PHILIPPINE GUIDELINES on PERIODIC HEALTH EXAMINATION

Adult Immunization

PERIODIC HEALTH EXAMINATION TASK FORCE 2022-2023

As of 02 September 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

For any questions about this CPG, please contact arminmasbangmd@gmail.com.

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

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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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Participating Societies, Organizations, Agencies and Institutions

Philippine College of Physicians

Philippine Society for Microbiology and Infectious Diseases

Philippine Society of General Internal Medicine

Philippine Foundation for Vaccination

Philippine Academy of Family Physicians

Association of Municipal Health Officers of the Philippines

Philippine College of Occupational Medicine

Philippine Society of Public Health Physician

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List of Abbreviations

6-MPI	6-month persistent infection (Human papillomavirus)
AAHS	Amorphous Aluminium Hydroxyphosphate Sulfate
ACIP	Advisory Committee on Immunization Practices
AE	Adverse events
AIN	Anal Intraepithelial Neoplasia
AMHOP	Association of Municipal Health Officers
AMSTAR	A Critical Appraisal Tool for Systematic Reviews
AR	Adverse reactions
ATAGI	Australian Technical Advisory Group on Immunization
BRPEP	Bohol Rabies Prevention and Elimination Project
CAP	Community Acquired Pneumonia
CAPiTA	Community Acquired Pneumonia Immunization Trial in Adults
CDC	Center for Disease Control and Prevention
CF	Case Fatality Rate
CI	Confidence interval
CIN	Cervical Intraepithelial Neoplasia
COI	Conflict of Interest
CP	Consensus Panel
CPG	Clinical Practice Guideline
DALY	Disability adjusted life year
DOH	Department of Health
DPCB	Disease Prevention and Control Bureau
EIA	Enzyme Immunoassay
ELISA	Enzyme-Linked Immunosorbent Assays
ERE	Evidence Review Experts
EtD	Evidence to Decision
EUGMS	European Geriatric Medicine
EVASCG	ESCMID Vaccine Study Group
FAMA	Fluorescent-antibody-to-membrane-antigen
FDA	Food and Drug Administration
GBMSM	Gay bisexual men who have sex with men
GBS	Guillain-Barré Syndrome
GMTs	Geometric mean titer
GRADE	Grading Of Recommendations, Assessment, Development and Evaluation
HAV	Hepatitis A virus
HCW	Healthcare worker
HDCV	Human diploid cell culture rabies vaccine
HiB	Haemophilus influenzae b
HIV	Human immunodeficiency virus
HPV	Human Papillomavirus
IBCM	Integrated Bite Case Management
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
ID	Intradermal (route of vaccination)
ILI	Influenza-Like Illness
IM	Intramuscular (route of vaccination)
IPD	Invasive Pneumococcal Disease
IQR	Interquartile Range
IRR	Incidence Rate Ratio
JE	Japanese encephalitis
JECV	Live chimeric Japanese encephalitis vaccine
JE-MB	Mouse brain-derived Japanese encephalitis vaccine
LMIC	Low to Middle Income Country

MBC	Memory-B cell
MCV	Meningococcal Conjugate Vaccine
MD	Mean difference
MeSH	Medical Subject Headings
MMR	Measles, Mumps, and Rubella (vaccination)
MNTE	Maternal and Neonatal Tetanus Elimination
MPX/Mpox	Monkeypox
MSM	Men who have sex with men
MVA-BN	Modified vaccinia Ankara strain
NNV	Number Needed to Vaccinate
OCV	Oral cholera vaccine
OPA	Opsonophagocytic Activity
OR	Odds Ratio
PCECV	Purified chick embryo cell vaccine
PCP	Philippine College of Physicians
PCR	Polymerase Chain Reaction
PCV13	Pneumococcal Conjugate Vaccine
PeIN	Penile Intraepithelial Neoplasia
PEP	Post-exposure prophylaxis
PFV	Philippine Foundation for Vaccination
PICO	Population, Intervention, Comparator and Outcome
PPSV23	Pneumococcal Polysaccharide Vaccine
PRP	Polyribosyl ribitol phosphate
PrEP	Pre-exposure prophylaxis
PrEP+PEP	Pre-exposure with post-exposure prophylaxis
PSA	Philippine Statistics Authority
PSGIM	Philippine Society of General Internal Medicine
PSMID	Philippine Society for Microbiology and Infectious Diseases
PVRV	Purified vero-cell rabies vaccine
QALD	Quality-adjusted life days
QALY	Quality-adjusted life years
RABV	Rabies virus
RCT	Randomized control trials
RD	Risk difference
RevMan	Review Manager - Cochrane
RFFIT	Rapid fluorescent focus inhibition test
RIG	Rabies immunoglobulin
RR	Risk ratio
RVNA	Rabies virus neutralizing antibodies
RZV	Recombinant Zoster Vaccine
SAE	Serious adverse events
SCR	Seroconversion Rate
SD	Standard Deviation
SRR	Seroresponse Rate
STATA	A general-purpose statistical software package developed by StataCorp for data manipulation, visualization, statistics, and automated reporting
STD	Sexually transmitted disease
TCV	Typhoid Conjugate Vaccine
Td	Tetanus Toxoid
TDaP	Tetanus, diphtheria, acellular pertussis (vaccine)
TIV	Trivalent Inactivated Vaccine
VaIN	Vaginal Intraepithelial Neoplasia
VE	Vaccine Efficacy
VIN	Vulvar Intraepithelial Neoplasia
Vi-rEPA	Vi Polysaccharide bound to recombinant *Pseudomonas Aeruginosa* Exoprotein A
Vi-TT	Vi Tetanus Toxoid

UVV	Universal varicella vaccination
VSV	Varicella-zoster virus
WHO	World Health Organization
WTP	Willing-to-pay threshold
YF	Yellow fever
YLD	Years Lost due to Disability
YLL	Years of Life Lost
ZVL	Zoster Vaccine Live

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Executive Summary

This Clinical Practice Guideline on Immunization of Adults 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 evidence to address immunization among adults. The CPG provides forty-one (41) recommendations on prioritized questions in the screening for certain disease conditions.

Recommendations are based on the appraisal of the best available evidence on each of the eight identified clinical questions. The CPG is intended to be used by general practitioners and specialists in the primary care setting, policy makers, employers and administrators, allied health practitioners, and even patients. The guideline development process followed the widely accepted Grading of Recommendations, Assessment, Development, and Evaluation or the GRADE approach including GRADE Adolopment,[1] a systematic process of adapting evidence summaries and the GRADE Evidence to Decision or EtD[2] framework. 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.

This CPG recommends giving a certain vaccine if the strength of recommendation is strong, while it suggests giving a certain vaccine if the strength of recommendation is weak.

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

References

1. Schünemann HJ, Wiercdioch 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-Adolopment. Journal of Clinical Epidemiology. 2017;81:101–10. doi:10.1016/j.jclinepi.2016.09.009
2. Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. Grade evidence to decision (ETD) frameworks: A systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. BMJ. 2016;i2089. doi:10.1136/bmj.i2089

Summary of Recommendations

Table 1. Summary of recommendations

RECOMMENDATIONS	STRENGTH OF RECOMMENDATION	CERTAINTY OF EVIDENCE
CHOLERA VACCINE		
Should cholera vaccine be given to asymptomatic apparently healthy adults?		
Among asymptomatic apparently healthy adults traveling to cholera-endemic areas, we **recommend giving** oral cholera vaccine.	Strong	Moderate
Among asymptomatic apparently healthy adults, we **suggest against** giving oral cholera vaccine.	Weak	Moderate
Among asymptomatic healthcare workers, we **suggest against** giving oral cholera vaccine due to insufficient evidence.	Weak	Very Low
HAEMOPHILUS INFLUENZAE B (HIB) VACCINE		
Should haemophilus influenzae B (HiB) vaccine be given to asymptomatic apparently healthy adults?		
Among asymptomatic apparently healthy adults, we **recommend against** giving Haemophilus influenzae B vaccine.	Strong	Low
Among asymptomatic healthcare workers, we **recommend against** giving Haemophilus influenzae b vaccine due to insufficient evidence.	Strong	Very Low
Among adults with anatomical and functional asplenia, we **suggest giving** Haemophilus influenzae b vaccine.	Weak	Low
Among pregnant women, we **suggest against** giving Haemophilus influenzae b vaccine.	Weak	Low
HEPATITIS A VACCINE		
Should hepatitis A vaccine be given to asymptomatic apparently healthy adults?		
Among apparently healthy adults, we **suggest giving** hepatitis A vaccination using a 2-dose series (0,6 months)	Weak	Low
HERPES ZOSTER VACCINE		
Should herpes zoster vaccine be recommended to apparently healthy adults?		
Among apparently healthy elderly aged ≥ 60 years old, we **suggest** herpes zoster vaccine.	Weak	Low

HIGH-DOSE INACTIVATED INFLUENZA VACCINE

Should high-dose influenza vaccine be given over standard-dose influenza vaccine among older adults?		
High-dose inactivated influenza vaccine is not available locally, precluding the panel from making a recommendation on its use.		

HUMAN PAPILLOMAVIRUS (HPV) VACCINE

Should HPV vaccine be recommended to apparently healthy adults?		
Among apparently healthy asymptomatic females aged 18 to 26 years who have not been vaccinated or who have not yet completed the vaccine series, we **recommend** HPV vaccination.	Strong	Moderate
Among apparently healthy asymptomatic adults aged 27 to 45 years, we **suggest against** routine catch-up vaccination. The decision to vaccinate people in this age group should be made on an individual basis.	Weak	Low
Among apparently healthy asymptomatic males aged 18 to 26 years who have not been vaccinated or who have not yet completed the vaccine series, we **suggest** HPV vaccination.	Weak	Very Low
Among pregnant patients, we **suggest against** HPV vaccination.	Weak	Very Low
Among apparently healthy asymptomatic sex workers, there is **insufficient evidence to recommend** HPV vaccination.	N/A	Very Low

INFLUENZA VACCINE

Should influenza vaccine be recommended to apparently healthy adults?		
Among healthy adults, pregnant women, and elderly (≥65 years old), we **suggest** annual influenza vaccination using inactivated influenza vaccine	Weak	Low
Among healthcare workers, we **suggest** annual influenza vaccination using inactivated influenza vaccine.	Weak	Very Low

JAPANESE ENCEPHALITIS VACCINE

Should Japanese encephalitis vaccine be given to asymptomatic apparently healthy adults?		
Among asymptomatic apparently healthy adults, we **suggest giving** Japanese encephalitis virus vaccine.	Weak	Low

MEASLES VACCINE

Should measles-containing vaccine be recommended to apparently healthy adults?		
Among healthy adults (non-pregnant or unvaccinated), we **recommend giving** measles-containing vaccine.	Strong	Very Low

MENINGOCOCCAL VACCINE

Should meningococcal vaccine be given to asymptomatic apparently healthy adults?		
Among asymptomatic apparently healthy adults, we **suggest against** giving meningococcal MenACWY vaccine.	Weak	High
Among asymptomatic apparently healthy young adults (18-25 y/o), we **suggest against** giving meningococcal MenB vaccine.	Weak	Moderate
Among adults with high risk of contracting meningococcal disease*, we **suggest giving** meningococcal MenACWY vaccine.	Weak	Moderate
Among adults with high risk of contracting meningococcal disease**, we **suggest giving** meningococcal MenB vaccine.	Weak	Very Low

**Individuals living in close close quarters/proximity, asplenic patients, microbiologists (increased exposure)*
***Young adults in crowded dormitories*

MONKEYPOX VACCINE

Should monkeypox vaccine be given to asymptomatic apparently healthy adults?		
Among apparently healthy adults, we **suggest against** monkeypox vaccine.	Weak	Low
Among adults with high risk* for exposure to monkeypox, we **suggest against** giving monkeypox vaccine.	Weak	Very Low

**Healthcare workers responding to monkeypox outbreak, laboratory personnel who are handling monkeypox virus, individuals with multiple sexual partners, and men having sex with men (MSM)*

PNEUMOCOCCAL

Should pneumococcal vaccine be recommended to apparently healthy adults?		
Among apparently healthy adults ≥ 65 years of age, we **recommend** the use of PPSV 23.	Strong	Moderate
Among apparently healthy adults ≥ 65 years of age, we **suggest** the use of PCV 13.	Weak	Moderate
Among apparently healthy adults between 18-64 years of age, we **suggest** the use of PCV 13	Weak	Low

Among apparently healthy adults between 18-64 years of age, there is **insufficient evidence to recommend** the use of PPSV 23	N/A	Low

RABIES VACCINE

Should pre-exposure rabies vaccine be given to asymptomatic apparently healthy adults?		
Among asymptomatic apparently healthy adults, we **suggest against** giving pre-exposure rabies vaccine.	Weak	Very Low
Among healthcare workers with high risk of exposure to rabies, we **suggest giving** pre-exposure rabies vaccine.	Weak	Very Low
Among adults with high risk of exposure to rabies, we **suggest giving** pre-exposure rabies vaccine.	Weak	Very Low

TETANUS VACCINE

Should tetanus vaccine be recommended to apparently healthy adults		
Among healthy adults with complete primary series, we **recommend giving** any tetanus-toxoid-containing vaccine every 10 years.	Strong	Low
Among pregnant women with complete primary series, we **suggest giving** any tetanus toxoid-containing vaccine during each pregnancy.	Weak	Low
Among pregnant women with unknown status or incomplete series, we **suggest giving** primary series with Tdap followed by any tetanus-toxoid-containing vaccine.	Weak	Low
Among healthy adults with unknown status or incomplete series, we **suggest giving** primary series with Tdap followed by any tetanus-toxoid-containing vaccine.	Weak	Very Low

TYPHOID VACCINE

Should typhoid vaccine be recommended to apparently healthy adults?		
Among healthy adults, we **suggest** the use of Vi polysaccharide intramuscular vaccine.	Weak	Low
Among healthcare workers, we **suggest against** the routine use of typhoid vaccines.	Weak	Very Low
Among healthy adults, there is **insufficient evidence to recommend** for or against Vi-TT intramuscular vaccines.	N/A	Very Low

VARICELLA VACCINE

Should varicella vaccine be given to asymptomatic apparently healthy adults?		
Among asymptomatic apparently healthy adults, we **suggest against** giving varicella vaccine	Weak	Very Low

Among asymptomatic healthcare workers, we **suggest against** giving varicella vaccine.	Weak	Very Low

1. Introduction

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

Due to the evolving technology, scientific evidence, and health policies, there is a pressing need to update this guideline. This 2023 Philippine Guidelines supports the objectives stated in the Universal Health Care Act,[2] which gives all Filipinos access to quality and affordable medical services, including primary care benefits. Since immunization plays a vital role in protecting individuals and communities from preventable infectious diseases, this guideline on adult immunization was included.

Immunization is one of the most convenient preventive measures in acquiring vaccine-preventable diseases. However, immunity from childhood can wear off over time and adults are at risk for different diseases; thus, the importance of providing guidance on which vaccinations should be recommended to the adult population. Recommendations were made on sixteen (16) vaccinations (cholera, *Haemophilus influenzae* B, hepatitis A, herpes zoster, human papilloma virus, influenza (2 vaccines), Japanese encephalitis, measles, meningococcal, monkeypox, pneumococcal, rabies, tetanus, typhoid, and varicella), taking into consideration the general outcomes of vaccine efficacy, safety, and cost-effectiveness.

This guideline focuses on adult immunization among apparently healthy adults and those with high risk conditions In the guideline development, evidence-based recommendations for the prioritized health screening were formulated using the GRADE Evidence-to-Decision (EtD) framework.[4,5] 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 the equity, applicability, and feasibility lenses.

The evidence collated to answer the research questions on adult immunization are used in formulating the recommendations.

The target users of this guideline include primary care providers, general physicians, and specialists. This also target the regulatory agencies and policymakers in the national government.

References

1. Dans A, Morales D. Philippine Guidelines on Periodic Health Examination (PHEX): Effective Screening for Diseases among Apparently Healthy Filipinos. Manila: The Publications Program; 2004.
2. Duque F, Villaverde M, Morales R. Implementing Rules and Regulations of the Universal Health Care Act (Republic Act No. 11223). In: Health Do, editor.: PhilHealth.
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2. Objective, Scope, Target Population and Target users

2.1. Objectives

The main objective of this guideline is to provide update in current evidence on the efficacy, safety, cost efficiency, and utility of various vaccines.

2.2. Scope and Purpose

This clinical practice guideline is an update of the previous systematic synthesis and summary of evidence addressing immunization among adults. Recommendations were made on sixteen (16) vaccinations (cholera, *Haemophilus influenza* B (HIB), hepatitis A, herpes zoster, human papilloma virus (HPV), influenza, Japanese encephalitis, measles, meningococcal, influenza, monkey pox, pneumococcal, rabies, tetanus, typhoid, and varicella). Primary considerations were outcomes of vaccine efficacy, safety, and cost-effectiveness. The publication and dissemination of this guidelines will aid and help physicians and allied medical professionals both in private and more in the government or resource limited settings to prioritize effective preventive vaccination programs utilizing evidence-based decision making tailored fit to local and available clinical and epidemiologic evidence.

2.3. Target Population

The main target of this update includes apparently healthy adults and those with increased risks and vulnerable population to acquire these vaccine preventable diseases.

2.4. Intended Users

These recommendations may greatly benefit healthcare professionals particularly in the public health units, those in primary care practice, and administrative sector of the health programs implementation. This can be use by general physicians and specialists, as well.

3. CPG 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:

- Risk of bias
- Important inconsistency of results
- Some uncertainty about directness
- High probability of reporting bias
- Sparse data/Imprecision
- Publication bias

Additional factors that may increase quality are:

- All plausible residual confounding, if present, would reduce the observed effect
- Evidence of a dose-response gradient
- Large effect

3.3. Composition of the CPG Panel

The Steering Committee convened the Consensus Panel (CP) considering possible conflicts of interests of each panel member. To ensure fairness and transparency, the composition was guided by the DOH manual.[1] Content experts and other key stakeholders were invited to join the CP. The key stakeholders included policymakers, patient advocates, allied medical practitioners, and physicians from different settings (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 framework[3]

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

Three independent stakeholders were identified and the reviewed the draft guidelines on the content, clarity, acceptability, applicability and feasibility of the recommendations. The AGREE-REX checklist was used for the said review. Their feedback was taken into consideration by the steering committee prior to finalizing the CPG. Concerns arising from the external review, the steering committee resolves technical issues and content in the manuscript.

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).

3.8. Editorial Independence

This project received financial support from the DOH. The DOH neither imposed any condition nor exerted any influence on the operations and the final output formulation.

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4. Recommendation and Evidence Summaries

4.1. Should cholera vaccine be given to asymptomatic apparently healthy adults?

RECOMMENDATIONS

Among asymptomatic apparently healthy adults traveling to cholera-endemic areas, we <u>recommend giving</u> oral cholera vaccine.
(strong recommendation, moderate certainty evidence)

Among asymptomatic apparently healthy adults, we <u>suggest against giving</u> oral inactivated cholera vaccine.
(weak recommendation, moderate certainty evidence)

Among asymptomatic healthcare workers, we <u>suggest against giving</u> oral cholera vaccine due to insufficient evidence.
(weak recommendation, very low certainty evidence)

Considerations

The consensus panel considered the following points during the formulation of the above recommendations:

- Despite having moderate certainty of evidence suggesting that oral inactivated cholera vaccines result in net benefit, the panel formulated a weak recommendation against using it for mass vaccinations as these types of cholera vaccines do not appear to be more cost-effective compared to public health measures (e.g., promoting proper sanitation and providing potable water to the public and affected areas). Mass vaccination using oral inactivated cholera vaccines may be considered in outbreak situations.
- A separate recommendation for healthcare workers was formulated due to their increased risk of exposure to the disease—associated with working in laboratories or cholera-endemic areas. Due to the lack of direct evidence on its efficacy for this specific population, the panel issued a weak recommendation against oral cholera vaccines.
- Oral cholera vaccines were strongly recommended in cholera-endemic areas due to the moderate certainty of evidence showing their effectiveness in reducing cholera infections and safety profile. Inactivated vaccines were primarily considered over live attenuated cholera vaccines as the comparative effectiveness of the latter is still being investigated. For injected cholera vaccine types, no recommendation was made since they are no longer available in the Philippines.

Key Findings

- Evidence for this guideline question was obtained from at least 24 studies that compared cholera vaccines against placebo. No direct evidence was found specifically for healthcare workers. Benefits and risks were analyzed according to the type of cholera vaccine used (e.g., injected, inactivated oral, live oral). Certainty of evidence regarding benefits and risks was rated moderate to high.

- Injected cholera vaccines were more effective compared to placebo in reducing cholera cases and cholera deaths for up to 2 years. However, they were associated with significantly more mild adverse events (e.g., malaise, vomiting, unspecified local and systemic reactions).
- Oral inactivated cholera vaccines were more effective compared to placebo in reducing cholera infection up to 2 years and hospitalization rates up to 1 year after administration. They did not significantly reduce all-cause mortality or cholera deaths. Safety data have not demonstrated any clinically significant increase in adverse events compared to placebo in healthy adults as well as in pregnant women.
- Live, oral cholera vaccines were more effective compared to placebo in terms of eliciting immune responses after 10 days. One RCT showed no significant benefit in terms of reducing cholera cases and all-cause mortality. They significantly increased the risk of mild adverse events in younger adults. The certainty of evidence examined vaccine effect on clinical outcomes (e.g., reducing cholera cases, cholera deaths).

Introduction

Cholera, caused by the toxin-producing strains of the gram-negative bacterium *Vibrio cholerae*, causes an acute secretory diarrheal disease with profound fluid and electrolyte losses in the stool.[1] About 3 million cholera cases and 100,000 cholera deaths are estimated to occur annually in endemic countries.[2] The current global burden of cholera remains largely unknown, but actual prevalence estimates may be higher due to underreporting.[2] Particularly in South Asia, cholera remains a continuous threat leading to increased health and economic burden due to gaps in water, sanitation, hygiene, surveillance, and oral cholera vaccine use.[3] In resource-rich settings, cholera cases are generally seen or reported among travelers to cholera-endemic regions.[2]

In the Philippines, the DOH Epidemiology Bureau – Philippine Health Statistics recorded a total of 60 cases per 100,000 population in 2019, with most cases coming from MIMAROPA region.[4] However, the recent typhoons that struck various provinces this 2022 have led to a resurgence of cases. Since the start of the year, a total of 3,729 cases of cholera have already been documented, which is 282% higher compared to the data during the same period last year.[5,6] Of these cases, 33 people have already died from the disease, with Central Luzon, Western Visayas, and Eastern Visayas surpassing the epidemic threshold levels of cholera in their respective regions.[5] Resurgence of cholera has been linked to the torrential rains and flooding that caused the destruction of water pipes and contamination of drinking water.[5,6]

A local study published in 2015 documented the largest confirmed cholera outbreak in the Philippines in June 2012 where 3,390 possible cases and 19 deaths were reported in Virac, Catanduanes.[7] Of the 7 outbreak reports from 2008-2013, V. cholerae O1 El Tor Ogawa was identified in rectal swabs of all patients, with 5 of the 7 investigated outbreaks occurring in areas with breakdowns in water infrastructure.[7]

Results

Characteristics of Included Studies

Evidence for this guideline question was obtained from at least 24 studies that compared cholera vaccines against placebo. No direct evidence was found specifically for healthcare workers. Benefits and risks were analyzed according to the type of cholera vaccine used (e.g., injected, inactivated oral, live oral). Certainty of evidence regarding benefits and risks was rated moderate to high.

Table 1. Benefits and harms of cholera vaccines for healthy adults

Outcomes	No. of Studies (Participants)	Effect Estimate	Interpretation	Certainty of Evidence
Injected cholera vaccine				
All adults				
Cholera cases (7 months)	14 (2,027,740)	RR 0.45 [0.38, 0.53]	Favors cholera vaccine	High
Cholera cases (1 year)	11 (1,442,165)	RR 0.55 [0.44, 0.68]	Favors cholera vaccine	High
Cholera cases (2 years)	5 (699,268)	RR 0.58 [0.44, 0.75]	Favors cholera vaccine	High
Cholera cases (3 years)	1 (14,059)	RR 0.61 [0.22, 1.68]	Inconclusive	Moderate
All-cause mortality	2 (26,743)	OR 0.99 [0.72, 1.34]	No significant difference	High
Cholera deaths	4 (807,600)	OR 0.52 [0.26, 1.04]	Inconclusive	Moderate
All adverse events	6 (27,612)	RR 1.51 [1.22, 1.86]	Favors control	Moderate
Oral inactivated cholera vaccine				
All adults				
Cholera cases (6-12 months)	6 (517,328)	RR 0.54 [0.43, 0.69]	Favors cholera vaccine	Moderate
Cholera cases (2 years)	7 (433,997)	RR 0.36 [0.30, 0.44]	Favors cholera vaccine	Moderate
All-cause mortality	2 (246,242)	RR 0.83 [0.64, 1.08]	Inconclusive	Moderate
Cholera deaths	2 (220,534)	RR 0.73 [0.03, 16.4]	Inconclusive	Moderate
Hospitalization	2 (167,249)	RR 0.40 [0.28, 0.57]	No significant difference	Moderate
Adverse events	4 (26,965)	RR 1.13 [0.88, 1.44]	Favors cholera vaccine	Moderate
Pregnant women (pregnant at the time of vaccination)				
Adverse events	1 (465)	RR 0.97 [0.58, 1.61]	No significant difference	Moderate
Pregnant women (pregnant after vaccination)				
Adverse events	1 (576)	RR 1.02 [0.67, 1.55]	No significant difference	Moderate
Oral live attenuated cholera vaccine				
Cholera cases (4 years)	(1 (224,120)	RR 0.86 [0.57, 1.30]	Inconclusive	Moderate
Death	1 (67,508)	OR 1.03 [0.82, 1.29	Inconclusive	Moderate
Adverse events	4 (4,567)	RR 0.99 [0.75, 1.30]	No significant difference	Moderate
Immunogenicity	5	Greater antigen-specific memory B cell and anamnestic lipopolysaccharide specific responses; higher seroconversion rates after 10 days	Favors cholera vaccine	Moderate

CI confidence interval; OR odds ratio; RR risk ratio

Injected Cholera Vaccine

Assessed were 11 RCTs coming from a high-quality systematic review published in 2010 that evaluated the effectiveness of injected cholera vaccines (killed whole cell or purified antigen) compared to placebo.[11] Primary outcomes included incidence of cholera cases, all-cause mortality, cholera deaths, and a number of adverse events. Of the 16 total RCTs originally included in this review, 5 were excluded in the analysis, as they only included children. The trials were conducted between 1965-1978. Overall risk of bias for efficacy outcomes was rated low, while risk of bias for safety trials was rated high due to poor reporting of surveillance methods and frequency.

Efficacy outcome: Incidence of cholera cases (follow-up: 7 months and 1, 2, 3 years)
The injected cholera vaccine was significantly more effective than placebo in reducing cholera cases for at least up to 7 months after immunization (risk ratio [RR] 0.45, 95% CI 0.38 to 0.53, I^2=41%; N=2,027,740; 14 RCTs). Reduction in cholera infections were noted also up to 1 year (RR 0.55, 95% CI 0.44 to 0.68, I^2=56%; N=1,442,165; 11 RCTs) and 2 years (RR 0.58, 95%CI 0.44 to 0.75; N=699,268; 5 RCTs). However, the vaccine was not significantly efficacious at 3 years (RR 0.61, 95%CI 0.22 to 1.68; N=14,059; 1 RCT).

Efficacy outcome: Mortality (follow-up: 1 year)
Injected cholera vaccines reduced cholera deaths by about 50% after 1 year follow-up (OR 0.52, 95% CI 0.26 to 1.04, I^2=0%; N=807,600; 4 RCTs). However, it did not reduce all-cause mortality (OR 0.99, 95% CI 0.72 to 1.34; I^2=0%; N=26,743; 2 RCTs).

Safety outcome: Adverse effects
Overall, injected cholera vaccine was associated with significantly more non-severe/non-life-threatening adverse events compared to inert or active placebo (13.9% vs. 10.4%; RR 1.51, 95% CI 1.22 to 1.86, I^2=86%; N=27,612; 6 RCTs). Specifically, the vaccine caused more malaise (at 10.9%) compared to inert placebo (at 2.5%) (RR 4.36, 95% CI 1.79 to 10.6; N=998; 1 RCT). Compared to active placebo, it caused more vomiting (1.5% vs. 0.1%; RR 10.4, 95% CI 1.34 to 81.22; N=1,393; 1 RCT), unspecified systemic reactions (13.2% vs. 5.8%; RR 2.30, 95% CI 1.10 to 4.80; N=419; 1 study), and local reactions (40% vs. 11.5%; RR 3.48, 95% CI 2.14 to 5.63; N=419; 1 study).

Oral Inactivated Cholera Vaccine
There are currently 3 WHO pre-qualified oral vaccines available[8] – a monovalent, whole-cell plus recombinant vaccine (WC-rBS, available as Dukoral®) and two bivalent whole cell vaccines (BivWC, available as Shanchol™ or Euvichol®). Dukoral, administered with a buffer solution, is usually used for travelers, while Shanchol™ and Euvichol® are the vaccines currently available for mass vaccination. Both vaccines require at least 2 doses for full protection and can be given among children ages 1 year and older (Shanchol™ or Euvichol®) or 2 years and older (Dukoral®).[8]

Evidence for inactivated oral cholera vaccines (OCVs) were obtained from 8 RCTs. Of these, 6 RCTs17[9,10,12] appeared in two high-quality systematic reviews evaluating the efficacy of oral inactivated cholera vaccines.[13,14] Both systematic reviews document protection against cholera in the short-term period (at least 6 months) and an extended protection for at least two[13] to three years.[14] Updated search yielded 2 additional trials.[15,16] Overall, serious risk of bias was noted due to poor follow-up rates and the use of passive surveillance for measuring outcomes.

Efficacy outcome: Incidence of cholera cases (follow-up: 6-12 months, 2 years)
Based on pooled data from 6 RCTs[9,12,15,18,19,21] conducted between 1988 to 2015, two doses of inactivated oral cholera vaccines were more effective than placebo in reducing cholera cases within the first 6 months to 1 year (RR 0.54, 95% CI 0.43 to 0.69, I^2=39%; N=517,328; 6 RCTs). Trials that assessed vaccine effectiveness after 2 years have shown the vaccine to be more effective than placebo in reducing cholera cases (RR 0.36, 95% CI 0.30 to 0.44, I^2=21%; N=433,997; 7 RCTs).[10,12,16,17-19,21]

Efficacy outcome: Hospitalization rates (follow-up: 1 year)
Pooled data from two studies[9,19] showed that oral inactivated cholera vaccine was more effective than placebo in reducing hospitalization risk (RR 0.40, 95% CI 0.28 to 0.57, I^2=0%; N=167,249; 2 RCTs).

Efficacy outcome: Mortality (follow-up: 1 year)
No significant difference between inactivated oral cholera vaccine and placebo in terms of all-cause death in (RR 0.83, 95% CI 0.64 to 1.08, I^2=34%; N=246,242; 2 RCTs). Effects on reducing cholera-related deaths were likewise not statistically significant (RR 0.73, 95% CI 0.03 to 16.41, I^2 = 73%, N=220,534), but certainty of these effect estimates are very low due to inconsistency (I^2=73%) and imprecision (i.e., wide CIs).

Safety outcome: Adverse effects

Adverse effects for all individuals
Based on 4 RCTs,[9,10,22,23] no significant difference was found between the vaccine and placebo in terms of rates of adverse events after the first or second doses (0.77% vs. 0.69% for placebo; RR 1.13, 95% CI 0.88 to 1.44, I^2=0%; N=26,965; 4 RCTs). Rate of adverse events for either Dukoral® or Shanchol™ were not more than 0.2%, with the most commonly reported symptoms being abdominal pain, headache, fever, nausea, or stomach gurgling. All adverse effects were generally described as mild.[13]

Adverse effects for pregnant women
Data on the safety of bivalent whole cell vaccine (Shanchol™) were reported in a 2018 RCT.[23] Women of child-bearing age (13-49 years) enrolled in the large RCT in Bangladesh[21] were divided into two cohorts: pregnant women during vaccination (n=465) and pregnant women after vaccination (n=576).[23] Incidence of adverse pregnancy outcomes (i.e., miscarriage, stillbirth, preterm births, low birth weight, abortion risk) were compared in placebo and Shanchol™ recipients for both cohorts.

Results from this study suggest that a single dose of Shanchol™ was not associated with adverse pregnancy outcomes in women who were pregnant during vaccination (11.3% vs 11.5% for placebo; RR 0.97, 95% CI 0.58-1.61) and in those who were pregnant after vaccination (14.1% vs 13.0% for placebo; RR 1.02, 95% CI 0.67-1.55). Rates of miscarriage, stillbirths, abortion, and preterm delivery were not significantly different in placebo and cholera vaccine recipients.[23] Certainty of evidence for this outcome was downgraded to moderate due to imprecision.

Oral Live Cholera Vaccine
CVD 103-HgR is an oral, live, attenuated, single-dose oral vaccine for cholera infection. It is currently being considered for travelers to cholera-endemic areas due to reports of high vaccine efficacy (90%) within 10 days post ingestion of a single dose.[24] In this review, we found 5 studies evaluating the safety[25-27] and immunogenicity[25-29] of CVD 103-HgR.

Efficacy outcome: Incidence of cholera cases (follow-up: 1, 2, 3 years)
One RCT from Indonesia provided efficacy data for CVD 103-HgR vaccine.[27] Cholera cases were not significantly reduced in the group that were given the vaccine (RR 0.83, 95% CI 0.53 to 1.40; N=56,030; 1 RCT). The certainty of this effect may have been influenced by imprecision from low cholera rates in this study (65/56030 adults).

Efficacy outcome: All-cause mortality

The Indonesian RCT showed no significant difference between vaccine and control groups in terms of reduction of deaths (OR 1.03, 95% CI 0.82 to 1.29; N=67,508). Data on deaths for this trial included combined data for adults and children.

Efficacy outcome: Immunogenicity

Based on one study,[28] live OCVs induced antigen-specific memory B cell (MBC) responses. The anamnestic lipopolysaccharide specific responses may contribute to long-term protection and provide correlates of the duration of vaccine-induced protection. Two other immunogenicity studies showed that the vaccine elicited significant antibody responses in younger adults[29] as early as 10 days after vaccination, with seroconversion rates of 94% in the vaccine group versus 4% in the placebo group.[25,26] Although similar seroconversion rates were seen among older adults (90.4%), GMT levels after 10 days were 4 times lower than in younger adults, suggesting less robust immune response with increasing age. The Indonesian RCT also showed significantly greater seroconversion rates after 10 days in vaccine recipients (60% vs. 4% in placebo).[27]

Safety outcome

Pooled data from 3 RCTs showed that live OCVs did not elicit more adverse events than placebo (RR 0.99, 95% CI 0.75 to 1.30; I^2=85%; N=4,549; 3 RCTs). Different effect estimates were noted between age groups.

In younger adults (< 45 years old), more adverse events were noted in those who received the vaccine (RR 1.15, 95% CI 1.01 to 1.30; I^2=24%; N=4,154; 2 studies).[26,27] Most adverse events were mild and resolved within 1-3 days. One of the 2 RCTs found diarrhea (i.e., >=4 stools over a 24-hr period) to occur in 3.9% of vaccine recipients, compared to only 1.2% in placebo. One vaccine recipient infected with *E. coli* developed severe diarrhea which required treatment in an emergency room.

On the other hand, older adults (46-64 years old) exhibited lesser adverse events in the vaccine group compared to the placebo group (36.1% vs. 50.5%; RR 0.72, 95%CI 0.56 to 0.92; N=395; 1 study).[25] Most were mild and lasted only for 1 or 2 days. There were no differences in unsolicited adverse events and no study-related serious adverse events.

Recommendations from Other Groups

Based on the 2018 local guidelines of the Philippine Society for Microbiology and Infectious Diseases (PSMID), oral cholera vaccine is **not routinely** given to adults; however, it was strongly recommended as an adjunct to standard epidemic response protocol for cholera despite the low quality of evidence.[30]

International guidelines (ACIP, Australia and WHO) recommend routine cholera vaccines only to healthy adults traveling to an area with active cholera transmission.[31-33] These guidelines do not have specific recommendations regarding routine cholera vaccination among asymptomatic healthy individuals in the general population.

Table 2. Recommendations on cholera vaccination from other groups.

Group	AGREE II Appraisal	Recommendation for Immunocompetent Adults	Basis for Recommendation/s	
			Strength	Quality of Evidence
PSMID 2018[30]	56.3	Cholera vaccine is effective among adults up to three years after completion of vaccination.	Strong	Moderate
		Oral cholera vaccine may be given as an additional measure to standard epidemic response protocol for cholera.	Strong	Low
		Cholera vaccine is not routinely given.	Strong	Low
		Oral cholera vaccine may be given to patients who are pregnant, immunocompromised, or even those with HIV among pregnant women if there is high risk of exposure (i.e., outbreak, endemic, travel).	Weak	Low
US ACIP 2022[31]	79.1	ACIP recommends CVD 103-HgR (single-dose, live attenuated oral cholera vaccine derived from V. cholerae O1), the only cholera vaccine licensed for use in the United States, for prevention of cholera among travelers aged 2–64 years to an area with active cholera transmission.	Evidence Category A	
Australian immunization handbook 2020[32]	93.75	Routine cholera vaccination of travelers is not recommended. Cholera vaccination (2 doses, 1-6 weeks interval between doses) is recommended for travelers: ● Who have high risk of exposure to cholera (e.g., humanitarian aid workers) ● Who have a higher risk of acquiring diarrheal disease due to a medical condition (e.g., achlorhydria) ● Who have a higher risk of severe or complicated diarrheal disease—poorly or uncontrolled diabetes, inflammatory bowel disease, HIV or other immunocompromising conditions, significant cardiovascular disease If there is an ongoing risk of cholera, a single booster dose is recommended up to 2 years after finishing the primary course. If the interval between primary immunization and the booster dose is more than 2 years, repeat the primary course.	Basis for recommendations not included in the available handbook	
WHO Recommendations for Routine Immunization 2017[33]	79.1	In cholera-endemic countries, vaccination of the entire population (throughout a country regardless of risk) is usually not warranted. Vaccination policies and strategies should be guided by an assessment of the risk of cholera and targeted to cholera hotspots. Strategies targeting specific age groups at higher risk of disease may be considered.	Basis for recommendation not available	

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

Cost

A 2018 study summarized the evidence for all economic evaluation from inception up to December 2015.[27] Majority of the studies included were from third world countries. Among these, it was found that oral cholera vaccine was cost-effective compared to no intervention. However, it appears to be less cost-effective when compared to promoting good drinking water and sanitation.

Oral cholera vaccination was deemed cost-effective when targeted to high-risk populations including patients without access to clean and safe drinking water and healthcare facilities.[23,27,34] The most influential factors affecting cost-effectiveness of an oral cholera vaccination program would be: (1) local cholera incidence, (2) vaccine coverage, (3) herd protection, and (4) vaccine price. [27]

The oral cholera vaccine's herd protection effect is evident when implemented as a mass vaccination program. Both studies in Malawi and Bangladesh,[23,34] despite limited duration of protection, concluded that mass cholera vaccination can have a significant impact on reducing cholera incidence in the entire population. This included those not vaccinated as a result of herd effects. This implies that it can be a cost-effective means of controlling the disease, especially until more long-term measures, such as improved water and sanitation infrastructure, are put in place.[23,34]

Cholera vaccines are also available in the Philippines with Dukoral® and Shanchol™ approved for distribution locally.[35] Cholera vaccines are available at PHP 300-800 per dose; the government estimates a composite cost of PHP 1,300 per person per vaccination program including vaccination cost and ancillaries.[36] Meanwhile, a 2020 published study estimating the economic burden of cholera among Asian countries estimate around USD 20.2 million in out-of-pocket expenditures, USD 8.5 million in public sector costs, and USD 12.1 million in lost productivity in 2015.[37]

Patient Values and Preference, Equity, Acceptability, and Feasibility

In the Philippines, there are no published local data to date evaluating the Filipino's knowledge, attitudes, and perceptions on oral cholera vaccine although cholera affects a large proportion of the provinces in the country especially areas without access to proper sanitation and potable water.[7]

In Malawi, a 2014-2015 cholera outbreak evaluated the feasibility and acceptability of conducting a mass oral cholera vaccine (OCV) program on top of other public health measures. The program was deemed feasible and acceptable with a 91.9% turnover from the target population especially during outbreaks.[38] In another qualitative study in Zambia, including adults without cholera vaccines, there were perceived differences with the acceptability and feasibility of the OCV programs. While all patients agree that cholera vaccination programs are efficacious, some of the identified barriers to OCV programs are perceived susceptibility, observable outcomes of vaccination, and circulating community narratives.[39] The same findings were congruent with another qualitative study among low socio-economic group of people in urban Dhaka, Bangladesh.[40] In both studies,[39,40] the knowledge, attitude, and practices on cholera and cholera vaccine were associated with perceived susceptibility to cholera with both studies recommending strengthening health education activities to improve knowledge and attitude towards vaccination.[39,40]

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4.2. Should *Haemophilus influenzae* B (HiB) vaccine be given to asymptomatic apparently healthy adults, asplenic patients, healthcare workers, and pregnant women?

RECOMMENDATIONS

Among asymptomatic apparently healthy adults, we <u>recommend against giving</u> *Haemophilus influenzae b* vaccine.
(strong recommendation, low certainty evidence)

Among asymptomatic healthcare workers, we <u>recommend against giving</u> HiB vaccine due to insufficient evidence.
(strong recommendation, very low certainty evidence)

Among adults with anatomical and functional asplenia, we <u>suggest giving</u> HiB vaccine.
(weak recommendation, low certainty evidence)

Among pregnant women, we <u>suggest against giving</u> HiB vaccine.
(weak recommendation, low certainty evidence)

Considerations

The consensus panel considered the following points during the formulation of the above recommendations:

- Despite evidence suggesting possible increase in immune responses from vaccination, mass HiB vaccination was not recommended due to the already high protection levels (i.e., antibodies for HiB) among unvaccinated individuals and the uncertainty in the data related to local seroprevalence of the disease in adults. A similar recommendation against HiB vaccination was issued for healthcare workers. There is no conclusive data justifying that this subpopulation is considered a high-risk group for contracting HiB infection.
- Despite the low certainty of evidence showing its effectiveness, the panel voted to suggest giving the HiB vaccine to adults with either anatomical or functional asplenia due to their higher risk of experiencing HiB-related disease complications.
- For pregnant women, the present recommendations by the panel contrast with existing local guidelines from PSMID. Additional cohort studies beyond those considered in the PSMID Guideline were considered in this CPG. Low certainty of evidence suggests that HiB vaccination may not be beneficial for this subpopulation.

Key Findings

- Three RCTs investigated the effect of Hib vaccination on healthy, asymptomatic adults, Likewise, 3 RCTs investigated vaccine effect on pregnant women. 2 quasi-experimental studies focused on asplenic patients. No study was found specifically investigating the effects of Hib vaccination on healthcare workers.
- Hib vaccination significantly increased total serum antibody concentration (anti-PRP) in healthy adults. After 1 month, 98% of vaccinated subjects reached antibody levels >1 µg/mL. After 12 months, 93% of vaccinated subjects continued to show antibody levels >1

μg/mL. Similarly, serum IgG1, serum IgG2, serum IgM, and serum IgA were significantly higher 1 month after vaccination.

- In asplenic patients and pregnant women, vaccination produced antibody levels that were significantly higher than pre-vaccination levels; however, the magnitude of this change varied depending on when antibody measurements were taken. Furthermore, a higher proportion of healthy adults and infants born to vaccinated mothers reached protective antibody levels.
- No serious adverse events were reported in all subgroups. Only mild adverse events were observed, of which pain at the injection site was the most common.
- For healthy adults, there was moderate certainty of evidence supporting the vaccine's efficacy (downgraded for serious indirectness in outcome) and low certainty of evidence for its safety. For asplenic patients, certainty of evidence for immunogenicity was very low (very serious risk of bias, imprecision, and serious indirectness). For pregnant women, certainty of evidence regarding benefits and harms of the Hib vaccine was low (serious risk of bias related to allocation concealment and blinding, serious indirectness in outcome).

Introduction

Haemophilus influenzae serotype b (Hib) is a non-motile, non-spore forming gram-negative coccobacilli commonly found in the nose and throat. It can invade the body and cause meningitis, epiglottitis, pneumonia, and septic arthritis. It exists in encapsulated/typeable (classified as a to f) and non-encapsulated/non-typeable forms. Encapsulated *Haemophilus influenzae* are more likely to cause invasive infections. Before the introduction of its vaccine, Hib was known to cause 95% of all invasive diseases commonly encountered in infants and children.[1]

The capsular polysaccharide of *Haemophilus influenzae* type b is polyribosyl ribitol phosphate (PRP), an important virulence factor enabling development of invasive disease.[2] Current vaccines against Hib are polysaccharide conjugated vaccines, which stimulate development of bactericidal antibodies against the PRP capsule (anti-PRP antibodies).[3] Conjugated vaccines generate more robust and longer lasting immune responses than vaccines made purely of PRP.

Newborns are protected by maternal antibodies. Children aged 3 months to 5 years lack bactericidal activity mediated by type b capsule-specific antibodies in their blood, making them uniquely susceptible to Hib meningitis.[4] Generally, healthy unvaccinated adults are well protected against invasive Hib disease; invasive Hib disease is extremely rare in healthy adults.[5] In 97% of healthy unvaccinated adults, circulating IgG antibodies against Hib capsular polysaccharide were above protective level for invasive Hib disease, which was defined as 0.15 μg/ml based on one study.[2] The same study showed that 56% of healthy unvaccinated adults have functionally active serum antibodies.[2] Another landmark study showed that 81% of healthy adults had antibody levels of ≥1 μg/ml, a correlate of protection in the vaccinated adult population.[6] These pioneering studies demonstrated that antibody levels greater than 0.15 and 1.0 μg/ml are the minimum protective and the long-term protective antibody concentrations.[7]

Haemophilus influenzae disease was estimated to have an annual incidence of 1.70 cases per 100,000 people based on data from the United States from 2009 to 2015.[8] New cases were recorded mostly among adults aged ≥65 years (6.30 per 100,000) and children aged <1 year (8.45 per 100,000). Higher risk for the disease was associated with increasing age: 3.48 per 100,000 adults aged 65-69 years; 4.65 among persons aged 70-74 years; 6.48 among persons aged 75-79 years; 8.56 among persons aged 80-84 years; and 13.56 among persons aged ≥85

years.[8] Hib accounts only for 0.8% of strains in patients aged ≥65 years. Most strains were non-typeable (79.3%) or non-b serotypes (19.9%).[8] Furthermore, most of the patients (74%) have at least one underlying condition. Commonly cited comorbidities were chronic obstructive pulmonary disease, atherosclerotic cardiovascular disease, diabetes, and chronic heart failure.[8]

Data from Europe showed similar characteristics. Based on data from 2007-2014, the mean annual notification rate was 0.6 cases/100,000 population.[9] Patients <1 month of age were the most affected, with notification rate of 23.4 cases/100,000 population. Non-typeable H. influenzae (NTHi) was also the leading strain, accounting for 78% of all cases. Hib vaccination appears to be successful since the reduction of cases was greatest among young children. Now, majority of Hib cases in Europe occur in older adults (>60) with comorbidities.[9] The mean annual notification rates for majority of adults (age groups 20-29 and 40-59) were the lowest, with 0.2 case per 100,000.[9]

Data on the epidemiology of Hib in Asian adults are lacking. Studies on Asians have focused on children less than 5 years old. One population-based study published in 2000 done in the Philippines showed that the annual incidence of Hib meningitis in central Manila was 95 per 100,000 children, with high case fatality rate (11%) and high rate of sequelae (15%).[10] According to a review done in 2009, this was the highest incidence recorded among Asian countries.[11] Data from a study in a rural area (Bohol) also showed that Hib is the most common cause of bacterial meningitis in children aged less than 5 years.[12] This was further corroborated by a review of hospital-based studies done in 2000 showing that Hib is a major cause of bacterial meningitis and/or pneumonia in children from the Philippines, India, Thailand, Malaysia, Indonesia, and Vietnam. Singapore and Hong Kong, in contrast, had lower incidence of Hib infection compared with their counterparts.[13]

Results

Characteristics of Included Studies

Studies on healthy adults

Of the 6 total RCTs originally included in this review, 3 were excluded in our analysis as they included children. Evidence for the effects of Hib vaccination on healthy adults was taken from three RCTs.[14-16] Two of these trials were performed in the United States (Granoff 1984[14]; Lottenbach 2004[16]), while the remaining trial was done in Cuba (Toraño 2006[15]). The two US studies[14,16] involved young adults (20-35 years) while the Cuban study[15] focused on older adults (64-92 years).

All 3 RCTs did not have a placebo-control group. These studies compared different types of Hib vaccines (e.g., PRP vs. PRP-conjugate, Quimi-Hib vs. Vaxem-Hib). Primary outcomes included immunogenicity outcomes (e.g., pre-vaccine and post-vaccine total concentrations of Hib anticapsular antibody or anti-PRP, IgG concentrations, proportion of subjects attaining >4-fold increase in antibody titers), local adverse events, and systemic adverse events. Since no study compared Hib with placebo, values for the unvaccinated individuals were derived instead from the recorded proportions or antibody concentrations pre-vaccination.

Studies on special populations

Studies on healthcare workers
No study about the vaccination of healthcare workers against Hib was found. Currently, there is no specific recommendation by any health organization for the Hib vaccination of healthcare workers since working in a healthcare setting is not considered a risk for Hib infection.[17,18]

Studies on patients with functional or anatomical asplenia
No RCT or quasi-RCT comparing the effects of Hib conjugate vaccines versus placebo in people with sickle cell disease (SCD) was found in a moderate-quality 2018 Cochrane systematic review by Allali et al.[19] Evidence for this review was therefore obtained from 2 non-randomized clinical trials (Li Volti 1999[20], Molrine 1999[21]).

Studies on pregnant women
A moderate-quality systematic review[22] published by Cochrane in 2015 synthesized the available evidence on the effectiveness and safety of Hib conjugate vaccines compared with no vaccine among pregnant patients. Only 1 quasi-RCT conducted in the United States (Glezen 1992) was found eligible.[23] In this trial, 217 pregnant women were given either capsular polysaccharide vaccine or placebo/saline during prenatal visit at 34-36 gestational weeks. Two RCTs of unclear risk of bias were found after an updated search.[24,25]

Outcomes

Table 1. Benefits and harms of *Haemophilus influenzae* B vaccination in healthy adults, asplenic patients, and pregnant women

Outcomes	No. of Studies (Participants)	Effect Estimate [95% CI]	Interpretation	Certainty of Evidence
Subgroup 1: Healthy adults				
Total change in serum anti-PRP antibody levels (1 month)	2 RCTs (310)	Mean difference [MD] 15.69 µg/mL higher (13.2 lower to 44.58 higher)	Inconclusive	Low
Total change in serum anti-PRP antibody levels (2 months)	1 RCT (60)	MD 1.52 µg/mL higher (1.31 higher to 1.74 higher)	Benefit	Moderate
Total change in serum anti-PRP antibody levels (12 months)	2 RCTs (310)	MD 4.95 µg/mL higher (2.66 lower to 12.56 higher)	Inconclusive	Low
Seroconversion rate* (1 month)	1 RCT (248)	RR 2.51 [2.01 to 3.13]	Benefit	Moderate
Seroconversion rate* (12 months)	1 RCT (243)	RR 2.38 [1.90 to 2.97]	Benefit	Moderate
Adverse reactions	2 RCTs (205)	No serious adverse events for vaccine group. Injection site pain – 32.7%; fever – 15%; normal hematological, hepatic, renal parameters	Harm	Low
Subgroup 2: Asplenic patients				
Total change in serum anti-PRP antibody levels (1 month) – asplenic patients before and after vaccination	1 observational (102)	MD 21.21 µg/mL higher (82.36 lower to 124.78 higher)	Inconclusive	Very Low
Difference in anti-PRP antibody levels (1 month)	1 observational (51)	MD 16.3 µg/mL lower	Inconclusive	Very Low

– vaccinated asplenic patients vs. vaccinated healthy adults		(225.06 lower to 192.46 higher)		
Adverse reactions	1 observational (102)	No immediate adverse reactions were observed. All adverse events were mild, resolved spontaneously, and nonserious†	Harm	Low
Subgroup 3: Pregnant Patients				
Total change in serum anti-PRP antibody levels	1 RCT (197)	MD 8.53 µg/mL higher (5.55 higher to 11.51 higher)	Benefit	Low
Adverse reactions	3 RCTs (342)	No serious adverse events reported[16] Only injection site pain in 15% of subjects 1-2 days after vaccination[17,18]	Harm	Low
Adverse pregnancy outcomes				
Preterm delivery	1 RCT (213)	RR 1.28 [0.12 to 13.86]	Equivalent	Low
Fetal distress	1 RCT (213)	RR 1.23 [0.67 to 2.26]	Equivalent	Low
Intubation	1 RCT (213)	RR 1.03 [0.55 to 1.95]	Equivalent	Low
Neonatal jaundice	1 RCT (213)	RR 1.01 [0.52 to 1.97]	Equivalent	Low

CI confidence interval; MD mean difference; PRP polyribosyl ribitol phosphate; RCT randomized controlled trial; RR risk ratio
**total serum anti-PRP ≥ 1.0 µg/mL*
†actual estimates were not reported in the study

Subgroup 1: Healthy adults

Efficacy

Immunogenicity: seroconversion rate (1 month)
More vaccinated respondents reached a total serum anti-PRP Ab greater than 1.0 µg/ml after 1 month (98.4% vs. 39.2%; RR 2.51; 95% CI 2.01 to 3.13) and 12 months (93.2% vs. 39.2%; RR 2.38; 95%CI 1.90 to 2.97).[16]

Increase in total serum antibody levels (1 and 2 months)
Based on two studies, participants who received Hib polysaccharide vaccines exhibited an increase in their total serum anti-PRP Ab levels at 1 month (MD 15.69 µg/mL; 95% CI -13.20 to 44.58 µg/mL) and 12 months (MD 4.95 µg/mL; 95% CI -2.66 to 12.56 µg/mL).[1,3] One study reported significantly higher total serum anti-PRP Ab (µg/mL) after 2 months post-vaccination in young adults given PRP-D conjugate vaccine (MD 1.52 µg/mL; 95% CI 1.31 to 1.74).[14]

Increase in total serum IgG anti-PRP antibodies (1 month)
No significant difference in total serum IgG antibodies against Hib 1 month post-vaccination was observed (MD 33.29 µg/mL; 95% CI -58.49 to 125.07 µg/mL).[14,15] However, when analyzed individually, there is significantly higher concentration of serum IgG1 (MD 1.30 µg/mL; 95% CI 0.44 to 2.16 µg/mL) and serum IgG2 (MD 3.74 µg/mL; 95% CI 2.30 to 5.18 µg/mL) in vaccinated individuals 1 month after vaccination.[16] There is also significantly higher concentration of serum IgM (MD 3.68 µg/mL; 95% CI 2.83 to 4.53 µg/mL) and serum IgA (MD 5.15 µg/mL; 95% CI 3.8 to 6.5 µg/mL) in vaccinated individuals 1 month after vaccination.[15]

Safety
Two studies reported no serious adverse event for any of those vaccinated. Pain at the injection site was the most reported reaction, occurring in 32.7% of the respondents.[14,15] One study

reported mild fever (37-37.9°C) in 15% of the total respondents and one case of fever above 38°C and slight headache.[15] This study also reported normal values for hematological, hepatic, and renal parameters for all vaccinated respondents.[15]

Certainty of evidence on benefits and harms
Overall certainty of evidence for efficacy was moderate due to serious indirectness in the comparisons for the included trials. Risk of bias for efficacy outcomes was rated low. Certainty of evidence for harm was rated low due to high risk of bias associated with poor reporting of surveillance methods and frequency as well as serious indirectness.

Subgroup 2: Patients with anatomical or functional asplenia

Efficacy
Mean Day 28 post-vaccination concentration of anti-PRP was higher than pre-vaccination levels in splenectomized patients, though with low certainty (MD 21.21 µg/mL; 95% CI -82.36 to 124.78).[21] In addition, the mean Day 28 post-vaccination concentration of anti-Hib did not significantly differ between splenectomized and non-splenectomized patients; the immune response of both groups reached protective levels (MD: -16.30; 95% CI -225.06 to 192.46).[21]

Several experimental studies show that splenectomized adults have lower immune response to Hib vaccination compared to healthy adults, indicated by significantly lower relative sizes (%) of lymphocyte subpopulations and IgM responses.[19,20] However, vaccination is still advised since asplenic patients still develop positive immune response after vaccination, supporting the recommendation for vaccination before splenectomy.

Safety
In the study by Li Volti 1999, Hib vaccine was reportedly well-tolerated and no immediate adverse reactions were observed. All adverse events were mild, resolved spontaneously, and non-serious; however, actual estimates were not reported in the study.[20]

Certainty of evidence on benefits and harms
Overall certainty of evidence for efficacy was very low due to very serious risk of bias, imprecision, and serious indirectness in the comparisons for the included trials. Risk of bias for efficacy outcomes was rated high due to the lack of randomization, allocation concealment, and blinding.

Subgroup 3: Pregnant patients

Efficacy

Increase in antibody levels
Vaccinated mothers have significantly higher total anti-PRP antibody concentrations than unvaccinated mothers (9.44 vs. 0.91 µg/mL; MD 8.53 µg/mL, 95% CI 5.55 to 11.51 µg/mL).[25] Furthermore, infants born to mothers who were given the Hib vaccine had significantly higher geometric mean antibody concentration compared to those who were given placebo (2.73 vs. 0.33 µg/mL; MD 2.40 µg/mL, 95% CI 1.08 to 3.72 µg/mL).[22] This finding is supported by other quasi-experimental studies which showed that maternal Hib vaccination yielded significantly higher levels of infant anti-PRP antibodies compared to unvaccinated mothers (MD 1.63 µg/mL; 95% CI 0.83 to 2.43 µg/mL).

Seroconversion rates
More infants in the vaccine group exhibited antibody concentrations ≥ 5 µg (40% vs. 5%; RR 8.00, 95% CI 1.95 to 32.78).[23] In terms of mean cord anti-PRP levels, a higher proportion of infants exhibited anti-PRP levels ≥ 1.0 µg/mL among vaccine recipients (RR 7.36, 95% CI 3.48 to 15.60).[24,25]

Reduction in Hib disease incidence
The possibility of reduction of risk to Hib disease in infants with maternal immunization was raised, but this actual clinical outcome has not yet been assessed.

Safety

Mild adverse events
No reactions were reported in the Glezen 1992 trial.[23] Pain at the injection site was the most common complaint 1-2 days after vaccination.[24,25] One study reported swelling at the injection site in 15% of the respondents; this occurred a day following vaccination.[25] None of the mothers in both studies reported fever.

