87 per vial	PHP 167.44-312.50 per vial

^aBased on the 2022 Philippine Drug Price Reference Index²⁵

Table 43 shows the list of registered hepatitis B products by the Philippine Food and Drug Administration (FDA) and their corresponding prices (if available). This list was updated by the FDA as of 07 December 2022.

Table 43. Registered hepatitis B vaccines in the Philippine FDA vaccine list²⁶

Generic Name	Brand Name	Manufacturer	Unit Cost Estimates*
Monovalent vaccine			
Recombinant hepatitis B vaccine	Bevac	Biological E. Limited (India)	PHP 50.00
	Hepliv	Bharat Biotech International Limited (India)	PHP 190.00
	Revac-B+	Bharat Biotech International Limited (India)	PHP 350.00
	Genevac-B (Adult)	Serum Institute of India Limited (India)	PHP 390.00
	Genevac-B (Pediatric)	Serum Institute of India Limited (India)	PHP 250.00

	Amvax-B (Adult)	Amson Vaccines & Pharma Private Limited (Pakistan)	PHP 570.00
	Amvax-B (Pediatric)	Amson Vaccines & Pharma Private Limited (Pakistan)	PHP 310.00
	Euvax B (multidose)	LG Chem Limited (Korea)	PHP 840.00
	Engerix B	GlaxoSmithKline Biologicals SA (Belgium)	PHP 610.00
	Engerix B Junior	GlaxoSmithKline Biologicals SA (Belgium)	PHP 350.00

Combination vaccines

HAV-HepB	Twinrix Adult	GlaxoSmithKline Biologicals SA (Belgium)	PHP 1,650.00
DTP-HepB-Hib	Eupenta	LG Chem Limited (Korea)	PHP 60.00
DTwP-HepB-Hib	Shan 5	Shantha Biotechnics Limited (India) Sanofi Healthcare India Private Limited (India)	PHP 360.00
	Combe Five	Biological E. Limited (India)	PHP 255.00
DTwP-HepB-Hib-Influenza B	Easyfive TT	Panacea Biotec Limited – Vaccine Division (India)	PHP 405.00
DTaP-HepB-IPV-Hib	Infanrix Hexa	GlaxoSmithKline Biologicals SA (Belgium)	PHP 2,200.00
	Hexaxim	Sanofi Pasteur (France)	PHP 2,300.00

aP acellular pertussis vaccine; D diphtheria vaccine; HAV hepatitis A vaccine; HepB hepatitis B vaccine (recombinant); Hib *Haemophilus influenzae* type B conjugate vaccine; IPV inactivated polio vaccine; P pertussis vaccine (unspecified); T tetanus vaccine; wP whole cell pertussis

Note: Unit cost estimates may vary over time depending on the present market price and/or inflation rates

Patient's Values and Preference, Equity, Acceptability, and Feasibility

There is no published local data yet on the impact of an additional HBV vaccine booster on health equity. However, a local survey published in 2020 on the timeliness of vaccination in the Philippines revealed that the proportion of infants who received the vaccines at the recommended age tended to decrease with vaccine doses in a series at a given age.²⁷ This may affect decision-making in requiring further hepatitis B booster doses in healthy children. There is no direct data available on the acceptability of an additional HBV vaccine booster to key stakeholders, including patients, healthcare providers, and immunization programs. There is no evidence yet that HBV booster vaccination can already be implemented in the clinical setting of the country.

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4.10. Can Pneumococcal Conjugate Vaccine brands be interchanged to complete the primary series? Can Pneumococcal Conjugate Vaccine brands be interchanged as booster dose?

RECOMMENDATION

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 booster dose in PCV13-primed children

(weak recommendation, very low certainty evidence)

Consensus Issues

The panelists recognized the immunogenicity and efficacy of pneumococcal conjugate vaccines interchanged 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 outweigh the risk of harm but some panelists believe that more high-quality evidence on cost-effectiveness of giving different vaccine brands, equity, acceptability, and feasibility are needed to make a strong recommendation.

Key Findings

Two observational studies evaluated the vaccine effectiveness (VE) of pneumococcal conjugate vaccine against invasive pneumococcal diseases (IPD). A study from Canada found similar VE against IPD between a PHiD-CV-only schedule, a PCV13-only schedule, or a mixed PHiD-CV+PCV13 schedule. A study from Taiwan found similar VE in PCV13-only schedule and mixed PCV7/PHiD-CV+PCV13 schedule, and lower VE for PHiD-CV-only schedule. 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 13 pneumococcal serotypes. For PCV10-SII and PCV13 booster, there was no significant difference in the 10 common serotypes. For PCV13 and PCV15, there was no significant difference in IgG response for 13 common serotypes. No difference in adverse events was seen between mixed and single-brand schedules.

Overall certainty of evidence was very low due to indirectness, serious risk of bias, inconsistency, and imprecision for three of the critical outcomes (vaccine efficacy, immunogenicity, and adverse events)

Introduction

Diseases caused by *Streptococcus pneumoniae* are usually divided into invasive pneumococcal diseases (IPD) when the organism is isolated from sterile sites (meningitis, bacteremia, bacteremic pneumonia) and non-invasive diseases (non-bacteremic pneumonia, sinusitis, and otitis media).¹ According to the World Health Organization, 294,000 of the estimated 5.83 million deaths among children <5 years of age globally were caused by pneumococcal infections with an additional 23,300 deaths estimated to have occurred in children living with HIV. The WHO further states that disease and mortality rates are higher in developing countries than in industrialized settings, with most deaths occurring in Africa and Asia.² The burden of pneumococcal disease in the Philippines remains high, as described by numerous studies across different time periods.¹ In a 2013 prospective surveillance study of 5940 children aged 28 days to <60 months living in urban areas in the Philippines, 47 IPD cases were identified.³

To address this burden, the pneumococcal conjugate vaccine (PCV) was included in the National Immunization Program (NIP) in 2015. PCV13 (Prevnar13) was the vaccine previously used in the NIP. It had a 3+0 vaccination schedule given at 6,10, and 14 weeks old. PCV13 has been recently replaced with PHiD-CV (Synflorix) using the same schedule.⁴ PHiD-CV and PCV13 are also available in the private sector. Other brands such as PCV10-SII (Pneumosil) and PCV15 (Vaxneuvance) were also recently approved by the Philippine FDA in 2022. Table 44 lists the pneumococcal serotypes included, as well as other characteristics of the vaccines. The availability of different PCV brands and the switch in the NIP provide impetuses for this review.

Table 44. Characteristics of available pneumococcal conjugate vaccines

		PHiD-CV (Synflorix)	PCV13 (Prevnar13)	PCV10-SII (Pneumosil)	PCV15 (Vaxneuvance)
		Carrier Protein			
		Protein D (except where indicated)	CRM197	CRM197	CRM197
Included Serotype	1	X	X	X	X
	3		X		X
	4	X	X		X
	5	X	X	X	X
	6A		X	X	X
	6B	X	X	X	X
	7F	X	X	X	X
	9V	X	X	X	X
	14	X	X	X	X
	18C	X Tetanus toxoid	X		X

	19A		X	X	X
	19F	X Diphtheria toxoid	X	X	X
	23F	X	X	X	X
	22F				X
	33F				X

To monitor the impact of pneumococcal vaccination, surveillance of IPD and *Streptococcus pneumoniae* serotypes causing disease is done; however, there is limited Philippine data for this. The Health Technology Assessment Council (HTAC) used surveillance data from the Research Institute for Tropical Medicine (RITM) in its 2020 document evaluating PCVs available in the country.⁵ Figure 1 shows the prevalence of pneumococcal serotypes before

and after the introduction of PCV13 in the NIP. The ten common serotypes found in both PCV10 and PCV13 accounted for approximately 42% of IPD isolates.⁵ The 2021 report⁶ of the Antimicrobial Resistance Surveillance Program (ARSP) isolated 23 *Streptococcus pneumoniae* from submitted samples and identified 14 serotypes/serogroups with the most common being serotypes 3, 4, 23, 6, 19A, 10, 11, and 34 and penicillin-resistant serotypes being serotypes 6, 19, and 23.

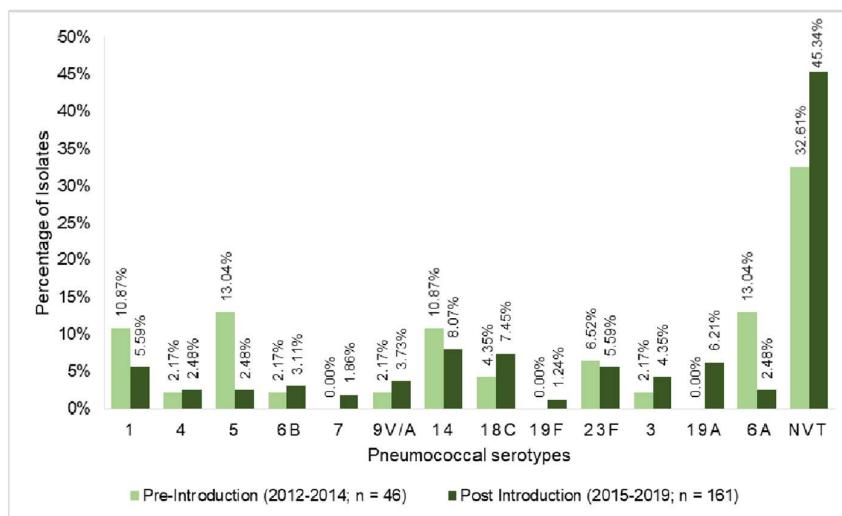


Figure 1. Percentage of isolates causing vaccine type and non- vaccine type IPDs in children less than 5 years old, pre and post PCV13 introduction, 2012-2019 (Source: RITM, 2020); figure lifted from HTA Report⁵

Review Methods

A systematic search of Pubmed was done until 08 February 2023 using a combined MeSH and free text search using the terms: “pneumococcal conjugate vaccine, invasive pneumococcal disease, *Streptococcus pneumoniae*, vaccine interchangeability.”

Only studies conducted in the pediatric age group and randomized controlled trials (RCT) that compared the four above-mentioned PCV brands were included. Outcomes of interest

included vaccine efficacy defined as incidence of invasive pneumococcal disease (IPD), immunogenicity, and adverse events. Reference lists of systematic reviews were also reviewed for relevant studies. For outcomes where no RCTs were found, observational studies were also researched. Case-control studies were appraised using the Newcastle-Ottawa Assessment Scale while RCTs were appraised using Cochrane risk of bias criteria.

Results

Characteristics of Included Studies

No randomized controlled trials evaluated vaccine efficacy against IPD from using interchanged brands in a primary series compared to single-brand schedules. 2 case-control studies^{7,8} evaluating vaccine effectiveness (VE), and 5 RCTs^{9,10,11,12,13} and 1 open-label comparative study¹⁴ evaluating immunogenicity were found.

Two trials^{9,10} enrolled infants ≤2 months old to investigate immunogenicity after primary series. 5 studies^{9,11,12,13,14} were conducted on infants ≤12-15 months old to examine booster dose effect on immunogenicity.

Six studies^{7,8,9,10,11,14} included interchangeability of PHID-CV and PCV13 in their comparisons. One study¹² compared PCV13 and PCV10-SII interchanged as boosters; another study¹³ included PCV13 and PCV15. Outcome assessed by the case-control studies was vaccine effectiveness, and the trials evaluated safety and immunogenicity measured via serotype-specific IgG levels and Opsonophagocytic Activity (OPA). The WHO Position Paper on Pneumococcal conjugate vaccines in infants and children under 5 years of age states, "WHO has defined serological criteria for non-inferiority that should be used in the primary analysis of studies of immunological responses to PCV. The criteria are: (i) the percentage of PCV recipients with serotype-specific immunoglobulin G $\geq 0.35 \mu\text{g/mL}$ ("percentage of responders") in a WHO reference assay (or an alternative, well-justified thresh-old based on a specific in-house assay) and (ii) the serotype-specific immunoglobulin G geometric mean concentration (GMC) measured 4 weeks after completion of the primary infant vaccination series... it is reasonable to use the proportion of infants with an antibody concentration $\geq 0.35 \mu\text{g/mL}$ as a marker of efficacy." This outcome was pooled, when applicable, for the included studies. Given the overlapping evidence for the primary and booster studies, the two research questions will be discussed concurrently.

Efficacy Outcomes

Vaccine effectiveness against IPD

Two case-control studies evaluated vaccine effectiveness against IPD using a mixed schedule versus a single-brand schedule. The study from Canada⁷ (Deceuninck, 2015) included IPD cases in children 2-59 months old during 2005-2013 and determined the vaccine effectiveness of ≥2 doses in its outcome. The study from Taiwan⁸ (Su, 2017) included IPD patients ≤5 years old from 2007-2013 with vaccine effectiveness of age-appropriate number of vaccine doses in its outcomes. Data could not be pooled because of missing data for controls from one of the studies.⁷ Deceuninck et. al.⁷ found similar VE against IPD between a PHID-CV-only schedule (VE 75%, 95% CI 51 to 87%), a PCV13-only schedule (VE 65%, 95%CI 29 to 83%), and a mixed PHID-CV+PCV13 schedule (VE 66%, 95% CI 23 to 85%). Su,⁸ on the other hand, found similar VE in PCV13-only schedule (VE 80%, 95% CI 65 to 89%) and mixed PCV7/PHID-CV+PCV13 schedule (VE 85%, 95% CI 66 to 93%), but a lower VE for PHID-CV-

only schedule (VE 50%, 95% CI 51 to 87%). Both studies were scored as good quality using the Newcastle-Ottawa Scale.

Immunogenicity - Primary series (PHiD-CV and PCV13)

Two randomized controlled trials evaluated the immunogenicity of a mixed versus single-brand schedule of PCV. One RCT⁹ (delos Santos, 2020) evaluated a 2+1 schedule of PHiD-CV and PCV13 with the primary series given at 2 and 4 months in the following manner: PCV13-PHiD-CV, PCV13-PCV13, and PHiD-CV-PHiD-CV with immunogenicity measured a month after the primary series. Another RCT¹⁰ (Leach, 2021) measured immunogenicity in a novel 4+0 mixed schedule of PHiD-CV at 1, 2, and 4 months and PCV13 at 6 months of age compared to children receiving single-brand 3+0 regimens of PHiD-CV or PCV13 at 2, 4, and 6 months of age. Both studies measured IgG against 10 common serotypes found in both vaccines and 3 serotypes found only in PCV13.

Pooled analysis of immunogenicity after the primary series measured via IgG showed no significant difference between mixed schedule and single-brand schedule for all of the 10

common serotypes (1,4,5,7F, 6B, 9V,14,18C,19F, 23F) and 2 of the 3 PCV13-only serotypes (6A, 19A). Immunogenicity was significantly different for mixed schedule over PCV 13-only schedule for only one serotype, serotype 3 (RR 1.99, 95% CI 1.05 to 3.79).

Table 45. Vaccination schedules of included studies evaluating immunogenicity for primary and booster doses

Study	Schedule	Treatment/Control vaccine received
Delos Santos, 2020	2+1 given at 2, 4 months (with 12 months booster)	PrPr+S (single brand primary, mixed booster)
		PrS+S (mixed)
		SS+S*
Leach, 2021	4+0 (mixed) given at 1, 2, 4, 6 months	SSSPr (mixed)
	3+0 (single brand) given at 2, 4, 6 months	SSS PrPrPr
Truck, 2016	2+1 (Booster)	PrPr+Pr (single brand)
		PrPr+S (mixed)
Urbancikova, 2017 (Slovakia)	2+1 (Booster)	PrPr+Pr (single)
		SySy+Pr (mixed)
Urbancikova, 2017 (Czech Republic)	3+1 (Booster)	PrPrPr+Pr (single)
		SySyPr+Pr (mixed)

Pr PCV Prevnar13; S PHiD-CV Synflorix

Immunogenicity - Booster dose (PHiD-CV and PCV13)

Three^{9,11,14} studies compared immunogenicity between a mixed schedule—infants given a booster using a different brand from their primary series—and those given a booster with the same brand as that given during the primary series. The above-mentioned RCT⁹ (delos

Santos, 2020) used a 2+1 schedule and had the following arms:

PCV13-PHiD-CV-PHiD-CV, PCV13-PCV13-PHiD-CV, and PHiD-CV-PHiD-CV-PHiD-CV. Another RCT¹¹ randomized infants who received PCV13 into either a PHiD-CV or PCV13 booster using a 2+1 schedule. An open-label study¹⁴ done in two countries, one with a 3+1 schedule and the other with 2+1 schedule, enrolled infants who have received either PHiD-CV or PCV13 in their primary series and gave both groups a PCV13 booster.

Pooled analysis of immunogenicity measured via IgG (4 studies, n=568) showed no significant difference between mixed schedule and single-brand schedule for 10 common serotypes (1,4,5,7F,6B, 9V,14,18C,19F, 23F) as well as the 3 PCV13-only serotypes (3, 6A, 19A).

Immunogenicity - Booster dose (PCV10-SII and PCV13)

One phase I/II study¹² (Clarke, 2020) evaluated PCV13-primed toddlers (12-15 months old) who were randomized to receive PCV10-SII or PCV13 as a booster. IgG immunogenicity following the booster immunization measured by GMC ratio against all 10 common serotypes showed no significant differences between those who were given PCV-SII or PCV13 booster.

Table 46. Immunogenicity (geometric mean concentration of serotype-specific IgG) PCV10-SII Booster vs. PCV 13 booster

Serotype	PCV10-SII Booster N=17 GMC (95% CI)	PCV13 Booster N=47 GMC (95% CI)	PCV10-SII/PCV13 GMC ratio (95% CI)	p-value
1	4.59 (3.90, 5.87)	6.09 (4.51, 10.75)	0.75 (0.51, 1.46)	0.265
5	2.30 (1.57, 3.72)	3.35 (2.46, 5.35)	0.69 (0.41, 1.31)	0.206
6A	13.33 (9.62, 22.49)	15.83 (11.64, 26.80)	0.84 (0.51, 1.69)	0.566
6B	15.77 (11.51, 23.96)	19.16 (14.98, 30.46)	0.8 (0.53, 1.43)	0.446
7F	9.17 (7.42, 12.12)	12.35 (8.83, 19.74)	0.74 (0.48, 1.23)	0.219
9V	2.35 (1.57, 3.45)	2.35 (1.57, 3.45)	0.60 (0.34, 1.14)	0.097
14	14.55 (8.23, 21.52)	8.28 (6.19, 13.82)	1.76 (0.91, 2.98)	0.071
19A	9.76 (6.71, 12.62)	13.68 (6.06, 22.64)	0.71 (0.38, 1.56)	0.344
19F	9.75 (7.36, 12.75)	12.87 (8.46, 22.39)	0.76 (0.44, 1.32)	0.328
23F	6.84 (4.28, 10.54)	10.49 (7.70, 19.64)	0.65 (0.35, 1.25)	0.204

CI confidence interval; GMC geometric mean concentration

Immunogenicity - Primary and booster dose (PCV13 and PCV15)

A phase III study¹³ (Bili, 2022) evaluated interchangeability between PCV13 and PCV15. Subjects were randomized into five study arms: groups 1 and 5 received a complete 4-dose regimen of PCV13 or PCV15 at 2, 4, 6, and 12–15 months old; groups 2, 3, and 4 started with PCV13 and were given PCV15 at doses 4, 3, and 2, respectively. Serotype-specific antibodies were assessed one month following both the primary series and the booster dose. IgG response levels measured 1 month after primary and booster series for the 13 shared serotypes between PCV13 and PCV15 showed no significant difference between mixed PCV13-PCV15 and single-brand intervention groups (Table 47).

Table 47. Immunogenicity (IgG response levels) 1 month after vaccination series for the 13 shared serotypes

Outcome	Effect Estimate Risk Ratio [95% CI]
Serotype 1	1.01 [0.99, 1.02]
Serotype 3	0.97 [0.78, 1.20]
Serotype 4	0.96 [0.93, 1.00]
Serotype 5	0.99 [0.97, 1.01]
Serotype 6A	0.99 [0.97, 1.01]
Serotype 6B	1.02 [0.99, 1.05]
Serotype 7F	1.00 [0.99, 1.01]
Serotype 9V	0.98 [0.96, 1.01]
Serotype 14	1.00 [0.96, 1.04]
Serotype 18C	1.01 [0.99, 1.03]
Serotype 19A	0.99 [0.97, 1.01]
Serotype 19F	1.00 [0.99, 1.01]
Serotype 23F	0.97 [0.93, 1.01]

CI confidence interval

Safety Outcomes

Adverse events (any)

Pooled analysis of adverse events from studies by Clarke¹² and Urbancikova¹⁴ (n=299) showed no significant difference between mixed and single-brand schedules (RR 0.76, 95% CI 0.48 to 1.21).

Other adverse event outcomes were also reported in the RCTs. Delos Santos et al.⁹ reported incidence of Grade 3 adverse events (AEs) during the primary doses to be 8.7% in infants receiving two primary PCV13 doses, 16.9% in infants receiving two primary PHiD-CV doses, and 11.4% in infants receiving a primary series consisting of one PCV13 dose followed by one PHiD-CV dose. During the PHiD-CV booster period, incidence was 16.5% (2 PCV13 primary dose + PHiD-CV booster), 11.6% (single-brand PHiD-CV group), and 13.8% (mixed PCV13- PHiD-CV primary + PHiD-CV booster group). Trück¹¹ reported the reactogenicity of the booster to be similar regardless of whether participants had received PHiD-CV or PCV-13. Clarke¹² reported that the most common treatment emergent adverse events (TEAEs) in toddlers who received boosters were infections (44.6% PCV10-SII, 50.0% PCV13), particularly upper respiratory tract infections and gastrointestinal disorders (16.1% PCV10-SII, 10.7% PCV13), including diarrhea. Bili¹³ reported that the proportion of participants with AEs were generally comparable across intervention groups.

Serious Adverse Events

Pooled analysis of SAEs from four studies^{9,10,13,14} showed no significant difference between mixed and single-brand schedules (RR 1.05, 95% CI 0.80 to 1.38).

Other RCTs also reported SAEs. Leach¹⁰ reported 73 serious adverse events (SAEs) including one death, 62 SAEs were unrelated, nine were unlikely to be related including the one death, and two were possibly related. Trück¹¹ reported 5 SAEs (febrile illness, suspected meningococcal sepsis, viral gastroenteritis, viral wheeze, and febrile convulsion) during the study with none considered related to studied vaccines. This included all participants and did not mention which vaccine groups the participants were in. Clarke¹² reported 2 toddlers in the PCV10-SII group and one in the PCV13 group had a mild or moderate vaccine-related TEAE (mild diarrhea and moderate rash following PCV10-SII). Two severe SAEs occurred—one (gastroenteritis) in the PCV10-SII group and one (pneumonia) in the PCV13 group, both of which were deemed unrelated to vaccination and resolved without sequelae. Four severe TEAEs occurred, including two cases of microcytic anemia in the PCV10-SII group deemed unrelated to vaccination.

Table 48. Summary of benefits and harms of PCV

Outcomes	No. of Studies (No. of Participants)	Effect Size	Interpretation	Certainty of Evidence
Vaccine effectiveness against IPD (any serotypes)	1 (n=516)	PHiD-CV 75% (51-87% 95% CI)	Similar VE	Low
		PCV13 65% (29-83% 95% CI)		
		PHiDCV+PCV13 66% (23-85% 95% CI)		
	1 (n=523)	PCV7/PHiD-CV 50% (33-63%, 95% CI)	Similar VE for mixed and PCV13-only	Low
		PCV13 only 80% (65-89, 95% CI)		
		PCV7/PHiD-CV+PCV13 85% (66-93%, 95% CI)		
Immunogenicity (IgG) primary series (PHiD-CV and PCV13)	2 (n=593)	Serotype 1 RR 1.00 [0.98, 1.01]	Equivalent (except serotype 3 showing benefit for mixed schedule)	Low
		Serotype 4 RR 1.00 [0.99, 1.02]		
		Serotype 5 RR 1.00 [0.97, 1.03]		
		Serotype 6B RR 1.12 [1.00, 1.26]		
		Serotype 7F RR 1.00 [0.98, 1.01]		
		Serotype 9V RR 1.01 [0.99, 1.03]		
		Serotype 14 RR 1.00 [0.98, 1.02]		
		Serotype 18C RR 1.00 [0.97, 1.02]		

		Serotype 19F RR 1.01 [0.99, 1.03]				
		Serotype 23F RR 0.98 [0.89, 1.07]				
		Serotype 3 RR 1.99 [1.05, 3.79]				
		Serotype 6A RR 1.13 [0.80, 1.59]				
		Serotype 19A RR 1.10 [0.90, 1.33]				
Immunogenicity (IgG) Booster (PHiD-CV and PCV13)	4 (n=568)	Serotype 1 RR 1.00 [0.98, 1.02]	Equivalent	Low		
		Serotype 4 RR 1.00 [0.99, 1.02]				
		Serotype 5 RR 0.97 [0.91, 1.05]				
		Serotype 6B RR 1.00 [0.97, 1.02]				
		Serotype 7F 1.00 [0.98, 1.01]				
		Serotype 9V RR 0.99 [0.94, 1.04]				
		Serotype 14 RR 1.00 [0.99, 1.02]				
		Serotype 18C 1.00 [0.99, 1.02]				
		Serotype 19F RR 1.00 [0.99, 1.02]				
		Serotype 23F 1.00 [0.98, 1.02]				
		Serotype 3 1.16 [0.82, 1.62]				
		Serotype 6A RR 0.91 [0.82, 1.02]				
		Serotype 19A 1.01 [0.98, 1.04]				
Immunogenicity Booster dose (PCV10-SII and PCV 13)	1 RCT (n=34)	Serotype	GMC ratio (95% CI)	p-value	Equivalent	Low
		1	0.75 (0.51, 1.46)	0.265		
		5	0.69 (0.41, 1.31)	0.206		
		6A	0.84 (0.51, 1.69)	0.566		
		6B	0.8 (0.53, 1.43)	0.446		
		7F	0.74 (0.48, 1.23)	0.219		
		9V	0.60 (0.34, 1.14)	0.097		
		14	1.76 (0.91, 2.98)	0.071		
		19A	0.71 (0.38, 1.56)	0.344		
		19F	0.76 (0.44, 1.32)	0.328		

		23F	0.65 (0.35, 1.25)	0.204		
Immunogenicity (IgG) (PCV13 and PCV15)	1 RCT (n=872)	Serotype 1 RR 1.01 [0.99, 1.02] Serotype 3 RR 0.97 [0.78, 1.20] Serotype 4 RR 0.96 [0.93, 1.00] Serotype 5 RR 0.99 [0.97, 1.01] Serotype 6A RR 0.99 [0.97, 1.01] Serotype 6B RR 1.02 [0.99, 1.05] Serotype 7F RR 1.00 [0.99, 1.01] Serotype 9V RR 0.98 [0.96, 1.01] Serotype 14 RR 1.00 [0.96, 1.04] Serotype 18C RR 1.01 [0.99, 1.03] Serotype 19A RR 0.99 [0.97, 1.01] Serotype 19F RR 1.00 [0.99, 1.01] Serotype 23F RR 0.97 [0.93, 1.01]	Equivalent	Moderate		
Adverse event (any)	2 (299)	RR 0.76 [0.48, 1.21]		Inconclusive	Very Low	
Serious adverse event (SAE)	4 (1,802)	RR 1.05 [0.80, 1.38]		Inconclusive	Very Low	

CI confidence interval; IgG immunoglobulin G; PCV pneumococcal conjugate vaccine; RCT randomized controlled trial; RR relative risk; SAE serious adverse event; VE vaccine effectiveness

Certainty of Evidence

Both case-control studies were scored as good quality using the Newcastle-Ottawa Scale. The overall certainty of evidence was rated very low due serious risk of bias, indirectness, inconsistency and imprecision for three of the critical outcomes (vaccine efficacy, immunogenicity and adverse events outcomes).

Recommendations from Other Groups

Table 49. Summary of other groups' recommendations for PCV

Group	Recommendation	Strength of Recommendation/Certainty of Evidence
World Health Organization (WHO) ¹⁵ (2021)	<p>Available evidence (IVAC Evidence Dossier 2019¹⁶) suggests that countries can use PCVs interchangeably in routine programmes when continuing the entire series with the same product is not feasible.</p> <p>Given limited evidence on interchangeability, once a PCV vaccination programme has been initiated, product switching may be recommended in the event of substantial changes in the epidemiological or programmatic factors that determined the original choice of product, such as increase in the burden of disease from a serotype(s) better covered by an available alternative vaccine formulation.</p>	None mentioned
US Centers for Disease Control and Prevention ¹⁷	<p>Interchangeability of Combination Vaccines from Different Manufacturers:</p> <ul style="list-style-type: none"> ACIP prefers that doses of vaccine in a series come from the same manufacturer; however, if this is not possible or if the manufacturer of doses given 	None mentioned

	<p>previously is unknown, providers should administer the vaccine that they have available.</p> <ul style="list-style-type: none"> CDC recommends PCV13 or PCV15 for all infants as a series of 4 doses. CDC recommends PCV13 or PCV15 vaccination for children 2 through 4 years old who are unvaccinated or received an incomplete pneumococcal conjugate vaccine (either PCV13 or PCV15) series. PCV13 and PCV15 can be used interchangeably for children who are healthy or have underlying conditions. PCV15 is not indicated for children who have received 4 doses of PCV13 or another age appropriate complete PCV13 series. 	
New Zealand ¹⁸	The Ministry of Health recommends that those who started with PCV10 may complete with PCV13. Children aged 24–59 months who have not received any PCV, or only one dose of PCV10 before the age of 12 months, are recommended to receive two doses of PCV13 given 8 weeks apart rather than one dose as given on the PCV13 (Prevenar 13) datasheet.	None mentioned
Australia ¹⁹	There is no specific data on the interchangeability of 10vPCV (not used in Australia) and 13vPCV. It is preferable to complete a primary course of pneumococcal conjugate vaccine with the same formulation. However, if a child started their vaccination course with 10vPCV (for example, children born overseas), it is acceptable to complete the course with 13vPCV.	None mentioned
India - National Operational Guidelines, Introduction of Pneumococcal Conjugate Vaccine ²⁰	No mention of interchangeability (PCV10-SII and PCV13 are both used in the Universal Immunization Programme).	None mentioned
PPS-PIDSP Immunization Calendar 2023 ²¹	No mention of interchangeability (all four brands are mentioned in the PCV schedule).	None mentioned

Ongoing Studies and Research Gaps

No ongoing studies were identified in clinical registries for studies evaluating PCV interchangeability. Local surveillance research addressing pneumococcal disease is needed to identify the current prevailing serotypes in the Philippines, as well as to determine the role of vaccination in the prevalence of IPD. The role of PCV10-SII and PCV15, as they are newer vaccines, should be studied by vaccine effectiveness studies (prevention of IPD); including their benefit and safety as part of mixed regimens.

Additional Considerations for Evidence-to-Decision (EtD) Phase

Cost

No local studies compared the cost-effectiveness of a mixed schedule against single-brand schedules. For the actual cost of the vaccine, data was obtained from UNICEF and CDC.

Table 50. PCV pricing from UNICEF and US CDC

UNICEF ^a	
Preparation	Cost
PCV 13 single dose vial presentation	USD 3.30 (PHP 183.00)
PHiD-CV two dose vial presentation	USD 3.050 (2019 data) (PHP 169.34)
PCV10-SII one dose vial presentation	USD 2.90 (PHP 161.00)

CDC ^b	
Preparation	Cost
PCV 13 10 pack-1 dose syringe	USD 158.18
PCV 15 10 pack-1 dose syringe	USD 162.27

^aGavi Pricing 2023 from <https://www.unicef.org/supply/documents/pneumococcal-conjugate-vaccine-pcv-price-data>

^bCost/dose from <https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html>

The 2021 WHO report¹⁵ on PCV products states that “PCV pricing varies by product and procurement method. PCV public market prices per dose for PHiD-CV and PCV13 range from USD 3 for Gavi countries through UNICEF to USD 132 in the USA. PCV10-SII has the lowest Gavi price of all PCVs (USD 2.95, 1 dose/vial; USD 2.00, 5 doses/vial) and is expected to be the lowest-price option for non-Gavi countries, though data on non-Gavi pricing are not yet available.”

Patient’s Values and Preference, Equity, Acceptability, and Feasibility

UNICEF reports 51% coverage for the third dose of PCV in 2021 in the Philippines. There are no studies that compared patient or provider preference comparing mixed versus single-brand schedules. The HTAC report⁵ states that “results of the interviews and survey on ethical and social impact assessment showed that patient group and leaders of marginalized communities generally prefer PCV10 over PCV13 due to its advantage in enabling more equitable access to vaccines by allowing more vaccines to be purchased thus enabling the achievement of greater population coverage and better public health outcomes. Civil society organizations (CSOs), however, prefer PCV13 to PCV10 due to its perceived benefit in terms of clinical outcomes. PCV13 has an advantage in the confidence of health workers and public perception on quality of service from NIP and NITAG compared with PCV10.” HTAC reports that for the 2020 nationwide implementation of PCV13 vaccination, 61% of the NIP budget was allocated for PCV alone, with the remaining 39% of the budget shared by eight other types of vaccines.

The International Vaccine Access Center evidence dossier¹⁶ that summarizes studies on interchangeability of vaccines and has been a reference of the WHO in its 2021 report¹⁵ states: “Among the currently WHO prequalified PCV options (Synflorix, Prevenar 13 and Pneumosil) several programmatic characteristics are similar or identical, alleviating some of the potential challenges that face product switches (e.g., administration, liquid formulation, schedule, storage temperature, VVM). Other critical components—such as cold chain space, doses per container, price, and shelf life—differ by product and may require additional planning for countries choosing to switch or incorporate multiple products. Additionally, the program will need to determine which states or districts receive each vaccine, whether they will run down existing vaccine stocks, if and how to retrain health care workers, and if previously produced

information, education, and communication (IEC) and training materials are still valid or need to be revised."

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4.11. Should pertussis-containing vaccines be given as booster among children and adolescents who received complete DPT primary immunizations?

RECOMMENDATION

We suggest giving 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.

(weak recommendation, very low certainty evidence)

Consensus Issues

Pertussis-containing vaccine booster doses are beneficial. Studies show that the acellular pertussis-containing vaccines have better safety profile compared to the whole cell pertussis-containing vaccine. The panel recognizes that both types of pertussis vaccines are effective in reducing incidence of pertussis in the country.

The benefits outweigh the risk of harm, but some panelists believe that more 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 are 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.

Key Findings

This review based the evidence of vaccine effectiveness (VE), safety, and immunogenicity of pertussis-containing vaccines on the results of several studies. Pertussis-containing (DTaP) booster vaccinations during childhood compared to no or under vaccination is protective against pertussis, but protection declines over time. Delay in vaccination among children who received the recommended number of vaccine doses was not associated with increased pertussis risk. Pertussis-containing (Tdap) booster vaccination among adolescents decreases the odds of developing pertussis disease; however, its effectiveness wanes over time. Acellular pertussis vaccines pose a significantly lower risk of convulsions and hypotonic hyporesponsive episodes compared to whole cell vaccines. Compared to placebo, acellular pertussis vaccines as primary immunizations do not pose a higher risk for serious adverse events. Tdap vaccines have a significantly higher incidence of injection-site pain than non-pertussis vaccines.

Introduction

Pertussis or whooping cough is a highly contagious, vaccine-preventable respiratory tract infection caused by a Gram-negative bacteria *Bordetella pertussis* with the highest severity and mortality occurring among infants and young children <5 years old.^{1,2} In the Philippines, it was found to be the most common cause of atypical pneumonia among hospitalized children with case fatality rates ranging from 10-15%.²

The vaccine effectiveness (VE) of pertussis-containing vaccines in preventing pertussis-related complications and deaths is well-documented, with benefits spanning from infancy^{1,3} up to early childhood.⁴ The true burden of pertussis among older children and adolescents in the Philippines is unknown; however, several surveillance studies involving neighboring Asian countries (China, Japan, South Korea, Taiwan, and Thailand) report that pertussis-related infections and outbreaks still occur in these population presenting with persistent cough.⁵ Waning vaccine immunity may possibly contribute to the development of pertussis among older children and adolescents despite adequate vaccination early in life. Likewise, adolescents and adults are considered important reservoirs of infection for infants and other vulnerable household members.

Pertussis-containing vaccines are typically given in combination with diphtheria and tetanus toxoid, either in whole-cell or acellular form (DTaP/Tdap), or in further combination with other vaccines (Hib, IPV, HepB). Diphtheria-Pertussis-Tetanus, or DPT, is routinely administered to infants and children as part of the primary series of the DOH Expanded Program on Immunization (EPI), given at 6, 10, and 14 weeks of age with a minimum interval of four weeks in between doses.⁶ The Pediatric Infectious Disease Society of the Philippines (PIDSP) recommends a booster series until adolescence with the following schedule: 12-23 months (DTP), 4-7 years (DTP), and 9-15 years (Tdap), with 4 years as an ideal minimum interval between booster doses. The PIDSP defines “fully immunized” as receipt of 5 doses of DTP, or 4 doses of DTP if the 4th dose was given on or after the 4th birthday. This review explores the vaccine effectiveness, safety, and cost-benefit of giving pertussis-containing vaccines as a booster for children and adolescents who received their complete primary immunizations.

Review Methods

A systematic search was done on 26 September 2022 and 09 February 2023 using MEDLINE, Cochrane Library, and Google Scholar with a combined MeSH and free text search. The search was limited to published studies that evaluated the safety, efficacy/effectiveness, and immunogenicity of pertussis-containing vaccines (DTaP and Tdap) compared to placebo, no vaccine, or any non-pertussis-containing vaccine. Separate searches at different time points were done for either intervention.

The vaccine intervention should have been intended as a “booster,” which is defined as the administration of a vaccine after an earlier primer dose during infancy and/or childhood, and for the case of the Philippines, “receipt of the primary series consisting of 3 doses during infancy” according to the EPI. Considering that there are variations on the dosing schedule for other countries, this review is limited to the reporting country’s prescribed immunization practices. A separate search was done for cost evaluation studies.

The Cochrane Handbook for Systematic Reviews of Interventions was used to assess risk of bias for randomized (RoB2) and non-randomized intervention (ROBINS-I) studies⁷, and AMSTAR 2 to critically appraise meta-analysis/systematic reviews.⁸

Results

Characteristics of Included Studies

This review based the evidence of vaccine effectiveness (VE), safety, and immunogenicity of pertussis-containing vaccines on the results of several studies. Appendix A lists

Characteristics of Included Studies. Appendix B shows the appraisal for the Risk of Bias of included studies, and Appendix D shows the GRADE evidence profile for the certainty of evidence for each outcome.

Table 51. Summary of outcomes for pertussis-containing vaccines

Outcomes	Population (Age range)	Evidence Basis	Certainty of Evidence
Vaccine effectiveness	Children (DTaP) (2 months to 12 years)	1 Meta-analysis (Chit et al., 2018)	Low to very low
		1 Cohort study (Rane et al., 2021)	Very low
	Adolescents (Tdap) (11-19 years)	2 Cohort studies (Acosta et al., 2012; Breakwell et al., 2016)	Low
Vaccine safety (Serious adverse events)	Children (DTaP and DTwP) (2 months to 7 years old)	1 Cochrane meta-analysis (Zhang et al., 2014)	Low to Very Low
	Adolescents (Tdap) (10-18 years)	1 RCT (Pichichero et al., 2005)	Moderate
Vaccine immunogenicity	Adolescents (Tdap) (10-18 years)	1 RCT (Pichichero et al., 2005)	Moderate

RCT randomized controlled trial

Data on VE of the pertussis-containing vaccines given as boosters during childhood (DTaP) was based on the results of one systematic review/meta-analysis completed in 2018.⁹ The meta-analysis included three observational studies (1 cohort, 2 case control study) and sought to determine the risk of pertussis since the last dose of the 5-dose DTaP. In addition, one population-based retrospective cohort study published in 2021 reported the association of undervaccination and delayed vaccination of the 5-dose DTaP primary series on the risk of acquiring pertussis disease among children.¹⁰

Data on safety of pertussis-containing booster vaccines during childhood was based on a 2014 Cochrane meta-analysis that included 52 safety trials with a total of 136,541 participants.¹¹ The results of the meta-analysis covered a broad range of local and serious safety outcomes for two comparisons: (1) acellular versus whole cell pertussis vaccine, and (2) acellular versus placebo. The meta-analysis did not cover the safety of whole cell vaccines alone versus placebo. Subgroup analysis was done according to the immunization schedule, whether the vaccine was given as a complete infant primary series or as the fourth or fifth booster during childhood. This review reports critical safety outcomes (i.e., serious adverse events) that were associated with receipt of the primary series, and the first and second booster during childhood.

Data on VE, safety, and immunogenicity of the Tdap vaccine given as boosters during adolescence were based on the results of two observational cohort studies and one randomized controlled trial. Two observational, matched case-control studies in the US investigated the VE of the Tdap vaccine against pertussis among adolescents (10-18 years old) who have completed their primary series.^{12,13} One randomized controlled trial¹⁴ reported immunogenicity and safety data among fully immunized adolescents after 1 month of receipt of Tdap vaccine. The pertussis antibody response pre- and post-vaccination were measured in the form of pertussis toxoid (PT), filamentous hemagglutinin (FHA), and pertactin (PRN), the components that contribute to the virulence of Pertussis. Geometric Mean Concentrations (GMCs) exceeding the predefined lower limit of 80% was used to demonstrate a booster response.

Vaccine Effectiveness

Pertussis-containing (DTaP) booster vaccinations during childhood compared to no or under vaccination are protective against pertussis, but protection declines over time.

Compared to no vaccine, five doses of DTaP (3 primary doses at infancy, 2 booster doses during childhood) reduce the absolute risk of pertussis, with a relative risk of 0.09 (95% CI: 0.07-0.11) in the first 2 years after series completion. Protection declines over time reaching an RR of 0.39 (95% CI: 0.27-0.56) after 6 years of series completion. In the meta-analysis by Chit et al., they calculated that the absolute VE was estimated at 91% (95% CI: 87%-95%) and declined 9.6% per year.⁹ The certainty of evidence for this outcome is rated low to very low due to indirectness, serious risk of bias for selection, and confounding bias, and presence of significant heterogeneity of two reported outcomes. See Table 52.

Table 52. Estimated relative risk of pertussis after 5 doses of DTaP vaccine according to the number of years since last receipt

Number of Years Since Receipt of 5-dose DTaP Vaccination	Basis (No. of studies, no. of participants)	Effect Estimate RR [95% CI]	Interpretation	Certainty of Evidence
1 to 2 years	1 meta-analysis (3 studies, $I^2= 26.01$)	0.09 [0.07-0.11]	Benefit	Low
2 to 3 years	1 meta-analysis (3 studies, $I^2= 31.75$)	0.12 [0.10-0.16]	Benefit	Low
3 to 4 years	1 meta-analysis (3 studies, $I^2= 0$)	0.17 [0.15-0.20]	Benefit	Low
4 to 5 years	1 meta-analysis (3 studies, $I^2= 58.64$)	0.25 [0.18-0.35]	Benefit	Very Low
6 years	1 meta-analysis (2 studies, $I^2= 63.78$)	0.39 [0.27-0.56]	Benefit	Very Low

CI confidence interval; RR relative risk

Likewise, under vaccination of childhood booster doses was found to be significantly associated with a high risk of pertussis, with an adjusted relative risk of 3.2 (95% CI: 2.3-4.5) for the first booster, and 4.6 (95% CI: 2.6-8.2) for the second booster.¹⁰ However, delay in

vaccination among children who received the recommended number of vaccine doses was not associated with pertussis risk. The certainty of evidence for this outcome is very low due to indirectness to the healthcare question, serious risk of bias (confounding, selection, and missing data), and imprecision (Table 53).

Table 53. Estimated relative risk of pertussis: Comparing children who were under vaccinated or vaccinated with delay with those who received age appropriate and timely DTaP vaccine

Booster Dose	Basis (No. of studies, no. of participants)	Effect Estimate RR [95% CI]	Interpretation	Certainty of Evidence
First Booster				
Under vaccinated with or without delay	1 cohort study (N=258,675)	3.2 [2.3-4.5]	Benefit	Very Low
Delayed vaccination	1 cohort study (N=221,928)	0.8 [0.5-1.4]	Inconclusive	Very Low
Second Booster				
Under vaccinated with or without delay	1 cohort study (N=134,950)	4.6 [2.6-8.2]	Benefit	Very Low
Delayed vaccination	1 cohort study (N=111,387)	1.3 [0.5-3.6]	Inconclusive	Very Low

CI confidence interval; RR relative risk

Pertussis-containing (Tdap) booster vaccination among adolescents decreases the odds of developing pertussis disease; however, its effectiveness wanes over time.

Pooled analysis of two observational studies showed that receiving a booster dose of Tdap vaccine during adolescence decreases the odds of developing illness for up to 58% (OR 0.42 95% CI 0.35 to 0.52, $I^2=0\%$). Subgroup analysis on the duration of protection conferred by Tdap booster vaccination shows protection wanes over time (OR 0.42 95% CI 0.36 to 0.49, $I^2=59\%$), with results showing moderate heterogeneity. Vaccine effectiveness after less than 12 months is around 71% (OR 0.29 95% CI 0.22 to 0.38) compared to 55% by 12-23 months post-vaccination (OR 0.45, 95% CI 0.35 to 0.58). Vaccine effectiveness for Tdap is lowest at 46% by 2 to 4 years post-vaccination (OR 0.54 95% CI 0.43 to 0.69).^{12,13} The certainty of evidence for this outcome is low due to indirectness to the healthcare question and serious risk of bias (confounding, selection, and missing data). (Table 54).

Table 54. Estimated odds of developing pertussis after Tdap booster vaccination according to number of months post-vaccination

Number of Years Since Receipt of Tdap Vaccination	No. of Studies (No. of participants)	Effect Estimate (95% CI)	Interpretatio n	Certainty of Evidence
Overall	2 observational studies (2,654)	OR=0.42 (0.35-0.52) VE=58%	Benefit	Low
Less than 12 months post- vaccination	2 observational studies (1,167)	OR=0.28 (0.22-0.38) VE=71%	Benefit	Low

12-23 months post-vaccination	2 observational studies (1,273)	OR=0.45 (0.35-0.58) VE=55%	Benefit	Low
24-46/47 months post-vaccination	2 observational studies (1,272)	OR= 0.54 (0.43-0.69) VE=46%	Inconclusive	Low

CI confidence interval; OR odds ratio; VE vaccine effectiveness

Vaccine immunogenicity data were reported by one randomized controlled trial,¹⁴ the pertussis antibody responses pre- and post-vaccination were measured among the adolescents who received Tdap as a booster after 1 month. Pertussis antigens were in the form of pertussis toxoid (PT), filamentous hemagglutinin (FHA), and pertactin (PRN)—the components that contribute to the virulence of pertussis. Tdap was found to elicit significant increases in anti-PT, anti-FHA, and anti-PRN geometric mean concentrations (GMCs), exceeding the predefined lower limit of 80% to demonstrate a booster response. The certainty of evidence for this outcome is moderate due to unclear risk of bias for selection bias (allocation concealment) in the trial. See Table 55.³

Table 55. Summary of outcomes for vaccine immunogenicity among adolescents

Outcomes	No. of Studies (No. of participants)	Booster response ³ (95% CI)	Interpretation	Certainty of Evidence
Antibody responses to PT 1 month post-vaccination	1 RCT (N=2,677)	84.5% (83.0 to 85.8)	Benefit	Moderate
Antibody responses to FHA 1 month post-vaccination	1 RCT (N=2,744)	95.1% (94.2 to 95.9)	Benefit	Moderate
Antibody responses to PRN 1 month post-vaccination	1 RCT (N=2,752)	95.4% (94.5 to 96.1)	Benefit	Moderate

CI confidence interval; FHA filamentous hemagglutinin; PRN pertactin; PT pertussis toxoid; RCT randomized controlled trial

Booster response for PT, FHA, and PRN was defined as: (1) an antibody concentration \geq 20 EL.U./mL in adolescents who were seronegative (antibody concentrations <5.0 EL.U./mL) before vaccination, or (2) at least a fourfold increased antibody concentration in adolescents who were seropositive with pre-vaccination antibody concentrations ≥ 5.0 EL.U./mL and <20 EL.U./mL, or (3) at least a two-fold increased antibody concentration in adolescents who were seropositive with pre-vaccination antibody concentrations ≥ 20 EL.U./mL.