Serious adverse events
No serious adverse events were likewise seen in mothers (anaphylaxis and premature labor).[24,25] In terms of adverse pregnancy outcomes, Hib-vaccinated mothers did not differ significantly than those given placebo for rates of preterm delivery (RR 1.28, 95% CI 0.12 to 13.86), fetal distress (RR 1.23, 95% CI 0.67 to 2.26), intubation (RR 1.03, 95% CI 0.55 to 1.95), and neonatal jaundice (RR 1.01, 95% CI 0.52 to 1.97).[22]

Certainty of evidence on benefits and harms
Certainty of evidence on the efficacy and safety of Hib vaccination on pregnant women was rated low due to study design limitations in the included trials. Overall, the studies were appraised to have unclear risk of bias because allocation concealment and blinding were not mentioned in the study. Furthermore, data on efficacy could not be extracted from 1 study because the range or confidence intervals were not reported.[24]

Recommendations from Other Groups

Table 2 summarizes existing recommendations from various groups. The WHO does not have a specific recommendation regarding Hib vaccination in adults. The US Advisory Committee on Immunization Practices (ACIP), Immunization Action Coalition, and the Philippine Society for Microbiology and Infectious Diseases (PSMID) recommended Hib vaccination for adults who are asplenic or scheduled for splenectomy. ACIP also issued recommendations for other at-risk groups (e.g., HIV-infection adults, recipients of hematopoietic stem cell transplant).

Table 2. Recommendations from international and local CPGs

Group	Recommendations
World Health Organization (WHO, 2018)[26]	No direct statement on adult vaccination. Hib vaccine is not required for healthy children after 5 years of age.

US Advisory Committee on Immunization Practices (ACIP, 2022)[27]	Recommends Hib vaccination for adults at increased risk for invasive Hib disease: • Patients aged ≥15 months undergoing elective splenectomy: If unimmunized, give 1 dose prior to procedure. • Asplenic patients aged >59 months and adults: If unimmunized, give 1 dose. • HIV-infected adults: Hib vaccination is not recommended. • Recipients of hematopoietic stem cell transplant, all ages: give 3 doses (at least 4 weeks apart) beginning 6-12 months after transplant, regardless of Hib vaccination history.
Philippine Society for Microbiology and Infectious Diseases (PSMID, 2018)[28]	Hib vaccine is not routinely given to immunocompetent adults because of high titers of Hib antibody. *(Strong recommendation, very low quality of evidence)* Hib vaccine may be given to adults who are asplenic or scheduled for splenectomy. *(Weak recommendation, very low quality of evidence)* Hib vaccine is safe to be given among non-pregnant immunocompetent individuals. *(Strong recommendation, low quality of evidence)* Hib vaccine is not recommended for pregnant women. *(Strong recommendation, very low quality of evidence)*

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

Cost

Costs of Hib vaccination

Hib vaccines are available in combination with other vaccines, with Sanofi Pasteur-manufactured vaccines available locally. Pentaxim (DtacP-IPV-Hib) is priced at PHP 2,200/dose while Hexaxim (DTacp-IPV-HepBHib) is priced at PHP 2,300/dose.[29]

Cost-effectiveness of Hib vaccination

It is unknown whether Hib vaccination in adults would be cost-effective. Currently, all existing studies evaluating the cost-effectiveness of Hib vaccination concern only pediatric populations. A cost-benefit analysis in 2001 predicted that a 3-dose immunization schedule of Hib vaccination for Filipino children would prevent 553 cases and 61 deaths per year in a birth cohort of 100,000, saving around PHP 39 million for the government and PHP 255 million for the society.[30] A 2013 cost-effectiveness study forecasted that Hib vaccination for children in lower middle-income countries would prevent 3,003 cases and 405 deaths per year in a birth cohort of 1 million, translating to about USD 3.34 million (PHP 183 million) in savings for the society.[31]

Pneumonia incidence was identified to contribute most to the damage of Hib to the government; meningitis incidence was analyzed to be most impactful to society. The benefit of Hib vaccination appears to be consistent across geographic regions and income levels, as reflected in a 2017 systematic review. Eighty-five percent of the studies analyzed (23/27) showed cost-effectiveness of Hib vaccination for children.[32]

Patient Values and Preference, Equity, Acceptability, and Feasibility

In the Philippines, there are no published local data to date evaluating the knowledge, attitudes, and perceptions of Filipinos on Hib vaccine.

Patients with anatomic or functional asplenia are prioritized for Hib vaccination since the spleen is necessary for protection against encapsulated bacteria, of which *Haemophilus influenzae* is

part of. The absence of spleen makes the patients more susceptible to infections caused by these bacteria. However, current data on the epidemiology of *Haemophilus influenzae* infection among these subgroups of patients are lacking.[33] In terms of vaccination coverage in splenectomized patients, one systematic review found low anti-Hib vaccination coverage at 48.3% (95% CI 34.3 to 52.3%).[34] Suboptimal coverage was attributed to the lack of adherence to international guidelines by healthcare workers. Training of health professionals in the management of post-splenectomy was suggested.[34]

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4.3. Should hepatitis A vaccine be given to asymptomatic apparently healthy adults?

RECOMMENDATION

Among apparently healthy adults, we <u>suggest giving</u> Hepatitis A vaccination using a 2-dose series (0, 6 months).
(weak recommendation, low certainty evidence)

Considerations

The consensus panel considered the following points during the formulation of the above recommendation:

- Despite the available evidence showing that Hepatitis A vaccination in all healthy adults results in net benefit, a weak recommendation was made due to uncertainty in local endemicity status of the Philippines for Hepatitis A among adults. The panel pointed out that estimating the actual disease burden in adults is challenging—factoring in the potential impact of the existing routine Hepatitis A vaccination for children.
- The vaccine appeared to be cost-effective for countries with high endemicity for Hepatitis A; however, local health economic evaluations still need to be completed. Additionally, the panel mentioned the uncertainty related to which seroconversion levels are associated with actual protection from the disease.

Key Findings

- The hepatitis A virus (HAV) is transmitted via direct human-to-human contact or through the consumption of food and water contaminated with fecal particles. It is considered a major cause of acute viral hepatitis which can eventually lead to acute liver failure and death. Globally, there are approximately 1.4 million cases of hepatitis, with 27,731 deaths in 2010. Prior to the advent of the hepatitis A vaccine in the United States, tens of thousands were being infected, peaking at 59,606 cases in 1971. After the first licensed vaccine, the annual number of cases in the United States dropped by 92% (1995-2010), with several outbreaks occurring due to person-to-person and food-related incidents occurring within the last 5 years.[1-4]
- Based on the Department of Health 2019 data, 1,047 cases of viral hepatitis were recorded (1 per 100,000 Filipinos).[5] Mindanao (CARAGA - 6.2%, SOCCSKSARGEN - 4.7%, Zamboanga Peninsula - 5%) had the highest proportion of documented cases. Mortality rate associated with viral hepatitis ranged from 0.8 to 1.0 per 100,000 population, with at least 1,061 deaths.[5] Southeast Asian serosurveys conducted in the 1980s revealed that half of adolescents and more than 90% of 40-year-olds had anti-HAV in Malaysia and the Philippines. There was little evidence of changes in seroprevalence in the said countries, as well as Indonesia and Vietnam.[5]
- The prevalence of Hepatitis A outbreaks centers around low-endemic regions with poor immunization rates or few previous infections.[1-4] Individuals at the highest risk for contracting the disease include: persons using illegal injection drugs, those who travel to places endemic for hepatitis A, incarcerated populations, men who have sex with men, persons with occupational risk of infection, and persons at high risk for developing

complications from a hepatitis A infection (patients with chronic liver disease or infected with HIV).[4,6]

- Young children who contract the infection are usually asymptomatic. Older children and adults commonly present with symptoms. The most commonly seen symptoms are malaise, fatigue, anorexia, vomiting, abdominal discomfort, diarrhea, and jaundice, which is clinically indistinguishable from acute hepatitis of another viral origin. The estimated case fatality ratio varies with age from 0.1% in <15 years-old children, to 0.3% among persons aged 15-39 years-old, to 2.1% among older adults (≥40 years-old).[4,7]

Results

Characteristics of Included Studies[8-14]

Evidence evaluating hepatitis A vaccination was obtained from 1 systematic review (indirectly) and 6 randomized controlled trials (directly) addressing the research question. Characteristics of included studies can be found in Table 1.

Table 1. Benefits and harms of pre-exposure hepatitis A vaccine for healthy adults

Outcomes	No. of Studies (participants)	Effect Estimate [95% CI]	Interpretation	Certainty of Evidence
Subgroup 1: Healthy adults				
1-3 doses vs. placebo				
Incidence of hepatitis A	9 (732,380)	RR 0.09 [0.05 to 0.17]	Benefit	Low
Lack of sero-protection	2 (739)	RR 0.01 [0.00 to 0.03]	Benefit	Low
All-cause mortality	1 (38,157)	RR 0.14 [0.62 to 3.16]	Inconclusive	Low
Local adverse events	3 (1,559)	RR 1.21 [0.86 to 1.70]	Inconclusive	Low
Systemic adverse events	3 (1,559)	RR 0.98 [0.68 to 1.41]	Inconclusive	Low
2-dose vs. 3-doses				
Incidence of hepatitis A	1 (55)	RR 1.00 [0.93 to 1.07]	Equivalent	Low
Local adverse events				
Pain	1 (55)	1.18 [0.79 to 1.76]	Inconclusive	Low
Swelling	1 (55)	0.22 [0.01 to 4.43]	Inconclusive	Low
Soreness	1 (55)	0.84 [0.21 to 3.39]	Inconclusive	Low
Rash	1 (55)	0.37 [0.04 to 3.36]	Inconclusive	Low
Redness	1 (55)	0.37 [0.04 to 3.36]	Inconclusive	Low
Systemic adverse events				
Headache	1 (55)	1.12 [0.25 to 5.05]	Inconclusive	Low
Fever	1 (55)	1.12 [0.07 to 16.95]	Inconclusive	Low
Fatigue	1 (55)	1.12 [0.17 to 7.36]	Inconclusive	Low
Dizziness	1 (55)	1.12 [0.07 to 16.95]	Inconclusive	Low
Nausea/vomiting	1 (55)	3.33 [0.14 to 78.42]	Inconclusive	Low
Diarrhea	1 (55)	3.33 [0.14 to 78.42]	Inconclusive	Low
Subgroup 2: Healthy adults with exposure to index cases				
Incidence of hepatitis A	1 (146)	RR 0.21 [0.05 to 0.93]	Benefit	Very Low
Serious adverse events	1 (146)	Could not be estimated	Inconclusive	Very Low
Subgroup 3: Patients living with HIV				
Seroconversion rate	3 (412)	49% to 93.9% after 1 month of 2nd dose[10, 12] 82.6% for 3 doses vs 69.4% 2 doses[11]	Benefit	Low
Minor adverse events	2 (310)	RR 1.89 [0.39, 9.12]	Inconclusive	Low
Serious adverse events	2 (310)	Could not be estimated	Inconclusive	Moderate
Subgroup 4: Persons experiencing homelessness				
Seroconversion rate	1 (100)	56/57 (98.2%)	Favors vaccine	Very Low
Compliance	1 (100)	73/100 (73%)	Favors vaccine	Very Low

CI confidence interval; HIV human immunodeficiency virus; RR risk ratio

Outcomes

Healthy Adults: Vaccine vs. Placebo/No Vaccine[8]

Comparison 1: Vaccine vs. placebo/no vaccine

A 2012 high quality (based on AMSTAR 2) Cochrane systematic review assessed the benefits and harms of pre-exposure hepatitis A vaccines in adults and children (N=825,937). This review included 11 RCTs (4 English, 7 Chinese) comparing the effect of any type of inactivated or live attenuated hepatitis A vaccine with placebo or no intervention for the following outcomes: all-cause mortality, mortality from hepatitis A, incidence of hepatitis A, lack of sero-protection (anti-HAV antibody titer < 20 mIU/L), and adverse events. Ten out of the 11 studies recruited only healthy children. Overall risk of bias across included studies was serious, with at least 50% of studies showing high risk of bias for allocation concealment, blinding, and other biases (e.g., cluster RCTs, performing analysis that is different from original allocation of participation).

Efficacy

Mortality

All-cause mortality was not significantly reduced in those who received hepatitis A vaccines compared to control (0.07% vs. 0.05%) based on 1 trial (Innis 1994; RR 0.14, 95% CI 0.62 to 3.16) that involved children. No outcomes reported on hepatitis A-related mortality.

Incidence of hepatitis A

Nine RCTs (Werzberger 1992, Innis 1994, Mayorga Perez 2003, Jiang 1995, Jiang 2001, Li 2000, Meng 2000, Riedermann 1992, Yuan 1995) have demonstrated significant benefit in reducing hepatitis A cases (RR 0.09, 95% CI 0.05 to 0.17; N=732,380; 9 RCTs). Subgroup analyses showed benefit across different vaccine types, regions of endemicity, dose regimens, and follow-up durations (up to 5 years). However, certainty of evidence regarding benefit is rated low for this outcome due to indirectness (8 of 9 studies included only children) and risk of bias issues.

Seroprotection

Low certainty of evidence from 2 RCTs showed that inactivated hepatitis A vaccines had a significant effect on conferring sero-protective anti-HAV IgG (RR 0.01, 95% CI 0.00 to 0.03; N=739; 2 RCTs).

Safety

Compared to placebo, inactivated hepatitis A vaccines did not significantly increase the risk of non-serious local adverse events (RR 1.21, 95% CI 0.86 to 1.70; N=1,559) as well as non-serious systemic adverse events (RR 0.98, 95% CI 0.68 to 1.41; N=1,559) based on low certainty of evidence from 3 RCTs. No evidence was found investigating adverse events specifically for live attenuated hepatitis A vaccines.

Comparison 2: Two-dose vs. three-dose series

One RCT compared the immunogenicity and safety of a 2-dose series versus a 3-dose series of Hepatitis A vaccine among 55 healthy young (20-26 years old) adult volunteers.[10] Group 1 (n=26) was given 2 doses of Hepatitis A vaccine at 0 and 24 weeks, while Group 2 (n=29) was given 3 doses at 0, 2, and 24 weeks. Outcomes measured were seroconversion (at 2, 4, 24, 28 and 52 weeks) and adverse effects.

Efficacy
Seroconversion rates for both groups reached 100% at the 28th and 52nd week.

Safety
Only mild adverse events, mostly local, were noted for both groups within 3 days of vaccination. These included pain at injection site, fatigue, dizziness, nausea, fever, headache, rashes, and the like. Differences in the rates of adverse events between groups were non-significant.[10]

Healthy Adults with Exposure to Index Cases
Very low certainty of evidence from 1 unblinded RCT in Italy assessed the effect of vaccination on reducing the incidence of secondary hepatitis A infections in 146 healthy household contacts of people with sporadic HAV infection (index cases).[9] All age groups were included, with 60% (88) being at least 15 years of age. No patient with a positive IgM anti-HAV or who was symptomatic was included; only susceptible patients were followed up and their results analyzed. Only one dose of intramuscular hepatitis A vaccine (Havrix) was given. The presence of hepatitis A infection was measured by taking serum samples at enrolment, at 14 days, and 45 days after vaccination. Risk of bias for this RCT was high due to issues with allocation concealment, blinding of participants, and incomplete outcome reporting.

Efficacy

Incidence of hepatitis A
At the end of follow up, 10/75 (13.3%) in the unvaccinated group, and 2/71 (2.8%) in the vaccinated group developed secondary hepatitis A infection (RR 0.21, 95% CI 0.05 to 0.93). Subgroup analysis by age showed that only 1 patient more than 18 years of age developed hepatitis A infection in the unvaccinated group, and none in the vaccinated group.[9]

Safety
No serious adverse events were noted for both groups. However, certainty of evidence for this outcome was very low and affected by the low sample size. The study did not report data on mild adverse events.[9]

Patients Living with HIV
Three randomized controlled trials provided evidence on the safety and efficacy of hepatitis A vaccine in adult patients living with HIV.[11-13] Heterogeneity in groups, comparison, and outcomes precluded pooling of results. All three studies were double-blind, randomized controlled trials and included adult patients living with HIV with various CD4+ count levels.

Comparison 1: 2-dose series vs. placebo

Efficacy
An RCT in the United States by Kemper et al. in 2003 evaluated the effects of 2-doses of hepatitis A vaccine (Havrix 1440; 0 and 6 months) compared to placebo on seroconversion rates, anti-HAV titers, CD4 cell counts, plasma HIV RNA loads, and adverse events up to 9 months.[10] Patients were stratified by CD4 cell counts: <200, 200-499, and ≥500 cells/mm^3. Overall frequency of seroconversion was 49% at 7 months and 52% at 9 months. Seroconversion rate was affected by CD4+ count—lower seroconversion rates were observed for patients with <200 CD4+ counts (9.1% or 1/11 subjects) compared to those with 200-499 (68.8%; 11/16) and ≥500 CD4+ counts (66.7%; 8/12).[11]

A 2004 RCT by Wallace et al. assessed the effect of 2 injections of VAQTA compared to placebo among 90 patients living with HIV and 90 healthy control subjects.[13] Outcomes were HAV titers at weeks 0 through 52, mean change in CD4 cell counts, mean change in HIV RNA loads, and adverse reactions within 14 days after vaccination. HIV patients were further stratified by CD4 cell count (<300 cells/mm^3, ≥300 cells/mm^3). However, no data was available for HIV-infected subjects given the placebo. 93.9% of patients (46/49) living with HIV had protective antibodies 1 month after completing the 2-dose series (0, 6 months) of hepatitis A vaccine (Havrix) while all healthy controls (72/72) developed antibodies.

Safety
Based on the 2 RCTs, HAV vaccines were found to be safe (RR 1.89, 95% CI 0.39 to 9.12; I^2=95%). No vaccine-related serious adverse events were reported. Kemper et al.[11] found that the proportion of minor injection site soreness was significantly higher in the Havrix vaccine group compared to the placebo group (36.6% vs. 9.3%; RR 3.95, 95% CI 2.09 to 7.49; N=220). In contrast, Wallace et al.[13] noted similar proportion of minor adverse events in the VAQTA vaccine group and placebo (57% vs. 60%; RR 0.94, 95% CI 0.65 to 1.36; N=90). Adverse events were non-serious; no significant difference was observed between groups in terms of frequency of infections and HIV-related events after vaccination.[11,13]

Comparison 2: 3-dose vs. 2-dose series

Efficacy
The 2008 HEPAVAC trial conducted by Launay and colleagues in France compared the immunological efficacy and safety of 3-dose hepatitis A vaccine series (Havrix 1440; at 0, 1, 6 months) compared to 2 dose-series (0, 6 months) among 95 patients with HIV.[12] Outcomes were assessed after 28 weeks. For efficacy, seroconversion rates at 28 weeks did not significantly differ between 3-dose (82.6%) and 2-dose (69.4%) groups (*P*=0.13), although 3-dose group exhibited higher GMTs through weeks 24, 28, and 72.

Safety
In terms of safety, both doses were tolerated and did not result in significant changes in CD4+ and plasma HIV-1 RNA levels.

Persons Experiencing Homelessness

Efficacy
One prospective cohort study evaluated the efficacy of hepatitis A vaccine among homeless people (N=100, age 18-72 years) in Australia.[13] Outcomes included compliance to vaccination schedule and seroconversion. Participants were given a 2-dose series (0, 6-12 months) of hepatitis A vaccine (Havrix) in a medical clinic for homeless and disadvantaged persons.

Safety
Seventy-three patients (73%) completed the schedule within 18 months of their 1st dose (median interval between doses=193 days. Of the 57 previously non-immune patients, 56 (98.2%) had detectable antibodies on follow-up (median follow-up=193 days [IQR 182-238]). Adverse events were not reported; however, three documented withdrawals were noted: 1 developed a medical condition, 1 died due to causes unrelated to the study, 1 patient was withdrawn from the study as a precautionary measure after an event post-vaccination.[14]

Certainty of evidence on the benefits and risks of hepatitis A vaccination in this subgroup of patients was downgraded to very low due to risk of bias issues (i.e., high attrition, non-blinding) and indirectness.

Recommendations from Other Groups

Generally, routine Hepatitis A vaccination is recommended by most infectious medical societies and international guidelines both for healthy and at risk individuals. The table below details the recommendations of each organizing body.

Table 2. Recommendations from international and local CPGs

Guidelines	Recommendation for Vaccination	Grade of Recommendation
Prevention of Hepatitis A Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP, 2020)[29]	Recommends HepA vaccination for HIV-infected persons ≥1 year old.	Effectiveness of the intervention (Grade B) Safety of the Intervention (Grade B)
	Recommends routine HepA vaccination; catch-up at any age for unvaccinated children and adolescents aged 2-18 years.	Effectiveness of the intervention (Grade B) Safety of the intervention (Grade B)
	Recommends the vaccination of pregnant women who are at risk for HAV infection during pregnancy or having a severe outcome from HAV infection.	Not mentioned
	Recommends vaccination of persons with chronic liver disease: ● Persons with hepatitis B virus (HBV) infection ● Hepatitis C virus (HCV) infection ● Cirrhosis ● Fatty liver disease ● Alcoholic liver disease ● Autoimmune hepatitis ● Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level persistently greater than twice the upper limit of normal	Not mentioned
	Recommends vaccination in settings providing services to adults in which a high proportion of persons have risk factors for HAV infection.	Not mentioned
Recommendations of the Advisory Committee on Immunization Practices for Use of Hepatitis A Vaccine for Persons Experiencing Homelessness (ACIP, 2018)[30]	Recommends routine (2- or 3- dose) bivalent (HepA and HepB) immunization for homeless people aged 1 year above.	Reduction in disease burden (Grade C) Serious adverse events (Grade C) Evidence to recommendation framework was applied, which declared that the desirable consequences clearly outweigh undesirable consequences in most settings.
World Health Organization: WHO Position Paper on Hepatitis A Vaccines (WHO, 2022)[31]	Recommends the following: ● For ≥ 12 months old: HAV vaccine be introduced into national immunization schedules.	

	• For ≥ 18 months old: Live attenuated vaccines administered as a single subcutaneous dose. • For > 40 years: Vaccination with inactivated vaccines using 2-dose schedules.	
Philippine Society for Microbiology and Infectious Diseases (PSMID, 2018)	Hepatitis A vaccination can prevent hepatitis A infection in immunocompetent individuals.	Strong recommendation, moderate quality of evidence (9 RCTs from 1 SR)

HAV hepatitis A virus; HIV human immunodeficiency virus; RCT randomized controlled trial; SR systematic review

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

Cost

Cost of vaccination

Table 3. Cost estimates for Hepatitis A vaccine in the Philippines

Treatment/Intervention	Cost
Hepatitis A Vaccine (Adult) (Havrix JR, GSK)[a]	• 1 pax – PHP 3,599 • 2-5 pax – PHP 3,399/pax • 6-10 pax – PHP 3,099/pax
Hepatitis A & B Vaccine (Twinrix, GSK)[a]	• 1 pax – PHP 3,699 • 2-5 pax – PHP 3,499/pax • 6-10 pax – PHP 3,199/pax
Hepatitis A (Adult)[b] (Vaqta, Havrix)	Approximately PHP 2,100/10 pack – 1 dose syringe
Hepatitis A & B (Twinrix)[b]	Approximately PHP 3,700/10 pack – 1 dose syringe
Personnel/Service Fee[a]	• NCR – PHP 1,399 • Cavite, Rizal, and Bulacan – PHP 1,799 • Laguna – PHP 1,999 • Batangas – PHP 2,999

[a]Pricing obtained from Juan Medical (https://juanmedical.ph/service/hepatitis-a-b/) (0960-291-7278; 0969-168-1957)
[b]Pricing obtained from CDC Vaccine price list (https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html) converted to PHP from USD based on Dec 2022 exchange rates

Cost-effectiveness

No local cost-effectiveness studies were found. Most of the available economic studies on hepatitis A vaccination found it to be generally cost-effective compared to passive immunization.[14-19] However, the cost effectiveness of hepatitis A vaccination for the general population is complex and highly influenced by vaccine price as well as regional endemicity the disease.[15-20]

A 2008 systematic review of 31 cost-effectiveness studies showed an ICER of <$ 20,000 (~PHP 1.1 million) per QALY or life-year gained for universal vaccination.[19] More favorable ICERs were produced for vaccination in children and high-incidence areas. For targeted vaccination, cost effectiveness was highly dependent on the risk of infection.[20]

One cost-utility analysis of hepatitis A vaccination among healthcare workers in Israel estimated that the cost of preventing a hepatitis A case was lowest for screening prior vaccination among 18- to 39-year-old healthcare workers (USD 6,240) and highest for mass vaccination of nurses ≥39 years (USD 61,858).[17] Both interventions were associated with high cost per quality-adjusted life-year (QALY) gained. Thus, selective vaccination of healthcare workers was proposed and

mass vaccination was recommended only once the cost of hepatitis A vaccine was reduced to at least USD 23 (~PHP 1,200).[17]

Single-dose vaccination may be considered in middle-income countries given their relatively limited financial resources.[21] One cost-effectiveness study in Indonesia compared one- versus two-dose vaccines in children.[15] Both options were found to be cost-effective from a societal perspective, with one-dose vaccination being the most cost-effective option over two-dose vaccination.[15]

Estimates of cost-effectiveness varied depending on the endemic status of the countries where studies are conducted. High-endemic areas tend to have a higher incidence of HAV infection among children, which subsequently leads to high levels of population immunity. On the other hand, countries with low or very low endemicity typically benefit more from the vaccination of high-risk populations. Countries with transitional endemicity tend to have more localized outbreaks.[6,7]

Patient Values and Preference, Equity, Acceptability, and Feasibility

No direct evidence or qualitative studies were available regarding the acceptability as well as patient values and preferences towards hepatitis A vaccination in the Philippines.

One study done in Sydney, Australia by Poulos[14] explored the general acceptability, completion rates, and immunogenicity of the standard vaccination schedule for hepatitis A and B vaccines among 201 persons subject to homelessness. Most of the patients (73%) completed their hepatitis A vaccines, with 98% showing serological response after 18 months of follow up.[14] To achieve good compliance rates among high-risk groups, the study recommended including vaccination as part of routine care, counseling, and having an accessible clinic to patients. Another study among homeless individuals in the US also highlighted the need for improving access to public showers and establishing higher levels of trust between patients and healthcare providers.[22]

Timely vaccination for HAV to prevent secondary cases was found to be feasible based on one cohort study in Italy.[19] Of the 495 household contacts who participated, 65% were vaccinated within 4 days of the index case's hospitalization and 95% within 7 days.[23]

Several studies from various countries have emphasized the importance of improving awareness of vaccination guidelines among both healthcare professionals and target vaccine recipients to ensure the success of universal vaccination for hepatitis A.[24-27] One study that combined a systematic literature review with interview of policymakers identified major gaps in hepatitis A vaccine programs such as: limited economic and seroprevalence data, poor communication of the risks of hepatitis A and benefits of vaccination, and lack of political will, among others.[28]

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4.4. Should herpes zoster vaccine be recommended to apparently healthy adults?

RECOMMENDATION

Among apparently healthy elderly aged ≥60 years old, we <u>suggest</u> herpes zoster vaccine.
(weak recommendation, moderate certainty evidence)

Considerations

The consensus panel considered the following when formulating this recommendation:

- Herpes zoster is often underreported and not detected early in the country; thus, the true burden of herpes zoster locally remains unknown.
- Two herpes zoster vaccine preparations are available in the global market: (1) live attenuated vaccine (ZVL) and (2) recombinant vaccine (RZV). Evidence showed higher vaccine efficacy rates with RZV. However, only ZVL is currently available locally.
- Herpes zoster vaccines pose financial accessibility issues, with a market price of PHP 6,000 to 7,500 per shot or PHP 4,500 when procured in bulk. ZVL, the available preparation locally, requires one dose delivered subcutaneously.
- Evidence on the cost-effectiveness of herpes zoster vaccine included studies conducted abroad—posing applicability issues.

Introduction

Burden of the Disease

As primary varicella infection resolves, the virus establishes latency in the dorsal root ganglia and may reactivate to cause herpes zoster or shingles. While the primary infection manifests as a generalized rash, herpes zoster presents as vesicular rash confined to a single dermatomal distribution and is preceded by neuropathic pain for around three days.[1] It frequently involves the trigeminal, cranial, and cervical nerves; lumbosacral involvement is less common. Age, health, and immune status are factors that affect the presentation and course of herpes zoster.

About 3% of patients with zoster are hospitalized. Few studies provide data on zoster mortality, with only ~0.25 per million population in the US and Europe.[2] One epidemiologic cohort study in the USA involving immunocompetent adults 50 years and older estimated the incidence rate of herpes zoster at 9.92 (95% CI 9.82, 10.01) per 1,000 person-years.[3] The incidence rate increases with age, from 7.2 per 1,000 person-years in the 50- to 54-year-old group to 13.99 per 1,000 person-years in the 80 years old and above group. Herpes zoster-related hospitalizations occurred in 0.86% of study subjects (70/8,160), translating to 8.49 per 100,000 person-years (95% CI 6.72, 10.73). Case fatality was observed to be extremely low at 0.04% (18/40,893). Ten of these fatalities (55%) were individuals aged 80 years and above. The computed mortality rate in this cohort was 0.23 per 100,000 person-years (95% CI 0.14, 0.37). In the same study, the Kaplan-Meier curves were not statistically significantly different by age group using the log-rank test (P=0.12). The ten-year cumulative incidence rate for recurrence is shown in Table 1.

Table 1. Ten-year cumulative incidence for recurrence of herpes zoster per age group

Age (in Years)	Cumulative Incidence of Herpes Zoster	95% CI
50-59	11.11%	9.6-12.84
60-69	10.37%	8.87-12.11
70-79	9.23%	7.62-11.15
≥80	8.96%	5.79-13.74

CI confidence interval

In a review of data from Asia-Pacific countries including the Philippines, herpes zoster incidence is comparable to the Western population—3 to 10 per 1,000 person-years that increases above 40 and peaks around 70 to 80 years old with female preponderance.[4,5] As cited in Chen 2010,[4] the mean age of 221 herpes zoster patients in the Philippines is 43 years old, with 1.8% having hypertension, 8.1% having pulmonary disease, and 2.7% having cardiovascular disease.[6] Herpes zoster recurrence rate was between 2.3% to 8% with higher rates among women, immunocompromised individuals, individuals aged 50 to 70 years old, and those with postherpetic neuralgia. In the last cohort, 2.3% had postherpetic neuralgia for at least three months, 5% had ocular involvement, and 6.3% had secondary skin infections.[4,6]

Postherpetic neuralgia is considered to be the most debilitating sequelae of herpes zoster as it impairs quality of life. This complication increases with age and is estimated to occur in 18% among those older than 50 years and 33% among those older than 80 years of age.[7] Its diagnosis in the Philippines remains clinical. Management options include antivirals and analgesics; either local or systemic treatments may be used.[8]

No studies looked at herpes zoster incidence, hospitalization, and healthcare costs in the Philippines. Herpes zoster rate was 6.24 per 2,000 person-years in Taiwan in 2009[9] and 7.65 per 100,000 population in Thailand (Bureau of Epidemiology data) in 2014.[4] In Taiwan, the estimated healthcare cost related to herpes zoster treatment was USD 9.8 million in 2004.[10]

There is no epidemiologic data specific to healthcare workers.

Results

Characteristics of Included Studies

Data on the benefits and harms of herpes zoster vaccine were mainly based on a high-quality Cochrane meta-analysis published in 2019.[11]

Benefits and Harms of Herpes Zoster Vaccine

Two herpes zoster vaccine preparations are available in the global market. Zostavax (ZVL) is a live attenuated vaccine and is given subcutaneously as a single dose in the deltoid region. Shingrix (RZV) is a recombinant vaccine and is given intramuscularly in the deltoid region as two doses, two to six months apart. As of 2021, only ZVL is available in the country. These two vaccines have not been directly compared with each other. However, network meta-analyses show that RZV was superior to ZVL in reducing the incidence of herpes zoster and postherpetic neuralgia in patients over 60 years of age.[12,13]

The summary of all critical outcomes of herpes zoster vaccination among healthy adults is shown in Table 2.

Table 2. Benefits and harms of herpes zoster vaccine per subgroup of healthy adults[14-22]

Outcomes	No. of Studies (No. of Participants)	Effect Estimate (95% CI)	Interpretation	Certainty of Evidence
ZVL vs. Placebo				
Incidence of herpes zoster (3 year follow-up)	1 (38,546)	RR 0.49 (95% CI 0.43, 0.56)	Favors ZVL	Moderate
Incidence of postherpetic neuralgia	1 (38,501)	60-69 years old: VE 65.7% (95% CI 20.4%, 86.7%) ≥70 years old: VE 66.8% (95% CI 43.3%, 81.3%)	Favors ZVL	Moderate
Herpes-zoster related hospitalization	1 (6,616)	RR 0.81 (95% CI 0.25, 2.67)	Inconclusive	Moderate
Herpes-zoster related mortality	5 (50,820)	RR 1.01 (95% CI 0.92, 1.11)	Not significant	Moderate
Serious adverse events	4 (50,766)	RR 0.99 (95% CI 0.24, 4.15)	Inconclusive	Moderate
Local adverse events	4 (7,040)	Redness: RR 4.30 (95% CI 2.66, 6.94) Pain: RR 6.47 (95% CI 2.67, 15.7) Swelling: RR 5.84 (95% CI 4.95, 6.89) Warmth: RR 4.73 (95% CI 2.57, 8.74) Rash: RR 3.26 (95% CI 1.31, 8.11)	Favors placebo	Moderate
Systemic adverse events	5 (6,856)	Pruritus: RR 1.61 (95% CI 0.12, 22.4) Malaise: RR 1.00 (95% CI 0.07, 15.2) Headache: RR 1.00 (95% CI 0.15, 6.75)	Inconclusive	Moderate
RZV vs. Placebo				
Incidence of herpes zoster (3.2 year ff up)	2 (22,022)	RR 0.08 (95% CI 0.03, 0.23)	Favors RZV	Moderate
Incidence of postherpetic neuralgia (≥70 years old)	1 (22,131)	VE 88.8% (95% CI 68.7, 97.1%)	Favors RZV	Moderate
Herpes-zoster related hospitalization (≥70 years old)	1 (13,163)	VE 100% (95% CI -9.9, 100)	Not significant	Low
Herpes-zoster related mortality	2 (29,311)	RR 0.94 (95% CI 0.84, 1.04)	Not significant	Moderate
Serious adverse events	2 (29,311)	RR 0.97 (95% CI 0.91, 1.03)	Not significant	Moderate
Local adverse events	2 (9,769)	Redness: RR 28.9 (95% CI 22.6, 37.0) Pain: RR 7.14 (95% CI 6.58, 7.74) Swelling: RR 28.3 (95% CI 15.9, 50.2)	Favors placebo	Moderate
Systemic adverse events	2 (9,762)	Myalgia: RR 3.82 (95% CI 3.52, 4.16) Fatigue: RR 2.51 (95% CI 1.99, 3.17) Headache: RR 2.44 (95% CI 2.26, 2.63) Fever: RR 6.45 (95% CI 4.61, 9.04) Shivering: RR 4.35	Favors placebo	Moderate

		(95% CI 3.26, 5.81)		

CI confidence interval; RR risk ratio; RZV Shingrix; ZVL Zostavax

Incidence of herpes zoster (n=60,568; moderate certainty of evidence)
The incidence of herpes zoster was measured either by laboratory confirmation or by clinical diagnosis by a physician. The Oxman study[14] (n=38,546) showed that ZVL significantly reduced herpes zoster incidence after 3.1 years follow-up (relative risk [RR] 0.49; 95% confidence interval [CI] 0.43, 0.56). Two RCTs (n=22,022) that evaluated RZV after a 3.2-year follow-up period also showed significantly large reductions in herpes zoster incidence (RR 0.08; 95% CI 0.03, 0.23).[15,16]

Incidence of postherpetic neuralgia (n=60,632; moderate certainty of evidence)
A phase III clinical trial[14] (n=38,501) with a follow-up of 3.1 years showed that the vaccine efficacy (VE) of ZVL for postherpetic neuralgia was 65.7% (95% CI 20.4, 86.7) in persons aged 60-69 years, and 66.8% (95% CI 43.3, 81.3) in those ≥70 years old.

A phase III RCT by Cunningham[16] with 22,131 subjects showed that RZV reduced postherpetic neuralgia in adults aged 70 years old and above (VE 88.8%; 95% CI 68.7, 97.1), and in adults aged 50 years and above (VE 91.2%; 95% CI 75.9, 97.7).

Herpes zoster-related hospitalization (n=20,229; low to moderate certainty of evidence)
In one study, no significant difference was seen between the ZVL vaccine group and placebo in terms of herpes zoster-related hospitalizations (RR 0.81; 95% CI 0.25, 2.67; n=6,616).[14]

A pooled analysis[17] of 13,163 subjects comparing RZV vaccinees and placebo recipients showed no herpes zoster-related hospitalizations in the ZOE 50 study[15] in both arms. In the ZOE 70 study,[16] five placebo recipients and none in the vaccine arm had herpes zoster-related hospitalizations. Since there were no cases in the >50 years cohort, only the >70 cohort was analyzed. The VE was computed at 100% (95% CI -9.1, 100) with a wide confidence interval due to very few events of hospitalized cases.

Herpes zoster-related mortality (n=78,736; moderate certainty of evidence)
Moderate certainty evidence from five studies showed that there was no significant difference between ZVL and placebo groups in terms of herpes zoster-related mortality (RR 1.01; 95% CI 0.92, 1.11; n=50,820).[14,18-21]

For RZV (n=27,916), there were no events in both RZV and placebo groups, thus, labelled as zero-event studies.[17]

Serious adverse events (n=80,077; low/moderate/high certainty of evidence)
Serious adverse events include vaccine-related events that resulted to death, hospitalization, disability, extension of current hospitalization, or birth defects.

Evidence on ZVL came from four studies (n=50,766).[14,19-21] No difference between the two groups was found in terms of serious adverse events (RR 1.01; 95% CI 0.92, 1.11). Similarly, two RCTs (n=29,311) found that RZV did not cause significantly more serious adverse events compared to placebo (RR 0.97; 95% CI 0.91, 1.03).[15,16]

Local adverse events (n=16,787; moderate certainty of evidence)
Four clinical trials (n=7,040) studied the safety profile of ZVL.[14,18,19,22] However, variable events were measured in each trial such that the denominator would change depending on the number of trials that measured a particular event outcome. There was higher incidence of injection site

events in the vaccinated group compared to placebo (RR 3.73; 95% CI 1.93, 7.21). Documented local adverse events for ZVL include erythema (RR 4.30; 95% CI 2.66, 6.94) and pain (RR 6.47; 95% CI 2.67, 15.68). Three trials (n=6,879) had swelling and warmth as event outcomes.[14,18,22] Risk ratios were 5.84 (95% CI 4.95, 6.89) for swelling and 4.73 (95% CI 2.57, 8.74) for warmth. Only one study (n=6,616) had rash as outcome (RR 3.26; 95% CI 1.31, 8.11).[14]

This observation was mirrored in the RZV studies[15,16] which showed higher risk for any local reactions in the vaccine group (RR 6.89; 95% CI 6.37, 7.45; n=9,769). These include redness (RR 28.93; 95% CI 22.62, 37), pain (RR 7.14; 95% CI 6.58, 7.74), and swelling (RR 28.26; 95% CI 15.91, 50.20).

Systemic adverse events (n=16,881; moderate certainty of evidence)
Systemic adverse events were likewise higher in the vaccine groups compared to the placebo groups. For ZVL, a total of five trials (n=7,119) documented systemic adverse events, albeit with variable events measured.[14,18,19,21,22] Three trials (n=6,856) measured vaccine-related systemic events in general (RR 1.3; 95% CI 1.07, 1.58).[14,19,21] Two studies[18,22] measured systemic pruritus (RR 1.61; 95% CI 0.12, 22.42; n=263), one trial[18] measured general malaise (RR 1; 95%CI 0.07, 15.18; n=54), and another trial[21] measured headache (RR 1; 95% CI 0.15, 6.75; n=78).

For RZV, two trials (n=9,762) documented systemic adverse events including myalgia (RR 3.82; 95% CI 3.52, 4.16), fatigue (RR 2.51; 95% CI 1.99, 3.17), headache (RR 2.44; 95% CI 2.26, 2.63), fever (RR 6.45; 95% CI 4.61, 9.04), and shivering (RR 4.35; 95% CI 3.26, 5.81). Any systemic adverse events had a pooled risk ratio of 2.23 (95% CI 2.12, 2.34).

Recommendations from Other Groups

The Australian Technical Advisory Group on Immunisation (ATAGI) recommends shingles vaccination for immunocompetent elderly aged 60 years and above.[23] However, vaccination from age 50 years can be considered if they are at higher risk of disease.

Meanwhile, both the ATAGI[23] and the Advisory Committee on Immunization Practices (ACIP) of the US CDC[24] recommend that RZV should be used preferentially for immunocompetent adults aged 50 years old and above irrespective of prior receipt of ZVL, which is also the recommendation of the Philippine Society for Microbiology and Infectious Diseases (PSMID). ZVL remains a recommended vaccine for prevention of herpes zoster in immunocompetent adults aged 60 years and above (per ACIP) and in those 50 years and above (per ATAGI) if RZV is not available or affordable. In Australia, ZVL is funded under their National Immunization Program for people aged 70 to 79 years old. In the US, shingles vaccine is available under Medicare if the individual is enrolled in a standalone Part D drug plan or an extended Medicare plan that includes Part D coverage.

PSMID 2018 CPG on Adult Immunization[25] recommendations are for use at the individual level. The CPG recommendations were not analyzed at the population level. They recommend the use of ZVL in immunocompetent adults aged 60 years old and above without prior history of herpes zoster to prevent the disease, and for the same with prior history of herpes zoster infection to prevent the recurrence of the disease, albeit with different strengths of recommendations and qualities of evidence. The former has a stronger recommendation and a higher quality of evidence than the latter. Furthermore, PSMID recommends the use of RZV in immunocompetent adults aged 50 and above without prior history of herpes zoster to prevent the disease (strong recommendation, high quality of evidence).

In the 2014 WHO position statement[26] on varicella and herpes zoster vaccine, WHO stated that they were unable to offer any recommendation concerning the use of herpes zoster vaccine at that time due to the unknown burden of herpes zoster in most countries and insufficient use of that relatively new vaccine. Their advice was for those countries deciding to proceed with a herpes zoster vaccination program. The optimal age and dosing schedule should consider the age-dependent burden of disease, vaccine effectiveness, duration of protection, and cost-effectiveness. In their September 2020 update, there remains no recommendation on herpes zoster vaccine as part of routine immunization.[27]

All the aforementioned groups did not include zoster vaccine in their recommended vaccines for healthcare workers.[25,28-30]

Table 3 shows a summary of the recommendations on herpes zoster vaccination from other groups.

Table 3. Recommendations from other groups

Group	Recommendation	Strength of Recommendation and Certainty of Evidence
ACIP US CDC (January 2018)[31]	Shingrix (RZV) for use in immunocompetent adults aged ≥50 years, irrespective of prior receipt of varicella vaccine or Zostavax.	High certainty of evidence
	Zostavax (ZVL) remains a recommended vaccine for prevention of herpes zoster in immunocompetent adults aged ≥60 years.	
	Not part of the recommended vaccines for healthcare workers.	
Australian Technical Advisory Group on Immunisation (ATAGI) (2018, updated September 2021)[32]	Recommends vaccination for immunocompetent people from age 60 years. Vaccination from age 50 years can be considered.	High certainty of evidence
	Shingrix is preferred over Zostavax from age 50 and above for prevention of herpes zoster and its complications, due to its higher efficacy—given 2 doses with an interval of 2-6 months.	
	Single dose Zostavax is an effective alternative vaccine for adults aged ≥50 years who wish to reduce their risk of herpes zoster.	
	Not part of the recommended vaccines for healthcare workers.	
PSMID Immunization Handbook (2018)[33]	Shingrix for adults ≥50 years, for the prevention of herpes zoster and related complications, irrespective of prior receipt of varicella vaccine or ZVL.	Strong recommendation; high quality of evidence
	Zostavax for immunocompetent adults ≥60 years without prior history of herpes zoster to prevent the disease.	Strong recommendation; moderate quality of evidence
	Zostavax for immunocompetent adults >60 years old with prior history of herpes zoster infection to prevent the recurrent of disease.	Weak recommendation; low quality of evidence
	No mention of recommendation for healthcare workers.	-
WHO recommendations for routine immunization (September 2020)[36]	Herpes zoster vaccine is not part of the recommended routine immunization for any group (elderly, ages 50-60, and healthcare workers).	-

ACIP Advisory Committee on Immunization Practices; CDC Center for Disease Control; PSMID Philippine Society of Microbiology and Infectious Diseases; RZV Shingrix; WHO – World Health Organization; ZVL Zostavax

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

Cost

In the Philippines, ZVL costs approximately PHP 4,000 to 5,000. RZV is not available locally. No cost-effectiveness analysis has been done on herpes zoster vaccine in the Philippines and in developing countries.

A systematic review of 27 studies in high-income countries was published in 2018.[31] Fifteen out of 25 (60%) studies concluded that ZVL was cost-effective compared with no vaccine at a vaccine price ranging from USD 93 to USD 236 (2018 values). In the single RZV study[32] included in that review, RZV was found to be more effective and less costly when compared to ZVL, and cost-effective when compared to no vaccination. The included cost-effectiveness studies utilized various models and analytical perspectives. Factors included in the assumption of direct and indirect costs also varied as only seven studies accounted for vaccine adverse reactions in the medical costs.

Upon stratification by funding sources, studies in the systematic review that were industry-sponsored concluded that ZVL was cost-effective regardless of age of vaccination (six of them were conducted before study results regarding duration of protection were released in 2014). On the other hand, three out of 13 studies with other sources of funding (government, non-profit organizations or no funding) favored ZVL only in individuals aged ≥65 years old. The authors further noted that there were widely different incremental cost-effectiveness ratios (ICERs) across the studies due to the varied assumptions used.

A cost-effectiveness study done in Japan showed that vaccination against herpes zoster with RZV would be cost-effective compared with no vaccination for the Japanese population aged ≥65 years. This study was funded by GSK.[33] Another study was done in Canada whose model predicted that RZV is likely cost-effective in Canada for adults 60 years.[34]

Patient Values and Preference, Equity, Acceptability, and Feasibility

No local studies have examined patient values and preferences, equity, acceptability and feasibility for herpes zoster vaccine. Current herpes zoster vaccination coverage in the US is suboptimal at around 30%, which is lower than the 65% coverage achieved with pneumonia and influenza immunization of older adults.[35] This has been partially attributed to a financial barrier because out-of-pocket cost is incurred for herpes zoster vaccine via copayments.[36,37]

In Australia, after 17 months of implementation of zoster vaccine inclusion in the National Immunisation Program, uptake was only 34% in 70-year-old and 26% in 71- to 79-year-old age groups. The study mentioned that underreporting could be one of the reasons because the doses distributed was almost twice the number in the Immunisation Register.[38]

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4.5. Should high-dose influenza vaccine be given over standard dose Influenza vaccine among older adults?

High-dose inactivated influenza vaccine is not available locally, precluding the panel from making a recommendation on its use.

CONSIDERATIONS

High-dose inactivated influenza vaccine is not available locally, precluding the panel from making a recommendation on its use. The panelists recognized that high-dose may be suggested over standard dose inactivated influenza vaccine for the elderly population, whenever available. The burden of disease should be considered among other factors when choosing the appropriate dose for vaccination.

Key Findings

Administration of high-dose influenza vaccine in the elderly significantly reduced laboratory-confirmed influenza, all-cause hospitalization, and serious adverse events compared to standard dose influenza vaccine. There was no significant difference in all-cause mortality and systemic reactogenic events, but there was significantly increased local reactogenic events with high-dose influenza vaccine.

Introduction

Burden of the Disease

In the Philippines, adults 60 years and older comprise the majority (67.1%) of deaths from influenza. The same age group has the highest excess mortality rate from influenza at 44.63 per 100,000 (95% confidence interval [CI] 44.51, 44.69)—a much higher number compared to the estimated overall annual excess mortality rate of 5.09 per 100,000 individuals (95% CI 2.20, 5.09) in the country.[1]

In addition to mortality, viral influenza is associated with significant morbidity among adults older than 65 years of age. The most common complication is pneumonia either from primary influenza or from secondary bacterial infection. Influenza may also cause exacerbations of underlying chronic lung and cardiac diseases such as congestive heart failure and ischemic heart disease.[2] International guidelines recommend that antiviral treatment with a single neuraminidase inhibitor be started as soon as possible for this age group, if with documented or suspected influenza, irrespective of influenza vaccination history.[3]

A high-dose trivalent influenza vaccine was licensed by the US Food and Drug Administration (FDA) in 2009 for use among people 65 years and above.[4] A high-dose quadrivalent influenza vaccine was subsequently licensed in 2019, also for use in the same age bracket. This vaccine contains four times the amount of hemagglutinin antigen compared to a standard-dose influenza vaccine (60ug per virus in high-dose compared to 15ug per virus in standard-dose vaccine).[5]

Results

Characteristics of Included Studies

There were 12 primary RCTs and 4 secondary studies that evaluated the effectiveness and safety of high-dose compared to standard dose influenza among elderly individuals aged 65 years old and above.[1-16] Of the 12 primary RCTs, 7 involved medically stable elderly patients, 1 involved frail elderly, 2 involved long-term nursing home residents, and 2 involved elderly patients in general. Eleven RCTs evaluated high-dose inactivated trivalent influenza vaccine, while 1 RCT evaluated high-dose inactivated quadrivalent influenza vaccine. Nine RCTs used standard dose inactivated trivalent influenza vaccine as control, 2 used standard dose inactivated quadrivalent influenza vaccine, and 1 RCT used standard dose adjuvanted inactivated trivalent influenza vaccine. The outcomes reported include: laboratory-confirmed influenza, mortality, hospitalization, serious adverse events, and systemic and local reactogenic events.

Benefits and Harms of High-dose Influenza Vaccine

The summary table of all critical outcomes of high-dose influenza vaccination among the apparently healthy elderly population is shown in Table 1.

Table 1. Benefits and harms of high-dose compared to standard-dose influenza vaccine among the elderly

Outcomes	No. of Studies (No. of Participants)	Effect Estimate (95% CI)	Interpretation	Certainty of Evidence
Influenza	2 (41,141)	RR 0.76 (0.64, 0.90)	Favors high-dose	High
All-cause mortality	7 (101,292)	RR 0.99 (0.95, 1.03)	Equivalent	Moderate
All-cause hospitalization	3 (87,948)	RR 0.93 (0.90, 0.96)	Favors high-dose	Low
Serious adverse events	6 (46,491)	RR 0.92 (0.87, 0.98)	Favors high-dose	Moderate
Systemic reactogenic events	4 (5,639)	RR 1.19 (0.91, 1.55)	Inconclusive	Very low
Local reactogenic events	4 (5,639)	RR 1.47 (1.26, 1.73)	Favors standard dose	Low
Systemic adverse effects	5 (1,018)	RR 1.40 (0.82, 2.38)	No significant difference	Low

CI confidence interval; RR risk ratio

The summary of findings table and reasons for downgrading are found in Appendix 2. The forest plots are shown in Appendix 4.

Twelve primary randomized controlled trials (RCTs) and four secondary studies evaluated the effectiveness and safety of high-dose compared to standard dose influenza among elderly individuals aged 65 years old and above.[6-21] Of the 12 primary RCTs, seven involved medically stable elderly patients, one involved frail elderly, two involved long-term nursing home residents, and two involved elderly patients in general. Eleven RCTs evaluated high-dose inactivated trivalent influenza vaccine, while one RCT evaluated high-dose inactivated quadrivalent Influenza vaccine. As control, nine RCTs used standard dose inactivated trivalent influenza vaccine, two used standard dose inactivated quadrivalent influenza vaccine, and one used standard dose adjuvanted inactivated trivalent influenza vaccine. The outcomes reported include laboratory-confirmed influenza, mortality, hospitalization, serious adverse events, and systemic and local reactogenic events. The characteristics of included studies are found in Appendix 3.

Laboratory-confirmed influenza, all-cause hospitalization, and all-cause mortality

Pooled analysis showed that high-dose inactivated influenza vaccination significantly reduced laboratory-confirmed influenza (relative risk [RR] 0.76; 95% confidence interval [CI] 0.64, 0.90) and all-cause hospitalization (RR 0.93; 95% CI 0.90, 0.96) in the elderly compared to standard dose vaccine. No significant difference was found on all-cause mortality (RR 0.90; 95% CI 0.95, 1.03). Two secondary studies reported that the benefit of high-dose influenza vaccine in reducing laboratory-confirmed influenza was irrespective of age, comorbidity, frailty of the elderly population, and previous season vaccination with high-dose or standard dose influenza vaccine.[19,20]

Adverse events

Significant reduction in serious adverse events (SAEs) was seen in high-dose (RR 0.92; 95% CI 0.87, 0.98) compared to standard dose influenza vaccination. Of all the SAEs reported, only eight were considered by the investigators to be vaccine related. Five SAEs occurred in the high-dose vaccine group, which included cardiac chest pain one day after vaccination, cranial nerve VI palsy one day after vaccination, hypovolemic shock from diarrhea one day after vaccination, exacerbation of Crohn's disease two days after vaccination, and acute disseminated encephalomyelitis 117 days after vaccination. Three SAEs occurred in the standard dose vaccine group, which included Bell's palsy 34 days after vaccination, immune thrombocytopenia 13 days after vaccination, and myasthenia gravis one month after vaccination.

No significant difference in systemic reactogenic events (RR 1.19; 95% CI 0.91, 1.55) was found, but high-dose influenza vaccination significantly increased the risk of local reactogenic events (RR 1.47; 95% CI 1.26, 1.71) compared to standard dose influenza vaccination.

Recommendations from Other Groups

Only one guideline mentioned the use of high-dose influenza vaccine among the elderly. The Advisory Committee on Immunization Practices (ACIP) 2020 guidelines recommend the use of any inactivated influenza vaccination, whether high-dose or standard dose, for persons aged 65 years old and above.[22]

Table 2. Recommendation on high-dose influenza vaccination from other groups

Group	Recommendation	Basis for recommendation
ACIP 2020[22]	For persons aged ≥65 years old, any age-appropriate inactivated influenza vaccine formulation (high-dose, standard dose, trivalent or quadrivalent).	Not indicated

ACIP Advisory Committee on Immunization Practices

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

Cost

A systematic review on the cost-effectiveness of high-dose influenza vaccine among persons aged 65 years old and above was published in March 2021.[23] Seven studies were included, six of which were done in the United States of America (USA) and one in Canada. All studies involved high-dose trivalent inactivated influenza vaccine. All similarly reported that high-dose influenza vaccine was cost-effective compared to standard dose influenza vaccine.[24-30] Another study done in Australia likewise reported that high-dose trivalent inactivated influenza vaccine was cost-

effective compared to standard dose.[31] The cost-effectiveness studies are summarized in Appendix 5.

In the Philippines, no local economic evaluation study has been done on high-dose influenza vaccines. Furthermore, high-dose influenza vaccines are not yet available locally.

The unit cost of standard-dose and high-dose influenza vaccines are shown in Table 3.

Table 3. Unit cost of influenza vaccine

Parameter	Type of Influenza Vaccine	
	High-dose	Standard dose
Unit cost of vaccine	PHP 3,063.05*[32]	PHP 600-800[33]

*Converted from USD (not locally available)

Patient Values and Preference, Equity, Acceptability, and Feasibility

A Philippine study published in 2020 evaluated the perceptions and attitudes of Filipinos towards influenza vaccination using focus group discussions.[34] The study identified eight barriers to influenza vaccination, namely:

1. Patient perception that vaccination is not a priority—responsibilities at home and work take precedence over vaccination;
2. Patient perception that they are at low risk of getting influenza;
3. Lack of awareness of the severity of influenza;
4. Lack of awareness that free influenza vaccines are provided by the government for qualified indigent elderly Filipinos;
5. Expensive cost of vaccines for some families;
6. Delayed vaccine availability a few months after the influenza season has already started;
7. Limited supply of free influenza vaccines; and
8. Improper storage that may compromise the efficacy of influenza vaccines.

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4.6. Should HPV vaccine be recommended to apparently healthy adults?

RECOMMENDATIONS

Among apparently healthy asymptomatic females aged 18 to 26 years who have not been vaccinated or who have not yet completed the vaccine series, we recommend HPV vaccination.
(strong recommendation, moderate certainty evidence)

Among apparently healthy asymptomatic adults aged 27 to 45 years, we suggest against routine catch-up vaccination. The decision to vaccinate people in this age group should be made on an individual basis.
(weak recommendation, low certainty evidence)

Among apparently healthy asymptomatic males aged 18 to 26 years who have not been vaccinated or who have not yet completed the vaccine series, we suggest HPV vaccination.
(weak recommendation, very low certainty evidence)

Among pregnant patients, we suggest against HPV vaccination.
(weak recommendation, very low certainty evidence)

Among apparently healthy asymptomatic sex workers, there is insufficient evidence to recommend HPV vaccination.
(very low certainty evidence)

Considerations

The consensus panel considered the following when formulating these recommendations:

- The evidence base included studies conducted abroad, which may have implications on applicability.
- The evidence showed that the optimal time for HPV vaccination to yield maximum effectiveness is before an individual's sexual debut. However, the studies included in the evidence base did not explicitly mention how HPV naivety was identified.
- Although bivalent HPV vaccine is still available in the country, the evidence base included studies only on quadrivalent and nonavalent HPV vaccines. No specific recommendation was made by the panel on which type of HPV vaccine should be used, citing that it should be a shared decision-making between the patient and physician. Factors that should be considered include: HPV naivety and risk of exposure of the patient, cost, and availability of the vaccine, among others.
- Among immunocompetent adults aged 16 to 26 years old, HPV vaccine prevents more critical outcomes in females compared to males; thus, the weak recommendation for males and strong recommendation for females.
- Among adults aged 27 to 45 years old, catch-up HPV vaccination showed low efficacy. Thus, vaccination in this age group should be made on an individual basis, taking into consideration the risk of exposure among others.
- Despite the risk of exposure among sex workers, the panelists unanimously voted that there is insufficient evidence to recommend HPV vaccination in this population due to

studies showing that HPV naivety affects vaccine efficacy. Additionally, vaccination has no benefit among those with HPV infection. However, the panelists recognized that HPV vaccine may still provide benefit to this group especially if the type of vaccine covers serotypes that the patient has not yet been exposed to.

Key Findings

Among female patients 16 to 26 years old who have not been vaccinated or who have not yet completed the vaccine series, evidence reviewed on the clinical outcomes available (i.e., 6-month persistent infection [6-MPI], cervical intraepithelial neoplasia [CIN] 2/3 or worse, vulvar intraepithelial neoplasia [VIN] 2/3, or vaginal intraepithelial neoplasia [VaIN] 2/3 or worse, anogenital warts) favors HPV vaccination (i.e., 4vHPV and 9vHPV). Among apparently healthy female asymptomatic adults aged 27 to 45 years who have not been vaccinated previously or who have not yet completed the vaccine series, there is limited evidence regarding benefit. Among pregnant patients, there is insufficient evidence on the possible benefits of HPV vaccination.

Among apparently healthy asymptomatic males aged 16 to 26 years who have not been vaccinated or who have not yet completed the vaccine series, evidence reviewed on the clinical outcomes available (i.e., 6-MPI, external genital lesion, all penile intraepithelial neoplasia [PeIN] lesions, and anogenital warts) favors HPV vaccination (i.e., 4vHPV and 9vHPV).

Among apparently healthy asymptomatic sex workers, there is insufficient evidence on the possible benefits of HPV vaccination.

HPV vaccination is generally safe and well tolerated. The safety profile and the spectrum of adverse events after vaccination in males are similar to those in females. For all HPV vaccines, injection site reactions are the most commonly reported adverse event.

Introduction

Burden of the Disease

Human papillomavirus (HPV), a sexually transmitted pathogen, is regarded as the most common viral infection affecting the reproductive tract and has been established to cause a variety of conditions for both men and women. Persistent infection with a specific type of HPV may lead to precancerous lesions that may eventually develop into cervical cancer in women when left untreated. It is also associated with oropharyngeal (i.e., head and neck) and anogenital (i.e., anus, vulva, vagina, and penis) cancers in both men and women.[1]

Worldwide, HPV types 16 and 18 are directly responsible for about three-fourths of all cervical cancer cases. In the Philippines, as of 2019, the annual number of cervical cancer cases is estimated to be at 7,190 with the annual deaths due to cervical cancer at 4,088.[2] Cervical cancer is the second most common cancer in females aged 15 to 44 years. Data on anogenital cancers other than cervical cancer are limited, but there is increasing evidence that strongly associates HPV DNA and infection with the development of anal, vulva, vaginal, and penile cancer.[3-7]

The association of these cancers with having previous HPV infections provides an opportunity for preventive strategies such as vaccination (i.e., HPV vaccination). In line with this, clinical studies[3-7] have shown that the optimal time for HPV vaccination to yield maximum effectiveness is before

an individual's sexual debut or in individuals who have not been infected with HPV (i.e., "HPV-naïve patients").

Different HPV types have varying propensity to infect certain body parts and develop into different associated diseases as shown in Table 1. HPV type 16 has the highest propensity to progress into cancer. It may infect the anogenital epithelium (i.e., penis, scrotum, perineum, anal canal, perianal region, vaginal introitus, vulva, and cervix) and other mucosal surfaces (i.e., oral mucosa).[8]

Specific HPV genotypes that cause persistent infection that ultimately progress to cancer (i.e., cervical cancer) include the following types: 31, 33, 45, 52, and 58. Meanwhile, HPV types 16 and 18 cause majority of the anal cancer cases and a significant proportion of oropharyngeal cancer, vulvar, vaginal, and penile cancer.[9]

Available vaccines offer different coverage in terms of the HPV types they target. The HPV quadrivalent vaccine targets HPV types 6, 11, 16, and 18 while the HPV nonavalent vaccine targets types 31, 33, 45, 52, and 58 in addition to the four types covered by the quadrivalent vaccine.[8]

Table 1. Most common and selected HPV types with associated diseases[8]

Disease	HPV Type Frequently Associated
Cutaneous warts	
Common and plantar warts	1, 2, 4
Flat wart	3, 10
Butcher's Wart	7, 2
Condyloma acuminata	6, 11
Squamous intraepithelial lesions (cervix, vagina, vulva, anus, and penis)	
Low grade	16, 31, 6, 11
High grade	16, 31, 52, 18, 33, 45, 58
Oropharyngeal cancer	16
Anal cancer	16

Outcomes

Benefits and Harms of HPV Vaccine

Nine randomized controlled trials were included in this review. Appendix 3 shows a summary of the characteristics of these studies.

Subgroup 1: Immunocompetent females aged 16 to 26 years old

Table 2. Benefits and harms of HPV vaccination among immunocompetent females aged 16 to 26 years old

Outcomes	No. of Studies (No. of Participants)	Effect Estimate	Interpretation	Certainty of Evidence
Efficacy outcomes				
4vHPV vs. placebo for HPV 6-, 11-, 16-, and 18-related outcomes				
6-month persistent infection	1 RCT (10) (n=551)	VE 89.0% (95% CI 70.0, 97.0)	Favors 4vHPV	Moderate[a]
CIN 2/3 or worse	1 RCT (11) (n=15,729)	VE 98.2% (95% CI 93.3, 99.8)	Favors 4vHPV	Moderate[a]
VIN2/3, or VaIN 2/3 or worse	1 RCT (11) (n=15,802)	VE 100.0% (95% CI 82.6, 100.0)	Favors 4vHPV	Moderate[a]
Anogenital warts	1 RCT (12) (n=15,344)	VE 98.9% (95% CI 96.1, 99.9)	Favors 4vHPV	High

9vHPV for HPV 6-, 11-, 16-, and 18-related outcomes (immunobridging studies used)				
6-month persistent infection	1 RCT (10) (n=551)	VE 89.0% (95% CI 70.0, 97.0)	Favors 4vHPV	Moderate[b]
CIN 2/3 or worse	1 RCT (11) (n=15,729)	VE 98.2% (95% CI 93.3, 99.8)	Favors 4vHPV	Moderate[b]
VIN2/3, or VaIN 2/3 or worse	1 RCT (11) (n=15,802)	VE 100.0% (95% CI 82.6, 100.0)	Favors 4vHPV	Moderate[b]
Anogenital warts	1 RCT (12) (n=15,344)	VE 98.9% (95% CI 96.1, 99.9)	Favors 4vHPV	High
9vHPV vs. 4vHPV for HPV 31-, 33-, 45-, 51-, and 58-related outcomes				
6-month persistent infection	1 RCT (13) (n=11,896)	VE 96.0% (95% CI 94.6, 97.1)	Favors 9vHPV	Moderate[c]
CIN 2/3, VIN2/3, or VaIN 2/3 or worse	1 RCT (13) (n=12,033)	VE 97.4% (95% CI 85.0, 99.9)	Favors 9vHPV	Moderate[c]
CIN 2/3 or worse	1 RCT (13) (n=11,892)	VE 97.1% (95% CI 83.5, 99.9)	Favors 9vHPV	Moderate[c]
Safety outcomes				
4vHPV vs. Placebo				
Overall local/injection site adverse events	6 RCT (22) (n=11,610)	RR 1.14 (95% CI 1.12, 1.16)	Favors comparator	High
Overall systemic event/general symptoms	6 RCT (22) (n=11,688)	RR 1.01 (95% CI 0.98, 1.04)	Not significant	High
Serious adverse events any time[d]	7 RCT (22) (n=22,979)	RR 0.81 (95% CI 0.65, 1.02)	Not significant	High
Deaths	7 RCT (22) (n=22,665)	RR 1.54 (95% CI 0.73, 3.2)	Not significant	High
9vHPV vs. 4vHPV				
Overall local/injection site adverse events	1 RCT (19) (n=500)	RR 1.07 (95%CI 1.05, 1.08)	Favors comparator	High
Overall systemic event/general symptoms	1 RCT (19) (n=500)	RR 1.01 (95% CI 0.98, 1.04)	Not significant	Moderate
Serious adverse events any time[d]	1 RCT (19) (n=500)	OR 1.22 (95% CI 1.0, 1.48)	Not significant	Low
Deaths	1 RCT (19) (n=500)	OR 1.20 (95% CI 0.37, 3.94)	Not significant	Low

4vHPV quadrivalent human papillomavirus vaccine; 9vHPV nonavalent human papillomavirus vaccine; CI confidence interval; CIN cervical intraepithelial neoplasia; RCT randomized controlled trial; OR odds ratio; RR risk ratio; VaIN vaginal intraepithelial neoplasia; VE vaccine efficacy defined as (1 − relative risk) × 100%; VIN vulvar intraepithelial neoplasia

[a]Downgraded due to indirectness of this outcome to the pre-specified in the review question (i.e., use of clinical surrogate outcome).

[b]Downgraded due to indirectness of this outcome to the pre-specified in the review question (i.e., use of clinical surrogate outcome); indirectness due to use of immunobridging to 4vHPV.

[c]Downgraded due to indirectness of this outcome to the pre-specified in the review question (i.e., use of clinical surrogate outcome).

[d]Serious events were defined as side effects that results in death, life-threatening, or requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or in congenital anomaly/birth defect.

4vHPV vs. placebo for HPV 6-, 11-, 16-, and 18-related outcomes

Persistent infection ≥6 months (1 RCT; n=551; high certainty of evidence)

Vaccination with 4vHPV significantly reduced persistent infection compared to placebo among women aged 16 to 23 years old (vaccine efficacy [VE] 89.0%; 95% confidence interval [CI] 70.0, 97.0).[10]

CIN 2/3 or worse (1 RCT; n=15,729; high certainty of evidence)

Vaccination with 4vHPV significantly reduced the development of cervical intraepithelial neoplasia (CIN) 2/3 or worse compared to placebo among women aged 16 to 23 years (VE 98.2%; 95% CI 93.3, 99.8).[11]

VIN 2/3, or VaIN 2/3 or worse (1 RCT; n=15,802; high certainty of evidence)
Vaccination with 4vHPV significantly reduced vulvar intraepithelial neoplasia (VIN) 2/3, or vaginal intraepithelial neoplasia (VaIN) 2/3 or worse, compared to placebo among women aged 16 to 23 years (VE 98.9%; 95% CI 96.1, 99.9).[11]

Anogenital warts (1 RCT; n=15,344; high certainty of evidence)
Vaccination with 4vHPV significantly reduced anogenital warts among women aged 16 to 23 years old (VE 98.9%; 95% CI 96.1-99.9).[12]

9vHPV vs. 4vHPV for HPV 31-, 33-, 45-, 52-, and 58-related outcomes
Data to evaluate the efficacy of 9vHPV vaccine on HPV type 31-, 33-, 45-, 52-, and 58-related clinical outcomes came from a large RCT that compared 9vHPV vaccine to 4vHPV vaccine among women aged 16 to 26 years old.[13]

Persistent infection ≥6 months (1 RCT; n=11,896; moderate certainty of evidence)
Vaccination with 9vHPV significantly reduced six-month persistent infection compared to 4vHPV among women aged 16 to 26 years (VE 96.0%; 95% CI 94.6, 97.1).[13]

CIN 2/3, VIN2/3, or VaIN 2/3 or worse (1 RCT; n=12,033; moderate certainty of evidence)
Vaccination with 9vHPV significantly reduced the composite of high-grade lesions (i.e., CIN 2/3 or worse, VIN 2/3 or worse, and VaIN 2/3 or worse) compared to 4vHPV among women aged 16 to 26 years (VE 97.4%; 95% CI 85.0, 99.9).[13]

CIN 2/3 or worse (1 RCT, n=11,892, moderate certainty of evidence)
Vaccination with 9vHPV vaccine significantly reduced the incidence of CIN 2/3 or worse for the additional HPV serotypes compared to 4vHPV among women aged 16 to 26 years (VE 97.1%; 95% CI 83.5, 99.9).[13]

9vHPV vaccine for HPV types 6-, 11-, 16-, and 18-related outcomes
Vaccine efficacy studies comparing the efficacy of 9vHPV versus placebo on HPV types 6, 11, 16, and 18 were not possible due to ethical concerns as previously approved vaccines (including 4vHPV vaccine) have shown protection against HPV 16 and 18—two of the most carcinogenic types. Hence, only studies that compared 9vHPV vaccine with 4vHPV vaccine were done. Consequently, indirect data from RCTs of 4vHPV vaccines (i.e., Kjaer et al., Dillner et al., Villa et al.) were used to infer the efficacy of 9vHPV vaccine for the prevention of HPV type 6-, 11-, 16-, and 18-related outcomes.[14]

Adverse events

4vHPV vaccine vs. placebo
Vaccination with 4vHPV vaccine significantly increased local/injection site adverse events compared to placebo among women aged 16 to 26 years (relative risk [RR] 1.14; 95% CI 1.12, 1.16; n=11,610; 6 RCTs; moderate certainty of evidence).[13]

No significant differences were noted in the overall systemic events and general symptoms (RR 1.01; 95%CI 0.98, 1.04; n=11,688; 6 RCTs; high certainty of evidence), serious adverse events (RR 0.81; 95% CI 0.65, 1.02; n=22,979; 7 RCTs; high certainty of evidence), and deaths (RR 1.54; 95% CI 0.73, 3.2; n=22,665; 7 RCTs; high certainty of evidence) among female patients aged 16 to 26 years who received the 4vPHV vaccine compared to placebo. It was noted by the study investigators that these deaths were unlikely to be related to the vaccine.[13]

9vHPV vaccine vs. 4vHPV vaccine

Vaccination with 9vHPV resulted in relatively more local/injection site adverse events (RR 1.07, 95% CI 1.05, 1.08; n=14,764; 1 RCT; high certainty of evidence) compared to 4vHPV among women aged 16 to 26 years. No significant differences in overall systemic events and general symptoms (RR 1.01, 95%CI 0.98, 1.04; n=14,764; 1 RCT; high certainty of evidence), and overall series adverse events (odds ratio [OR] 1.22, 95% CI 1.0-1.48; n=14,764 participants; 1 RCT; high certainty of evidence) were noted between 9vHPV vaccinees and 4vHPV vaccinees. Similarly, there was no significant difference in deaths among female patients aged 16 to 26 years who received the 9vPHV vaccine (6 out of 7,071 participants) compared to those who had 4vHPV vaccine (5 out of 7078 participants) with an OR of 1.20 (95% CI 0.37; 3.94; n=14,149; 1 RCT; high certainty of evidence). It was noted by the study investigators that these deaths were unlikely to be related to the vaccine.[15]

Subgroup 2: Immunocompetent males aged 16 to 26 years old

The summary of all critical outcomes of HPV vaccination among immunocompetent males aged 16 to 26 years old is shown in Table 3.

Table 3. Benefits and harms of HPV vaccination among immunocompetent males aged 16 to 26 years old

Outcomes	No. of Studies (No. of Participants)	Effect Estimate	Interpretation	Certainty of Evidence
Efficacy outcomes				
4vHPV vs. Placebo for HPV 6-, 11-, 16-, and 18-related outcomes				
6-month persistent infection	1 RCT (16) (n=2,790)	VE 85.6% (73.4, 92.9)	Favors 4vHPV	Moderate
External genital lesion	1 RCT (16) (n=2,805)	VE 90.4 (69.2, 98.1)	Favors 4vHPV	Moderate
Condyloma acuminatum	1 RCT (16) (n=2,805)	VE 89.4 (65.5, 97.9)	Favors 4vHPV	High
All PeIN lesions	1 RCT (16) (n=2,805)	VE 100.0 (-141.2, 100.0)	Favors 4vHPV	Very Low
Penile, perianal, or perianal cancer	1 RCT (16) (n=2,790)	Not estimable	-	Very Low
AIN (any grade) and anal cancer	1 RCT (17) (n=255)	VE 89.6 (57.2, 98.8)	Favors 4vHPV	High
Safety outcomes				
4vHPV vs. placebo				
Overall local/injection site adverse events	1 RCT (16) (n=3,895)	RR 1.12 (95% CI 1.06, 1.18)	Favors comparator	High
Overall systemic event/general symptoms	1 RCT (16) (n=5,008)	RR 0.99 (95% CI 0.90, 1.08)	Not significant	High
Serious adverse events any time	1 RCT (16) (n=5,162)	OR 0.69 (95% CI 0.29, 1.66)	Not significant	High
Deaths	1 RCT (16) (n=11,610)	RR 1.54 (95% CI 0.73, 3.2)	Not significant	High
9vHPV vs. 4vHPV				
Overall local/injection site adverse events	1 RCT (19) (n=500)	RR 1.07 (95%CI 1.05, 1.08)	Favors comparator	High
Overall systemic event/general symptoms	1 RCT (19) (n=500)	RR 1.01 (95% CI 0.98, 1.04)	Not significant	Moderate
Serious adverse events any time[a]	1 RCT (19) (n=500)	OR 1.22 (95% CI 1.0, 1.48)	Not significant	Low
Deaths	1 RCT (19) (n=500)	OR 1.20 (95% CI 0.37, 3.94)	Not significant	Low

4vHPV quadrivalent human papillomavirus vaccine; 9vHPV nonavalent human papillomavirus vaccine; AIN anal intraepithelial neoplasia; CI confidence interval; OR odds ratio; PeIN penile intraepithelial neoplasia; RCT randomized controlled trial; RR risk ratio; VE vaccine efficacy defined as (1 − relative risk) × 100%

[a]Serious events were defined as side effects that result in death, are life-threatening, or require inpatient hospitalization or prolongation of existing hospitalization, result in persistent or significant disability/incapacity, or result in congenital anomaly/birth defect.

4vHPV vs. placebo for HPV 6-, 11-, 16-, and 18-related outcomes

Persistent infection ≥6 months (1 RCT; n=2,790; high certainty of evidence)

Vaccination with 4vHPV decreased the incidence of HPV infection and related diseases for ≥6 months compared to placebo among males aged 16 to 26 years old (VE 85.6%; 95% CI 73.4, 92.9).[16]

External genital lesion (1 RCT; n=2,805; high certainty of evidence)

Vaccination with 4vHPV decreased the incidence of external genital lesion compared to placebo among males aged 16 to 26 years old (VE 90.4%; 95% CI 69.2, 98.1). External genital lesions included a diagnosis of condyloma acuminatum, HPV, and PIN (i.e., penile, perianal, or perineal intraepithelial neoplasia).[16]

Condyloma acuminatum (1 RCT; n=2,805; high certainty of evidence)

4vHPV vaccine decreased the incidence of condyloma acuminatum compared to placebo among males aged 16 to 26 years old (VE 89.4; 95% CI 65.5, 97.9).[16]

All PeIN lesions (i.e., PeIN1, PeIN2/3) (1 RCT; n=2,805; high certainty of evidence)

No significant differences were seen in the incidence of all penile intraepithelial neoplasia (PeIN) lesions (VE 100.0; 95% CI -141.2, 100.0), PeIN1 lesions (VE 100.0; 95% CI , 431.1, 100.0), and PeIN 2/3 lesions (VE 100.0; 95% CI -3,788.2, 100.0) among males aged 16 to 26 years old who were given the 4vHPV vaccine versus placebo.[16]

Penile, perianal, or perineal cancer (1 RCT, n=2,790, low certainty of evidence)

No observed penile, perianal, or perineal cancer was noted in both the 4vHPV vaccine arm and placebo arm within the study period. Data for these outcomes were not necessarily expected in clinical trials of current duration and size.[16]

AIN (any grade) and anal cancer (1 RCT; n=255; low certainty of evidence)

In the study by Goldstone et al. that assessed 4vHPV vaccine efficacy against disease related to HPV types 6, 11, 16, and 18, vaccination with 4vHPV significantly reduced the incidence of any grade of anal intraepithelial neoplasia (AIN) and anal cancer among males aged 16 to 24 years old (VE 89.6; 95% CI 57.2, 98.8).[17]

9vHPV vs. 4vHPV for HPV 31-, 33-, 45-, 52-, and 58-related outcomes

No direct evidence was found on the clinical efficacy of 9vHPV vaccine in males targeting HPV types 31-, 33-, 45-, 52-, and 58-related outcomes. As an alternative, two immunobridging studies[18,19] were used to derive the efficacy of 9vHPV in males aged 16 to 26 years old. A study by Huh et al.[13] was also used to evaluate the immunogenicity of 9vHPV vaccine in males aged 16 to 26 years old when compared to 4vHPV vaccine.

In the study by Castellsagué et al., efficacy estimates were compared between the 9vHPV vaccine given to heterosexual males aged 16 to 26 years old, and that given to females aged 16 to 26 years old. Immunogenicity data on 9vHPV vaccine in the males revealed non-inferior geometric mean titers (GMTs) for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 compared to the women at the seventh month post-vaccination.[18]

The study of Van Damme et al. that compared the immunogenicity and safety of 9vHPV vaccine versus the 4vHPV vaccine in males aged 16 to 26 years old showed that 9vHPV vaccine elicited HPV type 6, 11, 16, and 18 immune responses comparable to those given the 4vHPV vaccine.[19]

Adverse events

4vHPV vaccine vs. placebo
In a study by Giuliano et al. (n=3,895), vaccination with 4vHPV increased the overall local/injection site adverse events (RR 1.12; 95% CI 1.06, 1.18; high certainty of evidence) compared to placebo. These adverse events included pain at injection site (RR 1.29; 95% CI 1.04, 1.60; 2 RCTs; n=5,162), and redness at the injection site (RR 1.29; 95% CI 1.12, 1.27; 2 RCTs; n=5,162).[16]

No significant differences were noted between the treatment group and control group in terms of the overall systemic events and general symptoms (RR 0.99; 95% CI 0.90, 1.08; 2 studies; n=5,008; moderate certainty of evidence), and serious adverse events (OR 0.69; 95% CI 0.29, 1.66; very low certainty of evidence; vaccine n=8/2,574; control n=12/2,588; 2 RCTs). None of the serious adverse events were considered to be vaccine-related by the study assessors.

There were fewer deaths in the treatment group (3 deaths) compared to the control group (11 deaths) with an OR of 0.30 (95% CI 0.09, 1.01; n=5173; 2 RCTs; low certainty of evidence).[15]

9vHPV vs. 4vHPV
Vaccination with 9vHPV relatively increased local/injection site adverse events compared to 9vHPV among males aged 16 to 26 years old (RR 1.1; 95% CI 1.0, 1.22; n=500; 1 RCT). No recorded serious adverse events were recorded among males in the treatment arm (249 participants) while six events were recorded in the control arm (251 participants).[15]

No significant differences were seen in the overall systemic events and general symptoms observed among those who were given 9vHPV vaccine (101 out of 249 participants) compared to 4vHPV vaccine (100 out of 251 participants) with an RR of 1.02 (95% CI 0.82, 1.26; n=500; moderate certainty of evidence). Similarly, no significant difference in overall serious adverse events was observed among those given the 9vHPV vaccine (0 out of 249 participants) compared to 4vHPV vaccine (6 out of 251 participants) with an OR of 0.08 (95% CI 0.14, 2.61; n=500; moderate certainty of evidence).

No deaths were reported in the study done by van Damme et al. among males aged 16 to 26 years who were given 9vHPV vaccine (0 out of 249 participants) compared to 4vHPV vaccine (0 out of 251 participants).[15]

Subgroup 3: Immunocompetent females aged 27 to 45 years old
The summary of all critical outcomes of HPV vaccination among immunocompetent females aged 27 to 45 years old is shown in Table 4.

Table 4. Benefits and harms of HPV vaccination among immunocompetent females aged 27 to 45 years old

Outcomes	No. of Studies (No. of Participants)	Effect Estimate	Interpretation	Certainty of Evidence
Efficacy outcomes				
4vHPV vs. placebo for HPV 6-, 11-, 16-, and 18-related outcomes				
6-month persistent infection	1 RCT (18) (n=2,730)	VE 88.8% (95% CI 76.8, 95.4)	Favors 4vHPV	High

CIN 2/3 or worse	1 RCT (18) (n=2,760)	VE 83.3% (95% CI -37.6, 99.6%)	Not significant	Low
Anogenital warts	1 RCT (18) (n=2,760)	VE 100% (95% CI -9.8, 100.0)	Not significant	Moderate
Safety outcomes				
4vHPV vs. placebo				
Any adverse events	1 RCT (18) (n=3,778)	87.0% (1,645/1,890)	81.3% (1,535/1,888)	High
Injection site events (days 1–15)[a]	1 RCT (18) (n=3,778)	76.7% (1,450/1,890)	64.2% (1,213/1,890)	High
Systemic adverse events (days 1–15)[b]	1 RCT (18) (n=3,778)	59.3% (1,121/1,890)	60.1% (1,135/1,888)	High
Discontinuation due to adverse events	1 RCT (18) (n=3,778)	0.4% (7/1,890)	0.1% (2/1,888)	Moderate

4vHPV quadrivalent human papillomavirus vaccine; 9vHPV nonavalent human papillomavirus vaccine; CI confidence interval; CIN cervical intraepithelial neoplasia; RCT randomized controlled trial; VE vaccine efficacy defined as (1 − relative risk) × 100%; VIN vulvar intraepithelial neoplasia

[a]Injection site adverse events include pain, swelling, erythema and pruritus.

[b]Systemic events are defined as all events that are not correlated to the injection site and are not serious (they include principally headache, pyrexia and dizziness).

4vHPV vs. placebo for HPV 6-, 11-, 16-, and 18-related outcomes

Efficacy

A study by Castellsagué et al. showed that 4vHPV vaccine significantly reduced the following outcomes compared to placebo among females aged 27 to 45 years old: 6-month persistent infection (VE 88.8%; 95% CI 76.8, 95.4; high certainty of evidence), and CIN 2/3 or worse (VE 83.3%; 95% CI -37.6, 99.6%; low certainty of evidence). No significant decrease in anogenital warts was seen among those given the 4vHPV vaccine versus placebo (VE 100%; 95% CI 30.8, 100.0; moderate certainty of evidence).[18]

Safety

The same study by Castellsagué et al. showed that 4vHPV vaccine had higher any adverse events (RR 1.07; n=3,778; high certainty of evidence) and injection site events (RR 1.19; 95% CI 1.15, 1.25; n=3,778; high certainty of evidence) compared to placebo among females aged 27 to 45 years old. No significant differences in systemic adverse events (RR 0.99; 95% CI 0.94,1.04; n=3,778; high certainty of evidence) and discontinuation due to adverse events (RR 3.50; 95% CI 0.73, 16.81; n=3,778; moderate certainty of evidence) were seen between the 4vHPV group and placebo group.[18]

9vHPV vaccine for HPV types 31-, 33-, 45-, 52-, and 58-related outcomes

No studies were found on the efficacy of 9vHPV in females aged 27 and older.

Subgroup 4: Immunocompetent males aged 27 to 45 years old

4vHPV vs. placebo for HPV 6-, 11-, 16-, and 18-related outcomes

No studies were found on the efficacy of 4vHPV in females aged 27 and older.

9vHPV vaccine for HPV types 31-, 33-, 45-, 52-, and 58-related outcomes

No studies were found on the efficacy of 9vHPV in females aged 27 and older.

Subgroup 5: Special population: Pregnant Patients

Study protocols on HPV4 trials excluded women who were pregnant. However, 3,819 patients in these trials have reported at least one pregnancy. Adverse outcomes (i.e., cumulative spontaneous abortions, late fetal deaths, and congenital anomaly cases out of the total number

of known pregnancy outcomes [excluding elective terminations]) were observed in 22.6% (446/1,973) in the HPV4 group and 23.1% (460/1,994) in the aluminium adjuvant amorphous aluminium hydroxyphosphate sulfate (AAHS) control or placebo group. Congenital anomalies were observed in a total of 45 pregnancies that occurred in females who received the HPV4 vaccine, and 34 cases occurred in those who received AAHS control or placebo. For pregnancies estimated to occur within more than 30 days post-inoculation, 40 cases of congenital anomaly were observed in the HPV4 vaccine group versus 33 cases in the AAHS control or placebo group. HPV4 vaccines are classified as Pregnancy Category B based on animal studies on rats showing no evidence of impaired fertility or harm to the fetus.[20]

Currently, HPV vaccination (i.e., 4vHPV or 9vHPV) is not recommended in pregnant patients due to limited safety information. However, available data on the inadvertent use in women who were found to be pregnant after initiating the vaccination series does not indicate any increased risk in adverse pregnancy outcomes with HPV vaccination. The remainder of the vaccination series is recommended to be completed when the woman is no longer pregnant.[20]

Subgroup 6: Special population: Sex workers

No studies looked into the efficacy and safety of HPV vaccine (i.e., 4vPHV or 9vHPV vaccines) among sex workers. As discussed, clinical studies[3-7] have shown that the optimal time for HPV vaccination to yield maximum effectiveness is before an individual's sexual debut or in individuals who have not been infected with HPV (i.e., "HPV-naïve patients"). Available evidence on HPV vaccines have shown its role as prophylactic against HPV infections but do not affect existing infections.[21]

Subgroup 7: Catch-up vaccination among adults (unknown vaccination childhood series or incomplete vaccination series)

A population-based case-control study by Silverberg et al.[4] that assessed the effectiveness of 4vHPV in catch-up vaccination (i.e., vaccinating after the age of 14 years) against CIN2+ and CIN3+ showed significant protection among women offered catch-up vaccination at ages 14 to 20 years old. However, it was also observed that 4vHPV vaccination did not confer significant protection against CIN2+ and CIN3+ when the first dose was given at age 21 to 26 years.

Recommendations from Other Groups

Table 5 summarizes the recommendations on HPV vaccination from other groups.

Table 5. Recommendations on HPV vaccination from other groups

Group	Recommendation for immunocompetent adults	Basis for recommendation/s	
		Strength	Quality of evidence
PSMID 2018[22]	Quadrivalent and Nonavalent HPV Vaccine: Both vaccines are effective in preventing cervical cancer and anogenital warts among immunocompetent adult females and can be given until 26 years old.	Strong recommendation	High quality of evidence
American Cancer Society Guideline Adaptation 2020[23]	Providers should inform individuals aged 22 to 26 years who have not been previously vaccinated or who have not completed the series that vaccination at older ages is less effective in lowering cancer risk.	Not specified	Not specified
	The ACS does not endorse the recommendation for shared clinical decision making for adults aged 27 through 45 years because of the low effectiveness and low cancer prevention potential of vaccination in		

	this age group, the burden of decision making on patients and clinicians, and the lack of sufficient guidance on the selection of individuals who might benefit.		
Australian Immunization Handbook[24]	Vaccination of adults aged ≥19 years against HPV is not routinely recommended. However, some adults may benefit from HPV vaccination. When deciding whether to vaccinate adults, consider: their likelihood of previous exposure to HPV their future risks of HPV exposure.	Not specified	Not specified
German evidence and consensus based (S3) guideline: Vaccination recommendations for the prevention of HPV-associated lesions 2021[25]	We suggest to vaccinate HPV vaccine-naive adolescents aged 18 to 26 years against HPV, irrespective of their gender.	Weak recommendation for a procedure	Low
	We suggest to vaccinate HPV vaccine-naive adolescents aged 18 to 26 years against HPV, irrespective of their gender.	Weak recommendation against a procedure	Low
Guidance on HPV vaccination in EU countries: focus on boys, people living with HIV and 9-valent HPV vaccine introduction[26]	9vHPV vaccine is efficacious for at least six years in preventing six-month persistent HPV infection and high-grade cervical lesions due to types 31, 33, 45, 52 and 58 in females 16-26 years old not infected with HPV at time of vaccination.	Not stated	High
	No direct evidence of efficacy of 9vHPV vaccine against HPV-related infection and illness in males was found.	Not applicable	Not applicable
ACIP 2019[27]	Children and adults aged 9 through 26 years: HPV vaccination is routinely recommended at age 11 or 12 years; vaccination can be given starting at age 9 years. Catch-up HPV vaccination is recommended for all persons through age 26 years who are not adequately vaccinated.	Not specified	Not specified
	Adults aged >26 years. Catch-up HPV vaccination is not recommended for all adults aged >26 years. Instead, shared clinical decision-making regarding HPV vaccination is recommended for some adults aged 27 through 45 years who are not adequately vaccinated. HPV vaccines are not licensed for use in adults aged >45 years.	Not specified	Not specified

ACIP Advisory Committee on Immunization Practices; HPV human papillomavirus; PSMID Philippine Society of Microbiology and Infectious Diseases

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

Cost

Table 6 summarizes the current unit cost of 4vHPV and 9vHPV vaccines in the Philippines. The 4vHPV vaccine cost ranges from PHP 562.50 to PHP 4,800 per dose while 9vHPV vaccine cost ranges from PHP 6,750 to PHP 10,125 per dose.

Table 6. Unit cost of HPV vaccination

Parameter	Vaccination	
	Quadrivalent (4v-) HPV vaccine	Nonavalent (9v-) HPV vaccine
Unit cost of vaccine[28,29]	PHP 562.50 to Php 4,800 per dose	PHP 6,750 to PHP 10,125 per dose

HPV human papillomavirus

Patient Values and Preference, Equity, Acceptability, and Feasibility

A study done in 2018 by Santhanes et al. looked into factors affecting HPV vaccine hesitancy among women in the Southeast Asian region and Western Pacific region and found that concerns on adverse events of vaccination, shyness, fear of needles, and perceived embarrassment of receiving the vaccine were some of the highlighted issues in the population studied. Additionally, participants were reluctant to pay for the full course of the vaccines at the prevailing fair market price. The participants were influenced by recommendations or opinions of others such as family members, friends, and healthcare providers. Those who received support from these individuals were more likely to receive the vaccine. However, some of the studies reviewed showed that the doctors of the participants rarely discussed HPV vaccination with them.[30]

A study done by Young et al. in 2010 (n=435) on HPV vaccine acceptability among Filipinos found that the decision to get HPV vaccination was influenced by several factors: their mother (73%) and/or husband/partner (64%), knowledge that they can get protected from having HPV infection (82%) and/or cervical cancer (77%), and vaccine safety (58%). Female physicians were more likely to be trusted as a healthcare provided compared to male physicians in terms of providing HPV vaccine-related information, as well as whom they would be willing to receive the HPV vaccine from. In terms of cost, more than half (54%) of the participants indicated acceptance of HPV vaccination if vaccine can be acquired at low vaccine price (i.e., PHP 400 to PHP 800).[31]

In a study done by Young et al. in 2011 (n=143) among Filipino men, influence from their mother (69%) and/or father (64%) will affect their decision to get HPV vaccination. Additionally, 43% of the respondents indicated that a partner would influence their decision while only 24% reported that a healthcare worker would give influence. Protection from HPV infection (75%) and the need to stay healthy for the family (53%) were noted as influential factors for decision to get vaccinated. Other influential factors were their desire to protect sexual partners from HPV infection (40%) and vaccine safety (50%). More than half of the sample (53%) were willing to get vaccination from male physicians. In terms of cost as a factor for vaccine acceptance, 39.2% (n=56) of the respondents reported that they would accept the vaccine at a low price (i.e., PHP 400 to PHP 800). As the cost goes up, proportion of men accepting the vaccine decreases significantly.[32]

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4.7. Should influenza vaccine be recommended to apparently healthy adults?

RECOMMENDATIONS

Among healthy adults, pregnant women, and elderly (≥65 years old), we suggest annual influenza vaccination using inactivated Influenza vaccine.
(weak recommendation, low certainty evidence)

Among healthcare workers, we suggest annual influenza vaccination using inactivated Influenza vaccine.
(weak recommendation, very low certainty evidence)

Considerations

The consensus panel considered the following when formulating these recommendations:

- The evidence included studies with laboratory-confirmed influenza illness and influenza-like illness (i.e., clinically-diagnosed influenza) as outcomes. Emphasis was made on the utility of influenza vaccines in reducing influenza-like illness considering the current COVID-19 pandemic.
- Evidence came from studies conducted prior to the COVID-19 pandemic.
- There is a lack of data on the effect of influenza vaccination on COVID-19 infection and its related outcomes.
- The evidence base included studies where elderly was defined as individuals 65 years old and above. Two of the seven panelists disagreed with the specified age group because of conflict of interest. The Department of Health (DOH) currently targets the elderly aged 60 years old and above for influenza vaccination, while the Philippine Society of Microbiology and Infectious Diseases (PSMID) and Philippine Foundation for Vaccination (PFV) recommends influenza vaccination among ages 50 years old and above.
- There are public health concerns on the accessibility of trivalent or quadrivalent type of inactivated vaccine; thus, the panel opted not to make specific recommendations on these. Currently, there is a widespread use of the quadrivalent type in private practice because of trivalent vaccine shortages secondary to the latter being procured by DOH.
- Live attenuated vaccine is unavailable locally, precluding recommendations to be made on this vaccine. Because of its ease of intranasal administration, the panel recognized that it may be an alternative for healthy adults once it becomes available. However, concerns were raised on its high cost and its aerosol-generating administration considering the current COVID-19 pandemic. For the elderly, there is insufficient evidence to recommend live attenuated vaccine.

Key Findings

Administration of either inactivated or intranasal influenza vaccines in healthy adults showed significant benefit in reducing laboratory-confirmed influenza, and influenza-like illness compared with no vaccination. Inactivated vaccines showed no significant effect on hospitalization and missed working days.

Administration of inactivated influenza vaccine in pregnant women showed significant benefit in reducing infant and maternal laboratory-confirmed influenza, and maternal influenza-like illness, but no significant effect on infant and maternal mortality, infant hospitalization, and serious adverse events.

Administration of influenza vaccine in healthcare workers (HCWs) significantly reduced laboratory confirmed-influenza, but showed no significant effect on influenza-like illness, missed working days, and serious adverse events among HCWs (HCW-related outcomes). Influenza vaccination showed no significant effect on laboratory-confirmed influenza and hospitalization in the patients of these HCWs (patient-related outcomes) compared with no vaccination.

Administration of inactivated influenza vaccine in the elderly significantly reduced laboratory-confirmed influenza and influenza-like illness, with no significant difference in systemic adverse events. Live intranasal influenza vaccine showed trend towards benefit in laboratory-confirmed influenza, and trend towards harm in systemic adverse events, but the results were not statistically significant.

Introduction

Burden of the Disease

In the Philippines, the mean annual influenza incidence rate is 5.4 per 1,000 individuals in urban regions of the country.[1] Among adults, the greatest number of cases were reported in the 40- to 64-year-old age group (n=6,803), followed by the 65-year-old and above age group (n=4,702).[2] Influenza is estimated to account for an average of 5,347 excess deaths per year, majority of which (67.1%) occur among adults 60 years and older.[1]

Influenza illness has a substantial impact on health-related quality of life. In a study conducted in China, the average quality adjusted life days (QALD) loss was 1.62 days (SD 1.84).[3] Similar findings were noted in studies in the United Kingdom and England.[4,5]

Significant morbidity and mortality are associated with viral influenza, particularly among pregnant women, adults older than 65 years of age, and people with co-morbid illnesses. The most common complication is pneumonia either from primary influenza or from secondary bacterial infection. Influenza may also cause exacerbations of underlying chronic lung disease and cardiac diseases. Less common are neurologic sequalae such as Reye's syndrome, encephalomyelitis, transverse myelitis, aseptic meningitis, and Guillain-Barre syndrome.[6]

To halt the disease course, the Department of Health (DOH) in the Philippines advises the administration of antiviral medication within the first two days of illness.[7] International guidelines[8] specifically recommend that antiviral treatment with a single neuraminidase inhibitor be started as soon as possible for the following:

a. Adults with documented or suspected influenza who are hospitalized
b. Those with severe or progressive disease
c. Those with high risk of complications (i.e., immunocompromised or with chronic medical conditions)
d. Persons aged 65 years old and above
e. Pregnant women

Supportive treatment such as paracetamol for fever, rest, increased oral fluid intake, and consumption of nutritious food are also recommended.[7] On the other hand, antibiotics such as

vancomycin or linezolid may be prescribed among patients who develop secondary bacterial complications.[7,9]

Outcomes

Benefits and Harms of Influenza Vaccine

The summary of all critical outcomes of influenza vaccination among healthy adults is shown in Table 1.

Table 1. Benefits and harms of influenza vaccine per subgroup of healthy adults

Outcomes	No. of Studies (No. of Participants)	Effect Estimate (95% CI)	Interpretation	Certainty of Evidence
Healthy Adults				
Inactivated influenza vaccine				
Influenza	22 (61,512)	RR 0.41 (0.36, 0.47)	Favors vaccine	Moderate
Influenza like-illness	14 (25,702)	RR 0.84 (0.75, 0.95)	Favors vaccine	Moderate
Hospitalization	2 (2,308)	RR 2.89 (0.12, 70.68)	No significant difference	Low
Systemic adverse effects	5 (1,892)	RR 1.08 (0.88, 1.32)	No significant difference	Low
Live intranasal influenza vaccine				
Influenza	9 (11,579)	RR 0.47 (0.35, 0.62)	Favors vaccine	Moderate
Influenza like-illness	6 (12,688)	RR 0.90 (0.84, 0.96)	Favors vaccine	Moderate
Systemic adverse effects	5 (1,018)	RR 1.40 (0.82, 2.38)	No significant difference	Low
Pregnant Women				
Maternal outcomes				
Influenza	3 (10,123)	RR 0.47 (0.29, 0.77)	Favors vaccine	Moderate
Influenza like-illness	3 (6,720)	RR 0.81 (0.67, 0.99)	Favors vaccine	Moderate
Mortality	2 (7,886)	RR 0.62 (0.20, 1.90)	No significant difference	Low
Serious adverse events	2 (4,533)	RR 0.97 (0.70, 1.35)	No significant difference	Moderate
Infant outcomes				
Influenza	4 (10,270)	RR 0.64 (0.53, 0.78)	Favors vaccine	High
Influenza-like illness	3 (6,165)	RR 0.89 (0.73, 1.08)	No significant difference	Low
Hospitalization	1 (2,049)	RR 0.92 (0.75, 1.13)	No significant difference	Moderate
Mortality	2 (7,717)	RR 1.29 (0.98, 1.70)	No significant difference	Moderate
Serious adverse events	4 (10,173)	RR 1.08 (0.92, 1.28)	No significant difference	Low
Healthcare Workers				
HCW-related outcomes				
Influenza	1 (359)	RR 0.12 (0.04, 0.41)	Favors vaccine	Moderate
Influenza-like illness	1 (179)	RR 1.07 (0.62, 1.95)	No significant difference	Low
Adverse events	2 (606)	RR 5.34 (2.12, 13.41)	Favors placebo	Low
Serious adverse events	1 (359)	RR 0.14 (0.01, 2.73)	No significant difference	Low
Patient-related outcomes				
Influenza	2 (752)	RD 0 (-0.03, 0.03)	No significant difference	Low

Hospitalization	1 (3,400)	RD 0 (-0.02, 0.02)	No significant difference	Low
Mortality	4 (8,468)	5-13% in vaccine group, 6-22% in control group (not pooled)	No significant difference	Very low
Elderly				
Inactivated influenza vaccine				
Influenza	2 (2,040)	RR 0.44 (0.27, 0.71)	Favors vaccine	Low
Influenza-like illness	2 (2,537)	RR 0.64 (0.49, 0.84)	Favors vaccine	Moderate
Mortality	2 (2,537)	RR 0.99 (0.94, 1.04)	No significant difference	Moderate
Systemic adverse events (fever)	3 (2,519)	RR 1.58 (0.92, 2.71)	No significant difference	Moderate
Live intranasal influenza vaccine				
Influenza	1 (220)	RR 0.49 (0.21,1.17)	No significant difference	Very low
Systemic adverse events (fever)	1 (45)	RR 1.71 (0.09, 33.24)	No significant difference	Very low

CI confidence interval; RD risk difference; RR risk ratio

Subgroup 1: Healthy adults

A systematic review by Demicheli et al. published in 2018 synthesized the available evidence on the effectiveness and safety of influenza vaccines compared with no vaccine among healthy adults. This review was appraised to be of high quality using AMSTAR 2. Cochrane Library, MEDLINE, and Embase were searched until 31 December 2016. WHO international clinical trials registry platform (ICTRP) and ClinicalTrials.gov were searched until 01 July 2017. A total of 72 randomized controlled trials (RCTs) were included in the review. Out of the 72 included RCTs, 15.3% (11/72) were classified as low risk of bias, 9.7% (7/72) as high risk of bias, and 74.5% (54/72) as unclear risk of bias. There were 32 RCTs on trivalent inactivated vaccine (TIV), ten studies on monovalent inactivated vaccine, three studies on polyvalent inactivated vaccine, two studies on bivalent inactivated vaccine, 22 studies on live intranasal vaccine, and three studies on trivalent inactivated vaccine (TIV) and live intranasal vaccine. Results from the RCTs on trivalent inactivated and live intranasal vaccine were obtained for this review.[10]

Laboratory-confirmed influenza and influenza-like illness

Results of the systematic review showed that TIV significantly decreased laboratory-confirmed influenza (relative risk [RR] 0.41; 95% confidence interval [CI] 0.36, 0.47; n=61,512; 22 RCTs; moderate certainty of evidence) and influenza like-illness (RR 0.84; 95% CI 0.75, 0.95; n=25,702; 14 RCTs; moderate certainty of evidence) compared with no vaccination.

Live intranasal influenza vaccination similarly significantly decreased laboratory-confirmed influenza (RR 0.47; 95% CI 0.35, 0.62; number needed to vaccinate [NNV] 39; n=11,579; 9 RCTs; moderate certainty of evidence) and influenza-like illness (RR 0.90; 95% CI 0.84-0.96; NNV 46; n=12,688; 6 RCTs; moderate certainty of evidence) compared with no vaccination.

Hospitalization

Inactivated influenza vaccination showed no significant effect on hospitalization (RR 2.89; 95% CI 0.12, 70.68; n=2,308; 2 RCTs; low certainty of evidence) and missed working days (MD 0.01; 95% CI -0.08, 0.09; n=3,726; 4 RCTs; low certainty of evidence) compared with no vaccination.

Adverse effects

Inactivated influenza vaccination significantly increased the risk of combined local adverse effects (RR 2.42; 95% CI 1.80, 3.26; n=12,188; 10 RCTs; low certainty of evidence), but did not

significantly increase the risk of combined systemic adverse effects (RR 1.08; 95% CI 0.88,1.32; n=1,892; 5 RCTs; low certainty of evidence) compared with no vaccination.

Live intranasal Influenza vaccination similarly significantly increased the risk of combined local adverse events (RR 1.56; 95% CI 1.31, 1.87; n=4,921; 3 RCTs; high certainty of evidence), but did not significantly increase the risk of combined systemic adverse effects (RR 1.40; 95% CI 0.82-2.38; n=1,018; 5 RCTs; low certainty of evidence) compared with no vaccination.

Subgroup 2: Pregnant Women

The same 2018 systematic review by Demicheli et al. synthesized the evidence on the effectiveness of influenza vaccine among pregnant women.[11] Only one RCT was included in the review.[11] Three additional primary RCTs and seven secondary studies have been published since then.[12-21] Two primary RCTs involved pregnant women in the second and third trimester, while two other primary RCTs involved women in the third trimester. All studies involved the administration of trivalent inactivated influenza vaccine. As control, two studies used placebo, one study used meningococcal conjugate vaccine, and one study used pneumococcal polysaccharide vaccine. The outcomes reported include laboratory-confirmed influenza among infants and mothers, influenza-like illness among infants and mothers, serious adverse effects (SAE) among infants and mothers, and local and systemic reactogenic events. The secondary studies reported other outcomes such as infant hospitalization, influenza, and influenza-like illness among household contacts.

Infant and maternal influenza, and influenza-like illness

Pooled analysis showed that influenza vaccination of pregnant women led to a significant reduction on infant influenza (RR 0.64; 95% CI 0.53, 0.78; n=10,270; 4 RCTs; high certainty of evidence), maternal influenza (RR 0.47; 95% CI 0.29, 0.77; n=10,123; 3 RCTs, moderate certainty of evidence), and maternal influenza-like illness (RR 0.81; 95% CI 0.67-0.99; n=6,720; 3 RCTs; moderate certainty of evidence). No significant effect was seen on infant influenza-like illness (RR 0.89, 95% CI 0.73-1.08, n=6,165, 3 RCTs, low certainty of evidence).

Hospitalization and all-cause mortality

Influenza vaccination of pregnant women showed no significant reduction on infant hospitalization (RR 0.92; 95% CI 0.75, 1.13; n=2,049; 1 RCT; moderate certainty of evidence), infant all-cause mortality (RR 1.29; 95% CI 0.98, 1.70; n=7,717; 2 RCTs; moderate certainty of evidence), and maternal all-cause mortality (RR 0.62; 95% CI 0.20; 1.90; n=7,886; 2 RCTs; low certainty of evidence) compared with no vaccination.

Adverse events

Influenza vaccination of pregnant women showed no significant difference with no vaccination on serious adverse events among infants (RR 1.08; 95% CI 0.92, 1.28; n=10,173; 4 RCTs; low certainty of evidence) and mothers (RR 0.97; 95% CI 0.70-1.35; n=4,533; 2 RCTs; moderate certainty of evidence), and on laboratory-confirmed influenza among household contacts (RR 1.05; 95% CI 0.72, 1.54; n=7,097; 2 RCTs; low certainty of evidence).

Vaccine efficacy

A secondary study reported that vaccine efficacy did not vary by the timing of vaccination. The incidence risk ratios (IRR) for maternal influenza in pregnancy through six months postpartum were 0.62 (95% CI 0.35, 1.10) for those vaccinated at 17 to 25 weeks of gestation and 0.89 (95% CI 0.39, 2.00) for those vaccinated at 26 to 34 weeks of gestation. The IRRs for infant influenza were 0.73 (95% CI 0.51, 1.05) for those vaccinated at 17 to 25 weeks of gestation and 0.63 (95% CI 0.37, 1.08) for those vaccinated between 26-34 weeks of gestation.[20]

Subgroup 3: Healthcare workers

A systematic review by Thomas et al. published in 2016 reported the effects of influenza vaccines compared with no vaccine among HCWs in terms of influenza, hospitalization, and death of residents in long-term care institutions.[22] This review was appraised to be of moderate quality using AMSTAR 2. CENTRAL, MEDLINE, Embase and Web of Science were searched until October 2015. The Biological Abstracts and Science Citation Index-Expanded were searched until March 2013. A total of five studies were included, but only three cluster RCTs were included in the meta-analysis. All three RCTs had high risk of attrition bias and unclear risk for selection, performance, and detection bias.

Search of literature yielded no additional RCTs that reported patient-related outcomes of administering influenza vaccines among HCWs. Three RCTs evaluated the effect of influenza vaccine on HCW-related outcomes.[23-25] All studies involved HCWs in different hospital set-ups and administered trivalent inactivated influenza vaccine. As control, two studies used placebo alone, while one study used meningococcal conjugate vaccine, pneumococcal vaccine, or placebo.

HCW-related outcomes

Influenza vaccination significantly reduced laboratory confirmed-influenza among vaccinated HCWs (RR 0.12; 95% CI 0.04, 0.41; n=359; 1 RCT; moderate certainty of evidence). No significant effect on influenza-like illness (RR 1.07; 95% CI 0.62-1.95; n=179; 1 RCT; low certainty of evidence) and missed working days (MD -0.09 days; 95% CI -0.19, 0.02; n=538; 2 RCTs; moderate certainty of evidence) were found.

Influenza vaccination significantly increased adverse events (RR 5.34; 95% CI 2.12, 13.41; n=606; 2 RCTs; low certainty of evidence) but showed no significant difference on serious adverse events (RR 0.14, 95% CI 0.01-2.73, n=359, 1 RCT, low certainty of evidence) compared with no vaccination.

Patient-related outcomes

Influenza vaccination of HCWs showed no significant effect on laboratory-confirmed influenza (risk difference [RD] 0; 95% CI -0.03, 0.03; n=752; 2 RCTs; low certainty of evidence) and hospitalization for respiratory illness (RD 0, 95% CI -0.02, 0.02, n=3,400, 1 RCT, low certainty of evidence) among residents in long-term care institutions. The authors did not pool the results for all-cause mortality due to significant heterogeneity. The risk of death ranged from 5% to 13% in the vaccination group and 6% to 22% in the control group (n=8,468; 4 RCTs; very low certainty of evidence).

Subgroup 4: Elderly

Evidence for influenza vaccination in the elderly came from the systematic review by Demicheli et al.[10] A total of 75 studies were included in the review, with eight RCTs and 67 observational studies. The eight RCTs were analyzed separately in the meta-analysis. Out of the eight RCTs, 12.5% (1/8) had overall low risk of bias, 62.5% (5/8) as unclear risk of bias, and 25% (2/8) had high risk of bias. Two RCTs evaluated live intranasal vaccine and inactivated trivalent influenza vaccine, two RCTs evaluated inactivated trivalent vaccine, three RCTs evaluated inactivated monovalent vaccine, and one RCT evaluated inactivated quadrivalent vaccine. Search of literature for published articles since 2017 yielded no additional primary RCTs. One additional secondary study of an included RCT in the 2018 systematic review reported long-term mortality as an outcome.[26] Results from the RCTs on trivalent inactivated, quadrivalent inactivated, and live intranasal vaccine were obtained for this review.

Laboratory-confirmed influenza and influenza-like illness
Inactivated Influenza vaccination of the elderly significantly decreased laboratory-confirmed influenza (RR 0.44; 95% CI 0.27, 0.71; n=2,040; 2 RCTs; low certainty of evidence) and influenza-like illness (RR 0.64; 95% CI 0.49, 0.84; n=2,537; 2 RCTs; moderate certainty of evidence) compared with no influenza vaccination.

Live intranasal vaccination showed a trend towards benefit based on point estimates of laboratory-confirmed influenza but results were not statistically significant (RR 0.49; 95% CI 0.21, 1.17; n=220; 1 RCT; very low certainty of evidence).

Adverse events
Inactivated influenza vaccination of the elderly showed no significant difference in systemic adverse events such as fever (RR 1.58; 95% CI 0.92, 2.71; n=2,519; 3 RCTs; moderate certainty of evidence), nausea (RR 1.75; 95% CI 0.74, 4.12; n=672; 1 RCT; low certainty of evidence), general malaise (RR 1.19; 95% CI 0.87, 1.61; n=2,519; 3 RCTs; low certainty of evidence), headache (RR 1.08; 95% CI 0.77, 1.52; n=2,478; 2 RCTs; low certainty of evidence), and upper respiratory tract symptoms (RR 1.35; 95% CI 0.90, 2.01; n=713; 2 RCTs; low certainty of evidence). There was significant increase in local adverse effects, including sore arm (RR 3.62; 95% CI 2.63, 4.97; n=2,519; 3 RCTs, moderate certainty of evidence), and swelling/redness (RR 8.23; 95% CI 3.98, 17.05; n=1,806; 1 RCT, high certainty of evidence) among those given influenza vaccine.

Live intranasal Influenza vaccination showed a trend towards harm based on point estimates of adverse events. Results were not statistically significant for several adverse events including general malaise (RR 3.09; 95% CI 0.18, 53.20; n=45; 1 RCT; very low certainty of evidence), fever (RR 1.71; 95% CI 0.09, 33.24; n=45; 1 RCT; very low certainty of evidence), upper respiratory tract symptoms (RR 1.62; 95% CI 0.42, 6.29; n=45; 1 RCT; very low certainty of evidence), and lower respiratory tract symptoms (RR 2.91; 95% CI 0.41, 20.48; n=45; 1 RCT; very low certainty of evidence).

Mortality
Pooled analysis of two RCTs that reported the outcome of mortality showed no significant effect on all-cause mortality (RR 0.99; 95% CI 0.94, 1.04; n=2,537; 2 RCTs, moderate certainty of evidence) compared with no vaccination.

Recommendations from Other Groups

One local and six international guidelines recommend annual Influenza vaccination among adults.[27-33] Five guidelines specified prioritization of high-risk adults.[28,29,31-33] Table 2 summarizes the recommendations on influenza vaccination from other groups.

Table 2. Recommendations on influenza vaccination from other groups

Group	AGREE Rigor Domain Score	Recommendation	Basis for Recommendation
ACIP (2020)[27]	78.1	Routine annual influenza vaccination is recommended for all persons aged ≥6 months who do not have contraindications.	Not indicated
WHO (2020)[28]	72.9	For countries considering the initiation or expansion of programs for seasonal	Not indicated

		influenza vaccination, pregnant women should have the highest priority. Additional risk groups to be considered are elderly persons ≥65 years of age, individuals with specific chronic medical conditions, and healthcare workers.	
PSMID (2018)[29]	56.3	Inactivated influenza vaccine is routinely recommended in preventing influenza and influenza-like illness in immunocompetent adults.	Cochrane review on influenza vaccination 2014 (7 RCTs for influenza, 7 RCTs for influenza-like illness, 1 RCT for hospitalization) Strong recommendation Moderate quality of evidence
EVASG, EUGMS, WAidid (2016)[30]	56.3	Yearly influenza vaccination should be recommended for all healthy adults both for individual protection and for the overall reduction of disease burden and virus circulation. It is important to continue to ensure that the most vulnerable adults, for example those with cardiovascular disease, diabetes, pregnant, etc. are vaccinated.	Cochrane review on influenza vaccination 2014
Singapore Guidelines (2016)[31]	56.3	Influenza vaccination for healthy adults is recommended both for individual protection and for the overall reduction of disease burden and virus circulation. Among adults, vaccination is strongly recommended in the following high-risk populations: ● Aged 65 years and older ● Chronic pulmonary, cardiovascular, renal, hepatic, neurological, hematological or metabolic disorders ● Immunocompromised individuals ● Pregnant women ● Residents of chronic-care facilities ● Healthcare personnel ● Morbidly obese (BMI of 40 or greater) ● Household contacts and caregivers of children younger than 5 years of age and adults 50 years of age and older Household contacts and caregivers of people with medical conditions that put them at higher risk for severe complications from influenza.	Systematic review in 2012 (17 RCTs and 14 observational studies)
Australian Immunization Handbook (2021)[32]	93.75	Adults aged 65 years and older, pregnant women, healthcare workers, and people aged 6 months and above with medical conditions associated with an increased risk of influenza disease and	Not indicated Strong recommendation

		complications are strongly recommended to receive influenza vaccine every year.	
Indian CPG (2019)[33]	93.8	Routine influenza vaccination for adults: ● >50 years ● High risk adults, including healthcare workers, pregnant, and those with medical conditions that predispose to complications due to influenza The experts recommend the use of quadrivalent over trivalent inactivated influenza vaccine in developing nations such as India (Grade 2A).	Strong recommendation for HCWs, pregnant, people with diabetes, renal disease, liver disease, heart disease, long-term cortisone therapy, cancer. Conditional recommendation for people with hematologic conditions and HIV Usual practice point for adults >50 years 3 immunogenicity studies comparing QIV and TIV (Domachowske 2013, Kieninger 2013, Tinococa 2013)

ACIP Advisory Committee on Immunization Practices; CPG clinical practice guidelines; EVASG Escmid Vaccine Study Group; EUGMS European Geriatric Medicine Society; HCW healthcare worker; HIV human immunodeficiency virus; PSMID Philippine Society of Microbiology and Infectious Diseases; QIV quadrivalent inactivated influenza vaccine; RCT randomized controlled trial; TIV trivalent inactivated influenza vaccine; WAidid World Association for Infectious Diseases and Immunological Disorders; WHO World Health Organization

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

Cost

Evidence on the cost-effectiveness of influenza vaccines for adults was obtained from a 2018 systematic review of 30 cost-effectiveness studies as well as eight other studies in Southeast and East Asian countries. Of these, 12 were performed in Europe, nine in USA, three in Canada, three in China, one in Turkey, one in Thailand, one in Australia, and one in Israel. Seven studies assessed the effect of influenza vaccination in the general population, 11 among elderly, three among pregnant, one among adult healthcare workers, five among high-risk adult populations, and seven among children. All except one study reported that influenza vaccination is cost-effective. One study among pregnant women conducted in the USA reported a net negative societal benefit.[34]

The summary of cost-effective studies involving influenza vaccination of adult populations in Southeast and East Asian countries is shown in Appendix 5. All ten studies reported that influenza vaccination is cost-effective, with two studies involving all age groups, one study involving 50- to 64-year-old adults, one study involving the elderly and a proportion from other age groups, five in the elderly, and one in pregnant women.[35-44]

In the Philippines, no local cost-effectiveness study on Influenza vaccines has been published. The cost of each type of influenza vaccine is listed in Table 3.