Vaccine Safety

Acellular pertussis vaccines pose a significantly lower risk of convulsions and hypotonic hyporesponsive episodes compared to whole cell vaccines.

The 2014 Cochrane meta-analysis¹¹ compared safety outcomes for acellular versus whole-cell pertussis vaccines including all-cause mortality, deaths from infection, and convulsions. According to the report, the risk of death due to any cause did not differ significantly between acellular and whole-cell recipients with an RR 0.87 (95% CI 0.62 to 1.22). Likewise, the risk of death due to infection did not differ significantly between acellular and whole-cell

recipients (RR 0.97, 95% CI 0.23 to 4.16). The risk of convulsions and hypotonic hyporesponsive episodes after primary series immunization was significantly lower in acellular vaccine recipients compared to those immunized with whole-cell vaccines, with RR 0.47 (95% CI 0.31 to 0.73) for convulsions, and RR 0.26 (95%CI 0.08 to 0.81) for hypotonic hyporesponsive episodes. The certainty of evidence for this outcome is rated low due to unclear risk of bias (selection bias: allocation concealment) and presence of significant imprecision for some outcomes. See Table 56.

Table 56. Summary of safety outcomes comparing acellular vs. whole cell vaccines among infants and children

Outcomes	Basis (No. of studies, number of participants)	RR (95% CI)	Interpretation	Certainty of Evidence
All-cause mortality (Primary series only)	1 meta-analysis (16 studies, N=122451, I ² = 0%)	0.87 [0.62, 1.22]	Equivalent	Low
Death due to infection (Primary series only)	1 meta-analysis (13 studies, N=34498, I ² = 0%)	0.97 [0.23, 4.16]	Equivalent	Low
Convulsions (Boosters)	1 meta-analysis (11 studies, N=2647, I ² = N/A)	0.47 [0.31, 0.73]	Benefit (aP)	Low
Hypotonic hyporesponsive episodes (Primary series only)	1 meta-analysis (18 studies, N=121573, I ² = 50)	0.26 [0.08, 0.81]	Benefit (aP)	Low

CI confidence interval; RR relative risk

Compared to placebo, acellular pertussis vaccines as primary immunizations do not pose a higher risk for serious adverse events.

For vaccine safety comparing acellular pertussis vaccines versus placebo, the meta-analysis included all-cause mortality, death due to infection, convulsions, and hypotonic hyporesponsive episodes. No booster data were available. All-cause mortality and deaths due to infection did not differ significantly between acellular vaccines and placebo, with RR of 1.08 (95% CI 0.26 to 4.42) and RR of 1.21 (95% CI 0.19 to 7.80), respectively. There was no statistically significant difference between acellular and placebo recipients in terms of the risk of convulsion after primary series immunization (RR 0.46, 95%CI 0.02, 11.20). The risk of hypotonic hyporesponsive episodes after primary series immunization did not differ

significantly (RR 0.29, 95% CI 0.02 to 5.13).¹¹ The certainty of evidence for this outcome is rated low to very low due to unclear risk of bias (selection bias: allocation concealment) and presence of significant imprecision and heterogeneity for some outcomes. See Table 57.

Table 57. Summary of safety outcomes comparing acellular vaccines vs. placebo during primary series

Outcomes	Basis (No. of studies, number of participants)	RR (95% CI)	Interpretation	Certainty of Evidence

All-cause mortality (Primary series only)	1 meta-analysis (16 studies, N=122451, $I^2=0\%$)	1.08 (0.26, 4.42)	Equivalent	Low
Death due to infection (Primary series only)	1 meta-analysis (4 studies, N=25902, $I^2=0\%$)	1.21 (0.19, 7.80)	Equivalent	Low
Convulsions (Primary series only)	1 meta-analysis (4 studies, N=25901, $I^2=72\%$)	0.44 (0.12, 1.69)	Inconclusive	Very Low
Hypotonic hyporesponsive episodes (Primary series only)	1 meta-analysis (4 studies, N=25901, $I^2=52\%$)	0.29 (0.02, 5.13)	Inconclusive	Low

CI confidence interval; RR relative risk

Tdap vaccines have a significantly higher incidence of injection-site pain than non-pertussis vaccine.

Tdap vaccine was reported to have a significantly higher incidence of injection-site pain (grade 2 or 3) compared to those receiving non-pertussis-containing vaccines (RR 1.20, 95% CI 1.11 to 1.30).¹⁴ This may be in part due to the additional antigens contained in the vaccine. There were no significant differences observed among other reported symptoms post-vaccination such as redness, swelling, fever, headache, fatigue, and gastrointestinal symptoms. Overall, the study found that the Tdap vaccine had a comparable safety profile to that of theTd vaccine when administered to adolescents. The certainty of evidence for this outcome is moderate due to unclear risk of bias for selection bias (allocation concealment) and imprecision. See Table 58.

Table 58. Summary of safety outcomes comparing Tdap vaccines vs placebo among adolescents

Outcomes	No. of Studies (No. of participants)	RR (95% CI)	Interpretation	Certainty of Evidence
Local Symptoms				
Pain (grade 2 or 3) ¹	1 RCT (N=4,045)	1.20 (1.11 to 1.30)	Inconclusive	Moderate
Redness	1 RCT (N=4,045)	1.12 (0.97 to 1.29)	Inconclusive	Moderate
Swelling	1 RCT (N=4,045)	1.02 (0.88 to 1.18)	Equivalent	Moderate
General Symptoms				
Fever	1 RCT (N=4,043)	1.19 (0.89 to 1.59)	Inconclusive	Moderate
Headache (grade 2 or 3) ¹	1 RCT (N=4,043)	1.14 (0.88 to 1.47)	Inconclusive	Moderate
Fatigue (grade 2 or 3) ¹	1 RCT (N=4,043)	1.03 (0.81 to 1.29)	Equivalent	Moderate

Gastrointestinal symptoms (grade 2 or 3) ^{1,2}	1 RCT (N=4,043)	0.99 (0.72 to 1.35)	Inconclusive	Moderate
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CI confidence interval; RCT randomized controlled trial; RR relative risk

Recommendations from Other Groups

The World Health Organization provided a joint reporting of all vaccination schedules among multiple countries. To date, at least 55 countries have included pertussis-containing boosters (mainly Tdap) for older children and adolescents in their national immunization programs. The data can be accessed through their website at <https://immunizationdata.who.int>.¹⁵

Other recommendations for both DTaP and Tdap vaccines are given below (see Table 59):

Table 59. Summary of other groups' recommendations for DTaP and Tdap vaccines

Group	Recommendation	Basis for Recommendation
World Health Organization ¹⁵	WHO recommends the first dose be administered as early as 6 weeks of age; with subsequent doses given 4-8 weeks apart, at age 10-14 weeks and 14-18 weeks. A booster dose is recommended, preferably during the second year of life. Based on local epidemiology, further booster doses may be warranted later in life.	Not indicated
US CDC ¹⁸	(1) 5 doses of DTaP at 2, 4, and 6 months, around 15-18 months, and around 48-84 months; (2) Tdap given for children ages 7-10 years: a single dose for those who have not completed the five-dose DTaP series, or as part of a catch-up schedule; (3) Tdap given as a single dose among 11-18 years of age with preferred administration at 11 through 12 years of age.	Not indicated
Advisory Committee on Immunization Practices (ACIP), USA ¹⁷	All children should receive a series of DTaP at ages 2, 4, and 6 months, with boosters at ages 15-18 months and at 4-6 years. The fourth dose may be given as early as age 12 months if at least 6 months have elapsed since the third dose. Persons aged 11-18 years should receive a single dose of Tdap, preferably at a preventive care visit at ages 11-12 years. To ensure continued protection against tetanus and diphtheria, booster doses of either Td or Tdap should be administered every 10 years throughout life.	ACIP evidence to recommendation
Global Pertussis Initiative ¹⁹	Lacking robust data, we primarily recommend that brands of wP- or aP-containing combination vaccines should not be	Expert consensus (Multiple countries)

	<p>interchanged during primary immunization whenever possible. For the fourth dose in the second year of life, aP-containing vaccines may be interchanged, if necessary.</p> <p>Expanded vaccination should include adding booster doses to existing childhood schedules (preschool or adolescent) and booster doses for those specific adult subgroups that have the highest risk of transmitting <i>B. pertussis</i> infection to infants (i.e., new parents, other contacts of newborns, and health care workers).</p>	
Philippine Pediatric Society (PPS) and Pediatric Infectious Disease Society of the Philippines (PIDSP) ¹⁶	<p>The primary series consists of 3 doses with a minimum interval of 4 weeks.</p> <p>Booster series consists of 3 doses until adolescence with the following schedule:</p> <ul style="list-style-type: none"> ● 12-23 months (DTP) ● 4-7 years (DTP) ● 9-15 years (Td/Tdap) <p>Ideally, the minimum interval between booster doses should be at least 4 years</p> <p>For children who are fully immunized, Td or Tdap booster doses should be given every 10 years.</p> <p>For children age >7 years a single dose of Tdap can be given to replace due Td. Tdap can be administered regardless of the interval since the last tetanus and diphtheria-toxoid containing vaccine. Subsequent doses are given as Td or Tdap.</p>	Not indicated

Additional Considerations for Evidence-to-Decision (EtD) Phase

Cost

Tdap booster vaccination among adolescents is generally considered a cost-effective measure based on several cost-effectiveness, cost-utility, and economic impact models from developed countries (Netherlands, USA, UK, Canada).^{20,21,22,23} However, it should be noted that these estimations were done comparing Tdap to no vaccination. Appendix D summarizes the published findings from studies done in other countries.

In the latest National Immunization Program, the Philippines does not offer a booster dose against pertussis after the primary series of vaccinations. Recommended booster doses come in the form of Td vaccine, covering tetanus and diphtheria only, given as a two-dose schedule to school-age children 5-7 years and 12-15 years of age.¹⁶ Cost may be considered one important consideration as Tdap costs more than Td vaccines (see Table 60). Pricing data published by UNICEF showed that the usual awarded price per dose of Td vaccinations from multiple suppliers in 2021 range from USD 0.09 to 0.20 (PHP 5.30 to 12.00).²⁴

Table 60. Cost comparison of DTaP, Tdap, and Td vaccines in 2022²⁴

	Vaccine

	DTaP vaccine	Tdap vaccine	Td vaccine
Unit Cost	PHP 2,500 to 4,000.00/single-dose vial (Daptacel, Infanrix)	PHP 1,113.50 to 1,200.00/single-dose vial (Adacel, Boostrix)	Public: USD 0.09-0.20 (PHP 5.30 to 12.00) ^a Private: PHP 500.00

^aConversion rate: USD 1 = PHP 58.33

Although no cost-effectiveness studies comparing Tdap and Td vaccines have been done in the Philippines as of this writing, an economic impact study in the US investigated the implication and cost-effectiveness of replacing decennial Td boosters with Tdap in their country. Considering low incidence of pertussis cases among adults, Tdap vaccination would result in high costs per averted case (USD 111,540.00) and high cost of quality-adjusted life years saved (USD 8,972,848.00). If incidence was assumed to be higher (for example at 250/cases per 100,000 person-years), costs per averted case were lower at USD 984.00, and estimated cost per QALY saved ranged from USD971.00 (most favorable) to USD 217,370.00 (least favorable).²⁵ See Table 61.

Table 61. Cost-effectiveness of replacing Td boosters with Tdap in the US²⁵

Incidence (Pertussis cases per 100,000 person-years)	Total cost for Td boosters (Medical + non-medical)	Total cost for Tdap boosters (Medical + non-medical)	Cost per averted case for Tdap	Cost effectiveness ratio per QALY saved
2.5	USD 2,319,061.00	USD 1,855,769.00	USD 111,540.00 (high)	USD 8,972,849.00 (high)
250	USD 76,327,495.00	USD 60,882,923.00	USD 984.00	USD 81,678.00
500	USD 149,308,246.00	USD 119,084,363.00	USD 427.00	USD 35,474.00

QALY quality-adjusted life year

These findings confer a high degree of uncertainty as several factors affect these estimations such as the true pertussis incidence, degree of illness severity, vaccine effectiveness, and the impact of herd protection.

Patient's Values and Preference, Equity, Acceptability, and Feasibility

There is presently no data available on the values and acceptability of children, adolescents, and their families towards the use of Tdap or Td in situations where only Td vaccine is recommended. However, there is unpublished evidence in the US that Tdap is already being used in settings where Td only is recommended. No published data is available in the Philippine setting.

- Analysis of US commercial insurance claims indicated that in 2017 in adults aged 19 to 64 years, Tdap claims (n=716,638) were 12-fold more frequent than Td claims (n=61,468) (Truven Health Analytics, unpublished data, 2019 from ACIP).¹⁷
- In 2017, there were 441,075 doses of Tdap ordered by providers for adults for public sector purchases compared with 41,881 doses of Td ordered (CDC unpublished data, 2019 from ACIP).¹⁷

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25. Havers, F. P., Cho, B. H., Walker, J. W., & Hariri, S. (2020). Economic impact of implementing decennial tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccination in adults in the United States. *Vaccine*, 38(2), 380–387. <https://doi.org/10.1016/j.vaccine.2019.09.104>

5. Research Implications/Gaps

Many research questions from the identified clinical questions in this CPG were unanswered due to lack of published clinical research involving vaccines. 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.

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). Meta-analysis of RCTs indicated a tendency for risk of bias, heterogeneity, and inconsistency in the assessment and 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.

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. However, there were very limited studies that investigated: (1) psychosocial and cultural determinants of vaccine acceptability, and (2) 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 strengthen weak surveillance systems. To ensure high quality and robust data, regulatory agencies should provide specific guidance on the conduct of pediatric vaccine trials; 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.

With the release of this guideline, a total of 18 vaccines for the pediatric population has been discussed. It was agreed upon by the committee that users of this guideline may refer to the PIDSP/PPS/PFV Annual Childhood Immunization Schedule for guidance on the use of other vaccines not in the scope of the CPG.



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.

6. 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), health maintenance organizations (HMOs), and NGOs involved in a periodic health examination. The recommendations and the evidence summaries will be posted online.

The DOH planned to develop a simplified version of this CPG and make 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 task force 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. It also proposes to submit abridged and full-text copies to relevant journals under the auspices of PPS and PIDSP for publication.

7. 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. Panel recommendations took into considerations the different factors that affect vaccine uptake, storage and transfer requirements such as cold chain and vaccine availability which were the usual barriers to vaccination. The vaccines considered in this review were all locally registered under the Phil. FDA and has indications for use in children and adolescents up to 18 years of age. This CPG also does not necessarily supersede the recommendations from the specialty societies including Philippine Pediatric Society, Philippine Foundation for Vaccination and Pediatric Infectious Disease Society of the Philippines which was done annually. As such, the applicability of this guidelines still depend on the stakeholders, the national government programs and the prevailing recommendations for the pediatric population.

Although this CPG intends to influence the direction of health policies for the general population, adherence to the CPG and the impact of the recommendations can be assessed by qualitative studies using questionnaires and focal group discussions but it should not be the sole basis for recreating or abolishing practices that aim to improve the health conditions of all Filipino children.



8. Updating of the Guidelines

The recommendations herein shall hold until new evidence on screening, diagnosing, managing various risk factors or new vaccine preparations and diseases emerges, and contingencies dictate updating this Philippine Guidelines on Periodic Health Examination. This guideline will be updated after three (3) years.



9. Appendices

PERIODIC HEALTH EXAMINATION TASK FORCE ON PEDIATRIC IMMUNIZATION 2023

Task Force Steering Committee

Chair: Marimel G. Reyes-Pagcatipunan, MD, FPPS, FPIDSP

Co-Chair : Carmina A. Delos Reyes, MD, FPPS,FPIDSP

Members: Mary Antoinette 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

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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
(Philippine Foundation for Vaccination)
Rosemarie T. Santana-Arciaga, MD, FPPS, FPIDSP, MSc
(Pediatric Infectious Disease Society of the Philippines)
Mary Ann Bunyi, MD, FPPS, FPIDSP
(Pediatric Infectious Disease Society of the Philippines)
Teri-Marie Laude, MD, MsCM-FM
(Philippine Academy of Family Physicians)
Melissa Joyce Ramboanga, MD
(Philippine Ambulatory Pediatric Association)
Marysia Stella P. Tiongco-Recto, MD
(Philippine Society of Allergology, Asthma and Immunology)
Maria Teresa D. Villanueva, MD, FPPS
(Philippine Pediatric Society)
Maria Lourdes Bernadeth V. Manipon, RN
(Philippine Hospital Infection Control Nurse Association)
Bryan S. Posadas, RPh
(Philippine Pharmacists Association, Inc.)

Panel Meeting Facilitator: Mary Ann Abakan, MD, FPPS

Technical Writer: Korina Ada D. Tanyu, MD, FPPS

Administrative Officer: Jonalyn N. Nuqui



PERIODIC HEALTH EXAMINATION PHASE 3 CENTRAL COMMITTEE

Program Leader: Ian Theodore G. Cabaluna RPh, MD, GDip (Epi), MSc (cand.)

Co-Program Leaders: Marissa M. Alejandria, MD, MSc
Leonila F. Dans, MD, MSc

Central Steering Committee: Antonio L. Dans, MD, MSc
Dante D. Morales, MD
Beverly Lorraine C. Ho, MD
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Assistant Project Manager: Lea Galia, MD

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Maria Pamela Tagle
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Oversight Committee

Chair: Dante D. Morales, MD
Co-Chair: Antonio L. Dans, MD, MSc
Members: Angela Abanilla-Du, MD
Camilo G. Te, MD
Maria Vanessa V. Sulit, RN MSc

SUMMARY OF COI DECLARATIONS

Name	Designation	Society	COI Decision	Management
Rosemarie T Arciaga, MD	Medical Specialist	Pediatric Infectious Disease Society of the Philippines	B - Non-financial COI	To declare: - Lectures on vaccines (society initiated)
Cynthia A. Aguirre, MD	Medical Specialist	Philippine Foundation for Vaccination	A	No COI – allowed to participate
Melissa Joyce P. Ramboanga, MD	Medical Specialist	Philippine Ambulatory Pediatric Association	A	No COI – allowed to participate
Teri Marie P. Laude, MD	Medical Specialist	Philippine Academy of Family Physicians	A	No COI – allowed to participate
Marysia Stella T. Recto, MD	Medical Specialist	Philippine Society of Allergy, Asthma and Immunology	C (Financial COI – speakers bureau for Sanofi consumer health)	Cannot vote on question nos. 5 (Pertussis) & 9 (Rabies)
Maria Teresa D. Villanueva, MD	Medical Specialist	Philippine Pediatric Society	B Non-financial COI	To declare: - Current Member of PPS Immunization Committee
Mary Ann Bunyi, MD	Medical Specialist	Pediatric Infectious Disease Society of the Philippines	B Non-financial COI	To declare: - Past chairman of Immunization Committee - Authorship on paper on Pneumococcal Diseases in the Philippines
Maria Lourdes Bernadeth V. Manipon, RN	Registered Nurse	Philippine Hospital Infection Control Nurse Association	A	No COI – allowed to participate



Bryan S. Posadas, RPh	Registered Pharmacist	Philippine Pharmacists Association, Inc.	C Indirect / Intellectual COI: Academic status being faculty for Pharmacy, and Pharmacy Operations resource speaker.	Cannot vote on question #3 Hepatitis
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SEARCH STRATEGY

Question 1. Should rabies pre-exposure prophylaxis (PrEP) be given as routine vaccination for prevention of rabies infection in children and adolescents?

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	"Rabies"[Mesh] AND "Rabies Vaccine"[Mesh] Filters: March 26, 2021 to August 28, 2021 Filters: Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, Systematic Review, Child: birth-18 years, Newborn: birth-1 month, Infant: birth-23 months, Infant: 1-23 months, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years	November 9, 2022 10:00AM	112	3
Cochrane	MeSH descriptor: [Rabies] explode all trees AND MeSH descriptor: [Rabies Vaccines] explode all trees AND MeSH descriptor: [Pre-Exposure Prophylaxis] explode all trees	November 9, 2022 10:00AM	7	0
Google Scholar	rabies vaccine "pre exposure prophylaxis" -adult	November 9, 2022 10:00AM	26	0
ClinicalTrials.gov	Rabies vaccine Applied filters: Child (birth – 17)	November 9, 2022 10:00AM	43	0



Question 2. Among healthy children who completed the primary series of Haemophilus influenzae B (Hib) vaccination, is a booster dose of Hib vaccine needed?

Initial search strategy:

Pubmed/cochrane: haemophilus influenza (MESH) AND ((immunization OR vaccination) AND booster dose))

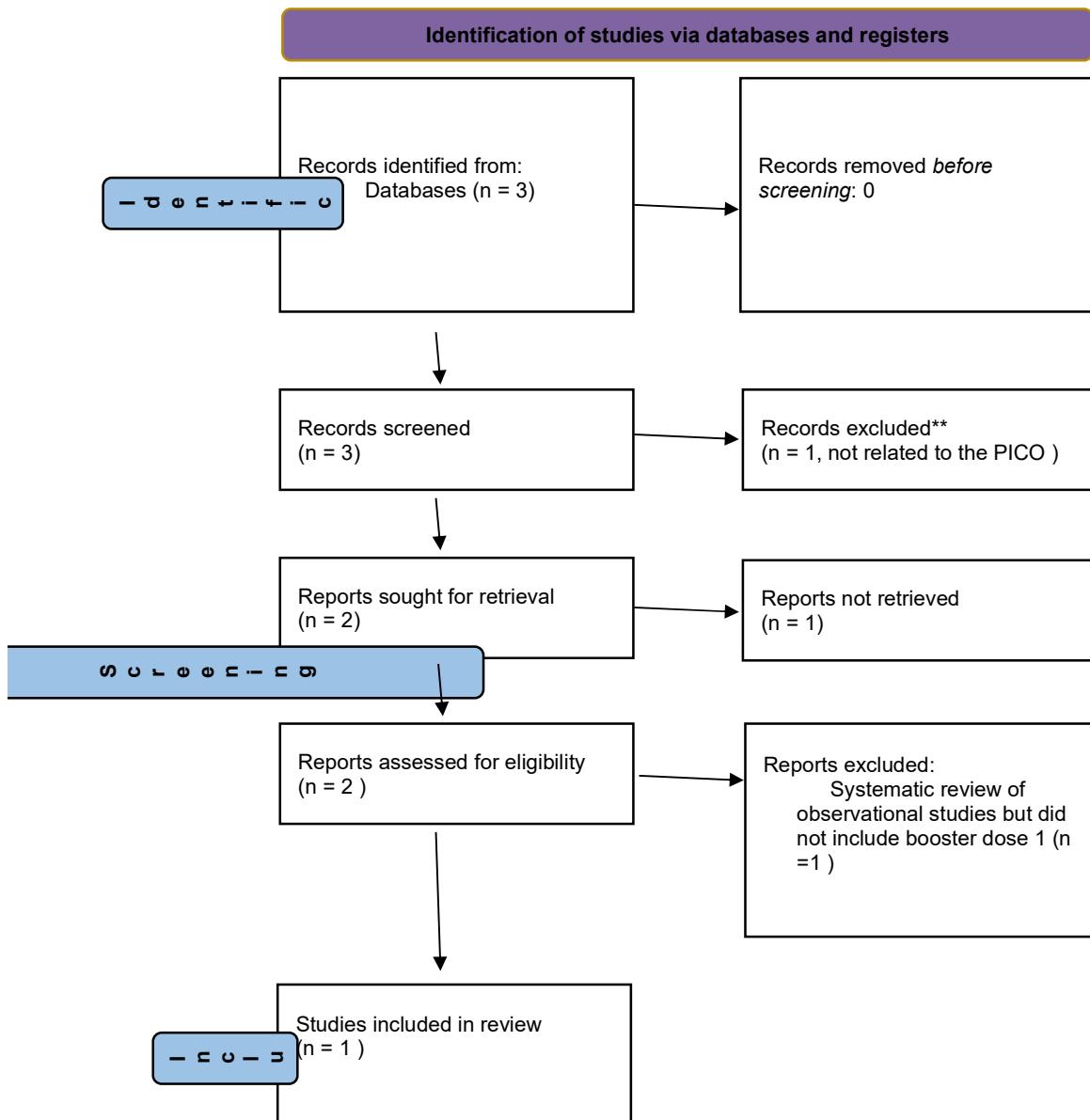
Filter: meta-analysis, systematic review

Updated search strategy (using meta-analysis search strategy)

(((((booster) AND (((immunization) OR (vaccination)) AND (randomizedcontrolledtrial[Filter])))) AND (((haemophilus influenzae) OR (H. influenza)) OR (hib)) AND (randomizedcontrolledtrial[Filter]))) AND (randomizedcontrolledtrial[Filter]))

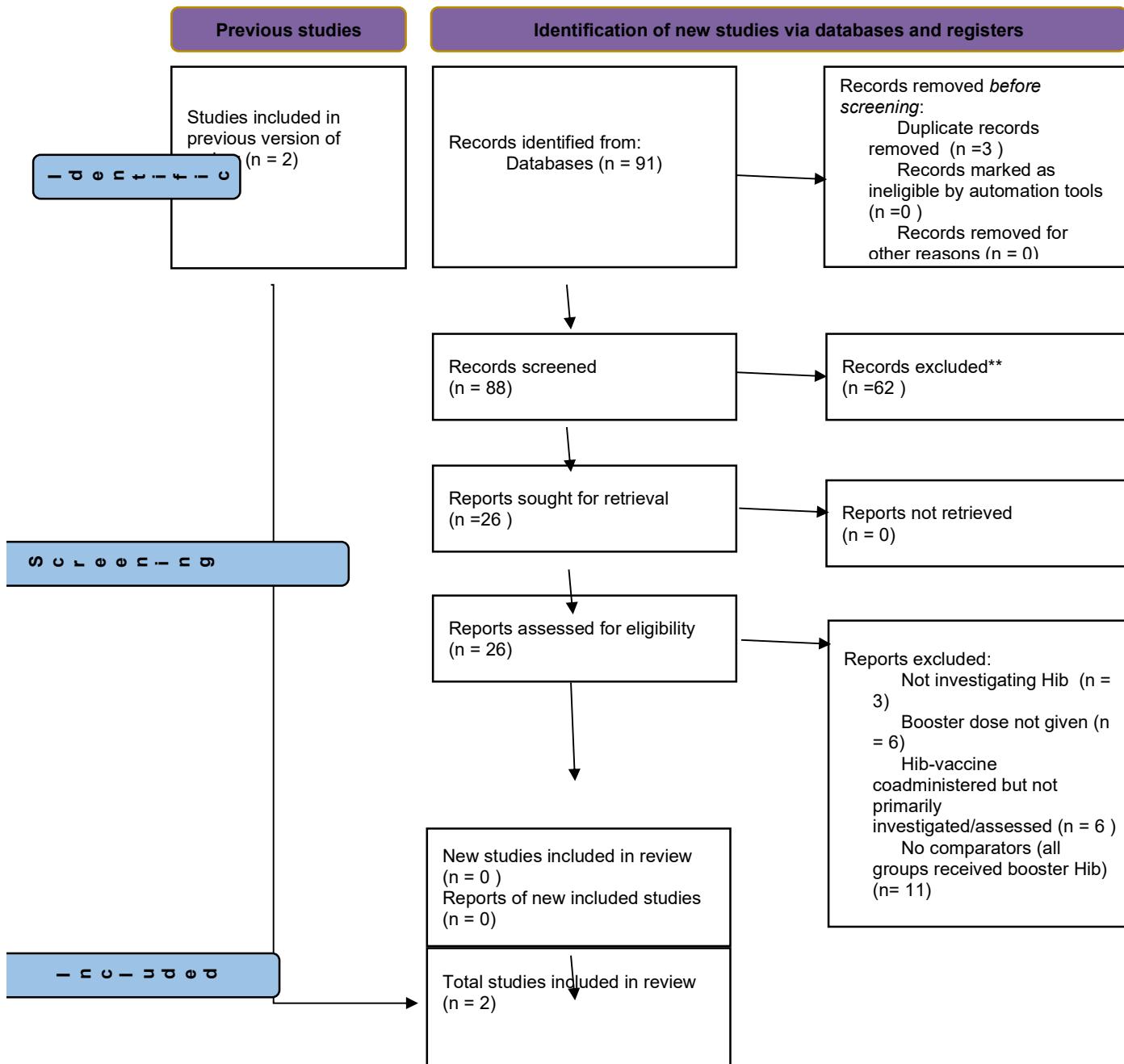
Added filter: 2012-2022

PRISMA Flow Diagram: Initial Search Strategy Result



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

PRISMA Flow Diagram: Updated Search Strategy Result



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71



Question 3. Should the Rotavirus vaccine be routinely given to infants for the prevention of Rotavirus gastroenteritis and its complications?

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
MEDLINE (Pubmed)	"Rotavirus Vaccines"[MeSH Terms] AND ((clinicaltrial[Filter] OR meta-analysis[Filter] OR randomizedcontrolledtrial[Filter]) AND (2020:2022[pdat]))"	February 2, 2023 11:00 AM	40	0
Cochrane Central Register of Controlled Trials CENTRAL	MeSH descriptor: [Rotavirus vaccine] explode all trees Filter: November 30, 2020 to October 24, 2022	February 2, 2023 1:00 PM	24	0
Google Scholar	Rotavirus AND vaccine AND clinical trial Filter: 2020 to 2022	February 2, 2023 2:00 PM	32	0
MedRxiv	Advanced search: "Rotavirus AND vaccine" Filter: November 30, 2020 to October 24, 2022	February 2, 2023 3:00 PM	153	0
ClinicalTrials.gov	Rotavirus vaccine	February 2, 2023 4:00 PM	101	0



Question 4. Should measles containing vaccines be given to apparently healthy children?

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{(Measles vaccine[MeSH Major Topic]) OR (Measles vaccine[MeSH Terms1]) OR (Measles containing vaccine[MeSH Terms]) AND CHILDREN} AND RANDOMIZED CONTROL TRIALS	October 10,2022 9:01AM	311	8
Cochrane	{Measles vaccine [Mesh] OR measles vaccine} AND children Filters: January 2012-September 2022	October 17,2022	167	3
Google Scholar	Measles Vaccine, children, RCT Filters:2018-2022	October 17,2022	949	5



Question 5. Should mumps containing vaccines be given to apparently healthy children?

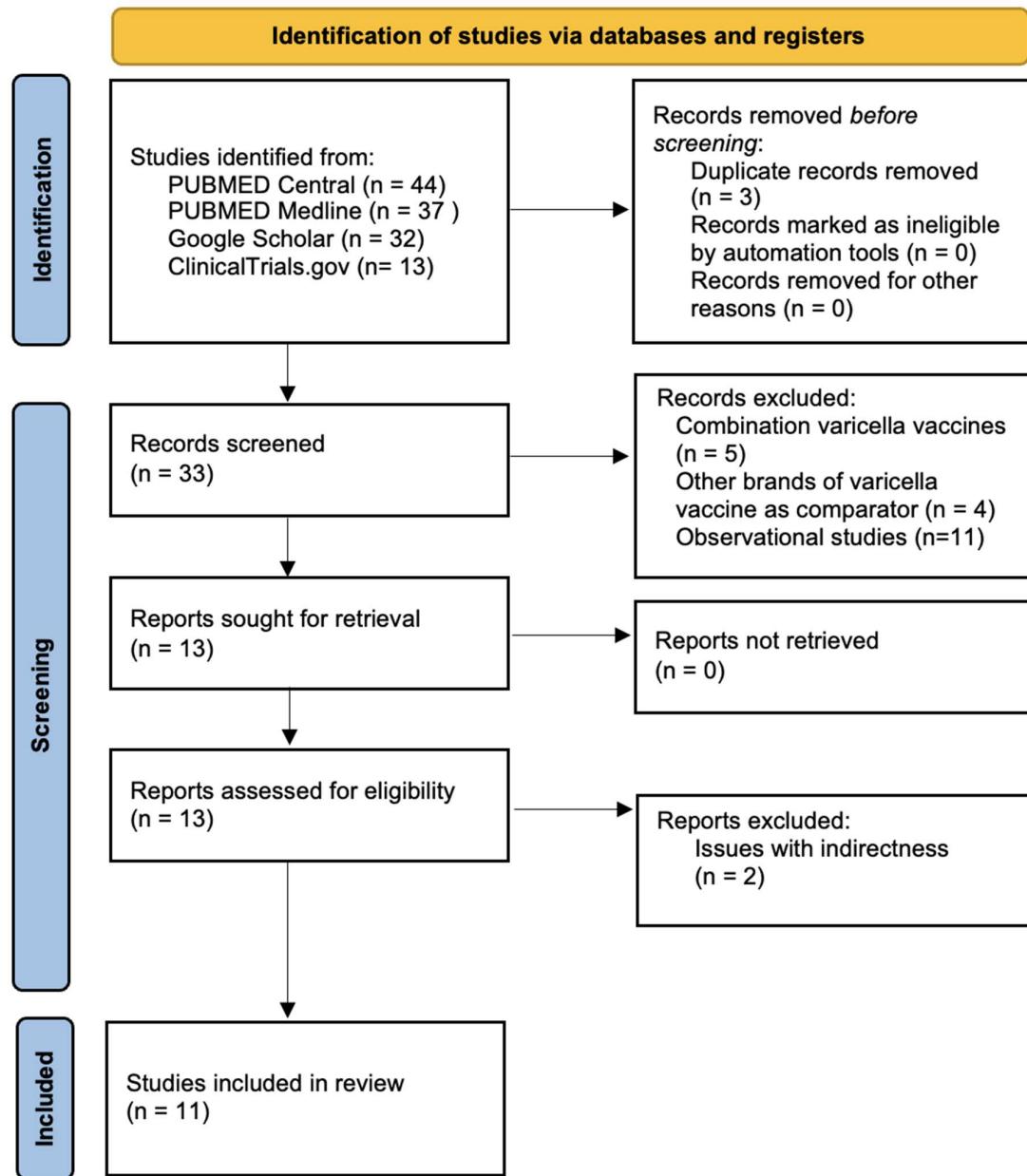
DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{(Measles vaccine[MeSH Major Topic]) OR (Measles vaccine[MeSH Terms1]) OR (Measles containing vaccine[MeSH Terms1]) AND CHILDREN} AND Meta Analysis, Randomized control trials Filters: January 2017-September 2022	October 10,2022 6:29PM	47	4
Cochrane	{Mumps vaccine [Mesh] OR mumpsvaccine} AND children Filters: January 2017-September 2022	October 17,2022	205	2
Google Scholar	Measles Vaccine, children, RCT Filters:2018-2022	October 17,2022	105	4



Question 6. Should varicella vaccine be recommended to apparently healthy children and adolescents?

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
PUBMED Medline	((("varicella immunization"[All Fields]) OR ("varicella vaccine"[All Fields])) OR ("chickenpox vaccine"[All Fields])) OR ("varicella vaccine administration"[All Fields] OR "varicella vaccine efficacy"[All Fields] OR "varicella vaccines"[All Fields]) AND (((("rct"[All Fields]) OR ("randomized control trial"[All Fields])) OR ("systematic review"[All Fields])) OR ("meta analysis"[All Fields]) AND (((("children"[All Fields]) OR ("school age"[All Fields])) OR ("adolescent"[All Fields])) OR ("child"[All Fields])) OR ("pediatric"[All Fields]))	October 1, 2022 4:23PM	37	18
PUBMED Central	((("varicella immunization"[All Fields]) OR ("varicella vaccine"[All Fields])) OR ("chickenpox vaccine"[All Fields])) OR ("varicella vaccine administration"[All Fields] OR "varicella vaccine efficacy"[All Fields] OR "varicella vaccines"[All Fields]) AND (((("rct"[All Fields]) OR ("randomized control trial"[All Fields])) OR ("systematic review"[All Fields])) OR ("meta analysis"[All Fields]) AND (((("children"[All Fields]) OR ("school age"[All Fields])) OR ("adolescent"[All Fields])) OR ("child"[All Fields])) OR ("pediatric"[All Fields]))	October 1, 2022 1:46PM	44	15
Google Scholar	Varicella vaccine OR chickenpox vaccine AND RCT	October 1, 2022 6:30PM	32	10
ClinicalTrials.gov	Varicella vaccine OR chickenpox vaccine	November 5, 2022 10:00PM	13	3

PRISMA Flow Diagram



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71



Question 7. Should BCG vaccine be routinely given at birth to healthy infants for the prevention of tuberculosis?

Step	Query	Result
1	Bacill* Calmette Guerin [tw] OR BCG [tw]	33,240
2	tuberculo* [tw] OR Mycobacterium [tw] OR TB [tw]	343,649
3	tuberculosis [mh]	204,045
4	#2 OR #3	344,046
5	#1 AND #4	21,116
6	randomized controlled trial [pt]	583,635
7	controlled clinical trial [pt]	673,858
8	randomized [tiab]	638,176
9	trial [tiab]	738,583
10	randomly [tiab]	398,333
11	placebo [tiab]	240,606
12	#6 OR #7 OR #8 OR #9 OR #10 OR #11	1,612,823
13	animals [mh] NOT humans [mh]	5,071,327
14	#12 NOT #13	1,472,356
15	#5 AND #14	769
16	child* [mh] OR neonat* [mh]	2,255,959
17	#15 AND #16	189
18	(meta-analysis [pt]) OR (systematic review [pt])	293,640
19	#5 AND #18	107

Question 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?

ELECTRONIC DATABASES	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
MEDLINE	("tetanus"[MeSH Terms] OR "tetanus"[All Fields] OR "tetanus toxoid"[MeSH Terms] OR ("tetanus"[All Fields] AND "toxoid"[All Fields]) OR "tetanus toxoid"[All Fields]) AND ((boostered"[All Fields] OR "boosterizing"[All Fields] OR "immunization, secondary"[MeSH Terms] OR ("immunization"[All Fields] AND "secondary"[All Fields])) OR "secondary immunization"[All Fields] OR "booster"[All Fields] OR "boosters"[All Fields]) AND ("vaccin"[Supplementary Concept] OR "vaccin"[All Fields] OR "vaccination"[MeSH Terms] OR "vaccination"[All Fields] OR "vaccinable"[All Fields] OR "vaccinal"[All Fields] OR "vaccinate"[All Fields] OR "vaccinated"[All Fields] OR "vaccinates"[All Fields] OR "vaccinating"[All Fields] OR "vaccinations"[All Fields] OR "vaccination s"[All Fields] OR "vaccinator"[All Fields] OR "vaccinators"[All Fields] OR "vaccine s"[All Fields] OR "vaccined"[All Fields] OR "vaccines"[MeSH Terms] OR "vaccines"[All Fields] OR "vaccine"[All Fields] OR "vaccins"[All Fields])) Filter: Child: birth – 18 years	22 Oct 2022 12:50PM	1,514	1
		15 Feb 2023 10:47AM	+8	
CENTRAL	MeSH descriptor: [Tetanus] explode all trees	22 Oct 2022 01:12PM	381	0
		15 Feb 2023 11:00AM		
HERDIN (herdin.ph)	Tetanus AND booster	22 Oct 2022 01:20PM	8	0
		15 Feb 2023 12:37PM		

Database: MEDLINE (PubMed)

Date: 22 October 2022 (Updated search: 15 February 2023)

No	Query	Filters	Search Details	Results	Time
6	#1 AND #4	Child: birth – 18 years	((("tetanus"[MeSH Terms] OR "tetanus"[All Fields] OR "tetanus toxoid"[MeSH Terms] OR ("tetanus"[All Fields] AND "toxoid"[All Fields]) OR "tetanus toxoid"[All Fields]) AND ((boostered"[All Fields] OR "boosterizing"[All Fields] OR "immunization, secondary"[MeSH Terms] OR ("immunization"[All Fields] AND "secondary"[All Fields])) OR "secondary immunization"[All Fields] OR "booster"[All Fields] OR "boosters"[All Fields]) AND ("vaccin"[Supplementary Concept] OR "vaccin"[All Fields] OR "vaccination"[MeSH Terms] OR "vaccination"[All Fields] OR "vaccinable"[All Fields] OR "vaccinal"[All Fields] OR "vaccinate"[All Fields] OR "vaccinated"[All Fields] OR "vaccinates"[All Fields] OR "vaccinating"[All Fields] OR "vaccinations"[All Fields] OR "vaccination s"[All Fields] OR "vaccinator"[All Fields] OR "vaccinators"[All Fields] OR "vaccine s"[All Fields] OR "vaccined"[All Fields] OR "vaccines"[MeSH Terms] OR "vaccines"[All Fields] OR "vaccine"[All Fields] OR "vaccins"[All Fields])))) AND (allchild[Filter]))	1,514	12:50:30



			Updated search	1,522	10:47:42	
5	#1 AND #4	("tetanus"[MeSH Terms] OR "tetanus"[All Fields] OR "tetanus toxoid"[MeSH Terms] OR ("tetanus"[All Fields] AND "toxoid"[All Fields]) OR "tetanus toxoid"[All Fields]) AND (("boostered"[All Fields] OR "boostering"[All Fields] OR "immunization, secondary"[MeSH Terms] OR ("immunization"[All Fields] AND "secondary"[All Fields]) OR "secondary immunization"[All Fields] OR "booster"[All Fields] OR "boosters"[All Fields]) AND ("vaccin"[Supplementary Concept] OR "vaccin"[All Fields] OR "vaccination"[MeSH Terms] OR "vaccination"[All Fields] OR "vaccinable"[All Fields] OR "vaccinal"[All Fields] OR "vaccinate"[All Fields] OR "vaccinates"[All Fields] OR "vaccinating"[All Fields] OR "vaccinations"[All Fields] OR "vaccination s"[All Fields] OR "vaccinator"[All Fields] OR "vaccinators"[All Fields] OR "vaccine s"[All Fields] OR "vaccined"[All Fields] OR "vaccines"[MeSH Terms] OR "vaccines"[All Fields] OR "vaccine"[All Fields] OR "vaccins"[All Fields]))		Updated search	2,430	12:50:16
4	#2 AND #3	("boostered"[All Fields] OR "boostering"[All Fields] OR "immunization, secondary"[MeSH Terms] OR ("immunization"[All Fields] AND "secondary"[All Fields]) OR "secondary immunization"[All Fields] OR "booster"[All Fields] OR "boosters"[All Fields]) AND ("vaccin"[Supplementary Concept] OR "vaccin"[All Fields] OR "vaccination"[MeSH Terms] OR "vaccination"[All Fields] OR "vaccinable"[All Fields] OR "vaccinal"[All Fields] OR "vaccinate"[All Fields] OR "vaccinated"[All Fields] OR "vaccinates"[All Fields] OR "vaccinating"[All Fields] OR "vaccinations"[All Fields] OR "vaccination s"[All Fields] OR "vaccinator"[All Fields] OR "vaccinators"[All Fields] OR "vaccine s"[All Fields] OR "vaccined"[All Fields] OR "vaccines"[MeSH Terms] OR "vaccines"[All Fields] OR "vaccine"[All Fields] OR "vaccins"[All Fields])		18,184	12:49:57	
3	Vaccination	"vaccin"[Supplementary Concept] OR "vaccin"[All Fields] OR "vaccination"[MeSH Terms] OR "vaccination"[All Fields] OR "vaccinable"[All Fields] OR "vaccinal"[All Fields] OR "vaccinate"[All Fields] OR "vaccinated"[All Fields] OR "vaccinates"[All Fields] OR "vaccinating"[All Fields] OR "vaccinations"[All Fields] OR "vaccination s"[All Fields] OR "vaccinator"[All Fields] OR "vaccinators"[All Fields] OR "vaccine s"[All Fields] OR "vaccined"[All Fields] OR "vaccines"[MeSH Terms] OR "vaccines"[All Fields] OR "vaccine"[All Fields] OR "vaccins"[All Fields])	Updated search	486,113	10:47:00	
2	Booster	"boostered"[All Fields] OR "boostering"[All Fields] OR "immunization, secondary"[MeSH Terms] OR ("immunization"[All Fields] AND "secondary"[All Fields]) OR "secondary immunization"[All Fields] OR "booster"[All Fields] OR "boosters"[All Fields]	Updated search	27,900	10:46:55	
1	Tetanus	"tetanus"[MeSH Terms] OR "tetanus"[All Fields] OR "tetanus toxoid"[MeSH Terms] OR ("tetanus"[All Fields] AND "toxoid"[All Fields]) OR "tetanus toxoid"[All Fields]	Updated search	30,584	10:46:49	

Database: Cochrane CENTRAL

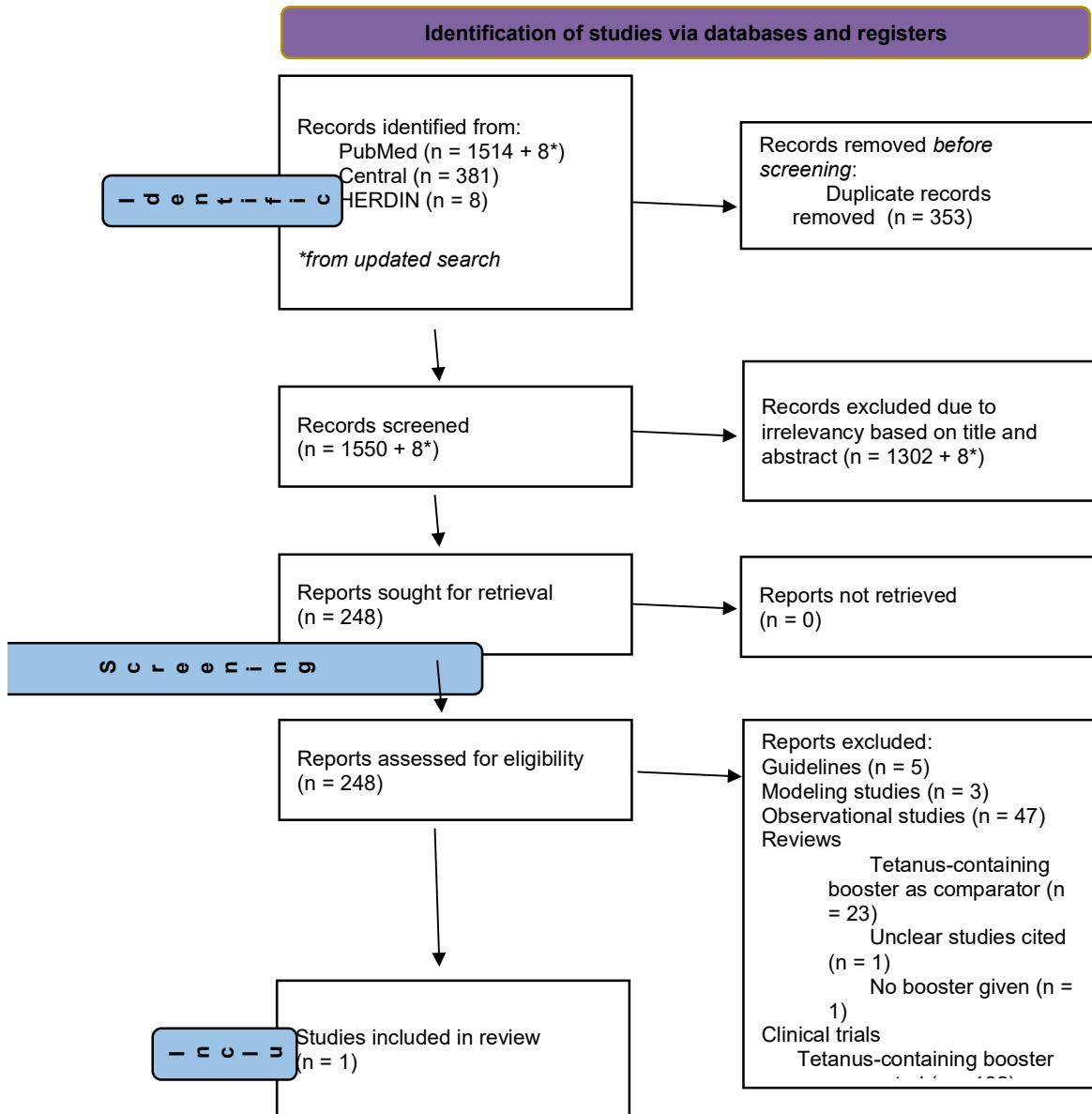
Date: 22 October 2022 (Updated search: 15 February 2023)

ID	Search	Hits
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#1	MeSH descriptor: [Tetanus] explode all trees	381
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PRISMA Flow Diagram

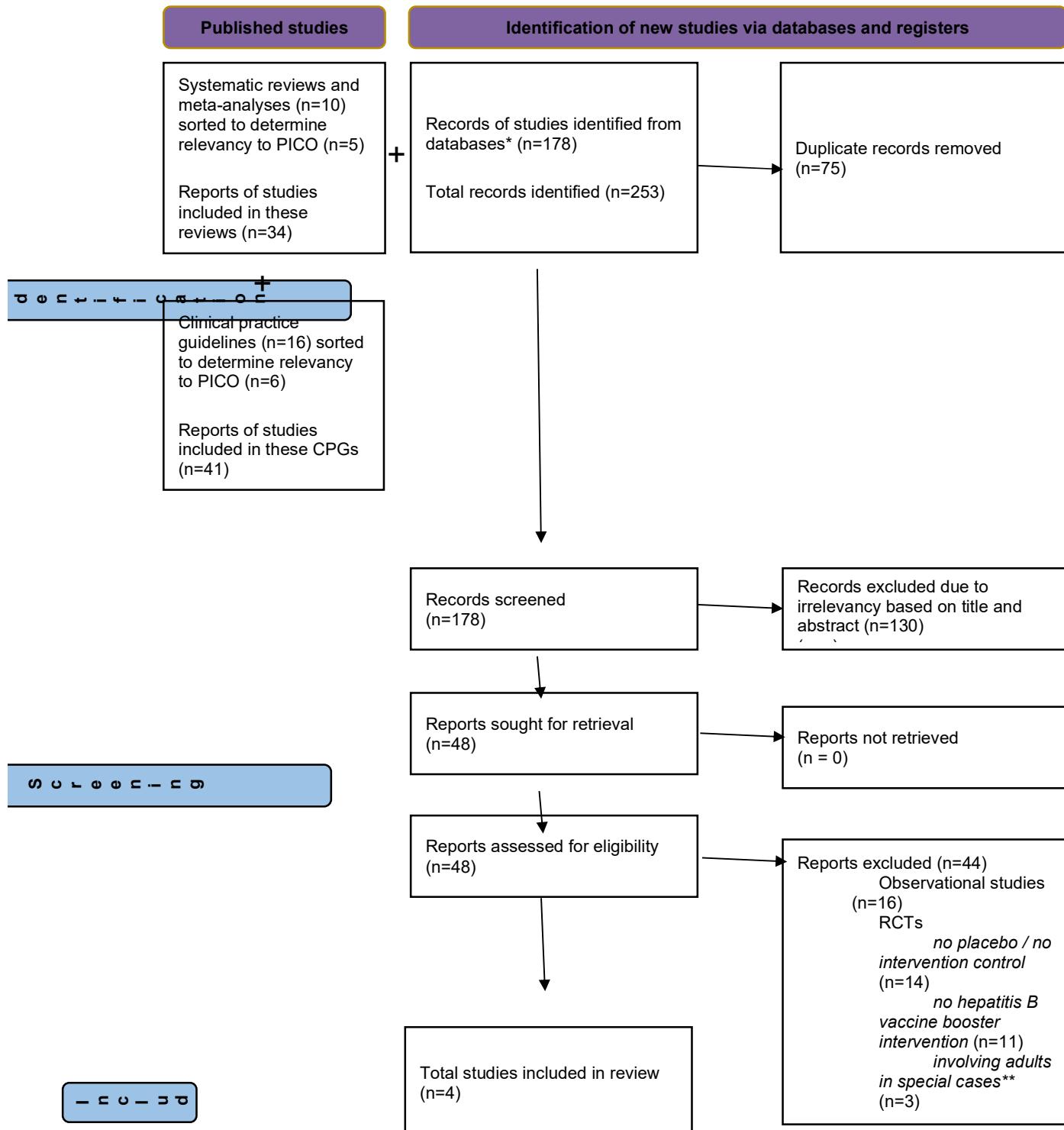


From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Question 9. Should Hepatitis B vaccine booster dose be given among children and adolescents who completed a 3-dose primary vaccination series during infancy?

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	(("hepatitis b vaccines" [MeSH Terms] OR "hepatitis b vaccin*" [Text Word] OR "hepatitis b immuniz*" [Text Word] OR "hbv vaccin*" [Text Word]) AND ("immunization, secondary" [MeSH Terms] OR "booster*" [Text Word] OR "revaccin*" [Text Word] OR "challenge dose" [Text Word])) AND ((("immunogenicity" [Text Word] OR "hbv dna positiv*" [Text Word] OR "hbv dna seropositiv*" [Text Word] OR "anti hbs positiv*" [Text Word] OR "anti hbs seropositiv*" [Text Word] OR "hbsag positiv*" [Text Word] OR "hbsag seropositiv*" [Text Word]) AND "hbeag positiv*" [Text Word]) OR "hbeag seropositiv*" [Text Word] OR "anti hbc seropositiv*" [Text Word] OR "anti hbc positiv*" [Text Word] OR "hepatitis b antigens" [MeSH Terms] OR "hepatitis b antibodies" [MeSH Terms] OR "Hepatitis B" [MeSH Terms] OR "acute Hepatitis B infection" [Text Word] OR "chronic Hepatitis B infection" [Text Word])) OR ((("hepatitis b vaccines" [MeSH Terms] OR "hepatitis b vaccin*" [Text Word] OR "hepatitis b immuniz*" [Text Word] OR "hbv vaccin*" [Text Word]) AND ("immunization, secondary" [MeSH Terms] OR "booster*" [Text Word] OR "revaccin*" [Text Word] OR "challenge dose" [Text Word])) AND ("Drug-Related Side Effects and Adverse Reactions" [MeSH Terms] OR "adverse event" [Text Word] OR "adverse reaction" [Text Word] OR "side effect" [Text Word])) OR ((("hepatitis b vaccines" [MeSH Terms] OR "hepatitis b vaccin*" [Text Word] OR "hepatitis b immuniz*" [Text Word] OR "hbv vaccin*" [Text Word]) AND ("immunization, secondary" [MeSH Terms] OR "booster*" [Text Word] OR "revaccin*" [Text Word] OR "challenge dose" [Text Word])) AND ("Cost-Benefit Analysis" [MeSH Terms] OR "cost effective*" [Text Word] OR "cost utility" [Text Word]))	February 18, 2023 8:30 AM	192	4
CENTRAL	MeSH descriptor: [Hepatitis B vaccine booster]	February 18, 2023 8:30 AM	4	0

PRISMA Flow Diagram



*See Search Strategy for details

***Special cases include: predialysis patients, non-responsive to primary series, medical students*

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

Question 10. Can Pneumococcal Conjugate Vaccine brands be interchanged to complete the primary series? Can Pneumococcal Conjugate Vaccine brands be interchanged as booster dose?

Database: MEDLINE (PubMed)

Search number	Query	Search Details	Results
1	(pneumococcal conjugate vaccine) AND (pneumococcal conjugate vaccine[MeSH Terms])	("pneumococcal vaccines"[MeSH Terms] OR ("pneumococcal"[All Fields] AND "vaccines"[All Fields]) OR "pneumococcal vaccines"[All Fields] OR "pneumococcal"[All Fields]) AND ("vaccines, conjugate"[MeSH Terms] OR ("vaccines"[All Fields] AND "conjugate"[All Fields]) OR "conjugate vaccines"[All Fields] OR ("conjugate"[All Fields] AND "vaccine"[All Fields]) OR "conjugate vaccine"[All Fields]) AND (("pneumococcal vaccines"[MeSH Terms] OR ("pneumococcal"[All Fields] AND "vaccines"[All Fields]) OR "pneumococcal vaccines"[All Fields] OR "pneumococcal"[All Fields]) AND "vaccines, conjugate"[MeSH Terms])	2,712
2	invasive pneumococcal disease[MeSH Terms]	("invasibility"[All Fields] OR "invisable"[All Fields] OR "invasion"[All Fields] OR "invasions"[All Fields] OR "invasive"[All Fields] OR "invasively"[All Fields] OR "invasiveness"[All Fields] OR "invasives"[All Fields] OR "invasivity"[All Fields]) AND "pneumococcal infections"[MeSH Terms]	4,200
3	streptococcus pneumoniae[MeSH Terms]	"streptococcus pneumoniae"[MeSH Terms]	24,451
4	#1 AND #3		1,414
5	#4 AND "interchange"		0
6	interchangeability AND #4		0
7	#1 AND #3 AND interchange		0
8	vaccine interchangeability	("vaccin"[Supplementary Concept] OR "vaccin"[All Fields] OR "vaccination"[MeSH Terms] OR "vaccination"[All Fields] OR "vaccinable"[All Fields] OR "vaccinal"[All Fields] OR "vaccinate"[All Fields] OR "vaccinated"[All Fields] OR "vaccinates"[All Fields] OR "vaccinating"[All Fields] OR "vaccinations"[All Fields] OR "vaccination s"[All Fields] OR "vaccinator"[All Fields] OR "vaccinators"[All Fields] OR "vaccine s"[All Fields] OR "vaccined"[All Fields] OR "vaccines"[MeSH Terms] OR "vaccines"[All Fields] OR "vaccine"[All Fields] OR "vaccins"[All Fields]) AND ("interchange"[All Fields] OR "interchangeability"[All Fields] OR "interchangeable"[All Fields] OR "interchangeably"[All Fields] OR "interchanged"[All Fields] OR "interchanges"[All Fields] OR "interchanging"[All Fields])	251
9	#4 AND #8		0
10	#1 AND #8		5
11	pcv10	"10 valent pneumococcal conjugate vaccine"[Supplementary Concept] OR "10 valent pneumococcal conjugate vaccine"[All Fields] OR "pcv10"[All Fields]	636
12	pcv13	"pcv13"[All Fields]	2,035
13	#8 AND #11		4
14	#8 AND #12		8



22	pcv10+pcv13	"pcv10+pcv13"[All Fields]	31
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Question 11. Should pertussis-containing vaccines be given as booster among children and adolescents who received complete DPT primary immunizations?

Database: **MEDLINE (PubMed)**

Date: 26 September 2022

Search number	Query	Filters	Results	Time
11	#5 and #8	Child: birth-18 years	55	02:02:06
9	#5 and #8		79	01:58:32
10	#5 and #8	Preschool Child: 2-5 years	13	01:56:28
8	#6 or #7		11,005,482	01:54:34
7	safety		808,824	01:54:27
6	effectiveness		10,655,003	01:54:23
5	#3 and #4		160	01:54:09
4	vaccine		470,296	01:54:01
3	#1 and #2		162	01:53:44
2	Td		693,085	01:53:30
1	Tdap		1,013	01:53:22

Database: **Cochrane CENTRAL**

Date: 26 September 2022

Search number	Query	Results	Time
9	Search #7 and #8	308	02:16:51
8	Search (randomized controlled trial) OR controlled clinical trial	591330	02:13:13
7	Search #5 and #6	1071	02:11:26
6	Search (effectiveness) OR safety	2126953	02:10:08
5	Search #3 and #4	1237	02:09:50
4	Search vaccine	492167	02:09:37
3	Search (Tdap) AND td	1314	02:09:18

Database: **MEDLINE (PubMed) and Cochrane CENTRAL**

Date: 09 February 2023

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
MEDLINE	Search: #1 AND #2 Filters: Randomized Controlled Trial, in the last 10 years, Child: birth-18 years ("pertussis vaccine"[MeSH Major Topic] OR "diphtheria tetanus acellular pertussis vaccines"[MeSH Major Topic] OR "diphtheria tetanus pertussis vaccine"[MeSH Major Topic] OR "Tdap"[All Fields]) AND ("safety"[MeSH Terms] OR "safety"[All Fields] OR "safeties"[All Fields] OR ("antigens"[MeSH Terms] OR "antigens"[All Fields] OR "immunogen"[All Fields] OR "immunogens"[All Fields] OR "immunogene"[All Fields] OR "immunogenes"[All Fields] OR "immunogenic"[All Fields] OR "immunogenes"[All Fields] OR "immunogenic"[All Fields])	February 9, 2023 2:16PM	125	2

	<p>Fields] OR "immunogenically"[All Fields] OR "immunogenicities"[All Fields] OR "immunogenicity"[All Fields] OR "immunogenity"[All Fields]) OR ("efficacies"[All Fields] OR "efficacious"[All Fields] OR "efficaciously"[All Fields] OR "efficaciousness"[All Fields] OR "efficacy"[All Fields])) AND ((y_10[Filter]) AND (randomizedcontrolledtrial[Filter]) AND (allchild[Filter]))</p> <p>Filters: Randomized Controlled Trials Filters: Meta-Analysis</p>			
CENTRAL	<p>("pertussis vaccine"[MeSH Major Topic] OR "diphtheria tetanus acellular pertussis vaccines"[MeSH Major Topic] OR "diphtheria tetanus pertussis vaccine"[MeSH Major Topic] OR "Tdap"[All Fields]) AND ("safety"[MeSH Terms] OR "safety"[All Fields] OR "safeties"[All Fields] OR ("antigens"[MeSH Terms] OR "antigens"[All Fields] OR "immunogen"[All Fields] OR "immunogens"[All Fields] OR "immunogene"*[All Fields] OR "immunogenes"[All Fields] OR "immunogenic"[All Fields] OR "immunogenically"[All Fields] OR "immunogenicity"[All Fields] OR "immunogenity"[All Fields]) OR ("efficacies"[All Fields] OR "efficacious"[All Fields] OR "efficaciously"[All Fields] OR "efficaciousness"[All Fields] OR "efficacy"[All Fields])) Filters: published in the last 10 years</p>	February 9, 2023 2:42PM	2525	2

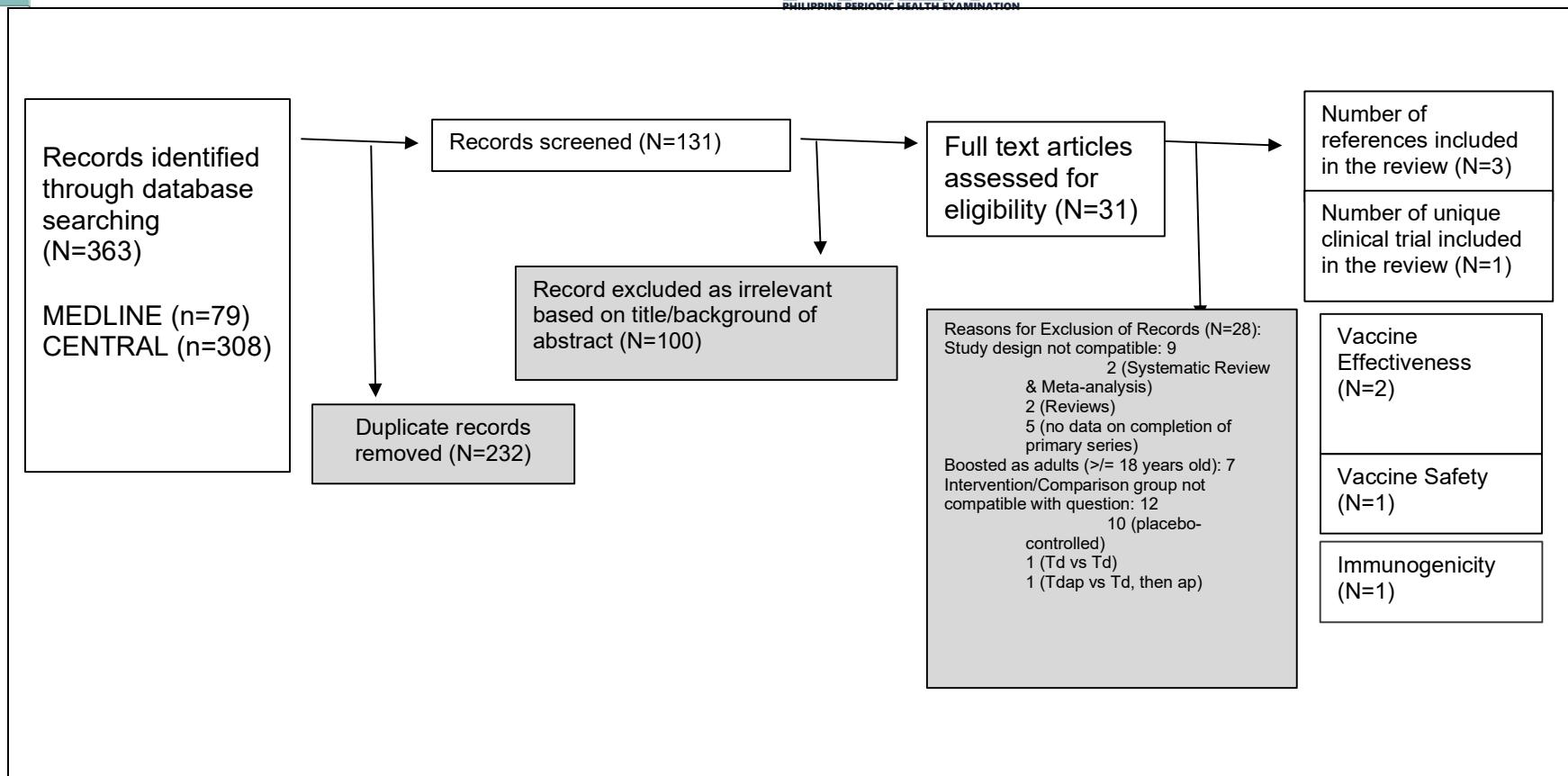


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University of the Philippines
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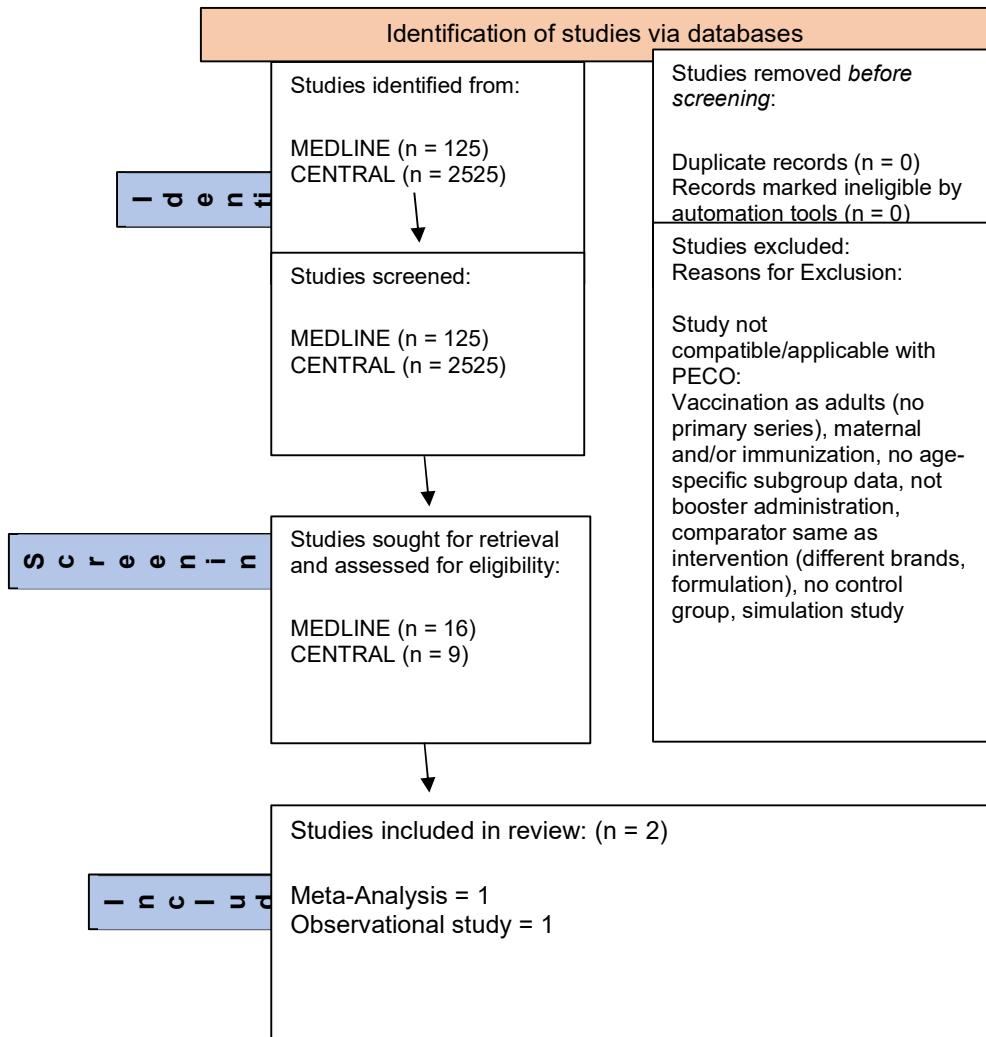


PRISMA FLOW DIAGRAM: Tdap Vaccination (26 September 2022)

Identification	Screening	Eligibility	Included
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PRISMA Flow Diagram: DTaP Vaccination PRISMA Diagram (09 February 2023)





LITERATURE APPRAISAL

Question 1. Should rabies pre-exposure prophylaxis (PrEP) be given as routine vaccination for prevention of rabies infection in children and adolescents?

Appendix A. Characteristics of Included Studies

Title/ Author	Study Design	Country	Number of Patients	Population	Intervention Group(s)	Control	Outcome
Lang 1997 Primary immunization with routine EPI schedule	Randomized controlled trial	Vietnam	84	Healthy 2-month old infants	DTP-IPV (2, 3 and 4mos) + 2 doses of PVRV IM (2, 4mos) (n=41) PVRV (Verorab, Pasteur Mérieux Connaught)	DTP-IPV (2, 3 and 4mos) (n=43) DTP-IPV (Tetraocq, Pasteur Mérieux Connaught, Lyon, France)	RVNA TITER Seroconversion definition: RVNA ≥ 0.5 IU/ml; Baseline: Control GMT 0.020 IU/ml (0/43) vs Intervention group GMT 0.015 IU/ml (0/41) 1month after primary vaccination: Control: (GMT 0.028 (0/43, 0%) vs Intervention Group GMT 20.09 (41/41, 100%)) Administration of PVRV with DTP-IPV proved safe, and elicited what are presumed to be protective antibody concentrations to all antigens in all 41 infants. ADVERSE REACTION No SAE Local Reactions Dose 1: Control 3/84 vs Intervention 0/41 Dose 3: Control 2/84 vs Intervention 0/41 Systemic reactions ($\geq 39.5^{\circ}\text{C}$, or $\geq 38.5^{\circ}\text{C}$, and lasting for ≥ 2 days) – NO SIGNIFICANT DIFFERENCE Dose1: 6/43 control vs 3/41 intervention Dose2: 4/43 control vs 2/41 intervention Dose3: 3/43 control vs 2/41 intervention
Lang 1999 Booster study at 1 year Continuation of Lang 1997 study	Randomized controlled trial	Vietnam	74	Healthy 2-month old infants	DTP-IPV (2, 3 and 4mos) + 2 doses of PVRV IM (2, 4mos) (n=36) PLUS booster of 1 dose PVRV IM at 17 months of age	DTP-IPV (2, 3 and 4mos) (n=38) PLUS booster of 1 dose DPT-IPV at 17 months of age	RVNA TITER Seroconversion definition: RVNA ≥ 0.5 IU/ml Prebooster at 17mos: Control GMT 0.040 IU/ml (0/38, 0%) vs Intervention group GMT 1.36 IU/ml (27/36, 75%) 2 weeks post-booster: Control GMT 0.060 IU/ml (0/38, 0%) vs Intervention group GMT 24.9 IU/ml (36/36, 100%)



					PVRV (Verorab, Pasteur Mérieux Connaught)	DTP-IPV (Tetraacq, Pasteur Mérieux Connaught, Lyon, France)	<p>One year after the primary series, 75% of the infants primed against rabies showed antibody titres greater than or equal to the 0.5 IU/ml seroconversion cut-off point.</p> <p>ADVERSE REACTION No SAE, no immediate reactions. Comparable systemic reaction rates for both groups [control 8/38 (21.1%) vs intervention 7/36 (19.4%)] Local reactions: No local reaction for PVRV (+) local AE to DPT-IPV control 2/39 vs intervention 3/37</p>
Chulasugandha 2006	Comparative Cost Analysis	Thailand			Cost of PREP with PEP boosters (No immunoglobulin required)	Cost of PEP without prior PREP	<p>PEP: \$28.75 to \$125.00. PrEP: \$2.00–7.25 + \$18.00–23.50 (PEP booster if required)</p> <ul style="list-style-type: none"> • PREP is cost-comparable with PEP when the probability of a dog bite is approximately 23%. • If ERIG is used, cost comparability occurred at 7% dog bite prevalence. • The lowest cost-comparability occurred in the group where HRIG is used at 3% dog bite prevalence <p>Conclusion: Not cost-effective</p>
Quiambao 2020	Comparative Cost Analysis	Philippines			Cost of PrEP + PEP program	PEP alone	<p>From both payer and societal perspectives, the resulting incremental cost-effectiveness ratios were 36,035 (US\$759) and 18,663 (US\$393) Philippine Pesos (PHP) quality-adjusted life-years gained respectively, which are both below the willingness-to-pay threshold of PHP140,255 (US\$2,953)</p> <p>Conclusion: universal PrEP program targeting 5-yo would be cost-effective in the Philippines</p>



Appendix B. Characteristics of Excluded Studies

Title/ Author	Study Design	Country	Number of Patients	Population	Intervention Group(s)	Control	Outcome
Angsuwatcharakon 2020	Randomized, open labelled, controlled-trial	Thailand	49	healthy Thai children aged 12–16 months (2:1)	Two 0.1 mL doses of PVRV ID at the deltoid region on days 0 and 28 (n=32) both groups received 1 dose of JE-CV on days 0 and 365	One 0.5 mL dose of PVRV IM on days 0, 7, and 28 (n=17)	RVNA TITER Seroconversion definition: RVNA ≥ 0.5 IU/ml; JEVNA at $\geq 1:10$ serum dilution D42: ID GMT 14.35 IU/ mL vs IM GMT 14.83 IU/mL Y1: ID GMT 1.5 IU/ mL (92.3%) vs IM GMT 2.00 IU/mL (92.3%) abbreviated (2-visit ID) rabies vaccination provided non-inferiority in antibody response comparing with the conventional rabies (3-visit) in toddlers. All children from both groups achieved RVNA > 0.5 IU/mL by 2 weeks after completion of rabies PrEP, without impact on JE-CV immunogenicity One year after rabies PrEP simultaneously administered with JE-CV, there was a high rabies seroprotective rate of 92.3% which was equal in both groups. ADVERSE EVENT No SAE. The most common local reactions in the group A (ID) were erythema and pruritus at the site of injection whereas the most common local reaction in the group B (IM) was pain at the injection site. All were mild.
Chantasisawad 2021	Randomized, open-label clinical trial	Thailand	67	Healthy children aged 3–9 years (2:2:1)	Group A PVRV IM at day 0, 7 with IIV4 (N=39) Group B PVRV IM at day 0, 28 with IIV4 (N=40) Group C PVRV IM at day 0, 7	No control group	RVNA TITER Seroconversion definition: RVNA ≥ 0.5 D42: 100% in all study groups Y1 (prebooster): Group A 82.9% vs Group B 82.9% vs Group C 94.1% Y1 (booster) + 7 days: 100% in all study groups adequate immune responses of rabies vaccine without interference with influenza vaccine in healthy children 3 to 9 years old. This finding suggests that 2 doses of IM CPRV with either 0,7 or

					(N=20)		0,28 regimens could be administered concomitantly with IIv4 in rabies-endemic countries ADVERSE EVENT No data
Chatchen 2017 Continuation of study by Pengsaa 2009	Randomized, open-label clinical trial	Thailand	68	Healthy children aged 4yo	Arm 1: PCECV 1.0 ml IM on D0, D7 and D28 (n=15) Arm 2: PCECV 0.5 ml IM on D0, D7 and D28 (n=18) Arm 3: PCECV 0.1ml ID on D0, D7 and D28 (n=20) Arm 4: PCECV 0.1ml ID on D0, and D28 (n=15) All groups with concomitant 0.25ml JEV SC on D0,7 All groups received booster at 1 year PCECV (Rabipur)	No control group	RVNA TITER Seroconversion definition: RVNA ≥ 0.5 Y4: GMT Full IM 14.9 IU/ml vs half IM 13.4 IU/ml vs 3ID 5.6 IU/ml vs 2ID 2.7 IU/ml Y5: GMT Full IM 11.8 IU/ml vs half IM 11.6 IU/ml vs 3ID 4.3 IU/ml vs 2ID 1.9 IU/ml Y6: GMT Full IM 9.6 IU/ml vs half IM 7 IU/ml vs 3ID 3.6 IU/ml vs 2ID 1.2 IU/ml Y7: GMT Full IM 5.6 IU/ml vs half IM 4.9 IU/ml vs 3ID 2.2 IU/ml vs 2ID 0.9 IU/ml Y8: GMT Full IM 4.3 IU/ml vs half IM 3.9 IU/ml vs 3ID 1.8 IU/ml vs 2ID 0.8 IU/ml IM and 3-ID regimens induced antibody titers above the seroprotective level throughout the study period but 2-ID group had sub-seroprotective titer of 6.7%, 13.4%, 25.0%, and 36.4% in year 5, 6, 7, and 8, respectively.
Janewongwirot 2019	Randomized, open-label clinical trial	Thailand	107	healthy children aged 2–12 years (3:1)	Group A - 2-dose PVRV IM (D0, D28) (N=78) (PVRV-Verorab 0.5ml IM)	Group B – 3-dose PVRV IM (D0, 7, and 28) (N=29)	RVNA TITER Seroconversion definition: RVNA ≥ 0.5 D42: 2-dose GMT 18.6 IU/mL (100%) vs 3-dose GMT 16.3 IU/mL (100%) Y1 (prebooster): 2-dose GMT 0.8 IU/mL (80%) vs 3-dose GMT 1.7 IU/mL (100%) Y1 + 7d (post booster at Y1): 2-dose GMT 20.9 IU/mL (100%) vs 3-dose GMT 22.2 IU/mL (100%) Two-dose primary rabies immunization provided adequate antibody at post primary vaccination and post booster. The results support 2-dose regimen of



							pre-exposure rabies immunization in the pediatric population. ADVERSE EVENT No data
Kamoltham 2007	Randomized, open-label, phase II clinical trial	Thailand	Phase 1 (n=703) Then randomized subset of 100 (1:1) Phase 2 147	healthy children aged 5-8 years	Group A 2-ID 0.1 mL PCECV on D0, 28 Group B 3-ID 0.1 mL PCECV on D0, 7, 28 PCECV - Rabipur® Phase 2 (booster dose) A1 and B1 (receive 2ID at D0 and D3) at Y1 A2 and B2 (receive 2ID at D0 and D3) at Y3 (ongoing study) A3 and B3 (receive 2ID at D0 and D3) at Y5 (ongoing study)	No control group	RVNA TITER Seroconversion definition: RVNA ≥ 0.5 Phase 1 D49 (3 weeks after primary): 2ID 42/43 (98%) vs 3ID 30/30 (100%) Phase 2 Y1 (prebooster): 2ID GMT 0.11 (6/84, 7%) vs 3ID GMT 0.33 (22/63, 35%) D7: 2ID GMT 4.69 (81/84, 96%) vs 3ID GMT 10.96 (61/61, 100%) D14: 2ID GMT 10.76 (81/81, 100%) vs 3ID GMT 22.12 (58/58, 100%) Y2: 2ID GMT 0.65 (51/77, 66%) vs 3ID GMT 22.12 (55/59, 93%) ADVERSE EVENT Only SAE were recorded. Local and systemic AE not recorded
Kamoltham 2011 long-term follow-up, the anamnestic response of Thai school children that received two (simulated) post-exposure booster doses of PCECV was investigated up to five years Subjects	Randomized, open-label, phase II clinical trial	Thailand		healthy children aged 5-8 years	Group A 2-ID 0.1 mL PCECV on D0, 28 Group B 3-ID 0.1 mL PCECV on D0, 7, 28 Phase 2 (booster dose) A1 and B1 (receive 2ID at D0 and D3) at Y1	No control group	RVNA TITER Seroconversion definition: RVNA ≥ 0.5 Y1 Prebooster: 2ID 6/84 (7%) vs 3ID 22/63 (35%) D7: 2ID GMT 4.69 (81/84, 96%) vs 3ID GMT 10.96 (61/61, 100%) D14: 2ID GMT 10.76 (81/81, 100%) vs 3ID GMT 22.12 (58/58, 100%) D365: 2ID GMT 0.65 (51/77, 66%) vs 3ID GMT 22.12 (55/59, 93%) Y3 Prebooster: 2ID 4/48 (8%) vs 3ID 24/60 (40%)



	were followed for 1, 3, or 5 years after primary PrEP given 2 booster doses at D0,3 to simulate PEP				A2 and B2 (receive 2ID at D0 and D3) at Y3 (ongoing study) A3 and B3 (receive 2ID at D0 and D3) at Y5 (ongoing study)		D7: 2ID 35/38 (73%) vs 3ID 58/60 (97%) D14: 2ID 47/47 (100%) vs 3ID 57/57 (100%) D365: 2ID 24/41, 59% vs 3ID 45/52 (87%) Y5 Prebooster: 2ID 10/82 (12%) vs 3ID 41/89% (46%) D7: 2ID 75/82 (91%) vs 3ID 88/89 (99%) D14: 2ID 79/79 (100%) vs 3ID 85/85 (100%) D365: 2ID 29/57 (51%) vs 3ID 59/62 (95%) a PrEP vaccination series using 2 or 3 doses of 0.1mL PCECV administered ID is safe and immunogenic in school children, and anamnestic responses occurred in all subjects after two booster doses were administered up to five years later.	
Khawplod 2007	Randomized, open-label, phase II clinical trial	Thailand	96	healthy volunteers aged 8 to 40	Group A – 2ID at D0,7,28 (adults) Booster 2ID (Y1, Y1+3days) n=16 Group B – 2ID at D0,3,7 (adults) Booster 2ID (Y1, Y1+3days) n=16 Group C – IM at D0,3,7 (adults) Booster 2ID (Y1, Y1+3days) n=20 Group D – 2ID at D0 (pedia 8-11yo) Booster 2ID (Y1, Y1+3days) n=14 Group E – PEP with TRC using PVRV 2ID at D0,3,7 and 1ID (D28 and 90) n=10	No control group	RVNA TITER Seroconversion definition: RVNA ≥ 0.5 Group D D0: GMT <0.03 Y1: GMT 0.41 IU/ml (5/13, 38%) Y1+7days: GMT 9.15 IU/ml (10/10, 100%) Y1+ 14days: BMT 51.96 (9/9, 100%) Even 0.1 mL of a WHO-accepted tissue culture rabies vaccine injected at two ID sites (both deltoid regions) conferred immune memory for at least 1 year. Two booster injections 1 year later resulted in an accelerated immune response	ADVERSE EVENT There were no reports of adverse side effects on aggressive questioning other than minor itching and erythema at injection sites. (no data provided)

					Group F – PEP with TRC using PCEV 2ID at D0,3,7 and 1ID (D28 and 90) n=20 PVRV		
Lang 1999	Randomized, open label controlled trial	Vietnam	240	healthy 2 – 5 month old	Group 1 DTP-IPV at 2, 3 and 4 months + IM PVRV at 2 and 4 months (n=117) PVRV - VERORAB	Group 2 DTP-IPV at 2, 3 and 4 months + 1ID PVRV at 2,3 and 4 months (n=116)	<p>RVNA TITER Seroconversion definition: RVNA ≥ 0.5 Baseline: IM GMT 0.033 (0%) vs ID GMT 0.032 (0%) D28: IM GMT 30.6 (100%) vs ID GMT 12.0 (100%)</p> <p>Although rabies antibody titers were higher in the IM group vs ID group, all infants in both groups had achieved >0.5 IU/ml. There was no evidence for any interference between DTP-IPV and rabies vaccine, supporting the interest of a low-dose ID PVRV pre-exposure regimen in infants living in rabies endemic developing countries.</p> <p>ADVERSE EVENT No SAE There was NO statistically significant difference between the 2 groups in the incidence of systemic events. Local reaction at the injection site was 6.0% in the ID group and 0.8% in the IM group ($P < 0.05$)</p>
Lang 2009 Booster study yearly up to 5 years	Open, single-centre, 5-year follow-up study	Vietnam	72	Healthy 2-month old infants	DTP-IPV (2, 3 and 4mos) + 2 doses of PVRV IM (2, 4mos) (n=41) + booster of DTP-IPV + PVRV at 1 year PVRV (Verorab, Pasteur Mérieux Connaught)	DTP-IPV (2, 3 and 4mos) (n=43) + booster of DTP-IPV alone at 1 year DTP-IPV (Tetraocq, Pasteur Mérieux	<p>RVNA TITER Seroconversion definition: RVNA ≥ 0.5 IU/ml; Intervention Group Y1: 30/33 (90.0%) Y2: 26/29 (89.7%) Y3: 20/30 (66.7%) Y4: 18/28 (64.3%) Y5: 19/30 (63.3%) <i>Control not included in the RVNA titer determination</i></p>



						Connaught, Lyon, France)	<p>Co-administration of PVRV with DTP-IPV elicited protective antibody concentrations to all antigens that persist for at least 5 years, with continued protection against rabies in over 60% of subjects □ integration of PrEP rabies vaccination into the EPI in countries where rabies is endemic.</p> <p>ADVERSE REACTION No SAE were reported during the 5-year follow-up period. (<i>No exact data/breakdown provided</i>)</p>
Pengsaa 2009	Phase II, pilot, randomized, open-label	Thailand	200	Healthy children 12 -18 months (n=200)	Arm 1: PCECV 1.0 ml IM on D0, D7 and D28 (n=44) Arm 2: PCECV 0.5 ml IM on D0, D7 and D28 (n=45) Arm 3: PCECV 0.1ml ID on D0, D7 and D28 (n=44) Arm 4: PCECV 0.1ml ID on D0, and D28 (n=44) All groups with concomitant 0.25ml JEV SC on D0,7 PCECV (Rabipur) All 4 rabies groups received a PCECV booster dose (0.1 mL ID or IM, 1.0 or 0.5 mL, according to primary route of administration	JE Vaccine on D0,7 (n=23) JEV (Biken)	<p>RVNA TITER Seroconversion definition: RVNA ≥0.5 IU/ml; JEVNA at ≥1:10 serum dilution</p> <p>[tested at baseline, D49, Y1 (before booster), Y1+7days, Y1 + 28days, Y2, and Y3)</p> <p>D49: Full IM GMT 22 IU/ml vs half IM GMT 29 IU/ml vs 3ID GMT 5.9 IU/ml vs 2ID GMT 5.9 IU/ml. All 4-rabies immunization schedule resulted RVNA ≥0.5 IU/ml</p> <p>Y1 (prebooster): Full IM GMT 4 IU/ml vs half IM GMT 3.7 IU/ml vs 3ID GMT 1.2 IU/ml vs 2ID GMT 0.5 IU/ml. IM maintained adequate RVNA concentration while 3ID (97%) and 2ID (61%)</p> <p>Y1+7: Full IM GMT 190 IU/ml vs half IM GMT 161 IU/ml vs 3ID GMT 25 IU/ml vs 2ID GMT 13 IM and ID adequate</p> <p>Y1 + 28days: IM and 3ID adequate, 2ID (no data)</p> <p>Y2: IM and 3ID adequate, 2ID (93%)</p> <p>Y3: IM and 3ID adequate, 2ID (80%)</p> <p><i>Control not included in the RVNA titer determination</i></p> <p>All regimens induced adequate immune responses at D49 after primary vaccination. By D7 after a single booster dose, all subjects elicited a rapid increase in RVNA concentrations. No evidence that either route or dose of concomitant administration of PCECV had an impact on JE antibodies at 1:10 serum dilution was detected.</p>



							ADVERSE EVENT No immediate adverse reactions occurred after vaccinations and both PCECV and JEV were well tolerated. A similar percentage of systemic reactions was seen in the children who received JEV alone, without significant differences. <i>(No exact data/breakdown provided)</i>
Quiambao 2022 Non-inferiority study	Multicenter, observer-blinded, controlled, randomized phase II study	Philippines	342	Children 2–11 years and adolescents aged 12–17 years (2:1)	PVRV-NG IM at D0,7 and 28 (n=229) PVRV-NG - a serum-free, highly purified Vero rabies vaccine with no animal or human components and low residual DNA content (Sanofi)	HDCV IM at D0,7 and 28 (n=113) HDCV (Imovax)	RVNA TITER Seroconversion definition: RVNA ≥ 0.5 IU/ml RVNA were measured at D0, D42 and 6 months D0 (prevaccine): PVRV-NG GMT 0.105 (4/229, 1.7%) vs HDCV GMT 0.102 (1/113, 0.88%) D42: PVRV-NG GMT 14.3 (226/226, 100%) vs HDCV GMT 17.2 (113/113, 100%) M6: PVRV-NG GMT 1.22 (204/224, 91.1%) vs HDCV GMT 1.54 (107/110, 97.3%) This study demonstrated the non-inferior immune profile of PVRV-NG compared with HDCV in a PrEP setting among children. PVRV-NG was well tolerated with no safety concerns. ADVERSE EVENT No immediate AEs Systemic reactions were similar in both groups (PVRV-NG 33.6% vs HDCV 37.2%) Fewer solicited injection-site reactions in the PVRV-NG group (28.4%) than in the HDCV group (44.2%)
Ravish 2013 Safety study	Single arm safety study	India	153	healthy children 5–10 y age	PCECV (Vaxirab) 3ID on D0,7, and 21	No control group	ADVERSE EVENT AEs recorded after every injection and 2 weeks after the last dose None of the study subjects dropped out due to adverse reactions Local AE pain at the injection site 15 (3.7%) redness 2 (0.5%) itching at the site of injection 1 (0.2%)



							<p>fatigue 1 (0.2%)</p> <p>Systemic AE fever 3 (0.7%) myalgia 2 (0.5%) allergy 1 (0.2%)</p> <p>Systemic AEs responsive to anti-inflammatory and antihistamines and were relieved within 1 day</p> <p>-</p>
Sabchareon 1999	Phase III, observer blinded, randomized controlled trial	Thailand	400	healthy children, 5–13 yo	3IM using CPRV on D0,7,28 and 365 (booster) (n=201) chromatographically purified rabies vaccine (CPRV) - Pasteur Me' rieux Connaught	3IM using HDCV on D0,7,28 and 365 (booster) (n=199) human diploid cell rabies vaccine (HDCV) - (movax)	<p>RVNA TITER Seroconversion definition: RVNA ≥ 0.5 IU/ml</p> <p>Primary Immunization D28 CPRV GMT 25.0 (195/195, 100%) vs HDCV 34.1 (190/190, 100%) D42 CPRV GMT 32.9 (195/195, 100%) vs HDCV 47.6 (190/190, 100%) M6: CPRV GMT 5.4 (182/188, 96.8%) vs HDCV 9.8 (186/186, 100%) Y1 (prebooster) CPRV GMT 2.2 (133/154, 88.1%) vs HDCV GMT 3.6 (149/154, 96.8%)</p> <p>Days after booster immunization D7 CPRV GMT 27.6 (146/146, 100%) vs HDCV GMT 42.3 (147/147, 100%) D14 CPRVGMT 31.9 (148/148, 100%) vs HDCV GMT 46.8 (151/151, 100%)</p> <p>CPRV has adequate immunogenicity for primary and booster PrEP in children and has a better safety profile than does HDCV</p> <p>ADVERSE EVENT Local and systemic reactions after primary and booster immunizations occurred significantly less frequently in the CPRV group. A severe allergic reaction (angioedema) was reported in only one child after booster immunization with HDCV</p>
Vien 2008	Randomized controlled trial	Vietnam	175	healthy	Children received a 1- and 5-year booster	No control group	RVNA TITER Seroconversion definition: RVNA ≥ 0.5 IU/ml



				children aged 16–20 months	either IM (0.5 ml dose) or ID (0.1 ml) with PVRV		During this 5-year follow-up, the rabies SPR in the ID. group was lower than in the IM group at all visits except 14d after both boosters, and the non-inferiority of the i.d. route was not demonstrated. At all-time points the GMT remained above the WHO recommended level for seroprotection and the majority had titers considered seroprotective in both groups.
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Appendix C. Grade Evidence Profile

Author(s): Reginald B. Balmeo, MD; Natasha Ann Esteban-Ipac, MD

Question: Rabies vaccine PrEP compared to Control for Rabies prevention

Setting: Community

Bibliography: Lang J, Duong GH, Nguyen VG, Le TT, Nguyen CV, Kesmedjian V, Plotkin SA. Randomised feasibility trial of pre-exposure rabies vaccination with DTP-IPV in infants. Lancet. 1997 Jun 7;349(9066):1663-5.; Lang J, Feroldi E, Vien NC. Pre-exposure purified vero cell rabies vaccine and concomitant routine childhood vaccinations: 5-year post-vaccination follow-up study of an infant cohort in Vietnam. J Trop Pediatr. 2009 Feb;55(1):26-31.

Nº of studies	Study design	Certainty assessment					Nº of patients		Effect		Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rabies vaccine PrEP	Control	Relative (95% CI)	Absolute (95% CI)		
Immunogenicity (1 and 17 months)												
2	randomised trials	serious ^a	serious ^b	not serious	serious ^c	none	9/77 (11.7%)	81/81 (100.0%)	RR 0.13 (0.07 to 0.23)	870 fewer per 1,000 (from 930 fewer to 770 fewer)	Very low	CRITICAL
GMT												
1	randomised trials	serious ^a	not serious	not serious	serious ^c	none	41	43	-	mean 20.07 higher (12.01 higher to 28.12 higher)	Low	CRITICAL
AE (local)												
1	randomised trials	serious ^a	not serious	not serious	serious ^c	none	0/41 (0.0%)	3/84 (3.6%)	RR 0.29 (0.02 to 5.47)	25 fewer per 1,000 (from 35 fewer to 160 more)	Low	CRITICAL
AE (systemic)												
1	randomised trials	serious ^a	not serious	not serious	serious ^c	none	3/41 (7.3%)	6/43 (14.0%)	RR 0.52 (0.14 to 1.96)	67 fewer per 1,000 (from 120 fewer to 134 more)	Low	CRITICAL

CI: confidence interval; RR: risk ratio

Explanations

a. issues on allocation concealment and the study design used to administer both the DPT-IPV and the DTP-IPV plus Verorab IM precludes blinding from the personnel and participants

b. high heterogeneity I² = 89%

c. sample size low (events <300)



Appendix D. Forest Plot

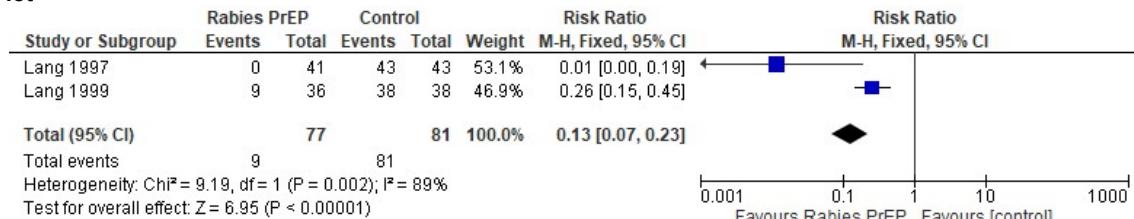


Figure 1. Effect of rabies PrEP compared to no rabies vaccine on immunogenicity at 1 and 17 months post vaccination



Question 2. Among healthy children who completed the primary series of *Haemophilus influenzae B (Hib)* vaccination, is a booster dose of Hib vaccine needed?