Table 3. Unit cost of influenza vaccine

Parameter	Type of influenza vaccine		
	Inactivated quadrivalent	Inactivated trivalent	Live intranasal
Unit cost of vaccine	PHP 600-800[45]	PHP 450-500*	PHP 821.91 to 1,184.30**[46]

**Previous selling price in the Philippines (no longer locally available)*
***Converted from USD (not locally available)*

Patient Values and Preference, Equity, Acceptability, and Feasibility

A local study published in 2020 evaluated the perceptions and attitudes of Filipinos towards influenza vaccination using focus group discussions.[47] The study identified eight barriers to influenza vaccination, namely:

1. Patient perception that vaccination is not a priority—that responsibilities at home and work take precedence over vaccination;
2. Patient perception that they are at low risk of getting influenza;
3. Lack of awareness of the severity of influenza;
4. Lack of awareness that free influenza vaccines are provided by the government for qualified indigent elderly Filipinos;
5. Expensive cost of vaccines for some families;
6. Delayed vaccine availability a few months after the influenza season has already started;
7. Limited supply of free influenza vaccines; and
8. Improper storage that may compromise the efficacy of influenza vaccines.

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4.8. Should Japanese encephalitis vaccine be given to asymptomatic apparently healthy adults?

RECOMMENDATION

Among asymptomatic apparently healthy adults, we <u>suggest giving</u> Japanese encephalitis virus vaccine
(weak recommendation, low certainty evidence)

Considerations

The consensus panel considered the following points during the formulation of the above recommendations:

- Japanese encephalitis vaccination appears to produce net benefit among adults in terms of immunogenicity outcomes, but not actual protection from the disease. In addition, due to the disproportionate distribution of disease burden across the country, only a weak recommendation for mass vaccination was made by the panel.
- An increasing burden of the disease locally was noted, although present epidemiologic data shows that cases are only concentrated mostly in Regions 1, 2, and 3. Incidence is noted to be high especially in regions where people are exposed to rice fields or other areas where there is prevalence of the Culex mosquito. Asia has been stated as a hotspot and the above-mentioned regions in the Philippines are examples of these.

Key Findings

- Six RCTs investigated the effect of Japanese encephalitis virus (JE) vaccination on healthy, asymptomatic adults. All studies were performed in non-JE-endemic countries. No study was found specifically investigating the effects of Japanese encephalitis virus vaccination on healthcare workers, travelers to endemic areas, or microbiologists who handle the virus.
- JE vaccination significantly resulted in positive seroconversion rates in healthy adults. After 1 month, 91-100% of vaccine recipients had positive seroconversion rates (protective antibody levels against JE virus). JE vaccination was shown to provide long lasting immunity as recipients had protective titers even at 60 months. The certainty of evidence regarding immunogenicity is moderate due to indirectness in the study population and there were no clinical outcomes measured
- Local, systemic, and serious adverse events in JE vaccine recipients were comparable to those reported by placebo recipients. Most of the adverse events observed were mild, with pain at the injection site being the most reported. Only one of the serious adverse events (acute viral illness 8 days after a dose of live chimeric JE vaccine [JECV]) was deemed to be possibly vaccine-related. No deaths occurred in any of the studies. The certainty of evidence regarding the effect estimates for safety was low due to imprecision, inconsistency, as well as indirectness in the study population, since the studies were done in non-endemic countries.

Introduction

Japanese encephalitis (JE), a vector-borne flavivirus disease, is the leading cause of viral encephalitis in Asia and is endemic in the Philippines.[1] JE virus is transmitted to humans through the bite of an infected mosquito, primarily Culex species. The virus is maintained in an enzootic cycle between mosquitoes and amplifying vertebrate hosts, primarily pigs and wading birds.[2] Although JE is considered mainly a rural disease, transmission can still occur in urban areas under the appropriate ecological conditions. Major risk factors for JE in humans have been identified as: proximity to rice fields, pig rearing—particularly backyard farming—bird migration from endemic countries, mosquitoes, and stagnant waters.[3,4]

According to WHO, the annual incidence of clinical disease varies both across and within endemic countries, ranging from <1 to >10 per 100 000 population or higher during outbreaks. An estimated 68,000 clinical cases of JE occur globally each year. According to a systematic review of the epidemiology of JE in the Philippines done in 2014-2018 by Lopez et al., majority of JE cases occurred in children below 15 years of age, while individuals older than 18 years comprised 15% of cases.[5] The JE virus was found to be the causative agent in 7% to 18% of clinical meningitis and encephalitis cases, and 16% to 40% of clinical encephalitis cases.[6] Such cases are among the notifiable diseases being actively surveyed per region in the country, with a case fatality rate as high as 40%.[7]

The Acute Meningitis-Encephalitis Syndrome (AMES) is used as a surrogate for JE cases in surveillance. It was included in the Philippine Integrated Disease Surveillance and Response or PIDSR by the DOH and the Philippine Epidemiology Bureau in 2015. According to the latest PIDSR annual report in 2021, a total of 2736 AMES cases were reported and 112 (4.1%) of these cases tested positive for Japanese encephalitis via ELISA. However, majority of AMES cases (84%) were not tested. For the profile of the 112 confirmed cases, ages ranged from less than 1 to 64 years of age with a median of 7 years of age. Region I (27, 24%), Region II (26, 23%), and Region V (20, 18%) reported the highest number of confirmed JE cases across all regions. These three regions account for majority (65%) of confirmed JE cases in the country. There were 4 confirmed JEV deaths for that year notably from regions III, V, CAR and NCR.[6] All regions in the country reported AMES cases while majority of the regions in the country had positive JEV cases.

The latest data available is the 01-21 January 2023 data wherein the Philippines had an AMES incidence rate of 0.12 per 100,000 population with the highest cases reported in Regions III (19 cases, 0.15/100,000) and VI (18 cases. 0.22/100,000), but Regions IX (13cases, 0.33 per 100, 000) and II (13 cases, 0.24 per 100,000) had the highest incidence rates.[8]

JE carries a high mortality rate of 15-40% and frequently causes long term neurologic sequelae. Permanent neurologic or psychiatric sequelae can occur in 30–50% of symptomatic cases.[7] It predominantly affects children, but any age can be affected.[7] Recently however, according to several articles, JE has reemerged, predominantly affecting unvaccinated adults aged 40 years or older thereby demonstrating a shift in age distribution toward older populations.[9] As observed in Japan and South Korea, there has been a gradual shift to a greater proportion of cases in adults. Moreover, more than 90% of JE cases in Taiwan in recent years were older than 20 years.[10] Older age is an important risk factor for clinical illness with the risk of neuro-invasive illness five to tenfold higher in people aged 50 and older compared with older children and young adults.[11]

JE poses a risk not only to humans in endemic areas but also to travelers and microbiologists who handle the live virus. Because no treatment exists for this disease, prevention of this infection

is important.[5] WHO currently recommends that JE vaccination be integrated into national immunization schedules in areas where JE disease is recognized as a public health issue.[12] WHO considers JE vaccination even if confirmed cases are low but the environment is suitable for JE virus transmission, as there is little evidence to support JE reduction disease burden from interventions other than human vaccination.[7,10] Improved understanding of the risk of acquiring JE infection for travelers (representing the full spectrum from asymptomatic infection to non-localizing febrile illness to overt encephalitis) through sero-epidemiological studies is needed for future vaccination guidelines.[10]

Characteristics of Included Studies

Studies on healthy adults

Evidence for the effects of JE vaccination on healthy adults was taken from 6 RCTs.[1,13-17] Trials were performed in non-JE-endemic areas, such as Australia,[13,16,17] USA,[13,15] and Austria.[14] One RCT had study sites in Australia, Austria, Germany, Israel, New Zealand, and USA.[1] All studies focused on healthy adults at least 18 years of age, all of which had no history of a flavivirus infection and vaccination against Japanese encephalitis.

The included RCTs compared either inactivated or live attenuated JE vaccines against placebo.[13,16] Primary outcomes assessed were immunogenicity (seroconversion rates, geometric mean titers of neutralizing antibodies against JE) and safety (local adverse events, systemic adverse events. and serious adverse events). A safety study compared placebo versus the inactivated cell culture derived JE vaccine or IC51.[1] One study investigated the immunogenicity and safety of the inactivated cell culture derived JE vaccine or IC51 and hepatitis A vaccine or HavRix when administered alone or concomitantly to healthy subjects versus a combination with placebo.[14] One study compared the live recombinant JE vaccine (Chimerivax) given alone or concomitantly with yellow fever (YF) vaccine with that of placebo.[15] The last study evaluated the safety, tolerability and immunogenicity of a live attenuated Japanese encephalitis chimeric virus vaccine co-administered with live attenuated yellow fever (YF) vaccine or administered sequentially to placebo.[17]

Studies on special populations (healthcare workers, travelers to endemic countries, laboratory personnel)

No study was found specifically on healthcare workers and laboratory personnel. WHO does not consider healthcare workers at special risk of contracting JE, except for those working in endemic areas or involved in vector control.[18] In a laboratory setting, it is unknown whether vaccination provides protection after accidental percutaneous, or theoretically, mucosal or inhalational exposures.[19] For travelers to JE-endemic areas, evidence was only available for children from non-endemic areas.[20]

Outcomes

Healthy Adults

Efficacy

Immunogenicity: Seroconversion rate (1 month)

Almost all vaccinated respondents (97.1%) had positive seroconversion rates or attained protective antibody levels after 1 month of vaccination compared with placebo (1.8%) (RR 51.9 [95% CI 44.1 to 53.9], I^2=24%; n=550, 4 RCTs).

Immunogenicity seroconversion rate > 2 months (6, 12, 24 and 60 months)
Only one RCT looked at the long-term immune response after a single dose of a live chimeric JE vaccine (JECV).[16] This study concluded that JECV is safe, well-tolerated, and that a single dose provides long-lasting immunity. Additionally, it states that a booster dose, compared with a single dose, provided only a marginally higher residual seroprotection rate at month 60. With regards to giving a second dose of the live chimeric JE vaccine, another study concluded that a second dose of the JECV had no booster effect.[15]

The seroprotection rate after 1 JECV dose was 97% (95% CI 93 to 99%) at 6 months, 95% (95% CI 87 to 99%) at 1 year, 90% (95% CI 81 to 96%) at 2 years, and 93% (95% CI 82 to 99%) at 5 years. For booster dose of JECV, the seroprotection rate was 100% (95% CI 96 to 100%) at 7 months, 99% (95% CI 93 to 100%) at 1 year, 99% (95% CI 92 to 100%) at 2 years, and 97% (95% CI 85 to 100%) at 5 years.

Safety

Local adverse events
JE vaccination is comparable to placebo in terms of incidence of local adverse events, with rates of 29.5% among vaccine recipients and 25.5% in the placebo recipients (RR 1.11 [95% CI 0.74 to 1.66]; n=875, I^2=59%, 4 RCTs). The most common adverse events reported by vaccinated individuals were pain on the injection site and erythema of the injection site.

Systemic adverse events
In terms of systemic adverse events, no significant difference was noted between JE vaccine and placebo (28.3% vs. 37% in placebo; RR 0.81 [95% CI 0.63 to 1.05]; I^2=46%, n=798; 3 RCTs). Most participants reported experiencing headache, fatigue, and malaise.

Serious adverse events
No significant difference was noted in rates of serious adverse events in vaccinated respondents (1.37%) and the control group (0.01%) (RR 1.04 [95% CI 0.45, 2.38], I^2=35%, n=5464; 6 RCTs). Only 1 case of acute viral illness resulting in hospital admission 8 days was deemed possibly related to JECV vaccination due to the temporal association.[16]

Certainty of evidence on benefits and harms
Overall certainty of evidence for efficacy (immune response) was moderate due to low risk of bias, but also for indirectness. Certainty of evidence for safety was rated low due to imprecision resulting in wide confidence intervals and due to indirectness as well.

Table 1. Benefits and harms of Japanese encephalitis virus vaccination in healthy adults

Critical Outcomes	No. of Studies (No. of Participants)	Effect Estimate [95% CI]	Interpretation	Certainty of Evidence
Healthy adults				
Immune response: Seroconversion rate after 1 month	4 RCTs (n=550)	RR 39.6 [12.0, 130.2]	Beneficial	Moderate
Systemic adverse events	3 RCTs (n=798)	RR 0.81 [0.63, 1.05)	Equivalent	Low
Serious adverse events	6 RCTs (n=5104)	RR 1.04 [0.45, 2.38]	Inconclusive	Low

CI confidence interval; RCT randomized controlled trial

Recommendations from Other Groups

Table 2 summarizes existing recommendations from various groups. The Philippine Society for Microbiology and Infectious Diseases (PSMID) issued a weak recommendation in favor of vaccination for all children and adults if without contraindications. The WHO and CDC has no direct statement regarding routine vaccination of healthy adults, but recommends vaccination for certain subgroups (e.g., travelers to endemic areas, laboratory workers at risk of exposure to JE).

Table 2. Recommendations from international and local CPGs

Group	Recommendations	Strength of Recommendation, Certainty of Evidence
World Health Organization (WHO, 2019)[12,21]	Healthy adults ● No direct statement on healthy adult vaccination, including booster recommendation. ● Recommends having strong JE prevention and control activities, including JE immunization in all regions where the disease is a recognized public health priority, along with strengthening surveillance and reporting mechanisms. ● Vaccination should be considered even if the number of JE-confirmed cases is low. Travelers ● Recommends travelers spending extensive time in JE-endemic areas to get vaccinated before travel, along with personal preventive measures which includes using mosquito repellents, long-sleeved clothes, coils, and vaporizers. Healthcare workers ● Healthcare workers are generally not at special risk of contracting JE. Workers at high-risk in endemic areas, such as those involved in vector control, should be vaccinated. Immunocompromised persons ● Inactivated Vero cell-derived JEV can be used in immunocompromised persons including HIV-infected individuals, but the immune response may be lower than in fully immunocompetent persons.	Not available
US Advisory Committee on Immunization Practices (US ACIP 2019, 2022)[22,23]	Healthy adults ● No statement regarding routine JE vaccination among healthy adults. U.S. Travelers ● Vaccination is recommended for travelers with higher risk itineraries to further reduce risk of infection. Such itineraries include: (1) moving to a JE-endemic country for residence, (2) longer-term (e.g., ≥1 month) travel to a JE-endemic area, (3) frequent travel countries where JE occurs. ● Vaccination should be considered for travelers spending less than one month in a country where JE occurs, if they will visit rural areas and have an increased risk for mosquito bites and are not sure of their travel plans. ● JE vaccine is not recommended for travelers with very low-risk itineraries, such as shorter-term travel limited to urban areas or outside of a well-defined JE virus transmission season.	Not available

	● The decision on vaccination should be individualized and consider the following: ○ Risks related to the specific travel itinerary ○ Likelihood of future travel to countries where JE is endemic ○ High morbidity and mortality of JE ○ Availability of an effective vaccine ○ Possibility (but low probability) of serious adverse events after vaccination ○ Traveler's personal perception and tolerance of risk Laboratory workers ● Vaccination is recommended for all laboratory workers with a potential for exposure to JE viruses other than SA14-14-2 JE vaccine virus. ● Vaccination is generally not required for those who work only with SA14-14-2; those working with high volumes or concentrations of the virus or passaging virus should undergo individual risk assessment by local biosafety committee. ● Not required for workers handling routine clinical samples. The vaccine is given as a 2-dose series (Inactivated JE vaccine). A booster dose is recommended after a year for people who remain at risk.	
Philippine Society for Microbiology and Infectious Diseases (PSMID, 2018)[21]	The vaccine can be given at any time if without contraindications (i.e., severe allergic reaction, hypersensitivity to any vaccine component such as protamine sulfate): • To children 9 months and above, including adults • Travelers going to Bangladesh, Bhutan, Brunei, Burma, Cambodia, China, India, Indonesia, Japan, Korea, Laos, Malaysia, Nepal, Papua New Guinea, Philippines, Singapore, Taiwan, Thailand, Timor Leste, Vietnam • No booster dose needed in immunocompetent adults • Single-dose administration, subcutaneous route	Weak recommendation, high quality of evidence[†]

[†]Torresi 2010 Vaccine 28(50), 7993-8000

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

Cost

Costs of JE vaccination

The only FDA approved JE vaccine in the Philippines is the live attenuated recombinant (vero cell derived) vaccine under the brand name Imojev manufactured by Sanofi Pasteur. It is given as a single dose subcutaneously. Imojev is priced at PHP 1,700/dose.[24]

As for the other JE vaccine types not readily available in the Philippines, the cost of the inactivated SA-14- 14-2 JE vaccine under the brand name Ixiaro manufactured by Valneva, USA, Inc. is USD 295 (approximately PHP 16,100) per 0.5mL suspension. For this type of vaccine, 2 doses are required for a primary regimen, bringing the total cost to around USD 590 (PHP ~32,450).[25] This is the only JE vaccine licensed and available in the United States; hence, this is the vaccine being referred to in the CDC recommendation.[22]

For the oldest type of vaccine, the mouse brain-derived Japanese encephalitis vaccine or JE-MB, its production was discontinued in 2006. The remaining supplies are now limited and not readily for sale in the market. JE-MB had been manufactured in Japan by The Research Foundation for

Microbial Diseases of Osaka University (Biken, Osaka, Japan).[25] Since it is no longer being produced, it has been substituted by the newer types of JE vaccines.

Cost-effectiveness of JE vaccination

It is unknown whether JE vaccination in adults would be cost-effective. In the Philippines, a 2020 cost-effectiveness analysis concluded that vaccinating children with live attenuated JE vaccine (Imojev) would be cost-effective, reduce long-term costs associated with the disease, and improve health outcomes compared to no vaccination.[26] Among the three vaccination strategies evaluated by the study, JE vaccination via national campaign followed by national routine delivery was seen as the most cost-effective strategy with a cost per disability adjusted life year (DALY) averted of USD 233 (PHP 12,815) and USD 29 (PHP 1,595) from the government and societal perspectives, respectively. JE vaccination was predicted to prevent 27,856 to 37,277 cases, 5,571 to 7,455 deaths, and 173,233 to 230,704 DALYs among children under five over 20 consecutive birth cohorts. Total incremental costs of vaccination versus no vaccination over 20 birth cohorts were USD 230,000 to 440,000 (PHP 12.6 to 24 million) annually from the societal perspective and USD 2.2 to 2.7 million (PHP 121 to 148 million) from the governmental perspective.[26]

Patient Values and Preference, Equity, Acceptability, and Feasibility

Feasibility

Currently, there are four types of JE vaccines: the inactivated mouse brain derived vaccine (oldest class), inactivated cell derived vaccine, live attenuated, and the live recombinant (chimeric) vaccine.[7] A 2021 network meta-analysis comparing these vaccine classes found that all vaccines demonstrated similar safety profiles, but live chimeric and inactivated Vero cell vaccines were most immunogenic.[27]

The only available Philippine FDA-registered JE vaccine in the country is the live recombinant (chimeric) vaccine. The vaccine has already been introduced in Regions I, II, III, and the Cordillera Administrative Region (CAR) in 2019 following the recognition of the disease as a public health priority.[6] Children 9 months old to less than 5 years old were eligible to be vaccinated. Immunization campaigns are scheduled before the start of the rainy season where JE disease activity is at its peak.

Local data on the epidemiology of Japanese encephalitis is lacking among the following subgroups of patients: healthy adults, healthcare workers, travelers to endemic areas, and microbiologists at risk of exposure. An immunization campaign targeting these subgroups is also not yet available.

Patient values and preferences

There are no published local data to date evaluating the knowledge, attitudes, and perceptions of Filipinos on JE vaccine.

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4.9. Should measles-containing vaccine be recommended to apparently healthy adults?

RECOMMENDATION

Among healthy adults (non-pregnant or unvaccinated), we recommend giving measles-containing vaccine.
(strong recommendation, very low certainty evidence)

Considerations

The consensus panel considered the following when formulating this recommendation:

- Studies on the efficacy of measles vaccine among healthy adults are lacking. The evidence base used indirect data involving the pediatric population; thereby, posing applicability issues.
- The evidence base included studies where two doses of measles-containing vaccine (MCV) were administered to participants. This may have applicability issues since one dose is sufficient to confer lifelong immunity among adults. In clinical practice, a single dose is administered to healthy adults while the two-dose regimen, given one month apart, is suggested only for high-risk groups including healthcare workers.
- Evidence on the cost-effectiveness of measles-containing vaccines came from simulated or hypothetical birth cohorts.
- Measles vaccination is part of the Expanded Program on Immunization of the Department of Health through the administration of MMR vaccine starting at nine months up to 12 months old, followed by a booster through MR vaccine given at school-age (i.e., grade levels one and seven). However, school-based vaccination efforts only reached a quarter in 2019 due to the COVID-19 pandemic. Additionally, surveillance by DOH showed low rates of fully immunized children, recording only 60% in 2020. With this, there is an expected increase in the population of measles-susceptible individuals.
- Despite very low certainty of evidence, the panelists were unanimous in recommending measles vaccine to healthy adults due to: (1) the airborne transmission of measles; thereby, having a highly infectious nature, (2) the high morbidity and mortality rates associated with it, and (3) the expected increase of adult population susceptible to measles secondary to currently low vaccination rates.

Key Findings

- Indirect evidence from nine observational studies showed that giving two doses of MCV compared with no vaccination yielded an overall median vaccine efficacy of 94.1% (IQR 88.3-98.3%). At a risk ratio of 0.03 (95% CI 0.02-0.08; I2=60%), studies showed that giving 2-dose MCV significant reduced measles incidence compared to no vaccine.
- Measles seroconversion rates for people ≥7 years old ranged from 96%-100%. The results showed that an MMR vaccine, even if given outside the recommended age, is still immunogenic for measles.
- Among healthcare workers, data from indirect studies showed that receipt of standard titer MCV was associated with a reduction in all-cause mortality (RR 0.74,95% CI 0.51 1.07) from four clinical trials.

Introduction

Burden of the Disease

Measles is a highly contagious acute infection characterized by fever, cough, coryza, conjunctivitis, rash, and enanthem that may lead to severe complications including encephalitis.[1] The introduction of vaccine programs in the 1960s brought dramatic decline in the number of cases proving effectiveness of the routine measles, mumps, and rubella (MMR) immunization.[2,3]

In the Philippines, 2019 data showed that there were 2.31 deaths per 100,000 cases of measles.[4] A surveillance report of the Department of Health (DOH) issued in July 2019 reported 208% higher number of measles cases compared to the same period in 2018. Ages of cases ranged from less than one month to 88 years old. Age groups with the greatest number of cases were: 1 to 4 years old, 6 to 8 months old, and less than 6 months old. Majority of the cases were not vaccinated. There were 538 deaths out of the 39,856 measles cases, translating to a case fatality rate (CFR) of 1.3%.[5]

No specific antiviral therapy is given for measles. Medical care is supportive, with the goal of relieving symptoms and addressing complications.[6] However, reports have shown that adults with measles are at increased risk of mortality compared with older children, and measles in pregnancy is associated with premature labor and spontaneous abortion.[1,7]

Measles vaccine usually offers long-term immunity, but antibody titers have been shown to decrease over time.[1,8-10] Anamnestic response to revaccination of people with waning antibody titers after primary vaccination suggests continued immunity.[1,11]

Characteristics of Included Studies

Randomized controlled trials (RCTs) investigating the effect of measles-containing vaccines (MCV) in an otherwise healthy adult population are limited. Most of the extant literature involve pediatric populations. No direct studies comparing MCV with placebo in terms of its effect on reducing measles incidence, all-cause mortality, and hospitalization rates among healthy adults were found. To inform this review, indirect evidence was obtained from three systematic reviews.

Two systematic reviews by Pawaskar et al.[12] and Nyaku et al.[13] used RCTs on the efficacy, immunogenicity, and safety of MMR II vaccines in healthy children and adults. To obtain data related to the effectiveness of measles-containing vaccines administered under routine field conditions, a 2011 systematic literature review by Uzicanin and Zimmerman that summarized all eligible studies from 1963 to 2010 was included.[12]

Outcomes

Benefits and Harms of Measles-Containing Vaccine

The summary of all critical outcomes of measles vaccination among healthy adults is shown in Table 1.

Table 1. Benefits and harms of measles vaccine per subgroup of healthy adults

Outcomes	No. of Studies (No. of Participants)	Effect Estimate	Certainty of Evidence
Healthy adults			
Incidence of measles	9 (n=4,387)	VE 94.1% (IQR 88.3, 98.3%)	Very Low
Immunogenicity	8 (n=1,325)	Range across studies: 96% to 100%	Low
Adverse events	7 (n=1,225)	Range across studies: Fever – 5.2% to 8.7% Injection site reactions – 2% to 33.3%	Low
Healthcare workers			
All-cause mortality	4 (n=17,190)	RR 0.74 (95% CI 0.51, 1.07)	Low

CI confidence interval; IQR interquartile range; RR risk ratio; VE vaccine efficacy

Subgroup 1: Healthy adults

Incidence of measles (Adapted from Uzicanin and Zimmerman, 2011; 9 studies; n=4,387; very low certainty of evidence)

Nine observational studies from this review showed that giving two doses of MCV compared with no vaccination yielded an overall median vaccine efficacy (VE) of 94.1% (interquartile range [IQR] 88.3, 98.3%).[14]

To produce risk ratios, data were extracted from nine observational studies from the review. Studies showed that giving two-dose MCV significantly reduced measles incidence compared to no vaccination (relative risk [RR] 0.03; 95% CI 0.02, 0.08; I^2=60%).

Immunogenicity and seroconversion (Adapted from Pawaskar et al., 2021 and Nyaku et al., 2021; 8 studies; n=1,325; low certainty of evidence)

Eight studies were included in the Pawaskar et al. review, among which seven studies were on ages seven years old and above. Five of the seven studies gave MMR vaccine as a second dose, one gave it as a single dose, and the remaining study was unspecified.[12] In the Nyaku et al. review, two out of the 15 studies were done in ages seven years old and above. One study was already included in the Pawaskar et al. review, while the other included study was unique.[13]

The eight total studies analyzed in the two systematic reviews found that the measles seroconversion rates for ages seven years old and above ranged from 96% to 100%. Results showed that an MMR vaccine is still immunogenic for measles even if given outside the recommended age. Table 2 shows the immunogenicity rates.

Table 2. Immunogenicity of an MMR vaccine among individuals ≥7 years of age, adapted from Pawaskar et al., 2021[12] and Nyaku et al., 2021[13]

Author	Country	Population (N) receiving MMR	Age (Years)	Timeframe Post-vaccination	Immunogenicity (Seropositivity, Measles)
Abu-Elyazeed[a]	USA, Estonia, Slovakia	457 with at least one previous dose of MMR vaccine	25.6 (mean)	42 days	99.1% SRR defined as ≥200 mIU/mL (ELISA)
Gothefors	Sweden	150 who had a first dose of MMR II in their 2nd year	11-12 (range)	40 days	100% SCR defined as appearance of detectable antibody activity in initially seronegative subjects (ELISA)

Diaz-Ortega	Mexico	62 (MMR II via injection) All received one dose of MMR II at 1–2 years	6.72 (mean)	1 month, 1 year	1 month: 100% SCR defined as ≥120 mIU/mL (PRN) 1 year: 100%
Diaz-Ortega	Mexico	100 (not specified if prevaccinated or unvaccinated)	18-25 (range enrolled)	2 months, 1 year	2 months: 96% SCR defined as ≥120 mIU/mL (PRN) 1 year: 95%
Sarno	Mexico	40 (standard syringe); 12/40 had received prior measles vaccine, 1/40 MMR at 12 months of age	11.1 (mean)	12 weeks	100% above baseline
Dos Santos	Brazil	219 previously vaccinated and unvaccinated	8.92 (mean)	21-30 days	99.5% SPR, threshold not defined (ELISA)
Cassidy	USA	97 (all vaccines at visit 1), 100 (HB at visit 1, Td and MMR II at 4.5 months) [dose 2]	11-12 (range)	6 weeks	100%, defined as ≥120 IU/ml (EIA)
Diaz-Ortega[b]	Mexico	100 (given 1 dose of MMR II)	18-25 (range)	21 days	96%

ELISA enzyme-linked immunosorbent assay; EIA enzyme immunoassay; MMR measles, mumps, rubella; SCR seroconversion rate; SRR seroresponse rate; Td tetanus, diphtheria
[a]Studies that were included in both reviews by Pawaskar et al. (2021) and Nyaku et al. (2021)
[b]Studies that were included only in Nyaku et al. (2021)

Adverse events (Adapted from Pawasakr et al., 2021; 7 studies; n=1,225; low certainty of evidence)

Reported adverse reactions to MMR vaccine include fever, rash, lymphadenopathy, joint complaints, hypersensitivity reactions, development of immune thrombocytopenia (ITP), and seizures.[12] Pawaskar et al. investigated the safety data in the seven included studies on ages seven years old and above. The adverse events reported in these studies include fever ≥38˚C (5.2%-8.7%), injection site reactions (2%-33.3%), and measles/rubella-like rash after the second dose (0.4%). Overall, this study suggests that the MMR vaccine is safe and well tolerated by recipients seven years old and above. No serious adverse events were documented in the studies included in the review.[12]

Subgroup 2: Healthcare workers

All-cause mortality (Adapted from Higgins et al., 2016; 4 studies; n=17,190; low certainty of evidence)

Data from indirect studies showed that receipt of standard titer MCV was associated with a reduction in all-cause mortality (RR 0.74; 95% CI 0.51, 1.07) from four clinical trials.[15]

Measles outbreaks in hospital settings are driven by factors such as low MCV coverage among the health human resource, low knowledge about measles, delay in measles hospital case reporting, and the lack of proper measles case management.[16] Strict use of alcohol-based hand sanitizer and rapid isolation are both insufficient measures to prevent measles outbreak in a hospital setting, while vaccination is the only reliable means to prevent nosocomial measles infection.[17] Nosocomial measles infection in low-resource settings can be reduced through a mandatory two-dose measles immunization of all healthcare workers.[18] The measles immunization status of healthcare workers should also be documented.

Recommendations from Other Groups

There are one local and three international guidelines that recommend influenza vaccination among adults (Table 3). The Philippine Society for Microbiology and Infectious Diseases (PSMID) recommends giving one dose of MMR vaccine for immunocompetent adults and as post-exposure prophylaxis to be given within 72 hours after exposure. PSMID also recommends giving two doses for adults at high risk of transmission.[19]

The Australian Immunisation Handbook (2021) recommends the administration of two doses for (a) adolescents and (b) adults born during or since 1966 who did not receive two doses of MCV, specifically: healthcare workers, childhood educators and carers, people working in long-term care facilities, people working in correctional facilities, and travelers.[20] WHO recommends giving two doses of MCV against one dose on healthy adults with unknown history of prior measles infection. MCVs or proof of measles immunization is required as a condition for enrollment into training and employment, and must be offered to measles-susceptible adults like travelers and health workers.[21] The ACIP recommends one dose of MMR for healthy adults with no evidence of immunity to measles. ACIP also recommends administering one to two doses for persons with unknown history of prior infection. Lastly, ACIP recommends two doses for those born in 1957 or later with no known evidence of immunity to measles.[2]

For healthcare workers, two doses of an MCV should be administered right away if they have no laboratory evidence of measles immunity.[22] International guidelines also recommend two doses of measles-containing vaccines for adults at high risk of transmission among healthcare workers.[2,19,23,24]

Table 3. Recommendations on measles-containing vaccination from other groups

Recommendations for Measles Vaccine	Guideline 1: PSMID 2018	Guideline 2: Australian Immunisation Handbook 2021	Guideline 3: WHO Routine Immunization 2020	Guideline 4: USA ACIP 2013
AGREE Rigor Domain Score	56.3	93.75	72.9	78.1
Overall quality assessment–				
Population subgroup 1: Healthy adults with unknown history of prior measles infection single dose	Strong recommendation; low quality of evidence 1 dose MMR vaccine for immunocompetent adults; 1 dose within 72 hours as post-exposure prophylaxis Basis for recommendation: ACIP	[a]	[a]	No rating 1 dose for no evidence of immunity to measles, mumps, or rubella; 1-2 doses for those with unknown history of prior infection Basis for recommendation: MMWR
Population subgroup 2: Healthy adults with unknown history of prior measles infection two doses	[a]	No rating 2 doses for adolescents and adults born during or since 1966 are recommended to	Strong recommendation; high level of scientific evidence 2 doses of measles containing vaccine	No rating 1-2 doses for those with unknown history of prior infection

		have received for catch-up vaccination/unknown history - 4 weeks apart. Basis for recommendation: Not indicated	are more effective than one dose in protecting against measles. Basis for recommendation: Not indicated	Basis for recommendation: Not indicated
Population subgroup 3: Healthcare workers single dose	[a]	[a]	[a]	[a]
Population subgroup 4: Healthcare workers two doses	No rating 2 doses for adults at high risk of transmission Basis for recommendation: ACIP	Strong recommendation 2 doses of measles- containing vaccine for HCW Basis for recommendation: 4 studies	No rating All HCWs should be immune to measles and proof/documentation of immunity or immunization should be required as a condition of enrollment into training and employment; offer to adults known or likely to be susceptible (HCWs, travelers). Basis for recommendation: Not indicated	No rating 2 doses for those born in 1957 or later with no evidence of immunity to measles, mumps and rubella (at least 4 weeks apart for measles) 2 doses for those born before 1957 with no evidence of immunity to measles, mumps, or rubella (at least 4 weeks apart for measles) Basis for recommendation: MMWR

ACIP Advisory Committee on Immunization Practices; HCW healthcare workers; MMWR Morbidity and Mortality Weekly Report; PSMID Philippine Society of Microbiology and Infectious Disease; WHO World Health Organization
[a]No recommendations

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

Cost

Economic analyses of the current measles vaccination program in East China and in the USA concluded that the national two-dose MMR vaccination program is highly cost-beneficial and results in substantial cost savings compared with the absence of the program.[25,26] Appendix 5 shows the detailed characteristics of these studies.

Patient Values and Preference, Equity, Acceptability, and Feasibility

Before the development and availability of measles vaccine in the 1960s, outbreaks of measles occurred predictably every year in the United States and other temperate regions.[27] In 2019, measles outbreaks have persisted in the USA and globally with over 400,000 confirmed cases, reflecting an overturn of decades of progress toward measles elimination in many countries.[28] Although safe and effective vaccine has been available over six decades, vaccine hesitancy and social and political unrest globally have led to under-vaccination.[27] Vaccine hesitancy is one of the contributors to low vaccination coverage in both developed and developing countries.[27,29,30]

Determinants of measles vaccine hesitancy were identified in a qualitative study in Sudan[29] and were summarized as:

1. Contextual influences (geographic barriers, religious beliefs);
2. Individual and group influences (beliefs and attitudes of parents about health and prevention; past experiences in vaccination; lack knowledge and awareness; perception of a lack of risk and low benefit of vaccination among guardians); and
3. Vaccine and vaccination-specific factors (vaccination program, schedules and mode of delivery, role of healthcare professional).

In the Philippines, DOH declared measles outbreak in five regions with a nearly eight-fold increase in number of cases since 2018. There has been a decline in the first dose of vaccine in the past decade, from above 80% in 2008 to below 70% in 2017. Initial figures for 2018 indicated further decrease leading to more children becoming susceptible to measle infection. WHO estimated that at least 2.6 million Filipino children under five years are not protected from measles. Multiple factors were identified that contributed to the low immunization coverage in the Philippines:

1. Inadequacy of service delivery including limited immunization sessions at the primary care level and inaccessibility issues in hard-to-reach areas; and
2. Decreased vaccine confidence.[30]

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4.10. Should meningococcal vaccine be given to asymptomatic apparently healthy adults?

RECOMMENDATIONS

Among asymptomatic apparently healthy adults, we <u>suggest against giving</u> meningococcal MenACWY vaccine.
(weak recommendation, high certainty evidence)

Among asymptomatic apparently healthy young adults (18-25 years old), we <u>suggest against giving</u> meningococcal MenB vaccine.
(weak recommendation, moderate certainty evidence)

Among adults with high risk of contracting meningococcal disease*, we <u>suggest giving</u> meningococcal MenACWY vaccine.
(weak recommendation, moderate certainty evidence)

Among adults with high risk of contracting meningococcal disease, we <u>suggest giving</u> meningococcal MenB vaccine.**
(weak recommendation, very low certainty evidence)

*Individuals living in close quarters/proximity, asplenic patients, persons handling *Neisseria meningitidis* isolates
**Young adults in crowded dormitories

Considerations

The consensus panel considered the following points during the formulation of the above recommendations:

- Despite the net benefit, a weak recommendation against giving the vaccine for all apparently healthy adults was formulated due to the low prevalence of the disease, low rates of infection, low endemicity, and high costs that accompanied the vaccination process. In addition, the panel also mentioned that there are existing prophylactic interventions for those infected with meningococcal disease.
- For individuals considered to be at high risk of contracting meningococcal disease, vaccination using either MenB or MenACWY vaccines was suggested. These include individuals living in close quarters, asplenic patients, and persons handling *Neisseria meningitidis* isolates (i.e., microbiologists, pathologists, etc.).

Key Findings

- 1 RCT compared the immunogenicity and safety of MenACWY with control (Tdap) in healthy adults 11 to 55 years old (mean age 24.7 years old). Indirect evidence regarding safety of MenACWY vaccines was also obtained from 8 RCTs comparing different types of MenACWY vaccines as well as 1 systematic review of observational studies. For MenB vaccines, evidence for this review was based on 2 RCTs.
- MenACWY vaccines showed benefit in terms of eliciting immune response against serogroups A, C, W, and Y 28 days post-vaccination. Although there were significantly

more systemic adverse events and injection site reactions in the vaccine group, no serious adverse events were reported. Evidence from eight other trials exhibited similar results in terms of safety and immunogenicity. Four observational studies reported real-world safety data of MenACWY among pregnant women. Findings suggest that there is no increased risk of pregnancy- or birth-related adverse events. The certainty of evidence was high across outcomes, except for serious adverse events in pregnant women which was rated very low due to serious imprecision, risk of reporting bias, and observational study design limitations.

- MenB vaccines were more effective compared to placebo control in terms of immunogenicity. Significantly more subjects exhibited protective antibody titer levels at 2 months and 12 months based on 1 RCT that evaluated MenB-4C vaccine. No serious adverse events related to the vaccine were reported. Certainty of evidence was moderate.
- One RCT that compared MenB-FHbp versus control group (HAV vaccine), on the other hand, showed benefit in terms of seroconversion at 28 days. The certainty of evidence is moderate. There is inconclusive evidence showing that the MenB-FHbp vaccine causes serious adverse events. The certainty of evidence is low due to imprecision and risk of bias.

Introduction

Neisseria meningitidis (meningococcus) is a significant source of deadly bacterial infections, which frequently manifest as meningitis or meningococcemia.[1] Invasive meningococcal disease affects all ages, especially infants less than 1 year old, adolescents, and the elderly. Serogroups C, W, and X account for the majority of endemic and epidemic meningococcal illness.[2]

The endemicity of meningococcal disease is low (<2 cases/100,000 per year) according to the World Health Organization.[2] All of the five serogroups (A/B/C/W/Y) were already identified in the country.[1] Serogroup B was identified as the most common isolate based on a local study investigating the prevalence of meningococcal nasopharyngeal carriage in Filipinos 5-24 years old living in an urban setting.[3] The DOH Epidemiology Bureau – Philippine Health Statistics has documented 84 cases of meningococcal infections in 2019, corresponding to a rate of 0.1 per 100,000 population.[1] Majority of the cases (73/84 or 87%) were recorded from Mindanao.[1] The Cordillera outbreak was caused by serogroup A, whereas the other two epidemics (Davao and Makati) were caused by serogroup B.[1] The rate of disease remain unchanged in 2020.[3] However, the cases were concentrated in a different region (CALABARZON).[3] Apart from age group and geographical locations, there were no local records of prevalence of *N. meningitidis* infection within populations at high risk, such as those with frequent or close contact with cases.

In a meta-analysis, risk factors associated with contracting invasive meningococcal disease were HIV-infected (RR 4.77, 95% CI 2.16 to 10.5), HIV-infected among the 25 to 44 years (RR 11.88, 95% CI 7.79 to 18.10), passive home smoke exposure (adjusted OR 2.37, 95% CI 1.11 to 5.07), high crowding index (OR 1.67, 1.16 to 2.41), crowded living space (OR 2.78, 95% CI 1.25 to 6.21).

Epidemiology and vaccination policies have changed over time. There has also been a switch from using monovalent conjugate vaccine to quadrivalent conjugate vaccines for meningococcal disease. In other countries, there are two types of meningococcal vaccines that are currently registered and recommended[4,5] and cover different serogroups: (1) quadrivalent (A, C, W, Y) meningococcal (MenACWY) vaccines conjugated to different protein carriers such as diphtheria toxoid (MenACWY-D), tetanus toxoid (MenACWY-TT), and modified cross-reacting material (MenACWY-CRM)[6-15] and (2) recombinant meningococcal B (MenB) vaccines.[5]

Characteristics of Included Studies

MenACWY Vaccines

Nine RCTs evaluated the immunogenicity and safety of various MenACWY vaccines among healthy adults.[6,7,9-13,15,16] Only 1 RCT compared quadrivalent, single dose of MenACWY-DT (Menactra®) against an active control (tetanus/diphtheria/acellular pertussis [Tdap] vaccine) among 300 healthy adults aged 11 to 55 years.[11] The remaining 8 RCTs compared different types of MenACWY vaccines. Data from one systematic review of various observational studies was also used to obtain safety outcomes on special population groups.[17]

MenB vaccines

Two randomized trials[16-18] investigated the effects of recombinant protein vaccines for serogroup B among adults, of whom majority were younger adults (18 to 25 years old). One trial compared MenB-4C vaccine compared to placebo (saline)[19] while another assessed MenB-FHbp using HAV vaccine as control.[20] Both RCTs included immunogenicity and number of adverse events as their primary outcomes. Similar to MenACWY, the proportion of those who achieved at least four-fold increase in antibody titers postvaccination over the total number of participants in the intervention and control group were compared. The high relative effect in the summary of findings for seroconversion rate indicates a better vaccine response.

One observational study[21] also investigated the effect of MenB-4C vaccine in a university outbreak in USA. Majority of the cohort were undergraduate students with mean age of 21 years who were living in an on-campus dormitory and were previously vaccinated with MenACWY vaccines.

Outcomes

Benefits and Harms of Measles-Containing Vaccine

The summary of all critical outcomes of meningococcal vaccination is shown in Table 1.

Table 1. Benefits and harms of meningococcal vaccination.

Critical Outcomes	No. of Studies (No. of Participants)	Effect Estimate [95% CI]	Interpretation	Certainty of Evidence
MenACWY vaccines				
Seroconversion rate – MenA (28 days)	1 RCT (295)	RR 8.38 [4.48 to 15.69]	Benefit	High
Seroconversion rate – MenC (28 days)	1 RCT (296)	RR 10.93 [5.61 to 21.28]	Benefit	High
Seroconversion rate – MenW (28 days)	1 RCT (295)	RR 7.54 [4.43 to 12.84)	Benefit	High
Seroconversion rate – MenY (28 days)	1 RCT (295)	RR 6.03 [3.06 to 11.89]	Benefit	High
Serious adverse events	1 RCT (298)	No SAEs reported in either control or vaccine group	No significant harm	High
Serious adverse events (Pregnant women)	4 observational (234)	No increased risk of pregnancy or birth-related adverse events.	Inconclusive	Very low
MenB vaccines				
MenB-4c Seroconversion rate (2 months)	1 RCTs (389)	RR 1.52 [1.37 to 1.68]	Benefit	Moderate
MenB-4c Seroconversion rate (12 months)	1 RCT (389)	RR 1.88 [1.59 to 2.22]	Benefit	Moderate

MenB-4c Serious adverse events (6 months)	1 RCT (581)	No SAEs related to vaccination	No significant harm	Moderate
MenB-FHbp Seroconversion rate (28 days)	1 RCT (3,293)	RR 8.48 [6.95 to 10.35)	Benefit	Moderate
MenB-FHbp Serious adverse events (6 months)	1 RCT (3,293)	RR 1.00 [0.50 to 1.95]	Inconclusive	Low

CI confidence interval; RCT randomized controlled trial; RR risk ratio; SAE serious adverse events

MenACWY VACCINES

Efficacy

Immunogenicity (Seroconversion rate at 1 month)
Immunogenicity is characterized as vaccine response which is commonly defined as at least four-fold increase in antibody titers from pre-vaccination status observed 1 month post-vaccination.[11] The proportion of those who achieved at least four-fold increase in antibody titers postvaccination over the total number of participants in the intervention and control group were compared. The high relative effect (i.e., higher RR values) in the summary of findings for seroconversion rate indicates a better response.

Clinical investigation has confirmed the immunogenicity of MenACWY-D in individuals with age up to 55 years (n=300) from different serogroups (MenA: RR 8.38, 95% CI 4.48 to 15.69; MenC: RR 10.93, 95% CI 5.61 to 21.28; MenW: RR 7.54; 95% CI 4.43 to 12.84; MenY: RR 6.03, 95% CI 3.06 to 11.89).[11] The certainty of this evidence is high.

The evidence for high-risk groups with MenACWY-D vaccination is similar to the aforementioned clinical investigation. However, the certainty of evidence was downgraded to moderate due to indirectness in terms of population (i.e., adults with frequent or close contact with cases such as healthcare or laboratory workers, students living in close quarters, and military recruits).

Safety

Adverse events (For healthy adults)
In the Korean RCT that compared MenACWY with Tdap, no reported serious adverse events were reported in both groups.[11] Solicited injection site reactions were recorded in 66/199 subjects (33.2%) in the MenACWY group versus 72/99 (72.7%) in Tdap group. Rates of systemic reactions in the MenACWY group were likewise lower than the Tdap group for both solicited (36.7% vs. 51.5%) and unsolicited adverse events (8.5% vs. 9.0%). Pain (32.2%), myalgia (25.6%), upper respiratory tract infection (1.5%) were the most common AEs reported in the MenACWY group. All were mild and resolved spontaneously. The certainty of evidence for these AEs is high.[11]

Indirect evidence from other studies comparing different meningococcal vaccines showed similar results regarding safety outcomes. There were no vaccine-related serious adverse events. The most common local AEs were injection site pain and erythema, while the most common systemic adverse events found among adults were myalgia, headache and fatigue. These AEs were mild to moderate and resolve within 3 days.[6-10,12-15]

One cohort study[22] (N=12,589,910) with more than 3 million young adults (19-21 years old) evaluated the risk of Guillain-Barré syndrome (GBS) and concluded that there was no evidence

of an increased risk of GBS due to MenACWY-D vaccines. No confirmed cases of GBS occurred within 6 weeks after vaccination.

Adverse events (For other/special populations)

Pregnant women
Four observational studies[23-26] included in a 2020 systematic review[27] reported real-world safety data of MenACWY among pregnant women. Overall findings suggest that there is no increased risk of pregnancy- or birth-related adverse events with MenACWY vaccines. However, the certainty of evidence on harm is very low due to serious risk of bias and imprecision. All studies were only descriptive in nature and poor reporting of outcomes and exposure data prevented a detailed appraisal of the results.

A study by Zheteyeva et al. in 2013 recorded 103 adverse events (17 spontaneous abortions [16.5%], 1 congenital anomaly [1%]) among pregnant women inadvertently exposed to MenACWY vaccines.[26] Another cohort study by Becerra-Culqui et al. in 2020 identified 2 cases of spontaneous abortions (16.7%) and 1 induced abortion (5.3%) among 92 women who were vaccinated during the pregnancy period.[23] Myers et al. in 2017 identified 14 pregnant women exposed to MenACWY-CRM; 3 reports included limited information on birth outcomes that were in all cases normal.[25] In a study by Hansen and research team, MenACWY-D safety in large integrated health care system was examined.[28] They identified 25 pregnancy exposures with 12 live births (1 infant with dermoid cyst), 5 elective abortions, and 1 fetal death.

Hematopoietic cell transplant patients
Among adults who had hematopoietic cell transplantation (n=67) with a median age of 58 years, there were no adverse events documented within 60 days of MenACWY-D vaccine administration.[29]

MenB VACCINES

<u>Efficacy</u>

Immunogenicity: MenB-4C vaccine
Based on moderate certainty of evidence from 1 RCT[18] involving 581 healthy young adults, 99% to 100% of MenB-4C recipients had hSBA titers ≥4 against all serogroup B strains after 2 months compared to 65% in the control group (RR 1.52; 95% CI 1.37 to 1.68; n=389). This proportion remained high even after 12 months (84.9% vs. 45.2%; RR 1.88; 95% CI 1.59 to 2.22).[18]

Immunogenicity: MenB-FHbp vaccine
The relative effect of 3 doses of MenB-FHbp (Trumenba® administered at 0, 2, 6 months) compared with control from one large RCT[17] indicates benefit as observed 28 days postvaccination (RR 8.48, 95% CI 6.95 to 10.35; N=3,293). No data was available regarding long-term effects of the vaccine from this trial.

Case of meningococcal infection (high-risk group)
One observational study[21] revealed that within the 2 academic years after MenB4C vaccination program, there had been no reported case of serogroup B meningococcal infection among the university students living in on-campus dormitories who had high risk from an outbreak setting. The serious risk of selection and detection biases due to lack of multiple sources of population, absence of comparator or controls, and failure to describe those who did not receive vaccination is worth noting in this very low certainty evidence.

Safety

No vaccine-related SAEs were reported within 6 months in one trial involving 192 MenB-4C vaccine recipients. Certainty of evidence for harm for MenB-4C is rated moderate due to serious risk of bias.

In the trial of MenB-FHbp vaccine, SAEs were reported by 1.3% (33/2471) of the subjects in the vaccine group and 1.3% (11/822) in the control group (RR 1.00; 95% CI 0.50 to 1.95; N=3,293). Of these 33 SAEs, 3 (0.1% of all vaccine recipients) were considered vaccine-related: dystonia, multiple sclerosis, and pyrexia. Certainty of evidence for harm for MenB-FHbp is low due to serious risk of bias and imprecision.

In one observational study[21] specific to a high-risk group, the certainty of evidence for the report of rhabdomyolysis 1 day after the MenB-4C vaccination is very low due to the study's identified biases. See Appendix 4 for the detailed assessment.

Recommendations from Other Groups

Local guidelines from the Philippine Society for Microbiology and Infectious Diseases in 2018 issued a weak recommendation against routine meningococcal vaccination for immunocompetent adults based on low quality of evidence. However, meningococcal vaccination was strongly recommended for high-risk populations such as those with specific medical conditions, travelers to high-endemic areas, and workers handling *N. meningitidis* isolates. A weak recommendation in favor of vaccination was also given for adults living in close quarters. Similarly, guidelines from Australia and the United States recommend giving meningococcal vaccines for high-risk groups (see Table 2 for details).

Table 2. Recommendations of different guidelines on meningococcal vaccination among adults

Group	Recommendations	Strength of recommendation; quality of evidence
Australian Immunization Handbook (2022)	Recommends full primary course with ongoing booster doses MenACWY + full primary course MenB for: ● Defects in complement components (e.g., factor H, D, properdin) ● Current or future treatment with eculizumab ● Functional or anatomical asplenia, sickle cell disease, other haemoglobinopathies, congenital or acquired asplenia ● HIV (regardless of disease stage or CD4+ cell count ● Haemotopoeitic stem cell transplant Recommends 1 dose MenACWY for: ● People travelling to, or living in, parts of the world where epidemics of serogroups ACWY meningococcal disease occur, particularly the 'meningitis belt' of sub-Saharan Africa ● People travelling to mass gatherings, such as pilgrims travelling to the Hajj ● Laboratory workers with ongoing occupational exposure risks who have previously received a quadrivalent meningococcal polysaccharide vaccine vaccinated at least 2 years after most recent dose of 4vMenPV Recommends 1 dose MenACWY + 2 doses MenB vaccine for: ● Young adults (<24 years) living in 'close quarters' (e.g., new military recruits, students)	Strong, N/A

Philippine Society for Microbiology and Infectious Diseases (PSMID, 2018)	Routine vaccination is not recommended in immunocompetent adults. ● Should the elderly, 65 years old and older, choose to have meningococcal vaccination, the quadrivalent polysaccharide vaccine is the recommended vaccine and found to be immunogenic in older adults. There is limited data on the use of the quadrivalent polysaccharide-protein conjugate vaccine for immunocompetent elderly individuals.	Weak, low
	Recommendations vaccination for high-risk groups: ● Adults traveling from low-endemic to endemic and hyperendemic areas for meningococcal disease ● Adults traveling specifically to the African meningitis belt (Benin, Burkina Faso, Burundi, Cameroon, Chad, Cote d'Ivoire, Central African Republic, Democratic Republic of Congo, Eritrea, Ethiopia, Gambia, Ghana, Guinea, Guinea Bissau, Kenya, Mali, Maurotania, Niger, Nigeria, Rwanda, Senegal, South Sudan, Sudan, Tanzania, Togo and Uganda) ● Patients with anatomic or functional asplenia ● Immunocompromised patients including persons with HIV ● Patients with complement component or properdin deficiencies ● Personnel handling N. meningitidis isolates, such as microbiologists, medical technologists, or pathologists ● Close contacts of meningococcal disease patients ● Outbreak control settings	Strong, moderate
	Recommends vaccination for other population subgroups: ● Students living in dormitories ● Unvaccinated students ● Military personnel	Weak, low
US Advisory Committee on Immunization Practices (2022)	Recommends 1 or 2 doses for MenACWY depending on indication and 2 or 3 doses for MenB depending on vaccine and indication: ● Anatomical or functional asplenia (including sickle cell disease), HIV infection, persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use: 2-dose series MenACWY-D (Menactra, Menveo, or MenQuadfi) at least 8 weeks apart and revaccinate every 5 years if risk remains ● Travel in countries with hyperendemic or epidemic meningococcal disease, or microbiologists routinely exposed to Neisseria meningitidis: 1 dose MenACWY (Menactra, Menveo, or MenQuadfi) and revaccinate every 5 years if risk remains ● First-year college students who live in residential housing (if not previously vaccinated at age 16 years or older) or military recruits: 1 dose MenACWY (Menactra, Menveo, or MenQuadfi) Adults should receive a MenB vaccine if they are at increased risk for serogroup B meningococcal disease due to: ● Complement component deficiency (e.g., C5-C9, properdin, factor H or D) ● Functional or anatomic asplenia (including sickle cell disease) ● Taking complement inhibitor (e.g., Soliris® or Ultomiris®) ● Working in specific professions or settings ● Microbiologists routinely exposed to Neisseria meningitidis (boost with MenB after 1 year, then every 2–3 years thereafter; boost with MenACWY every 5 years) ● Being a part of a community experiencing a serogroup B meningococcal disease outbreak Those who remain at increased risk need regular booster doses.	N/A

	• Give booster for MenB vaccine 1 year after series completion and then every 2 to 3 years thereafter • For those at increased risk due to an outbreak who previously received the MenB vaccine series, recommend giving booster dose if a year or more has passed since primary series completion.	

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

Cost

There are no cost-effectiveness studies on meningococcal vaccines for the Philippine context. A few studies[30-33] reported conflicting conclusions regarding the cost-effectiveness of universal vaccination for meningococcal disease, with more favorable results seen in situations where vaccine prices are low and the incidence of the disease is high (including outbreak settings).

The cost-effectiveness of different meningococcal vaccination strategies in Burkina Faso was examined in a modeling study.[34] Compared to the current base policy in the country (serogroup A vaccination at 9 months with reactive vaccination for outbreak situations), the study found that a nationwide catch-up campaign including individuals up to 29 years old is cost-effective and would avert 78% to 87% of meningococcal cases at a vaccine price of USD 4 per dose. In Chile, implementing a mass 4CMenB campaign was found cost-effective for controlling a hypothetical outbreak situation at a vaccine cost of USD <18.[19]

One economic modelling study from the United States estimated the cost-effectiveness of universal vaccination versus no vaccination targeted to college-aged young adults. Due to the high incremental cost per gain in quality-adjusted life years (USD 13.9 million per QALY) as well as the low incidence of *N. meningitidis* serogroup B, the study concluded that universal vaccination was not cost-effective.[30] In Germany, universal vaccination with Bexsero® (cost: €96) against serogroup B meningococcal disease was not seen to be cost-effective (i.e., all ICERs were >€500,000 per QALY) due to its low incidence.[20]

Patient Values and Preference, Equity, Acceptability, and Feasibility

No studies were found examining patient values and preference regarding meningococcal vaccination in the Philippines, as well as studies evaluating the acceptability and equity implications of mass vaccination.

Meningococcal vaccinations are not included in the Philippine Expanded Immunization Program; however, current data support their use in high-risk children.[31-33] The following vaccines were reported to be available in the country: MCV4 (MenACWY-D, Menactra™; Sanofi Pasteur; MenACWY-TT, Nimenrix®, Pfizer; and MenACWY-CRM) and MPSV4.[31]

Certain populations have been found to be at a higher risk for exposure to *N. meningitidis*. The calculated attack rate for the disease was higher among microbiologists (13/100,000) compared to the general adult population (0.2/100,000) based on the study in the USA between 1996 to 2001.[4,35] As such, vaccination for all meningococcal subgroups (1 dose MenACWY using Menveo or Nimenrix, and 2 doses MenB using either Bexsero or Trumenba) is advised for these laboratory workers.[5,25]

Another high-risk group are travelers to or residents of regions where meningococcal disease is hyperendemic or epidemic, such as the meningitis belt of sub-Saharan Africa.[4,5] Proof of

vaccination is also an entry requirement for pilgrims wanting to attend the annual Hajj in Mecca, Saudi Arabia.[5,36]

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4.11.1. Should monkeypox vaccine be given to apparently healthy adults?
4.11.2. Should monkeypox vaccine be given to asymptomatic healthcare workers?

RECOMMENDATIONS

Among apparently healthy adults, we <u>suggest against giving</u> monkeypox vaccine.
(weak recommendation, low certainty evidence)

Among adults with high risk* of exposure to monkeypox, we <u>suggest against giving</u> monkeypox vaccine.
(weak recommendation, very low certainty evidence)

*High risk groups: Healthcare workers responding to monkeypox outbreak, laboratory personnel who are handling monkeypox virus, people with multiple sexual partners, and men having sex with men (MSM)

Considerations

The consensus panel considered the following points during the formulation of the above recommendations:

- Routine vaccination for monkeypox (mpox) among the general population was not recommended primarily due to the low and decreasing disease burden as well as issues in vaccine access. The DOH no longer procured mpox vaccines since only 4 cases have been documented as of August 2022. The only commercially available vaccines are the modified vaccinia Ankara strain (MVA-BN - ACAM2000), stockpiled by the United States, and LC16m8, stockpiled by Japan.
- There was only very low certainty of evidence suggesting that vaccination offers protection from the current mpox disease. In addition, studies made use of vaccines developed for smallpox.
- Mpox vaccination was also not recommended for individuals considered to have high risk of exposure to mpox due to the very low certainty of its effectiveness as well as issues with vaccine access and implementation. The following individuals were identified as belonging in the high risk group based on existing epidemiologic studies: healthcare workers responding to mpox outbreak, laboratory personnel who are handling mpox virus, people with multiple sexual partners, and men having sex with men (MSM).