Appendix A. Characteristics of Included Studies

Review Year Journal	Review aim	Search strategy	PICO	Data Analysis
Low et al., 2013 <i>Pediatr Infect Dis J</i>	To review relative effects of different Hib vaccine schedules	<p>Database: 21 electronic databases <ul style="list-style-type: none"> - 5 peer reviewed database (AIM, Cochrane, LILACs, IndMED, Medline) - 3 trial registries - 11 vaccine manufacturer databases - 2 regulatory authority websites Language restriction: no mention (Covered trials across 15 countries) Strategy: available via supplemental document Last date of search: Initial search until May 2010 Updated search of Medline database until 2012 Exclusion criteria: Studies where both schedule and PRP-conjugated molecule differed between available comparison groups making comparison of effect attributable to vaccine schedule alone impossible </p>	<p>Population: Children vaccinated with PRP-T, PRP-OMP, or PRP-HbOC at less than 6 yrs of age</p> <p>Intervention: Vaccinated at following schedules: 3p+0 vs 2p+0 3p+0 vs 2p+1 3p+1 vs 2p+1 3p+1 vs 3p+0</p> <p>Outcome: Invasive Hib disease (either alone such as Hib meningitis, pneumonia, epiglottitis, etc, or as a combined outcome) OR Seropositivity after vaccination (measured at threshold values of 0.15 and 1.0 ug/mL) OR Mean geometric mean concentration (GMC) of PRP antibody</p> <p>Study design: RCTS or quasi-randomized</p>	<p>Risk of bias: Assessed in terms of blinding, allocation concealment, and manner of analysis (whether ITT/mITT or PP)</p> <p>Publication Bias: Not done (using funnel plot or Egger test) because few trials were available for most analyses</p> <p>Statistical analysis: DerSimonian and Laird random-effects meta-analysiss in STATA Heterogeneity described using I² statistic</p> <p>3p+1 versus 3p schedules (Based on 2 trials (Canada and Europe) <i>Europe (Knuf): used DTaP-HBV-IPV/Hib (Infarix)</i> <i>Canada (Scheifele)2: used DTaP/IPV//PRP-T (Pentacel)</i></p>



Appendix B. Appraisal of Included Systematic Reviews/Meta-analyses

AMSTAR Items	Low (2013)
<i>Date of last search</i>	
<i>Rating of overall confidence in the results of the review⁶</i>	High
1. Research questions, inclusion criteria include PICO components	YES
2.* Protocol registered before commencement of the review	YES
3. Selection of study designs to be included were explained	YES
4.* Adequacy of literature search	YES
5. Study selection done by at least 2 reviewers	YES
6. Data extraction done by at least 2 reviewers	YES
7.* Justification for excluding individual studies	YES
8. Described included studies in adequate detail	YES
9.* ROB from individual studies being included in the review	YES
10. Reported sources of funding for studies included	YES
11.* Appropriateness of meta-analytical methods	YES
12. Potential impact of ROB in individual studies	YES
13.* Consideration of ROB when interpreting review results	YES
14. Sufficient explanation of heterogeneity	YES
15.* Assessment of presence and likely impact of publication bias	NO
16. Reported potential COI sources, funding they received	YES

Appendix C. GRADE Evidence Profile
Hib vaccine booster compared to no booster in healthy completely immunized infants

Bibliography:

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no booster	With hib vaccine booster		Risk with no booster	Risk difference with hib vaccine booster

Geometric mean concentration

449 (1 RCT)	serious ^a	not serious	serious ^b	not serious	none	⊕⊕○○ Low	at 16months of age, 3p+1 had GMC of 29.92ug/mL (95% CI 24.58-36.43), while the group that has yet to receive a booster dose had a GMC of 0.32ug/mL (95% CI 0.25-0.41)			
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Seropositivity

444 (1 RCT)	serious ^a	not serious	very serious ^{b,c}	not serious	none	⊕○○○ Very low	1 month after the booster dose was given (3p+1) - 1.0ug/mL: risk difference 0.59 (95% CI 0.52-0.67) - 0.15ug/mL: risk difference 0.16 (95% CI, 0.11-0.22)			
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CI: confidence interval

Explanations

- a. study design with incomplete information about randomization and allocation
- b. PICO is not direct, information needed to answer the study question was extrapolated from available data
- c. no explanation how values were extrapolated



Question 3. Should the Rotavirus vaccine be routinely given to infants for the prevention of Rotavirus gastroenteritis and its complications?

Appendix A. Appraisal of Included Systematic Reviews/Meta-analyses

AMSTAR Items	Bergman (2021)
1. Did the research question and inclusion criteria for this review include the components of PICO?	Yes
2. Did the report contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes
5. Did the review authors perform study selection in duplicate?	Yes
6. Did the review authors perform data extraction in duplicate?	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes
8. Did the review authors describe the included studies in adequate detail?	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias in individual studies that were included in the review?	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of ROB in individual studies on the results of the meta-analysis or other evidence synthesis?	No
13. Did the review authors account for ROB in primary studies when interpreting or discussing the results of the review?	Yes



14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
15. If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received?	Yes
Overall assessment	High



Appendix B. GRADE Evidence Profile

Author(s): AP Zamora

Question: Rotavirus vaccination compared to No vaccination for Prevention of Rotavirus gastroenteritis

Setting: Outpatient

No of studies	Study design	Certainty assessment					No of patients		Effect		Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rotavirus vaccination	No vaccination	Relative (95% CI)	Absolute (95% CI)		
Severe Rotavirus gastroenteritis (up to 2 years follow-up)												
23	randomised trials	not serious	serious ^a	not serious	not serious	none	708/44911 (1.6%)	1489/37779 (3.9%)	RR 0.30 (0.22 to 0.40)	28 fewer per 1,000 (from 31 fewer to 24 fewer)	⊕⊕⊕○ Moderate	CRITICAL
Severe all-cause AGE (up to 2 years follow-up)												
12	randomised trials	not serious	serious ^a	not serious	not serious	none	2724/26476 (10.3%)	2975/22859 (13.0%)	RR 0.78 (0.68 to 0.90)	29 fewer per 1,000 (from 42 fewer to 13 fewer)	⊕⊕⊕○ Moderate	CRITICAL
All-cause mortality (follow-up: range 2 months to 2 years)												
48	randomised trials	not serious	not serious	not serious	serious ^b	none	394/112565 (0.4%)	307/97402 (0.3%)	RR 1.02 (0.88 to 1.18)	0 fewer per 1,000 (from 0 fewer to 1 more)	⊕⊕⊕○ Moderate	CRITICAL
Serious adverse event: Intussusception (follow-up: range 2 months to 2 years)												
43	randomised trials	not serious	not serious	not serious	serious ^b	none	63/113486 (0.1%)	59/99150 (0.1%)	RR 0.87 (0.61 to 1.25)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	CRITICAL
Serious adverse events (follow-up: range 2 months to 2 years)												
51	randomised trials	not serious	not serious	not serious	not serious	none	6407/110221 (5.8%)	5364/95851 (5.6%)	RR 0.92 (0.88 to 0.96)	4 fewer per 1,000 (from 7 fewer to 2 fewer)	⊕⊕⊕⊕ High	CRITICAL

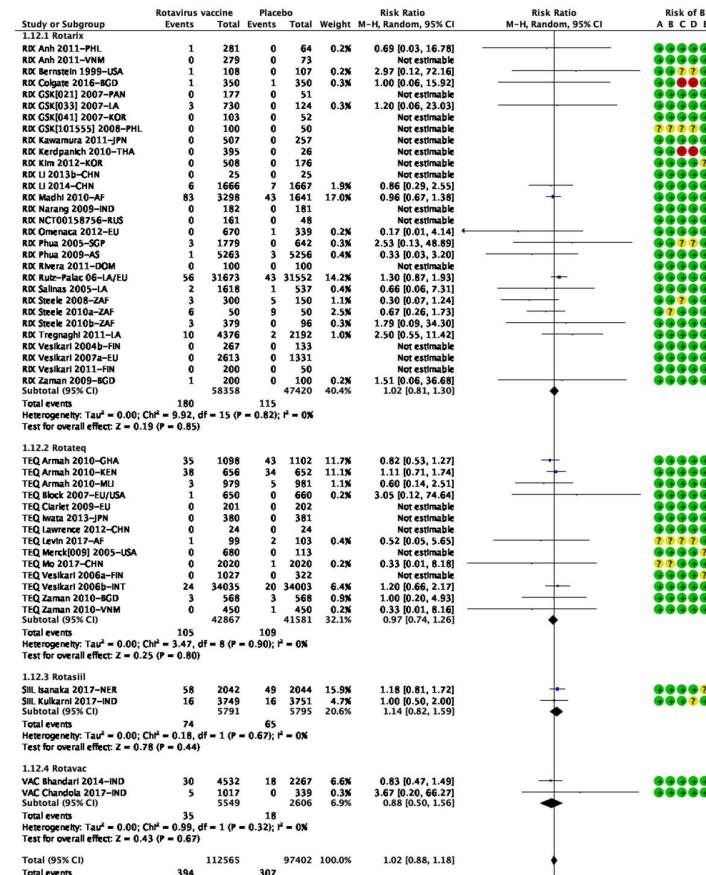
No of studies	Study design	Certainty assessment					No of patients	Effect		Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Rotavirus vaccination	No vaccination		
Rotavirus gastroenteritis of any severity (up to 2 years follow up)											
18	randomised trials	not serious	serious ^a	not serious	not serious	none	1929/27561 (7.0%)	2823/21962 (12.9%)	RR 0.46 (0.37 to 0.57)	69 fewer per 1,000 (from 81 fewer to 55 fewer)	Moderate
Rotavirus gastroenteritis requiring hospitalization (up to 2 years follow up)											
8	randomised trials	not serious	serious ^a	not serious	not serious	none	134/22864 (0.6%)	365/19967 (1.8%)	RR 0.20 (0.08 to 0.48)	15 fewer per 1,000 (from 17 fewer to 10 fewer)	Moderate
All-cause AGE requiring hospitalization (up to 2 years follow-up)											
2	randomised trials	not serious	serious ^a	not serious	not serious	none	182/7817 (2.3%)	266/6550 (4.1%)	RR 0.52 (0.27 to 0.99)	19 fewer per 1,000 (from 30 fewer to 0 fewer)	Moderate

CI: confidence interval; RR: risk ratio

Explanations

- a. High I²
- b. Wide confidence interval

Appendix C. Risk of Bias Appraisal



Favours Rotavirus vaccine Favours Placebo

Figure 1. All-cause mortality, subgroup analysis according to brand of vaccine (Follow-up: 2 months to 2 years)

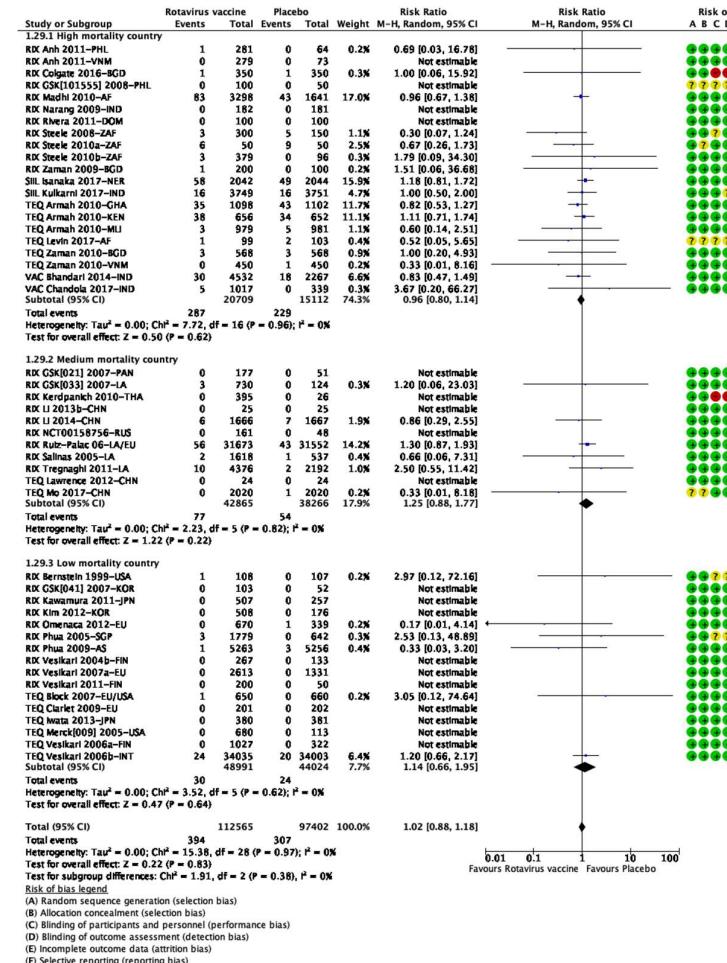


Figure 2. All-cause mortality, subgroup analysis according to country-based under-five mortality rate (Follow-up: 2 months to 2 years)



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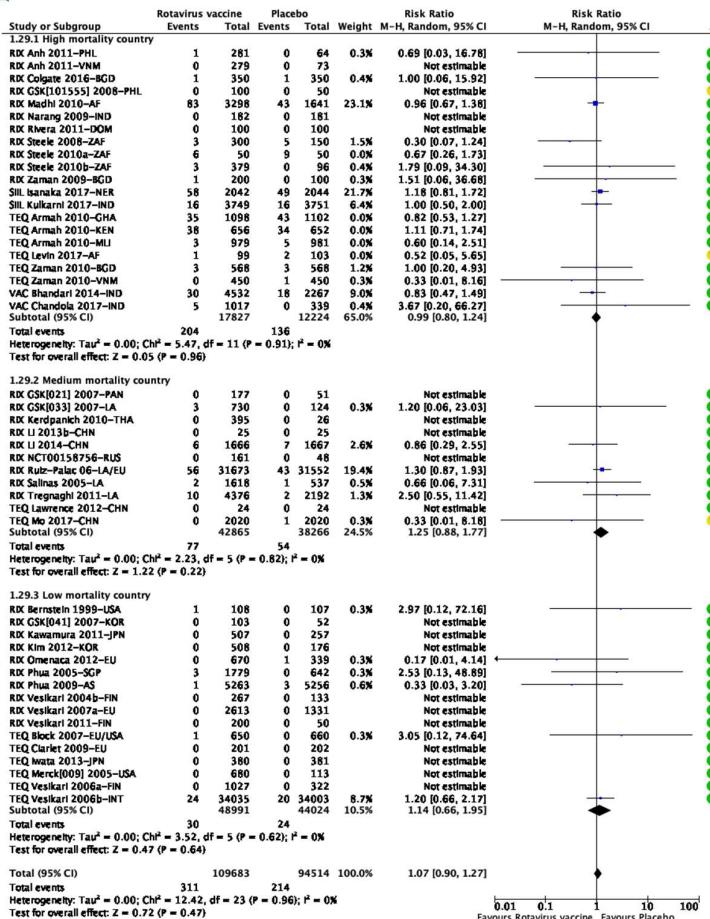
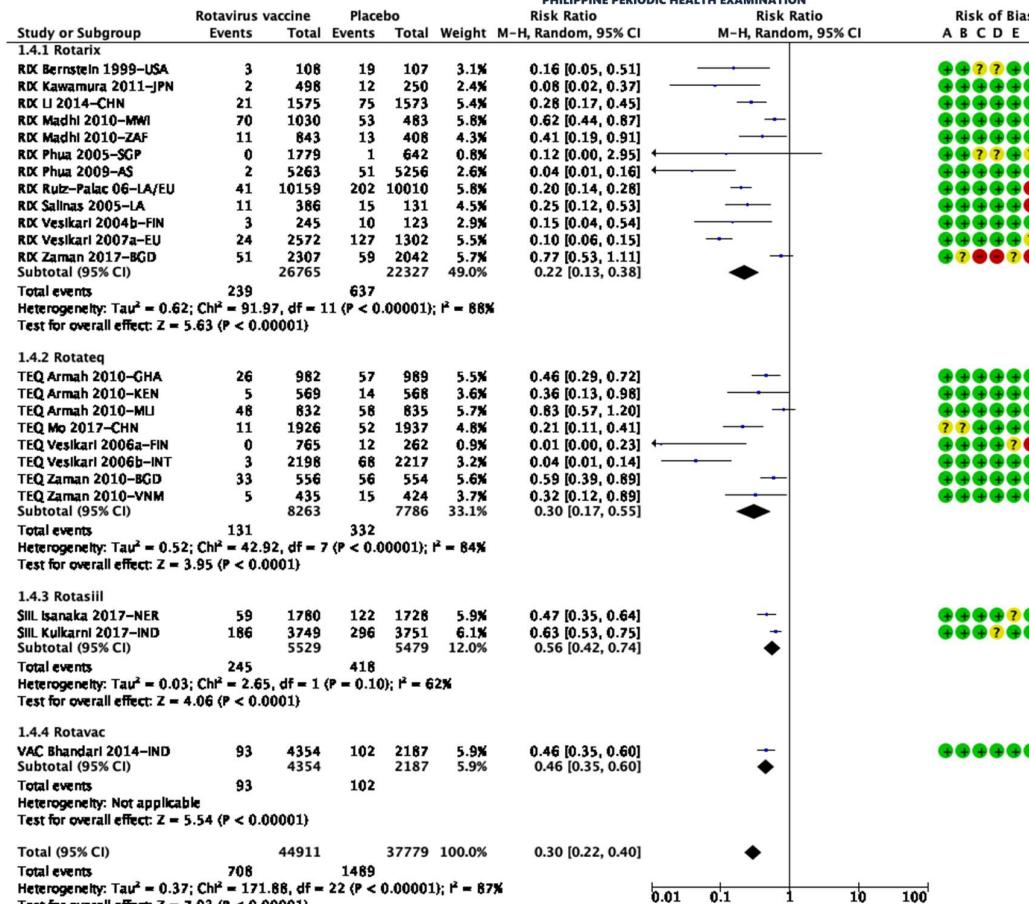


Figure 3. All-cause mortality, sensitivity analysis excluding studies which enrolled patients with HIV infection or exposure (RIX Steele 2010a, TEQ Armah 2010-GHA, TEQ Armah 2010-KEN, TEQ Armah 2010-MLI, TEQ Levin 2017-AF)

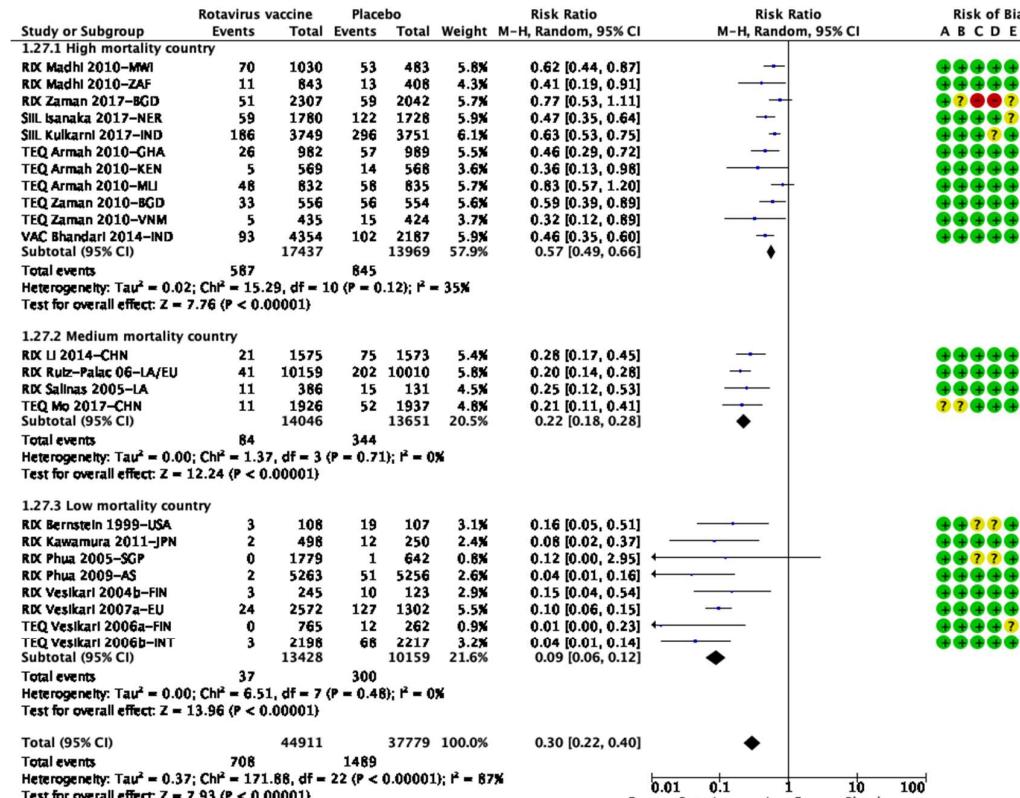
- (A) Random sequence generation (selection bias)
 - (B) Allocation concealment (selection bias)
 - (C) Blinding of participants and personnel (performance bias)
 - (D) Blinding of outcome assessment (detection bias)
 - (E) Incomplete outcome data (attrition bias)



Test for overall effect: $Z = 7.93$ ($P < 0.001$)
Test for subgroup differences: $\chi^2 = 1.00$
Risk of bias legend:

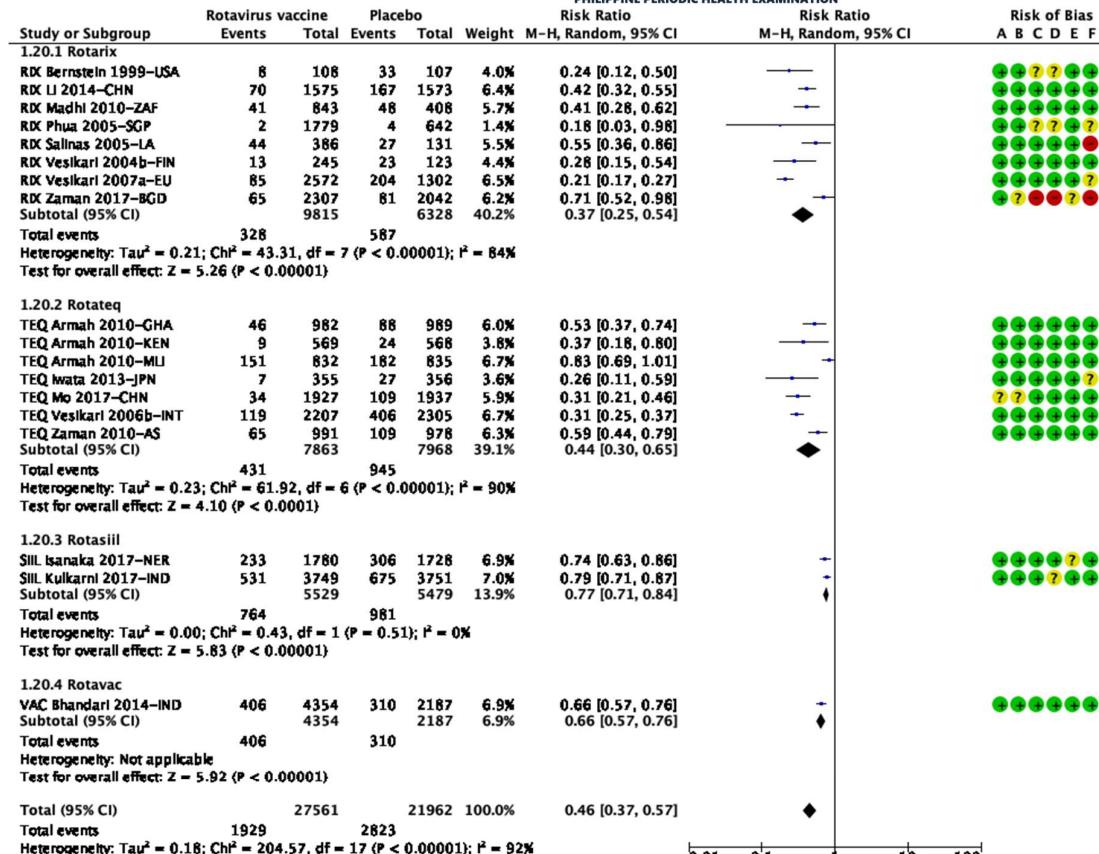
- (A) Random sequence generation (selection)
- (B) Allocation concealment (selection)
- (C) Blinding of participants and personnel (performance)
- (D) Blinding of outcome assessment (detection)
- (E) Incomplete outcome data (attrition)
- (F) Selective reporting (reporting bias)

Figure 4. Severe rotavirus gastroenteritis, subgroup analysis according to brand of vaccine (up to 2 years follow-up)



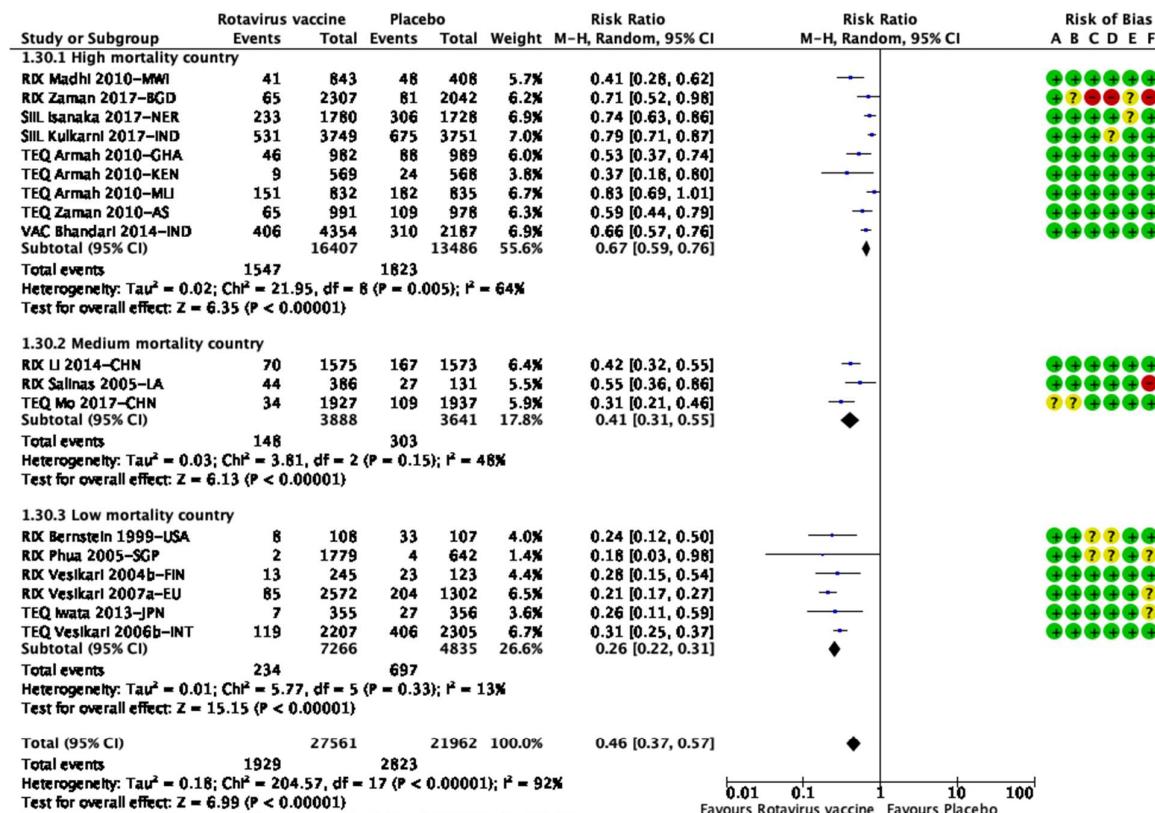
- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)

Figure 5. Severe rotavirus gastroenteritis, subgroup analysis according to country-based level of under-five mortality rate (up to 2 years follow-up)



Risk of bias legend
 (A) Random sequence generation (selection bias)
 (B) Allocation concealment (selection bias)
 (C) Blinding of participants and personnel (performance bias)
 (D) Blinding of outcome assessment (detection bias)
 (E) Incomplete outcome data (attrition bias)
 (F) Selective reporting (reporting bias)

Figure 6. Rotavirus gastroenteritis of any severity, subgroup analysis according to brand of vaccine (up to 2 years follow-up)



Test for subgroup differences

- Risk of bias legend**

 - (A) Random sequence generation (selection bias)
 - (B) Allocation concealment (selection bias)
 - (C) Blinding of participants and personnel (performance bias)
 - (D) Blinding of outcome assessment (detection bias)
 - (E) Incomplete outcome data (attrition bias)
 - (F) Selective reporting (reporting bias)

Figure 7. Rotavirus gastroenteritis of any severity, subgroup analysis according to country-based level of under-five mortality rate (up to 2 years follow-up)

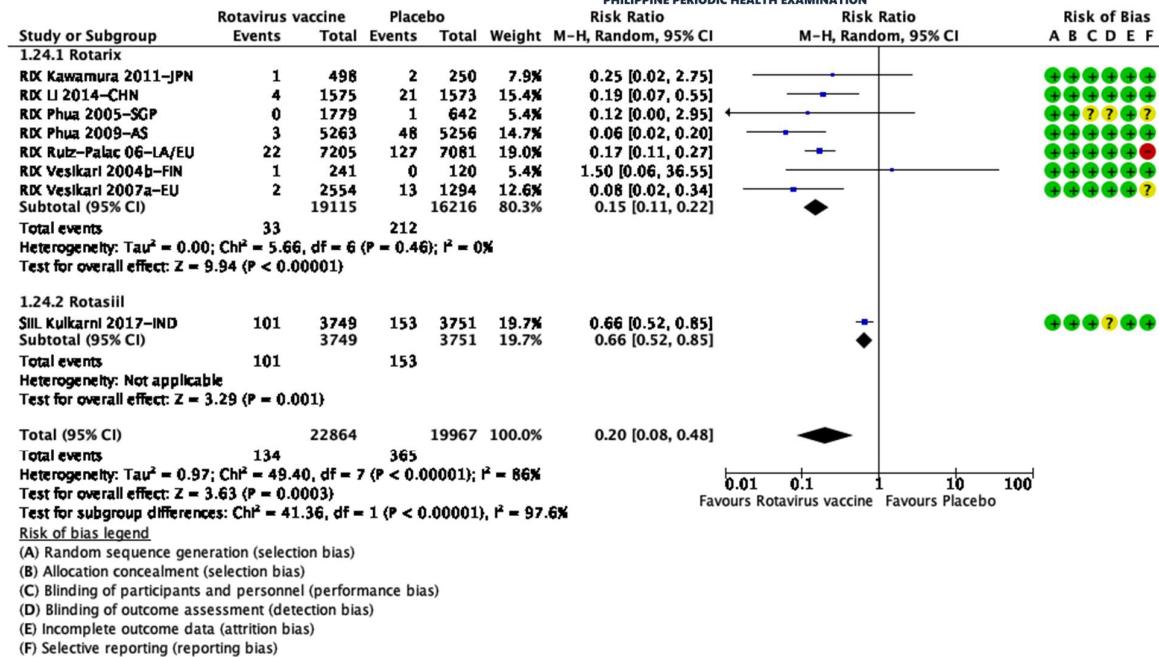
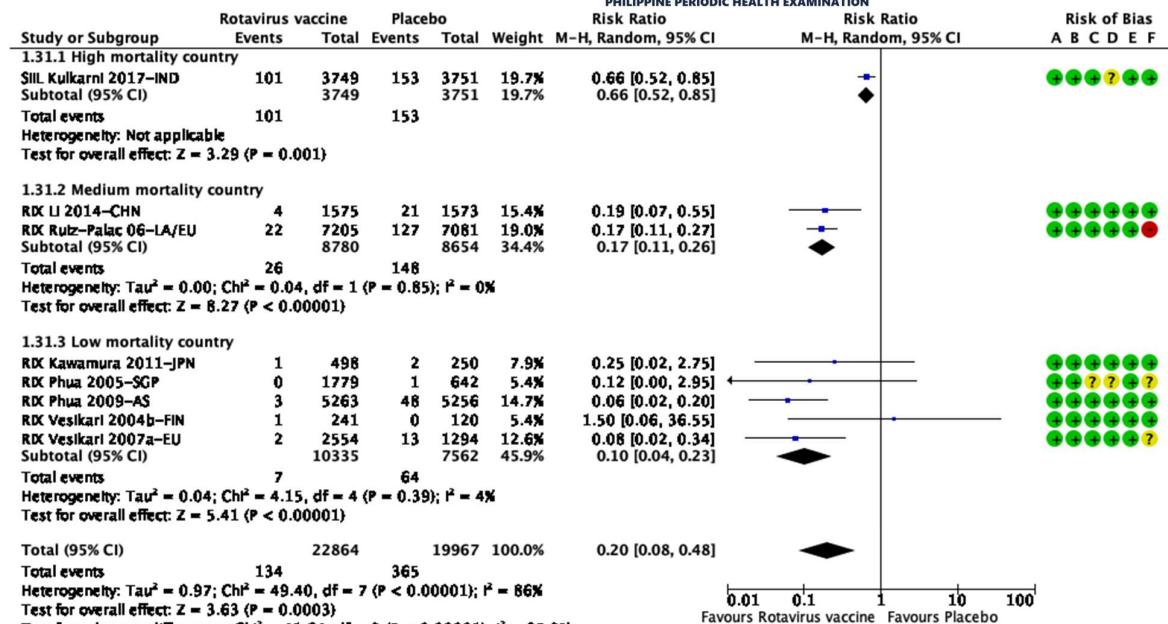


Figure 8. Rotavirus gastroenteritis requiring hospitalization, subgroup analysis according to brand of vaccine (up to 2 years follow up)



- Risk of bias legend
 (A) Random sequence generation (selection bias)
 (B) Allocation concealment (selection bias)
 (C) Blinding of participants and personnel (performance bias)
 (D) Blinding of outcome assessment (detection bias)
 (E) Incomplete outcome data (attrition bias)
 (F) Selective reporting (reporting bias)

Figure 9. Rotavirus gastroenteritis requiring hospitalization, subgroup analysis according to country-based level of under-five mortality rate (up to 2 years follow up)

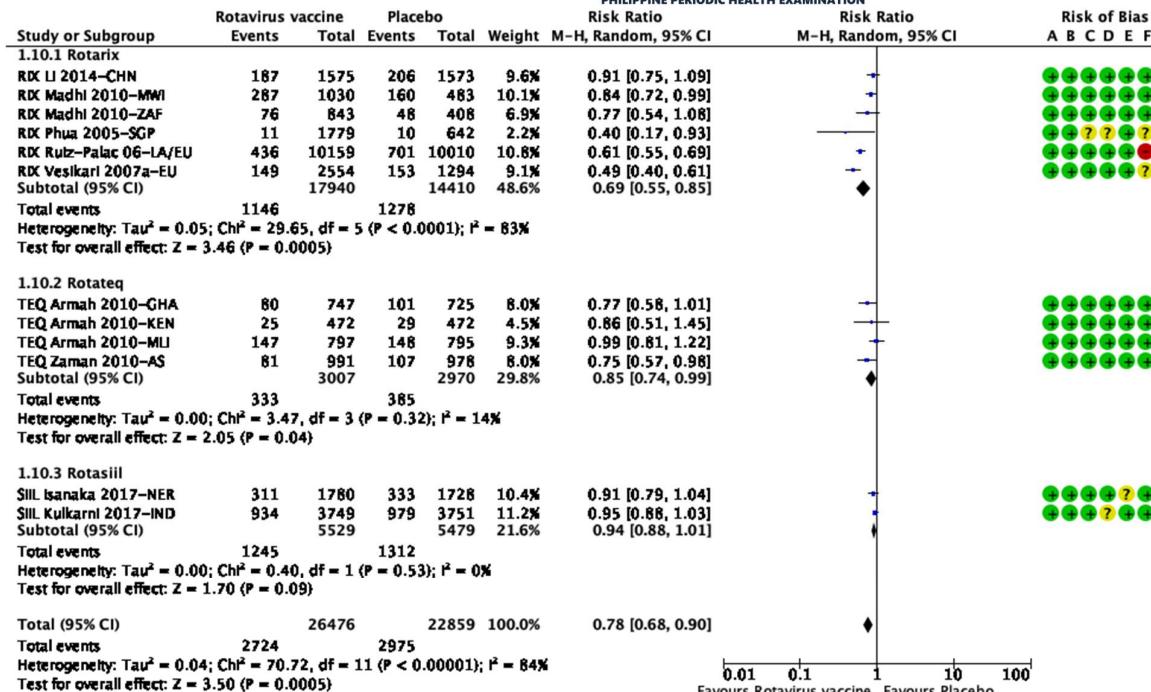


Figure 10. Severe all-cause acute gastroenteritis, subgroup analysis according to brand of vaccine (up to 2 years follow-up)

- Risk of bias legend**

 - (A) Random sequence generation (selection bias)
 - (B) Allocation concealment (selection bias)
 - (C) Blinding of participants and personnel (performance bias)
 - (D) Blinding of outcome assessment (detection bias)
 - (E) Incomplete outcome data (attrition bias)
 - (F) Selective reporting (reporting bias)

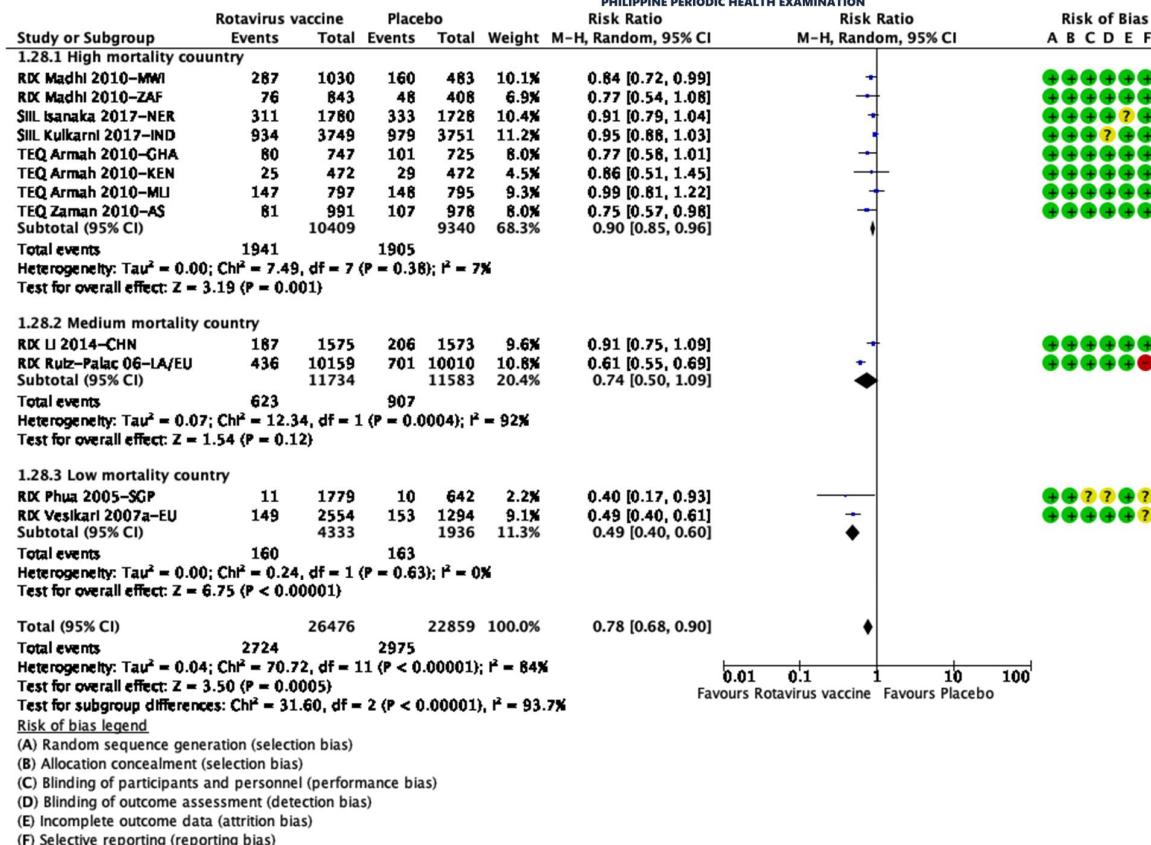
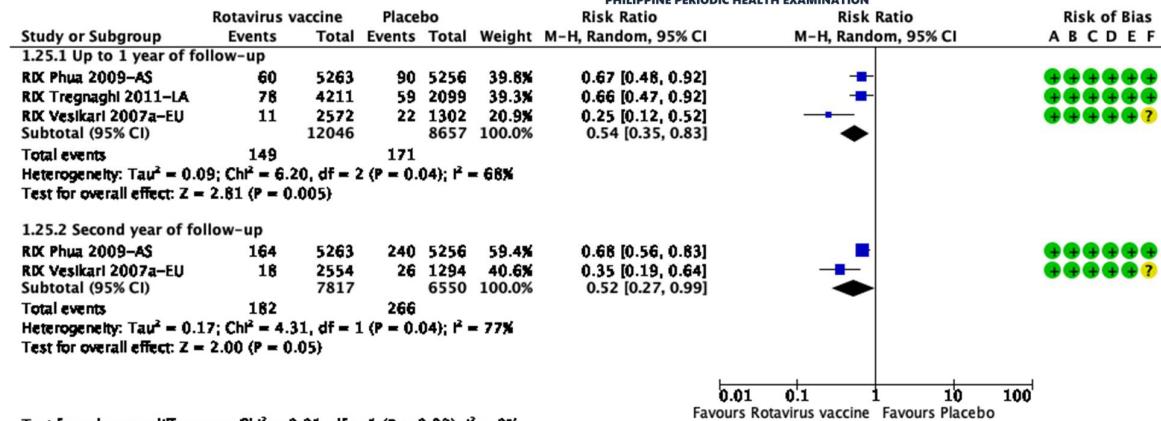


Figure 11. Severe all-cause acute gastroenteritis, subgroup analysis according to country-based level of under-five mortality rate (up to 2 years follow-up)



Test for subgroup differences: $\chi^2 = 0.01$, df = 1 ($P = 0.92$), $I^2 = 0\%$

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)

Figure 12. All-cause AGE requiring hospitalization

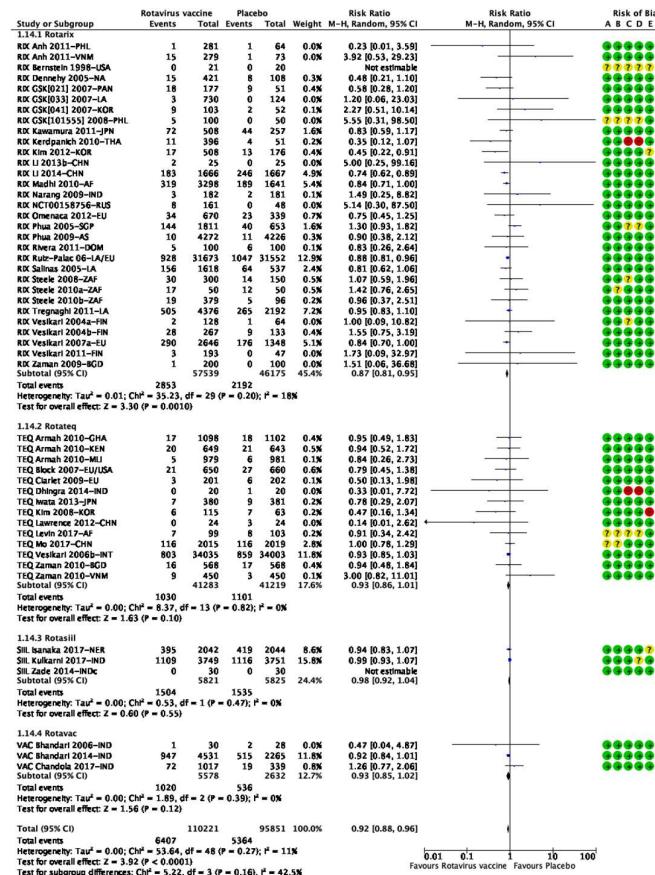


Figure 13. Serious adverse events (all cases)



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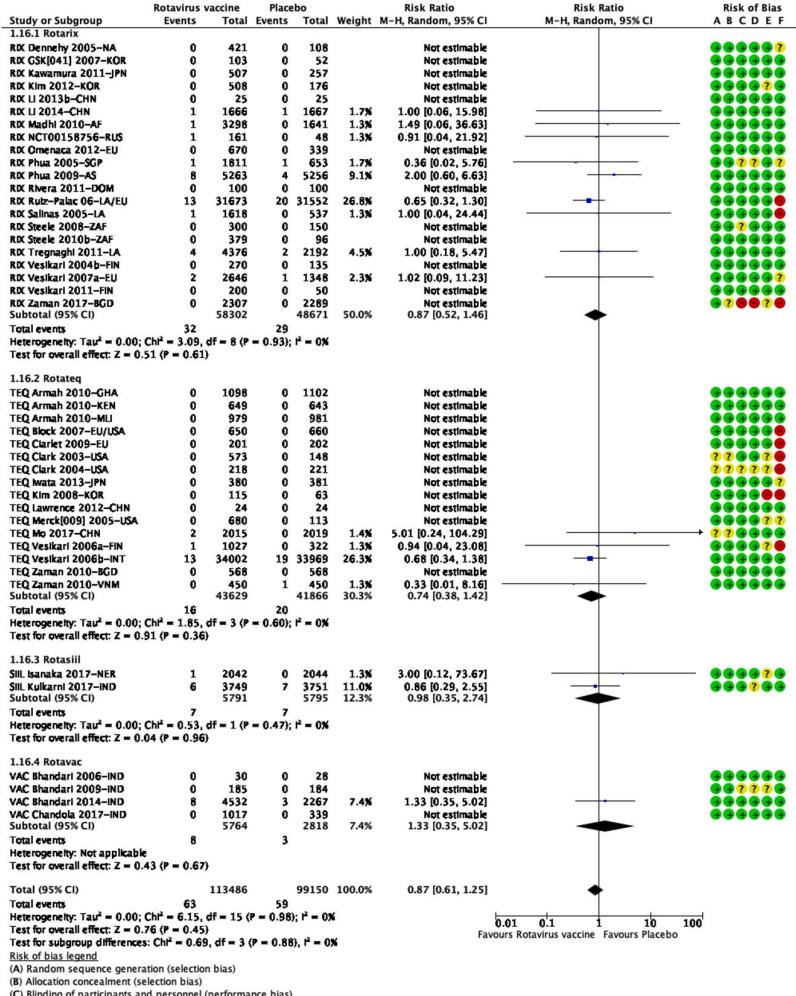
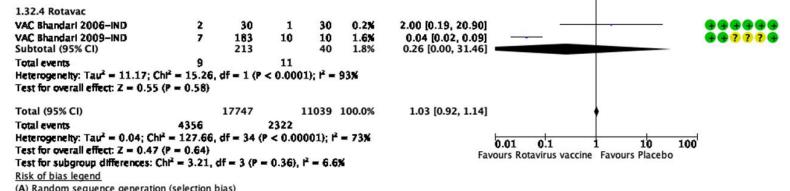
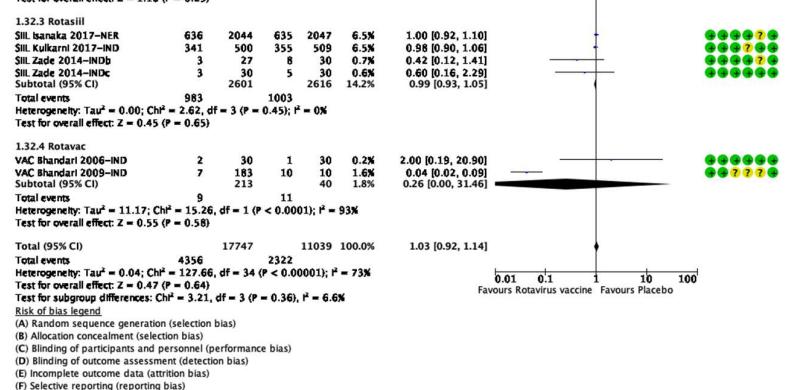
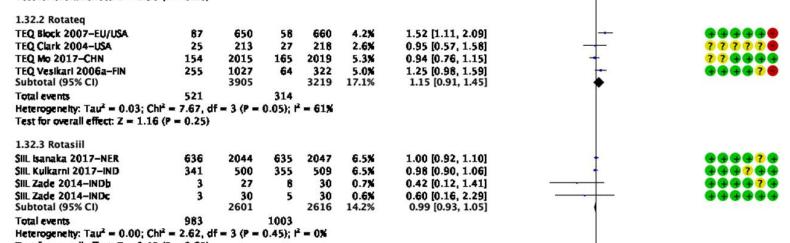
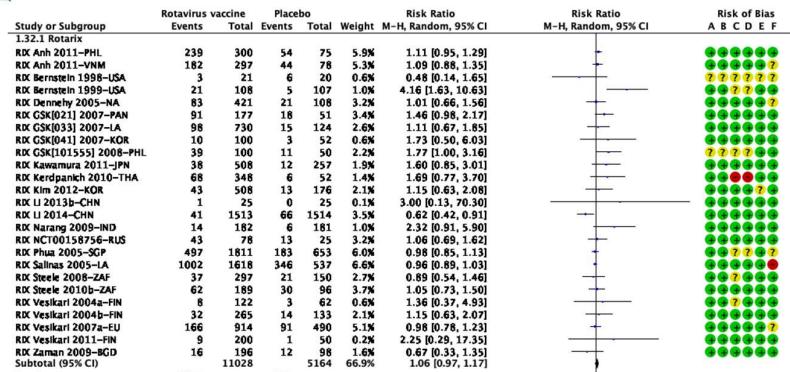