Key Findings

- The current mpox outbreak mostly affected high risk groups including gay and bisexual men having sex with men, individuals with high risk sexual behaviors, healthcare workers, and those working in laboratories handling mpox virus. There are three available vaccines being used today against mpox: ACAM2000®, MVA-BN (Jynneos®, Imvamune,Imvanex), and LC16m8.
- For healthy adults, 3 studies were reviewed. All studies were completed prior to the current outbreak. One RCT was able to show that MVA-BN can increase total and neutralizing antibody titers after 2, 4, 6, and 8 weeks and 6 months postvaccination; antibodies can persist even after 2 years. Surveillance data involving 987,209 administered MVA-BN doses (JYNNEOS) revealed only 2 cases of myocarditis within 30 days and 3 cases of

anaphylaxis within 24 hrs. The certainty of evidence regarding the efficacy of mpox vaccination among healthy adults is low (downgraded from moderate certainty due to serious indirectness). Safety was also rated low due to serious imprecision and indirectness.

- For individuals who are considered at high risk for mpox, the evidence base by the WHO/SAGE guidelines published last 16 November 2022 was adapted. A rapid review of 39 studies was done. Immunogenicity data using seroconversion rates after 30 days for each vaccine types were as follows: ACAM2000: 79% to 97% (n=317), LC16m8: 60% to 100% (n=331) and MVA-BN: 62.4% (n=753). In terms of safety outcomes, ACAM2000 can be associated with rare but serious AE, such as myopericarditis (269 cases of myopericarditis across 8 studies with n=1,743,620). Local and systemic AEs were frequently reported among vaccinated subjects with MVA-BN (up to 99%); there were no reported cases of myocarditis or serious AEs for this vaccine. LC16m8 vaccine is also associated with high rates of local and systemic AEs (up to 99% of vaccines); autoinoculation in 0.4 of vaccines was noted (14/3489) and no other SAEs (including cardiac-related SAEs) were reported. The overall effectiveness of mpox vaccination among high risk individuals is very low. Safety estimates are also of very low certainty. Reasons for downgrading include design limitations from included observational studies, indirectness, and imprecision.

Introduction

Monkeypox virus is a DNA virus of the *Orthopoxvirus* genus that is related to the variola virus that causes smallpox. It was first described in humans in 1970 in the Democratic Republic of Congo. There have been multiple instances of sporadic outbreaks in Africa that were thought to have originated from contact with wildlife reservoirs, especially rodents.[1] The virus causes mpox that typically begins with fever, followed by the development of multiple popular, vesiculopustular, and ulcerative lesions on the face and body and prominent lymphadenopathy.[2] More atypical presentations that include oral, genital, and/or anal lesions with or without fever, or systemic symptoms were noted during the current 2022 outbreak.[3] Complications of mpox include pneumonitis, encephalitis, keratitis, and secondary bacterial infections. The current global outbreak has disproportionately affected men who are gay or bisexual and other men who have sex with men accounting for about 85% of the total reported case. Healthcare workers make up about 4.2% of the current outbreak.

On 23 June 2022, the World Health Organization (WHO) declared mpox as an evolving threat of moderate public concern due to the increasing number of cases and affected member states.[4,5] From 01 May 2022 to 14 March 2023, a total of 86,516 mpox cases have been recorded globally, with 111 (0.13%) deaths.[6] In the Philippines, only 4 cases and zero deaths were recorded between 29 July 2022 to 22 August2022. Globally, the weekly number of cases being reported to WHO are noted to be decreasing.[4]

Smallpox vaccines used during the global smallpox eradication programs may provide protection against mpox.[6] To prevent infections, countries are advised to intensify surveillance and implement public health measures. However, global smallpox vaccination programs ended in 1980 when smallpox was declared eradicated. Currently, there are three types of vaccines that may be used for mpox prevention.

The first vaccine is ACAM2000™,[7] a second generation live-attenuated smallpox vaccine that is replication- competent. It is administered by percutaneous scarification using a bifurcated needle,

given as a single dose vaccine. The second vaccine is MVA-BN (modified vaccinia Ankara-Bavarian Nordic; JYNNEOS®/Imvamune®/Imvanex®)[8] a third-generation non-replicating smallpox vaccine administered for two doses as a subcutaneous injection. The third vaccine is LC16m8, a third-generation smallpox vaccine modified attenuated lister strain of vaccinia. Protective efficacy of these vaccines was evaluated in various animal studies[9] using mouse, rabbit and monkey models. Data from these studies demonstrated that mice,[10] rabbits, and monkeys[11] were protected against lethal challenges with mpox virus when immunized with smallpox vaccines.

Incidence of mpox after vaccination had been documented in some observational studies. In a study by Payne et al. that was conducted from 31 July to 03 September 2022, in 32 U.S. jurisdictions, among males aged 18-49 years old eligible for JYNNEOS vaccination, mpox incidence was 14 times as high among unvaccinated males compared with those who had received a first vaccine dose ≥14 days earlier. Breakthrough infections have also been documented among subjects vaccinated with a single dose of MVA-BN in one study in Belgium (5 cases out of 1,408 individuals)[12] and another in France (12 cases out of 276).[13]

Characteristics of Included Studies

Studies on Healthy Adults

Three studies provided data on the efficacy of smallpox vaccines for healthy adults.[14-16] Studies were performed in Germany[14] and in the United States.[15-16] All were completed before the June 2022 mpox outbreak. Two studies used the modified vaccinia Ankara strain (MVA-BN) vaccine[14,16] and one study used the LC16m8 (attenuated Lister strain).[15] Since only the phase 2 RCT study by Ilchmann 2022 involved a comparison of the MVA-BN vaccine with placebo, the remaining 2 studies were excluded from the analysis.[3]*

Ilchmann et al., 2022 compared the immunogenicity and safety of 1 and 2 doses of MVA-BN against tris buffer placebo in 753 healthy adults age 18-55 years old (204 with prior smallpox vaccination, 549 without vaccination history).[14] Total and neutralizing serum antibody titers measured by ELISA and PRNT after 2, 4, 6, and 8 weeks, and 6 months postvaccination. Safety outcomes were assessed up to 2 weeks post- vaccination. In a small subset of the original participants (n=306/753 or 40.6%), the persistence of antibodies after 2 years was measured. The effect of MVA-BN booster dose was also evaluated in a smaller subset of participants (152/306 or 49.6%).

Studies on Healthy Populations with High Risk of Exposure to Monkeypox

Evidence to inform recommendations for high-risk groups was obtained from the rapid review of 39 studies used in the WHO/SAGE Guidelines (16 November 2022) on monkeypox. This guideline was appraised to be of good methodological quality based on AGREE-II tool (85.7% on rigour of development domain, 86.7% overall quality score). High risk individuals include the following:

a. Immunocompetent adult gay or bisexual men who have sex with men (GBMSM)
b. Others with multiple sex partners
c. Health workers at high risk of exposure
d. Laboratory personnel working with orthopox viruses

[3]*The other two studies had different objectives: Overton et al.[16] aimed to assess the consistency of 3 MVA-BN vaccine production lots, while Kennedy et al.[15] compared LC16m8 with Dryvax smallpox vaccine. Safety data was also obtained from Vaccine Adverse Event Reporting System (VAERS) and Vaccine Safety Datalink (VSD) for JYNNEOS vaccine recipients in the US from May 22 to October 21, 2022 (n=987,294 doses).[17]

The WHO/SAGE evidence review included 39 studies comparing primary preventive vaccination (pre- exposure) with one dose of ACAM2000, LC16m8, and MVA-BN vaccine compared to no intervention or placebo. Outcomes of interest were the following: reduction in mpox infections, immunogenicity, local and systemic adverse events, and serious adverse events. There were no peer-reviewed RCTs found evaluating the clinical effectiveness/efficacy of any of the three types of vaccines against mpox; indirect evidence from observational studies and animal studies were used as bases for the reported effect estimates.

Outcomes

Subgroup 1: Asymptomatic Healthy Adults

Efficacy

Seroconversion (2-6 weeks)
Approximately half of all participants seroconverted for neutralizing antibodies (nAb) at week 2. By the 4th week, seroconversion rate was highest at 62.4% for the 1-dose group. The 2-dose group exhibited peak seroconversion (89.2%) by week 6. In subjects with prior smallpox vaccination, 78.5% were seroconverted by week 2. In the placebo group, seroconversion rates remained low throughout the duration of the study (1.1 to 3.4%). The resulting relative risk (RR) for each vaccine group compared to placebo are: 1-dose - RR 22.4 (95% CI 9.4 to 53.6), 2-dose - RR 26.9 (95% CI 12.2 to 59.1), prior vaccination - RR 28.4 (95% CI 11.9 to 67.7).

Peak nAb GMT levels were as follows: 7.2 [95% CI 5.5 to 9.4] at 4 weeks for 1 dose, 45.6 [95% CI 35.1 to 59.3] at 6 weeks for 2 doses, and 175.1 [95% CI 140.0 to 219.1] at 2 weeks for subjects with prior vaccination. Peak total antibody titers were comparable in the 2-dose and the prior vaccination groups at 568.8 [95% CI 473.3 to 683.6] and 495.8 [95% CI 431.8 to 569.4], respectively.

Immunogenicity at 6 months and 2 years
Six months postvaccination, seroconversion rates based on nAb levels dropped to 23.6% in the 1-dose group and 65.2% in the 2-dose group. At 2 years, nAb GMTs were similar to baseline/prevaccination levels. Seroconversion rates in terms of total antibody titers were 37.9% at 6 months and 42.9% at 2 years for the 1-dose group, and 73.0% at 6 months, and 71.7% at 2 years for the 2-dose group.

Data from the MVA-BN lot consistency trial by Overton et al.[16] also showed high seroconversion rates for both nAb (99.2% or 980/988 subjects) and total antibodies (98.6% of 974/988 subjects) measured 2 weeks after administration of the second dose.

Safety

Local and systemic adverse events
More unsolicited local and systemic adverse events were noted in vaccinated subjects compared to the placebo group within a 6-month follow-up period (33.5% vs. 12.7%; RR 2.64 [95% CI 1.75 to 3.97]; n=545; 1 RCT).[14,18] Most of these AEs were mild or moderate (injection site reactions, chills, urticaria).

Among the 152 vaccinated subjects included in the long-term follow-up (2 years), 51.3%

experienced at least 1 unsolicited AE, with 13.2% being vaccine-related AEs. All were mild or moderate, including injection site warmth (3.9%), lymphadenopathy (2%), chills (1.3%), dizziness (1.3%), injection site irritation (1.3%), and nasopharyngitis (1.3%). In the study by Overton,[16] the recorded vaccine-related local and systemic AEs were 91.2% (1030/1129) and 66.8% (754/1129).

Serious adverse events
Compared to placebo, the rate of SAEs was not significantly higher in the vaccine recipients (RR 3.49 [95% CI 0.18 to 67.21].[14,18] No vaccine-related SAEs were observed in the Overton et al. study,[16] while 1 (0.1%) case of sarcoidosis was documented by Ilchmann et al.[14] A total of 5 possibly related cardiac AEs of special interest were also found by Ilchmann et al. (3 palpitations, 2 tachycardia).[14] No case of myo- or pericarditis was documented.

Surveillance data collected between 22 May to 21 October 2022 involving 987,209 participants given MVA-BN doses (JYNNEOS) revealed only 2 cases of myocarditis within 30 days and 3 cases of anaphylaxis within 24 hrs.[17]

Certainty of evidence
Overall, the certainty of evidence regarding the efficacy of mpox vaccination is low. Efficacy estimates are of moderate certainty with downgrading due to serious indirectness (immunogenicity outcomes not based on MPX-specific neutralizing antibodies), while safety was rated low due to serious imprecision (wide confidence intervals) and indirectness.

Table 1. Benefits and harms of mpox vaccination in healthy adults

Critical Outcomes	No. of Studies (No. of Participants)	Effect Estimate [95% CI]	Interpretation	Certainty of Evidence
Seroconversion rate (4-6 weeks)	1 RCT (753)	1 dose MVA-BN: RR 22.4 [9.4, 53.6][c] 2 dose MVA-BN: RR 26.9 [12.2, 59.1[d]	Benefit	Moderate
Serious adverse events[a] (6 months)	1 RCT (545)	RR 3.49 (0.18, 67.21)	Inconclusive	Low
Local and systemic adverse events[b]	1 RCT (545)	RR 2.64 (1.75, 3.97)	Harm	Moderate

CI confidence interval; MVA-BN (modified vaccinia Ankara-Bavarian Nordic; JYNNEOS®/Imvamune®/Imvanex®); RCT randomized controlled trial; RR risk ratio
[a]Serious adverse events (AE) and AEs of special interest (cardiac events)
[b]At least 1 unsolicited AE related to vaccination
[c]62.4% of participants seroconverted for neutralizing antibodies (nAb) at week 2. Higher RR values favor vaccination.
[d]89.2% of participants seroconverted for nAb at week 6. Higher RR values favor vaccination.

Subgroup 2: Healthy Adults with High Risk of Exposure to Monkeypox

Efficacy

Prevention of mpox infection
For MVA-BN, no peer reviewed randomized controlled trials evaluating the clinical efficacy of primary preventive vaccination versus no vaccination against mpox has been completed yet. A preprint study (23 September 2022) in Israel involving a retrospective cohort of 1,970 male subjects who are receiving HIV- pre-exposure prophylaxis or diagnosed HIV-positive showed that out of 873 subjects given one dose of MVA-BN, 3 developed mpox infections versus 15 among the unvaccinated subjects. Vaccine efficacy was estimated at 79% (95%CI 24% to 94%).[19]

Similarly, no clinical effectiveness study using ACAM2000 is currently available. Indirect evidence on this vaccine's efficacy for preventing mpox infections was taken from animal studies and surveillance data from the Democratic Republic of the Congo (2005-2007). People born before 1980 (end of the official national mass smallpox vaccination program) vaccinated against smallpox with first generation vaccines had 5.2-fold lower risk of mpox than those unvaccinated (0.78 vs 4.05 per 10,000), which represented a smallpox pre-exposure vaccine effectiveness against monkeypox of 80.7% (95%CI 68.2 to 88.4%).[20]

Immunogenicity
Seroconversion rates (non-MPXV specific) at 30 days for ACAM2000 vaccinees ranged from 76% to 97% (n=317).[21-24] For LC16m8, seroconversion rate ranged from 60% to 100% at 30 days from vaccination (n=331).[15,25,26] For MVA-BN, data on immunogenicity is provided by Ilchmann[14] which was described in the previous section.

Safety
For the MVA-BN vaccine, local and systemic AEs were frequently reported among vaccinated subjects (up to 99%) based on very low to low certainty evidence from 6 studies (n=5,921). However, there are no cases of myopericarditis or serious adverse events (SAE) requiring hospitalization reported among 9,713 MVA- BN vaccinees from 19 clinical studies. Most common local AEs were injection site pain (up to 85%), redness (61%), pruritus (18%), swelling (52%), as well as induration and itching (43%). Frequent systemic AEs included muscle pain (43%), fatigue (30%), and headache (34.8%).

Although adverse events were generally mild to moderate, ACAM2000 can be associated with rare but serious AE, such as myopericarditis. The rapid review reported a total of 269 cases of myopericarditis across 8 studies (n=1,743,620 vaccines). Five cases of generalized vaccinia, one case of eczema vaccinatum, one case of progressive vaccinia, and five cases of autoinoculation were reported in four studies (n=843,744). Two out of the 1,732,264 ACAM2000 vaccine deaths were attributed to the vaccine (dilated cardiomyopathy, liver and adrenal gland necrosis, rhabdomyolysis).[27,28]

The LC16 vaccine was also associated with high rates of local and systemic AEs (up to 99% of vaccines) based on one RCT[15] and two cohort studies.[25,26] No serious adverse events were reported, including cardiac-related SAEs, although the two observational studies documented autoinoculation in 0.4% of vaccinees (14/3489).

Certainty of evidence
The overall certainty of evidence regarding the effectiveness of mpox vaccination using either ACAM2000, MVA-BN, or LC16m8 is very low. Safety estimates are also of very low certainty. Reasons for downgrading include design limitations from the included observational studies, indirectness (no studies demonstrating MPXV-neutralizing antibodies in vaccinated subjects), and imprecision (insufficient sample size or low event rates for serious adverse events).

Table 2. Benefits and harms of mpox vaccination among high-risk individuals for mpox including gay and bisexual men having sex with men, multiple sex partner, and healthcare workers (based on WHO/SAGE 16 November 2022 Guidelines)

Critical Outcomes	No. of Studies (No. of Participants)	Impact*	Certainty of Evidence
Prevention of mpox/ vaccine efficacy	1 (873)	MVA-BN: 3 vaccinated subjects developed mpox infections versus 15 in the unvaccinated group. Vaccine efficacy was estimated at 79% (95% CI 24% to 94%) ACAM2000: Vaccine efficacy 80.7% (95% CI 68.2 to 88.4%)	Very low
Seroconversion rates (1 month)	5 (1012)	ACAM2000: 76% to 97% (n=317) LC16m8: 60% to 100% (n=331) MVA-BN: 62% to 89.2% (n=364)	Very low
Serious adverse events	19 (9713)	ACAM 2000: 269/1,743,620 myopericarditis; 5 vaccinia, 1 eczema vaccinatum, 1 progressive vaccinia, 5 autoinoculation out of 843,744 subjects; 2/1,732,264 deaths LC16: No cardiac-related SAEs, autoinoculation in 0.4% of vaccinees (14/3,489). MVA-BN: no SAEs or deaths	Very low

CI confidence interval; MVA-BN (modified vaccinia Ankara-Bavarian Nordic; JYNNEOS®/Imvamune®/Imvanex®)
*Evidence was based on observational studies.

Ongoing Clinical Trials

Several ongoing studies involving mpox vaccination were currently registered at clinicaltrials.gov. A Phase 2 randomized trial (NCT 05512949) to evaluate the immunogenicity of dose reduction strategies of the MVA-BN mpox vaccine aims to enroll at least 210 participants in order to evaluate two intradermal regimens for the vaccine compared to the standard subcutaneous regimen in healthy adults 18-50 years of age in the USA. A target trial emulation study (NCT05522296) is also being conducted to assess the protection of pre-exposure vaccination against infection with mpox in real-world individuals with risk factors for mpox. This study aims to enroll 4,638 participants in different countries in Europe. At least 4 other trials (from Phase II-IV) are currently being conducted using JYNNEOS.

Recommendations from Other Groups

Table 3 summarizes existing recommendations from various groups. Current guidelines from the WHO (November 2022), US Advisory Committee on Immunization Practices (US ACIP; June 2022), Australian Technical Advisory Group on Immunisation (ATAGI; December 2022), and National Advisory Committee on Immunization Canada all recommend mpox vaccine only for individuals at high risk of exposure.

Table 3. Recommendations from international and local CPGs.

Group	Recommendations	Strength of Recommendation, Certainty of Evidence
WHO Emergency Response, Immunization, Vaccines and Biologicals, Strategic Advisory Group of Experts on Immunization (WHO SAGE, 16 November 2022)[29]	**Primary preventive (pre-exposure) vaccination (PPV)** Mass vaccination is not recommended for outbreaks of monkeypox, and vaccination is not recommended for the general public. Vaccination is recommended for groups at high risk for exposure to mpox. High-risk groups include: ● Gay, bisexual, men who have sex with men with multiple sexual partners ● Individuals with multiple casual sexual partners ● Sex workers ● Health workers at risk of repeated exposure ● Laboratory personnel working with *orthopoxviruses* ● Clinical laboratory and healthcare personnel performing diagnostic testing for monkeypox ● Outbreak response team members Not recommended for groups at risk of developing severe disease: ● Children ● Pregnant women ● Immunocompromised persons **Post-exposure preventive vaccination (PEPV)** Recommended for contacts of cases, ideally within 4 days of first exposure and up to 14 days in the absence of symptoms. **Choice of vaccine** For healthy adults: non-replicating (MVA-BN) minimally replicating (LC16), or replicating vaccinia-based vaccines (ACAM2000) 2-dose, subcutaneous, 0.5mL dose, 4 weeks apart for MVA-BN; single dose using scarification method with bifurcated needle for LC16 and ACAM2000™ For immunocompromised adults, pregnant, breastfeeding women: MVA-BN	No strength of recommendation; very low certainty of evidence
US Advisory Committee on Immunization Practices, CDC (ACIP CDC, 3 June 2022)[30]	**PPV** JYNNEOS® and ACAM2000™ are recommended for persons at risk for occupational exposure to orthopoxvirus: ● Research laboratory personnel ● Clinical laboratory personnel performing diagnostic testing for orthopoxviruses ● Designated response team members ● Healthcare personnel who administer ACAM2000™ or care for patients infected with orthopoxviruses (based on shared clinical decision-making) Recommends JYNNEOS® booster dose for persons who are at ongoing risk for occupational exposure ● Every 2 years for exposure to more virulent orthopoxviruses ● Every 10 years for exposure to less virulent orthopoxviruses	No strength indicated; Moderate certainty for disease prevention and low certainty for SAEs (3 RCTs, 15 observational studies)

Australian Technical Advisory Group on Immunisation (ATAGI, 12 December 2022)[31]	**PPV** Recommended for at risk populations: ● Gay, bisexual and other men who have sex with men (GBMSM) age ≥ 16 ● Patients living with HIV ● Sex workers ● Immunocompromised ● Healthcare workers who have not received smallpox vaccine in the past and will be administering ACAM2000™ ● Healthcare workers categorised by public health authorities as high risk mpox contact in the past 14 days ● Laboratory workers with ongoing risk of occupational exposure Not recommended for wider vaccination of the general population or low-risk GBMSM. **PEPV** Vaccination may be considered for high-risk contacts (e.g., healthcare workers, household contacts, sexual contacts, or contacts in other settings with identified risk for transmission) within 4 days of first exposure JYNNEOS® is preferred over ACAM2000™ for PEPV due to its more favorable safety profile and comparative ease of administration. Vaccination either using JYNNEOS® or may be used for PPV or PEPV. A shared clinical decision-making approach is appropriate, based on a joint assessment of individual risks, benefits, and vaccine availability.	No strength indicated
National Advisory Committee on Immunization (NACI Canada June 2022)[32]	NACI recommends Imvamune as: 1. Post-exposure prophylaxis (PEP) using a single dose of Imvamune may be offered to individuals with high-risk exposure to probable or confirmed cases of mpox. 2. Pre-exposure Prophylaxis (PrEP) may be offered to personnel working with replicating orthopoxviruses that pose a risk for human health (vaccinia or monkeypox) in laboratory settings and who are at high risk of occupational exposure. 3. Imvamune may be offered to the following population if recommended to receive vaccine based on exposure risk: a. Individuals who are immunocompromised due to disease or treatment b. Individuals who are pregnant c. Individuals who are lactating d. Children and youth <18 years of age e. Individuals with atopic dermatitis	"Discretionary" *

*Strength of NACI recommendation is based on factors not isolated to strength of evidence (e.g. public health need). A "discretionary" recommendation means that the wording that was used is "may/may not be offered" and that known/anticipated advantages are closely balanced with known/anticipated disadvantages, OR uncertainty in the evidence of advantages and disadvantages exist. A discretionary recommendation may be considered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.

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

Cost

Costs of mpox vaccination

In a study that was published in 2016, a total cost analysis for using replicating and nonreplicating smallpox vaccines was done.[33] It is estimated that for ACAM2000® smallpox vaccine (Sanofi Pasteur Biologics, France) total cost will be at USD 139 (approximately PHP 7,459.87). The cost of a single dose of JYNNEOS® smallpox and mpox vaccine (Bavarian Nordic, Denmark) was USD 130 (approximately PHP 6,976.65). However, these vaccines are not yet commercially available.

Cost-effectiveness of mpox vaccination

In a 2022 cost-benefit analysis of three interventions for mpox (no intervention, quarantine, vaccination), mpox vaccination was found to be the best intervention to mitigate further spread of the disease.[34] Costs included direct costs of the intervention, mortality cost, productivity losses, and indirect costs. The authors concluded that vaccination would entail a huge direct cost at the beginning (USD 36,000,000 versus USD 161,200 for quarantine and USD 0 for no intervention) but would effectively reduce transmission rate, prevent deaths, and saves the economy from the disease's financial burden in terms of productivity loss from work absenteeism and premature deaths.[34]

Patient Values and Preference, Equity, Acceptability, and Feasibility

Acceptability and equity considerations

Certain behaviors place individuals at increased risk of exposure to mpox virus (e.g., proximity of contact, sexual activities, household members or behaviors that cause exposure to body fluids or fomites). Some populations are at increased risk for severe mpox disease due to biological factors like level of immunity (e.g., HIV patients) and social factors that may intersect. Any combination of these factors has the potential for disproportionate consequences for specific populations characterized by increased rates of infection, disease, and severe illness.[32]

A systematic review of 11 studies involving a total of 8,045 participants estimated the pooled mpox vaccination acceptance rate of 56% (95% CI 42 to 70%) and vaccination hesitancy of 24% (95% CI 8 to 40%).[35] Lower vaccine acceptance rates were also found in Asian countries (50%) than in Europe (70%), possibly due to the incidence and associated perception of risk. Subgroup analysis showed variations across different populations with low acceptance rate in the general population (43% [95% CI 35 to 50%]) and healthcare workers (63% [95% CI 42 to 70%]), and high acceptance rate in the LGBTI community (84% [95% CI 83 to 86%].

Vaccine acceptance rate among men having sex with men (n=2618) was found to be high (90.2%) based on a July 2022 cross-sectional study in China.[36] The main influencing factors found to facilitate vaccine acceptance included knowledge about monkeypox, knowledge of prevention measures, concerns about their susceptibility to mpox infection, and possible contact with people and animals in epidemic areas. In the subset of patients with self-reported HIV infection, education and poor condom use also affected vaccine acceptance.

In another survey from June to August 2022 involving healthcare workers in France and Belgium (n=397, mean age 43.3 years, 65% women), acceptance of MPX vaccination was low at 55.4%.[37] This was attributed by the authors to complacency, pandemic fatigue, confidence in guidelines issued by authorities, and perceptions of exposure risk. Only 31% stated that they would get

vaccinated as soon as possible and 25% would probably get vaccinated, while 22% were undecided. In case of spread of mpox to the general population, acceptance rate increased to 79%; however, higher acceptance rates were found in physicians and pharmacists (84.7%) than nurses (70.7%).

Feasibility

Currently, only MVA-BN can be procured. ACAM2000 has its reserves within the USA Strategic National Stockpile and keeps the vaccine as an emergency response to a bioweapon threat.[38] LC16m8 is available only in Japan; while MVA-BN/JYNNEOS is only produced in a single firm in Denmark, with 16.4 million doses produced to date and sold to various government entities.[29]

There is no ongoing global plan to supply vaccine doses to low- to middle-income countries (LMICs). Meanwhile, the major bulk of doses is either held or pre-ordered by high income countries (HICs).[39] The USA holds most doses, with remaining supply secured by Europe, the UK, Canada, and Australia. Nations with the highest number of cases, such as the UK[40] and several other European countries, are gradually running out of vaccine supplies, despite having the required resources to acquire new vaccines since manufacturing cannot keep up with demand. Locally, the Philippine government is in talk with other ASEAN states for possible procurement of mpox vaccine.[41]

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4.12. Should pneumococcal vaccine be recommended to apparently healthy adults?

RECOMMENDATIONS

Among apparently healthy adults ≥ 65 years of age, we <u>recommend</u> the use of PPSV 23.
(strong recommendation, moderate certainty evidence)

Among apparently healthy adults ≥ 65 years of age, we <u>suggest</u> the use of PCV 13.
(weak recommendation, moderate certainty evidence)

Among apparently healthy adults between 18-64 years of age, we <u>suggest</u> the use of PCV 13.
(weak recommendation, low certainty evidence)

Among apparently healthy adults between 18-64 years of age, there is <u>insufficient evidence to recommend</u> the use of PPSV 23.
(insufficient evidence to recommend, low certainty evidence)

Considerations

The consensus panel considered the following when formulating these recommendations:

- The evidence base included studies on immunocompetent adults without comorbidities. This is in contrast to the current recommendations of the Philippine Society of Microbiology and Infectious Diseases (PSMID) and Philippine Foundation for Vaccination (PFV) on pneumococcal vaccines, which are based on studies among immunocompetent adults with stable comorbidities.
- The outcomes in the evidence base were measured after a single dose of either PCV13 or PPSV23. This was noted by the panel because PPSV23 is administered every five years while PCV13 is administered as a single dose in clinical practice.
- The local prevalence of pneumococcal serotypes was an important consideration for the panelists. Due to the lack of pneumococcal surveillance studies up to date, the panel used the Antimicrobial Resistance Surveillance Program Annual Report in 2020 as a basis, which showed that the locally prevailing serotypes varied per year. However, the panel also noted that the report had a small sample size and that it is an antimicrobial resistance surveillance rather than a prevalence study.
- Despite the evidence showing PCV13 as non-inferior to PPSV23 among immunocompetent adults 65 years old and above, two panelists voted against recommending the former vaccine for this age group because the serotypes covered by PCV13 are more commonly isolated in the younger population.
- One panelist voted against the use of PCV13 among immunocompetent adults between 18 to 64 years old due to its low efficacy in this subgroup.

Key Findings

- Among immunocompetent adults ≥65 years of age, PCV13 decreased the incidence of pneumococcal pneumonia (high certainty of evidence) and invasive pneumococcal disease (high certainty of evidence) compared to placebo, while it had no impact on all-cause mortality (moderate certainty of evidence). PCV13 was associated with greater incidence of non-serious adverse events (high certainty of evidence) compared to placebo. PPSV23 also significantly decreased invasive pneumococcal disease (moderate certainty of evidence) but not pneumococcal pneumonia (moderate certainty of evidence). In terms of immunogenicity, PCV13 was non-inferior to PPSV23 (high certainty of evidence) with more frequent local reactions in PCV13 than PPSV23 (high certainty of evidence).
- Among immunocompetent adults 18 to 64 years of age, observational studies showed that PCV13 decreased the incidence of invasive pneumococcal disease (low certainty of evidence) and was associated with more local adverse events (low certainty of evidence) compared to placebo. One RCT showed that it had no impact on reducing pneumonia incidence (moderate certainty of evidence). Immunogenicity studies revealed that PCV13 produced robust immune response among adults ≥18 years of age, with the highest responses observed in the youngest age groups (low certainty of evidence). In addition, PCV13 was non-inferior to PPSV23, with greater immune response seen among 50 to 59 years old compared to those 60 to 64 years old (high certainty of evidence).

Introduction

Burden of the Disease

Pneumonia is a disease from the infection of the tiny air sacs of the lungs. When infected, patients present with symptoms of cough, fever, chills, and difficulty of breathing. Global data in 2017 found pneumonia to have the highest rates among ages 70 years and older, and to be the leading cause of mortality in children under five years old.[1] In the Philippines, pneumonia remains one of the leading causes of morbidity and mortality. According to the Philippine Statistics Authority (PSA), it is the fifth leading cause of mortality in the country, with 32,600 cases or 5.7% of all deaths in 2020.[2] A local study published in 2015 also showed a high economic burden of community acquired pneumonia (CAP) among adults, with PHP 8.48 billion for CAP-moderate risk (MR) and PHP 643.76 million for CAP-high risk (HR).[3]

The morbidity and mortality rates from pneumonia may be reduced through various methods, including: controlling air pollution, controlling undernutrition, and improving access to health care.[1] Another important intervention that can highly impact the rates of cases is vaccination. Vaccination with pneumococcal polysaccharide vaccine protects 50% to 85% of healthy adults against invasive pneumococcal disease.[4,5] In children, PCV13 had a moderate impact in reducing the overall and vaccine type invasive pneumococcal disease.[6] Guidelines on the role of pneumococcal vaccination for specific subgroups (immunocompromised, patients with multiple comorbidities, and high-risk patients) have been established,[7-11] but data on its role among apparently healthy asymptomatic adults remains limited.

Characteristics of Included Studies

Evidence on the benefits and harms of pneumococcal vaccines was obtained from nine studies. Four randomized controlled trials (RCTs) focused on the elderly (≥65 years old), among which were three studies[12-14] that compared PCV13 against placebo and one[15] that compared PCV13 against PPSV23. Five studies focused on younger adults (18 to 64 years old), among which were three observational studies[16-18] that assessed the efficacy and safety of PCV13, and two RCTs that compared PPSV23 against placebo[19] or PCV13.[20] Data on PPSV23 for the elderly were also taken from a high-quality 2017 systematic review.[21]

Outcomes

Benefits and Harms of Pneumococcal Vaccine

The summary of critical outcomes of pneumococcal vaccination among healthy adults is shown in Table 1.

Table 1. Benefits and harms of pneumococcal vaccine per subgroup of healthy adults

Outcomes	No. of Studies (No. of Participants)	Effect Estimate (95% CI)	Interpretation	Certainty of Evidence
Immunocompetent adults ≥65 years old				
PCV13 vs. Placebo				
All-cause mortality	1 (84,496)	RR 0.89 (0.34, 2.30)	No significant difference	Moderate
Community-acquired pneumonia	1 (84,496)	RR 0.78 (0.63, 0.97)	Favors PCV13	High
Invasive pneumococcal disease	1 (84,496)	RR 0.51 (0.34, 0.77)	Favors PCV13	High
Adverse events	1 (2,011)	RR 1.37 (1.08, 1.74)	Favors placebo	High
Serious adverse events	1 (2,011)	RR 1.18 (0.82, 1.68)	No significant difference	High
PPSV23 vs. Placebo				
Community-acquired pneumonia	4 (22,282)	RR 0.36 (0.20, 0.65)	Favors PPSV23	Moderate
Invasive pneumococcal disease	4 (22,282)	RR 0.75 (0.35, 1.62)	No significant difference	Moderate
PPSV23 vs. PCV13				
Immunogenicity	1 (737)	PCV13 was non-inferior to PPSV23	No significant difference	High
Adverse events	1 (737)	RR 0.60 (0.45, 0.80)	Favors PPSV23	High
Immunocompetent adults 18-64 years old				
PCV13 vs. Placebo				
Invasive pneumococcal disease	1 (7,640)	74% (-78%, -70%) decrease in incidence	Favors PCV13	Low
Adverse events	2 (1,340)	95.8% to 96% (mostly local reactions, non-severe)	Favors placebo	Low
Immunogenicity	1 (831)	Robust immune response among adults (18-29 years)	Favors PCV13	Low

PPSV23 vs. PCV13				
Immunogenicity	1 (1,234)	PCV13 was non-inferior to PPSV23 for all 12 common serotypes	No significant difference	High
PPSV23 vs. Placebo				
Community-acquired pneumonia	1 (152, 723)	HR 1.136 (0.92, 1.40)	No significant difference	Moderate

CI confidence interval; HR hazard ratio; PCV pneumococcal conjugate vaccines; PPSV pneumococcal polysaccharide vaccine; RR relative risk

Subgroup 1: Immunocompetent Adults Aged ≥65 Years Old

All-cause mortality

PCV13 vs. placebo (1 RCT; n=84,496; moderate certainty of evidence)
An RCT[12] in Netherlands investigated the efficacy and safety of PCV13 compared to placebo among immunocompetent adults ≥65 years of age. PCV13 did not significantly reduce deaths from any cause (relative risk [RR] 0.89; 95% confidence interval [CI] 0.34, 2.30). However, the low mortality rates in either group preclude any conclusions to be made regarding the vaccine effect.

Incidence of pneumonia

PCV13 vs. placebo (1 RCT; n=84,496; high certainty of evidence)
Data from the CAPiTA RCT[12,13] showed that PCV13 immunization significantly reduced the incidence of pneumococcal pneumonia (RR 0.78; 95% CI 0.63, 0.97) among immunocompetent adults ≥65 years of age with no prior pneumococcal vaccination history.

PPSV23 vs. placebo (4 RCTs; n=22,282; moderate certainty of evidence)
A high quality systematic review[21] summarized the impact of PPSV23 compared to placebo on pneumococcal pneumonia in four RCTs. Pooled estimates showed no significant reduction in pneumonia incidence (RR 0.75; 95% CI 0.35, 1.62). The certainty of evidence was downgraded to moderate owing to inconsistency across estimates reported in the studies (I^2=78%). Only one of the four RCTs showed benefit, but this involved very old and frail nursing home residents. Sensitivity analysis involving only two of four trials showed a significant benefit in pneumonia incidence reduction (RR 0.36; 95% CI 0.20, 0.65).

Invasive pneumococcal disease

PCV13 vs. placebo (1 RCT; n=84,496; high certainty of evidence)
Data from the CAPiTA RCT[12,13] showed that PCV13 immunization reduced the episodes of invasive pneumococcal disease (IPD) across all serotypes among immunocompetent adults ≥65 years of age with no prior pneumococcal vaccination history (RR 0.51; 95% CI 0.34, 0.77).

PPSV23 vs. placebo (4 RCTs; n=22,282; moderate certainty of evidence)
Four RCTs included in the high-quality systematic review[22] showed that PPSV23 significantly reduced IPD incidence (RR 0.27; 95% 0.08, 0.90). The certainty of this effect was rated moderate due to imprecision associated with wide confidence intervals.[21]

Immunogenicity

PCV13 vs. PPSV23 (1 RCT; n=737; high certainty of evidence)
A multi-center RCT in Japan[15] investigated the non-inferiority of PCV13 compared to PPSV23 among immunocompetent, vaccinated adults ≥65 years of age. The obtained functional antibody response, measured using opsonophagocytic activity (OPA) geometric mean titers (GMTs), showed that PCV13 was non-inferior to PPSV23 for all 12 serotypes, and was statistically higher for nine of the 12 serotypes common between the vaccines (see Appendix 2 GRADE Evidence Profile for the specific values). The study supports that PCV13 has the potential for improved clinical efficacy caused by PCV13-associated serotypes.

Adverse events

PCV13 vs. placebo (1 RCT: n=2,011; high certainty of evidence)
The same RCT[12] in Netherlands evaluated the adverse events occurring within four weeks after vaccination among all participants, and within six months after vaccination among participants in a safety subgroup. Adverse events within one month of vaccination were significantly higher in the PCV13 group than in the placebo group (RR 1.37; 95% CI 1.08, 1.74). However, most were local reactions including local injection-site reactions and muscular pain. The risk for serious adverse events were comparable between PCV13 and placebo groups (RR 1.18; 95% CI 0.82, 1.68).

PCV13 vs. PPSV23 (1 RCT; n=737; high certainty of evidence)
PCV13 was associated with more frequent local reactions (RR 0.60; 95% CI 0.45, 0.80) compared to PPSV23 immunization among immunocompetent adults ≥65 years of age.[15]

Subgroup 2: Immunocompetent Adults Aged 18 to 64 Years Old

Incidence of pneumonia

PPSV23 vs. placebo (1 RCT; n=152,723; moderate certainty of evidence)
PPSV23 vaccination showed no significant effect on all-cause radiographically-confirmed pneumonia among immunocompetent and healthy young adult military trainees between 17 to 20 years of age (HR 1.136; 95% CI 0.919, 1.404).[19]

Invasive pneumococcal disease

PCV13 (no comparator) (1 case control; n=632; low certainty of evidence)
PCV13 immunization reduced the incidence of PCV13 type invasive pneumococcal disease by 74% (95% CI -78%, -70%) among immunocompetent adults between 19 to 64 years of age without chronic medical conditions.[17]

Immunogenicity

PCV13 vs. PPSV23 (1 RCT; n=1,234; high certainty of evidence)
An RCT on the immunogenicity of pneumococcal vaccines compared a total of 831 subjects between 60 to 64 years of age that received either PCV13 (n=417) or PPSV23 (n=414) to an additional group with subjects between 50 to 59 years of age (n=403) that received PCV13. PCV13 was non-inferior to PPSV23 for all 12 common serotypes and was statistically significantly greater for eight of the 12 common serotypes (1, 4, 6B, 7F, 9V, 18C, 19A, 23F), with a difference in proportions of 39.2% (95% CI 33.0%, 45.1%). The immunogenicity in the 50- to 59-year-old

cohort was non-inferior to that of the 60- to 64 year-old cohort for all 13 serotypes, and was statistically significantly greater for nine serotypes (see Appendix 2 GRADE Evidence Profile for the specific values).[20]

PCV13 (no comparator) (1 prospective cohort; n=1,316; low certainty of evidence)
A prospective cohort found that immune responses to PCV13 were robust in adults ≥18 years of age, with the highest responses observed in the youngest subgroup. Based on safety and immunologic profile, PCV13 may serve an important therapeutic role in younger adults, particularly those with underlying medical conditions who have an increased risk of serious pneumococcal infections.[16]

Adverse events

PCV13 (2 observational studies; n=1,340; low certainty of evidence)
Two observational studies showed that PCV13 was well tolerated, without serious adverse events documented and with local reactions (pain in injection site, redness, swelling, and limitation of activities) as the most common adverse events.[16,18] At least one systemic event was reported by 96% of adults aged 18 to 49 years old and 83% of adults aged 60 to 64 years old. The most commonly reported systemic events were generalized muscle pain, headache, and fatigue, with events lasting for less than six days.[16]

Recommendations from Other Groups

There is one local guideline[7] and four international guidelines[8-11] with relevant recommendations on pneumococcal vaccine as summarized in the table below. Clinical practice guidelines (CPG) from India, USA, and Saudi Arabia have no recommendation on pneumococcal vaccines for adults below 64 years old.[8-10] All five CPGs recommended PCV13 and PPSV23 for healthy elderly. However, the population of immunocompetent adults for these guidelines included patients with stable comorbidities (e.g., heart failure, diabetes, etc.).

Table 2 summarizes the recommendations on pneumococcal vaccines from other groups

Table 2. Recommendations on pneumococcal vaccination from other groups

Group	GRADE Rigor Score	Recommendation for Immunocompetent Adults	Basis for Recommendation/s	
			Strength	Quality of Evidence
Immunocompetent elderly				
PSMID 2018[7]	56.3	PPSV23[a] and PCV13[b] can be administered routinely to immunocompetent elderly patients to prevent invasive pneumococcal disease.[12,32]	Strong	Moderate
		PPSV23[a] can be administered routinely to immunocompetent adults, especially the elderly, to prevent pneumococcal disease.[12,32]	Strong	Low
		PCV13 can be administered routinely to immunocompetent adults in preventing pneumococcal pneumonia.[12,32]	Strong	Moderate
		PPSV23 and PCV13 may be recommended to immunocompetent adults, especially the elderly, in preventing mortality.[12,32]	Strong	Low
Indian CPG 2019[8]	79.1	PPSV23 vaccination is recommended in all adults above age 65.[33]	Grade 2A	
ACIP 2021[9]	78.1	PPSV23 vaccination (1 dose) is recommended in all adults aged ≥65 years.[34]	Grade 2A	

		PCV13 vaccination is recommended based on shared clinical decision-making for adults aged ≥65 years who do not have immunocompromised condition and who have not previously received PCV13.[17]	No recommendation (no evidence cited with the recommendation)
STS 2016[10]	75	All healthy, vaccine naïve adults ≥50 years of age should receive one dose of PCV13 followed by PPSV23 after 1 year or more.[35,36]	Evidence Category A
Immunocompetent elderly			
Australian Immunisation Handbook 2021[11]	93.75	Non-indigenous adults without risk conditions for pneumococcal disease are recommended to receive PCV13 ≥70 years of age.	Basis for recommendations not included in the available handbook
		Aboriginal and Torres Strait Islander adults without risk conditions are recommended to receive PCV13 at age ≥50 years followed by a PPSV23 after 1 year.	
Immunocompetent adults 19-64 years old			
Indian CPG 2019[8]	79.1	Pneumococcal vaccination (PCV13 and PPSV23) is usually not recommended for healthy individuals under the age of 65 years.	No recommendation (no evidence cited with the recommendation)
		No recommendation for adults between 19 to 64 years old without underlying medical condition.	No basis available
ACIP 2021[9]	78.1	No recommendation for adults between 19 to 64 years old without underlying medical condition.	No basis available
STS 2016[10]	75	No recommendation for adults between 19 to 64 years old without underlying medical condition.	No basis available
Australian Immunisation Handbook 2021[11]	93.75	No recommendation for adults between 19 to 64 years old without underlying medical condition.	Basis for recommendations not included in the available handbook

ACIP Advisory Committee on Immunization Practices; PSMID Philippine Society of Microbiology and Infectious Diseases; STS Saudi Thoracic Society

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

Cost

Table 3. Cost-effectiveness studies of pneumococcal vaccines among healthy adults

Setting	Cost-effective (Yes/No)				Conclusion
	PCV13	**PPSV23**	**Sequential PCV13-PPSV 23**	**PCV13 vs. PPSV23**	
Immunocompetent Adults ≥65 Years Old					
Korea (2017)[25]	YES (USD 4,529 per QALY)	YES (USD 25,786 per QALY)	YES (USD 1,228 per QALY)	YES, PCV13 > PPSV23 (USD 797 per QALY)	Vaccination with PCV13 alone, PPSV23 alone, and sequential PCV13-PPSV23 are cost-effective options for elderly aged ≥65 years old, regardless of the age and risk groups. However, PCV13 vaccination is more cost-effective compared to PPSV23 vaccination alone.
Sweden (2020)[26]	YES for ≥75 y/o (€200,000 per QALY)	YES for ≥75 y/o (€29,500 per QALY)	[a]	[a]	Either PCV13 or PPSV23 vaccination is unlikely to be cost-effective for elderly aged ≥65 years old, but can be cost-effective for those aged ≥75 years old in a Swedish setting.
	NO for ≥ 65 y/o	NO for ≥ 65 y/o	[a]	[a]	
England (2016)[27]	NO	[a]	[a]	[a]	PCV13 vaccination is efficacious for elderly aged ≥65 years old. However, the absolute incidence of vaccine-type disease will likely become very low due to wider benefits of the childhood PCV13 vaccination program, such that a specific PCV13 vaccination program targeting the immunocompetent elderly would not be cost-effective.
Immunocompetent adults ≥50 years old					
Belgium (2016)[28]	NO	[a]	NO	NO	PCV13 vaccination is unlikely to be cost-effective compared with either no vaccination or in combination with PPSV23 versus PPSV23 alone for elderly aged ≥ 50 years old.
Immunocompetent adults 50-64 years old					
Korea, (2017)[25]	NO	NO	[a]	[a]	Neither PCV13 nor PPSV 23 is cost-effective in the low-risk group.
Immunocompetent adults 18-65 years old					
South Africa (2020)[29]	[a]	[a]	[a]	YES, PCV13 > PPSV23 (USD 771 per QALY)	PCV13 is more cost-effective compared to PPSV23 for adults aged 18-65 years old.[b]

QALY Quality Adjusted Life Years

[a]No data

[b]The study population is heterogeneous in terms of the risk for pneumococcal disease (ranging from low- to high-risk, with more patients having moderate- to high-risk features).

Patient Values and Preference, Equity, Acceptability, and Feasibility

Research conducted by the University of the Philippines Population Institute evaluated the awareness of vaccines (pneumococcal and flu) as well as the level of vaccination among Filipinos aged ≥60 years (n=5,985).[30]

Filipinos showed low level of awareness regarding influenza and pneumococcal vaccines. Only four in ten respondents were aware of pneumococcal vaccines, while four out of ten were aware of influenza vaccines. Of those who were aware of vaccination for pneumococcal disease, only 53% have actually been vaccinated, which translates to only 20% of Filipinos ≥60 years of age having protection against pneumonia in the next five years after vaccination. In addition, around 19% of respondents who were aware of the vaccines did not get vaccinated with either pneumococcal or influenza vaccines. This was observed among older age groups, males, rural residents and less educated respondents.[31] This reflects that treatment rather than prevention is prioritized especially in limited settings.[31]

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4.13. Should pre-exposure rabies vaccine be given to asymptomatic healthy adults?

RECOMMENDATIONS

Among asymptomatic healthy adults, we <u>suggest against giving</u> pre-exposure rabies vaccine.
(weak recommendation, very low certainty evidence)

Among healthcare workers with high risk of exposure to rabies, we <u>suggest giving</u> pre-exposure rabies vaccine.
(weak recommendation, very low certainty evidence)

Among adults with high risk of exposure, we <u>suggest giving</u> pre-exposure rabies vaccine.
(weak recommendation, very low certainty evidence)

Considerations

The consensus panel considered the following points during the formulation of the above recommendations:

- Only a weak recommendation was made for routine pre-exposure rabies vaccination due to the very low certainty of evidence on efficacy. Included studies did not specify risk categories among populations or target groups included. Uncertainties surrounding which geometric mean titer (GMT) levels offer protection from disease as well as duration of immunity were also pointed out by the panel.
- Intramuscular (IM) and oral routes were deemed to be equipotent, thus no specific recommendations on the routes were drafted.

Key Findings

- No studies were found comparing pre-exposure rabies vaccination with placebo or no vaccination among asymptomatic apparently healthy adults. Indirect evidence for this guideline question was obtained from 11 RCTs that compared variations in the schedule, route, and type of pre-exposure rabies vaccination. Efficacy outcomes were expressed as geometric mean titer (GMTs) or seroconversion rates at 1 year of follow-up or less. The overall certainty of evidence regarding efficacy ranged from low to moderate, while certainty of evidence on safety outcomes ranged from very low to low.
- In terms of vaccine schedule, an abbreviated schedule did not show a significant difference compared to standard regimen for efficacy and safety outcomes regardless of age, risk group, or type of rabies vaccine. In terms of route of administration, intradermal and intramuscular routes demonstrated similar safety and efficacy profiles. Finally, different types of rabies vaccines (PVRV and PCECV) showed no significant difference in safety and efficacy.

Introduction

Rabies, caused by rabies virus (RABV) genotype 1, carries the highest fatality rate among all viral encephalitis and is one of the most common fatal infections in the world.[1] Based on 2019 data from the Department of Health, animal bites were ranked 8th among the top 10 leading causes of morbidity in the Philippines, accounting for 89,082 cases or 83 per 100,000 population.[2] There were 283 rabies deaths that year, corresponding to a mortality rate of 0.3 per 100,000 population, with most cases (n=216; 76%) occurring in adults.[2]

A retrospective study of medical records from San Lazaro Hospital, a national referral center for infectious disease in the Philippines, reported 1,839 rabies cases from 1987 to 2006.[3] All patients died and 98.6% had an animal bite or scratch exposure. Two-thirds of cases were recorded in adults and men. Almost all patients (n=1,831; 99.5%) came from indigent sectors of society. Regarding the animal bites, dog bites (n=1,638; 97.1%) outnumbered cat bites (n=49; 2.9%). Most dogs were considered "stray" (64.5%; n=1,057), while 35.5% (n=581) were unvaccinated domesticated pet dogs. About one-fourth of cases came from NCR. No notable decline in rabies epidemiology was observed in an extension of this retrospective study (2006-2015).[4]

Characteristics of Included Studies

Eleven randomized controlled trials (RCTs) investigating the effects of pre-exposure rabies vaccination among adults were included in the review.[5–15] Six of these were open-label trials.[7,8,10–13] Most (n=6) were conducted in Asian countries[8–13], with two completed in the Philippines.[12,13] The search strategy and detailed characteristics of these studies are summarized in Appendix 2 and 3, respectively.

A total of 2,554 healthy adults from 11 trials were included in the analysis. Most studies (n=8; 73%) recruited healthy adults from the general population aged 18-50 years with no prior history of rabies vaccination,[6–8,10,12–15] while four studies (36%) included older adults aged 50 years or above.[7,11–13] Three trials investigated the effects of rabies vaccination on healthy students or professionals at risk (n=908) for vaccination (e.g., veterinary medicine students, animal bite clinic staff).[5,8,9]

The included trials compared either one of the two locally-available vaccine types–purified Vero-cell rabies vaccine (PVRV) and purified chick embryo cell vaccine (PCECV). All studies used active interventions as comparators and were heterogeneous in terms of vaccination schedule/regimen, administration route, and vaccine manufacturer. Four studies compared abbreviated (2-1-1 or 2-1) versus standard (1-1-1 or 1-1-1-1-1) vaccination regimens,[8,10,11,14] while 6 trials compared intradermal (ID) versus intramuscular (IM) administration routes.[5-7,9,13,15] Only 2 studies directly compared different vaccine types (i.e., PVRV vs PCECV).[12,14] Eight studies on vaccine types which are not available in the Philippines (i.e., human diploid cell culture vaccine) were excluded in this review.

All studies provided data on rabies virus neutralizing antibodies (RVNA), geometric mean titer (GMT; IU/mL), and percentage of seroconversion (using $\geq$0.5 IU/mL as the cut-off point), measured using rapid fluorescent focus inhibition test (RFFIT). Local and systemic adverse events, serious adverse events, and mortality events resulting from rabies vaccine were reported by these studies. Short term follow-up periods across trials ranged from 7-90 days after the first vaccination, while longer follow-up periods ranged from 6 months to 2 years.

Appendix 5 shows the risk of bias assessment for each study. Most studies (n=9; 82%) were assessed to have high risk of detection bias for safety outcomes due to reporting of subjective outcomes for adverse events (e.g., pain, pruritus).

Outcomes

The summary of benefits and harms of pre-exposure rabies vaccination among healthy adults is shown in Table 1.

Table 1. Benefits and harms of pre-exposure rabies vaccine for healthy adults

Outcomes	No. of Studies (No. of Participants)	Effect Estimate [95% CI]	Interpretation	Certainty of Evidence
Comparison 1: By vaccination schedule (abbreviated vs. standard)				
PVRV				
All adults				
% Seroconversion* (90 days)	1 (173)	RR 1.00 [0.98, 1.02]	Equivalent	Moderate
High-risk populations (students)				
GMT (45 days)	1 (173)	MD 0.39 [-1.93, 2.71]	Inconclusive	Low
GMT (1 year)	1 (86)	MD 1.14 [-0.71, 2.99]	Inconclusive	Low
% Seroconversion* (45 days)	1 (44)	RR 1.00 [0.92, 1.09]	Equivalent	Moderate
% Seroconversion* (1 year)	1 (86)	RR 0.96 [0.87, 1.05]	Equivalent	Moderate
Local and systemic adverse events (any)	1 (181)	RR 1.15 [0.76, 1.76]	Abbreviated regimen is as good as standard regimen or worse	Very low
PCECV				
All adults				
GMT (45 days)	2 (530)	MD -0.99 [-4.01, 2.03]	Inconclusive	Low
% Seroconversion* (42-90 days)	3 (577)	RR 1.00 [0.99, 1.01]	Equivalent	Moderate
Local adverse events (any)	2 (1221)	RR 0.99 [0.89, 1.11]	Equivalent	Low
Systemic adverse events (any)	2 (1221)	RR 0.87 [0.72, 1.04]	Abbreviated regimen is as good as standard regimen or better	Low
Younger adults (18-50 years)				
GMT (42 days)	1 (139)	MD -0.90 [-9.92, 8.12]	Inconclusive	Low
GMT (13 months)	1 (200)	MD 0.10 [-0.82, 1.02]	Inconclusive	Low
% Seroconversion* (42-90 days)	2 (186)	RR 1.00 [0.97, 1.03]	Equivalent	Moderate
% Seroconversion* (13 months)	1 (200)	RR 0.95 [0.88, 1.03]	Equivalent	Moderate
Local adverse events (any)	1 (824)	RR 1.00 [0.95, 1.06]	Equivalent	Low
Systemic adverse events (any)	1 (824)	RR 0.86 [0.71, 1.05]	Abbreviated regimen is as good as standard regimen or better	Low
Older adults (> 50 years)				
GMT (43 days)	1 (391)	MD -1.00 [-4.20, 2.20]	Inconclusive	Low
% Seroconversion* (43 days)	1 (391)	RR 1.00 [0.99, 1.01]	Equivalent	Moderate
Local adverse events (any)	1 (397)	RR 0.78 [0.45, 1.35]	Inconclusive	Low

Systemic adverse events (any)	1 (397)	RR 0.91 [0.72, 1.04]	Equivalent	Low
Comparison 2: By route of administration (intradermal vs. intramuscular)				
PVRV				
All adults				
GMT (21 days)	1 (73)	MD 1.67 [-1.47, 4.81]	Inconclusive	Low
GMT (1 year)	1 (71)	MD 0.06 [-0.33, 0.45]	Equivalent	Low
% Seroconversion* (21-90 days)	2 (128)	RR 0.99 [0.92, 1.05]	Equivalent	Moderate
% Seroconversion* (1 year)	1 (71)	RR 1.14 [0.75, 1.71]	Inconclusive	Low
Local adverse events (any)	2 (205)	RR 1.11 [0.55, 2.24]	Inconclusive	Very low
Systemic adverse events (any)	2 (205)	RR 0.44 [0.10, 1.86]	Inconclusive	Very low
High-risk populations (students and healthcare workers)				
Local adverse events (any)	2 (727)	RR 1.19 [0.71, 2.00]	Inconclusive	Very low
Systemic adverse events (any)	2 (727)	RR 1.00 [0.67, 1.48]	Inconclusive	Very low
PCECV				
All adults				
GMT (77 days)	1 (24)	MD 1.08 [-2.33, 4.49]	Inconclusive	Low
GMT (365 days)	1 (22)	MD -0.02 [-0.43, 0.39]	Equivalent	Low
% Seroconversion* (21-90 days)	2 (62)	RR 1.00 [0.92, 1.09]	Equivalent	Moderate
% Seroconversion* (365-756 days)	2 (60)	RR 0.92 [0.72, 1.18]	Equivalent	Moderate
Local and systemic adverse events (any)	1 (24)	RR 1.38 [0.89, 2.12]	ID is as good as IM or worse	Very low
Comparison 3: By vaccine type (PVRV vs. PCECV)				
All adults				
GMT (90 days)	1 (119)	MD -1.05 [-2.46, 0.36]	PVRV is as good as PCECV or worse	Low
% Seroconversion* (90 days)	2 (165)	RR 1.00 [0.97, 1.03]	Equivalent	Moderate
Local adverse events (any)	1 (119)	RR 3.38 [0.36, 31.52]	Inconclusive	Very low
Systemic adverse events (any)	1 (119)	RR 0.38 [0.08, 1.78]	Inconclusive	Very low

CI confidence interval; GMT geometric mean titer; ID intradermal; IM intramuscular; MD mean difference; PCECV purified chick embryo cell vaccine; PVRV purified Vero-cell rabies vaccine; RR risk ratio
*% Seroconversion cut-off value: ≥0.5 IU/mL

Comparison 1: By Schedule (Abbreviated vs. Standard Regimens)

Efficacy

PVRV

For PVRV, the risk ratios (RR) of seroconverted healthy adults in the abbreviated regimen (2-1-1) compared to the standard regimen (1-1-1) were equivalent (RR 1.99 [95% CI 0.92 to 1.02]; N=173; 1 RCT).[14] The certainty of evidence was moderate due to serious indirectness.

Among veterinary medicine students, the mean differences (MD) in the RVNA GMT between abbreviated regimen (2-1) and standard regimen (1-1-1-1-1, Essen) were inconclusive after 45 days (MD 0.39 IU/mL, 95% CI -1.93 to 2.71; N=173; 1 RCT)[8] and after one year of vaccination (MD 1.14 IU/mL, 95% CI -0.71 to 2.99; N=86; 1 RCT).[8] The certainty of evidence was low due to serious indirectness and imprecision.

Seroconversion rates of veterinary medicine students on either abbreviated (2-1) or standard (2-1-1) regimens were comparable after 45 days (RR 1.00, 95% CI 0.92 to 1.09; N=4; 1 RCT)[8] and after one year of vaccination (RR 0.96, 95% CI 0.87 to 1.05; N=86; 1 RCT).[8] The certainty of evidence was downgraded to moderate due to serious indirectness.