Figure 14. Severe adverse events: Intussusception



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Total (95% CI) 17747 11039 100.0% 1.03 [0.92, 1.14]

0.01 0.1 1 10 100

Favours Rotavirus vaccine Favours Placebo

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)

Figure 15. Reactogenicity to rotavirus vaccine manifesting as fever

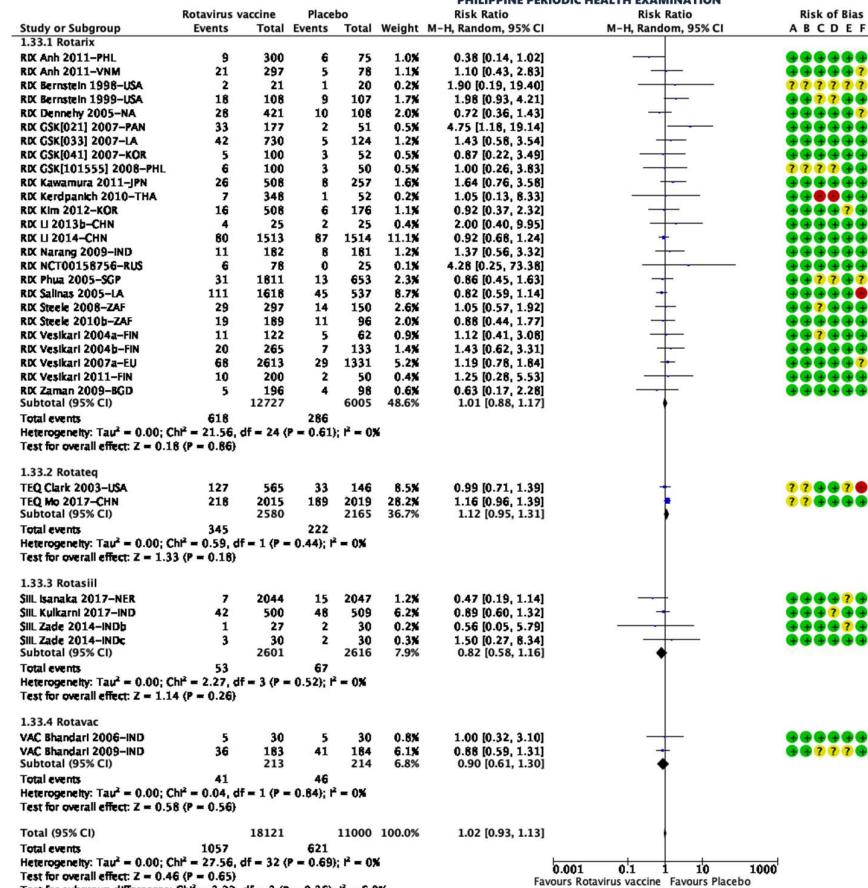


Figure 16. Reactogenicity to rotavirus vaccine manifesting as diarrhea

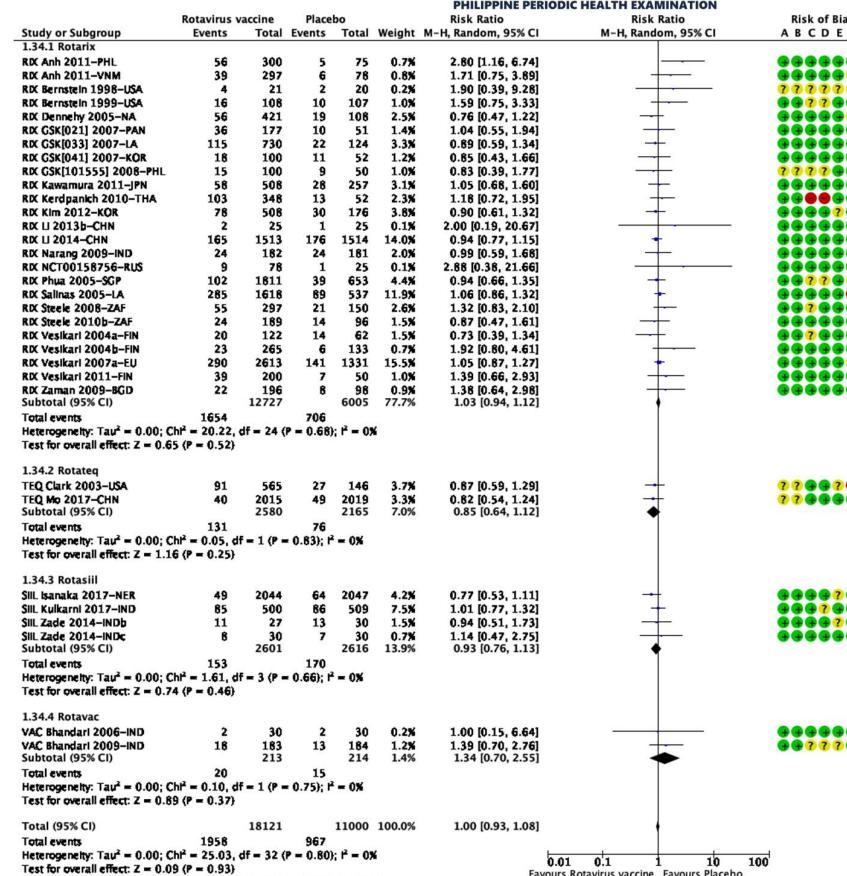


Figure 17. Reactogenicity to rotavirus vaccine manifesting as vomiting

KIND OF BIAS REPORTED

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)

Question 4. Should measles containing vaccines be given to apparently healthy children?

Appendix A. Characteristics of Included Studies

Study ID	Patients	Intervention	Outcome	Method
Marolla, 1998	N=3050, aged 1-7 yo	With measles vaccination (MMR vaccine)	Clinical Diagnosis of Measles infection(1995-1996)	Retrospective Cohort
Barrabeig, 2011 (Spain)	N=1121	1 st dose of Measles vaccine at 9-12 mo 2 nd dose 15 mo (MMR vaccine)	Clinical diagnosis and Laboratory confirmed measles	Retrospective cohort
Bhuniya, 2013 India	N=68, 9-59 months	Measles vaccination based on records, undeclared vaccine type	Clinical diagnosis and Laboratory confirmed measles	Retrospective cohort
Choe, 2017 South Korea	N=14,465, 19-44yo (vaccinated at 8-17yo, in 2001)	MR orMMR give during cath up vaccination from records	Laboratory confirmed measles	Retrospective cohort
La Torre, 2017, Italy	N=11,004 Vaccinated at 1-3yo	MMR Vaccine (1 or 2 doses) via records	Hospitalization with Measles (via records)	Retrospective cohort
Musa, 2018	N=5,084 of School aged children (0-14, >14)	MMR vaccine via records	Clinical diagnosis and Laboratory confirmed measles	Retrospective cohort
Ong, 2007 Singapore	N=1309, aged 8-14 yo	MMR vaccine, 1 dose based on records	Laboratory confirmed measles	Retrospective cohort
Wichmann, 2007 Germany	N=1,098 10-12=485 3-15=460 16-21=152	Measles containing vaccine not specified	Clinical diagnosis	Retrospective cohort
Bloom, 1975	N=282, 11mo -4yo 7-21 days post vaccination	MMR vs placebo	Adverse Events: Temp, rash, coryza, lymphadenopathy, rhinitis, cough, local reactions limb and joint symptoms	RCT, double blind
Lerman, 1981	N=502, 15mo-15yo 4 days- 6 weeks	1 dose MMR vaccine (Arm 2&3) vs placebo	Local reactions, Fever, Respiratory symptoms, rash, Lymphadenopathy, sore eyes, joint symptoms	RCT, double blind
Schwarz, 1975 North and South America	N=1481 7-21 days	MMRvs Placebo	Axillary and rectal temperature, rash, lymphadenopathy, conjunctivitis, otitis media, coryza, rhinitis, pharyngitis, cough, headache, parotitis, orchitis, arthralgia, paraesthesia, site adverse events, hypersensitivity.	Multicenter, RCT, Double blind



Appendix B. Grade Evidence Profile

Question: Should measles-containing vaccine be given to apparently healthy children?

Author(s): Castor, Fides Roxanne and Esteban-Ipac Natasha Ann

Question: Measles Containing vaccine compared to No Measles containing vaccine for Apparently healthy children

Bibliography: Di Pietrantonj C, Rivetti A, Marchione P, Debalini MG, Demicheli V. Vaccines for measles, mumps, rubella, and varicella in children. Cochrane Database of Systematic Reviews. 2021;2021(11).

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Measles Containing vaccine	No Measles containing vaccine	Relative (95% CI)	Absolute (95% CI)		

Vaccine Effectiveness with One Dose of Measles Containing Vaccine

7	observational studies	serious	not serious	not serious	not serious	very strong association	40/8838 (0.5%)	211/3201 (6.6%)	RR 0.05 (0.02 to 0.13)	63 fewer per 1,000 (from 65 fewer to 57 fewer)	⊕⊕⊕○ Moderate	
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Vaccine effectiveness with Two Doses

5	observational studies	serious ^a	not serious	not serious	not serious	very strong association	60/16063 (0.4%)	107/5541 (1.9%)	RR 0.04 (0.01 to 0.28)	19 fewer per 1,000 (from 19 fewer to 14 fewer)	⊕⊕⊕○ Moderate	
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CI: confidence interval; RR: risk ratio

Explanations

a. Included studies have unclear or high risk of bias in terms of cohort selection, comparability and assessment of outcome



Appendix C. Grade Evidence Profile

Evaluating Vaccine Safety

Author(s): Fides Roxanne Castor, MD and Natasha Ann Esteban-Ipac, MD

Bibliography: Di Pietrantonj C, Rivetti A, Marchione P, Debalini MG, Demicheli V. Vaccines for measles, mumps, rubella, and varicella in children. Cochrane Database of Systematic Reviews. 2021;2021.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Measles Containing vaccine	No Measles containing vaccine	Relative (95% CI)	Absolute (95% CI)	
Vaccine Safety- Rash											
3	randomised trials	serious ^a	not serious	not serious	not serious	strong association	110/869 (12.7%)	15/287 (5.2%)	RR 2.05 (1.21 to 3.48)	55 more per 1,000 (from 11 more to 130 more)	⊕⊕⊕⊕ High
Vaccine Safety- Lymphadenopathy											
3	randomised trials	serious ^a	not serious	not serious	serious ^b	none	43/869 (4.9%)	6/287 (2.1%)	RR 1.32 (0.52 to 3.33)	7 more per 1,000 (from 10 fewer to 49 more)	⊕⊕○○ Low
Vaccine Safety- Coryza											
2	randomised trials	serious ^a	not serious	not serious	not serious	none	12/586 (2.0%)	9/245 (3.7%)	RR 0.45 (0.12 to 1.63)	20 fewer per 1,000 (from 32 fewer to 23 more)	⊕⊕⊕○ Moderate
Vaccine Safety- URTI											
2	randomised trials	serious ^a	not serious	not serious	not serious	none	73/586 (12.5%)	65/245 (26.5%)	RR 0.31 (0.06 to 1.56)	183 fewer per 1,000 (from 249 fewer to 149 more)	⊕⊕⊕○ Moderate
Vaccine safety- Cough											



Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Measles Containing vaccine	No Measles containing vaccine	Relative (95% CI)	Absolute (95% CI)	
2	randomised trials	serious ^a	not serious	not serious	serious ^b	none	12/586 (2.0%)	2/245 (0.8%)	RR 1.99 (0.45 to 8.81)	8 more per 1,000 (from 4 fewer to 64 more)	⊕⊕○○ Low

Vaccine safety- Temperature (axillary)

1	randomised trials	serious ^c	not serious	not serious	not serious	none	34/244 (13.9%)	12/176 (6.8%)	RR 2.04 (1.09 to 3.83)	71 more per 1,000 (from 6 more to 193 more)	⊕⊕⊕○ Moderate
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Vaccine safety- Temperature (Rectal)

1	randomised trials	serious ^c	not serious	not serious	not serious	none	94/142 (66.2%)	22/28 (78.6%)	RR 0.84 (0.67 to 1.06)	126 fewer per 1,000 (from 259 fewer to 47 more)	⊕⊕⊕○ Moderate
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Vaccine safety- Temperature (measurement site not reported)

2	randomised trials	serious ^a	not serious	not serious	not serious	none	117/443 (26.4%)	14/77 (18.2%)	RR 1.36 (1.04 to 1.81)	65 more per 1,000 (from 7 more to 147 more)	⊕⊕⊕○ Moderate
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CI: confidence interval; RR: risk ratio

Explanations

- a. One included study had a high risk of bias for attrition and selective reporting
- b. Very Wide Confidence Interval
- c. Study has unclear risk of bias regarding Random sequence Generation Allocation, Attrition,Selective Reporting

Appendix D. Forest Plots

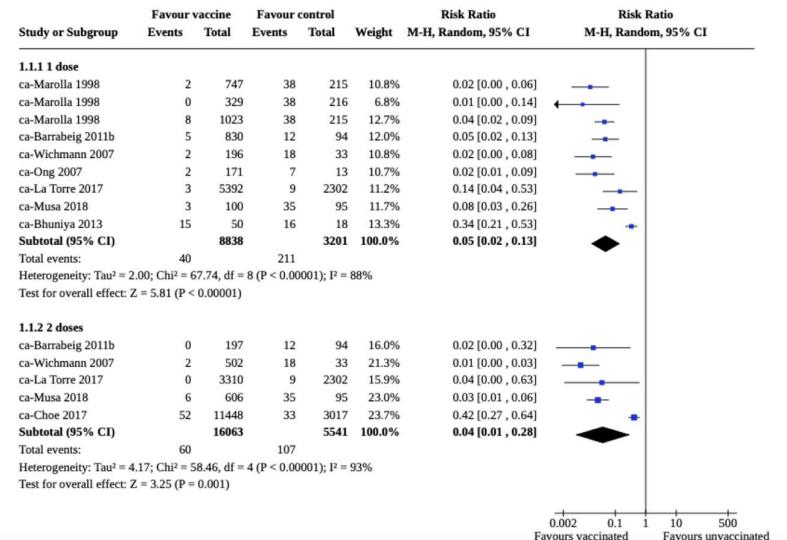


Figure 1. Effectiveness against Incidence of Measles

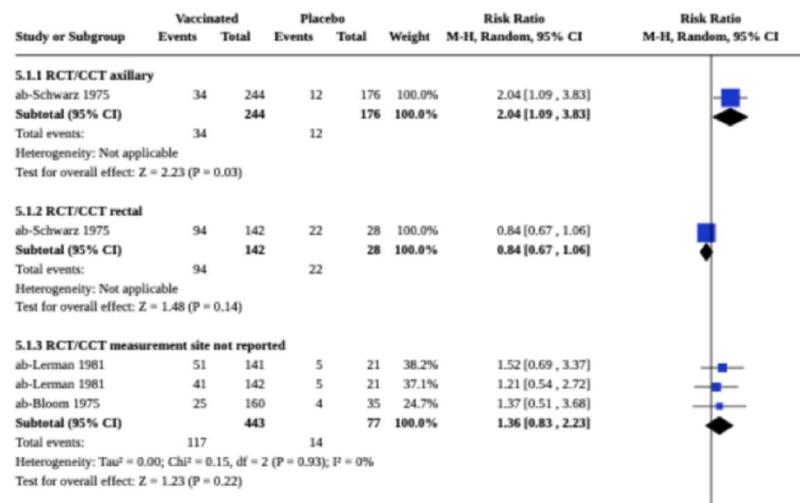


Figure 2. Measles: Adverse event (Temperature)

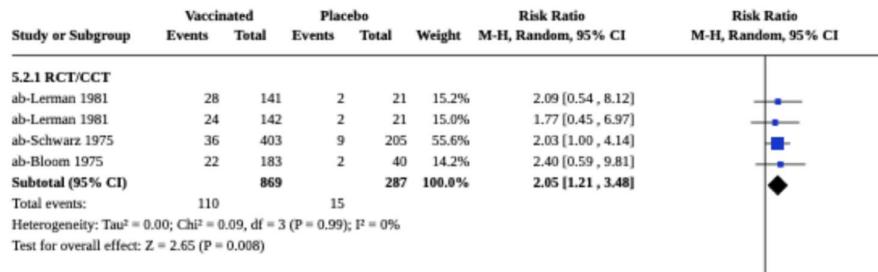


Figure 3. Measles: Adverse event (Rash)

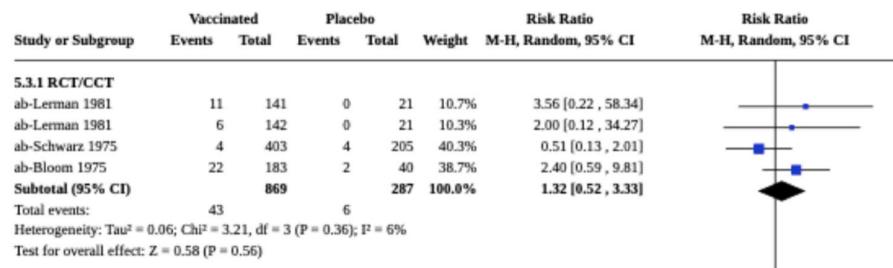


Figure 4. Measles: Adverse event (Lymphadenopathy)

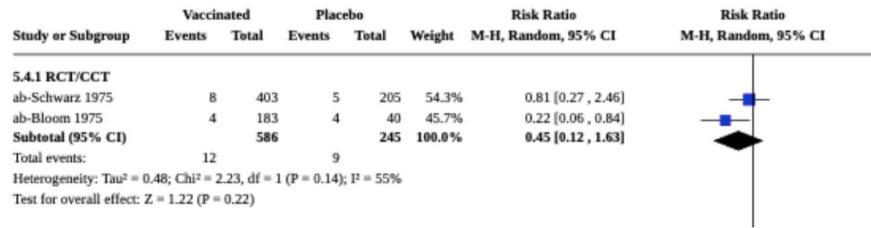


Figure 5. Measles: Adverse event (Coryza)

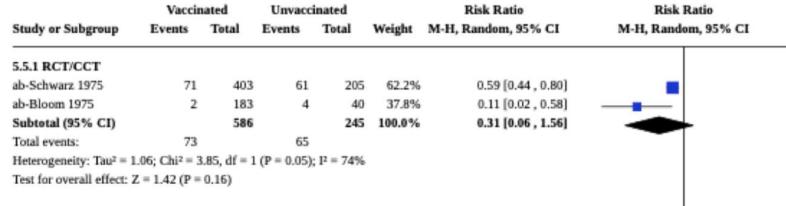


Figure 6. Measles: Adverse event (URTI)

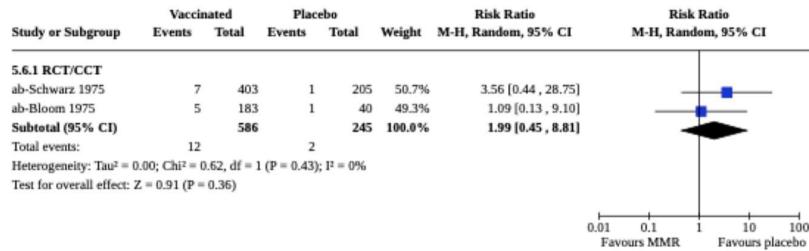


Figure 7. Measles: Adverse event (Cough)

Question 5. Should mumps containing vaccines be given to apparently healthy children?

Appendix A. Characteristics of Included Studies

Study ID	Patients	Intervention	Outcome	Method
Chamot, 1998, Switzerland	N=265 1-30 days from exposure	MMR different strains	Clinical diagnosis of mumps	Retrospective Cohort
Greenland, 2012	N=989	MMR via registry	Clinical diagnosis (self report)	Retrospective cohort
La Torre, 2017, Italy	N=11,004 Vaccinated at 1-3yo	MMR Vaccine (1 or 2 doses) via records	Hospitalization with Mumps (via records)	Retrospective cohort
Livingston, 2013	N=2176	MMR via registry	Clinical diagnosis or Laboratory confirmed mumps	Retrospective cohort
Ma, 2018, China	N=1908 6-15 yo	MMR, Jeryl Lynn strain	Clinical Diagnosis of mumps	Retrospective cohort
Schlegel, 1999 Switzerland	N=165 5-13 y	MMR, 3 strains via vaccination certificates	Clinical Diagnosis of mumps	Retrospective cohort
Snijers, 2012	<19 yo	MMR Jeryl Lynn Strain	Clinical diagnosis of mumps as report	Retrospective cohort
Takla, 2014	N=108	MMR Jeryl Lynn Strain	Clinical diagnosis or Laboratory confirmed mumps	Retrospective cohort
Ong, 2005 Singapore	N=2539+2533 5-12 yo	MMR, 3 strains, from health booklet	Clinical diagnosis of mumps	Retrospective cohort
Compes-Dea, 2014, Spain	N=235 16-17 yo	MMR Jeryl Lynn or Rubin strain b vaccine record	Laboratory confirmed mumps	Retrospective cohort
Lopez-Hernandez, 2000, Spain	N=775 3-15 yo	MMR strain not reported	Clinical diagnosis of mumps	Retrospective cohort
Bloom, 1975	N=282, 11mo-4yo 7-21 days post vaccination	MMR vs placebo	Adverse Events: Temp, rash, coryza, lymphadenopathy, rhinitis, cough, local reactions limb and joint symptoms	RCT, double blind
Lerman, 1981	N=502, 15mo-15yo 4 days- 6 weeks	1 dose MMR vaccine (Arm 2&3) vs placebo	Local reactions, Fever, Respiratory symptoms, rash, Lymphadenopathy, sore eyes, joint symptoms	RCT, double blind
Schwarz, 1975 North and South America	N=1481 7-21 days	MMR vs Placebo	Axillary and rectal temperature, rash, lymphadenopathy, conjunctivitis, otitis media, coryza, rhinitis, pharyngitis, cough, headache, parotitis, orchitis, arthralgia, paresthesia, site adverse events, hypersensitivity.	Multicenter, RCT, Double blind

Appendix B. Grade Evidence Profile

Question: Should Mumps containing vaccine be given to apparently healthy children?

Author(s): Fldes Roxanne Castor, MD and Natasha Ann Esteban-Ipac, MD

Question: Mumps containing vaccine compared to no mumps vaccine for apparently healthy children

Bibliography: Di Pietrantonj C, Rivetti A, Marchionne P, Debalini MG, Demicheli V. Vaccines for measles, mumps, rubella, and varicella in children. Cochrane Database of Systematic Reviews. 2021;2021

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mumps containing vaccine	no mumps vaccine	Relative (95% CI)	Absolute (95% CI)		
Vaccine Efficacy												
6	observational studies	serious ^a	not serious	not serious	not serious	strong association	68/6690 (1.0%)	175/3225 (5.4%)	RR 0.28 (0.13 to 0.62)	39 fewer per 1,000 (from 47 fewer to 21 fewer)	⊕⊕○○ Low	
Vaccine Efficacy - 2 doses												
5	observational studies	serious ^a	not serious	not serious	not serious	strong association	124/5097 (2.4%)	103/2695 (3.8%)	RR 0.14 (0.07 to 0.27)	33 fewer per 1,000 (from 36 fewer to 28 fewer)	⊕⊕○○ Low	
Vaccine Efficacy- unspecified doses												
4	observational studies	serious ^a	not serious	not serious	not serious	strong association	34/1297 (2.6%)	69/714 (9.7%)	RR 0.23 (0.14 to 0.35)	74 fewer per 1,000 (from 83 fewer to 63 fewer)	⊕⊕○○ Low	
Vaccine Efficacy- Mumps strain not specified or Mixed												
2	observational studies	serious ^b	not serious	not serious	not serious	none	86/729 (11.8%)	9/40 (22.5%)	RR 0.52 (0.29 to 0.94)	108 fewer per 1,000 (from 160 fewer to 14 fewer)	⊕○○○ Very low	

CI: confidence interval; RR: risk ratio

Explanations

a. unclear risk for comparability and assessment of outcome

b. One study included had high risk of bias for comparability and assessment of outcome

Appendix C. Grade Evidence Profile

Evaluating Vaccine Safety

Author(s): Fldes Roxanne Castor, MD and Natasha Ann Esteban-Ipac, MD

Bibliography: Di Pietrantonj C, Rivetti A, Marchionne P, Debalini MG, Demicheli V. Vaccines for measles, mumps, rubella, and varicella in children. Cochrane Database of Systematic Reviews. 2021;2021

Nr of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty assessment		Nr of patients		Effect		Certainty
							Measles Containing vaccine	No Measles containing vaccine	Relative (95% CI)	Absolute (95% CI)			
Vaccine Safety- Rash													
3	randomised trials	serious ^a	not serious	not serious	not serious	strong association	110/869 (12.7%)	15/287 (5.2%)	RR 2.05 (1.21 to 3.48)	55 more per 1,000 (from 11 more to 130 more)	⊕⊕⊕⊕ High		
Vaccine Safety- Lymphadenopathy													
3	randomised trials	serious ^a	not serious	not serious	serious ^b	none	43/869 (4.9%)	6/287 (2.1%)	RR 1.32 (0.52 to 3.33)	7 more per 1,000 (from 10 fewer to 49 more)	⊕⊕○○ Low		
Vaccine Safety- Coryza													
2	randomised trials	serious ^a	not serious	not serious	not serious	none	12/586 (2.0%)	9/245 (3.7%)	RR 0.45 (0.12 to 1.63)	20 fewer per 1,000 (from 32 fewer to 23 more)	⊕⊕⊕○ Moderate		
Vaccine Safety- URTI													
2	randomised trials	serious ^a	not serious	not serious	not serious	none	73/586 (12.5%)	65/245 (26.5%)	RR 0.31 (0.06 to 1.56)	183 fewer per 1,000 (from 249 fewer to 149 more)	⊕⊕⊕○ Moderate		
Vaccine safety- Cough													
2	randomised trials	serious ^a	not serious	not serious	serious ^b	none	12/586 (2.0%)	2/245 (0.8%)	RR 1.99 (0.45 to 8.81)	8 more per 1,000 (from 4 fewer to 64 more)	⊕⊕○○ Low		
Vaccine safety- Temperature (axillary)													
1	randomised trials	serious ^c	not serious	not serious	not serious	none	34/244 (13.9%)	12/176 (6.8%)	RR 2.04 (1.09 to 3.83)	71 more per 1,000 (from 6 more to 193 more)	⊕⊕⊕○ Moderate		
Vaccine safety- Temperature (Rectal)													
1	randomised trials	serious ^c	not serious	not serious	not serious	none	94/142 (66.2%)	22/28 (78.6%)	RR 0.84 (0.67 to 1.06)	126 fewer per 1,000 (from 259 fewer to 47 more)	⊕⊕⊕○ Moderate		
Vaccine safety- Temperature (measurement site not reported)													
2	randomised trials	serious ^a	not serious	not serious	not serious	none	117/443 (26.4%)	14/77 (18.2%)	RR 1.38 (1.04 to 1.81)	65 more per 1,000 (from 7 more to 147 more)	⊕⊕⊕○ Moderate		

CI: confidence interval; RR: risk ratio

Explanations

- a. One included study had a high risk of bias for attrition and selective reporting
- b. Very Wide Confidence Interval
- c. Study has unclear risk of bias regarding Random sequence Generation Allocation, Attrition, Selective Reporting

Appendix C. Forest Plots

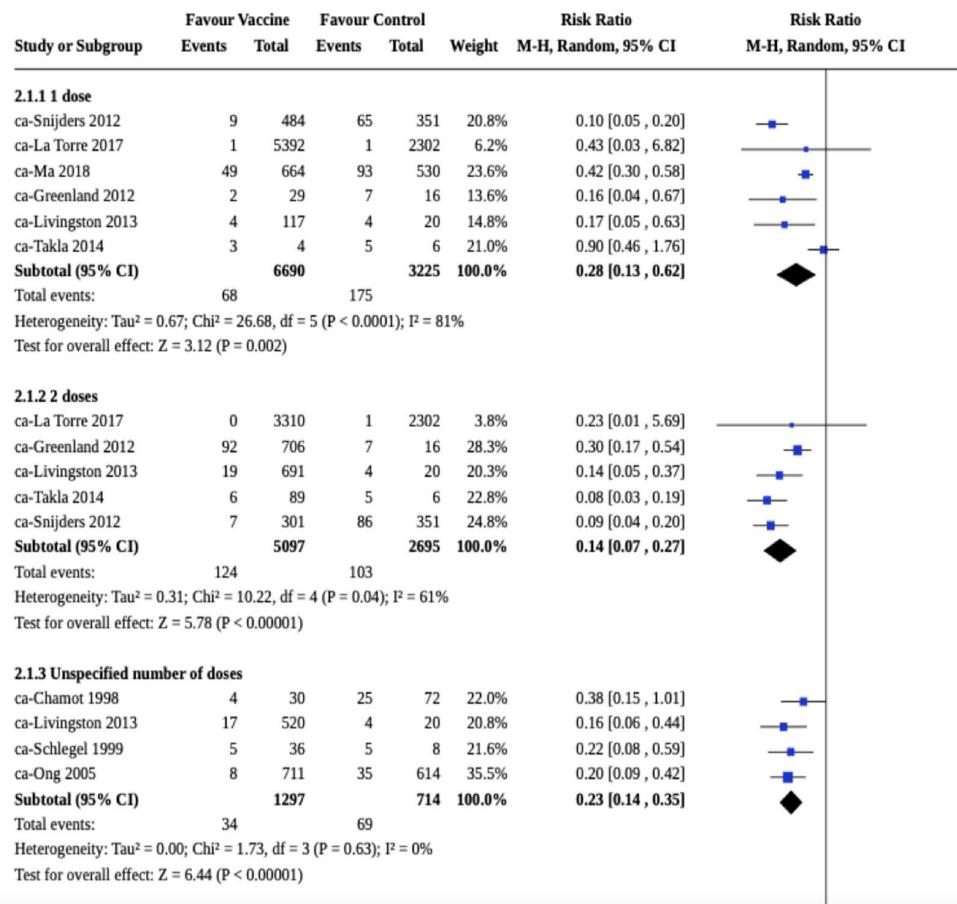


Figure 1. Vaccine effectiveness against mumps (Jeryl Lynn strain)

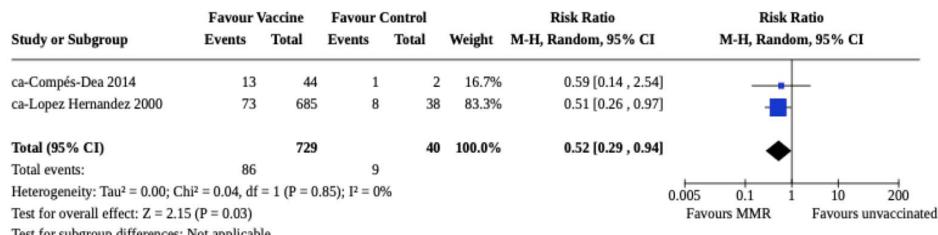


Figure 2. Vaccine effectiveness against mumps (Unspecified or mixed strain)

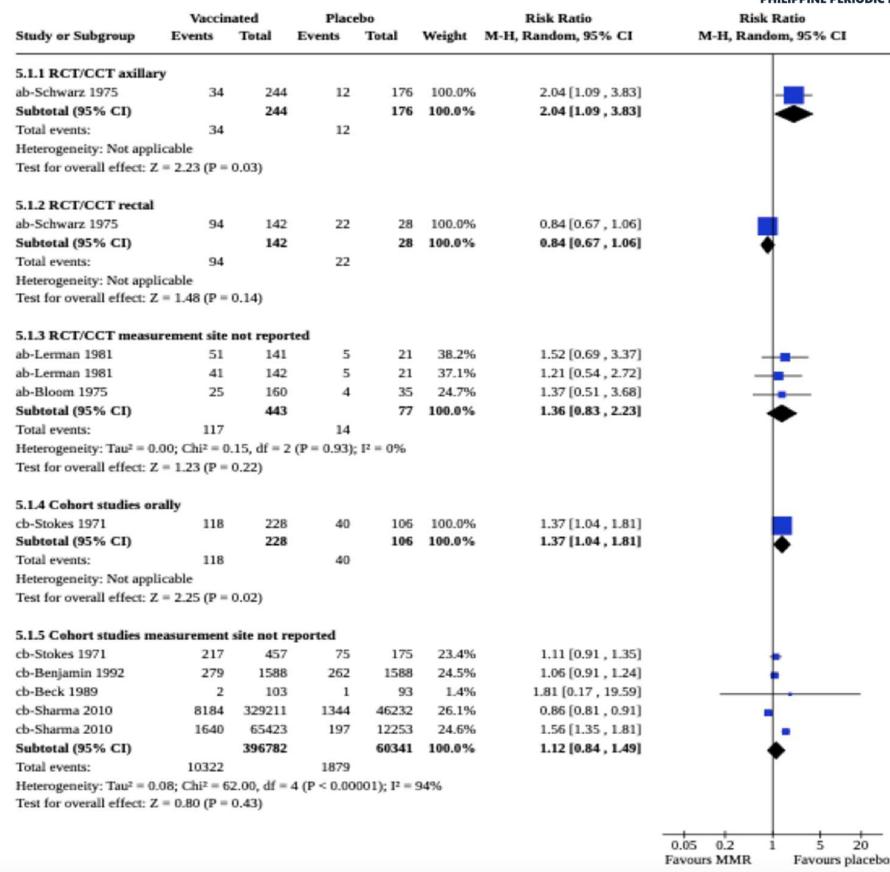


Figure 3. Mumps: Adverse event (Temperature)

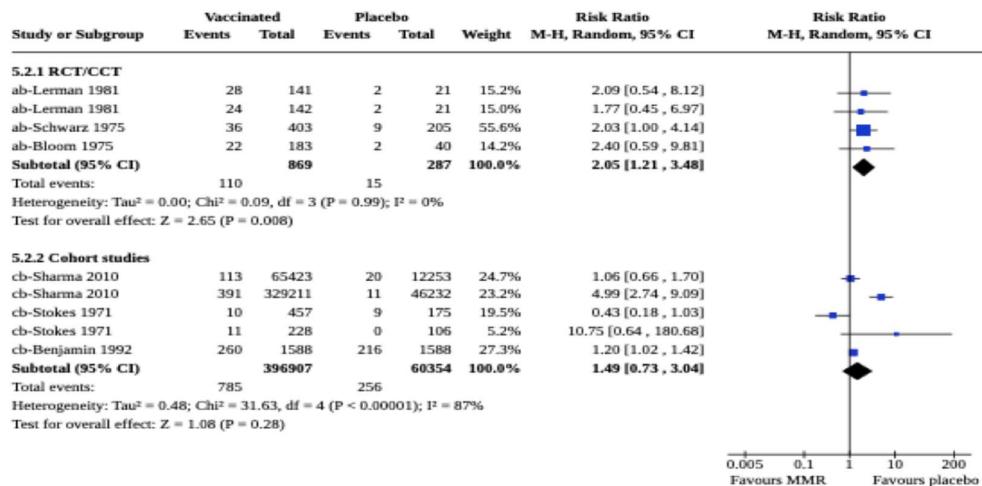


Figure 4. Mumps: Adverse event (Rash)

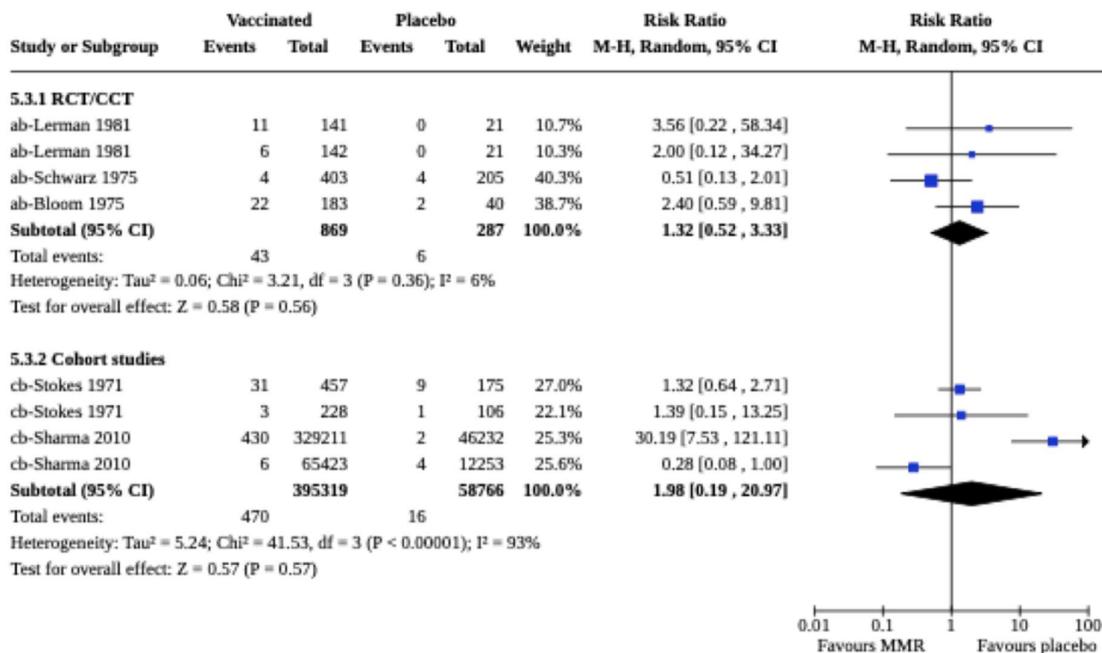


Figure 5. Mumps: Adverse event (Lymphadenopathy)

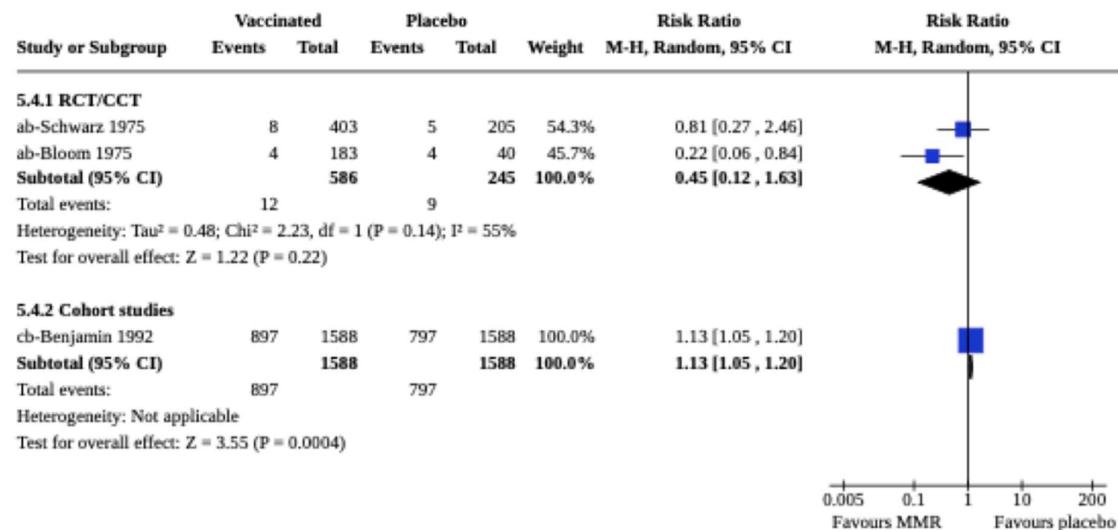


Figure 6. Mumps: Adverse event (Coryza)

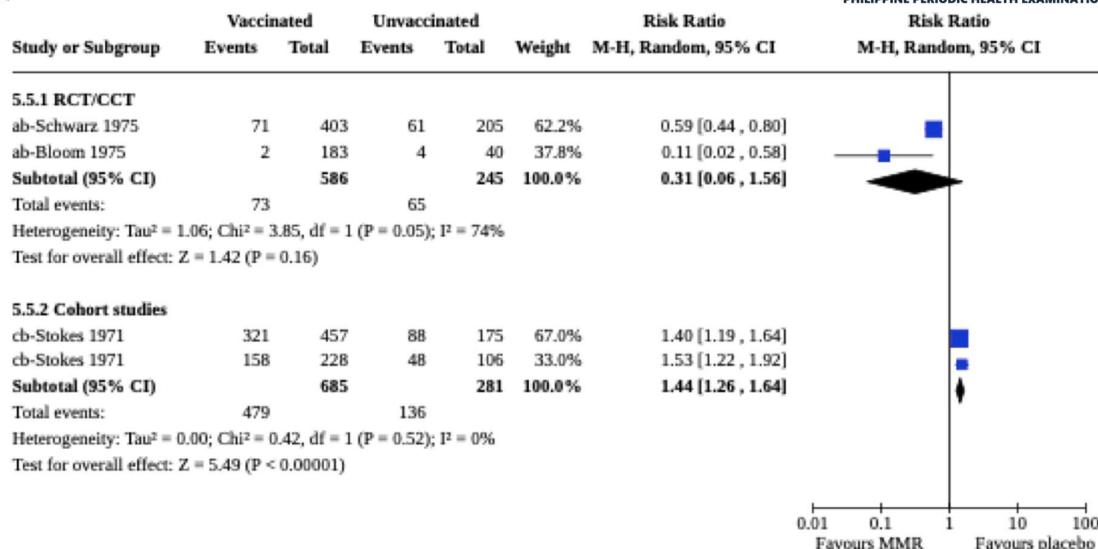


Figure 7. Mumps: Adverse event (URTI)

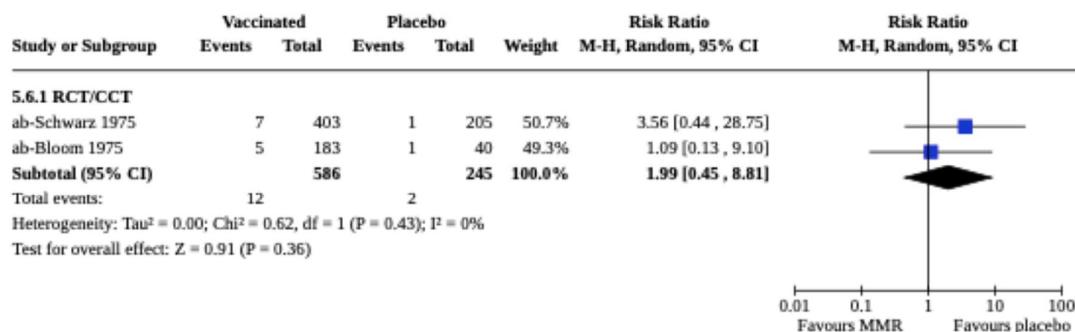


Figure 8. Mumps: Adverse event (Cough)

Question 6. Should varicella vaccine be recommended to apparently healthy children and adolescents?

Appendix A. Characteristics of Included Studies

One dose varicella vaccine vs placebo/non varicella containing vaccine

Primary Author	Year	Setting	Age (No. of participants)	Vaccine Formulation/Virus Strain	Control	Outcome	Timing of Outcome Collection	Antibody Measurement
Weibel	1984	USA	1-14 y/o (N = 956)	Oka/Merck	placebo	Immunogenicity (GMT, seroconversion); Incidence (attack rate); Safety (fever, rash, local)	Day 0, 60	IFA
Kuter	1991	USA	1-14 y/o (N = 332)	Oka/Merck	placebo	Incidence (attack rate lab confirmed); Immunogenicity (GMT, seroconversion)	2-6 years	gpELISA
Varis	1996	Finland	10-30mos (N = 513)	Oka strain	placebo	Immunogenicity (GMT, seroconversion); Incidence (serologically and clinically confirmed)	Day 35-63 (target 42 days)	IFA
Parment	2003	Sweden	11-12y/o (N = 1231)	Varilrix (Oka/GSK)	MMR (MSD)	Immunogenicity (GMC, seropositivity); Safety (Local vs general)	Day 0, 56	IFA, gpELISA
Gatchalian	2004	Philippines	12-24mos (N = 300)	Okavax (Oka/Biken)	MMR (Trimovax)	Immunogenicity (GMT, seroconversion); safety (immediate and delayed local vs systemic)	Day 0, 42	gpELISA
Ferrera	2009	France, Italy	12-15mos (N = 507)	VARIVAX (Oka/Merck)	MMR	Safety (erythema, pain, swelling, rash)	Day 0, 42	N/A
Hao	2019	China	1-12y/o (N = 5997)	Oka strain	placebo	immunogenicity (GMT, seroconversion, seropositivity); efficacy (clinical and lab confirmed varicella infection); safety (local vs systemic)	Day 0, 30	IFA

Two doses varicella vaccine vs one dose varicella vaccine

Primary Author	Year	Setting	Age (No. of Participants)	Vaccine	Control	Outcome	Timing of Outcome Collection
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Kosuwon	2004	Thailand	13-29 y/o (186 subjects)	2 dose Varilrix	GSK	1 dose Biken	Seroconversion, GMT, Local injection symptoms (pain, redness, swelling), General symptoms (fever, rash)	Day 0, 42
Kuter	2004	Philadelphia	12mos-12 y/o (2196 subjects)	2 dose Varivax		1 dose Varivax	Incidence, Seroconversion, GMT	1 – 10 years
Ngai	1995	Philadelphia	12mos-12 y/o (2196 subjects)	2 dose Varivax		1 dose Varivax	Seroconversion, GMT, Incidence, Adverse events (fever, rash)	6 weeks – 1 year
Watson	1995	Philadelphia	12mos-12 y/o (200 subjects)	2 dose Varivax		1 dose Varivax	GMT, Cell-mediated immune response	6 weeks – 1 year

Appendix B. Grade Evidence Profile

1 dose varicella vaccine compared to placebo/nonvaricella containing vaccine for healthy children and adolescents

Bibliography:

Certainty assessment							Summary of findings			
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects
							With placebo/nonvaricella containing vaccine	With 1 dose varicella vaccine		
7556 (4 RCTs)	not serious	not serious	not serious	not serious	strong association ^a	⊕⊕⊕⊕ High	146/3764 (3.9%)	12/3792 (0.3%)	RR 0.08 (0.05 to 0.15)	39 per 1,000 36 fewer per 1,000 (from 37 fewer to 33 fewer)

Incidence of varicella disease (follow-up: range 30 days to 6 years; assessed with: clinically and serologically diagnosed)

7556 (4 RCTs)	not serious	not serious	not serious	not serious	strong association ^a	⊕⊕⊕⊕ High	146/3764 (3.9%)	12/3792 (0.3%)	RR 0.08 (0.05 to 0.15)	39 per 1,000 36 fewer per 1,000 (from 37 fewer to 33 fewer)
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Seroconversion (follow-up: range 30 days to 60 days; assessed with: IFA, gpELISA)

2113 (4 RCTs)	not serious	not serious	not serious	not serious	very strong association ^{a,b}	⊕⊕⊕⊕ High	19/1043 (1.8%)	1029/1070 (96.2%)	RR 51.68 (33.26 to 80.30)	18 per 1,000 923 more per 1,000 (from 588 more to 1,000 more)
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Geometric Mean Titers (follow-up: range 42 days to 63 days)

1922 (3 RCTs)	not serious	serious ^c	not serious	not serious	none ^d	⊕⊕⊕○ Moderate	948	974	-	The mean geometric Mean Titers was 0 SD MD 29.85 SD higher (from -42 higher to 35.28 higher)
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Safety (local adverse events) (follow-up: range 30 days to 60 days; assessed with: redness and pain)

7446 (4 RCTs)	not serious	not serious	not serious	serious ^e	none ^a	⊕⊕⊕○ Moderate	163/3761 (4.3%)	190/3685 (5.2%)	RR 1.33 (1.10 to 1.61)	43 per 1,000 14 more per 1,000 (from 4 more to 26 more)
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Safety (systemic adverse events) (follow-up: range 30 days to 60 days; assessed with: fever)

6490 (3 RCTs)	not serious	not serious	not serious	serious	none ^a	⊕⊕⊕○ Moderate	495/3296 (15.0%)	460/3194 (14.4%)	RR 0.94 (0.83 to 1.05)	150 per 1,000 9 fewer per 1,000 (from 26 fewer to 8 more)
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CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

a. The studies included have been sponsored by pharmaceutical companies such as MSD, Sanofi and Sinovac. There are however no noted bias in reporting of results and journal selection

b. The magnitude of effect across studies is very large as reflected by RR >5

c. Wide variance of point estimates across studies with high level of heterogeneity might be due to difference in baseline titers of the subjects recruited, and the difference in the duration of follow-up extraction

d. The wide confidence interval might be due to low baseline titers of the participants recruited (low event rate)

e. The wide CI may be due to low event rate of adverse events whether local or generalized across studies

2 dose varicella vaccine compared to 1 dose for healthy children and adolescents

Bibliography:

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With 1 dose	With 2 dose varicella vaccine		Risk with 1 dose	Risk difference with 2 dose varicella vaccine
4339 (2 RCTs)	not serious	serious ^a	not serious	not serious	strong association	⊕⊕⊕⊕ High	93/2217 (4.2%)	19/2122 (0.9%)	RR 0.16 (0.03 to 0.79)	42 per 1,000	35 fewer per 1,000 (from 41 fewer to 9 fewer)

Incidence of Varicella Disease (follow-up: range 42 days to 180 days; assessed with: Presence of varicella-like symptoms such as vesicular rash and fever)

4339 (2 RCTs)	not serious	serious ^a	not serious	not serious	strong association	⊕⊕⊕⊕ High	93/2217 (4.2%)	19/2122 (0.9%)	RR 0.16 (0.03 to 0.79)	42 per 1,000	35 fewer per 1,000 (from 41 fewer to 9 fewer)
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Seroconversion (assessed with: gpELISA >0.3 to 5 units/mL)

2429 (4 RCTs)	serious ^b	not serious	not serious	not serious	none	⊕⊕⊕○ Moderate	1283/1322 (97.0%)	1099/1107 (99.3%)	RR 1.02 (1.00 to 1.03)	970 per 1,000	19 more per 1,000 (from 0 fewer to 29 more)
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Geometric Mean Titers

2807 (4 RCTs)	serious ^b	serious ^c	not serious	not serious	none	⊕⊕○○ Low	1516	1291	-	-	SMD 0.83 SD higher (0.2 higher to 1.47 higher)
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CI: confidence interval; RR: risk ratio; SMD: standardised mean difference

Explanations

a. The heterogeneity may be due to the differences in outcome measures such as varying duration of follow-up, different intervals between doses, and different brands of vaccines used.

b. High risk of bias noted in randomization, allocation concealment, and blinding.

c. The heterogeneity is due to wide variance of point estimates across studies due to different scales used in measuring GMT, difference in the vaccines used across the studies, along with different duration of follow-up.

Appendix C. Forest Plots

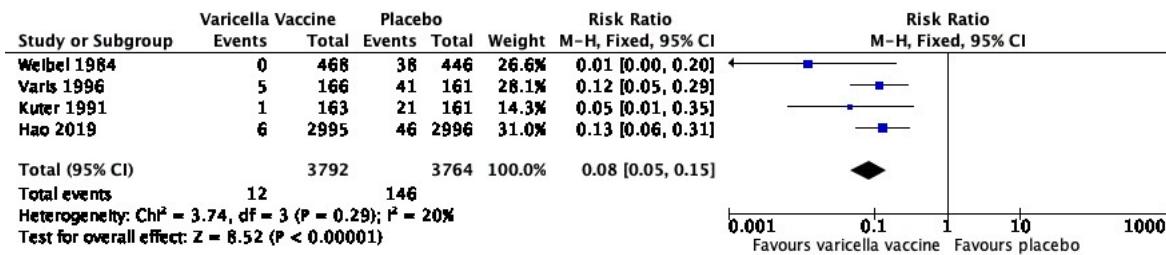


Figure 1. Effect of one dose monovalent varicella vaccine on incidence of varicella disease

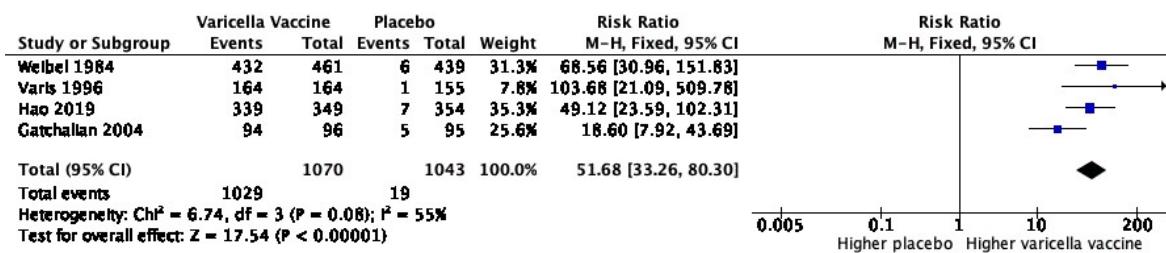


Figure 2. Effect of one dose monovalent varicella vaccine on seroconversion

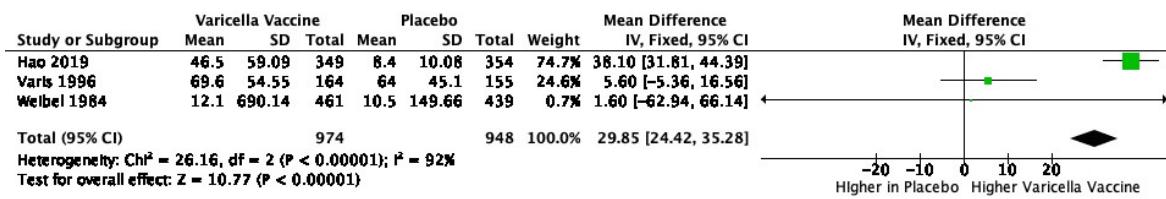


Figure 3. Effect of one dose monovalent varicella vaccine on geometric mean titers

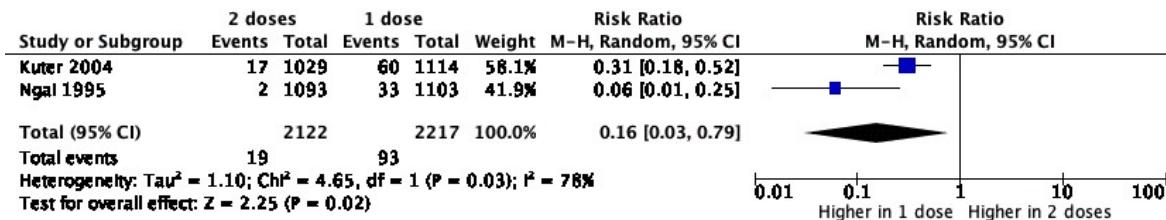


Figure 4. Effect of two doses varicella vaccine versus one dose on incidence of varicella disease

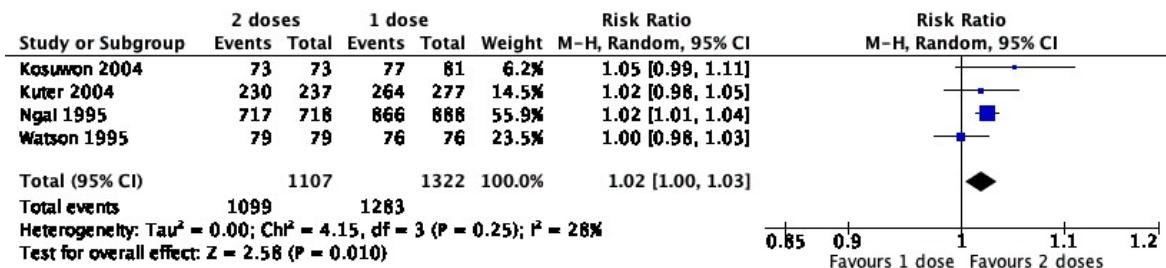


Figure 5. Effect of two doses varicella vaccine versus one dose on seroconversion

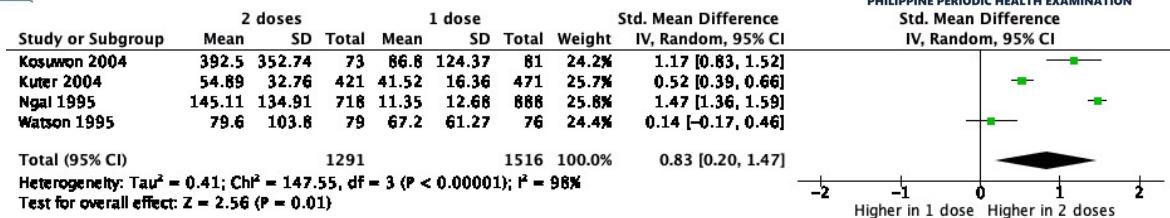


Figure 6. Effect of two doses varicella vaccine versus one dose on geometric mean titers

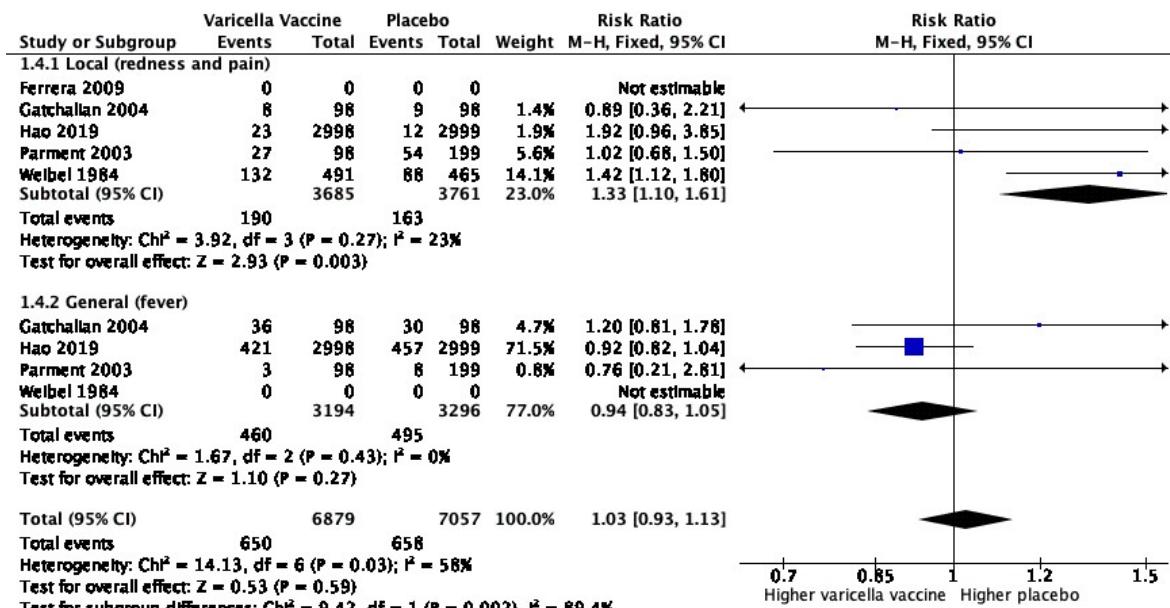


Figure 7. Effect of one dose monovalent varicella vaccine on adverse events (local and generalized)

Question 7. Should BCG vaccine be routinely given at birth to healthy infants for the prevention of tuberculosis?

Appendix A. Characteristics of Included Studies

Title/Author	Study design	Country	Number of participants	Population	Intervention Group(s)	Control	Outcomes
Mangtani et al.	Systematic review and meta-analysis of randomized and quasi-randomized trials (18 studies from 1933-1998) 6 RCTs included	6 countries	40,106	All ages (only included studies involving BCG vaccine at birth)	BCG vaccine	No BCG vaccine	Efficacy against pulmonary TB, miliary or meningeal TB
Martinez et al.	Systematic review and meta-analysis (26 cohort studies from 1998-2019)	17 countries	18,175	All ages (only included studies involving BCG vaccine at birth)	BCG vaccine	No BCG vaccine	Effectiveness against extrapulmonary TB; all-cause mortality
Farajnia et al.	Cross-sectional study	Iran	358	Patients (6 months to 96 years) with PTB (with at least one AFB+ sputum sample)	History of BCG vaccination (presence of BCG scar)	No BCG vaccination (no BCG scar)	Presence of TB symptoms
Trollfors et al.	Retrospective cohort study	Sweden	1,117	0 to 17 year-old immigrants arriving in Sweden	History of BCG vaccination (presence of BCG scar)	No BCG vaccination (no BCG scar)	LTBI
Abubakar et al.	Systematic review and meta-analysis (20 RCTs from 1933-1997)	6 countries	50,900	All ages (included RCTs involving BCG vaccine at birth)	BCG vaccine	No BCG vaccine	Mortality from TB
Roy et al.	Systematic review and meta-analysis (14 cohort studies)	5 countries	3149	All ages (included RCTs involving BCG vaccine at birth)	BCG vaccine	No BCG vaccine	LTBI
Dourado et al.	Randomized controlled trial	Brazil	71,718	Children 7-14 years	1 dose BCG	2 doses BCG	Adverse effects
Richardus et al.	Randomized controlled trial	Bangladesh	14,828	All ages	1 dose BCG	2 doses BCG	Adverse effects



Appendix B. Grade Evidence Profile

Question: Should BCG vaccine be routinely given at birth to healthy infants for the prevention of tuberculosis?

Author(s): Francesca Mae T. Pantig, Natasha Ann Esteban-Ipac

Setting: Outpatient

No of studies	Study design	Certainty assessment						No of patients		Effect		Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCG vaccine	no BCG vaccine	Relative (95% CI)	Absolute (95% CI)			
BCG vaccine against pulmonary TB													
5	randomised trials	very serious ^a	serious ^b	not serious	not serious	none	48/19084 (0.3%)	111/21022 (0.5%)	OR 0.045 (0.011 to 0.193)	5 fewer per 1,000 (from 5 fewer to 4 fewer)	⊕○○○ Very low		CRITICAL
BCG vaccine against extrapulmonary TB													
14	observational studies	very serious ^c	not serious	not serious	serious ^d	none	106/40318 (0.3%)	38/15865 (0.2%)	not estimable		⊕○○○ Very low		CRITICAL
BCG vaccine against meningeal / miliary TB													
2	randomised trials	very serious ^a	not serious	not serious	not serious	none	0/3388 (0.0%)	9/3265 (0.3%)	OR 0.412 (0.329 to 0.516)	2 fewer per 1,000 (from 2 fewer to 1 fewer)	⊕⊕○○ Low		CRITICAL
BCG vaccine against latent TB infection													
7	observational studies	very serious ^c	serious ^e	not serious	not serious	none	531/2196 (24.2%)	378/953 (39.7%)	not estimable		⊕○○○ Very low		CRITICAL
BCG vaccine against TB-related mortality													
5	observational studies	very serious ^a	not serious	not serious	serious ^d	none	10/25554 (0.0%)	28/25346 (0.1%)	not estimable		⊕○○○ Very low		CRITICAL
BCG vaccine against all-cause mortality													
4	observational studies	very serious ^c	not serious	not serious	not serious	none	35/16786 (0.2%)	15/1401 (1.1%)	not estimable		⊕○○○ Very low		CRITICAL
Adverse events													
2	randomised trials	serious ^f	not serious	very serious ^g	serious ^d	none	22/18337 (0.1%)	53/67820 (0.1%)	not estimable		⊕○○○ Very low		CRITICAL

CI: confidence interval; OR: odds ratio



Institute of Clinical Epidemiology, National Institutes of Health
University of the Philippines
Evidence to Decision Framework Evidence Summary
Version 3, 12 December 2023



Explanations

- a. Downgraded two levels due to high risk of selection and detection bias. Many of the included trials were conducted before standardized RCT methods were developed. Most trials did not guarantee concealment of allocation or blinding of trial personnel and participants.
- b. Downgraded one level due to serious inconsistency and significant heterogeneity ($I^2=70\%$)
- c. Downgraded one level due to serious risk of selection, confounding and recall bias.
- d. Downgraded one level due to serious imprecision and wide range of confidence interval
- e. Downgraded one level due to serious inconsistency and significant heterogeneity ($I^2=68\%$). The method of diagnosing TB infection varied across studies.
- f. Downgraded two levels due to serious risk of selection and reporting bias.
- g. Downgraded two levels due to serious indirectness. Studies compared adverse events of one dose BCG vs two doses BCG (re-vaccination) in older children

Appendix C. Forest Plots

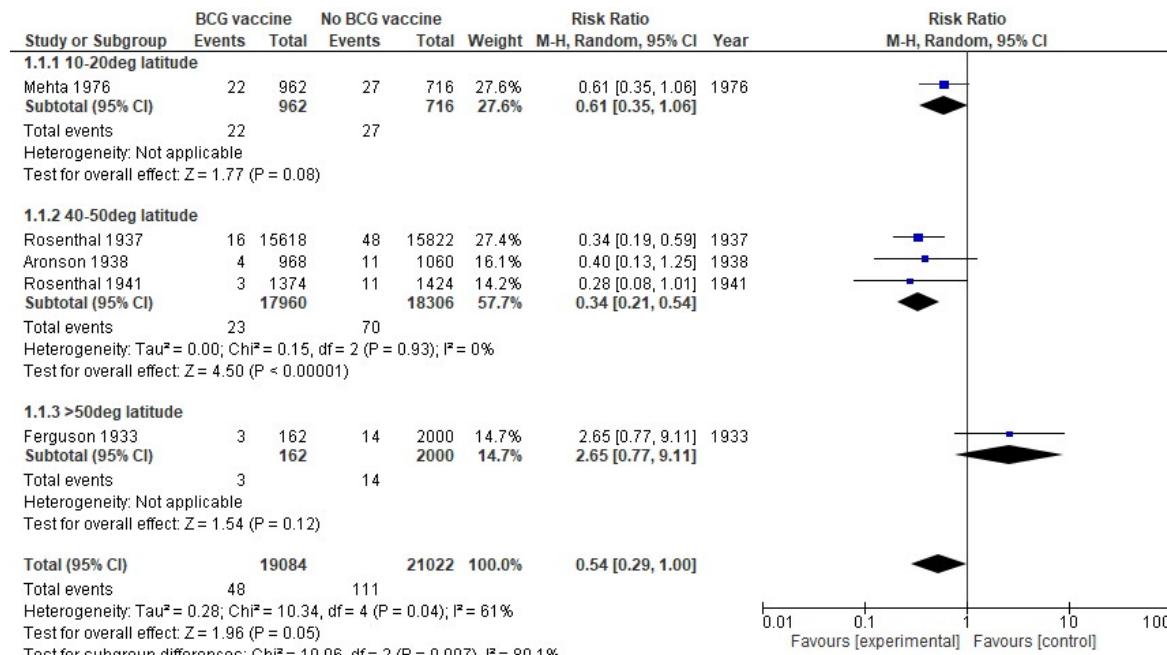


Figure 1. Efficacy of BCG vaccination at birth against pulmonary TB



Figure 2. Effectiveness of BCG vaccine against extrapulmonary tuberculosis

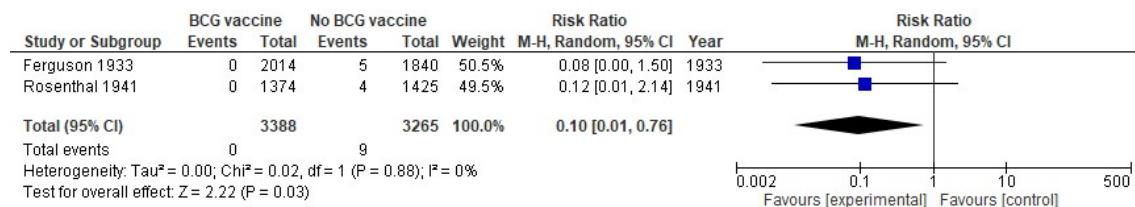


Figure 3. Efficacy of BCG vaccination at birth against meningeal/miliary TB

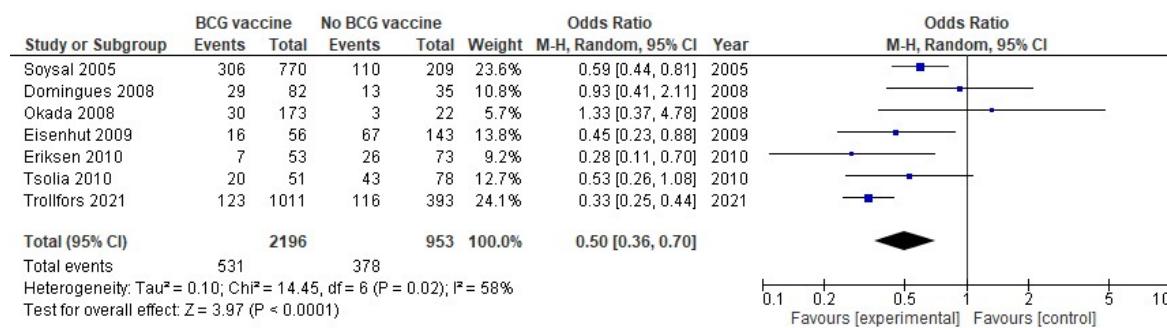


Figure 4. Effectiveness of BCG vaccine against latent TB infection

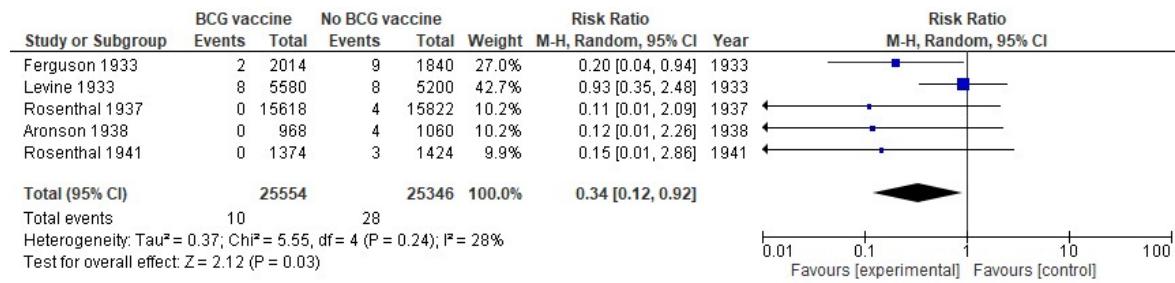


Figure 5. Efficacy of BCG vaccine against TB-related mortality

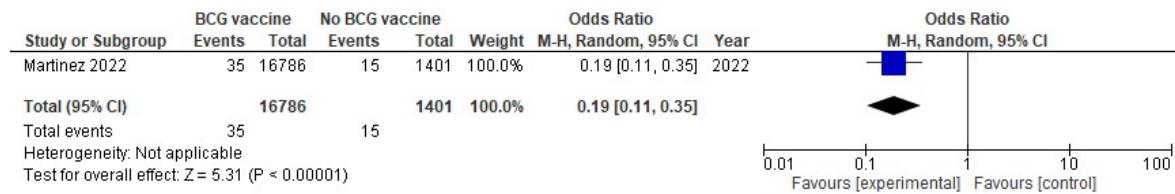


Figure 6. Effectiveness of BCG vaccine against all-cause mortality

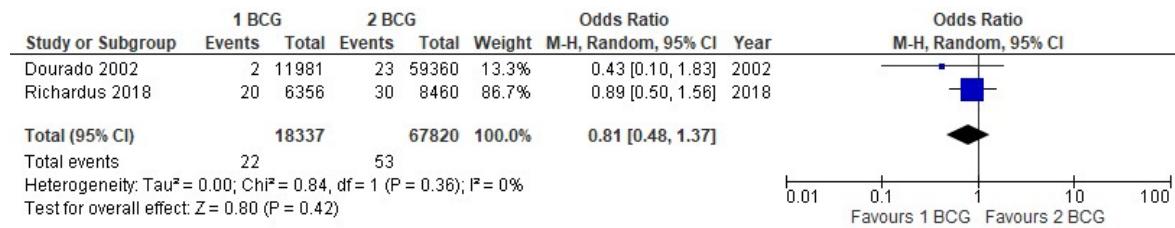


Figure 7. Adverse effects after 1 dose vs 2 doses of BCG vaccine

Question 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?

Appendix A. Characteristics of Included Studies

Title/Author	Study design	Country	Number of patients	Population	Intervention Group(s)	Control
Nolan et al. (2009) Booster vaccination of toddlers with reduced antigen content diphtheria-tetanus-acellular pertussis vaccine	RCT	Australia	n = 48	Healthy children 18-20 months old who completed primary vaccination	DTPa (<i>Infanrix™</i>) or dTpa (<i>Boostrix™</i>)	Hepatitis A vaccine (HAV)
Outcomes						
Pre-booster immunogenicity: Infanrix (n=16): 87.5% Boostrix (n=16): 81.3% HAV (n=16): 75%	Pre-booster GMT: Infanrix (n=16): 0.489 (0.243-0.988) Boostrix (n=16): 0.237 (0.129-0.436) HAV (n=15): 0.360 (0.142-0.914)			General symptoms reported: Infanrix: 11 (68.8%) Boostrix: 15 (93.8%) HAV: 15 (93.8%) Irritability Grade 3 related Infanrix: 3 (18.8%) Boostrix: 4 (25.0%) HAV: 2 (12.5%)	Drowsiness Infanrix: 3 (18.5%) Boostrix: 8 (50%) HAV: 3 (18.8%) Fever Infanrix: 7 (43.8%) Boostrix: 13 (81.3%) HAV: 8 (50%)	Loss of Appetite Infanrix: 6 (37.5%) Boostrix: 6 (37.5%) HAV: 6 (37.5%) Local symptoms reported: Infanrix: 16 (100%) Boostrix: 16 (100%) HAV: 16 (100%) Pain Infanrix: 5 (31.3%) Boostrix: 10 (62.5%) HAV: 6 (37.5%) Redness Infanrix: 14 (87.5%) Boostrix: 11 (68.8%) HAV: 8 (50%) Swelling Infanrix: 9 (56.3%) Boostrix: 11 (68.8%) HAV: 6 (37.5%)
Post-booster immunogenicity: Infanrix (n=15): 100% Boostrix (n=16): 100% HAV (n=15): 73.3%	Post-booster GMT: Infanrix (n=15): 5.631 (4.154-7.632) Boostrix (n=16): 4.869 (3.852-6.154) HAV (n=15): 0.365 (0.140- 0.951)					

Appendix B. GRADE Evidence Profile

Question: Tetanus toxoid-containing vaccine booster compared to placebo / no booster for healthy children

Author(s): Paul Sherwin O. Tarnate, MD, DPPS, DPIDSP; Patricia Marie D. Isada, MD, DPPS; Natasha Ann R. Esteban-Ipac, MD, FPPS, DPSAMS

Bibliography: Nolan T, Ruff TA, Lambert SB, Buttery J, O'Grady KA, Streeton C, et al. Booster vaccination of toddlers with reduced antigen content diphtheria-tetanus-acellular pertussis vaccine. *Vaccine*. 2009;27(18):2410–3.

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tetanus toxoid-containing vaccine booster	placebo / no booster	Relative (95% CI)	Absolute (95% CI)		
Seroprotection (follow-up: 1 month)												
1	randomized trial	serious ^a	not serious	not serious	serious ^b	none	32/32 (100.0%)	11/16 (68.8%)	RR 1.46 (1.05 to 2.03)	316 more per 1,000 (from 34 more to 708 more)	⊕⊕○○ Low	CRITICAL
Immunogenicity (follow-up: 1 month; assessed with: geometric mean concentration of tetanus antibody titers)												
1	randomized trials	serious ^a	not serious	not serious	serious ^b	none	31	15	-	MD 4.87 higher (3.77 higher to 5.97 higher)	⊕⊕○○ Low	CRITICAL
Serious Adverse Events (follow-up: 1 month)												
1	randomized trials	serious ^a	not serious	not serious	serious ^b	none	There were no serious adverse events that occurred throughout this study.				⊕⊕⊕○ Low	CRITICAL
General Adverse Events (follow-up: 15 days)												
1	randomized trials	serious ^a	not serious	not serious	very serious ^{b,c}	none	7/32 (21.9%)	2/16 (12.5%)	RR 1.75 (0.41 to 7.48)	94 more per 1,000 (from 74 fewer to 810 more)	⊕○○○ Very Low	IMPORTANT
Local Adverse Events (follow-up: 15 days)												
1	randomized trials	serious ^a	not serious	not serious	very serious ^{b,c}	none	6/32 (18.8%)	1/16 (6.3%)	RR 3.00 (0.39 to 22.85)	125 more per 1,000 (from 38 fewer to 1,000 more)	⊕○○○ Very Low	IMPORTANT
Fever (follow-up: 15 days)												
1	randomized trials	serious ^a	not serious	not serious	very serious ^{b,c}	none	5/32 (15.6%)	4/16 (25.0%)	RR 0.63 (0.19 to 2.01)	93 fewer per 1,000 (from 203 fewer to 252 more)	⊕○○○ Very Low	IMPORTANT
Drowsiness (follow-up: 15 days)												
1	randomized trials	serious ^a	not serious	not serious	very serious ^{b,c}	none	11/32 (34.4%)	3/16 (18.8%)	RR 1.83 (0.59 to 5.66)	156 more per 1,000 (from 77 fewer to 874 more)	⊕○○○ Very Low	IMPORTANT
Irritability (follow-up: 15 days)												
1	randomized trials	serious ^a	not serious	not serious	very serious ^{b,c}	none	20/32 (62.5%)	8/16 (50.0%)	RR 1.25 (0.71 to 2.19)	125 more per 1,000 (from 145 fewer to 595 more)	⊕○○○ Very Low	IMPORTANT
Loss of Appetite (follow-up: 15 days)												

Certainty assessment							No of patients		Effect		Certainty	Importance	
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tetanus toxoid-containing vaccine booster	placebo / no booster	Relative (95% CI)	Absolute (95% CI)			
1	randomized trials	serious ^a	not serious	not serious	very serious ^{b,c}	none	12/32 (37.5%)	6/16 (37.5%)	RR 1.00 (0.46 to 2.17)	0 fewer per 1,000 (from 203 fewer to 439 more)		Very Low	IMPORTANT

Redness (follow-up: 15 days)

1	randomized trials	serious ^a	not serious	not serious	very serious ^{b,c}	none	25/32 (78.1%)	8/16 (50.0%)	RR 1.56 (0.93 to 2.64)	280 more per 1,000 (from 35 fewer to 820 more)		Very Low	IMPORTANT
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Pain (follow-up: 15 days)

1	randomized trials	serious ^a	not serious	not serious	very serious ^{b,c}	none	15/32 (46.9%)	6/16 (37.5%)	RR 1.25 (0.60 to 2.60)	94 more per 1,000 (from 150 fewer to 600 more)		Very Low	IMPORTANT
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Swelling (follow-up: 15 days)

1	randomized trials	serious ^a	not serious	not serious	very serious ^{b,c}	none	20/32 (62.5%)	6/16 (37.5%)	RR 1.67 (0.84 to 3.31)	251 more per 1,000 (from 60 fewer to 866 more)		Very Low	IMPORTANT
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CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

- a. some concerns on biases arising from the randomization process and allocation concealment
- b. optimal sample size for this study not met
- c. no appreciable benefit or appreciable harm of the intervention over control

Question 9. Should Hepatitis B vaccine booster dose be given among children and adolescents who completed a 3-dose primary vaccination series during infancy?

Appendix A. Characteristics of Included Studies

Author	Study Design	Country	Number of patients	Population	Intervention Groups	Control	Outcome
Poovorawan 1997	Randomized controlled trial	Thailand	38	Infants born to HBeAg positive mothers (but all infants are HBsAg negative at baseline)	Primary vaccines + Hepatitis B booster at month 60	Primary vaccines + no booster	HBV seroprotection
Qu 2014	Population-based, cluster-randomized, controlled trial	China	63,615	Adolescents who have received primary vaccination series of hepatitis B during infancy	Hepatitis B booster	No hepatitis B booster	Primary liver cancer Acute-on-chronic liver failure Mortality HBV seroprotection HBsAg seropositivity
Van der Sande 2007	Randomized controlled trial	Gambia	492	Adolescents who have received primary vaccination series of hepatitis B during infancy	Hepatitis B booster	No hepatitis B booster	HBV seroprotection Adverse events after immunization
Wu 2011	Randomized placebo-controlled trial	China	156	Participants who have received primary vaccination series of hepatitis B at 5-9 years of age	Hepatitis B booster	No hepatitis B booster	HBV seroprotection Anti-HBc seropositivity

Appendix B. GRADE Evidence Profile

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hepatitis B vaccine booster	no booster dose	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow-up: median 25 years)												
1	randomised trials	not serious	not serious	serious ^a	not serious	none	6/33947 (0.0%)	17/29668 (0.1%)	RR 0.31 (0.12 to 0.78)	0 fewer per 1,000 (from 1 fewer to 0 fewer)		Moderate
Acute on chronic liver failure (follow-up: median 25 years)												
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	3/33947 (0.0%)	6/29668 (0.0%)	RR 0.44 (0.11 to 1.75)	0 fewer per 1,000 (from 0 fewer to 0 fewer)		Low
Primary liver cancer (follow-up: median 25 years)												
1	randomised trials	not serious	not serious	serious ^a	not serious	none	3/33947 (0.0%)	14/29668 (0.0%)	RR 0.19 (0.05 to 0.65)	0 fewer per 1,000 (from 0 fewer to 0 fewer)		Moderate
HBV seroprotection (Anti-HBs ≥10IU/L)												
4	randomised trials	serious ^c	serious ^d	not serious	serious ^b	none	372/537 (69.3%)	104/324 (32.1%)	RR 1.85 (0.97 to 3.52)	273 more per 1,000 (from 10 fewer to 809 more)		Very low
HBsAg seropositivity												
1	randomised trials	not serious	not serious	not serious ^e	serious ^f	none	11/577 (1.9%)	25/398 (6.3%)	RR 0.30 (0.15 to 0.61)	44 fewer per 1,000 (from 53 fewer to 24 fewer)		Moderate
Anti-HBc seropositivity												
1	randomised trials	not serious	not serious	not serious	very serious ^{b,f}	none	3/77 (3.9%)	5/63 (7.9%)	RR 0.49 (0.12 to 1.98)	40 fewer per 1,000 (from 70 fewer to 78 more)		Low
Local or systemic adverse events related to vaccination (follow-up: range 2 weeks to 12 months)												
1	randomised trials	not serious	not serious	serious ^g	not serious	none	0/264 (0.0%)	0/182 (0.0%)	not estimable			Moderate

Explanations

- a. some participants in the control group did not receive catch-up primary vaccinations
- b. wide confidence interval
- c. one study had high risk of bias (missing outcome data) and some risk of bias on 2 domains (randomization and deviations from intended interventions)
- d. there was considerable heterogeneity among the studies
- e. study had a subset of participants in the control group who had catch-up HBV primary vaccination
- f. low number of events
- g. some enrolled participants were seropositive for HBsAg and/or anti-HBc at baseline



Hepatitis B vaccine booster compared to no booster dose for children and adolescents who completed a 3-dose primary vaccination series

Patient or population: children and adolescents who completed a 3-dose primary vaccination series

Setting: Outpatient setting

Intervention: Hepatitis B vaccine booster

Comparison: no booster dose

Outcome Nº of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
			Difference			
All-cause mortality follow-up: median 25 years Nº of participants: 63615 (1 RCT)	RR 0.31 (0.12 to 0.78)	0.1%	0.0% (0 to 0)	0.0% fewer (0.1 fewer to 0 fewer)	⊕⊕⊕○ Moderate ^a	Hepatitis B vaccine booster probably results in little to no difference in all-cause mortality.
Acute on chronic liver failure follow-up: median 25 years Nº of participants: 63615 (1 RCT)	RR 0.44 (0.11 to 1.75)	0.0%	0.0% (0 to 0)	0.0% fewer (0 fewer to 0 fewer)	⊕⊕○○ Low ^{a,b}	The evidence suggests that hepatitis B vaccine booster results in little to no difference in the development of acute on chronic liver failure.
Primary liver cancer follow-up: median 25 years Nº of participants: 63615 (1 RCT)	RR 0.19 (0.05 to 0.65)	0.0%	0.0% (0 to 0)	0.0% fewer (0 fewer to 0 fewer)	⊕⊕⊕○ Moderate ^a	Hepatitis B vaccine booster probably results in little to no difference in the development of primary liver cancer.
HBV seroprotection (Anti-HBs ≥10IU/L) Nº of participants: 861 (4 RCTs)	RR 1.85 (0.97 to 3.52)	32.1%	59.4% (31.1 to 100)	27.3% more (1 fewer to 80.9 more)	⊕○○○ Very low ^{b,c,d}	Hepatitis B vaccine booster may increase or have little to no effect in terms of HBV seroprotection (Anti-HBs ≥10IU/L) but the evidence is very uncertain.
HBsAg seropositivity Nº of participants: 975 (1 RCT)	RR 0.30 (0.15 to 0.61)	6.3%	1.9% (0.9 to 3.8)	4.4% fewer (5.3 fewer to 2.4 fewer)	⊕⊕⊕○ Moderate ^{e,f}	Hepatitis B vaccine booster probably reduces HBsAg seropositivity slightly.
Anti-HBc seropositivity Nº of participants: 140 (1 RCT)	RR 0.49 (0.12 to 1.98)	7.9%	3.9% (1 to 15.7)	4.0% fewer (7 fewer to 7.8 more)	⊕⊕○○ Low ^{b,f}	Hepatitis B vaccine booster may result in a slight reduction in anti-HBc seropositivity.
Local or systemic adverse events related to vaccination (Adverse events) follow-up: range 2 weeks to 12 months Nº of participants: 446 (1 RCT)	not estimable	0.0%	0.0% (0 to 0)	0.0% fewer (0 fewer to 0 fewer)	⊕⊕⊕○ Moderate ^g	There were no local or systemic adverse events related to HBV booster vaccination according to 1 published RCT involving 446 participants.

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

CI: confidence interval; RR: risk ratio



Hepatitis B vaccine booster compared to no booster dose for children and adolescents who completed a 3-dose primary vaccination series

Patient or population: children and adolescents who completed a 3-dose primary vaccination series

Setting: Outpatient setting

Intervention: Hepatitis B vaccine booster

Comparison: no booster dose

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)		Certainty	What happens
			Difference		

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: 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.

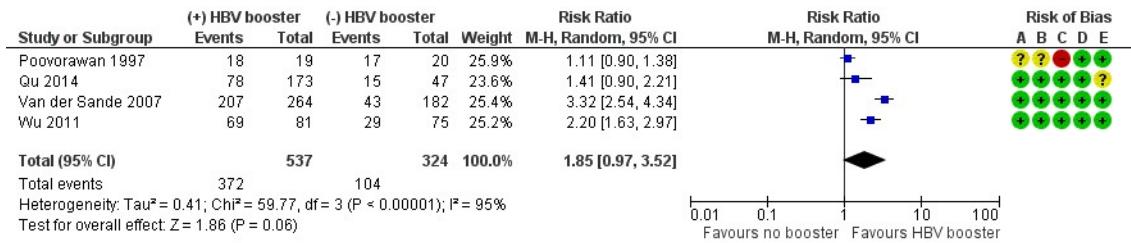
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

- a. some participants in the control group did not receive catch-up primary vaccinations
- b. wide confidence interval
- c. one study had high risk of bias (missing outcome data) and some risk of bias on 2 domains (randomization and deviations from intended interventions)
- d. there was considerable heterogeneity among the studies
- e. study had a subset of participants in the control group who had catch-up HBV primary vaccination
- f. low number of events
- g. some enrolled participants were seropositive for HBsAg and/or anti-HBc at baseline

Appendix C. Forest Plots



Risk of bias legend

- (A) Randomization process
- (B) Deviations from the intended interventions
- (C) Missing outcome data
- (D) Measurement of the outcome
- (E) Selection of the reported result

Figure 1. Effect of HBV vaccine booster compared to no booster on HBV seroprotection



Appendix D. Cost-Effectiveness Studies and Articles

Author	Year	Country	Population	Intervention	Control	Cost-effective? (Y/N)	
Prakash <i>et al.</i>	2005	India	Hypothetical cohort of 100,000 infants in year 0	Hepatitis B EPI	No vaccination	YES. Excluding indirect costs, the cost utility ratio was \$27.36 per DALY gained. This cost may decrease with changes in the HBsAg carrier state, followed by improvement of vaccination coverages, and decreasing cost of vaccine to about \$0.60.	
Tilson <i>et al.</i>	2008	Ireland	Hypothetical cohort of 100,000 population	6-component vaccine (including hepatitis B)	Monovalent hepatitis B vaccine	YES. At a cost of €29.00 per dose of the 6-component vaccine, universal infant hepatitis B vaccination is cost effective, and compares favorably with other preventive programs.	
Wang <i>et al.</i>	2018	China	Hypothetical cohort of 10-year-old children born to HBSA6872-positive mothers	HBV vaccine booster given at 10 years of age	No booster	YES. Cost-effective ratios were found to be less than US\$ -6961 to US\$ -6872 per QALY gained (Note: GDP per capita in China in 2016 was US\$ 8126).	
Simms <i>et al.</i>	2019		This commentary on the Wang <i>et al.</i> study emphasized that "It will be important [...] to confirm the earlier findings on breakthrough infection reported by Wang <i>et al.</i> by randomising individuals at age 10 years to receive either a booster vaccine or no booster, provided these individuals received full-dose timely vaccination at birth and were born to HBsAg-positive mothers."				
Bhattacharya <i>et al.</i>	2021		This analysis of available evidence that included the study by Wang <i>et al.</i> emphasized cost-effectiveness as an integral part of vaccination programs. Considering low vaccination awareness, small coverage, high disease burden, and high treatment cost, it was suggested that India should introduce hepatitis B booster vaccine into its health program.				

Question 10. Can Pneumococcal Conjugate Vaccine brands be interchanged to complete the primary series? Can Pneumococcal Conjugate Vaccine brands be interchanged as booster dose?