PCECV
The mean difference in RVNA GMT of younger adults aged 18-50 years who received the abbreviated PCECV regimen (2-1-1) compared to standard regimen (1-1-1) were inconclusive after 42 days (MD -0.90 IU/mL, 95% CI -9.92 to 8.12; N=139; 1 RCT)[10] and up to 13 months (MD 0.10 IU/mL, 95% CI -0.82 to 1.02; N=200; 1 RCT)[10] of vaccination. In older adults > 50 years old, the mean difference was also inconclusive for either type of regimens (MD -1.00 IU/mL, 95% CI -4.20 to 2.20; N=391; 1 RCT)[11] after 43 days. No data was found on immune response for PCECV in older adults after 1 year. The certainty of evidence was low due to serious indirectness and imprecision.

Comparable seroconversion rates were noted for abbreviated and standard PCECV regimens after 90 days of follow-up at 99.7% vs 100% respectively (RR 1.00, 95% CI 0.99 to 1.01; N=577; 3 RCTs) for healthy adults across age groups.[10,11,14] At 13 months follow-up, similar results were noted in one trial among younger adults (90% vs. 95% respectively; RR 0.95, 95% CI 0.88 to 1.03, 1 RCT), suggesting equivalence of the two regimens.[10] The certainty of evidence as moderate due to serious indirectness.

Safety

PVRV
Safety data was reported in 1 RCT involving 181 healthy veterinary students. The risk ratio for combined local and systemic adverse events suggests that the abbreviated regimen (2-1) is as good as the standard regimen (1-1-1-1-1) or worse (16% vs. 14%; RR 1.15, 95% CI 0.76 to 1.76; N=181; 1 RCT).[8] All adverse events were classified as mild and subsided within 72 hours of vaccination without requiring medical treatment. Most common adverse events noted were pain, pruritus, headache, fever, malaise, and sleepiness. The certainty of evidence was very low due to serious indirectness, imprecision, and high risk of detection bias.

PCECV
Based on 2 RCTs involving 1,221 Chinese adults,[10,11] the risk ratios of local adverse events (67% vs. 56%; RR 0.99, 95% CI 0.89 to 1.11) and systemic adverse events (RR 0.87, 95% CI 0.72 to 1.04) suggest that abbreviated regimen is as good as standard regimen or better. Similar effect estimates were noted regardless of age group of participants. All events were classified as mild and non-fatal. Most common adverse events included pain, fever, and headache. The certainty of evidence was low due to high risk of detection bias and serious indirectness.

Comparison 2: By Route of Administration (Intradermal vs. Intramuscular)

Efficacy

PVRV
For PVRV, the mean difference in the RVNA GMT levels of healthy adults under ID and IM after 21 days was inconclusive (MD 1.67 IU/mL, 95% CI -1.47 to 4.81; N=73; 1 RCT).[13] After one year, the mean difference became comparable for ID and IM routes (MD 0.06 IU/mL, 95% CI -0.33 to 0.45; N=71; 1 RCT).[13] The certainty of evidence was low due to serious indirectness and imprecision.

Comparable seroconversion rates were observed for ID and IM routes at 21-90 days of follow-up (97% vs. 98%, respectively, RR 0.99, 95% CI 0.92 to 1.05; N=128; 2 RCTs).[13,15] Although the

proportion of seroconverted adults in the intradermal and intramuscular routes were reduced after one year, the results were still comparable for both groups (60% vs. 53%, RR 1.14, 95% CI 0.75 to 1.71; N=71; 1 RCT).[13] The certainty of evidence ranged from low to moderate due to serious indirectness and imprecision.

PCECV
For PCECV, the mean difference in GMT levels between ID and IM routes among healthy adults after 77 days was inconclusive (MD 1.08 IU/mL, 95% CI -2.33 to 4.49; N=24; 1 RCT). The mean difference in GMT of ID and IM routes was comparable after one year (MD -0.02 IU/mL, 95%CI -0.43 to 0.39], 1 RCT).[7] The certainty of evidence was low due to serious indirectness and imprecision.

All participants in both groups exhibited seroconversion after 21-90 days of vaccination (RR 1.00, 95% CI 0.92 to 1.09; N=62; 2 RCTs). After 1-2 years, the proportion of seroconverted participants in both groups were lower (77% for intradermal vs. 87% for intramuscular) but still comparable (RR 0.92, 95% CI 0.72 to 1.18; N=60; 2 RCTs).[6,7] The certainty of evidence was moderate and was downgraded due to serious indirectness.

Safety

PVRV
Among adults from the general population, the risk ratios for local adverse events (28% for ID vs. 24% for IM; RR 1.11, 95% CI 0.55 to 2.24; N=205; 2 RCTs)[13,15] and systemic adverse events (13% vs 15%; RR 0.44, 95% CI 0.10 to 1.86; N=205; 2 RCTs)[13,15] were inconclusive for ID and IM PVRV. Most common adverse events included pain, erythema, and fever. All were mild and non-fatal. The certainty of evidence was very low due to high risk of detection bias, serious indirectness, and serious imprecision.

Among students and healthcare workers at risk for rabies, risk ratios were also inconclusive for ID and IM PVRV in terms of local adverse events (RR 1.19, 95% CI 0.71 to 2.00; N=727; 2 RCTs)[5,9] and systemic adverse events (RR 1.00, 95% CI 0.67 to 1.48; N=727; 2 RCTs.[5,9] The certainty of evidence was downgraded due to serious indirectness, imprecision, and high risk of detection bias.

PCECV
One trial involving 24 healthy adults compared the safety profile of ID and IM routes for PCECV.[7] Higher adverse events (combined local and systemic) were noted in the ID group (92% vs. 67% for IM), suggesting that ID route is as good as IM route or worse (RR 1.38; 95% CI 0.89 to 2.12).[7] No serious adverse events were reported.[7] It should be noted that the certainty of evidence was very low due to high risk of detection bias, serious indirectness, and serious imprecision.

Comparison 3: By Type of Vaccine (PVRV vs. PCECV)

Efficacy
The mean difference in the RVNA GMT levels of healthy adults after 90 days suggests that PVRV is as good as PCECV or worse (MD -1.05 IU/mL; 95% CI -2.46 to 0.36; N=119; 1 RCT).[12] The certainty of evidence was downgraded to low due to serious indirectness and imprecision.

In terms of seroconversion rates after 90 days, 2 RCTs showed no significant difference between PVRV and PCECV (RR 1.00, 95% CI 0.97 to 1.03; N=165) with 100% seroconversion.[12,14] No

efficacy data was available for longer follow-up periods. The certainty of evidence was moderate (downgraded due to serious indirectness).

Safety

One local trial involving 119 adults showed inconclusive findings between PCECV and PVRV in terms of local adverse events (RR 3.38, 95% CI 0.36 to 31.52) and systemic adverse events (RR 0.38, 95% CI 0.08 to 1.78).[12] For both groups, not more than 11% of participants reported experiencing mild adverse events. Most reported adverse events included pain, erythema, itching, fever, dizziness, and headache.[12] The certainty of evidence was very low due to serious indirectness, imprecision, and high risk of detection bias.

Recommendations from Other Groups

The World Health Organization (WHO),[16] the US Advisory Committee on Immunization Practices (ACIP),[17] and the Philippine Society for Microbiology and Infectious Diseases (PSMID)[18] all recommend the use of pre-exposure rabies vaccination among individuals at risk for rabies virus exposure such as: persons working with live rabies virus in research or vaccine production facilities, persons who interact with possibly rabid animals, and selected travelers to areas where rabies virus is endemic in dogs.[17]

WHO recommends either a 2-site intradermal vaccination (days 0, 7) or 1-site intramuscular vaccination (days 0, 7).[16] ACIP recommends 2 intramuscular doses of HDCV or PCECV.[17] They also provided recommendations on checking of titers and booster vaccination based on risk. PSMID recommended the use of PVRV or PCECV based on a meta-analysis of 11 studies among children.[18]

Table 2. Recommendations from international and local CPGs

Group	Recommendations
World Health Organization (WHO, 2018)[16]	Recommends PrEP for individuals at high risk of rabies virus exposure: ● Those in highly endemic settings with limited access to timely and adequate PEP ● Individuals at occupational risk ● Travelers who may be at risk of exposure Recommends the following PrEP schedule: ● Intradermal: 2-site given on days 0 and 7 ● Intramuscular: 1-site, given on days 0 and 7
US Advisory Committee on Immunization Practices (ACIP, 2022)[17]	Recommends PrEP for individuals with elevated risk for unrecognized or recognized rabies virus exposures including higher risk or unusual exposures (e.g., aerosolized virus): ● 2 IM doses of HDCV or PCECV on days 0 and 7 ● A 1-time titer/booster dose is advised for persons with risk for only recognized rabies exposure ● Checking of titers every 6 months or 2 years (minimum acceptable rabies antibody titer is 0.5 IU/mL) depending on the risk category
Philippine Society for Microbiology and Infectious Diseases (PSMID, 2018)[18]	Recommends PrEP for individuals at risk for rabies virus exposure: ● Schedule: days 0, 7, 21/28 ● Route: ID, 0.1 mL; or IM, 0.5 mL PVRV or 1.0 mL for PCECV ● 3 doses of pre-exposure vaccination of PCECV shows immunogenicity in 100% by day 28 ● At risk populations include the following: ○ Healthcare workers directly caring for rabies patients ○ Individuals directly involved in rabies control ○ Personnel in rabies diagnostic laboratories ○ Pet owners and household members

	○ Animal handlers ○ Field workers such as dog vaccinators/catchers ○ Veterinarians and veterinary students ○ Children 5-14 years old living in areas where there is high incidence of rabies ○ Spelunkers *(Strong recommendation, moderate quality of evidence)*

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

Cost

Costs related to rabies vaccination

Costs of rabies vaccine and related treatments taken from a local economic evaluation in 2020 are listed in Table 3.[19] The total costs of vaccinating one adult against rabies range from PHP 3,507-4,462. Cost estimates were obtained from the study by Quiambao, et al.,[19] which used costs of the rabies vaccine and rabies immunoglobulin (RIG) administered through the public sector and borne by the Department of Health.

Table 3. Costs of pre- and post-exposure prophylaxis and treatments associated with rabies

Vaccines/Procedures	**Unit Cost (PHP)**[19]	**Total Cost (PHP)**
PVRV (per vial)	365 x 2	730
PCECV (per vial)	730 x 2	1460
Consultation	50-125 x 3	150-375
Vaccine administration (per visit)	35 x 3	105
eRIG skin test	41	41
Transportation and meals (per visit of one patient and one caregiver)	329 x 3	1,092
Productivity loss (per visit)	463 x 3	1,389
GRAND TOTAL (cost of vaccinating one adult against rabies)		**3,507-4,462**

eRIG equine rabies immunoglobulin; hRIG human immunoglobulin; PCECV purified chick embryo cell vaccine; PVRV purified Vero-cell rabies vaccine

Cost-effectiveness studies

One econometric modeling study among 5-year-old children compared pre-exposure with post-exposure prophylaxis (PrEP+PEP) program versus post-exposure prophylaxis (PEP) program for rabies vaccine in the Philippines. PEP was more cost-effective than no vaccination at an incremental cost-effectiveness ratio (ICER) of PHP 18,663 per quality-adjusted life-years (QALYs) gained. Adding PrEP to PEP resulted in an ICER of PHP 36,035/QALY gain.[19] Both programs were cost-effective since they fall below the willingness-to-pay threshold (PHP 140,255). The study also concluded that using an abbreviated (2-2) PrEP intradermal regimen among children in school-based settings would be more cost-effective when compared to standard (2-2-2-0-0) PEP regimen. In contrast, the World Health Organization (WHO) mentioned in their 2018 position paper on rabies vaccines that a large-scale PrEP immunization would be substantially more expensive when compared to other rabies prevention strategies such as PEP with mass dog vaccination campaigns.[16]

Another econometric modeling study conducted in the Netherlands compared different PrEP regimens recommended by the WHO, intramuscular versus intradermal vaccination routes, and subsequent post-exposure vaccination among high-risk groups.[20] Intradermal vaccinations in combination with current WHO recommendations was the least costly strategy. Similar results were found by a modeling study evaluating the cost-effectiveness of PEP strategies in low-income countries.[21] Switching from intramuscular to intradermal vaccine regimen would improve affordability and accessibility of PEP among animal bite victims.

Patient Values and Preference, Equity, Acceptability, and Feasibility

Several local studies evaluated the effectiveness of rabies prevention programs in various regions of the country. A case study of the Integrated Bite Case Management (IBCM) in Albay, Bicol found the following strategies to be beneficial in rabies prevention and treatment: (1) investigations of suspicious biting incidents, (2) triage of patients, (3) investigation of suspect dogs, and (4) targeted field investigations.[22] The Bohol Rabies Prevention and Elimination Project (BRPEP) reported a significant reduction in human rabies deaths from 0.77 per 100,000 population in 2007 to zero per 100,000 in 2009.[23] Mass vaccinations and continuous surveillance activities were found to be effective in halting the spread of the virus on the island. A follow-up study described the knowledge, skills, and practices of Filipinos after the implementation of BRPEP. A large proportion (94%) of households in Bohol heard about the program, but specific knowledge on rabies was limited.[24] Personal experience (e.g., knowing someone with rabies) and employment had the greatest impact on the participants' knowledge on and attitudes towards rabies. A cross-sectional study of 727 randomly selected households in Central Luzon reported that owning a dog was associated with higher rabies knowledge when compared to those with no dogs, while the level of education (either primary only or no education) was associated with lower knowledge on rabies.[25]

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4.14. Should tetanus vaccine be recommended to apparently healthy adults?

RECOMMENDATIONS

Among healthy adults with complete primary series, we recommend giving any tetanus-toxoid-containing vaccine every 10 years.
(strong recommendation, low certainty evidence)

Among pregnant women with unknown status or incomplete series, we suggest giving primary series with Tdap followed by any tetanus-toxoid-containing vaccine.
(weak recommendation, low certainty evidence)

Among pregnant women with complete primary series, we suggest giving any tetanus toxoid-containing vaccine during each pregnancy.
(weak recommendation, low certainty evidence)

Among healthy adults with unknown status or incomplete series, we suggest giving primary series with Tdap followed by any tetanus-toxoid-containing vaccine.
(weak recommendation, very low certainty evidence)

Considerations

The consensus panel considered the following when formulating these recommendations:

- Despite achieving the Maternal and Neonatal Tetanus Elimination (MNTE) status in 2017, the Philippines remains to have a significant burden of tetanus based on data from subsequent years. Additionally, tetanus has a high case fatality rate. For this reason, the panel was unanimous in recommending tetanus vaccines for healthy adults despite very low to low certainty of evidence.
- Local non-neonatal tetanus surveillance system is lacking, making underreporting of the total number of tetanus cases highly likely.
- The evidence included studies where the participants were able to complete the primary series, posing applicability issues in the local setting.
- Frequent administration of tetanus vaccine does not provide added benefit. Further, the vaccine is more reactogenic if administered closely. In the absence of wound, tetanus vaccine should be given every ten years.
- All but one panelist agreed with the dosing specified for the pregnant patients. The panelist who was against it cited that health centers currently follow a different vaccine schedule: two doses are given during the first pregnancy, and one dose is given for each of the second to fourth pregnancies. Subsequent pregnancies will no longer need tetanus vaccination once a total of five doses have been administered. However, this dosing schedule came from a recommendation by the World Health Organization (WHO) where the evidence base was one case report.

Key Findings

- Tetanus toxoid-containing vaccination showed significant benefit in increasing immune response rates, defined as having detectable antibody levels against the tetanus antigen one month after vaccination using the standardized enzyme-linked immunosorbent assays (ELISA), in healthy adults.
- Seven immunogenicity studies showed increased immune responses from any tetanus toxoid-containing vaccine compared with another vaccine or with no comparator. Individuals who were given tetanus vaccination experienced a small but increased risk of grade 3 adverse events (as much as 2.4%) that would cause difficulty or impairment in daily activities. The incidence of serious adverse events was estimated at 0.4 to 1.2% among those who received the vaccine.
- These effect estimates are all based on low certainty evidence due to imprecision and risk of bias issues.

Introduction

Burden of the Disease

Tetanus is caused by *Clostridium tetani*, a gram-positive spore-forming rod-shaped bacterium found in soil. Tetanus infection usually arises from skin cuts and abrasions, penetrating wounds, or drug injections. *C. tetani* produces tetanospasmin that binds to presynaptic membranes at neuromuscular junctions and undergoes retrograde transport. The toxin is then taken up by presynaptic inhibitory neurons and blocks the release of inhibitory neurotransmitters, thereby causing generalized or localized spasms, trismus, dysphagia, dyspnea, and autonomic nervous system disturbances such as hypertension, tachycardia, bladder and bowel dysfunction, and increased respiratory secretions. Management of the disease involves supportive care and administration of antitoxin and antibiotics.[1]

An estimated 34,683.73 (95% confidence interval [CI] 25,943.00, 48,457.09) deaths from tetanus were recorded worldwide in 2019.[2] In the same year, the Philippines reported only 78 cases of neonatal tetanus and 953 total cases of tetanus[3] but the lack of a local non-neonatal tetanus surveillance system makes underreporting of the total number of cases highly likely. The Department of Health (DOH) reported 15 cases of clinically-confirmed neonatal tetanus from January 1 to April 27, 2019.[4] Of these 15 cases, eight (53%) of the mothers were not vaccinated against tetanus, 4 (27%) had unknown vaccination status, and one (6%) had received a single dose of tetanus toxoid vaccine.

In 2017, the Philippines achieved the Maternal and Neonatal Tetanus Elimination (MNTE) status, defined as less than one neonatal tetanus case per 1,000 live births,[5] and this status was maintained in all regions.[4] However, neonatal tetanus in the Philippines still has a case-fatality rate of 47%.[4] Moreover, approximately 0.027 years of healthy life lost due to disability (YLDs) per 100,000, 26.06 years of life lost (YLLs) per 100,000, and 26.08 disability-adjusted life years (DALYs) per 100,000 were incurred by tetanus in 2019.[2]

Data on long-term outcomes of tetanus are unavailable because most cases that occur in low-middle income countries have limited surveillance programs for the disease.[1]

Characteristics of Included Studies

Evidence for this review was obtained from eight studies. Appendix 3 lists the characteristics of included studies. All studies focused on adults from 18 to 64 years old. Three[6-8] were randomized controlled trials (RCTs), among which one[9] was a sub-analysis of four different RCTs, one[10] was a multicenter RCT, and three were open-label trials.[11-13] Two[8,13] of the studies used tetanus toxoid (Td), one[7] used reduced diphtheria toxoid vaccine, while the other five studies [6,9,11,12] used tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine. All of the vaccines used contained 20IU (or 5Lf) tetanus toxoid.

No available studies compared any tetanus-toxoid containing vaccine against placebo in healthy non-pregnant adults. One study[8] on Td used an active comparator (standard Td available in the market) as their control, and another study[7] on Td used standard Td and a placebo as control. Both studies had no reported differences in the amount of tetanus toxoid contained between the experimental and the control vaccine. Among the studies that used Tdap, three[6,12,13] used no comparator, one[9] compared Tdap against a Tdap-IPV combination, and one[11] compared the efficacy of a Tdap booster to those who had taken a Tdap or Td booster ten years prior to the trial. One study described the safety profile of Tdap with the healthy pregnant population compared with placebo.[10]

Outcomes

Subgroup 1: Healthy Adults

The summary of all critical outcomes of tetanus vaccination among healthy adults is shown in Table 1.

Table 1. Benefits and harms of tetanus vaccine per subgroup of healthy adults

Outcomes	No. of Studies (No. of participants)	Effect Estimate	Interpretation	Certainty of Evidence
Incidence of tetanus	None	-	Inconclusive	-
All-cause mortality	None	-	Inconclusive	-
Any hospitalization	7 (3,664)	No reported hospitalizations that implicated the use of the vaccine as the causative agent	Inconclusive	-
Immune response rate	7 (3,664)	Pooled effect size 98.5% (95% CI 98.0, 98.9%)	Favors tetanus vaccine	Moderate
Grade 3 adverse events	4 (2,818)	Pooled incidence 1.8% (95% CI 1.4, 2.4%)	Favors control	Low
Serious adverse events	7 (3,664)	Pooled incidence 0.8% (95% CI 0.4, 1.2%)	Favors control	Low

CI confidence interval

Incidence of tetanus

No studies have focused on the incidence of tetanus as an outcome. Numerous patients in combat zones have been managed without tetanus immunoglobulin therapy.[14] Regardless, tetanus has not been reported in this group, and authors postulate that this may be due to their early wound care and primary immunization series.[14]

All-cause mortality

No studies have reported the incidence of mortality as an outcome of tetanus vaccination among healthy adults.

Any hospitalization

No studies have reported hospitalization specifically as an outcome of tetanus vaccination among healthy adults. However, several studies included hospitalizations as a component of "serious adverse events", which will be discussed below. Among the seven studies included, none reported any incidence of hospitalization as a result of the vaccination.

Immune response rate

Any tetanus toxoid-containing vaccine vs. another tetanus vaccine, or no comparator
(7 studies: 1 sub-analysis of 4 RCTs, 2 RCTs with 2 arms each, 1 RCT, 1 open label trial with 3 arms, 2 open label trials; n=3,664; moderate certainty of evidence)

Pooled data from the vaccine arm of seven randomized controlled trials[6-9,11-13] showed that immune response rates in adults were increased with vaccination using any tetanus toxoid-containing vaccine (ES 98.5%; 95% CI 98.0, 98.9%; I^2=0). This was defined in the studies as anti-tetanus antibody levels ≥0.1IU/ml after vaccination. However, this effect was based on moderate certainty of evidence. The quality of the studies was downgraded due to serious indirectness associated with the use of another tetanus vaccine as comparator[7-11] or no comparator used.[6,12,13]

Grade 3 adverse events

Any tetanus toxoid-containing vaccine vs. another tetanus vaccine or no comparator
(4 studies: 1 sub-analysis of 4 RCTs, 1 RCT with 2 arms, 2 open-label trials with 2 arms; n=2,818; moderate certainty of evidence)

Data from one sub-analysis of four RCTs, one RCT with two arms, and two open-label trials with two arms demonstrated that the pooled incidence of Grade 3 events observed among 2,818 vaccinated individuals was 1.8% (95% CI 1.4, 2.4%; I^2=0). The overall body of evidence providing this data was rated as low due to indirectness related to the use of non-standard definitions of "Grade 3 adverse events" across trials (i.e., any symptom that would cause difficulty or impairment in daily activities)[4*] and study design limitations as estimates came from intervention arms across studies.

Serious adverse events

Any tetanus toxoid-containing vaccine vs. another tetanus vaccine or no comparator
(6 studies: 1 sub-analysis of 4 RCTs, 3 RCTs with 5 arms, 1 open-label trial with 2 arms, 1 open label trial; n=3,329; very low certainty of evidence)

Tetanus toxoid-containing vaccines were well-tolerated. Pooled data from seven studies involving 3,329 patients estimated the incidence of serious adverse events (SAEs) at 0.8% (95% CI 0.4, 1.2%; I^2=0). SAEs probably have equal risk with tetanus toxoid vaccination versus control. Certainty of evidence was downgraded to low due to indirectness related to the use of different definitions for SAEs across trials and study design limitations as estimates came from intervention arms across studies.

[4]*The 2020 study by Asatryan had the following definitions: "grade 3 irritability - crying that could not be comforted or irritability preventing normal activity; grade 3 drowsiness - drowsiness preventing normal activity; grade 3 loss of appetite - not eating at all; grade 3 fever - temperature ≥40.0°C".[10] The 2011 study by Van Damme[7] and 2009 study by Blatter[13] defined "Grade 3 swelling as swelling >50 mm", while Asatryan[10] defined it as >20 mm.

For the purposes of this meta-analysis, “Severe Adverse Events” was defined as any symptom directly caused by the vaccination that would cause mortality, any hospitalization, prolonged in-patient hospitalization, or impairment or disability in daily activities. The studies by Asatryan and Van Damme narrowed their definitions to “any fatal event”.[9,12] The study by Lee did not specifically define which symptoms or conditions constitute severe adverse events, but the solitary SAE was noted to be acute gastroenteritis.[8]

Subgroup 2: Pregnant Women

Data on immune response rates in pregnant women were limited. No studies were found on the incidence of tetanus, all-cause mortality, and any hospitalization as an effect of tetanus vaccination. Its efficacy in preventing neonatal tetanus cases appears to be unclear. A multicenter RCT reported that tetanus toxoid-containing vaccines are relatively safe in pregnant women. Although some mild adverse events were significantly higher among pregnant women who received tetanus toxoid-containing vaccines, the risk of experiencing Grade 3 or more serious adverse events was not significantly increased with tetanus vaccination. These effect estimates are all based on low certainty evidence due to imprecision and risk of bias issues.

The effects of tetanus vaccination on various clinical outcomes in pregnant women are shown in Table 2.

Table 2. Summary of all critical outcomes of tetanus vaccination in pregnant women

Outcomes	No. of Studies (No. of Participants)	Effect Estimate	Interpretation	Certainty of Evidence
Incidence of tetanus	None	-	Inconclusive	-
All-cause mortality	None	-	Inconclusive	-
Any hospitalization	None	-	Inconclusive	-
Immunogenicity	None	-	Inconclusive	-
Prevention of neonatal tetanus (tetanus toxoid vs. polyvalent influenza vaccine)	1 RCT (n=1,182)	RR 0.12 (95% CI 0.00, 7.88) I^2=81.4%	Inconclusive	Low
Grade 3 adverse events (solicited)	1 multicenter RCT (n=687)	RRs for all types of AEs were comparable during and after pregnancy, except for pain during pregnancy RR 6.87 (95% CI 1.57, 30.0)	Inconclusive	Low
Grade 3 adverse events (unsolicited)	1 multicenter RCT (n=687)	During pregnancy: RR 2.33 (95% CI 1.13, 4.83) After pregnancy: RR 1.21 (95% CI 0.65, 2.26)	Inconclusive	Low
Serious adverse events	1 multicenter RCT (n=687)	RR 0.95 (95% CI 0.70, 1.30)	Inconclusive	Low

AE adverse event; CI confidence interval; RCT randomized controlled trial; RR risk ratio

Incidence of tetanus

No studies have reported the incidence of tetanus as an outcome of tetanus vaccination among pregnant women.

All-cause mortality
No studies have reported the incidence of mortality as an outcome of tetanus vaccination among pregnant women.

Any hospitalization
No studies have reported hospitalization as an outcome of tetanus vaccination among pregnant women.

Immune response rate
No studies have reported immunogenicity as an outcome of tetanus vaccination among pregnant women.

Adverse events

Tdap vs. placebo (1 multicenter RCT; n=687; moderate certainty of evidence)

Solicited adverse events
The incidences of the following solicited adverse events were significantly increased with administration of Tdap during pregnancy: pain (RR 3.65; 95% CI 2.79, 4.77; p<0.0001), redness (RR 2.23; 95% CI 1.62, 3.09; p<0.0001), swelling (RR 7.17; 95% CI 3.99, 12.88; p<0.0001), and fatigue (RR 1.21; 95% CI 1.00, 1.45; p=0.05).

Other adverse events were comparable in terms of risk: gastrointestinal symptoms (RR 1.81; 95% CI 0.84, 1.66; p=0.34), headache (RR 1.09; 95% CI 0.83, 1.43; p=0.53), and fever (RR 1.38; 95% CI 0.31, 6.11; p=0.67).

The incidences of the following solicited adverse events were significantly increased with administration of Tdap post-partum: pain (RR 4.96; 95% CI 3.68, 6.68; p<0.0001), redness (RR 2.83; 95% CI 1.98, 4.05; p<0.0001), swelling (RR 5.02; 95% CI 3.06, 8.26; p<0.0001), and fever (RR 1.96; 95% CI 1.08, 3.58; p=0.03). Fatigue, gastrointestinal symptoms, and headache incidence were comparable.

Unsolicited adverse events
Unsolicited adverse events in the pregnancy doses were not significantly different between vaccinated and unvaccinated groups (RR 1.09; 95% CI 0.90, 1.32; p=0.39), similar to the incidence of unsolicited adverse events in the postpartum group (RR 1.05; 95% CI 0.84, 1.31; p=0.67).[10]

Grade 3 adverse events

Tdap vs. placebo (1 multicenter RCT; n=687; moderate certainty of evidence)
Adverse events were considered grade 3 if they prevented normal activities. Grade 3 redness and swelling referred to more than 50 mm involvement, grade 3 pain referred to significant pain at rest or pain preventing normal activities, while grade 3 fever referred to a temperature of more than 39.0°C.[10] Either a single reduced antigen content Tdap dose at 27 to 36 weeks of gestation or a placebo was given in the pregnancy group. On the other hand, the post-pregnancy groups received the said Tdap vaccine or a placebo at less than 72 hours post-delivery. Grade 3 solicited adverse events were similar in the pregnancy and post-pregnancy groups.

Solicited adverse events
When Tdap was administered during pregnancy, the incidences of the following Grade 3 adverse events were not significantly different from the control group: pain (RR 15.36; 95% CI 0.88, 267.84; p=0.06), redness (RR 7.17; 95% CI 0.37, 138.22; p=0.19), swelling (RR 7.17; 95% CI 0.37, 138.22; p=0.19), fatigue (RR 1.23; 95% CI 0.37, 3.98; p=0.73), gastrointestinal symptoms (RR 1.03; 95% CI 0.20, 5.05; p=0.97), headache (RR 1.37; 95% CI 0.30, 6.07; p=0.67), and fever (RR 1.02; 95% CI 0.02, 51.45; p=0.99).

However, when Tdap was administered post-delivery, the incidence of Grade 3 adverse events was significantly higher but only for pain (RR 6.87; 95% CI 1.57, 30.00; p=0.01). Other than this, Grade 3 adverse events were comparable for redness (RR 6.87; 95% CI 0.35, 132.54; p=0.20), swelling (RR 8.84; 95% CI 0.47, 163.48; p=0.14), fatigue (RR 1.47; 95% CI 0.89, 2.41; p=0.12), gastrointestinal symptoms (RR 0.82; 95% CI 0.25, 2.65; p=0.74), headache (RR 0.79; 95% CI 0.21, 2.89; p=0.72), and fever (RR 0.33; 95% CI 0.03, 3.13; p=0.33).

Unsolicited adverse events
The risk of unsolicited Grade 3 adverse events from Tdap compared to placebo was significantly higher during pregnancy (RR 2.33; 95% CI 1.13, 4.83; p=0.022). but this risk was comparable for postpartum groups (RR 1.21; 95% CI 0.65, 2.26; p=0.54).

Serious adverse events

Tdap vs. placebo (1 multicenter RCT; n=687; moderate certainty of evidence)
A multicenter RCT reported pregnancy- and neonate-related adverse effects of interest.[5*] Tdap was found to be well-tolerated among pregnant women. Pregnancy- and neonate-related adverse events were not significantly different (RR 0.95; 95% CI 0.70, 1.30; p=0.75) in the Tdap (64/341 or 18.8%) and control group (69/346 or 19.9%). No maternal or neonatal deaths, gestational diabetes, eclampsia, neonatal hypoxic-ischemic encephalopathy, failure to thrive or growth deficiencies were observed in either of the groups.[10]

Prevention of neonatal tetanus

Tetanus toxoid vs. polyvalent influenza vaccine (1 RCT; n=1,182; low certainty of evidence)
Vaccination of pregnant women and women of childbearing age showed significant benefit in preventing deaths from neonatal tetanus. A 2015 systematic review by Demicheli et al.[15] included one RCT that assessed the effectiveness of one, two, or three doses of tetanus toxoid vaccine administered to women of childbearing age or pregnant women. Tetanus toxoid vaccine had an efficacy of 88% (95% CI -688%, 100%) in preventing deaths from neonatal tetanus (RR 0.12; 95% CI 0.00, 7.88; I^2=81.42%; P=0.02) compared to polyvalent influenza vaccine.

Recommendations from Other Groups

Three international (ACIP 2020, WHO 2018, Australian Immunisation Handbook) and one local (PSMID 2018) guidelines[16-19] recommend giving the tetanus vaccine to healthy adults with incomplete or unknown series. Table 3 shows a summary of the recommendation on tetanus vaccination from other groups.

[5]*These include gestational diabetes, pregnancy-related hypertension, premature rupture of membranes, preterm premature rupture of membranes, premature labor, premature uterine contractions, intrauterine growth restriction/poor fetal growth, pre-eclampsia, eclampsia, vaginal or intrauterine hemorrhage, maternal death, preterm birth, neonatal death, small for gestational age, neonatal hypoxic-ischemic encephalopathy, and failure to thrive/growth deficiency.

Table 3. Recommendations from other groups

Group	AGREE Rigor Domain Score	Recommendation	Strength	Quality
ACIP 2020[16]	78.1	Administer tetanus vaccine to healthy adults with completed series	Not indicated	5 RCTs (Halperin 2019; Kovac 2018; Brandon 2018; Jackson 2018; Theeten 2007) 1 case report (Shimabukuro 2015) 2 retrospective cohorts (Fortner 2018; Sukumaran 2015) 1 unpublished study (CDC 2019)
		Administer tetanus vaccine to healthy adults with incomplete/unknown series	Not indicated	
		Administer tetanus vaccine to pregnant women	Not indicated	
WHO 2017[17]	72.9	No recommendation for those with completed series	Not indicated	2 systematic reviews (Blencowe 2010; Demicheli et al. 2015) 1 meta-analysis (Bar-on et al 2012) 1 RCT (Zepp et al 2004) 1 case-control study (Silveira et al 2013) 1 case report (Zhou et al 2004)
		Administer tetanus vaccine to healthy adults with incomplete/unknown series. In women, if tetanus vaccination is started during adolescence or adulthood, a total of only 5 doses are required to obtain lifelong protection	Not indicated	
		Conditional recommendation. If a woman received 6 TTCV doses during childhood or 5 doses if first vaccinated during adolescence/adulthood before reproductive age, considered protected from birth-associated tetanus. Administer tetanus vaccine if with incomplete/unknown series.	Not indicated	
Australian Immuni-sation Handbook[18]	93.75	Administer tetanus vaccine to healthy adults with completed series at 10 years and 20 years after the primary course	Not indicated	1 Clinical Practice Guideline (ACIP, 2011) 4 RCTs (Theteen et al, 2007; Blatter et al, 2008; Turnbull et al, 2000; Pichichero et al, 2005)
		Administer dTpa to healthy adults with incomplete/unknown series	Not indicated	
		Administer dTpa vaccine as a single dose in each pregnancy, ideally early in the 3rd trimester	Not indicated	
PSMID 2018[19]	56.3	Administer tetanus vaccine to healthy adults with completed series if the last vaccination was 10 years ago	Weak	Low to moderate 10 clinical practice guidelines (WHO 2017; Society of Infectious Diseases Singapore 2016; ACIP 2006; Broder et al 2016; ACIP 2011; ACIP 2013; WHO nd; Public Health England 2006; CDC 2017; Immunization Action Coalition 2017) 1 systematic review (Hospenthal et al.)
		Administer tetanus vaccine to healthy adults with incomplete/unknown series. Primary series must include 1 dose of Tdap if unvaccinated or incompletely vaccinated	Strong	
		No further vaccination if with 5 doses of vaccine, including 3-primary series and 4th and 5th doses spaced at least 1 year. Otherwise, administer at least 2 doses of tetanus vaccine with an interval of at least 4 weeks between doses, the 2nd dose at least 2 weeks before birth, and the 3rd dose at least 6 months after 1st dose. Administer at least 1 dose of Td in subsequent pregnancies.	Strong	

		Administer dTpa to healthy adults with incomplete/unknown series.	Not indicated	
		Administer dTpa vaccine as a single dose in each pregnancy, ideally early in the 3rd trimester.	Not indicated	

ACIP Advisory Committee on Immunization Practices; PSMID Philippine Society of Microbiology and Infectious Diseases; WHO World Health Organization

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

Cost

Currently, there is insufficient evidence in both local and international publications to conclude the cost-effectiveness of tetanus vaccination in adults. Existing cost-effectiveness studies mostly focused on related outcomes like pertussis[20,21] and have different conclusions.[20-23] While there are no systematic reviews on the cost-effectiveness, cost-utility, or cost-benefit of administering tetanus vaccinations, individual studies on cost-effectiveness have been published and are summarized in Table 4.

Table 4. Summary of cost-effectiveness studies on tetanus vaccination

Study	Population	Method	Cost-Effectiveness of Tetanus Vaccination
Fernandes et al., 2019[20]	Healthy adults in Brazil	Dynamic model (health system perspective): (1) universal vaccination with single dose of Tdap at 20 years of age vs. (2) current practice (only pregnant women pertussis vaccination)	Not cost-effective (ICER of USD 8,459)
Havers et al.,2019[21]	Healthy adults >21 years old in the USA	Static cohort model: replaced Td with Tdap over the lifetime of 4,386,854 adults 21 years	Not cost-effective (Cost per QALY USD 81,678)
Griffiths et al.,2004[22]	Women 10-45 years old in Pakistan	State-transition model (public health sector perspective): followed each woman from birth to end of childbearing years comparing supplementary immunization activities vs. routine DTP & tetanus toxoid	Cost-effective (Cost per DALY averted USD 3.61)
Abu-Raya et al., 2020[23]	Pregnant women in Canada given Tdap	Part decision tree, part Markov model (cost-utility analysis): estimated long-term cost and QALYs	Cost-effective (if cost per vaccine <USD10)

DALY disability adjusted life year; ICER incremental cost-effectiveness ratio; QALY quality-adjusted life years

Ding et al.[24] found that Tdap vaccination in mothers resulted in a net cost-benefit for the society. In particular, overall societal benefits in the cohort of 3.6 million United States birth mothers ranged from USD 52.8 to 126.8 million, depending on the vaccination coverage level. However, the strategy would not generate net savings from a health care system perspective.

Other studies asserted the cost-effectiveness of tetanus vaccination when administered in pregnant patients. Griffiths et al.[22] assessed the incremental costs and effects of supplementary immunization activities versus routine DTP and tetanus toxoid vaccination and found that the cost per death averted was USD 117.00, and the cost per discounted DALY averted was USD 3.61. On the other hand, Abu-Raya et al.[23] conducted a cost-utility analysis using a base-case scenario with epidemiologic data in Canada from 2006 to 2015. A cost of CAN$44,301 per quality-adjusted

life year (QALY) was gained at an acquisition price per vaccine of CAN$12.50. The researchers then set a threshold of CAN$50,000 per QALY gained and found that Tdap vaccination was cost-effective if the cost was below CAN$14 in the next ten years. Computing the amount in US dollars using the average exchange rate in 2020 of 0.75, Tdap vaccination was cost-effective if the acquisition price was below USD 10. However, it should be noted that the study focused more on pertussis infections instead of tetanus that Tdap vaccination prevents.

Fernandes et al.[20] likewise found that introducing universal adult vaccination with Tdap (USD 7.01 per dose) in Brazil would not be a cost-effective intervention from a health systems perspective, due to an incremental cost-effectiveness ratio (ICER) of USD 8,459. However, this recommendation was largely driven by the burden of pertussis instead of tetanus infections. In a similar vein, Havers et al.[21] looked into the use of Tdap boosters instead of Td boosters in the United States and suggested that replacing Td with Tdap for the decennial booster would result in high cost per averted case at USD 984 and QALY saved at USD 81,678, at an incidence of 250 cases per 100,000 person years.

The local cost of tetanus vaccine is shown in Table 5.

Table 5. Unit cost of tetanus vaccination

Parameter	Vaccination
Unit cost of tetanus toxoid vaccine	Public Price: Php 28-108[25] Private Price: Php 400[26]

Patient Values and Preference, Equity, Acceptability, and Feasibility

Vaccine hesitancy was listed by the WHO as one of the top ten global health threats.[27] In the Philippines, previous public health crises such as the controversial deployment of Dengvaxia may have affected confidence in vaccination programs launched by the government as vaccination rates for infectious diseases have dropped from 2010 to 2015.[28]

Local research regarding factors affecting rates of tetanus toxoid immunization is limited. One such study conducted locally looked into the different factors associated with tetanus toxoid immunization among 60 urban poor women of reproductive ages (15-44 years old).[29] The study found that socioeconomic and demographic characteristics such as age, educational attainment, and occupation did not seem to influence willingness to be vaccinated. However, knowledge of the respondents on tetanus vaccination seemed to be limited or inaccurate.[29]

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4.15. Should typhoid vaccine be recommended to apparently healthy adults?

RECOMMENDATIONS

Among healthy adults, we <u>suggest</u> the use of Vi polysaccharide intramuscular vaccine.
(weak recommendation, low certainty evidence)

Among healthcare workers, we <u>suggest against</u> the routine use of typhoid vaccines.
(weak recommendation, very low certainty evidence)

Among healthy adults, there is <u>insufficient evidence to recommend</u> for or against Vi-TT intramuscular vaccines.
(insufficient evidence to recommend, very low certainty evidence

Considerations

The consensus panel considered the following when formulating these recommendations:

- Typhoid fever is endemic in the Philippines; thus, the importance of typhoid vaccination among healthy adults in the country. However, issues were raised on the efficacy, availability, and financial accessibility of typhoid vaccines.
- Among the four types of typhoid vaccine, only Vi polysaccharide intramuscular vaccine and Vi-TT intramuscular vaccine are available locally. The panelists were equally divided in recommending for or against the Vi-TT vaccine. Half were against it due its cost and the lack of direct studies among healthy adults. Contrary to this, those for Vi-TT cited that the vaccine may have utility locally, considering the endemicity of typhoid fever in the country. Recommending against it would preclude local experience that may generate efficacy data on the vaccine. After two rounds of voting, the panel could not reach consensus. They eventually decided unanimously that there is insufficient evidence to recommend for or against Vi-TT.
- The unavailability and lack of local experience on Ty21 oral vaccine and Vi-rEPA intramuscular vaccine precluded the panel from making recommendations on these vaccines. Additionally, there is expected shortage of Ty21 oral vaccine because its manufacturing was temporarily stopped in December 2020 for uncited reasons.
- The panel was unanimous in recommending Vi polysaccharide vaccine among healthy adults, but a weak recommendation was made due to its low efficacy and high cost.
- Typhoid vaccine does not offer 100% protection. The panel highlighted the importance of other preventive measures such as access to safe water, adequate sanitation, and hygienic food preparation. These preventive measures are also the reason why the panel was unanimous against routine typhoid vaccination among healthcare workers. Despite the risk of exposure of this group to typhoid fever, transmission could be prevented by proper hygiene and occupational safety measures.

Key Findings

- Live-attenuated (oral) and conjugated (parenteral) typhoid vaccines showed significant benefit in reducing laboratory-confirmed typhoid fever in patients living in or travelling to endemic areas. There was no increased risk for mortality, hospitalizations, and mild to severe adverse effects.
- No RCTs have evaluated the efficacy of typhoid vaccines specifically in healthcare workers (HCWs). Very low certainty evidence from a case series suggests that typhoid vaccine may not sufficiently provide protection of HCWs from the disease.

Introduction

Burden of the Disease

Typhoid fever, also known as enteric fever, is a multisystemic bacteremic disease caused by *Salmonella enterica* serotypes Typhi, Paratyphi A, B, and C. It is most commonly transmitted through the fecal-oral route from contaminated water or food sources. The disease is endemic in many Southeast Asian countries, most especially in areas where there is poor water and sewage sanitation. Globally, typhoid fever is estimated at 26 million cases while paratyphoid fever is estimated at five million cases, causing 215,000 deaths each year.[1] In 2019, an estimated 110,029.04 (95% confidence interval [CI] 52,810.45, 191,205.71) deaths occurred globally due to typhoid fever and 52,810.45 (95% CI 848.64, 3,373.42) estimated deaths were recorded in the Philippines alone.[2]

The incubation period of the disease is around six to thirty days with an insidious onset of disease. A gradually increasing fever from 38°C to 40°C can be observed spanning around a week, alongside malaise, fatigue, headaches, and anorexia. Abdominal pain, constipation, vomiting, and diarrhea may be observed, with the first two gastrointestinal symptoms being more common in children than adults. The disease may progress and present with myalgia, dry cough, sore throat, hepatosplenomegaly, and in some cases, a transient rose-colored maculopapular rash on the trunk. It has a case fatality ratio of around 10% to 30% for untreated cases, and <1% for treated cases.[1] Around 4% of untreated cases progress to become chronic carriers of the disease, which worsen the burden of disease.[3]

The diagnostic management for enteric fever consists of direct detection through culture or polymerase chain reaction (PCR), or indirect detection through antibody testing. Antibiotics remain the standard of management, with hospitalization being offered to those with moderate to severe illnesses or those in high-risk population groups (i.e., pregnant patients).

Currently, vaccination is indicated for the prevention of the disease in (a) chronic travelers to endemic areas, (b) persons with intimate exposure to positive cases, and (c) healthcare workers or microbiologists in close contact with the etiologic agent.[1,4] The vaccines available include the oral Ty21a live-attenuated vaccine and the intramuscular Vi polysaccharide vaccine (parenteral inactivated whole cell vaccine). Two new vaccines, namely the Vi-rEPA (Vi polysaccharide bound to recombinant *Pseudomonas aeruginosa* exoprotein A) vaccine and the Vi-TT (tetanus toxoid) conjugate vaccine are currently being studied for their efficacy in children and adults

Characteristics of Included Studies

Evidence for this review was obtained from a 2018 high-quality Cochrane systematic review[5], which is an update of an earlier review in 2014.[6] All four guidelines used in the 2018 review referenced the earlier 2014 review. A total of 17 randomized controlled trials (RCTs) were pooled from China (moderate risk), India (high risk), Pakistan (high risk), and South Africa (high risk) with respect to endemicity of the disease. Of these, there were seven RCTs on oral Ty21a vaccine, eight on intramuscular Vi polysaccharide vaccine, one on intramuscular Vi-rEPA, and one on intramuscular Vi-TT conjugate vaccine. The RCTs on oral Ty21a vaccine and intramuscular Vi polysaccharide vaccine were studied in children and adult populations, while the RCTs on the newer Vi-rEPA and Vi-TT vaccines focused on children.

Outcomes

Benefits and Harms of Typhoid Vaccine

The summary of all critical outcomes of typhoid vaccination among healthy adults is shown in Table 1.

Table 1. Benefits and harms of typhoid vaccine per subgroup of healthy adults

Outcomes	No. of Studies (No. of Participants)	Effect Estimate (95% CI)	Interpretation	Certainty of Evidence
Vi polysaccharide vaccine				
Laboratory-confirmed typhoid fever[a]	3-year cumulative: 1 (11,384)	RR 0.45 (0.30, 0.70)	Favors vaccine	Low
	Year 1: 3 (99,979)	RR 0.31 (0.26, 0.37)		High
	Year 2: 4 (194,969)	RR 0.41 (0.31, 0.55)		Moderate
	Year 3: 1 (11,384)	RR 0.50 (0.30, 0.70)		Low
All-cause mortality	4 (133,240) 2 clusters (64,904)	No reported mortalities	Inconclusive	Moderate
Hospitalization	4 (133,240) 2 clusters (64,904)	No reported hospitalizations	Inconclusive	Moderate
Fever	4 (132,261)	RR 0.98 (0.85, 1.14)	No significant difference	Moderate
Erythema	3 (132,261)	RR 1.15 (0.33, 4.03)	Inconclusive	Low
Swelling	3 (1,767)	RR 6.06 (1.07, 34.22)	Favors placebo	Moderate
Injection site pain	1 (667)	RR 7.98 (3.36, 17.24)	Favors placebo	Moderate
Ty21a oral vaccine				
Laboratory-confirmed typhoid fever	3-year cumulative 4 (235,239)	RR 0.50 (0.39, 0.65)	Favors vaccine	Moderate
	Year 1: 3 (76,296)	RR 0.55 (0.35,0.86)		Moderate
	Year 2: 3 (76,296)	RR 0.41 (0.29, 0.57)		Moderate
	Year 3: 3 (76,296)	RR 0.44 (0.25, 0.76)		Moderate
All-cause mortality	5 (235,239)	No reported mortalities	Inconclusive	Moderate
Hospitalization	5 (235,239)	No reported hospitalizations	Inconclusive	Moderate
Fever	2 (2,066)	RR 1.53 (0.86, 2.72)	Inconclusive	Moderate
Erythema	1 (1,190)	RR 2.94 (0.61, 14.12)	Inconclusive	Moderate
Mild adverse effects	2 (1,360)	RR 1.67 (1.03, 2.72)	Favors placebo	Moderate
Headache	1 (1,190)	RR 1.31 (0.75, 2.27)	Inconclusive	Moderate
Vomiting and GI symptoms	2 (2,066)	RR 0.61 (0.3, 1.24)	Inconclusive	Moderate
Vi-repa vaccine				

Laboratory-confirmed typhoid fever	3.8-year cumulative: 1 (12,008)	RR 0.11 (0.05, 0.23)	Favors vaccine	Moderate
	Year 1: 1 (12,008)	RR 0.06 (0.01, 0.25)		Moderate
	Year 2: 1 (12,008)	RR 0.13 (0.04, 0.44)		Moderate
All-cause mortality	1 (12,008)	No reported mortalities	Inconclusive	Moderate
Hospitalization	1 (12,008)	No reported hospitalizations	Inconclusive	Moderate
Fever	Dose 1: 1 (12,008)	RR 2.54 (1.69, 3.62)	Favors placebo	Moderate
	Dose 2: 1 (11,091)	RR 4.39, (2.85, 6.77)		Moderate
Erythema	1 (11,091)	RR 2.01 (0.19, 22.21)	Inconclusive	Moderate
Swelling	1 (11,091)	RR 20.15 (2.71, 150.08)	Favors placebo	Moderate
Vi-TT Vaccine				
Laboratory-confirmed typhoid fever	1 (1,626)	RR 0.06 (0.00, 1.01)	Inconclusive	Very low
Fever	1 (654)	RR 1.45 (0.63, 3.29)	Inconclusive	Moderate
Erythema	1 (654)	RR 0.92 (0.02, 46.42)	Inconclusive	Low
Swelling	1 (654)	RR 4.62 (0.54, 39.31)	Inconclusive	Low
Injection site pain	1 (654)	RR 1.39 (0.57 to 3.34)	Inconclusive	Moderate

CI confidence interval; GI gastrointestinal; RR relative risk

[a]The difference in quality of evidence between years is due to the different studies used during the first year (7-9), second year (8,10-12), and third year/cumulative three years result.

Subgroup 1: Immunocompetent Adults

Incidence of laboratory-confirmed cases

Vi Polysaccharide vs. placebo (7 RCTs; n=283,382; moderate certainty of evidence)
Vi Polysaccharide vaccination significantly reduced the three-year cumulative incidence (relative risk [RR] 0.45; 95% CI 0.30, 0.70; 1 RCT; n=11,384; low certainty of evidence), first-year post-vaccination incidence (RR 0.31; 95% CI 0.26, 0.37; 3 RCTs; n=99,979; high certainty of evidence), second-year post-vaccination incidence (RR 0.41; 95% CI 0.31, 0.55; 4 RCTs; n=194,969; moderate certainty of evidence), and third-year post-vaccination incidence (RR 0.50; 95% CI 0.32, 0.78; 1 RCT; n=11,384, low certainty of evidence) of laboratory-confirmed typhoid fever compared to placebo.[7-12]

Ty21a Live-attenuated vs. placebo (4 RCTs; n=235,239; moderate certainty of evidence)
Ty21a Live-Attenuated vaccination significantly reduced the three-year cumulative incidence (RR 0.50; 95% CI 0.39, 0.65; 4 RCTs; n=235,239), first-year incidence (RR 0.55; 95% CI 0.35, 0.86; 3 RCTs; n=76,296), second-year incidence (RR 0.41; 95% CI 0.29, 0.57; 3 RCTs; n=76,296), and third-year incidence (RR 0.44; 95% CI 0.25, 0.76; 3 RCTs; n=76,269) of laboratory-confirmed typhoid fever compared to placebo.[13-16]

Other typhoid vaccines: Vi-rEPA (1 RCT, n=12,008, moderate certainty of evidence)
Vi-rEPA vaccination significantly reduced the 3.8-year cumulative incidence (RR 0.11; 95% CI 0.05, 0.23, n=12,008), two-year cumulative incidence (RR 0.09; 95% CI 0.04, 0.22; n=12,008), first-year incidence (RR 0.06; 95% CI 0.01, 0.25; 1 RCT; n=12,008), and second-year incidence (RR 0.13; 95% CI 0.04, 0.44; n=12,008) of laboratory-confirmed typhoid fever compared to placebo.[17]

Other typhoid vaccines: Vi-TT (1 RCT; n=1,625; very low certainty of evidence)
No direct studies have evaluated Vi-TT in healthy adults. An RCT that tested the Vi-TT conjugate vaccine in children six months to 12 years old showed its ability to reduce the incidence of laboratory-confirmed typhoid fever (RR 0.06; 95% CI 0.00, 1.01; n=1,625). However, this effect is very uncertain especially for adults due to the high risk for bias, imprecision from wide confidence intervals, and indirectness (i.e., children being the study population) of the study.[18]

No studies have focused on clinically-suspected typhoid fever as an outcome. As such, no evidence could demonstrate the effectiveness of typhoid vaccine in preventing clinically-suspected enteric fever that is not confirmed through laboratory testing.

Severe adverse effects
Severe adverse effects were defined as events that led to death, in-patient hospitalization, prolongation of existing hospitalization, life-threatening, or those resulting in permanent or persisting disability or incapacity. No severe adverse effects were observed for Vi polysaccharide (4 RCTs; n=133,240; 2 cluster-RCTs; n=64,904), Ty21a live-attenuated oral (5 RCTs; n=235,239), Vi-rEPA (1 RCT; n=12,008),[5] and Vi-TT (1 RCT, n=654).[19] The same findings were noted for typhoid conjugate vaccines (Vi-CRM197) in two RCTs (n=315) that included a local safety trial in Filipino adults (n=75).[20,21]

Other adverse effects
Typhoid vaccine significantly increased the risk for mild adverse effects. Intramuscular vaccines (Vi polysaccharide and typhoid conjugate vaccines) increased the risk for swelling and pain in the injection site, but with equivalent risk for fever and erythema compared to placebo. Live oral vaccine (Ty21a) increased the risk for mild adverse effects overall, with fever as the most common side effect.

Vi Polysaccharide vs. placebo (4 RCTs; n=133,038; moderate quality of evidence)
Vi polysaccharide vaccination was associated with swelling (RR 6.06; 95% CI 1.07, 34.22; 3 RCTs; n=1,767; moderate quality of evidence),[9,22,23] and pain in the injection site (RR 7.98; 95% CI 3.36, 17.24; 1 RCT; n=667; moderate quality of evidence).[23] In contrast, the risk for fever (RR 0.98; 95% CI 0.84, 1.13; 3 RCTs; n=132,261; moderate quality of evidence)[9,12,19,20] and erythema (RR of 1.15; 95% CI 0.33, 4.03; 3 RCTs; n=132,261; low quality of evidence) were equivalent between the Vi polysaccharide and placebo arm.[12,22,23]

Ty21a Live-attenuated oral vs. placebo (3 RCTs; n=2,236; moderate quality of evidence)
Ty21a Live-Attenuated oral vaccine was associated with mild adverse effects in general (RR 1.67; 95% CI 1.03, 2.72; 3 RCTs; n=2,236; moderate quality of evidence), with fever (RR 1.53; 95% CI 0.86, 2.72; 2 RCTs; n=2,066; moderate quality of evidence) being the most common. It was not associated with increased risk of vomiting and other gastrointestinal symptoms (RR 0.61; 95% CI 0.3, 1.24; 2 RCTs; n=2,066; moderate quality of evidence). The risk for headache (RR 1.31; 95% CI 0.75, 2.27; 1 RCT; n=1190, moderate quality of evidence) and rash (RR 2.94; 95% CI 0.61, 14.12; 1 RCT; n=1,190, moderate quality of evidence) were inconclusive between the Vi polysaccharide and placebo arm.[13,15,16,24,25]

Other typhoid vaccines: Vi-rEPA (1 RCT; n=12,008; moderate quality of evidence)
Vi-rEPA vaccine was associated with increased risk for fever for the first dose (RR 2.54; 95% CI 1.69, 3.62; 1 RCT; n=12,008; moderate quality of evidence), fever for the second dose (RR 4.39; 95% CI 2.85, 6.77; 1 RCT; n=11,091; moderate quality of evidence), erythema (RR of 2.01; 95% CI 0.19, 22.21; 1 RCT; n=11,091; moderate quality of evidence for the second dose), and swelling

of the injection site (RR 20.15; 95% CI 2.71, 150.08; 1 RCT; n=11,091; moderate quality of evidence for the second dose) compared to placebo.[17]

Other typhoid vaccines: Vi-TT (1 RCT; n=654; low quality of evidence)
Vi-TT vaccine was associated with fever in 4.3% (14 subjects), pain at injection site in 3.6% (12 subjects), swelling at injection site in 1.5% (5 subjects), tenderness at injection site in 0.6% (2 subjects), and arthralgia in 0.3% (1 subject). Vi-TT vaccine did not significantly differ from ViPS vaccine on the frequency of adverse effects.[19]

A test typhoid conjugate vaccine (TCV) was compared with a comparator TCV. Overall, the test TCV showed no significant difference from the comparator TCV in terms of the frequency of adverse effects except for fever, which had a higher frequency in the test TCV than the comparator (p=0.05). The adverse effects observed in the test TCV include pain in 39.0% (23 adults), swelling in 5.1% (3 adults), redness in 5.1% (3 adults), fever in 8.5% (5 adults), diarrhea in 1.7% (1 adult), myalgia in 3.4% (2 adults), and arthralgia in 1.7% (1 adult). Irritation, URTI, malaise, headache, vomiting, nausea, and urticaria were not observed in the test group. Adverse effects observed in the comparator TCV include pain in 42.6% (26 adults), swelling in 1.6% (1 adult), redness in 3.3% (2 adults), irritation in 1.6% (1 adult), fever in 14.1% (17 adults), URTI in 1.6% (1 adult), diarrhea in 1.6% (1 adult), myalgia in 6.6% (4 adults), headache in 1.6% (1 adult), and arthralgia in 1.6% (1 adult). Malaise, vomiting, nausea, and urticaria were not observed in the comparator group.[20]

For TCV (Vi-CRM197), the reported adverse events include pain in 13 subjects (52.0%), tenderness in 14 subjects (56.0%), area of erythema/redness in four subjects (16.0%), area of swelling/induration in 6 subjects (24.0%), pruritus associated with injection in one subject (4.0%), fever in one subject (4.0%), headache in five subjects (20.0%), fatigue in two subjects (8.0%), myalgia in one subject (4.0%), and arthralgia in one subject (4.0%). Nausea/vomiting and chills did not occur. There were 21 events for pain, 28 for tenderness, 12 for erythema/redness, 13 for swelling, two for pruritus associated with injection, one for fever, seven for headache, two for fatigue, three for myalgia, and three for arthralgia. Vi-TT showed no significant difference in adverse events compared to TCV.[21]

Subgroup 2: Healthcare Workers
A 1947 case series described four cases of atypical typhoid fever among HCWs as a result of laboratory-associated exposure to *S. typhi* bacteria. The patients were fully immunized but the specific vaccine used was not indicated. There was no mention of the total population of the laboratory facilities these HCWs were working in, as well as the duration since the completion of immunization to the disease state. A very broad spectrum of disease was noted, ranging from influenza-like illness, pelvic inflammation, and nasopharyngitis. The most common symptoms were anorexia, fever, chills, headache, malaise, hyperhidrosis, and abdominal pain. All four patients eventually recovered well.[26]

Recommendations from Other Groups

Three international guidelines recommend typhoid vaccine for healthy adults and HCWs within endemic countries.[27-29] One local guideline also recommends typhoid vaccine for healthy adults, but does not recommend the routine use of the vaccine for healthy HCWs.[4]

Table 2 summarizes the recommendations on typhoid vaccination from other groups.