Appendix A. Characteristics of Included Studies

Study & Setting	Population	Interventions/Control	Outcomes
Deeuninck 2015 (Case-control) Canada	Laboratory-confirmed IPD cases in children 2–59 months old and matched controls	<ul style="list-style-type: none"> • PHID-CV • PHID-CV+PCV13 • PCV13 	Vaccine (≥ 2 dose) effectiveness against IPD based on 1) Any serotype, 2) 19A serotype, 3) PCV13-contained serotypes, 4) non-PCV13-contained serotype
Su 2016 (Case Control) Taiwan	IPD patients ≤ 5 years of age and matched controls	<ul style="list-style-type: none"> • PCV7/PHID-CV • PCV7/PHID-CV+PCV13 • PCV13 	Vaccine effectiveness against IPD based on 1) Any serotype, 2) 19A serotype, 3) non 19A serotype
de los Santos 2020 (RCT) Mexico	Healthy infants 6–12 weeks old, delivered at least 36 weeks gestational age	<p>Schedule: 2+1 (at 2,4 months old and booster at 12–15 months old)</p> <ul style="list-style-type: none"> • PrPr+Sy • PrSy+Sy • Sy only 	<ol style="list-style-type: none"> 1. Adverse Events (Primary outcome) 2. Immunogenicity (IgG, Serotype-specific pneumococcal opsonophagocytic activity (OPA)) of primary and booster vaccination 1 month after primary series and 1 month after booster 3. Antibody persistence 8–11 months after primary vaccination
Leach 2021 (RCT) Australia	Aboriginal infants at 28 to 38 days of age	<p>Schedule: 3+0 and 4+0</p> <p>PCV13 and PHID-CV at 2-4-6 months and mixed schedule PHID-CV at 1-2-4 plus PCV13 at 6 months</p>	Immunogenicity (IgG, OPA) for serotypes 3, 6A, 19A (PCV13-only serotypes) as primary outcomes, and other serotypes as secondary outcomes at 7 months
Bili 2023 (RCT) USA, Puerto Rico, Thailand, Turkey	Infants 2mo old	<p>Schedule: 3+1 (at 2, 4, 6, and 12–15 months)</p> <p>Pr only, PrPrPr+Vx PrPrVx+Vx PrVxVx+Vx Vx only</p>	<ol style="list-style-type: none"> 1. Safety 2. Immunogenicity (IgG) for shared and PCV15-only-serotypes at 1month after dose3 and 1month after dose4
Clarke 2020 (RCT) The Gambia	PCV13-vaccinated toddlers (12–15 months old)	<p>Schedule: 3+1 (6,10,14 weeks primary)</p> <p>Booster of either Pneumosil or Prevenar among Prevenar vaccinated toddlers</p>	<ol style="list-style-type: none"> 1. Safety 2. Immunogenicity (IgG, OPA) after 1 month
Urbancikova 2017 (Open-label) Czech Republic and Slovakia	Healthy children 12–15 months old (Czech Republic); Healthy children 11–12 months old (Slovakia)	Booster of Prevenar for those given either Sy or Pr in a 3+1 (Czech Republic) or 2+1 (Slovakia) schedule	<ol style="list-style-type: none"> 1. Safety 2. Immunogenicity (IgG, OPA) on PCV13-contained serotypes
Truck 2016 (RCT) UK	healthy 12-month-old children	<p>Schedule: 2+1</p> <p>Booster of Pr or Sy in Pr-primed children</p>	<ol style="list-style-type: none"> 1. Reactogenicity Immunogenicity to PHID-CV-contained serotypes



Appendix B. GRADE Evidence Profile

Certainty assessment							Effect	Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			

Effectiveness against IPD

2	observational studies	not serious ^{a,b}	not serious	not serious ^{c,d}	not serious	none	Deceuninck 2015 found similar VE against IPD between a PHID-CV-only schedule, a PCV13-only schedule, or a mixed PHID-CV+PCV13 schedule; Su 2017 found similar VE in PCV13-only schedule and mixed PCV7/PHID-CV+PCV13 schedule and lower VE for PHID-CV-only schedule.	⊕⊕○○ Low	CRITICAL
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Immunogenicity - Primary Series (PHiD-CV and PCV13)

2	randomised trials	not serious	serious ^e	not serious	serious ^f	none	Serotype 1 RR 1.00 [0.98, 1.01] Serotype 4 RR 1.00 [0.99, 1.02] Serotype 5 RR 1.00 [0.97, 1.03] Serotype 6B RR 1.12 [1.00, 1.26] Serotype 7F RR 1.00 [0.98, 1.01] Serotype 9V RR 1.01 [0.99, 1.03] Serotype 14 RR 1.00 [0.98, 1.02] Serotype 18C RR 1.00 [0.97, 1.02] Serotype 19F RR 1.01 [0.99, 1.03] Serotype 23F RR 0.98 [0.89, 1.07] Serotype 3 RR 1.99 [1.05, 3.79] Serotype 6A RR 1.13 [0.80, 1.59] Serotype 19A RR 1.10 [0.90, 1.33]	⊕⊕○○ Low	CRITICAL
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Immunogenicity – Booster Dose (PHiD-CV and PCV13)

4	randomised trials	serious ^g	serious ^e	not serious	not serious	none	Serotype 1 RR 1.00 [0.98, 1.02] Serotype 4 RR 1.00 [0.99, 1.02] Serotype 5 RR 0.97 [0.91, 1.05] Serotype 6B RR 1.00 [0.97, 1.02] Serotype 7F 1.00 [0.98, 1.01] Serotype 9V RR 0.99 [0.94, 1.04] Serotype 14 RR 1.00 [0.99, 1.02] Serotype 18C 1.00 [0.99, 1.02] Serotype 19F RR 1.00 [0.99, 1.02] Serotype 23F 1.00 [0.98, 1.02] Serotype 3 1.16 [0.82, 1.62] Serotype 6A RR 0.91 [0.82, 1.02] Serotype 19A 1.01 [0.98, 1.04]	⊕⊕○○ Low	CRITICAL
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Immunogenicity – Booster Dose (PCV10-SII and PCV13)

1	randomised trials	not serious	not serious	not serious	very serious ^f	none	Serotype PCV10-SII/PCV13 GMC ratio (95% CI) p-value 1 0.75 (0.51, 1.46) 0.265 5 0.69 (0.41, 1.31) 0.206 6A 0.84 (0.51, 1.69) 0.566 6B 0.8 (0.53, 1.43) 0.446 7F 0.74 (0.48, 1.23) 0.219 9V 0.60 (0.34, 1.14) 0.097 14 1.76 (0.91, 2.98) 0.071 19A 0.71 (0.38, 1.56) 0.344 19F 0.76 (0.44, 1.32) 0.328 23F 0.65 (0.35, 1.25) 0.204	⊕⊕○○ Low	CRITICAL
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Immunogenicity – Primary and Booster Dose (PCV13 and PCV15)

1	randomised trials	not serious	not serious	not serious	serious ^f	none	Serotype 1 RR 1.01 [0.99, 1.02] Serotype 3 RR 0.97 [0.78, 1.20] Serotype 4 RR 0.96 [0.93, 1.00] Serotype 5 RR 0.99 [0.97, 1.01] Serotype 6A RR 0.99 [0.97, 1.01] Serotype 6B RR 1.02 [0.99, 1.05] Serotype 7F RR 1.00 [0.99, 1.01] Serotype 9V RR 0.98 [0.96, 1.01] Serotype 14 RR 1.00 [0.96, 1.04] Serotype 18C RR 1.01 [0.99, 1.03] Serotype 19A RR 0.99 [0.97, 1.01] Serotype 19F RR 1.00 [0.99, 1.01] Serotype 23F RR 0.97 [0.93, 1.01]	⊕⊕⊕○ Moderate	CRITICAL
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Adverse Events (any)

1	comparative study	serious ^g	serious ^h	not serious	serious ^f	none	RR 0.76 [0.48,1.21]	⊕○○○ Very low	CRITICAL
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Serious Adverse Events

4	randomised trials	serious ^g	serious ^h	not serious	serious ^f	none	RR 1.05 [0.80, 1.38]	⊕○○○ Very low	CRITICAL
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Explanations

- a. case control study
- b. IPD cases and controls were selected and reviewed with minimal bias; Newcastle-Ottawa Scale GOOD
- c. schedule is different from Philippine NIP
- d. vaccine effectiveness was evaluated, instead of vaccine efficacy
- e. heterogeneity is seen in some serotype outcomes
- f. wide confidence intervals and/or small sample sizes
- g. unclear allocation concealment and blinding
- h. heterogeneity is high on meta-analysis

Appendix C. Forest Plots

Primary Series

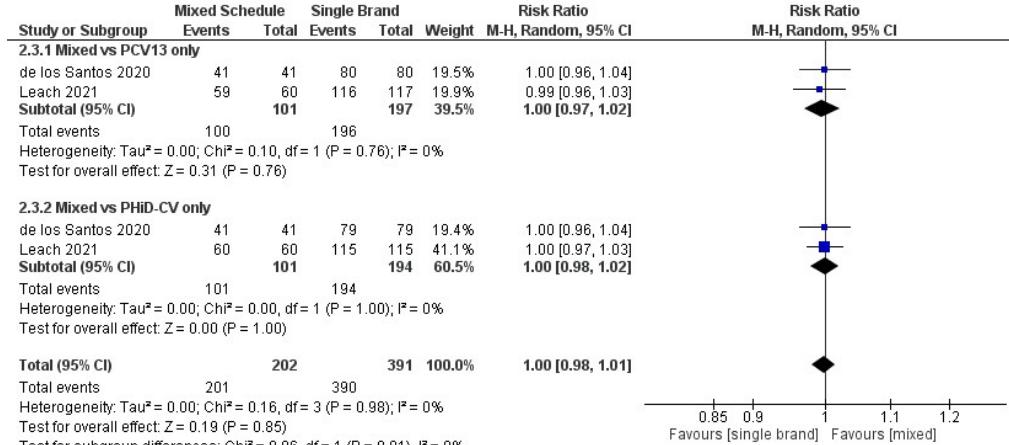


Figure 1. Forest plot of comparison: Immunogenicity (IgG), Serotype 1 IgG

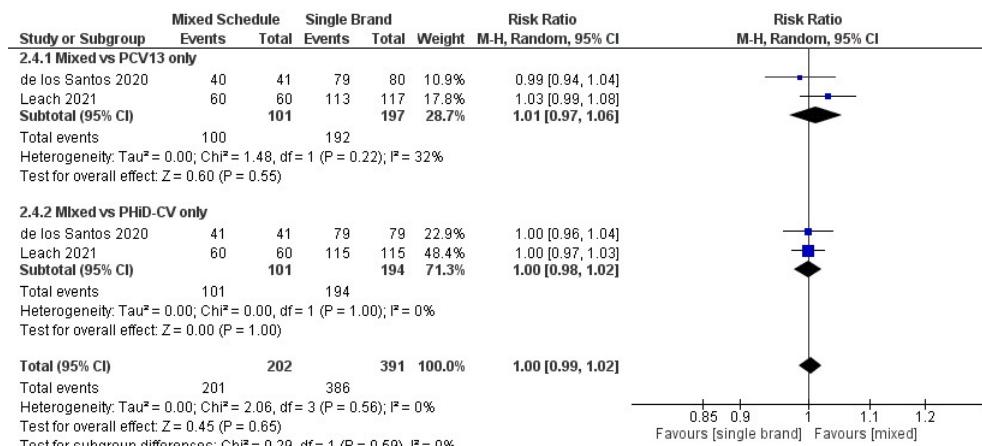


Figure 2. Forest plot of comparison: Immunogenicity (IgG), Serotype 4 IgG

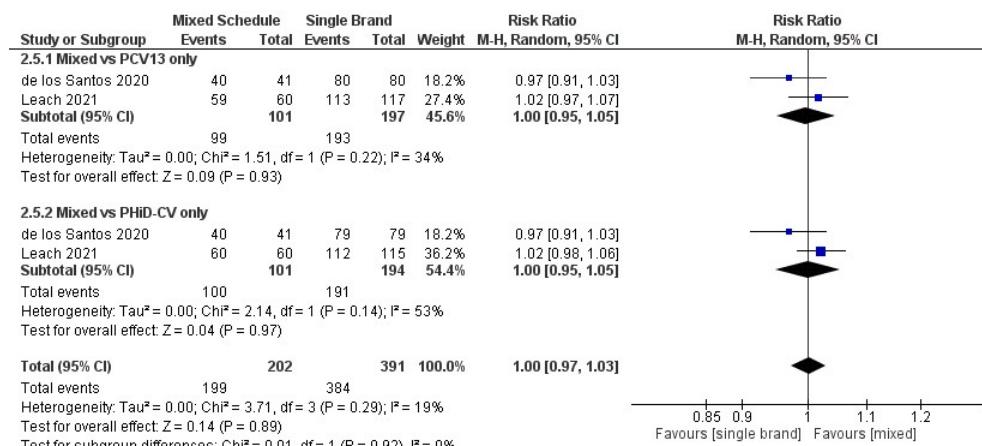


Figure 3. Forest plot of comparison: Immunogenicity (IgG), Serotype 5 IgG

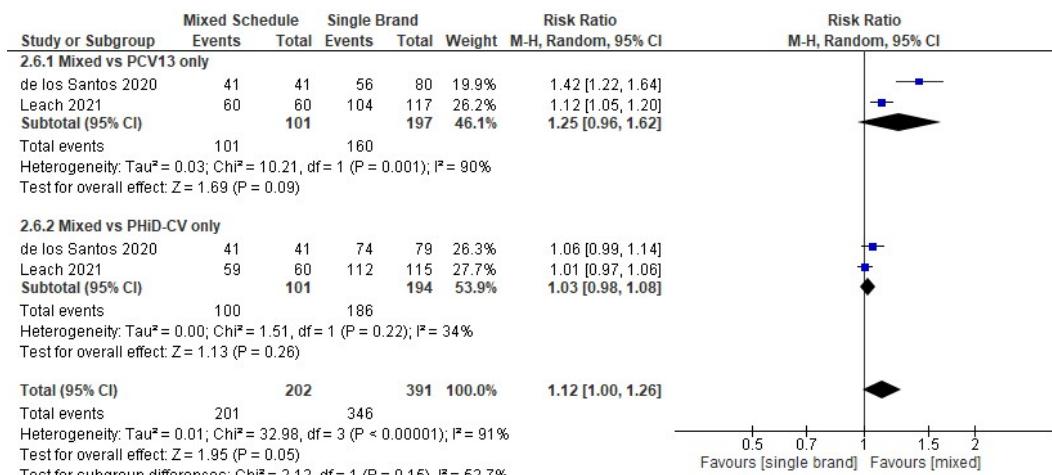


Figure 4. Forest plot of comparison: Immunogenicity (IgG), Serotype 6B IgG

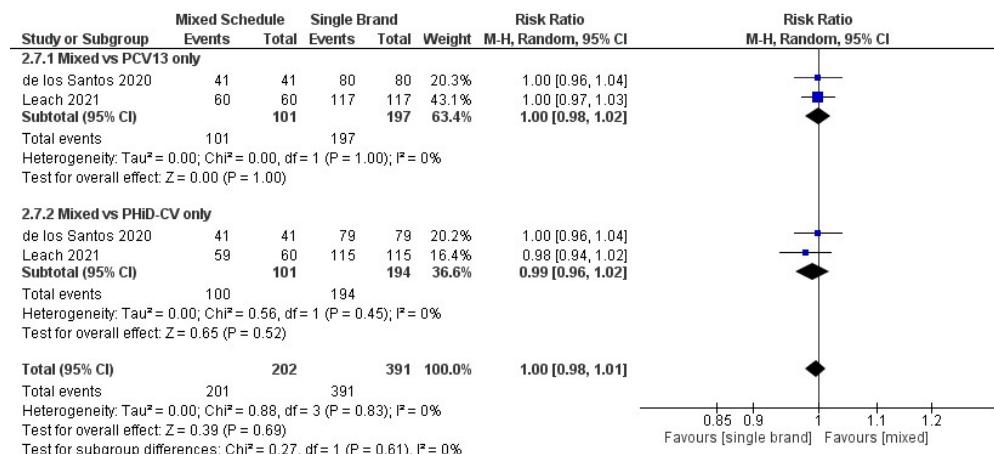


Figure 5. Forest plot of comparison: Immunogenicity (IgG), Serotype 7F IgG

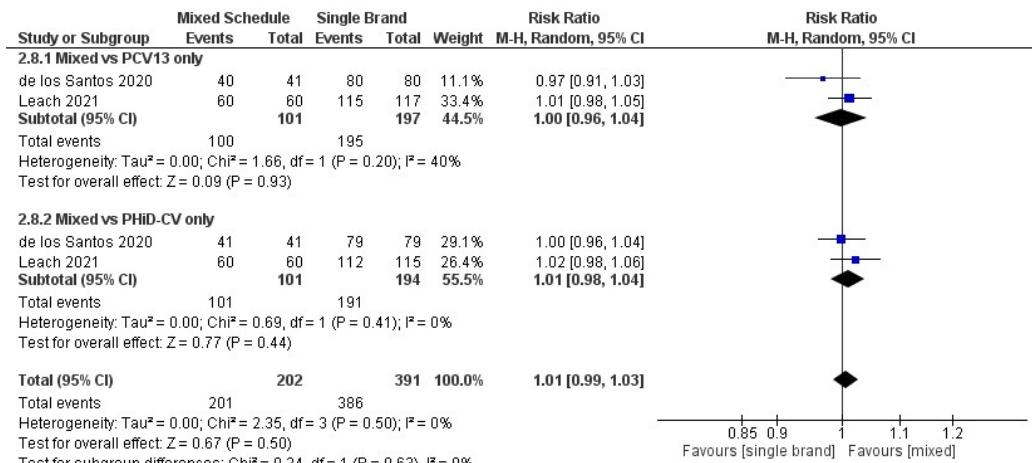


Figure 6. Forest plot of comparison: Immunogenicity (IgG), Serotype 9V IgG

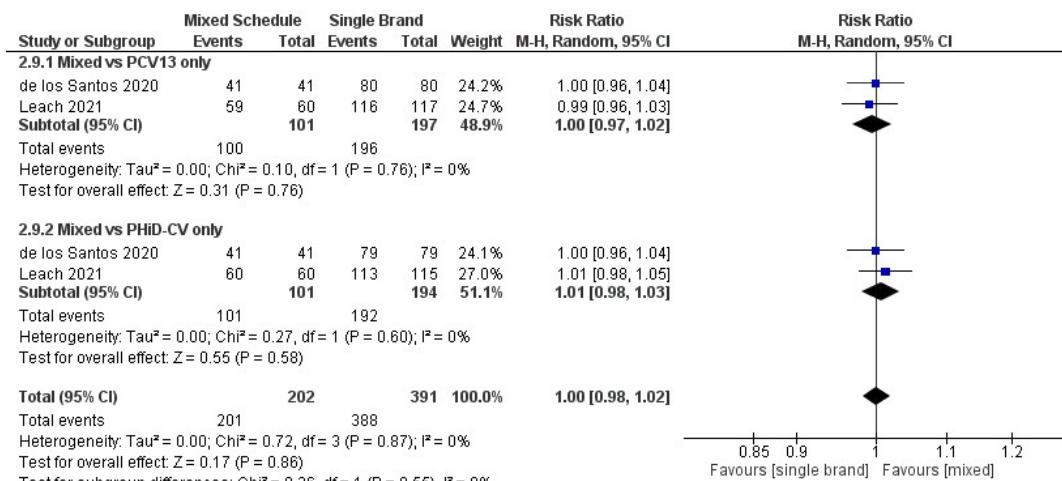


Figure 7. Forest plot of comparison: Immunogenicity (IgG), Serotype 14 IgG

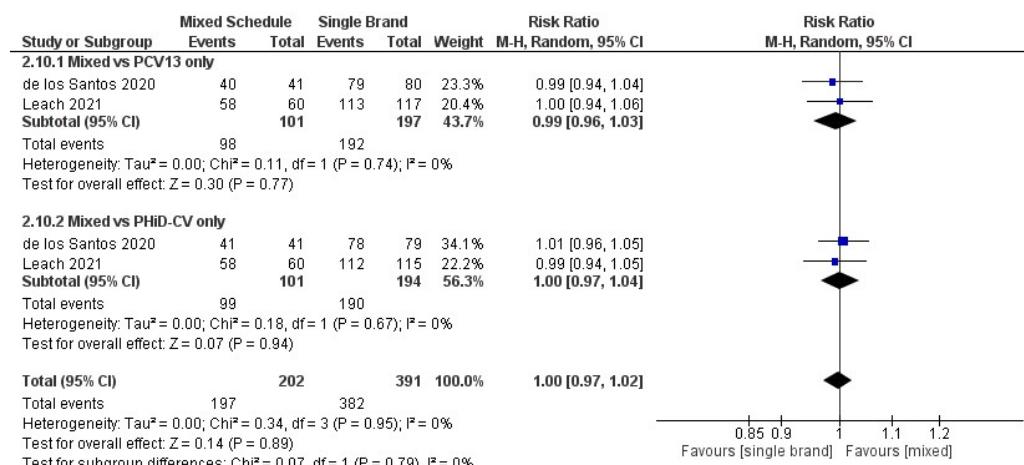


Figure 8. Forest plot of comparison: Immunogenicity (IgG), Serotype 18C IgG

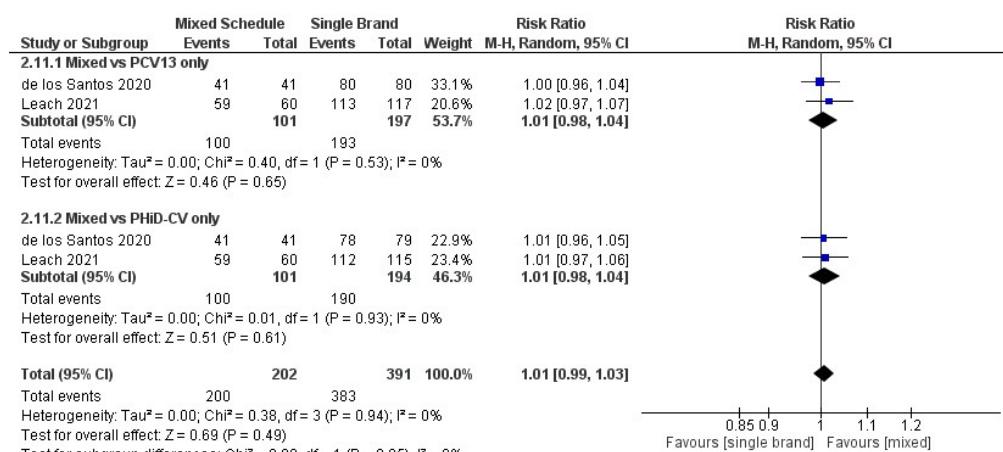


Figure 9. Forest plot of comparison: Immunogenicity (IgG), Serotype 19F IgG

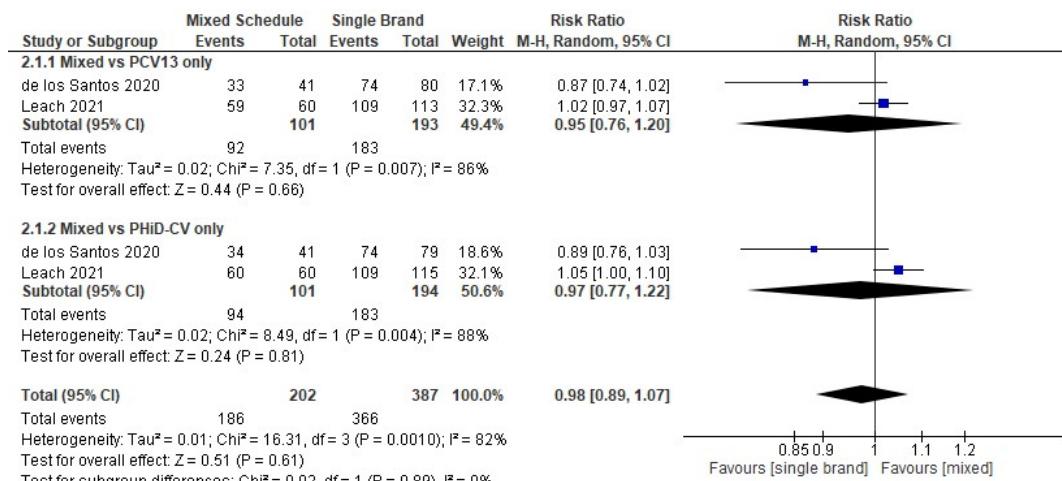


Figure 10. Forest plot of comparison: Immunogenicity (IgG), Serotype 23F IgG

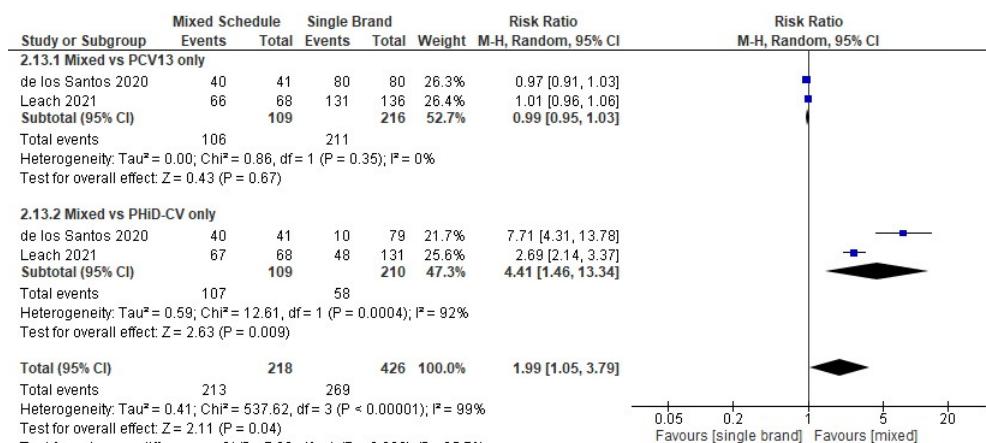


Figure 11. Forest plot of comparison: Immunogenicity (IgG), Serotype 3 IgG

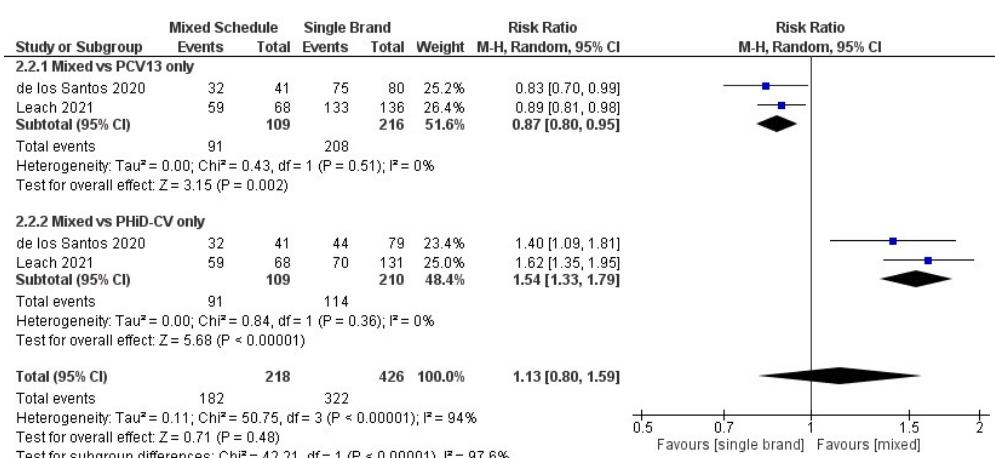


Figure 12. Forest plot of comparison: Immunogenicity (IgG), Serotype 6A IgG

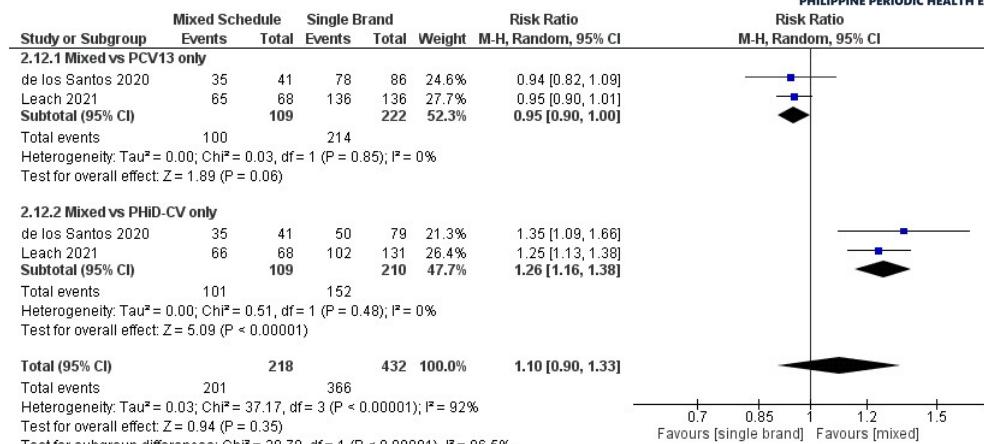


Figure 13. Forest plot of comparison: Immunogenicity (IgG), Serotype 19A IgG

Booster Doses

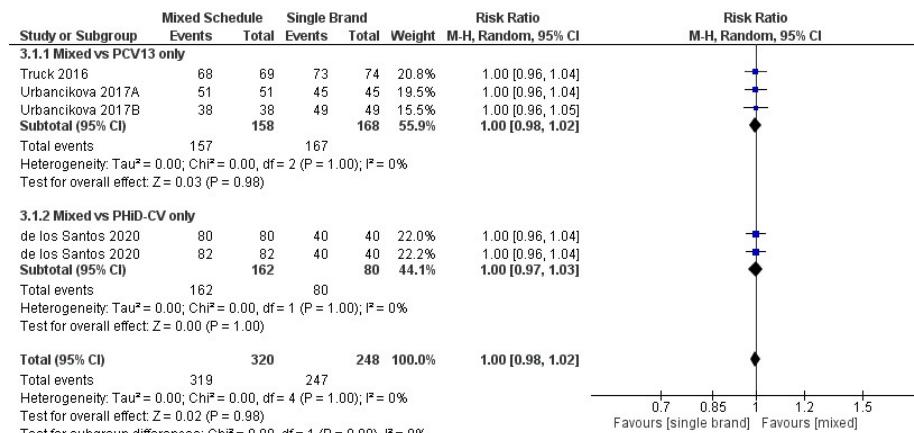


Figure 14. Forest plot of comparison: Booster Immunogenicity (IgG), Serotype 1 IgG

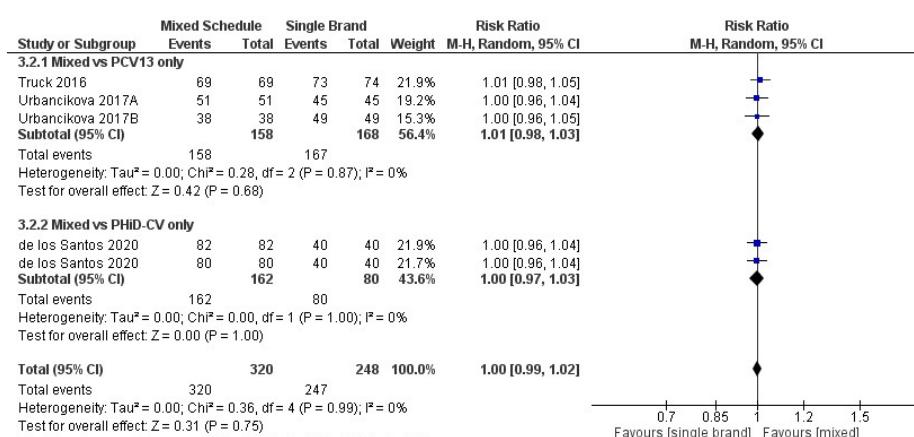


Figure 15. Forest plot of comparison: Booster Immunogenicity (IgG), Serotype 4 IgG

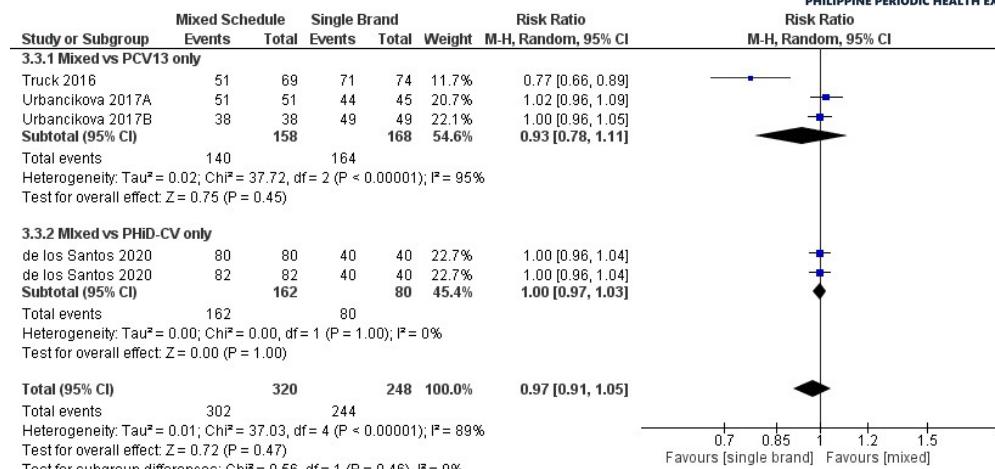


Figure 16. Forest plot of comparison: Booster Immunogenicity (IgG), Serotype 5 IgG

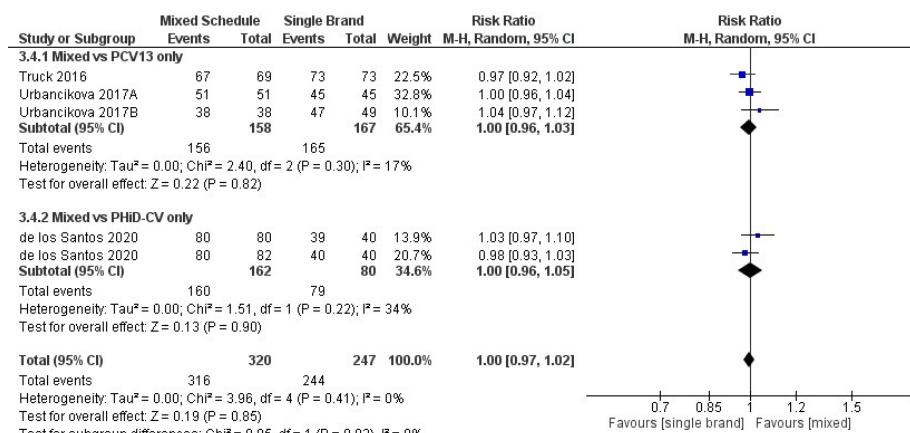


Figure 17. Forest plot of comparison: Booster Immunogenicity (IgG), Serotype 6B IgG

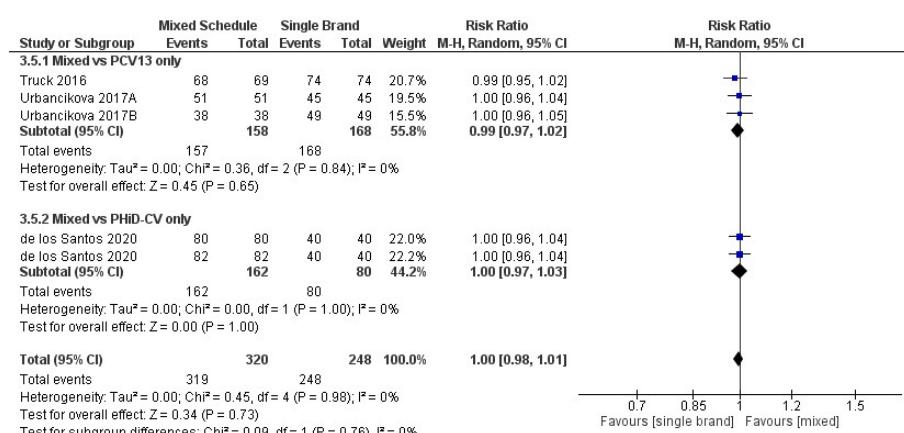


Figure 18. Forest plot of comparison: Booster Immunogenicity (IgG), Serotype 7F IgG

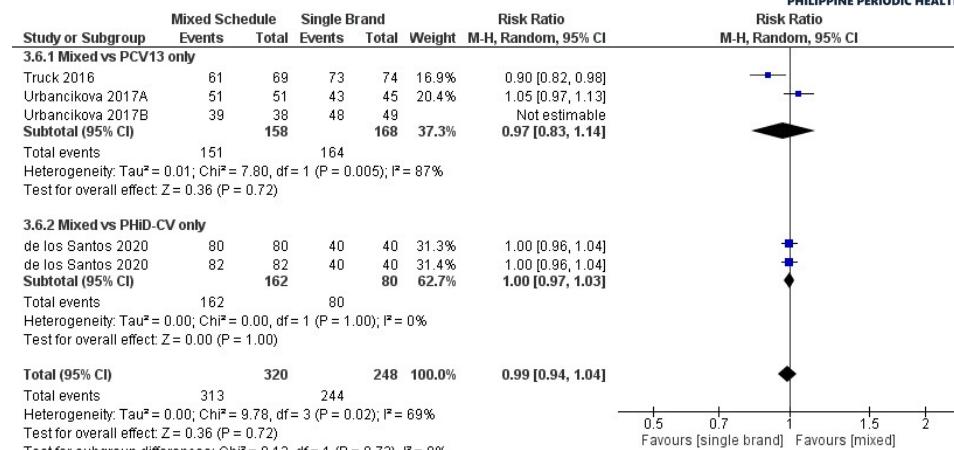


Figure 19. Forest plot of comparison: Booster Immunogenicity (IgG), Serotype 9V IgG

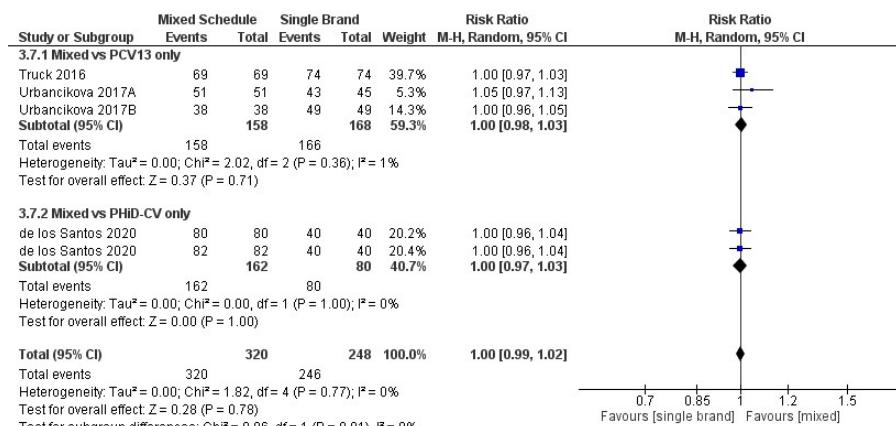


Figure 20. Forest plot of comparison: Booster Immunogenicity (IgG), Serotype 14 IgG

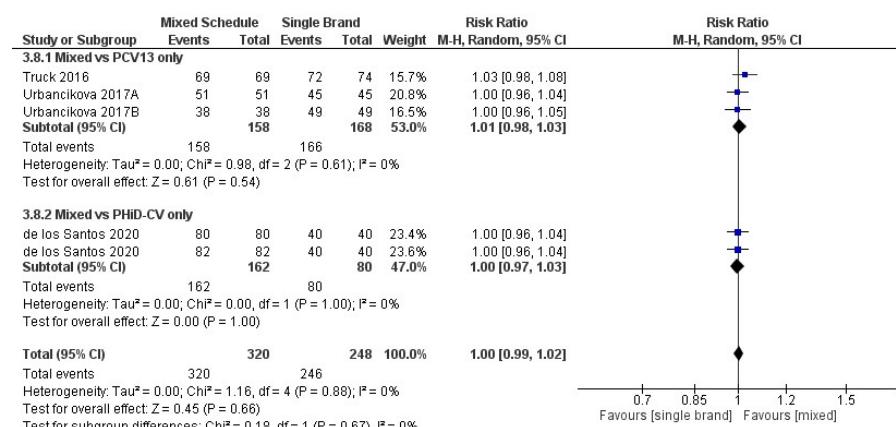


Figure 21. Forest plot of comparison: Booster Immunogenicity (IgG), Serotype 18C IgG

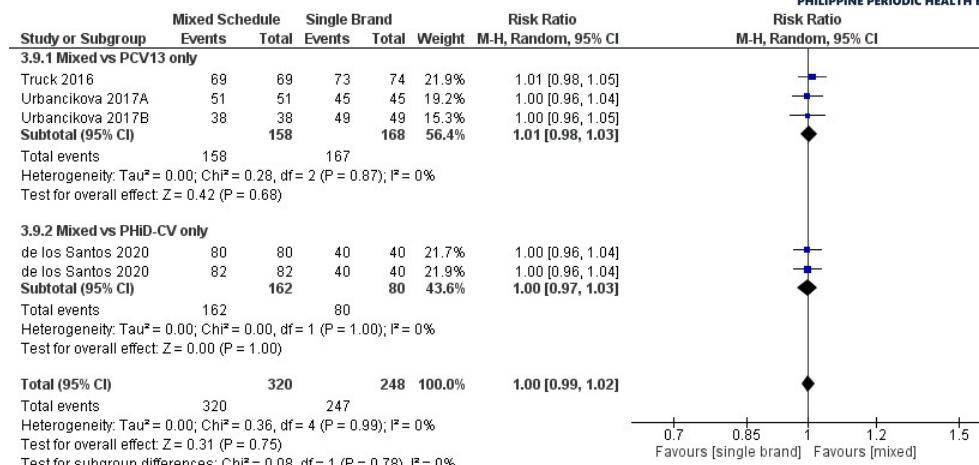


Figure 22. Forest plot of comparison: Booster Immunogenicity (IgG), Serotype 19F IgG

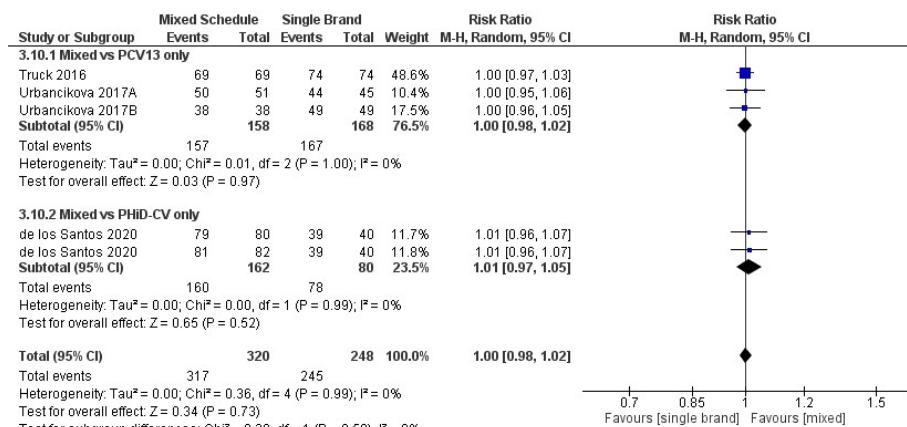


Figure 23. Forest plot of comparison: Booster Immunogenicity (IgG), Serotype 23F IgG

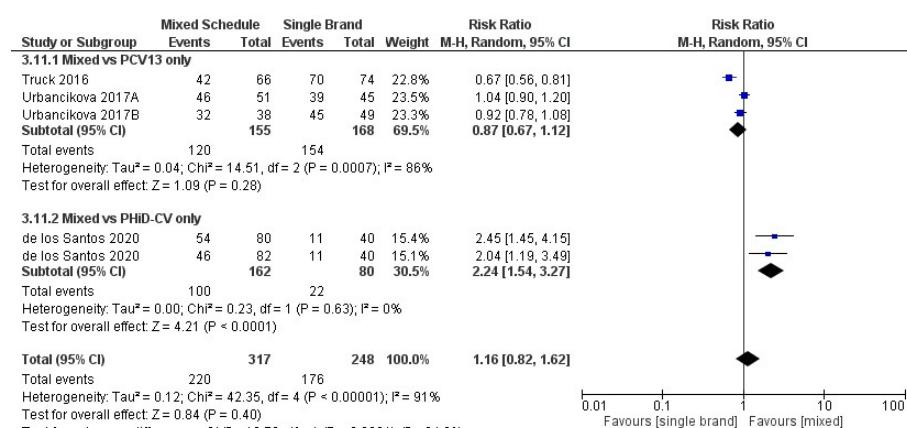


Figure 24. Forest plot of comparison: Booster Immunogenicity (IgG), Serotype 3 IgG

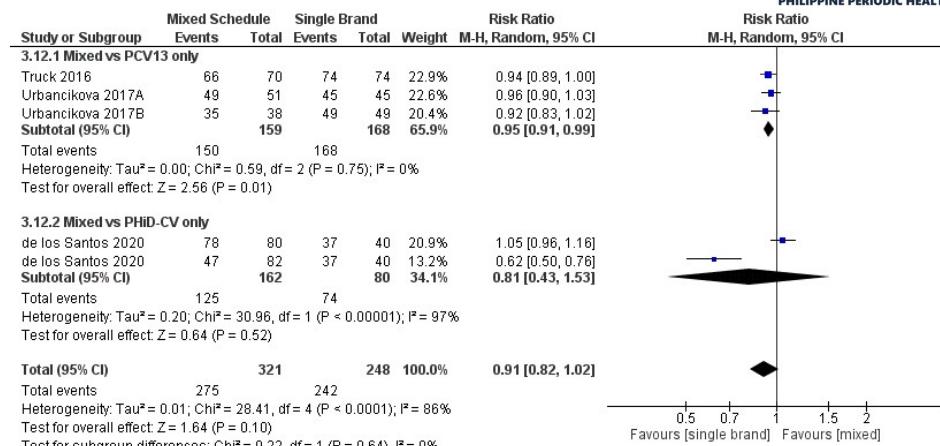


Figure 25. Forest plot of comparison: Booster Immunogenicity (IgG), Serotype 6A IgG

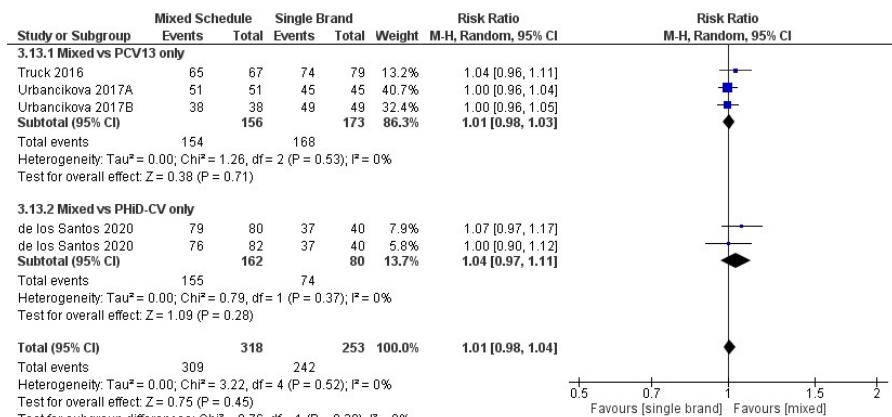


Figure 26. Forest plot of comparison: Booster Immunogenicity (IgG), Serotype 19A IgG

PCV13-PCV15 Primary Series (Bili 2022)

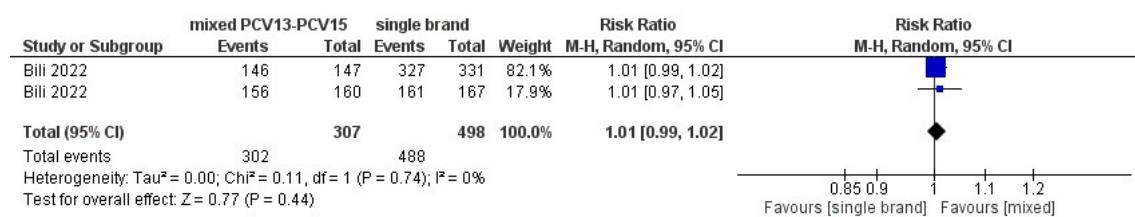


Figure 27. Forest plot of comparison: Immunogenicity (IgG) outcome: Serotype 1 IgG

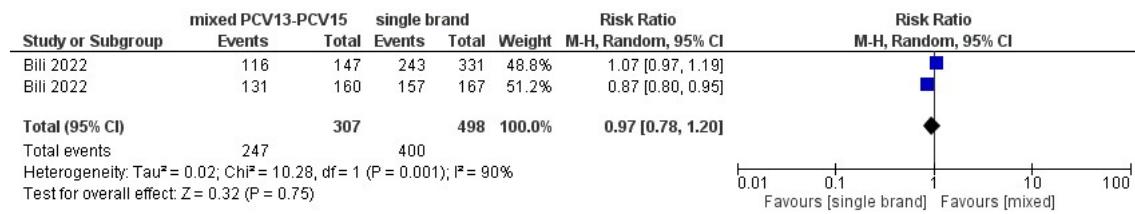


Figure 28. Forest plot of comparison: Immunogenicity (IgG) outcome: Serotype 3 IgG

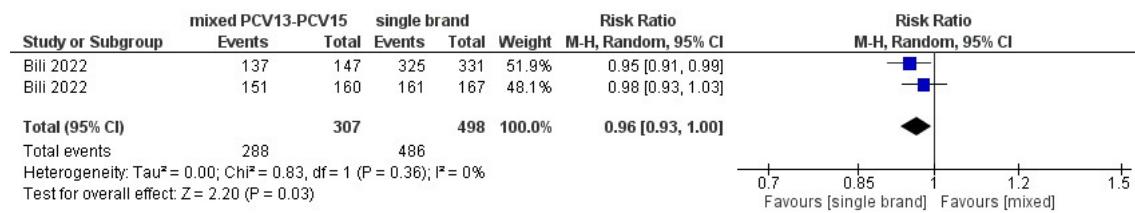


Figure 29. Forest plot of comparison: Immunogenicity (IgG) outcome: Serotype 4 IgG

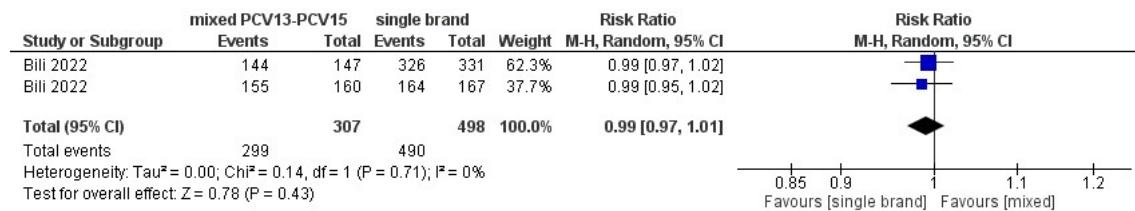


Figure 30. Forest plot of comparison: Immunogenicity (IgG) outcome: Serotype 5 IgG



Figure 31. Forest plot of comparison: Immunogenicity (IgG) outcome: Serotype 6A IgG



Figure 32. Forest plot of comparison: Immunogenicity (IgG) outcome: Serotype 6B IgG

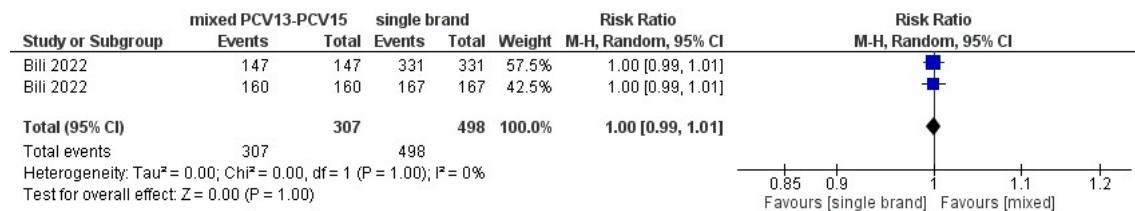


Figure 33. Forest plot of comparison: Immunogenicity (IgG) outcome: Serotype 7F IgG

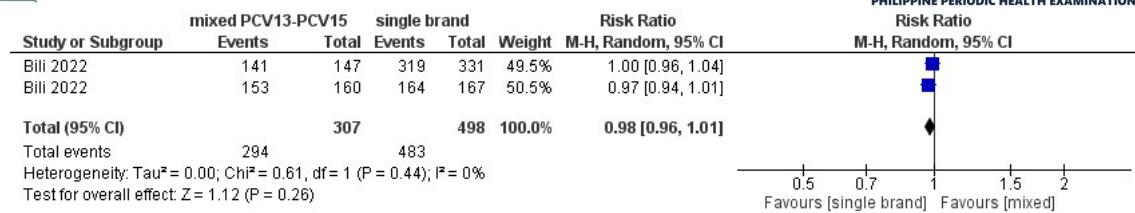


Figure 34. Forest plot of comparison: Immunogenicity (IgG) outcome: Serotype 9V IgG



Figure 35. Forest plot of comparison: Immunogenicity (IgG) outcome: Serotype 14 IgG



Figure 36. Forest plot of comparison: Immunogenicity (IgG) outcome: Serotype 18C IgG

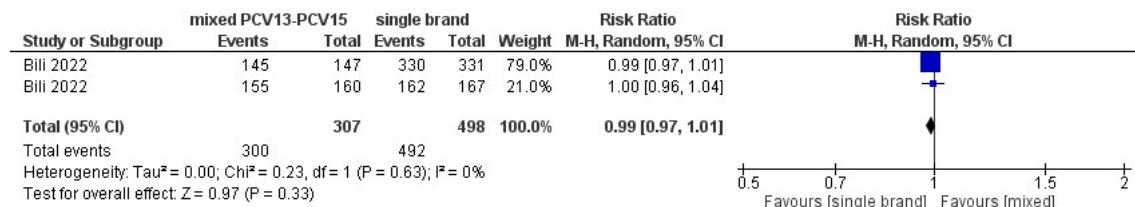


Figure 37. Forest plot of comparison: Immunogenicity (IgG) outcome: Serotype 19A IgG

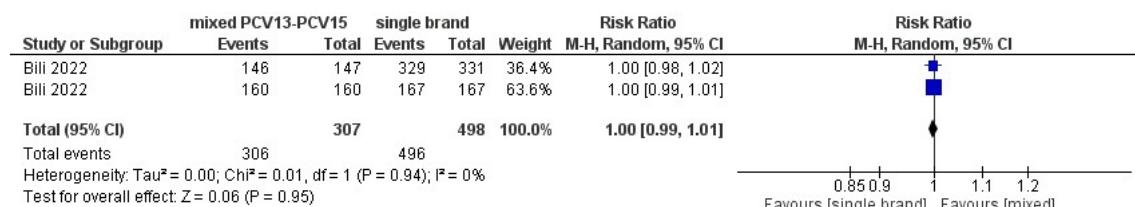


Figure 38. Forest plot of comparison: Immunogenicity (IgG) outcome: Serotype 19F IgG

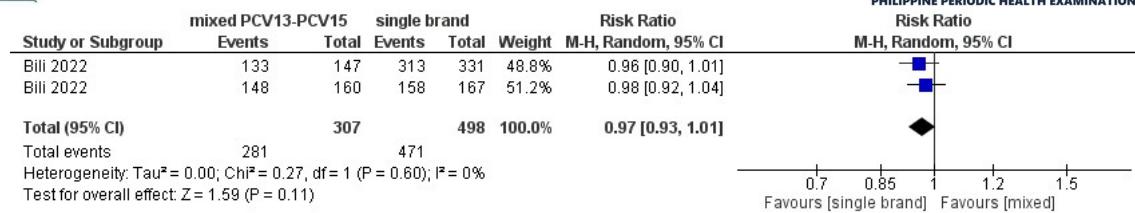


Figure 39. Forest plot of comparison: Immunogenicity (IgG) outcome: Serotype 23F IgG

Adverse Events

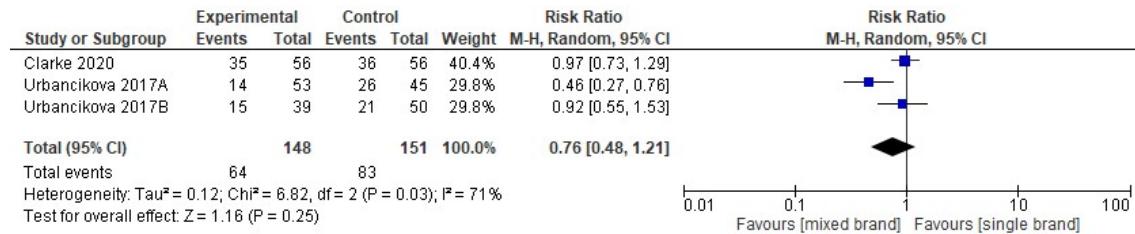


Figure 40. Forest plot of comparison: Outcome: Adverse events (Any)

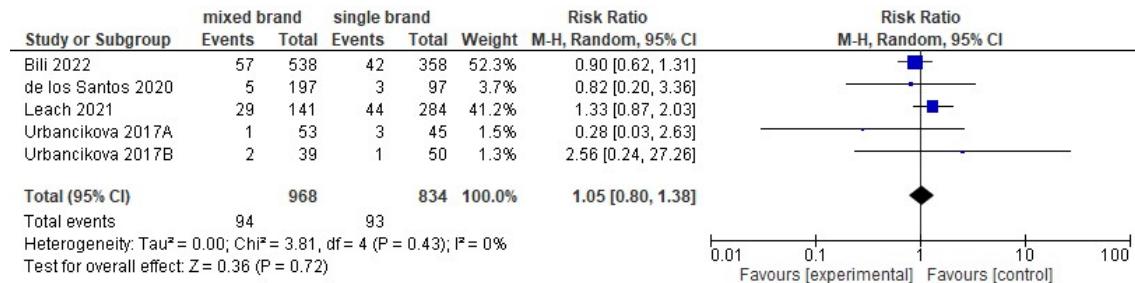


Figure 41. Forest plot of comparison: Outcome: Serious adverse events (SAEs)



Appendix D. Manufacturer's Recommendation on Interchangeability

Brand	Recommendation on Interchangeability	Reference
Synflorix	"Use of Synflorix and 13-valent PCV in the immunisation course of an individual: The use of Synflorix and PCV13 in the immunisation course of an individual (interchangeability) was assessed in a clinical study conducted in Mexico [...] for most of the 10 common serotypes 1 month post-priming and post-booster, observed percentages of infants reaching antibody concentrations $\geq 0.2 \mu\text{g/mL}$ and OPA titers above cutoffs were high for infants receiving both Synflorix and PCV13. No safety concern was identified when the vaccine was changed from PCV13 to Synflorix at the time of priming or boosting."	https://www.ema.europa.eu/en/documents/product-information/synflorix-epar-product-information_en.pdf
Prevnar13	No mention of interchangeability	https://www.ema.europa.eu/en/documents/product-information/prevenar-13-epar-product-information_en.pdf
Pneumosil	No mention of interchangeability	https://extranet.who.int/pqweb/file/25978905/download
Vaxneuvance	"Serotype-specific IgG GMCs at 30 days following the toddler dose were numerically similar for participants administered mixed regimens of VAXNEUVANCE® and Prevnar®13 and for participants administered a complete dosing regimen of Prevnar®13 for the 13 shared serotypes, as assessed by IgG GMC ratios."	https://www.merck.ca/en/wp-content/uploads/sites/20/2022/06/VAXNEUVANCE-PM_E.pdf



Question 11. Should pertussis-containing vaccines be given as booster among children and adolescents who received complete DPT primary immunizations?

Appendix A. Characteristics of Included Studies

Title/Author	Study Design	Country	Number of Patients	Population	Intervention Group(s)	Control	Outcomes
Vaccine Effectiveness							
DTaP Booster Dose (3 months to 9 years old)							
Acellular pertussis vaccines effectiveness over time: A systematic review, meta-analysis and modeling study [9] Chit et al 2018	Meta-Analysis	UK	(3 studies) 959 cases, 5443 controls	Infants & Children (2 months to 6 years)	5 dose DTaP	No booster	Vaccine Effectiveness (VE)
Association of Diphtheria-Tetanus–Acellular Pertussis Vaccine Timeliness and Number of Doses with Age-Specific Pertussis Risk in Infants and Young Children [10] Rane et al 2021	Observational retrospective cohort study	USA	316,404 patients	Children vaccinated with DTaP Age 3 months to 9 years	Under-vaccination (incomplete or no vaccination) or delayed vaccination	Receipt of DTaP according to Recommended Vaccine Schedule	absolute Risk Reduction Vaccine Effectiveness (VE) – suspected, probable, and confirmed pertussis
Tdap Booster Dose (10 to 18 years old)							
Tdap vaccine effectiveness in adolescents during the 2012 Washington State pertussis epidemic Acosta et al 2012	Matched case-control	USA	1,696 patients	Adolescents 11 to 19 years	DTaP primary series followed by Tdap booster	N/A	Vaccine Effectiveness (VE): Odds ratio
Pertussis Vaccine Effectiveness in the Setting of Pertactin-Deficient Pertussis Breakwell et al 2016	Matched case-control	USA	958 patients	Adolescents 11 to 19 years	DTaP primary series followed by Tdap booster	N/A	Vaccine Effectiveness (VE): Odds ratio



Vaccine Safety among Children							
Acellular vaccines for preventing whooping cough in children [11] Zhang et al 2014	Cochrane Meta-analysis	USA	52 RCTs (136,541)	Infants & Children Age 2 months to 7 years	DTaP booster	DTwP Placebo	Vaccine Safety (Adverse Events)
Vaccine Safety and Immunogenicity among adolescents							

Appendix B. Risk of Bias Appraisal

Title: Acellular pertussis vaccines effectiveness over time: A systematic review, meta-analysis and modeling study (Chit et al., 2018)

AMSTAR Item	Yes/No	Note
1. Did the research questions and inclusion criteria for the review include the components of PICO?	YES	
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	YES	CRITICAL
3. Did the review authors explain their selection of the study designs for inclusion in the review?	PARTIAL YES	
4. Did the review authors use a comprehensive literature search strategy?	PARTIAL YES	CRITICAL
5. Did the review authors perform study selection in duplicate?	YES	
6. Did the review authors perform data extraction in duplicate?	YES	
7. Did the review authors provide a list of excluded studies and justify the exclusions?	NO	CRITICAL
8. Did the review authors describe the included studies in adequate detail?	YES	
9. Did the review authors use a satisfactory technique for assessing the risk of bias (ROB) individual studies that were included in the review?	YES	CRITICAL
10. Did the review authors report on the sources of funding for the studies included in the review?	NO	
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	YES	CRITICAL
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	YES	
13. Did the review authors account for RoB in individual studies when inter the results of the review?	YES	CRITICAL
14. Did the review authors provide a satisfactory explanation for, and discuss heterogeneity observed in the results of the review?	NO	
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	YES	CRITICAL
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	NO	
Overall confidence in the results of the review:		
Low One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest (AMSTAR 2)		

Title: Association of Diphtheria-Tetanus-Acellular Pertussis Vaccine Timeliness and Number of Doses With Age-Specific Pertussis Risk in Infants and Young Children (Rane et al., 2021)

AMSTAR Item	Risk of Bias Assessment
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Bias due to confounding	YES
Bias in selection of participants into the study	PROBABLY NO
Bias in classification of interventions	NO
Bias due to deviations from intended interventions	PROBABLY YES
Bias due to missing data	PROBABLY YES
Bias in measurement outcomes	NO
Bias in selection of the reported result	NO
Overall Risk of Bias Judgement	Serious Risk of Bias The study is judged to be at serious risk of bias in at least one domain, but not at critical risk of bias in any domain.

Title: Acellular vaccines for preventing whooping cough in children (Zhang et al., 2014)

AMSTAR Item	Yes/No	Note
1. Did the research questions and inclusion criteria for the review include the components of PICO?	YES	
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	YES	CRITICAL
3. Did the review authors explain their selection of the study designs for inclusion in the review?	YES	
4. Did the review authors use a comprehensive literature search strategy?	YES	CRITICAL
5. Did the review authors perform study selection in duplicate?	YES	
6. Did the review authors perform data extraction in duplicate?	YES	
7. Did the review authors provide a list of excluded studies and justify the exclusions?	YES	CRITICAL
8. Did the review authors describe the included studies in adequate detail?	YES	
9. Did the review authors use a satisfactory technique for assessing the risk of bias (ROB) individual studies that were included in the review?	YES	CRITICAL
10. Did the review authors report on the sources of funding for the studies included in the review?	YES	
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	YES	CRITICAL
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	YES	
13. Did the review authors account for RoB in individual studies when interpreting the results of the review?	YES	CRITICAL
14. Did the review authors provide a satisfactory explanation for, and discuss heterogeneity observed in the results of the review?	YES	
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	YES	CRITICAL
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	YES	
Overall confidence in the results of the review:		
High No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest (AMSTAR 2)		

Title: Tdap vaccine effectiveness in adolescents during the 2012 Washington State pertussis epidemic (Acosta et al., 2012)

AMSTAR Item	Risk of Bias Assessment
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Bias due to confounding	YES
Bias in selection of participants into the study	PROBABLY YES
Bias in classification of interventions	NO
Bias due to deviations from intended interventions	PROBABLY NO
Bias due to missing data	PROBABLY NO
Bias in measurement outcomes	NO
Bias in selection of the reported result	NO
Overall Risk of Bias Judgement	Serious Risk of Bias

Title: Pertussis Vaccine Effectiveness in the Setting of Pertactin-Deficient Pertussis (Breakwell et al., 2016)

AMSTAR Item	Risk of Bias Assessment
Bias due to confounding	YES
Bias in selection of participants into the study	PROBABLY YES
Bias in classification of interventions	NO
Bias due to deviations from intended interventions	PROBABLY NO
Bias due to missing data	PROBABLY NO
Bias in measurement outcomes	NO
Bias in selection of the reported result	NO
Overall Risk of Bias Judgement	Serious Risk of Bias

Title: Acellular pertussis vaccine booster combined with diphtheria and tetanus toxoids for adolescents (Pichichero et al., 2005)

AMSTAR Item	Risk of Bias Assessment
Arising from randomization process	LOW
Deviations from the intended intervention (effect assignment to intervention)	LOW
Missing outcome data	LOW
Measurement of the outcome	SOME CONCERNS
Selection of the reported result	LOW
Overall Risk of Bias Judgement	Some Concerns

Appendix C. Forest Plots

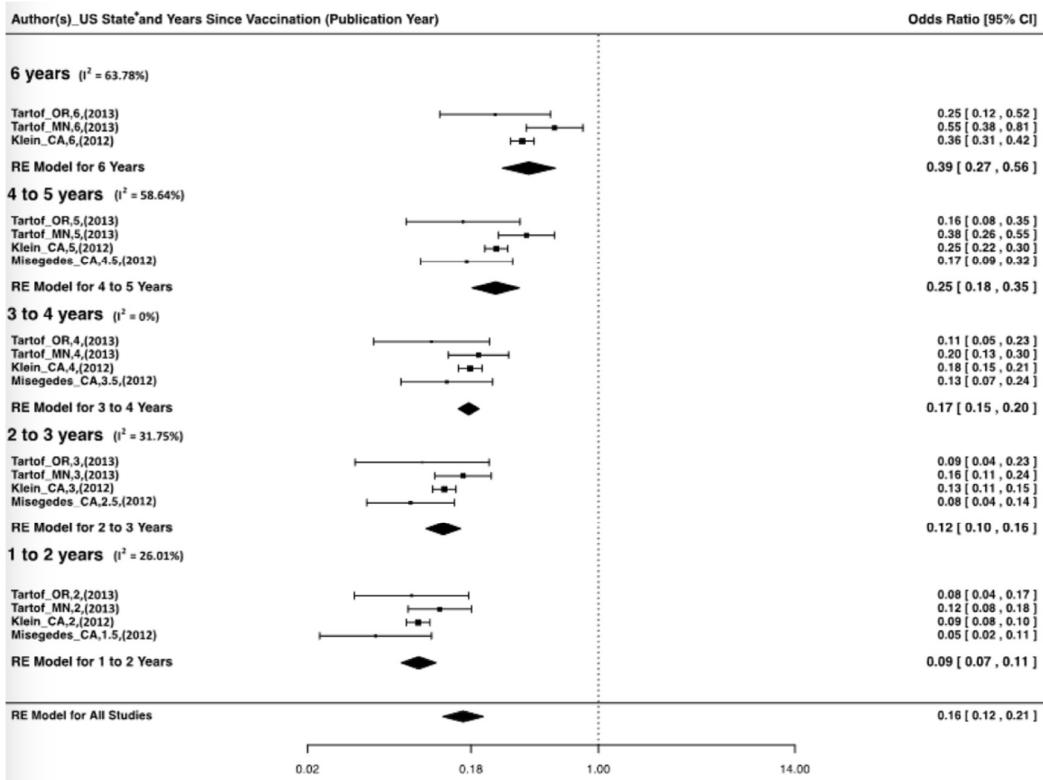


Figure 1. Estimated relative risk of pertussis after 5 doses of DTaP vaccine according to the number of years since last receipt

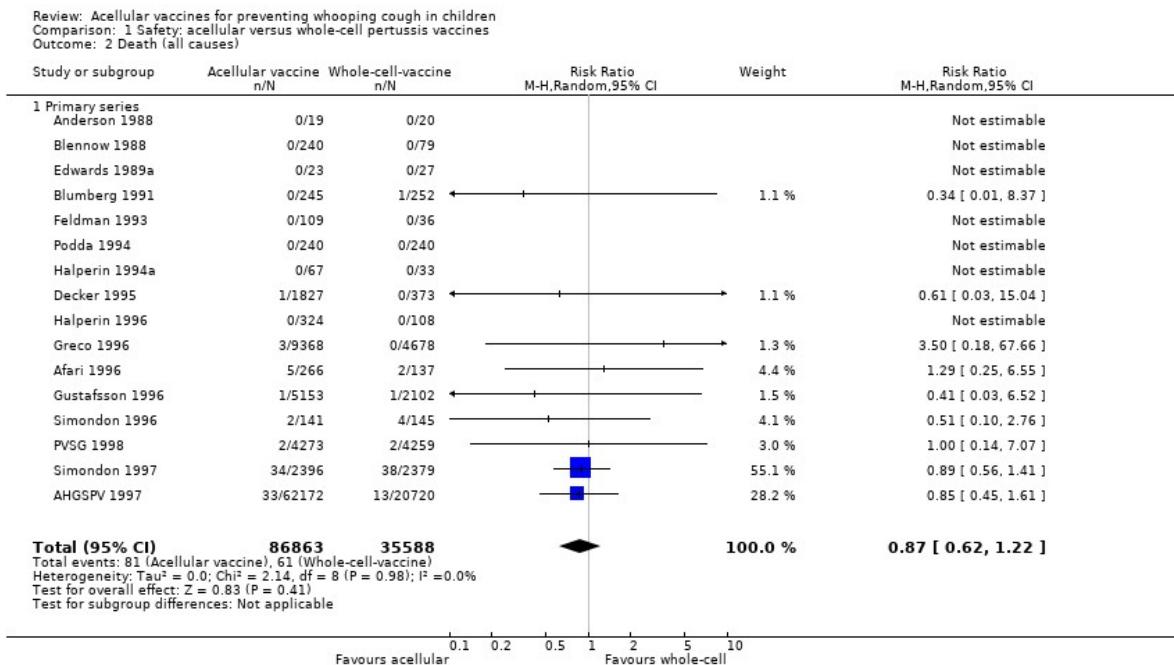


Figure 2. Acellular vaccines vs. whole cell vaccines: All-cause mortality – primary series (from Cochrane 2014)

Review: Acellular vaccines for preventing whooping cough in children
 Comparison: 1 Safety: acellular versus whole-cell pertussis vaccines
 Outcome: 3 Death (infection)

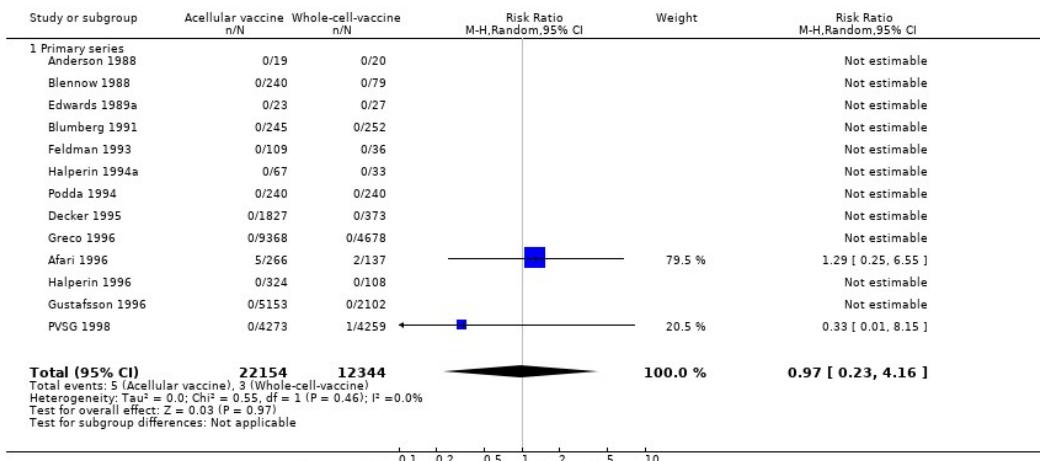


Figure 3. Acellular vaccines vs whole cell vaccines: Death from infection – primary series (from Cochrane 2014)

Review: Acellular vaccines for preventing whooping cough in children
 Comparison: 1 Safety: acellular versus whole-cell pertussis vaccines
 Outcome: 5 Convulsions

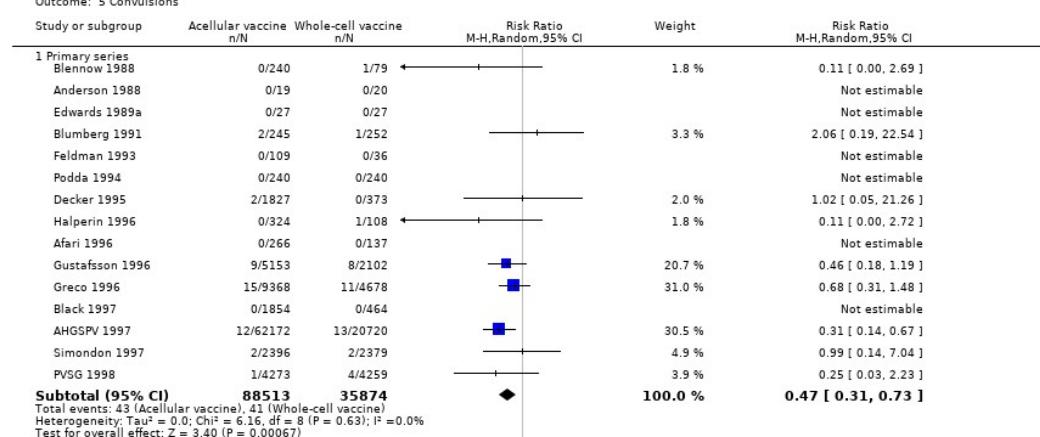


Figure 4. Acellular vaccines vs whole cell vaccines: Convulsions - primary series (from Cochrane 2014)

Review: Acellular vaccines for preventing whooping cough in children
 Comparison: 1 Safety: acellular versus whole-cell pertussis vaccines
 Outcome: 6 Hypotonic hyporesponsive episodes

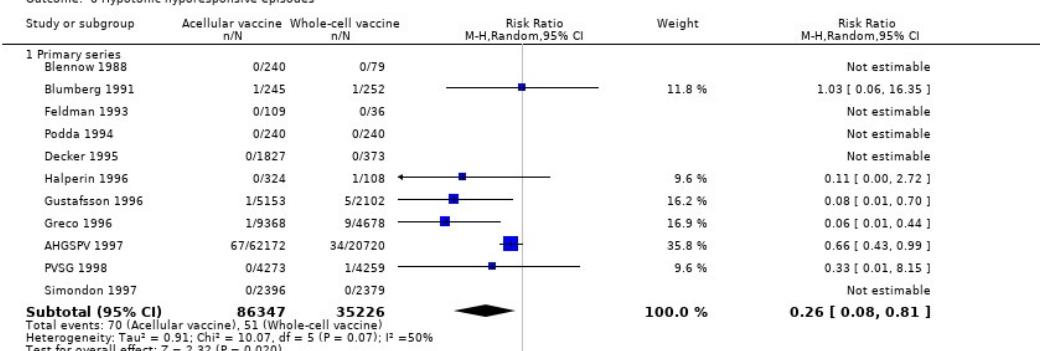


Figure 5. Acellular vaccines vs whole cell vaccines: Hypotonic hyporesponsive episodes – primary series (from Cochrane 2014)

Review: Acellular vaccines for preventing whooping cough in children
 Comparison: 2 Safety: acellular vaccines versus placebo/DT
 Outcome: 2 Death (all causes)

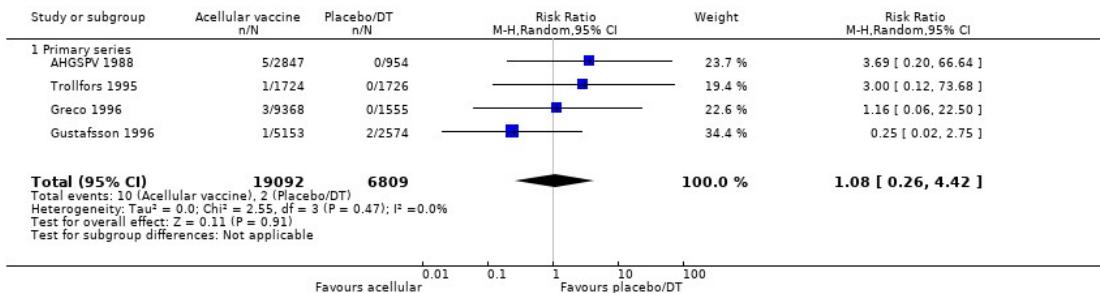


Figure 6. Acellular vaccines vs. placebo: All-cause mortality – primary series (from Cochrane 2014)

Review: Acellular vaccines for preventing whooping cough in children
 Comparison: 2 Safety: acellular vaccines versus placebo/DT
 Outcome: 2 Death (all causes)

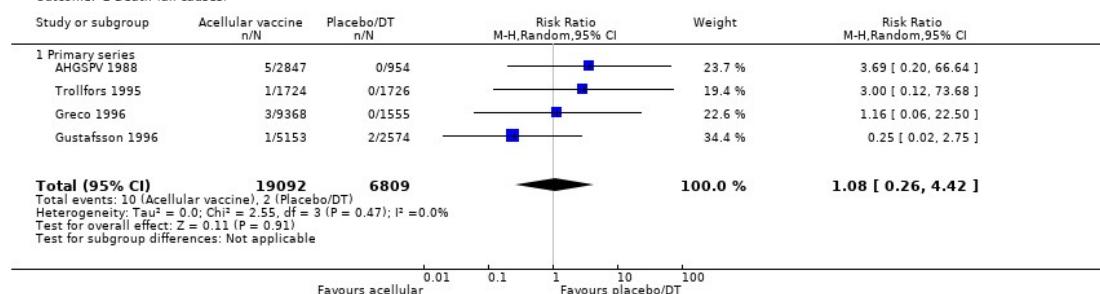


Figure 7. Acellular vaccines vs. placebo: Death from infection – primary series (from Cochrane 2014)

Review: Acellular vaccines for preventing whooping cough in children
 Comparison: 2 Safety: acellular vaccines versus placebo/DT
 Outcome: 5 Convulsions

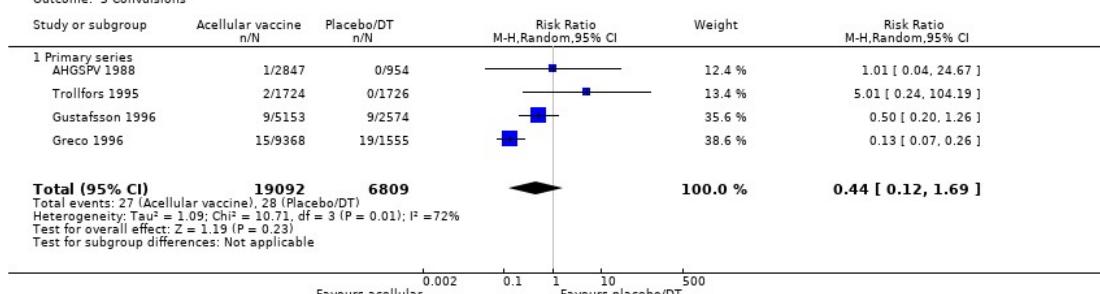


Figure 8. Acellular vaccines vs. placebo: Convulsions – primary series (from Cochrane 2014)

Review: Acellular vaccines for preventing whooping cough in children
 Comparison: 2 Safety: acellular vaccines versus placebo/DT
 Outcome: 6 Hypotonic hyporesponsive episodes

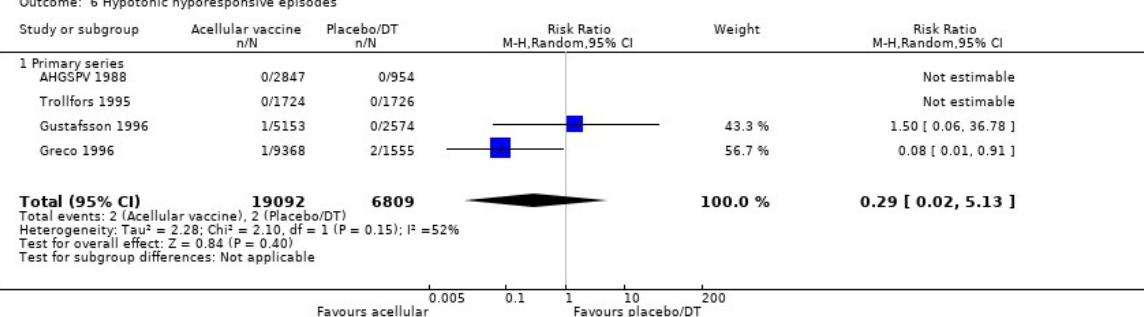


Figure 9. Acellular vaccines vs placebo: Hypotonic hyporesponsive episodes – primary series (from Cochrane 2014)

Appendix D. GRADE Evidence Profile

Certainty assessment							No of patient s	Effect		Certainty	Importanc e
No of studie s	Study design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns		DTaP None	Relativ e (95% CI)		

Vaccine Effectiveness: pertussis-containing booster (DTaP) against Pertussis disease during childhood in 1 to 2 years

3	observatio nal studies	seriou s ^a	not serious	serious	not serious	all plausible residual confounding would reduce the demonstrated effect	682 cases, 2016 control s 277 cases, 3,31 control s 403,38 9 cohort s, 547 cases	RR 0.09 [0.07- 0.11]	-	⊕⊕○ Low	CRITIC AL
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Vaccine Effectiveness: pertussis-containing booster (DTaP) against Pertussis disease during childhood in 2 to 3 years

3	observatio nal studies	seriou s ^a	not serious	serious	not serious	all plausible residual confounding would reduce the demonstrated effect	682 cases, 2016 control s 277 cases, 3,31 control s 403,38 9 cohort s, 547 cases	RR 0.12 [0.10- 0.16]	-	⊕⊕○ Low	CRITIC AL
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Vaccine Effectiveness: pertussis-containing booster (DTaP) against Pertussis disease during childhood in 3 to 4 years

3	observatio nal studies	seriou s ^a	not serious	serious	not serious	all plausible residual confounding would reduce the demonstrated effect	682 cases, 2016 control s 277 cases, 3,31 control s 403,38 9 cohort s, 547 cases	RR 0.17 [0.15- 0.20]	-	⊕⊕○ Low	CRITIC AL
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Vaccine Effectiveness: pertussis-containing booster (DTaP) against Pertussis disease during childhood in 4 to 5 years

3	observatio nal studies	seriou s ^a	serious	serious	not serious	all plausible residual confounding would reduce the demonstrated effect	682 cases, 2016 control s 277 cases, 3,31 control s 403,38 9 cohort s, 547 cases	RR 0.25 [0.18- 0.35]	-	⊕○○ Very Low	CRITIC AL
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Certainty assessment							No of patient s	Effect		Certainty	Importanc e
No of studies	Study design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Other consideratio ns		Relativ e (95% CI)	Absolu te (95% CI)		

Vaccine Effectiveness: pertussis-containing booster (DTaP) against Pertussis disease during childhood in 6 years

2	observatio nal studies	seriou s ^a	serious	serious	not serious	all plausible residual confounding would reduce the demonstrated effect	682 cases, 2016 control s 277 cases, 3,31 control s	RR 0.39 [0.27- 0.56]	-	⊕○○○ Very Low	CRITIC AL
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Vaccine Effectiveness: Undervaccination of pertussis-containing booster (DTaP) against Pertussis disease during childhood – First booster

1	observatio nal study	seriou s ^a	serious	serious	not serious	all plausible residual confounding would reduce the demonstrated effect	259,67 5 cohort size	RR 3.2 [2.3- 4.5]	-	⊕○○○ Very Low	CRITIC AL
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Vaccine Effectiveness: Undervaccination of pertussis-containing booster (DTaP) against Pertussis disease during childhood – Second booster

1	observatio nal study	seriou s ^a	serious	serious	not serious	all plausible residual confounding would reduce the demonstrated effect	134,95 0 cohort size	RR 4.6 [2.6- 8.2]	-	⊕○○○ Very Low	CRITIC AL
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Vaccine Safety: pertussis-containing vaccine versus whole cell during childhood (All-cause mortality – primary series only)

16	Randomize d trials	seriou s	not serious	not serious	serious	None	N= 12245 1 sampl e size	RR 0.87 [0.62, 1.22]	-	⊕⊕○○ Low	CRITIC AL
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Vaccine Safety: pertussis-containing vaccine versus whole cell during childhood (Death due to infection – primary series only)

13	Randomize d trials	seriou s	not serious	not serious	serious	None	N= 34498 sampl e size	RR 0.97 [0.23, 4.16]	-	⊕⊕○○ Low	CRITIC AL
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Vaccine Safety: pertussis-containing vaccine versus whole cell during childhood (Death due to infection – primary series only)

11	Randomize d trials	seriou s	not serious	not serious	serious	None	N= 2647 sampl e size	RR 0.46 [0.02, 11.20]	-	⊕⊕○○ Low	CRITIC AL
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Vaccine Safety: pertussis-containing vaccine versus whole cell during childhood (Death due to infection – primary series only)

18	Randomize d trials	seriou s	not serious	not serious	serious	None	N= 12157 3 sampl e size	RR 0.26 [0.08, 0.81]	-	⊕⊕○○ Low	CRITIC AL
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Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tdap	Td	Relative (95% CI)	Absolute (95% CI)		

Vaccine Effectiveness: pertussis-containing booster (Tdap) against Pertussis disease during adolescence

2	observational studies	very serious ^a	serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	482 cases 212 controls	OR 0.42 (0.35 to 0.52)	-	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕○	CRITICAL
											Low	

Vaccine Safety: Pain (grade 2 or 3)

1	randomised trial	serious	not serious	not serious	not serious	none	1538/3032 (50.7%)	427/1013 (42.2%)	RR 1.20 (1.11 to 1.30)	84 more per 1,000 (from 46 more to 126 more)	⊕⊕⊕○	Moderate
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Vaccine Safety: Redness

1	randomised trial	serious	not serious	not serious	not serious	none	664/3032 (21.9%)	198/1013 (19.5%)	RR 1.12 (0.97 to 1.29)	23 more per 1,000 (from 6 fewer to 57 more)	⊕⊕⊕○	Moderate
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Vaccine Safety: Swelling

1	randomised trial	serious	not serious	not serious	not serious	none	613/3032 (20.2%)	201/1013 (19.8%)	RR 1.02 (0.88 to 1.18)	4 more per 1,000 (from 24 fewer to 36 more)	⊕⊕⊕○	Moderate
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Vaccine Safety: Fever

1	randomised trial	serious	not serious	not serious	serious ^b	none	196/3030 (6.5%)	55/1013 (5.4%)	RR 1.19 (0.89 to 1.59)	10 more per 1,000 (from 6 fewer to 32 more)	⊕⊕○	Low
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Vaccine Safety: Headache (grade 2 or 3)

1	randomised trial	serious	not serious	not serious	not serious	none	235/3030 (7.8%)	69/1013 (6.8%)	RR 1.14 (0.88 to 1.47)	10 more per 1,000 (from 8 fewer to 32 more)	⊕⊕⊕○	Moderate
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Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tdap	Td	Relative (95% CI)	Absolute (95% CI)		

Vaccine Safety: Fatigue (grade 2 or 3)

1	randomised trial	serious	not serious	not serious	not serious	none	267/303 0 (8.8%)	87/101 3 (8.6%)	RR 1.03 (0.81 to 1.29)	3 more per 1,000 (from 16 fewer to 25 more)	 Moderate	
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Vaccine Safety: Gastrointestinal symptoms (grade 2 or 3)

1	randomised trial	serious	not serious	not serious	not serious	none	148/303 0 (4.9%)	50/101 3 (4.9%)	RR 0.99 (0.72 to 1.35)	0 fewer per 1,000 (from 14 fewer to 17 more)	 Moderate	
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CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio

Explanations

a. Possible selection, confounding and information bias b. Wide confidence intervals

AGREE REPORTING CHECKLIST (SELF-EVALUATION)

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

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
DOMAIN 1: SCOPE AND PURPOSE		
1. OBJECTIVES <i>Report the overall objective(s) of the guideline. The expected health benefits from the guideline are to be specific to the clinical problem or health topic.</i>	<input checked="" type="checkbox"/> Health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) <input checked="" type="checkbox"/> Expected benefit(s) or outcome(s) <input checked="" type="checkbox"/> Target(s) (e.g., patient population, society)	13, 15
2. QUESTIONS <i>Report the health question(s) covered by the guideline, particularly for the key recommendations.</i>	<input checked="" type="checkbox"/> Target population <input checked="" type="checkbox"/> Intervention(s) or exposure(s) <input checked="" type="checkbox"/> Comparisons (if appropriate) <input checked="" type="checkbox"/> Outcome(s) <input checked="" type="checkbox"/> Health care setting or context	13, 15
3. POPULATION <i>Describe the population (i.e., patients, public, etc.) to whom the guideline is meant to apply.</i>	<input checked="" type="checkbox"/> Target population, sex and age <input checked="" type="checkbox"/> Clinical condition (if relevant) <input type="checkbox"/> Severity/stage of disease (if relevant) <input type="checkbox"/> Comorbidities (if relevant) <input type="checkbox"/> Excluded populations (if relevant)	13, 15
DOMAIN 2: STAKEHOLDER INVOLVEMENT		
4. GROUP MEMBERSHIP <i>Report all individuals who were involved in the development process. This may include members of the steering group, the research team involved in selecting and reviewing/rating the evidence and individuals involved in formulating the final recommendations.</i>	<input checked="" type="checkbox"/> Name of participant <input checked="" type="checkbox"/> Discipline/content expertise (e.g., neurosurgeon, methodologist) <input checked="" type="checkbox"/> Institution (e.g., St. Peter's hospital) <input type="checkbox"/> Geographical location (e.g., Seattle, WA) <input checked="" type="checkbox"/> A description of the member's role in the guideline development group	117-118
5. TARGET POPULATION PREFERENCES AND VIEWS <i>Report how the views and preferences of the target population were sought/considered and what the resulting outcomes were.</i>	<input checked="" type="checkbox"/> Statement of type of strategy used to capture patients'/publics' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences) <input checked="" type="checkbox"/> Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups) <input checked="" type="checkbox"/> Outcomes/information gathered on patient/public information <input checked="" type="checkbox"/> How the information gathered was used to inform the guideline development process and/or formation of the recommendations	15-17, 22, 32, 42, 49, 56, 64, 73, 81, 90, 102, 112
6. TARGET USERS <i>Report the target (or intended) users of the guideline.</i>	<input checked="" type="checkbox"/> The intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators) <input checked="" type="checkbox"/> How the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)	15
DOMAIN 3: RIGOUR OF DEVELOPMENT		
7. SEARCH METHODS <i>Report details of the strategy used to search for evidence.</i>	<input checked="" type="checkbox"/> Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL) <input checked="" type="checkbox"/> Time periods searched (e.g., January 1, 2004 to March 31, 2008) <input checked="" type="checkbox"/> Search terms used (e.g., text words, indexing terms, subheadings) <input checked="" type="checkbox"/> Full search strategy included (e.g., possibly located in appendix)	16-17, 121-140
8. EVIDENCE SELECTION CRITERIA	<input checked="" type="checkbox"/> Target population (patient, public, etc.) characteristics <input checked="" type="checkbox"/> Study design	16-17

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
<i>Report the criteria used to select (i.e., include and exclude) the evidence. Provide rationale, where appropriate.</i>	<input checked="" type="checkbox"/> Comparisons (if relevant) <input checked="" type="checkbox"/> Outcomes <input type="checkbox"/> Language (if relevant) <input type="checkbox"/> Context (if relevant)	
9. STRENGTHS & LIMITATIONS OF THE EVIDENCE <i>Describe the strengths and limitations of the evidence. Consider from the perspective of the individual studies and the body of evidence aggregated across all the studies. Tools exist that can facilitate the reporting of this concept.</i>	<input checked="" type="checkbox"/> Study design(s) included in body of evidence <input checked="" type="checkbox"/> Study methodology limitations (sampling, blinding, allocation concealment, analytical methods) <input checked="" type="checkbox"/> Appropriateness/relevance of primary and secondary outcomes considered <input checked="" type="checkbox"/> Consistency of results across studies <input checked="" type="checkbox"/> Direction of results across studies <input checked="" type="checkbox"/> Magnitude of benefit versus magnitude of harm <input checked="" type="checkbox"/> Applicability to practice context	20-114
10. FORMULATION OF RECOMMENDATIONS <i>Describe the methods used to formulate the recommendations and how final decisions were reached. Specify any areas of disagreement and the methods used to resolve them.</i>	<input checked="" type="checkbox"/> Recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered) <input checked="" type="checkbox"/> Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures) <input checked="" type="checkbox"/> How the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote)	17-18
11. CONSIDERATION OF BENEFITS AND HARMS <i>Report the health benefits, side effects, and risks that were considered when formulating the recommendations.</i>	<input checked="" type="checkbox"/> Supporting data and report of benefits <input checked="" type="checkbox"/> Supporting data and report of harms/side effects/risks <input checked="" type="checkbox"/> Reporting of the balance/trade-off between benefits and harms/side effects/risks <input checked="" type="checkbox"/> Recommendations reflect considerations of both benefits and harms/side effects/risks	22, 30, 39, 46, 53, 62, 70, 79, 86, 98-99 109
12. LINK BETWEEN RECOMMENDATIONS AND EVIDENCE <i>Describe the explicit link between the recommendations and the evidence on which they are based.</i>	<input checked="" type="checkbox"/> How the guideline development group linked and used the evidence to inform recommendations <input checked="" type="checkbox"/> Link between each recommendation and key evidence (text description and/or reference list) <input checked="" type="checkbox"/> Link between recommendations and evidence summaries and/or evidence tables in the results section of the guideline	11, 16, 141-234
13. EXTERNAL REVIEW <i>Report the methodology used to conduct the external review.</i>	<input checked="" type="checkbox"/> Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence) <input checked="" type="checkbox"/> Methods taken to undertake the external review (e.g., rating scale, open-ended questions) <input checked="" type="checkbox"/> Description of the external reviewers (e.g., number, type of reviewers, affiliations) <input type="checkbox"/> Outcomes/information gathered from the external review (e.g., summary of key findings) <input checked="" type="checkbox"/> How the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations)	18
14. UPDATING PROCEDURE <i>Describe the procedure for updating the guideline.</i>	<input checked="" type="checkbox"/> A statement that the guideline will be updated <input checked="" type="checkbox"/> Explicit time interval or explicit criteria to guide decisions about when an update will occur <input checked="" type="checkbox"/> Methodology for the updating procedure	116
DOMAIN 4: CLARITY OF PRESENTATION		
15. SPECIFIC AND UNAMBIGUOUS RECOMMENDATIONS	<input checked="" type="checkbox"/> A statement of the recommended action	9, 11-12



CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
<i>Describe which options are appropriate in which situations and in which population groups, as informed by the body of evidence.</i>	<input checked="" type="checkbox"/> Intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) <input checked="" type="checkbox"/> Relevant population (e.g., patients, public) <input checked="" type="checkbox"/> Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply) <input checked="" type="checkbox"/> If there is uncertainty about the best care option(s), the uncertainty should be stated in the guideline	
16. MANAGEMENT OPTIONS <i>Describe the different options for managing the condition or health issue.</i>	<input checked="" type="checkbox"/> Description of management options <input type="checkbox"/> Population or clinical situation most appropriate to each option	11-12
17. IDENTIFIABLE KEY RECOMMENDATIONS <i>Present the key recommendations so that they are easy to identify.</i>	<input checked="" type="checkbox"/> Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms <input checked="" type="checkbox"/> Specific recommendations grouped together in one section	11-12
DOMAIN 5: APPLICABILITY		
18. FACILITATORS AND BARRIERS TO APPLICATION <i>Describe the facilitators and barriers to the guideline's application.</i>	<input checked="" type="checkbox"/> Types of facilitators and barriers that were considered <input checked="" type="checkbox"/> Methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation) <input checked="" type="checkbox"/> Information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography) <input checked="" type="checkbox"/> How the information influenced the guideline development process and/or formation of the recommendations	115-116
19. IMPLEMENTATION ADVICE/TOOLS <i>Provide advice and/or tools on how the recommendations can be applied in practice.</i>	<input checked="" type="checkbox"/> Additional materials to support the implementation of the guideline in practice. For example: <ul style="list-style-type: none"> ○ Guideline summary documents ○ Links to check lists, algorithms ○ Links to how-to manuals ○ Solutions linked to barrier analysis (see Item 18) ○ Tools to capitalize on guideline facilitators (see Item 18) ○ Outcome of pilot test and lessons learned 	121-234
20. RESOURCE IMPLICATIONS <i>Describe any potential resource implications of applying the recommendations.</i>	<input checked="" type="checkbox"/> Types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) <input checked="" type="checkbox"/> Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.) <input checked="" type="checkbox"/> Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course) <input checked="" type="checkbox"/> How the information gathered was used to inform the guideline development process and/or formation of the recommendations	23, 32, 41, 48, 55, 64, 72, 81, 88, 101, 112, 115-116
21. MONITORING/ AUDITING CRITERIA <i>Provide monitoring and/or auditing criteria to measure the application of guideline recommendations.</i>	<input checked="" type="checkbox"/> Criteria to assess guideline implementation or adherence to recommendations <input checked="" type="checkbox"/> Criteria for assessing impact of implementing the recommendations <input type="checkbox"/> Advice on the frequency and interval of	116



CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
	<p>measurement</p> <p><input checked="" type="checkbox"/> Operational definitions of how the criteria should be measured</p>	
DOMAIN 6: EDITORIAL INDEPENDENCE		
22. FUNDING BODY <i>Report the funding body's influence on the content of the guideline.</i>	<input checked="" type="checkbox"/> The name of the funding body or source of funding (or explicit statement of no funding) <input checked="" type="checkbox"/> A statement that the funding body did not influence the content of the guideline	3
23. COMPETING INTERESTS <i>Provide an explicit statement that all group members have declared whether they have any competing interests.</i>	<input checked="" type="checkbox"/> Types of competing interests considered <input checked="" type="checkbox"/> Methods by which potential competing interests were sought <input checked="" type="checkbox"/> A description of the competing interests <input checked="" type="checkbox"/> How the competing interests influenced the guideline process and development of recommendations	119-120