Table 2. Recommendations on typhoid vaccination from other groups

Group	AGREE Rigor Domain Score	Recommendation	Strength of recommendation	Quality of evidence
PSMID 2018[4]	50.8	Administer typhoid vaccine to immunocompetent adults living in endemic areas	Strong	Moderate 1 systematic review[6]
		Do not administer vaccine routinely to healthcare workers.	Strong	Weak 1 case series[26]
WHO 2018[27]	67.6	Programmatic use of typhoid vaccine is recommended. TCV is preferred at all ages. Consider use of ViPS in 2 years and older. Consider Ty21a for individuals more than 6 years.	Not indicated	1 meta-analysis, 5 RCTs[7,12,15,19]
		Typhoid vaccine is recommended for clinical microbiology laboratory staff with a recognized risk of occupational exposure to *S. typhi* (strength of recommendation not indicated)	Not indicated	
Australian Immunization Handbook[28]	70.25	Typhoid vaccine is recommended for military personnel and travellers to endemic regions as well as those living in an endemic region.	Not indicated	3 RCTs on Children[11,14,30], 1 RCT including adults[31], 2 case control[32,33], 1 cohort[34], 1 Descriptive[35]
		Typhoid vaccine is recommended for laboratory workers who routinely work with *Salmonella typhi.*	Not indicated	
ACIP 2015[29]	78.1	Conditional recommendation for those who live in or are travelling to endemic areas and for those with intimate contact with positive cases.	Conditional	2 Systematic reviews[6,11], 2 Challenge Studies[36,37], 2 RCTs[13,15]
		Typhoid vaccine is recommended for healthcare workers or those who routinely work with *Salmonella typhi*	Strong	

ACIP Advisory Committee on Immunization Practices; PSMID Philippine Society of Microbiology and Infectious Diseases; WHO World Health Organization

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

Cost

Evidence on the cost-effectiveness of typhoid vaccine was obtained from a 2019 systematic review of ten cost-effectiveness and five cost-of-delivery studies.[38] The cost-effectiveness studies were limited to children, and only one of the five cost-of-delivery studies was published. The cost of delivery was modeled to a hypothetical population of 700,000 adults and 300,000 children in a low to middle income country (LMIC). Findings showed that USD 671,000 in government investment would avert USD 60,000 in public treatment costs.

In the Philippines, no local cost-effectiveness study on typhoid vaccines has been published. International studies have focused on LMICs, but their scope has been limited to children. Their recommendations on cost-effectiveness are context-specific and largely depend on the typhoid burden, the cost of treating typhoid fever, and the price of typhoid vaccinations.

Typhoid vaccine costs PHP 2,000 in the country.[39]

Patient Values and Preference, Equity, Acceptability, and Feasibility

There are no international and local studies on the equity, acceptability, and feasibility of typhoid vaccination.

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4.16. Should varicella vaccine be given to asymptomatic apparently healthy adults?

RECOMMENDATIONS

Among asymptomatic apparently healthy adults, we <u>suggest against giving</u> varicella vaccine.
(weak recommendation, very low certainty evidence)

Among asymptomatic healthcare workers, we <u>suggest against giving</u> varicella vaccine.
(weak recommendation, very low certainty evidence)

Considerations

The consensus panel considered the following points during the formulation of the above recommendations:

- A weak recommendation against the routine vaccination of healthy adults was made by the panel primarily due to lack of epidemiological studies showing the degree of burden of varicella among adults. However, some clinicians in the panel have reported encountering more severe disease presentation in adults compared to children. In addition, the available evidence exhibited high uncertainty in the ability of vaccination to provide adequate levels of protection for disease prevention.
- The panel considered other costs associated with lost work days when adults would take care of a family member with varicella, as well as being at high risk of contracting the virus when exposed to afflicted family members.

Key Findings

- No RCTs were found comparing varicella vaccination with no vaccination or placebo. Evidence to address this guideline question was obtained from six observational studies evaluating the efficacy and safety of varicella vaccination on apparently healthy adults and one randomized controlled trial comparing different dosing schedules. Three other observational studies specifically investigated the efficacy and safety of varicella vaccines on healthcare workers. Only pooled rates of outcomes could be calculated as corresponding rates for unvaccinated adults could not be determined from the available studies.
- The crude attack rate or incidence of breakthrough varicella infection among vaccine recipients occurred in 7% of healthy adults and 9% of healthcare workers. These participants received two doses of varicella vaccine within an interval of 4 to 12 weeks. Among those with reported exposures, the varicella attack rate (proportion of subjects developing varicella) ranged from 9 to 21% in healthy adults and 3 to 17% in healthcare workers.
- Seroconversion rate was reported at 92% to 99% across all studies among healthy adults. Among healthcare workers, the pooled seroconversion rates were compared between 3 groups: short-term group (1-2 months) 95%, medium-term group (5-6 months) 94%, and long-term group (>6 months) 81%.
- No serious adverse events were reported for both healthy adults and healthcare workers. Only mild adverse events were observed such as local or injection-site related reactions,

fever, varicella or zoster-like rash, and other systemic adverse events like: headache, facial spasm, sore throat, chills, muscle pain and increase in body temperature.
- Certainty of evidence supporting the vaccine's efficacy and safety is very low.

Introduction

Varicella-zoster virus (VZV) is a Herpesviridae virus responsible for two clinical disorders. Varicella, often known as chickenpox, is the main illness and is caused by being exposed to someone who is sick with the virus. Recurrence of infection occurs in herpes zoster, often known as shingles, a frequent condition among the elderly and immunocompromised persons.[1] VZV is highly contagious, with secondary attack rates ranging from 61% to 100% in varicella patients. Person-to-person transmission occurs predominantly by inhalation of aerosols from vesicular fluid of skin lesions, direct contact with rash, and perhaps through contaminated respiratory tract secretions.[2] VZV can only be found in humans. Symptoms are typically moderate in children, but they can be fatal in adults and immunocompromised people of any age.[3] The period of transmissibility is expected to begin 1-2 days before the development of the rash and last 4-7 days after the commencement of the rash in immunocompetent patients.[4] Serious complications can occur, most commonly in infants, adults, and immunocompromised people. These include secondary bacterial infections of skin lesions, which at times can lead in bacteremia/sepsis, pneumonia, cerebellar ataxia, encephalitis, and hemorrhagic conditions; rarely (about 1 in 40,000 varicella cases), these complications may result in death.[4]

Without vaccination, almost everyone in the population acquires wild-type varicella infection by adulthood.[2] The incidence of disease has markedly decreased with more widespread use of the varicella vaccine. For a healthy unimmunized child, chickenpox-associated mortality is fewer than 2 per 100,000 cases. This risk increases by more than 15-fold for adults.[1] Breakthrough varicella infections can occur in vaccinated people and are usually mild in severity (lesser (<50) skin lesions, low to no fever, shorter rash duration). The rash may be atypical in appearance with fewer vesicles and predominance of maculopapular lesions.[4]

A vaccine based on live attenuated VZV (Oka strain) was developed and clinically tested in the 1970s and 1980s. It was first licensed in Germany and Sweden in 1984. The vaccines are available either as monovalent (varicella only), or in combination with measles, mumps and rubella (MMR) vaccine.[5] Varicella vaccine has been found beneficial in susceptible healthy adults, although less immunogenic than in children. Two doses are required to reach glycoprotein antigen-based enzyme-linked immunosorbent assay (gp-ELISA) ≥90%, with evidence of waning of antibody levels within a few years of vaccination.[5]

Seroprevalence and burden studies on varicella in the Philippines are sparse.[6,7] In a 1994 study by Barzaga and colleagues involving individuals aged 1-65 years old in Manila, the seroprevalence of varicella increased with age—30% in children < 5 years old, 57% in those > 15 years old, and up to 95% in adults >30 years old.[8] In an earlier study by Nassar & Touma 1986, 88% of adult expatriate Filipino nurses working in Lebanon showed seroconversion, compared with 97% of their Lebanese counterparts.[9] Data from the Philippine Health Statistics 2011 documented a total of 14,080 varicella cases or a rate of 32.4% per 100,000 population for all ages, with 47 total deaths across all ages (<0.01% per 100,000 population).[10] Among ages 15 and above, the total number of deaths is 38 (<0.01% per 100,000 population).[8] Varicella is listed as one of the ten leading causes of morbidity since 1989.[10]

Characteristics of Included Studies

Studies on Healthy Adults

Seven studies were included in this review.[11-17] All were observational (cohort) studies evaluating the outcomes of varicella vaccines. The study by Kuter et al. 1995,[11] which was a randomized controlled trial compared the effect of 2 different regimens of varicella vaccination (i.e., giving 2 doses 4 weeks apart versus 2 doses 8 weeks apart) involving 757 healthy adolescents and adults. A total of 1,737 healthy adults were included across the studies. Three studies[12,13,17] included adolescents (age ≥13) as participants.

Oka strain of the varicella vaccine was used in all studies. Majority used the vaccine produced by Merck Sharp and Dohme Corp.[13-18] One study used vaccines by either Merck Sharp and Dohme Corp and Smithkline Beecham.[12] Two doses of the varicella vaccine were given across all studies. In four studies,[11,12,14,17] the interval between 2 doses was 12 weeks. One study[16] had an interval of 6 weeks while two studies[13,15] had either 4- or 8-week intervals between two doses of vaccination.

The following efficacy outcomes were assessed:

1. Crude attack rate/incidence of breakthrough varicella infections,[11,12,17]
2. Varicella attack rate (proportion of subjects developing varicella among those with reported exposures),[11,13]
3. Seroconversion rate (i.e., proportion of participants reaching a certain VZV antibody titer level),[12,13,15-17]
4. Persistence of seropositivity / antibodies beyond 1 year (1.212, 518, 6 years[12]).

Safety data was also provided by 4 studies.[12-14,16] These included solicited and unsolicited local reactions (e.g., swelling, erythema, pain/tenderness, injection site rashes, pruritus), fever ≥ 39.0°C, varicella-like or herpes zoster-like rash, other systemic adverse events, and serious adverse events collected through self- report from the day of vaccination up to 6-8 weeks.

Studies on Healthy Healthcare Workers

Three studies were included in this review.[18-20] All were observational (cohort) studies participated by a total of 264 apparently healthy healthcare workers.

Oka strain of varicella vaccine was used in all studies. One study used vaccines by either Merck Sharp and Dohme Corp and Smithkline Beecham,[17] one study used vaccines by Smithkline Beecham,[18] and one study[20] used vaccines by Merck Sharp and Dohme Corp. Two doses of varicella vaccine were given in two studies,[18,20] while three doses were given in one study.

The efficacy outcomes assessed were (1) crude attack rate/incidence of breakthrough varicella infections,[20] (2) varicella attack rate (proportion of subjects developing varicella among those with reported exposures),[20] and (3) seroconversion rate (i.e., proportion of participants reaching a certain VZV antibody titer level).[18-20] Safety data was also provided by 2 studies[18,19] These included solicited and unsolicited local reactions (e.g., swelling, erythema, pain/tenderness, injection site rashes, pruritus), fever, varicella-like or herpes zoster-like rash, other systemic adverse events, and serious adverse events collected through self-report from the day of vaccination up to 6-8 weeks.

Outcomes

Since none of the included studies have compared varicella vaccination with no vaccination/control, the effect estimates reported in this evidence review only shows the pooled rates of the outcomes among vaccinated individuals. The rates of the outcomes in unvaccinated individuals could not be determined from the included studies.

Subgroup 1: Asymptomatic Healthy Adults

Efficacy

Incidence of breakthrough infections (crude attack rate)
Based on 3 studies (n=688), the pooled incidence rate of breakthrough varicella infections among vaccinated subjects is 7% (95% CI 5.0 to 10%; I^2=14.9%) within a follow-up period ranging from 2 months to 11.8 years. Zerboni et al 1998 recorded only 1 case (2.5%) out of 40 vaccinated healthy adults aged 13-45 years old[17] within 5 years. Ampofo et al. 2022 reported varying proportions of breakthrough infections among vaccinated healthy adults aged 22-41 years old depending on the number of doses received by the participants, with 8.7% (40/461) in those receiving only 1 dose, 2.2% (10/461) for those with 2 doses, and 6.1% (28/461) for those with 3 doses.[11] Gershon et al 1988 recorded 12 (6.4%) cases out of 187 vaccinated healthy adults aged 17-57 years old; 7 had household exposure, 4 were exposed while working in the hospital, and 1 school teacher was exposed in her classroom.[12]

The certainty of evidence that varicella vaccination is associated with lesser breakthrough infections is very low due to the high risk of bias observed in two of the studies included (e.g., participants received varying number of vaccine doses, exposures to individuals with varicella infection, and high number of dropout rates).

Varicella attack rate
In 2 studies (n=1,218), varicella attack rate among subjects with documented exposure to varicella cases was 14% (95% CI 9 to 21%; I^2=0%).[11,12] In the study by Kuter et al., 46 out of 757 (6.1%) vaccinated patients had an exposure to 1 or more individuals with varicella or shingles. Subsequently, 2 of these 46 exposed subjects (4.3%) developed varicella during the 6-12 months follow-up.[13] Ampofo et al., 2022 reported 89 out of 461 (19.3%) vaccinated patients with household exposure, and 19/89 (21%) eventually developed varicella 8 weeks to 9 years after vaccination.[11]

Seroconversion rate
Based on four studies (n=611) the pooled seroconversion rate was 96% (95% CI 92 to 99%; I^2=80.94%) measured 1.5 months post-vaccination. Participants with fluorescent-antibody-to-membrane-antigen (FAMA) titer ≥1:2, gpELISA units ≥ 5 or presence of VZV IgG antibodies as measured by ELISA were considered seropositive. Studies had heterogeneous follow-up periods for measuring seroconversion (i.e., 6 weeks, 1 year, yearly for up to 6 years), and measurement methods for determining seroconversion (e.g., FAMA titer ≥1:2, gpELISA units ≥ 5).

Dosing schedule did not appear to influence the seroconversion rates based on one study that showed a rate of 97% (199/205) in those vaccinated within a four-week interval and 99% (213/214) in the eight-week interval group.[13] Four weeks after the second dose, the seroconversion rates were similar but the geometric mean titer (GMT) levels (measured using

VZV gpELISA) were 1.6-fold higher when the second dose was administered at 8 weeks rather than 4 weeks.

Paradis et al.[16] reported data on seroconversion rates after 6 weeks for subjects with different seropositivity status at baseline. Seroconversion was defined as VZV antibody titer ≥5 gpELISA units/mL for subjects seronegative at baseline, and ≥4-fold rise in antibody titers for those seropositive at baseline. All 26/26 (100%) seronegative subjects were seroconverted at baseline, compared to 14/23 (60.9%) in the seropositive group. The corresponding GMT and geometric mean fold rise (GMFR) in antibody titer of seronegative patients using gpELISA were 71 (95% CI 47.9 – 104.2) and 173 (95% CI 120.9 – 246.2), respectively. For seropositive subjects, the GMT and GMFR of seropositive patients were 217 (95% CI 132.8 – 353.6) and 3 (95% CI 2.0 – 4.8), respectively.

Persistence of antibodies (1-6 years)
Three studies reported persistence of antibodies to VZV up to 1 to 6 years after vaccination.[12,13,17] Zerboni et al. reported that there was a significant increase in antibody concentration from 1 to 5 years, and antibodies to VZV were well preserved at a mean of 5 years following vaccination in adults.[17] Antibody levels were still detected up to 6 years, with 80% seropositivity rate in another study by Gershon et al.[21] Kuter et al. also reported persistence of antibody up to 1 year after the second dose for both four-week interval (97%, [31/32]) and eight-week interval group (98%, [50/51]).[13]

Safety
There were no reported serious adverse events for any of the vaccinated patients across all studies. Local or injection site-related reactions such as swelling, redness, pain or tenderness were the most reported reactions in four studies, occurring in 24% of the vaccinated patients.[11,13,14,16] Varicella- or zoster-like rash was reported in 4% of patients while fever occurred in 5% after 1 to 1.5 months.[12-14,16] Other systemic adverse events such as headache, facial spasm, sore throat, and increase in body temperature were reported as well in 11% of patients.[12,16]

Certainty of evidence on benefits and harms
The overall certainty in the evidence for the benefits and harms of varicella vaccination for the general population is very low. Rating was downgraded due to observational study design limitations, serious inconsistency (heterogeneity), and serious indirectness (no comparison with placebo).

Table 1. Benefits and harms of varicella vaccination in healthy adults

Critical Outcomes	No. of Studies* (No. of Participants)	Impact	Certainty of evidence
Incidence of breakthrough infections/crude attack rate) (2 months – 11.8 years)	3 (688)	Pooled estimate - 7% (95% CI 5 to 10%)	Very Low
Varicella attack rate (6 months – 11.8 years)	2 (1218)	Pooled estimate - 14% (95% CI 9 to 21%)	Very Low
Seroconversion rate (1.5 months – 6 years)	5 (1074)	Pooled estimate - 96% (95% CI 92 to 99%)	Very Low
Systemic adverse reactions (AEs) (1-1.5 months)	4 (1196)	Pooled estimates were as follows: ● Systemic adverse event: 11% (95% CI 8 to 16%) ● Fever: 7% (95% CI 3 to 13%) ● Varicella or zoster-like rash: 4% (95% CI 3 to 5%)	Low

Serious adverse events (SAEs) (1-1.5 months)	(2) 807	No SAEs reported in all studies	Low

CI confidence interval; SAE serious adverse events
*All studies only involved participants given the vaccine. One study was a randomized controlled trial comparing different vaccination schedules.

Subgroup 2: Asymptomatic Healthcare Workers

Efficacy

Incidence of breakthrough infections (crude attack rate)
Based on two studies (n=154), the pooled incidence rate of breakthrough varicella infections among vaccinated healthcare workers is 9% (95% CI 5-15%; I^2=0%) within a follow-up period ranging from 6 months to 8.4 years. Ndumbe recorded only 2 cases (5.8%) out of 34 vaccinated healthcare workers (38% with exposure to varicella patients) aged 18-21 years old within 3 years.[19] Saiman reported 12 cases (10%) out of 120 vaccinated healthcare workers aged 19-45 years old within 6 months to 8.4 years after the second dose. All 12 healthcare workers had mild to moderate illness, without complications.[20]

Varicella attack rate
In 1 study (n =120) by Saiman, 91 (76%) out of 120 vaccinees had known exposure to varicella cases. Among 22 healthcare workers with household exposure, 4 (8%) developed varicella 11 months to 8.4 years after vaccination. Among 72 healthcare workers with hospital exposure, 6 (8%) developed varicella.[20]

Seroconversion rate
Based on three studies (n=264), the pooled seroconversion rate for the 3 groups is 95% (95% CI 91 to 98%; I^2=19.99%) at 1-2 months, 94% (95% CI 89 to 97%; I^2=0%) at 5-6 months, 81% (95% CI 58 to 97%; I^2=92.48%) beyond 6 months. Participants with FAMA titer ≥1:2, immunofluorescent test ≥8 or appearance of ≥4 in subjects with an initially undetectable titer indirect immunofluorescent technique were considered seropositive in the three studies included.[18-20]

Safety
There were no reported serious adverse events for any of the vaccinated patients across all studies. Burgess et al. reported local site injections (e.g., redness, swelling, heat and pain, and systemic adverse events) and systemic adverse events (e.g., chills and muscle pains) during the 1.5 months follow-up in 47% and 2% of vaccinated healthcare workers, respectively.[16] Varicella-like rash and fever were reported in 2 studies (n=134) with pooled incidence of 7% (95% CI 3 to 12%; I^2=0%) and 1% (95% CI 0 to 4; I^2=0%), respectively.[18,19]

Certainty of evidence on benefits and harms
Overall certainty of evidence for efficacy and safety of varicella vaccination for healthcare workers was low to very low (local adverse events, seroconversion rate). Certainty was downgraded due to study design limitations (no study compared vaccination to no vaccination) or serious inconsistency (high heterogeneity estimates).

Table 2. Benefits and harms of varicella vaccination in healthy healthcare workers

Critical Outcomes	No. of Studies* (No. of Participants)	Impact	Certainty of evidence
Incidence of breakthrough infections/crude attack rate) (2 months – 3 months)	1 (120)	Pooled estimate: 9% (95% CI 5 to 14%)	Low

Varicella attack rate (2 months – 11.8 years)	1 (120)	Pooled estimate: 8% (95% CI 3 to 17%)	Low
Seroconversion rate (1 month – 4 years)	3 (264)	Pooled estimates were as follows: ● At 1-2 months: 95% (95% CI 91 to 98%) ● At 5-6 months: 94% (95% CI 89 to 97%) ● At >6 months: 81% (95% CI 58 to 97%)	Very low
Systemic adverse reactions (1.5 months)	2 (144)	Pooled estimates were as follows: Any systemic adverse events: 2% (95% CI 0 to 7%) Fever: 1% (95% CI 0 to 4%) Varicella or zoster-like rash: 2% (95% CI 3 to 12%)	Low

CI confidence interval
*Prospective cohort studies

Recommendations from Other Groups

Table 3 summarizes existing recommendations from various groups. The World Health Organization (WHO), US Advisory Committee on Immunization Practices (ACIP), Australian Immunisation Handbook, and UK recommended 2 doses of varicella vaccination for adolescents and adults without evidence of varicella immunity. The Philippine Society for Microbiology and Infectious Diseases (PSMID) recommended that varicella vaccine should not be routinely given to immunocompetent adults since no studies were conducted on varicella vaccine among adults comparing it with placebo. All groups recommended varicella vaccine for healthcare workers.

Table 3. Recommendations from international and local CPGs

Group	Recommendations	Strength of Recommendation, Certainty of Evidence
World Health Organization (WHO, 2014)[5]	● Countries with a high average age (≥15 years) of acquisition of infection, indicating a high proportion of susceptible persons in the population, could consider alternative vaccination strategies such as vaccination of adolescents and adults without evidence of varicella immunity. This strategy requires a 2-dose schedule. ● Countries should consider vaccination of potentially susceptible health-care workers (i.e., unvaccinated and with no history of varicella) with 2 doses of varicella vaccine, even if it is not included in the routine immunization schedule, in settings where the risk of severe varicella in the population in direct contact with the healthcare workers is high.	Not available
US Advisory Committee on Immunization Practices (ACIP, 2022)[22]	● Persons aged >13 years without evidence of varicella immunity should receive two 0.5-mL doses of single antigen varicella vaccine administered subcutaneously, 4-8 weeks apart. ● If >8 weeks elapse after the first dose, the second dose may be administered without restarting the schedule. Only single-antigen varicella vaccine may be used for vaccination of persons in this age group. ● Because of their increased risk for transmission to persons at high risk for severe disease or their increased risk of exposure, vaccination is especially	

	important for persons without evidence of immunity in the following groups: ○ Close contacts (e.g., healthcare personnel, household contacts) ○ Persons at high risk for serious complications ○ Persons who live or work in environments in which transmission of varicella zoster virus is likely (e.g., teachers, child-care workers, and residents and staff in institutional settings) ○ Persons who live and work in environments in which transmission has been reported (e.g., college students, inmates and staff members of correctional institutions, military personnel) ○ Nonpregnant women of childbearing age ○ Adolescents and adults living in households with children ○ International travelers	
Philippine Society for Microbiology and Infectious Diseases (PSMID, 2018)[23]	● Varicella vaccine should not be routinely given to immunocompetent adults. ● Healthcare workers without history of varicella infection should be given varicella vaccine. ● The vaccine is safe to be given to patients but is poorly immunogenic to those who underwent hematopoietic stem cell transplant. ● Varicella vaccine should not be given to HIV-infected adults regardless of their immunogenicity. ● Varicella vaccine may be given as post-exposure prophylaxis within 72 hours of exposure	Strong recommendation, very low quality of evidence
Australian Immunisation Handbook (2022)[24]	● All non-immune adolescents ≥14 years of age and adults are recommended to receive 2 doses of varicella vaccine.	Not available
	● Healthcare workers are strongly recommended to receive 2 doses of varicella vaccine if they are not immune.	Strong recommendation, Certainty of evidence not available
UK 2019	● Children from one year of age or older and adults should receive two doses of varicella vaccine, 4-8 weeks apart (and certainly not less than 4 weeks apart). ● Vaccinating non-immune healthcare workers who themselves will derive benefit as they will be protected from contact with infectious patients.	Not available

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

Cost

Costs of varicella vaccination

Varicella vaccines that are available locally are Varivax® (Merck Sharp and Dohme), Varilrix® (GlaxoSmithKline), and ProQuad® (Merck Sharp and Dohme). Varivax is priced at PHP 2,000/dose while Varilrix is priced at PHP 1,800/dose.[24] ProQuad®, which is a combined vaccine for varicella, measles, mumps and rubella, costs PHP 4,500/dose.[25]

Cost-effectiveness of varicella vaccination

Currently, all studies evaluating the cost-effectiveness of universal varicella vaccination for concern only pediatric populations. No cost-effectiveness studies have been done in the Philippine setting.

A systematic review by Unim et al. demonstrated that varicella vaccination could save €637 762 (infant strategy) to 53 million annually (combined infant and adolescent strategy).[26] In a cost-effectiveness study in the United Kingdom, 2-dose universal varicella vaccination (UVV) was noted to be a cost-effective alternative to no vaccination. Oka-recombinant immunotoxin Varilrix® and Varivax® vaccines produced similar impact on reducing varicella incidence. A high coverage 2-dose UVV appears to be the most effective strategy to reduce the burden associated with varicella. Cost-utility analyses show that 2-dose UVV with either GSK or MSD vaccine will be a cost-effective alternative to no vaccination.[27]

A cost-effectiveness analysis was performed among healthcare workers (physicians and nurses) aged less than 45 years old in Israel.[28] Results showed that screening and vaccination of susceptible workers using anamnestic selection (vaccinating those who test negative for VZV antibody) is expected to reduce future cases within 20 years since vaccination, from 58.3 to 33.0 with an incremental cost of USD 23,713 (approximately PHP 1.3 million) per avoided cases. Using serological tests to detect susceptible healthcare workers would prevent additional 5.7 cases with an incremental cost of USD 206,692 (approximately PHP 11.3 million) per avoided case. Vaccinating all healthcare workers without serotesting (vaccination of all serologically proven susceptible healthcare workers), raises the costs markedly, with almost identical effectiveness resulting in an incremental cost of USD 10.4 million (approximately PHP 571 million) per avoided case.[28]

Patient Values and Preference, Equity, Acceptability, and Feasibility

There were no published local data to date evaluating the knowledge, attitudes, and perceptions of Filipinos on varicella vaccination.

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5. Research Implications/Gaps

Although there were available studies on the efficacy and safety of the vaccines among apparently healthy adults, the efficacy outcomes for some vaccines were based on immunogenicity and seroconversion findings only and not prevention of disease (e.g., Japanese encephalitis vaccine, rabies vaccine, *Haemophilus influenzae* b), which reduced the certainty of the effect estimates. For some questions, the available evidence did not use a placebo control group. There were also limited RCTs specifically enrolling healthcare workers. Some of the RCTs that were available are more than 20 years, such as those of Hib vaccine. No studies were found comparing pre-exposure rabies vaccination with placebo or no vaccination among asymptomatic apparently healthy adults. Indirect evidence for this guideline question. No RCTs were found comparing varicella vaccination with no vaccination or placebo.

More vaccine trials should be conducted using hard outcomes to strengthen the evidence. Future studies could also investigate the resources required and cost-effectiveness of the vaccines especially in our country. More so, studies focusing on the acceptability of vaccines should also be conducted to address the challenges of vaccine implementation.

6. Dissemination and Implementation

Dissemination

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 plans 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.

Implementation

The SC will develop a program of monitoring to determine the best practices of relevant stakeholders regarding routine adult vaccination. Monitoring the use of this CPG may also be a subject of research by interested parties.

As one of the PHEX guideline, its recommendations will be incorporated into an online application that can be accessed by PCPs and patients. For any individual person, after provision of basic demographic data, the application will enumerate the recommended or suggested vaccines. Data on application usage can be used to measure uptake of the CPG.

7. Applicability Issues

The PHEX Task Force emphasizes some caveats of this CPG using equity and applicability. When considering an individual for vaccination, several important factors must be accounted for including: vaccine supply, age, eligibility, medical history, current health status, possible contraindications, and drug interactions. This CPG does not necessarily supersede the

consumers' (i.e., health professionals, hospital administrators, employers, payors, patients) values, settings, and circumstances, but can guide them to receive the effective and appropriate vaccines.

Although this CPG intends to influence the direction of health policies for the general population, it should not be the sole basis for recreating or abolishing practices that aim to improve the health conditions of many Filipinos, particularly individuals belonging to the workforce.

8. Updating of the Guidelines

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

9. Appendices

PERIODIC HEALTH EXAMINATION PHASE 2 TASK FORCE ON ADULT IMMUNIZATION 2021-2022

Task Force Steering Committee
Chair: Rosally P. Zamora, MD, FPCP, FPSMID
Internist and Adult Infectious Disease Specialist

Members: Jane Eflyn L. Bunyi, RPh, MD, OHP, DFM, FPAFP, CSPSH
Family Physician, Occupational Health Physician, Hypertension Specialist

Roberto Razo II, MD, FPSP, FPSPhys
Internist

Consensus Panel Members

Joannah Kaye B. Borallo, MD
Physician, representing Department of Health (DOH)

Hairam R. Encendencia, MD, MCHM
Family Physician, representing Association of Municipal Health Officers in the Philippines (AMHOP)

Ma. Charmian M. Hufano, MD
Internist and Adult Infectious Disease Specialist, representing, Philippine Society for Microbiology & Infectious Diseases (PSMID)

Imelda Astre Luna, MD
Pediatrician and Pediatric Infectious Disease Specialist, representing Philippine Foundation for Vaccination (PFV)

Ruperto Angel O. Navarro, MD
Internist, representing Philippine Society of General Internal Medicine (PSGIM)

Mario M. Panaligan, MD
Internist and Adult Infectious Disease Specialist, representing Philippine College of Physicians (PCP)

Marishiel Mejia-Samonte, MD
Family Physician, representing *Philippine Academy of Family Physicians (PAFP)*

Kim Patrick S. Tejano, MD
Physician, representing Department of Health (DOH)

Technical Working Group
Technical Coordinator: Howell Henrian G. Bayona, MSc
Evidence Review Experts: Aldrich Ivan Lois D. Burog, MD, MSc (cand.)
Carol Stephanie C.Tan-Lim, MD, MSc
Isabel Kristine M. Valdez, MD

	Jeriel Reyes De Silos, MD, MPM-HSD Jonathan P. Chan, MD Mithi Kalayaan S. Zamora, MD Kathryn Uy Roa, MD, MPH Renee Anne Karmela L. Feliciano, RN, MD Sen Kendrich N. Cua, MD
Consensus Panel Meeting Facilitator:	Bernadette Heizel D. Manapat-Reyes, MD, MHPEd
Technical Writer:	Aubrey Melody R. Rocimo, MD
Administrative Officer:	Cynthia Castro Lati
Central Steering Committee:	Antonio L. Dans, MD, MSc Dante D. Morales, MD Marissa M. Alejandria, MD, MSc Beverly Lorraine C. Ho, MD Aileen R. Espina, MD Maria Vanessa Villaruz-Sulit, RN, MSc
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
Project Leader:	Leonila F. Dans, MD, MSc
Co-Project Leader:	Marissa M. Alejandria, MD, MSc
Project Managers:	Ian Theodore G. Cabaluna, RPh, MD Josephine T. Sanchez, RN
Administrative Staff:	Lailanie Ann C. Tejuco Maria Pamela Tagle

PERIODIC HEALTH EXAMINATION PHASE 3 TASK FORCE ON ADULT IMMUNIZATION 2022-2023

Task Force Steering Committee	
Chair:	Armin N. Masbang, RMT, MD, FPCP, FPSMID *Internist and Infectious Disease Specialist*
Members:	Rosally P. Zamora, MD, FPCP, FPSMID *Internist and Infectious Disease Specialist*
	Jane Eflyn L. Bunyi, RPh, MD, OHP, DFM, FPAFP, CSPSH *Family Physician, Occupational Health Physician, Hypertension Specialist*
	Roberto Razo II, MD, FPCP, FPSPhys *Internist*

Rommel B. Punongbayan, MD, MBA, FPCP, DPCOM, CSPSH
Internist, Occupational Health Physician, Hypertension Specialist

Consensus Panel Members

Elmer D. Bondoc, RN, MN
Nurse, representing Philippine Nurses Association (PNA)

Marilou Claris, RPh
Pharmacist

James Dela Cruz, MD
Occupational Health Physician, representing Philippine Society of Public Health Physicians

Hairam R. Encendencia, MD
Family Physician, representing Association of Municipal Health Officers in the Philippines (AMHOP)

Ma. Charmian M. Hufano, MD
Internist and Adult Infectious Disease Specialist, representing, Philippine Society for Microbiology & Infectious Diseases (PSMID)

Imelda Astre Luna, MD
Pediatrician and Pediatric Infectious Disease Specialist, representing Philippine Foundation for Vaccination (PFV)

Edmyr M. Macabulos, MD
Occupational Health Physician, representing Philippine College of Occupational Medicine

Rupert Angel Navarro, MD
Internist, representing Philippine Society of General Internal Medicine (PSGIM)

Mario M. Panaligan, MD
Internist and Adult Infectious Disease Specialist, representing Philippine College of Physicians (PCP)

Marishiel Mejia-Samonte, MD
Family Physician, representing *Philippine Academy of Family Physicians (PAFP)*

Technical Working Group

Technical Coordinator: Howell Henrian G. Bayona, MSc
Evidence Review Experts: Aubrey Melody Rocimo, MD
Aldrich Ivan Lois Burog, MD
Bernard Demot, MD
Gina Antonina Eubanas, MD
Honey Jane Limos, MD
Kerwyn Jim Chan, MSc

	Mithi Kalayaan Zamora, MD Myzelle Anne Infantado Samantha Bartolo, MD Timothy Hudson David Carandang, MD Vanezah Leah Espino, MD
Consensus Panel Meeting Facilitator:	Bernadette Heizel D. Manapat-Reyes, MD, MHPEd
Technical Writer:	Alrenzo Ludwig Domingo
Administrative Officer:	Carlos Diego A. Rozul
Program Managers: Assistant Program Manager:	Josephine Sanchez, RN Lea Galia, MD
Administrative Staff:	Pamela Tagle Lailanie Tejuco Michelle Recana
COI Administrative Officer:	Ivy Cruz

PERIODIC HEALTH EXAMINATION PHASE 3 CENTRAL COMMITTEE

Program Leader: Co-Program Leaders:	Ian Theodore Cabaluna, MD, GDip, MSc (cand.) Leonila Dans, MD, MSc Marissa Alejandria, MD, MSc
Steering Committee Members:	Antonio Dans, MD, MSc Dante Morales, MD Diana Tamondong-Lachica, MD Aileen Espina, MD Maria Vanessa Sulit, RN, MSc
Program Manager: Assistant Program Manager:	Josephine Sanchez, RN Lea Galia, MD
Administrative Staff:	Pamela Tagle Lailanie Tejuco
COI Committee Members:	Dante Morales, MD Antonio Dans, MD, MSc Maria Vanessa Sulit, RN, MSc Angela Du, MD Camilo Te, MD Miriam Timonera, MD
COI Administrative Officer:	Ivy Cruz

Summary of COI Declarations

PERIODIC HEALTH EXAMINATION PHASE 2

Name	Affiliation	Summary of Declared Conflicts of Interest	Assessment
Hairam R. Encendencia, MD, MCHM (AMHOP)	Consensus Panelist	Municipal Health Officer – Agusan, Regional President – Association of Municipal Health Officers of the Philippines	Manageable A
Imelda Astre Luna, MD (PFV)	Consensus Panelist	CPG in infectious diarrhea for children, Handbook Childhood vaccine 2014, DOH – National Verification Committee on Measles Elimination, Medical Specialist 3 Quirino Labor, Lead Coordinator for SLMC Institute of Pediatrics and Child Health, past Chair of PPS – Committee on Immunization, Speaker on Vaccine awareness program (Voting member for questions 1 to 7); Research grants for vaccine studies (Observer, non-voting member for question 8)	Manageable A for Questions 1-7 Manageable B for Question 8
Joannah Kaye B. Borallo, MD (DOH)	Consensus Panelist	Medical Officer III – DOH DPCB Immunization Program (Observer, non-voting member)	Manageable B
Kim Patrick S. Tejano, MD (DOH)	Consensus Panelist	Medical Officer IV – DOH DPCB, Program Manager on National Immunization (Observer, non-voting member)	Manageable B
Ma. Charmain M. Hufano, MD (PSMID)	Consensus Panelist	RITM, DOH, stocks at Saint Luke's Medical Center and Dela Salle University Medical Center	Manageable A
Mario M. Panaligan, MD (PCP)	Consensus Panelist	Member DMSB – Avigan Trial, DOH, Head Infectious Disease JRMMC, Immediate Past President PSMID, PCP, board member of Philippine Hospital Infectious Control Society	Manageable A
Marishiel Mejia-Samonte, MD (PAFP)	Consensus Panelist	Medical Specialist III – UP-PGH DFM, Advocacy against Tb and Infectious Disease	Manageable A
Ruperto Angel O. Navarro, MD	Consensus Panelist	Proprietor – Medline Plus Clinics	Manageable A

PERIODIC HEALTH EXAMINATION PHASE 3

Name	Affiliation	Summary of Declared Conflicts of Interest	Assessment
Dr. Armin N. Masbang	Task Force Chair	No COI	A
Howell Henrian G. Bayona, MSc	Technical Coordinator	Technical Coordinator for Adult Immunization PHEX 2	B Non-Financial COI
Dr. Roberto A. Razo II	Steering Committee Member	SC of Adult Immunization PHEX 2	B Non-Financial COI
Rommel B. Punongbayan	Steering Committee Member	● Advisory board respiratory division asthma – GSK ● Pres-PSGIM ● Head - Advocacy & Social Responsibility, PCOM ● National Board-PCOM ● MSII-Bulacan Medical Center ● Technical Working Group & Author on COVID-19 for PCOM	B Non-Financial COI
Dr. Rosally P. Zamora	Steering Committee Member	No COI	A
Dr. Jane Eflyn Lardizabal-Bunyi	Steering Committee Member	No COI	A
Dr. Aubrey Melody Rocimo	ERE Topic: Varicella Vaccine	Technical Writer for Adult Immunization PHEX 2	B Non-Financial COI
Dr. Aldrich Ivan Lois Burog	ERE Topic: Encephalitis Vaccine	ERE for Adult Immunization PHEX 2	B Non-Financial COI
Dr. Mithi Kalayaan Zamora	ERE Topic: Cholera Vaccine	ERE for Adult Immunization PHEX 2	B Non-Financial COI
Dr. Timothy Hudson David Carandang	ERE Topic: Japanese B Encephalitis Vaccine; Haemophilus influenzae B Vaccine	No COI	A
Kerwyn Jim Chan	ERE Topic: Rabies Vaccine	No COI	A
Myzelle Anne Infantado	ERE Topic: Meningococcal Vaccine	No COI	A
Dr. Vaneza Leah Espino	ERE Topic: Hepatitis A Vaccine	No COI	A
Dr. Gina Antonina Eubanas	ERE Topic: Japanese Encephalitis Vaccine	No COI	A
Dr. Honey Jane Limos	ERE Topic: Varicella Vaccine	Cannot vote for questions on Varicella. Transfer to another question.	C Financial Conflict
Dr. Samantha Bartolo	ERE Topic: Japanese Encephalitis Vaccine	BSV has no vaccine for Japanese encephalitis. Lecture on Ampholip. PSMID, PSBIM, MO IV	B Non-Financial Conflict
Dr. Bernard Demot	ERE Topic: Monkeypox	Health promotion activity of the hospital for COVID-19 vaccination and health education regarding monkeypox.	B Non-Financial Conflict
Dr. Elmer Bondoc	Consensus Panel Member	No COI	A
Dr. Edmyr Macabulos	Consensus Panel Member	No COI	A
Dr. Hairam Encendencia	Consensus Panel Member	No COI	A

Dr. Rupert Angel Navarro	Consensus Panel Member	No COI	A
Dr. Marishiel Samonte	Consensus Panel Member	No COI	A
Dr. Marilou Claris	Consensus Panel Member	No COI	A
Dr. Charmain Hufano	Consensus Panel Member	IDS Specialist	B Non-Financial COI
Dr. James Dela Cruz	Consensus Panel Member	● Cebu Landmasters Inc, Central Inter-transport Logistics Corporation, Maxicare Health Corporation- logistics of the various clinics like ActiveOne and Maxicare ● Home Health Care Placement Inc. | July 2018 – September 2021 ● Led and managed the clinic for an off-shore US company. Initiated health programs including flu vaccination, confidential HIV screening, TB in the Workplace, and mental health promotion to almost 500 workers in a BPO work environment	B Non-Financial COI
Dr. Imelda Luna	Consensus Panel Member	● Sub-investigator hemophilus influenza B study ● MSD Speaker for MMR; Intellectual COI - Vaccine studies; Vaccine advocacy	C Financial COI Cannot vote on questions for Hepa A and Influenza B

Cholera Vaccine

Appendix 1. Evidence-to-Decision Summary

Burden	No	Probably No	Probably Yes	Yes (7)	Varies	Don't know (1)
Benefits	Trivial (1)	Small (3)	Moderate (2)	Large	Varies	Don't know (2)
Harms	Large	Moderate (3)	Small (3)	Trivial (2)	Varies	Don't know
Certainty of evidence	Very Low (4)	Low (3)	Moderate	High	No included studies (1)	
Balance of effects	Favors no vaccine	Probably favors no vaccine	Equivalent (2)	Probably favors vaccine (2)	Favors vaccine (2)	Varies (1)	Don't know (1)

Resources required	Large costs	Moderate costs (7)	Negligible costs and savings	Moderate savings (1)	Large savings	Varies	Don't know
Certainty of evidence (resources)	Very Low	Low (3)	Moderate (5)	High	No included studies		
Cost effectiveness	Favors no vaccine	Probably favors no vaccine (1)	Does not favor either	Probably favors vaccine (3)	Favors vaccine (3)	Varies	No included studies (1)
Equity	Reduced	Probably reduced	Probably no impact (1)	Probably increased (1)	Increased (2)	Varies (1)	Don't know (3)
Acceptability	No	Probably no	Probably yes (4)	Yes (2)	Varies	Don't know (2)	
Feasibility	No	Probably no (1)	Probably yes (6)	Yes (1)	Varies	Don't know	
Values	Important variability (2)	Possibly important variability (6)	Probably no important variability	No important variability			

Recommendation 1: **Asymptomatic apparently healthy adults**	STRONG against	WEAK against (1)	NO RECOMMENDATION (3)	WEAK in favor (3)	STRONG in favor (1)

Appendix 2. GRADE Summary of Findings Table

Grade Table 2.1. Injected cholera vaccines compared to placebo for apparently healthy adults

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	injected cholera vaccines	placebo	Relative (95% CI)	Absolute (95% CI)		
Cholera Cases – Up to 7 months												
14	Randomized trials	not serious	not serious	not serious	not serious	none	654/1427798 (0.0%)	509/599942 (0.1%)	**RR 0.45** (0.38 to 0.53)	**0 fewer per 1,000** (from 1 fewer to 0 fewer)	High	CRITICAL
Cholera Cases – Up to 1 year												
11	Randomized trials	not serious	not serious	not serious	not serious	none	525/971492 (0.1%)	416/470673 (0.1%)	**RR 0.55** (0.44 to 0.68)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	High	CRITICAL
Cholera Cases – Up to 2 years												
5	Randomized trials	not serious	not serious	not serious	not serious	none	105/428309 (0.0%)	129/270959 (0.0%)	**RR 0.58** (0.44 to 0.75)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	High	CRITICAL
Cholera Cases – Up to 3 years												
1	Randomized trials	not serious	not serious	not serious	serious[a]	none	6/6956 (0.1%)	10/7103 (0.1%)	**RR 0.61** (0.22 to 1.68)	**1 fewer per 1,000** (from 1 fewer to 1 more)	Moderate	CRITICAL
Death – All cause (year 1)												
2	Randomized trials	not serious	not serious	not serious	not serious	none	99/15413 (0.6%)	73/11330 (0.6%)	**OR 0.99** (0.72 to 1.34)	**0 fewer per 1,000** (from 2 fewer to 2 more)	High	CRITICAL
Death – Cholera (year 1)												
4	Randomized trials	not serious	not serious	not serious	serious[b]	none	22/616600 (0.0%)	14/191000 (0.0%)	**OR 0.52** (0.26 to 1.04)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	Moderate	CRITICAL
Adverse Events												
6	Randomized trials	serious[c]	not serious	not serious	not serious	none	2602/18721 (13.9%)	927/8891 (10.4%)	**RR 1.51** (1.22 to 1.86)	**53 more per 1,000** (from 23 more to 90 more)	Moderate	CRITICAL

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio; Explanations: a) CI crosses 1.0 b) wide Cis c) poor reporting of surveillance methods and frequency

GRADE Table 2.2. Oral inactivated cholera vaccines compared to placebo for asymptomatic apparently healthy adults

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral inactivated cholera vaccines	placebo	Relative (95% CI)	Absolute (95% CI)		
Oral Inactivated Vaccine (All-Types) Versus Placebo – Cholera Cases: First 6-12 months of follow up												
6	Randomized trials	serious[a]	not serious	not serious	not serious	none	182/264486 (0.1%)	296/252842 (0.1%)	**RR 0.54** (0.43 to 0.69)	**1 fewer per 1,000** (from 1 fewer to 0 fewer)	Moderate	CRITICAL
Oral Inactivated Vaccine (All-Types) Versus Placebo – Cholera Cases: First 2 years of follow up												
7	Randomized trials	serious	not serious	not serious	not serious	none	182/218508 (0.1%)	401/215489 (0.2%)	**RR 0.36** (0.30 to 0.44)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	Moderate	CRITICAL
Oral Inactivated Vaccine (All-Types) Versus Placebo – All-Cause Death 1 year												
2	Randomized trials	not serious	not serious	not serious	serious[b]	none	160/123257 (0.1%)	194/122985 (0.2%)	**RR 0.83** (0.64 to 1.08)	**0 fewer per 1,000** (from 1 fewer to 0 fewer)	Moderate	CRITICAL
Oral Inactivated Vaccine (All-Types) Versus Placebo – Cholera Death 1 year												
2	Randomized trials	not serious	not serious	not serious	serious[b]	none	5/110468 (0.0%)	15/110066 (0.0%)	**RR 0.73** (0.03 to 16.41)	**0 fewer per 1,000** (from 0 fewer to 2 more)	Moderate	CRITICAL
Oral Inactivated Vaccine (All-Types) Versus Placebo – Adverse Events												
4	Randomized trials	serious[c]	not serious	not serious	not serious	none	105/13557 (0.8%)	93/13408 (0.7%)	**RR 1.13** (0.88 to 1.44)	**1 more per 1,000** (from 1 fewer to 3 more)	Moderate	CRITICAL
Oral Inactivated Vaccine (All-Types) Versus Placebo – Hospitalization Rates												
2	Randomized trials	serious[d]	not serious	not serious	not serious	none	43/84001 (0.1%)	106/83248 (0.1%)	**RR 0.40** (0.28 to 0.57)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	Moderate	CRITICAL

CI: confidence interval; **RR:** risk ratio;
Explanations: a) High risk of bias for outcome reporting due to attrition; passive surveillance b) Wide Cis c) High risk of bias for safety outcome assessment method d) Sur 2009; No mention of the participants who may have moved out of the area and therefore been lost to follow up. Cases identified through passive surveillance at the polyclinics and hospitals.

GRADE Table 2.3. Live attenuated oral cholera vaccines compared to placebo for asymptomatic apparently healthy adults

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	live attenuated oral cholera vaccines	placebo	Relative (95% CI)	Absolute (95% CI)		
Cholera Cases (follow-up: 4 years)												
1	Randomized trials	not serious	not serious	not serious	serious[a]	none	83/111868 (0.1%)	94/112252 (0.1%)	**RR 0.86** (0.57 to 1.30)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	Moderate	CRITICAL
Death												
1	Randomized trials	not serious	not serious	serious[b]	not serious	none	159/33696 (0.5%)	155/33812 (0.5%)	**OR 1.03** (0.82 to 1.29)	**0 fewer per 1,000** (from 1 fewer to 1 more)	Moderate	CRITICAL
Adverse Events												
3	Randomized trials	not serious	serious[d]	not serious	not serious	none	1686/3568 (47.3%)	350/981 (35.7%)	**RR 0.99** (0.75 to 1.30)	**4 fewer per 1,000** (from 89 fewer to 107 more)	Moderate	CRITICAL
Immunogenicity (follow-up: 10 days after immunization; assessed with: GMT titers, seroconversion rates)												
5	Randomized trials and observational studies	serious[c]	not serious	not serious	not serious	None	Based on one study[30] • live OCVs induced antigen-specific memory B cell (MBC) responses • anamnestic lipopolysaccharide specific responses may contribute to long-term protection and provide correlates of the duration of vaccine-induced protection. Two other immunogenicity studies showed: • the vaccine elicited significant antibody responses in younger adults[31] as early as 10 days after vaccination, with seroconversion rates of 94% in the vaccine group versus 4% in the placebo group.[28, 29] • Similar seroconversion rates among older adults (90.4%) • GMT levels after 10 days were 4 times lower than in younger adults, suggesting less robust immune response with increasing age • significantly greater seroconversion rates after 10 days in vaccine recipients (60% vs. 4% in placebo).[34]				Moderate	CRITICAL

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio
Explanations: a) low event rates for cholera cases b) data included both children and adults for this outcome c) Two of 5 trials were non-RCTs d) different effect estimates for younger vs. older adults

Appendix 3. Characteristics of Included Studies

Appendix 3.1. Injected Cholera Vaccines

Systematic Reviews

Study ID	Search Methods	Inclusion Criteria	Data analysis	Included Studies
Graves 2010[12]	> 5 electronic databases (MEDLINE, EMBASE, LILACS, CENTRAL, Cochrane Infectious Disease Group Specialized Register) All articles from database inception to 1 Sep 2008 +Bibliographic search, handsearching in journal *Vaccine* from 1st issue up to 1997	**Study design:** RCT or quasi-RCTs **Population:** well adults or children irrespective of immune status or special risk category **Intervention:** killed whole cell cholera vaccines or other inactive subunit vaccines administered by injection **Control:** placebo, control vaccines, or no intervention **Outcomes:** cholera cases, all-cause deaths, cholera deaths, adverse effects	• > 2 authors performed study screening, data extraction, risk of bias assessment • Overall risk ratio (RR) used to reported relative rates • Pre-planned subgroup analysis by age group (< 5 yo and > 5 yo) • Individual ROB tables were not available but described as low risk in the text for efficacy outcomes and high risk for safety outcomes	Azurin 1965i Azurin 1965ii Azurin 1965iii Benenson 1968a Benenson 1968b-i Benenson 1968b-ii Burgasov 1976 Curlin 1975 (children) Das Gupta 1965a Das Gupta 1965b-i Das Gupta 1965b-ii McCormack 1969 (children) Mosley 1970-i (children) Mosley 1970-ii (children) Mosley 1970-iii (children) Oseasohn 1965 Pal 1980 PCC 1968 PCC 1973a-i PCC 1973a-ii PCC 1973a-iii PCC 1973a-iv PCC 1973b Saroso 1978i Saroso 1978ii Taneja 1965

Appendix 3.2. Inactivated Oral Cholera Vaccines

Systematic Reviews

Study ID	Search Methods	Inclusion Criteria	Data analysis	List of Included Studies
Sinclair 2011[14]	Electronic databases (MEDLINE, EMBASE, LILACS, CENTRAL, Cochrane Infectious Disease Group Specialized Register, metaRegister of Controlled Trials, WHO ICTRP) All articles from database inception to October 2010 +Bibliographic search, reference lists, contacting individual researchers	**Study design:** RCT or quasi-RCTs **Population:** well adults or children without cholera symptoms **Intervention:** any cholera vaccine administered orally **Control:** placebo, control vaccines, different dose or schedule of cholera vaccine, or no intervention **Outcomes:** cholera cases, cholera deaths, cases of severe dehydrating diarrhea, cases of all-cause diarrhea, deaths from severe dehydrating diarrhea, all-cause deaths, serious adverse effects leading to hospitalization or death, other adverse events	• > 2 authors performed study screening, data extraction, risk of bias assessment (Cochrane ROB tool) • Overall risk ratio (RR) used to report relative rates or vaccine efficacy (VE = (1-RR) x 100%) • Pre-planned subgroup analysis by age, time period of follow up, blood group (O vs other), type of vaccine, vaccine regimen used or doses received, challenge • Assessment of heterogeneity by forest plot visual analysis, I^2 statistic (50% cut off), Chi-squared test of heterogeneity • Assessment of reporting biases using funnel plot	**Studies on killed whole cell / inactivated vaccines (n=6)** Clemens 1988 Bangladesh Sanchez 1994 Peru Sanchez 1995 Peru Taylor 2000 Peru Trach 1997 Vietnam (cluster RCT) Sur 2009 India (cluster RCT)
Bi 2016[15]	MEDLINE, EMBASE, Scopus, Cochrane Review Library Search from inception up to July 2016 Consulted GTFCC Oral Cholera Vaccine Working Group to identify additional publications	**Study designs:** RCTs or pragmatic RCTs, case-control, cohort, case-cohort **Population:** non-specified **Intervention:** any oral cholera vaccine **Outcomes:** vaccine efficacy (relative reduction in medically attended confirmed cholera risk in vaccinated vs. unvaccinated, as measure in RCTs); vaccine effectiveness (relative reduction in risk of medically attended confirmed cholera cases in vaccinated vs. unvaccinated, measured in observational studies)	• 2 reviewers independently screened, extracted, appraised studies • Newcastle Ottawa Scale for observational studies; Cochrane ROB tool for RCTs • Assessment of publication bias using funnel plots • Subgroup analysis by number of vaccine doses, duration, and age group; primary analysis focused on efficacy of two-dose	**Studies on efficacy (RCTs; n=7)** Clemens 1990a Clemens 1990b Sanchez 1994 Peru Taylor 2000 Trach 1997 Sur 2009, 2011 Qadri 2015

Individual Trials

Study ID	Study Design	Setting	Population	Intervention	Comparator	Serotypes	Outcomes
Clemens 1988[17]	RCT	Bangladesh	N=89,596 (2 doses) N=62,285 (3 doses) Children aged 2-15 years and all women aged > 15 years, non-pregnant	Whole-cell or whole-cell with B-subunit (Dukoral®) 3 doses, 6 wks apart	Placebo	Inaba and Ogawa	• Incidence of cholera cases • Cholera deaths • Diarrhea cases • Adverse events within 3 days of 1st and 2nd doses
Qadri 2015[23]	Cluster-RCT, open label	Bangladesh	N = 268,896 All non-pregnant individuals > 1 yo; urban clusters	Whole-cell (Shanchol™) 2 doses 2 wks apart (n=94675) Vaccine + behavioral change (handwashing, chlorine treatment of drinking water) (n=92539)	Placebo	Inaba and Ogawa	• Vaccine effectiveness / Incidence of severely dehydrating cholera (1 year, 2 years) • Adverse events (day 14, day 28)
Qadri 2016; 2018[24,25]	RCT	Bangladesh	N=205,513 All non-pregnant individuals > 1 yo	Whole-cell (Shanchol™) 2 doses 2 wks apart	Placebo	Inaba and Ogawa	• Incidence of cholera cases (day 7-180) • Adverse events (day 0, day 28)
Khan 2019[26]	RCT	Bangladesh	N=71,202 Reproductive age women (13-49 yrs) among the Qadri RCT cohort Cohort 1: Pregnant during vaccination (n=550) Cohort 2: Pegnant after vaccination (n=773)	Whole-cell (Shanchol™) 2 doses 2 wks apart	Placebo	Inaba and Ogawa	• Adverse pregnancy outcomes (miscarriage, stillbirth, preterm delivery, low birth weight)
Sanchez 1994[18]	RCT	Peru	N=1426 All volunteers 17-65 yo	Whole-cell with B-subunit (Dukoral®) 2 doses 2 wks apart	Placebo	Not reported	• Incidence of cholera cases
Sur 2009[22]	Cluster-RCT	India	N=66,900 (3933 clusters) All non-pregnant individuals > 1 yo	Whole-cell (Shanchol™) 2 doses 2 wks apart	Placebo	Inaba and Ogawa	• Incidence of cholera cases (passive surveillance) • All-cause deaths • Serious adverse events within 14 days of vaccination • Adverse events within 14 days of each dose
Taylor 2000[20]	RCT	Peru	N=17,799 (2nd dose received; 14,997 with booster)	Whole-cell with B-subunit (Dukoral®)	Placebo	Inaba and Ogawa	• Cases of cholera identified through household surveillance or passive surveillance

Study ID	Study Design	Setting	Population	Intervention	Comparator	Serotypes	Outcomes
			All non-pregnant individuals 2-65 years	2 doses at day 1, 14; booster dose after 10 months			• Level of dehydration in patients with cholera • Adverse events after first dose; symptom inquiry at 2nd dose
Trach 1997[19]	Quasi-RCT	Vietnam	N=134,453 (22,653 households) All individuals aged > 1 year	Whole-cell (developed in Vietnam) 2 doses	No vaccine	Ogawa	• Cases of cholera requiring hospitalization • Cholera deaths • Number of visits to health facility for diarrhea treatment

Appendix 3.3. Live Attenuated Oral Cholera Vaccines

Study ID	Study Design	Setting	Population	Intervention	Comparator	Serotypes	Outcomes
McCarty 2019*[28]	RCT	United States	N=398 Healthy adults aged 46 to 64	Oral cholera vaccine (PXVX0200; Vaxchora®) (N=291)	Placebo (N=99)	Inaba	• Immunogenicity (serum vibriocidal antibody (SVA) response [4-fold rise in vibriocidal antibody], seroconversion rates at day 11; geometric mean titers at days 1 and 11) • Non-inferiority (versus Lot Consistency Study [10]) • Reactogenicity and safety
McCarty 2018**[29]	RCT	United States, Australia	N=3,077 Healthy adults aged 18 to 45	Oral cholera vaccine (PXVX0200) (N=2,734)	Placebo (N=343)	Inaba	• Safety and tolerability (systemic reactogenicity) • Immunogenicity (SVA seroconversion rates and geometric mean titers)
Haney 2018[30]	Quasi - RCT	United States	N=197 Healthy adults 18 to 45	Oral cholera vaccine (PXVX0200) Cohort 1: 10-day challenge (n=68) Cohort 2: 90-day challenge (n=66)	Placebo	Inaba	• Immunogenicity (antigen specific memory B cells – IgG, IgA) • Serum vibriocidal GMT
Islam 2018[31]	Quasi-experimental	United States	N=46 Healthy adults 18 to 45 yo 54% with Blood type O	Oral cholera vaccine (CVD 103-HgR) 5 x 10^8 CFU Cohort 1: 10-day challenge (n = 26) Cohort 2: 90-day challenge (n = 20)	Placebo	O1 Inaba	• Immunogenicity (serum IgM, IgA, IgG; seroconversion [>= 1.5-fold rise in ELISA units over baseline); - Cohort 1: day 0, 7, 10, 20, 38 - Cohort 2: day 0, 10, 28, 90, 100, 118, 180 • Vibriocidal seroconversion (>= 4-fold increase in reciprocal end-titer over day 0 value)
Richie 2000[34]	RCT	Indonesia	N=67,508 All non-pregnant individuals 2-41 years old	CVD 103-HgR (5 x 10^9 CFU lyophilized)	Placebo	Inaba	• Incidence of cholera (4 years; using hospital surveillance) • Adverse events (n=552 for 10-41 yo subjects) • All-cause mortality

Appendix 4. Forest Plots: Effects of Cholera Vaccines

Appendix 4.1. Injected Cholera Vaccines Versus Placebo

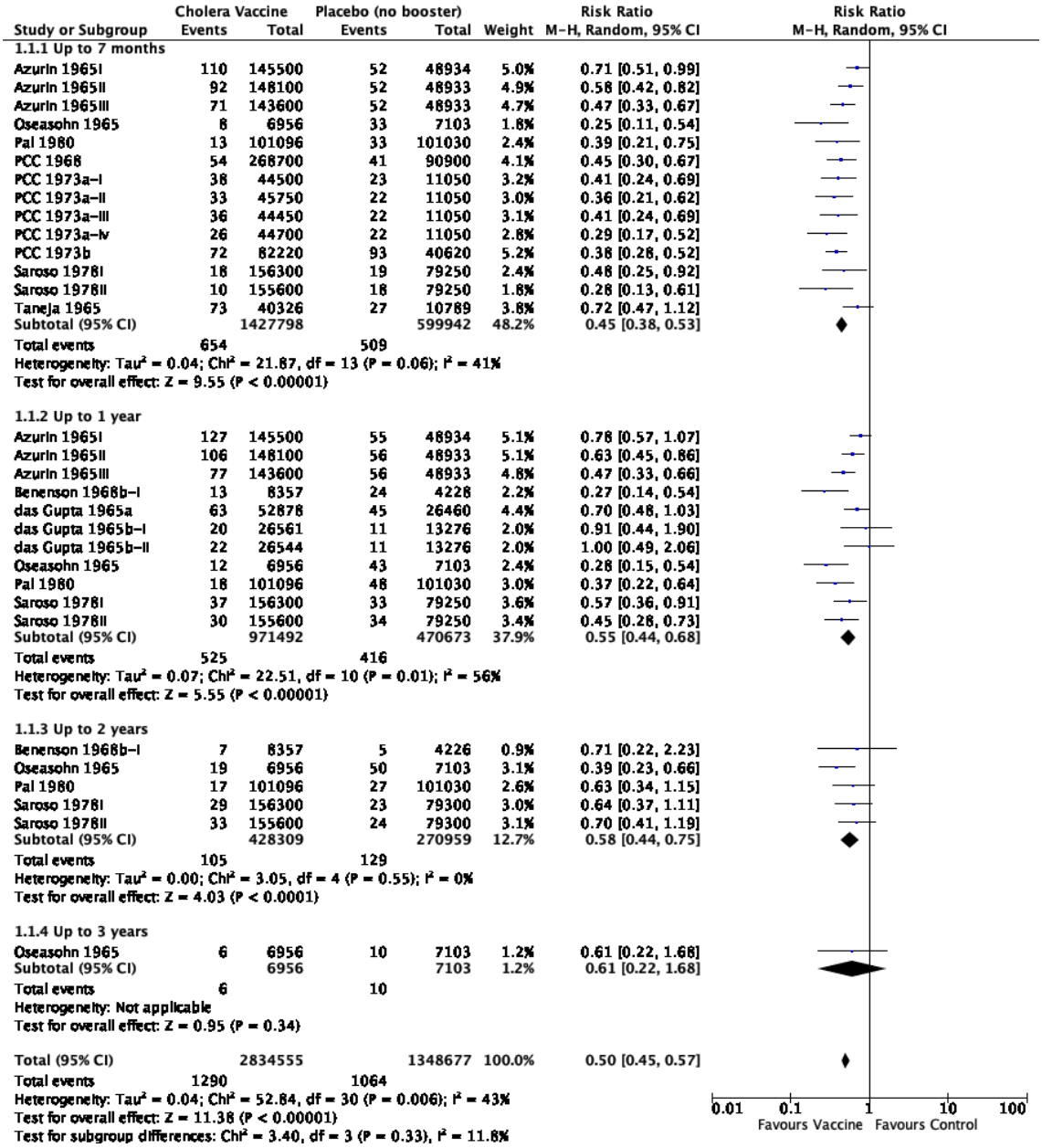


Figure 1. Outcome: Cholera Cases

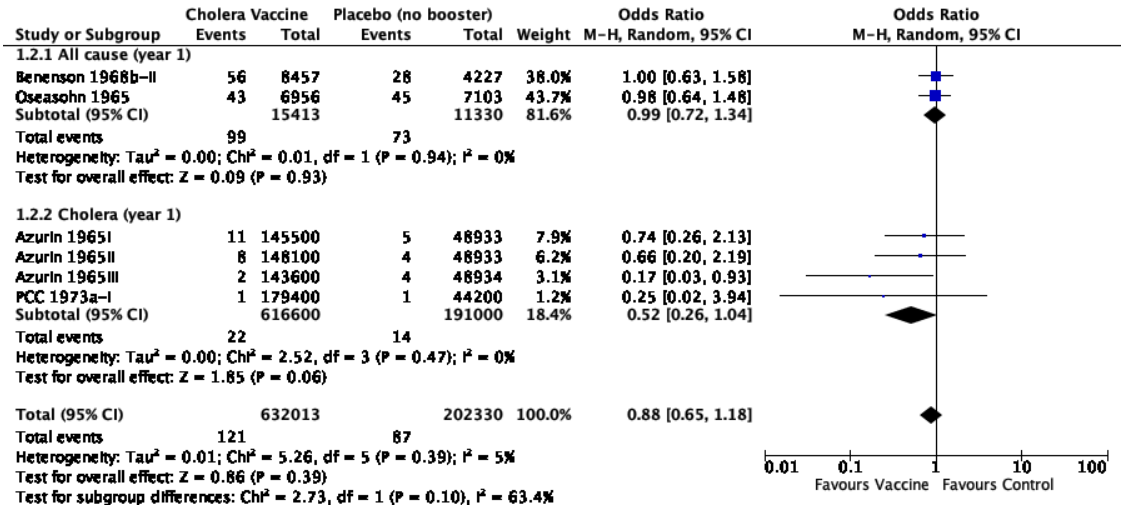


Figure 2. Outcome: All-cause deaths and cholera deaths

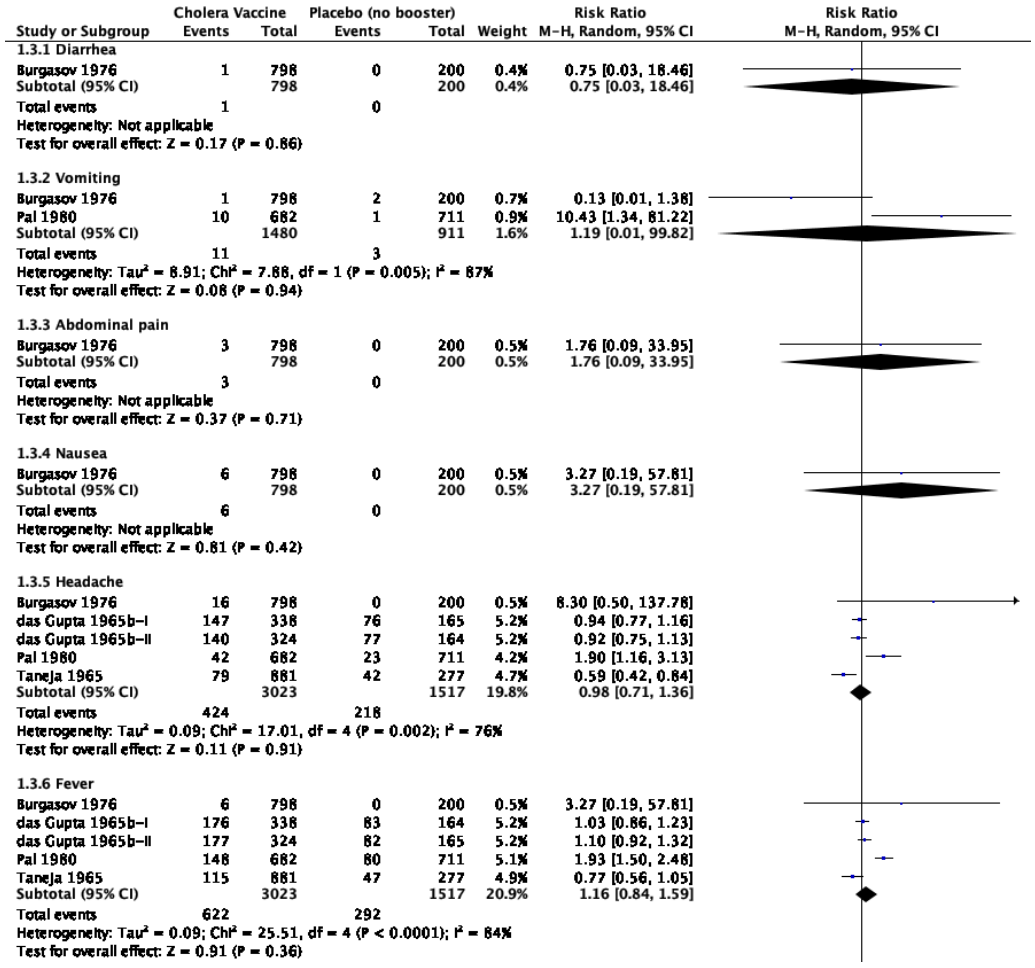


Figure 3. Outcome: Adverse events

Appendix 4.2. Oral Inactivated Cholera Vaccines Versus Placebo

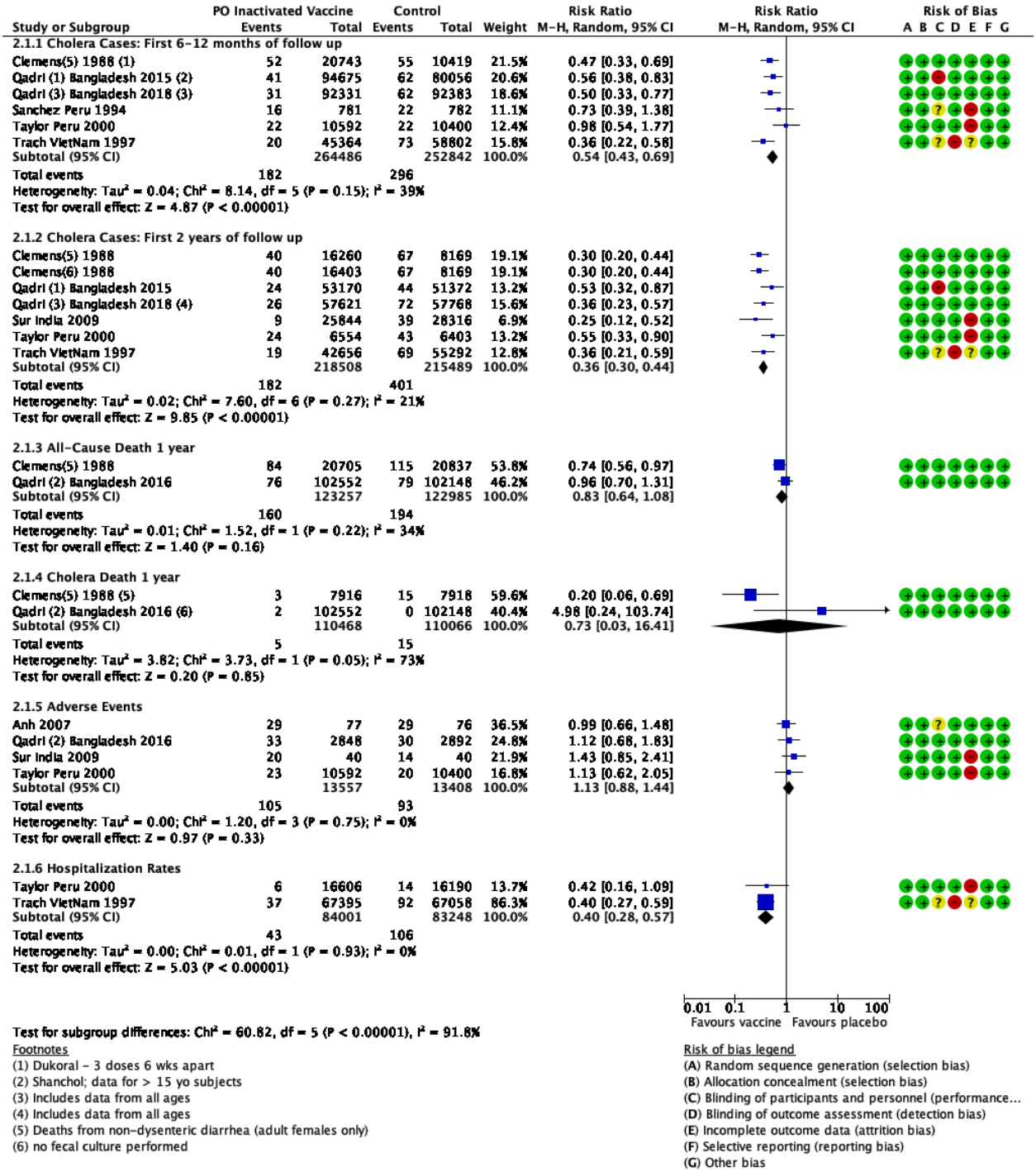


Figure 4. Outcome: Cholera Cases

Appendix 4.3. Live Oral Cholera Vaccine Versus Placebo

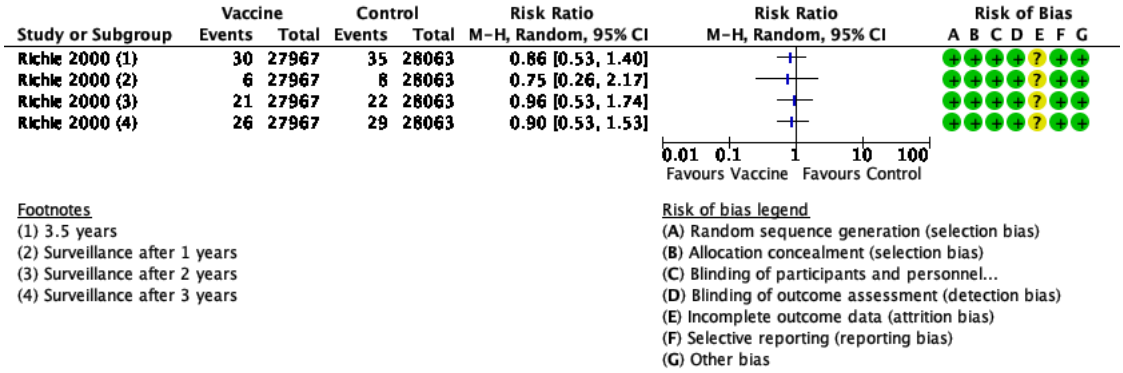


Figure 5. Outcome: Cholera cases

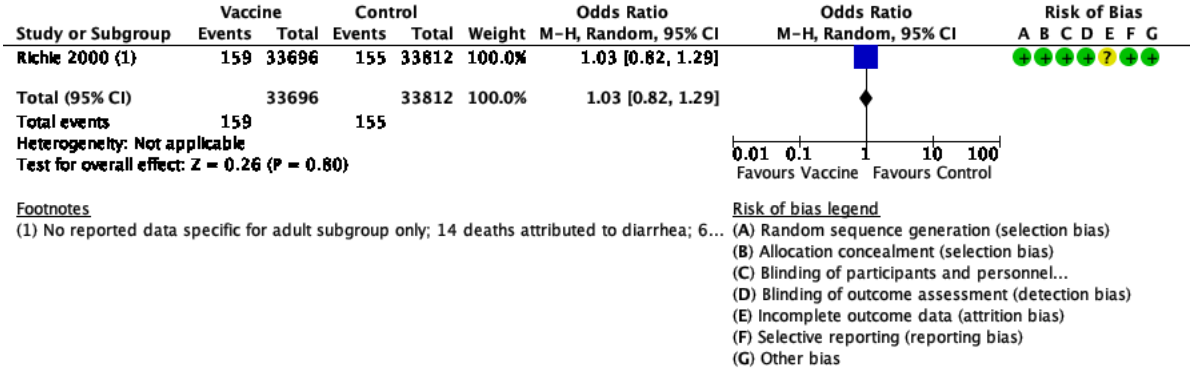


Figure 6. Outcome: All-cause deaths

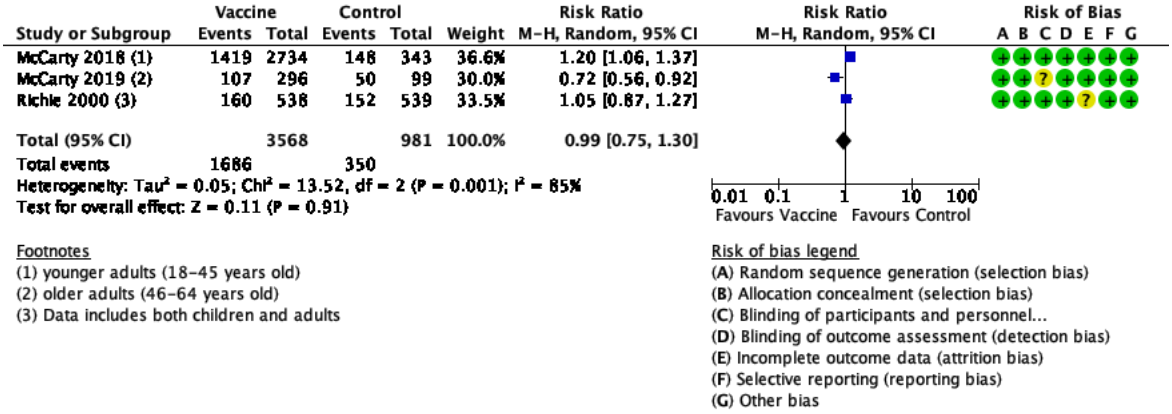


Figure 7. Outcome: Adverse effects

Haemophilus influenzae B Vaccine

Appendix 1. Evidence-to-Decision Summary

Burden	No (2)	Probably No	Probably Yes	Yes (3)	Varies (2)	Don't know
Benefits	Trivial (1)	Small (3)	Moderate (2)	Large	Varies (1)	Don't know
Harms	Large	Moderate	Small (7)	Trivial	Varies	Don't know
Certainty of evidence	Very Low	Low	Moderate	High	No included studies	
Balance of effects	Favors no vaccine	Probably favors no vaccine (1)	Equivalent (1)	Probably favors vaccine (1)	Favors vaccine (2)	Varies (2)	Don't know

Resources required	Large costs (3)	Moderate costs (4)	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence (resources)	Very Low	Low (1)	Moderate (4)		High (2)	No included studies	
Cost effectiveness	Favors no vaccine (1)	Probably favors no vaccine (1)	Does not favor either	Probably favors vaccine (2)	Favors vaccine	Varies (2)	No included studies (1)
Equity	Reduced	Probably reduced	Probably no impact (3)	Probably increased (1)	Increase	Varies (1)	Don't know (2)
Acceptability	No	Probably no (3)	Probably yes		Yes (1)	Varies	Don't know (3)
Feasibility	No (2)	Probably no	Probably yes (2)		Yes (1)	Varies	Don't know (2)

Recommendation 1: **Asymptomatic apparently healthy adults**	STRONG against (1)	WEAK against (3)	NO RECOMMENDATION (1)	WEAK in favor (2)	STRONG in favor

Appendix 2. GRADE Summary of Findings Table

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Post Hib-vaccination	Pre Hib-vaccination	Relative (95% CI)	Absolute (95% CI)		
SUBGROUP 1: HEALTHY ADULTS												
Total change in serum anti-PRP Ab (1 mo)												
2[1,3]	randomized trials	not serious	not serious	serious	serious	none	155	155	-	**MD 15.69 µg/mL higher** (13.2 lower to 44.58 higher)	Low	CRITICAL
Total change in serum anti-PRP Ab (2 mo)												
1[1]	randomized trials	not serious	not serious	serious	not serious	none	30	30	-	**MD 1.52 µg/mL higher** (1.31 higher to 1.74 higher)	Moderate	CRITICAL
Total change in serum anti-PRP Ab (12 mo)												
2[1,3]	randomized trials	not serious	not serious	serious	serious	none	155	155	-	**MD 4.95 µg/mL higher** (2.66 lower to 12.56 higher)	Low	CRITICAL
Total change in serum IgG (1 mo)												
2[1,3]	randomized trials	not serious	not serious	serious	very serious	none	110	110	-	**MD 33.29 µg/mL higher** (58.49 lower to 125.07 higher)	Very Low	CRITICAL

Appendix 3. Characteristics of Included Studies

Appendix 3.1. Asymptomatic, Apparently Healthy Adults

Author/ Year	Study design	Country	Number of patients	Population	Intervention Group(s)	Control	Outcomes	
							Efficacy	Safety
Granoff 1984	RCT	Missouri, USA	30	Healthy adults aged 22 to 28	PRP-D IM (n=15)	PRP IM (n=15)	Total concentrations of Hib anticapsular antibody, prevaccine, 1mo, 2mo and 12 month postvaccine IgG anti-PRP antibody serum dilution preventing bacteremia in at least 80% of rats	none
Lottenbach 2004	RCT	Missouri, USA	125	Healthy adults aged 64 to 92 with no unstable underlying medical condition	PRP conjugated to an outer-membrane protein complex of Neisseria meningitidis (PRP-OMP) IM (n=44) PRP conjugated to diphtheria toxoid (PRP-D) IM. (n=42)	PRP IM (n=39)	Total concentrations of Hib anticapsular antibody, prevaccine, 1mo and 12 month postvaccine Prevaccine and 1-month serum IgG1 and IgG2 anti-PRP antibody concentration Percentage of subjects having a twofold or greater IgG1 and IgG2 anticapsular response among vaccine groups Percentage of subjects with in vitro postvaccine Hib bactericidal activity (>50% colony-forming unit killing)	incidence of local reactions between vaccine groups
Toraño 2006	RCT	Cuba	80	Healthy males aged 20 to 35 years old and without history of chronic disease or vaccination with Hib vaccine.	Quimi-Hib vaccine: synthetic polyribosylribitol phosphate (sPRP) conjugated with tetanus toxoid IM (n = 60)	Vaxem-Hib: PRP coupled to the cross reacting mutant 197 (CRM197) carrier protein IM (n = 20)	IgA, IgG, and IgM anti-PRP antibodies in pre- and post-vaccination sera Proportion of volunteers who attained >4-fold increases in antibody titers Antibody specificity; relative antibody avidity	Proportion of local and systemic adverse events Clinical laboratory tests (hematological panel, hepatic, and renal functions)

Appendix 3.2. Asplenic or Functional Asplenia

Author/ Year	Study design	Country	Number of patients	Population	Intervention Group(s)	Control	Outcomes	
							Efficacy	Safety
Li Volti 1999	Quasi-experimental	Italy	102	Young individuals who are not seropositive for Hib-specific antibodies (anti-Hib) (mostly young adults)	PRP-tetanus Hib vaccine	--	Total antibodies against PRP Seroconversion rate Relative sizes (%) of lymphocyte subpopulations	Proportion of local and systemic adverse events
Molrine 1998	Quasi-experimental	Israel	51	Individuals who had undergone splenectomy	PRP Hib vaccine + bivalent meningococcal vaccine + 14-valent pneumococcal vaccine	--	IgG and IgM antibody concentrations to two pneumococcal capsular polysaccharides measured at 7-, 28-, and 180-days following immunization Total binding anti-Hib antibody was measured IgG, IgM, and IgA anti-Hib antibody concentrations	none

Appendix 3.3. Pregnant Women

Author/ Year	Study design	Country	Number of patients	Population	Intervention Group(s)	Control	Outcomes	
							Efficacy	Safety
Englund 1995	RCT	Texas, USA	54	Healthy women with a single fetus of estimated gestational ages of 32.5-36.0 weeks	PRP conjugated to an outer membrane protein complex of Neisseria meningitidis (PRP-OMP) IM (n=18) PRP conjugated to diphtheria toxoid (PRP-D) IM (n=19) PRP IM (n=13)	No vaccine (n=47)	Mean total PRP antibody Mean cord PRP antibody levels	Proportion of local and systemic adverse events
Glezen 1992	RCT	Texas, USA	213	Healthy pregnant women at 30-38 weeks of gestation	PRP IM (n=35)	Placebo (n=40)	levels of antibodies to PRP in cord sera	none
Mulholland 1996	RCT	Gambia	451	Pregnant women judged by clinic staff to be at 34 to 36 weeks' gestation by fundal height	PRP-T IM from mother in 3rd trimester to infant 1 mo after D3 (n=126) PRP-T IM in mother in 3rd trimester and IPV in infant until1 mo after D3 (n=125) MAC in mother in 3rd trimester and PRP-T IM in infant until1 mo after D3 (n=128)	---	Anti-PRP antibody measurements of maternal, cord, and infant blood.	Proportion of adverse effects on days 1 and 6 following vaccination for mothers and 1st 42 infants

Appendix 4. Forest Plots

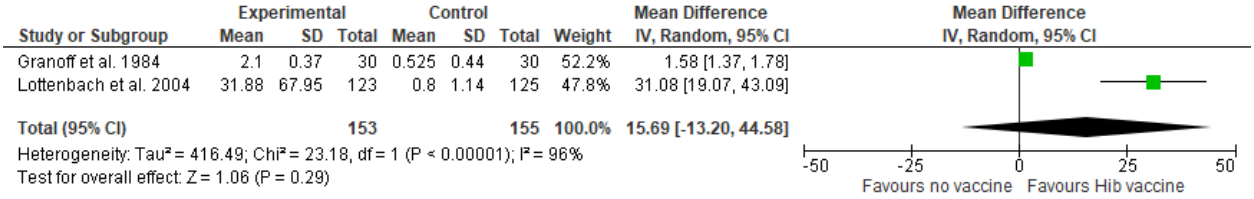


Figure 1. Total change in serum anti-PRP Antibody concentrations, 1-month post-vaccination

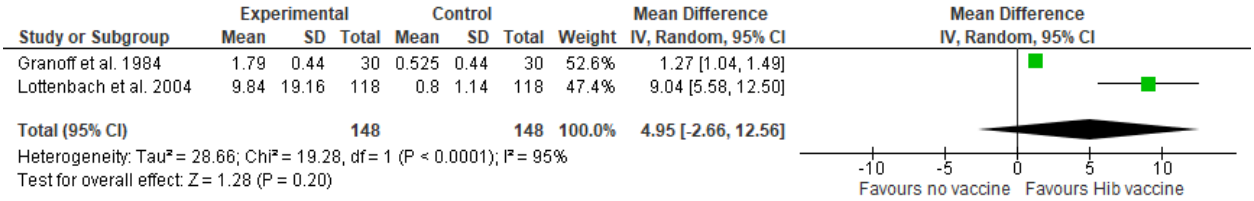


Figure 2. Total change in serum anti-PRP Antibody concentrations, 12-months post-vaccination

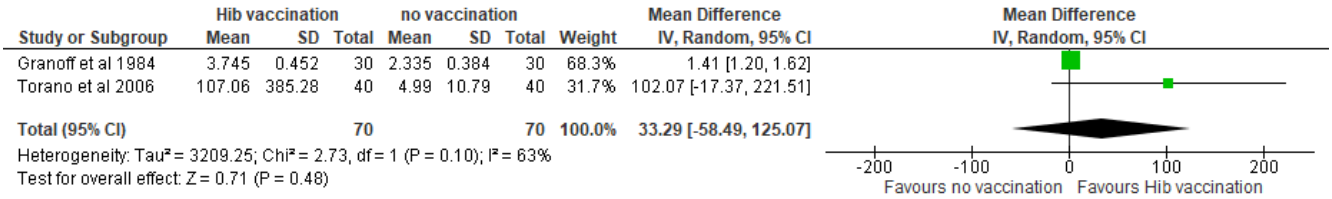
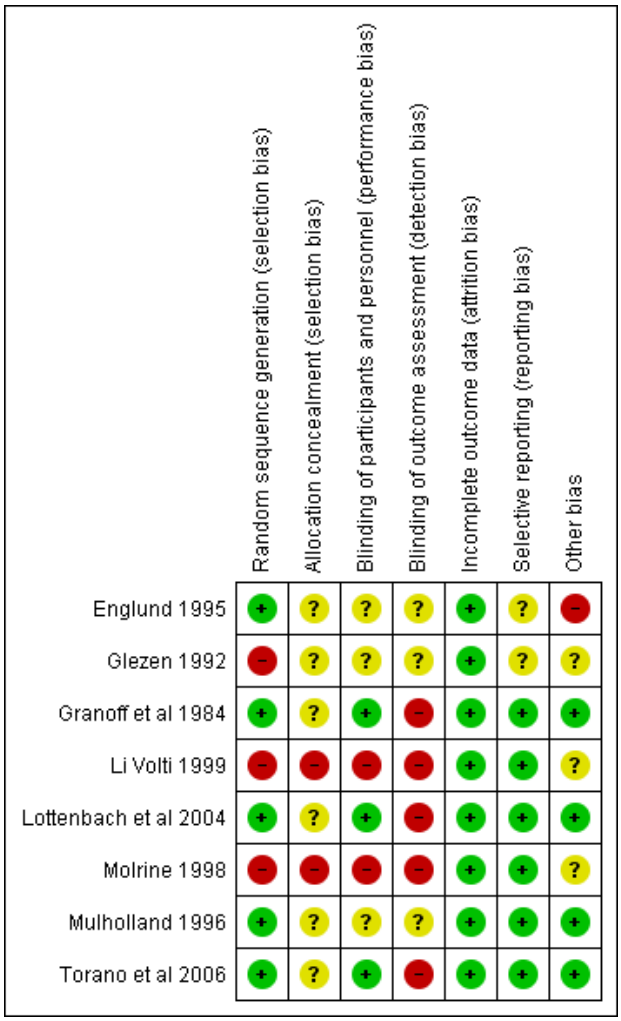


Figure 3. Total change in serum IgG Antibody concentrations, 1-month post-vaccination

Appendix 5. Risk of Bias Assessment of Included Studies



Hepatitis A Vaccine

Appendix 1. Evidence-to-Decision Summary

Burden	No (2)	Probably No	Probably Yes	Yes (2)	Varies (3)	Don't know (1)
Benefits	Trivial (1)	Small (4)	Moderate (1)	Large (2)	Varies	Don't know
Harms	Large (1)	Moderate	Small (4)	Trivial (3)	Varies	Don't know
Certainty of evidence	Very Low	Low (8)	Moderate	High	No included studies	
Balance of effects	Favors no vaccine	Probably favors no vaccine (1)	Equivalent (3)	Probably favors vaccine (3)	Favors vaccine (1)	Varies	Don't know

Resources required	Large costs (4)	Moderate costs (3)	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know (1)
Certainty of evidence (resources)	Very Low	Low (3)	Moderate (1)	High (4)	No included studies		
Cost effectiveness	Favors no vaccine (1)	Probably favors no vaccine	Does not favor either (1)	Probably favors vaccine (2)	Favors vaccine (1)	Varies (2)	No included studies (1)
Equity	Reduced (1)	Probably reduced	Probably no impact (2)	Probably increased	Increased	Varies (1)	Don't know (4)
Acceptability	No	Probably no (1)	Probably yes (4)	Yes	Varies (3)	Don't know	
Feasibility	No (1)	Probably no (3)	Probably yes (4)	Yes	Varies	Don't know	
Values	Important variability (2)	Possibly important variability (4)	Probably no important variability (2)	No important variability			

Recommendation 1: **Asymptomatic apparently healthy adults**	STRONG against	WEAK against (1)	NO RECOMMENDATION (1)	WEAK in favor (6)	STRONG in favor (1)

Appendix 2. GRADE Summary of Findings Table

GRADE Table 2.1. Healthy adults
(11 RCTs, n = **825,937** low certainty of evidence)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HepA vaccine	Placebo	Relative (95% CI)	Absolute (95% CI)		
1-3 doses vs. placebo												
Incidence of hepatitis A												
9	randomised trials	serious[a]	not serious	serious[b]	not serious	none	31/375726 (0.0%)	505/356654 (0.1%)	**RR 0.09** (0.05 to 0.17)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	Low	CRITICAL
Lack of sero-protection												
2	randomised trials	serious[c]	not serious	serious[b]	not serious	none	2/362 (0.6%)	367/377 (97.3%)	**RR 0.01** (0.00 to 0.03)	**964 fewer per 1,000** (from 944 fewer to --)	Low	CRITICAL
Mild local adverse event												
3	randomised trials	not serious	not serious	serious[b]	serious[d]	none	89/780 (11.4%)	76/779 (9.8%)	**RR 1.21** (0.86 to 1.70)	**20 more per 1,000** (from 14 fewer to 68 more)	Low	CRITICAL
Mild systemic adverse events												
3	randomised trials	not serious	not serious	serious[b]	serious[d]	none	49/780 (6.3%)	51/779 (6.5%)	**RR 0.98** (0.68 to 1.41)	**1 fewer per 1,000** (from 21 fewer to 27 more)	Low	CRITICAL
All-cause mortality												
1	randomised trials	not serious	not serious	serious[b]	serious[e]	none	14/20028 (0.1%)	10/20091 (0.0%)	**RR 1.40** (0.62 to 3.16)	**0 fewer per 1,000** (from 0 fewer to 1 more)	Low	CRITICAL
2-dose vs. 3-dose series												
Immunogenicity												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HepA vaccine	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	26/26 (100.0%)	29/29 (100.0%)	**RR 1.00** (0.93 to 1.07)	**0 fewer per 1,000** (from 70 fewer to 70 more)	Low	CRITICAL
Adverse event: local symptom (pain)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	18/26 (69.2%)	17/29 (58.6%)	**RR 1.18** (0.79 to 1.76)	**106 more per 1,000** (from 123 fewer to 446 more)	Low	CRITICAL
Adverse event: local symptom (swelling)												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	0/26 (0.0%)	2/29 (6.9%)	**RR 0.22** (0.01 to 4.43)	**54 fewer per 1,000** (from 68 fewer to 237 more)	Low	CRITICAL
Adverse event: local symptom (soreness)												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	3/26 (11.5%)	4/29 (13.8%)	**RR 0.84** (0.21 to 3.39)	**22 fewer per 1,000** (from 109 fewer to 330 more)	Low	CRITICAL
Adverse event: local symptom (rash)												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	1/26 (3.8%)	3/29 (10.3%)	**RR 0.37** (0.04 to 3.36)	**65 fewer per 1,000** (from 99 fewer to 244 more)	Low	CRITICAL
Adverse event: local symptom (redness)												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	1/26 (3.8%)	3/29 (10.3%)	**RR 0.37** (0.04 to 3.36)	**65 fewer per 1,000** (from 99 fewer to 244 more)	Low	CRITICAL
Adverse event: general symptom (headache)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	3/26 (11.5%)	3/29 (10.3%)	**RR 1.12** (0.25 to 5.05)	**12 more per 1,000** (from 78 fewer to 419 more)	Low	CRITICAL
Adverse event: general symptom (fever)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HepA vaccine	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	1/26 (3.8%)	1/29 (3.4%)	**RR 1.12** (0.07 to 16.95)	**4 more per 1,000** (from 32 fewer to 550 more)	Low	CRITICAL
Adverse event: general symptom (fatigue)												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	2/26 (7.7%)	2/29 (6.9%)	**RR 1.12** (0.17 to 7.36)	**8 more per 1,000** (from 57 fewer to 439 more)	Low	CRITICAL
Adverse event: general symptom (dizziness)												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	1/26 (3.8%)	1/29 (3.4%)	**RR 1.12** (0.07 to 16.95)	**4 more per 1,000** (from 32 fewer to 550 more)	Low	CRITICAL
Adverse event: general symptom (nausea/vomiting)												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	1/26 (3.8%)	0/29 (0.0%)	**RR 3.33** (0.14 to 78.42)	**0 fewer per 1,000** (no change)	Low	CRITICAL
Adverse event: general symptom (diarrhea)												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	1/26 (3.8%)	0/29 (0.0%)	**RR 3.33** (0.14 to 78.42)	**0 fewer per 1,000** (no change)	Low	CRITICAL

CI: confidence interval; **RR:** risk ratio; Explanations: a) Six studies had high risk of bias due to non-blinding of participants and outcome assessors, unclear bias on dropouts, b) Population included children instead of adults, c) Population included children instead of adults, d) 1 study had high risk of bias due to non-blinding of outcome assessors and participants, e) Downgraded due to wide confidence interval, effect estimate crossing line of no effect

GRADE Table 2.2. High Risk Individuals (with exposure): Vaccine versus Placebo
(1 RCT, n = 146, very low certainty of evidence)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HAV	placebo	Relative (95% CI)	Absolute (95% CI)		
Incidence of hepatitis A												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	2/71 (2.8%)	10/75 (13.3%)	RR 0.21 (0.05 to 0.93)	**105 fewer per 1,000** (from 127 fewer to 9 fewer)	Very Low	CRITICAL
Serious adverse events												
1	randomized trials	serious[a]	not serious	serious[b]	serious[c]	none	0/71	0/71	Not estimated	-	Very Low	CRITICAL

CI: confidence interval; **RR:** risk ratio, Explanations: a) downgraded due to non-blinding of participants and outcome assessors b) downgraded due to indirectness, study population included both healthy children and adults c) downgraded due to wide confidence interval

GRADE Table 2.3. Patients Living with HIV
(3 RCTs, n = 412, moderate certainty of evidence)

Certainty assessment							Impact				Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations						
Seroconversion rate												
3	randomised trials	serious[a]	serious[b]	not serious	not serious	none	Launay (2008) on immunogenicity of 2-dose (0, 6) vs. 3-dose (0, 1, 6) series of Hepatitis A vaccine (Vagta): • No significant change in CD4+ counts and HIV-1 RNA levels • Seroconversion at 4 weeks after last dose in both groups (69.4% or 34/49 in 2-dose group; 82.6% or 38/46 in 3-dose group) Wallace et al. (2004) on seroconversion rates between HIV patients and healthy control subjects (Havrix): • HIV-infected subjects – no data available after being given placebo; 93.9% or 46/49 patients developed antibodies 1-month after 2-dose series (0, 6) • Healthy control subjects (72) – 100% developed antibodies Kemper (2003) on efficacy and safety of Hepatitis A vaccination as 2-dose series based on CD4+ count • 49% at 7 months, 52% at 9 months • No data on placebo recipients • Efficacy directly proportional to CD4+ count				Low	CRITICAL
Serious adverse events												
2	randomised trials	not serious	serious[b]	not serious	not serious	none	No reported serious adverse event.				Moderate	CRITICAL
Minor adverse events												
2	randomised trials	not serious	serious[b]	not serious	serious[c]	none	75/172 (43.6%)	28/138 (20.3%)	RR 1.89 (0.39 to 9.12)	**181 more per 1,000** (from 124 fewer to 1,000 more)	Low	CRITICAL

CI: confidence interval. Explanations: a) downgraded due to high risk of bias for incomplete reporting of data b) downgraded due to heterogeneity in groups, comparison, and outcomes b) Downgraded for heterogeneity in groups and comparison, I^2 = 95% c) Wide confidence interval

GRADE Table 2.4. Persons Experiencing Homelessness
(1 clinical trial, n = 201, very low certainty of evidence)

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Immunogenicity									
1	Observational study	serious[a]	not serious	serious[c]	not serious	none	56/57 (98.2%) participants who completed 2-dose had detectable antibodies	Very low	CRITICAL
Compliance									
1	Observational study	serious[a]	not serious	serious[c]	not serious	None	73/100 (73%) completed the 2-dose series within 18 months of the 1st dose	Very low	IMPORTANT

Explanations: a) downgraded due to high risk of bias associated with observational study design limitations (non-randomization, non-blinding of participants, high attrition rate (only 73% completed 2-dose schedule); b) downgraded due to indirectness with population (Australian setting)

Appendix 3. Characteristics of Included Studies

Author/Year	Study Design	Setting/Country	No, of Patients	Population	Intervention	Control/ Comparator	Outcomes
Subgroup 1: Healthy individuals: Vaccine vs, placebo (1 SR with 11 RCTs, n = 825,937, Low Certainty of evidence)							
Innis 1994	Double blinded RCT	Thailand	38,157	Children 1 to 16 years old	Inactivated HAV vaccine (Havrix, SmithKine Beecham 0,1,12 months)	Placebo/no vaccine	Clinical Hepatitis A Adverse events Immunogenicity
Jiang 1995	Cluster RCT	Liuzhou China	62,698	School aged children 0-18 yrs old	Live attenuated HAV vaccine (H2 TCID50 10, LA-1 TCID50 10 – 0 months)	No vaccine	Clinical Hepatitis A Adverse events
Jiang 2001	Non-blinded RCT	Shanghai China	1080	Healthy children 7-12 yrs old	Live attenuated HAV vaccine (LA-1 TCID50 10 – 0 months)	No vaccine	Clinical Hepatitis A Adverse events
Li 2000	Cluster RCT	Shanghai	564,442	Healthy primary and secondary school students	Live attenuated HAV vaccine (H2 TCID50 10, LA-1 TCID50 10 – 0 months)	No vaccine	Clinical Hepatitis A Immunogenicity
Luo 2004	Quasi-randomized study	China	30,040	1-12 years old	Live attenuated HAV vaccine (LA-1 TCID50 10 – 0 months)	No vaccine	Clinical Hepatitis A Adverse events
Mayorga Perez 2003	Double blinded RCT	Nicaruaga	274	1.5 to 6 years old	Inactivated HAV vaccine (Virosome – 0 months)	placebo	IgM-HAV positive, clinical hepatitis, immunogenicity
Meng 2000	Non blinded RCT	Hebei China	12,036	1 to 12 years old	Live attenuated HAV vaccine (H2 TCID50 10 – 0 months)	No vaccine	Clinical Hepatitis A Immunogenicity
Riedemann 1992	Double blinded RCT	Chile	260	6 to 15 years old	Inactivated HAV vaccine (Havrix, GSK at 0,1,6 months)	placebo	Clinical hepatitis Adverse events Immunogenicity
Wezberger 1992	Double blinded RCT	New York	519	Seronegative children 0,1,6 months	Inactivated HAV vaccine (Merck at 0,1,6 months)	placebo	Clinical hepatitis Adverse events Immunogenicity
Wu 1996	Quasi-randomized study	China	54,746	Elementary students	Live attenuated HAV vaccine	No vaccine	Clinical Hepatitis A Adverse events Immunnogenecity

Author/Year	Study Design	Setting/Country	No, of Patients	Population	Intervention	Control/ Comparator	Outcomes
					(H2 TCID50 10, LA-1 TCID50 10 – 0 months)		
Yuan 1995	Cluster RCT	China	Total initially recruited unclear Vaccine group: 29,721 Unvaccinated: 31,964	Factory workers and primary students	Live attenuated HAV vaccine (LA-1 TCID50 10 – 0 months)	No vaccine	Clinical Hepatitis A Adverse events Immunnogenecity
Subgroup 2: High risk individuals (with exposure): Vaccine vs, placebo (1 RCT, n = 146, Very Low CoE)							
Saglioca 1999	Non blinded RCT	Naples, Italy	N = 146 75 vaccinated 71 unvaccinated	Healthy patients with an index case in the household < 15y: 58 > 15y: 88	Hepatitis A vaccine (1 dose)	No vaccine	Secondary HAV infection Serious adverse events
Subgroup 3: Two- versus Three- dose Regimen (1 RCT, n = 55, Low CoE)							
Lu 1999	RCT	Taiwan	N = 55 Group 1 - 26 Group 2 - 29	Healthy adult volunteers 20-26 years old with negative anti-HAV and no history of travel to hepatitis A endemic country	Group 1 – Hepatitis A vaccine 2-dose series (0, 24 weeks)	Group 2 – 3-dose series (0, 2, 24 weeks)	Immunogenicity Adverse effects
Subgroup 4: Patients Living with HIV (3 RCTs, n = 412, Moderate CoE)							
Launay 2008	Double blind RCT – multi center	France	N = 99	18-55 years old Mean: 38.8 years	HAVRIX, 2 doses 24 weeks apart	HAVRIX, 3 doses, weeks 0, 4, 24	GMT‡, mIU/mL: 138.2, 2-dose vs. 323.5, 3-dose group at 28 weeks No significant changes in CD4+ T-cell counts or plasma HIV-1 RNA levels during 28-week follow-up. Serious AE: There were no serious adverse events associated with the vaccine.

Author/Year	Study Design	Setting/Country	No, of Patients	Population	Intervention	Control/ Comparator	Outcomes
Wallace 2004	Double blind RCT – Single center	USA	N = 180 (90 HIV+; 90 HIV-)	21-45 years old Mean: 32.6 years HAV-seronegative Stratified by CD4 cell count (< 300, > 300 cells/mm^3)	VAQTA, 2 doses, week 0 and 24	Placebo	Seropositivity rates at 4 wks after 1st dose GMT‡, mIU/mL: 517 subjects with CD4+ <300 cells/mm3; 1959 subjects with ≥300 cells/mm3 Mild AE: Local reaction at injection site in 57% of VAQTA group and 60% of placebo group. Systemic adverse events (predominantly self-limited headache and fever) were more common among PWHIV who received VAQTA (37%) than among PWHIV who received placebo (23%). Only 3 subjects experienced clinically significant adverse events within 2 weeks after receipt of either vaccine dose. Only 1 of these 3 events (a severe headache) was thought to be vaccine-associated. There were no significant changes in complete blood counts or the results of liver function tests in any group at any point in this study. Serious AE: No adverse effect on either HIV viral load or CD4+ cell count found.
Kemper 2003	Double blind RCT – multicenter	USA	N = 133	22-65 years old Mean: 38 years HAV-seronegative HIV-positive on stable ART or no therapy for at least 1 mo Stratified by CD4 count (<200, 200-499, >500)	HAVRIX (1440 ELISA), 2 doses, 6 months apart n=68	Placebo, 2 doses, 6 months apart n=65	Protective antibody response to vaccination significantly associated with CD4+ cell counts ≥200 cells/mm3 Mild AE: Minor injection site soreness: 35% of vaccine doses administered versus 8% of placebo doses (P <0.01). Reported bacterial, viral, or fungal infections post-vaccination similar for

Author/Year	Study Design	Setting/Country	No, of Patients	Population	Intervention	Control/ Comparator	Outcomes
							patients receiving vaccine or placebo (24% vs. 26%, respectively; *P*>0.20). Within 4 days of vaccination, 1 subject (1.6%) in each group experienced severe headache; 1 subject (1.6%) in vaccine group experienced severe fatigue. Difference was non-significant, considered to be relatively mild AE. Authors concluded that the vaccine was well-tolerated in this population.
Subgroup 5: Persons experiencing Homelessness (1 clinical trial, n=201, Very Low CoE							
Poulos et al., 2010	Prospective cohort study	Sydney, Australia	N = 100	18-72 years old Mean: 42 years	Hepatitis A vaccine (Havrix) with interval of first and second dose of 193 days (IQR 182-238)	None	Compliance to vaccination Seroconverstion Outbreak was controlled No mention of the reduction of cases or % of hepatitis A cases after vaccination. *No information on AE however, with documented withdrawals: 1 developed a medical condition, 1 died due to causes unrelated to the study, 1 client withdrawn as a precautionary measure after an event post-vaccination.

Appendix 4. Forest Plots

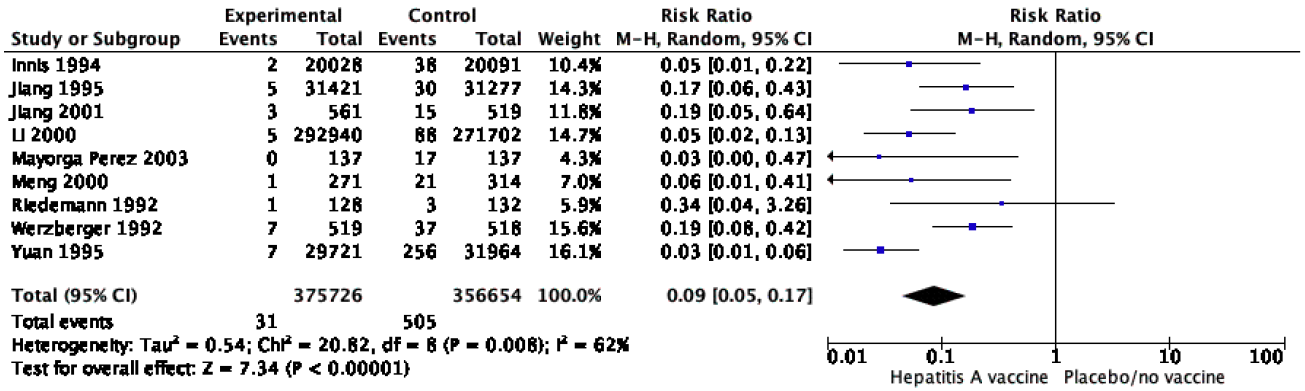


Figure 1. Outcome: Clinical Hepatitis A, Intervention: All vaccine types

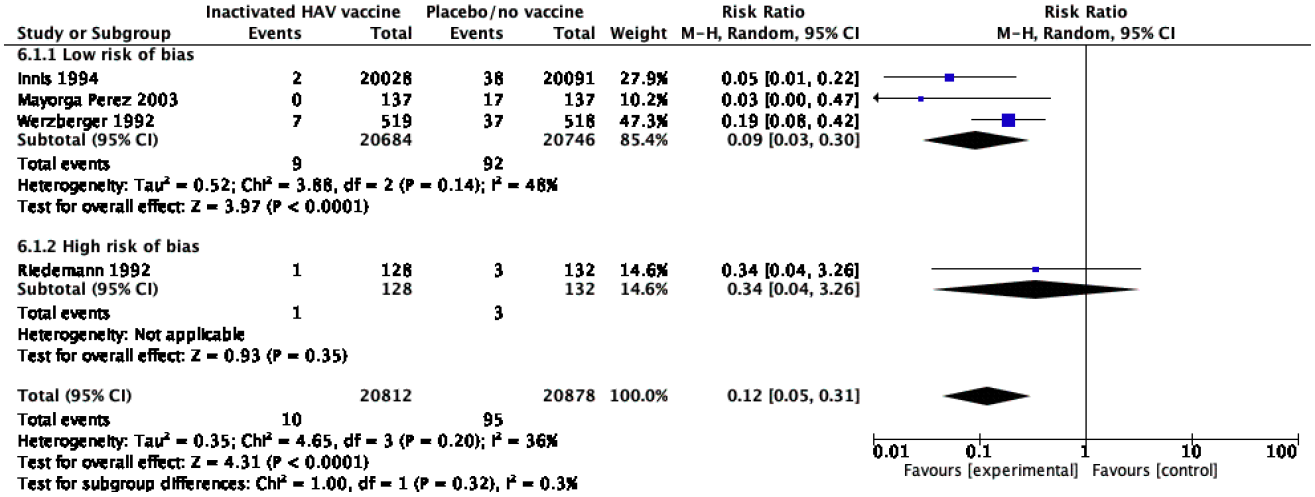


Figure 2. Outcome: Clinical Hepatitis A; Intervention: Inactivated HAV vaccine

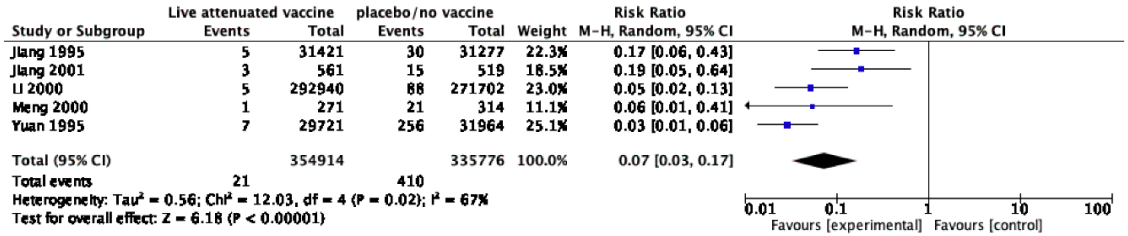


Figure 3. Outcome: Clinical Hepatitis A; Intervention: Live attenuated HAV vaccine

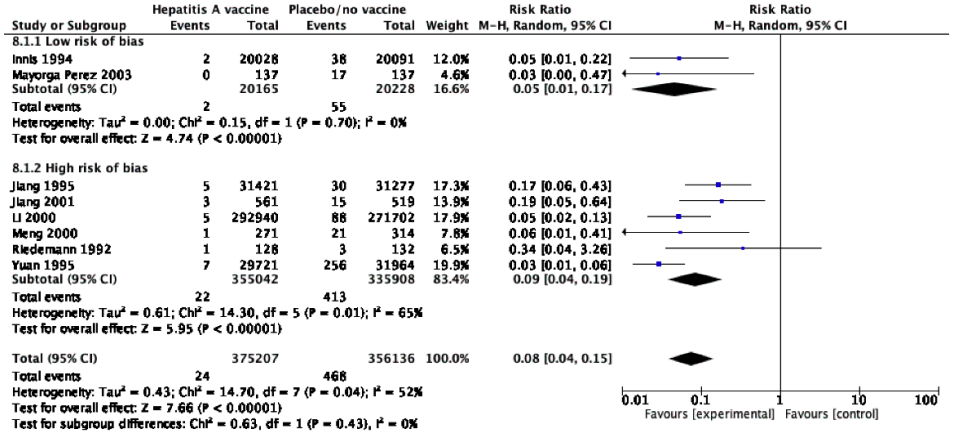


Figure 4. Outcome: Hepatitis A vaccine in high endemicity

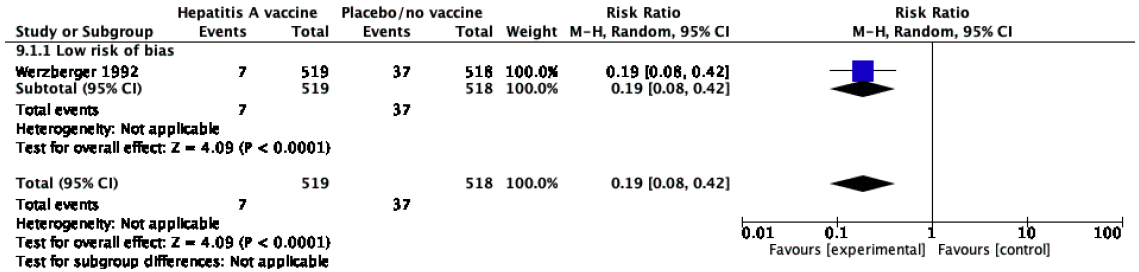


Figure 5. Outcome: Hepatitis A vaccine in low endemicity

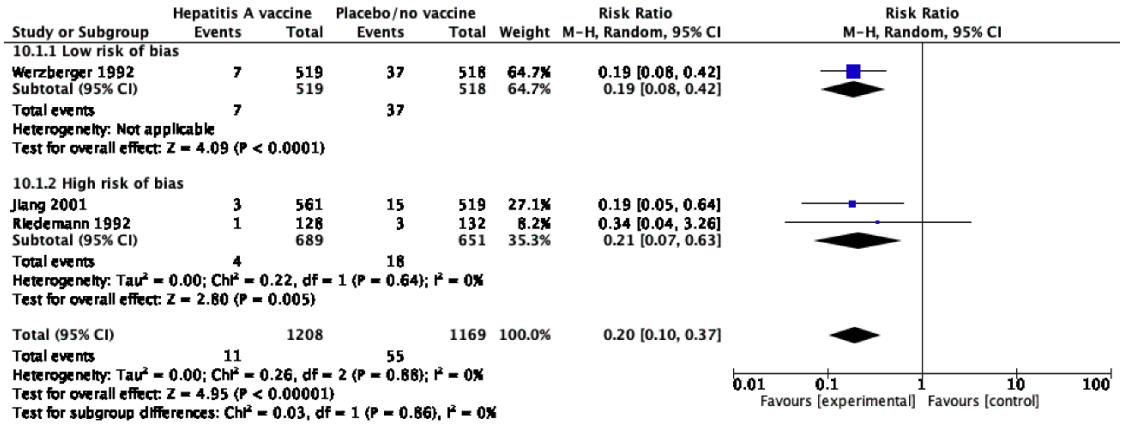


Figure 6. Outcome: Clinical Hepatitis A after 1 to 12 months follow-up

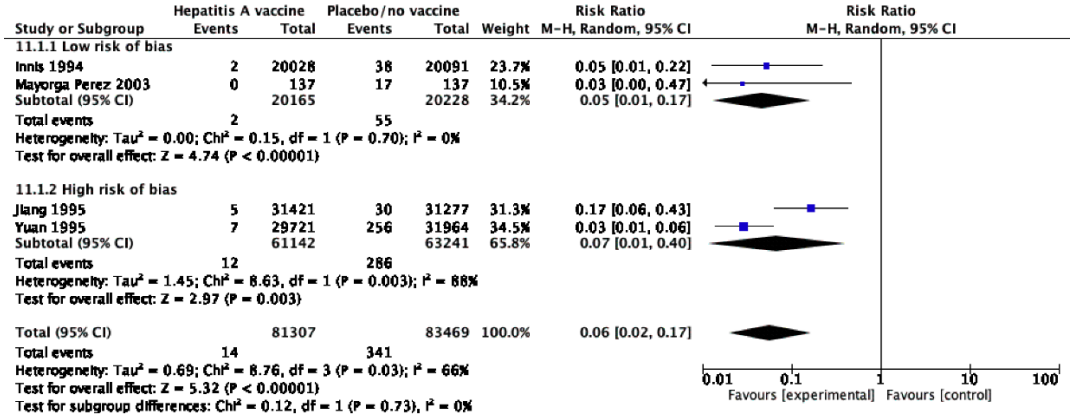


Figure 7. Outcome: Clinical Hepatitis A after 13 to 24 months follow-up

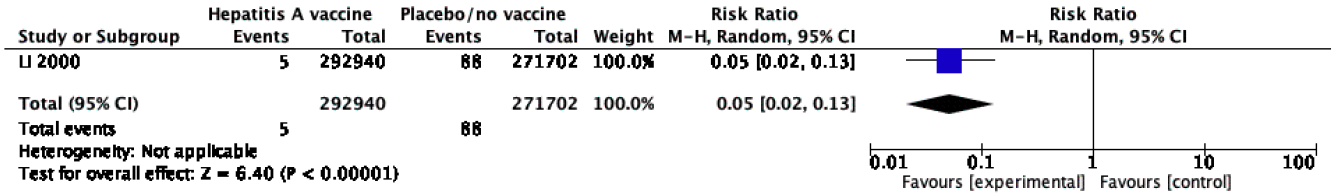


Figure 8. Outcome: Clinical Hepatitis A after 25 to 36 months follow-up

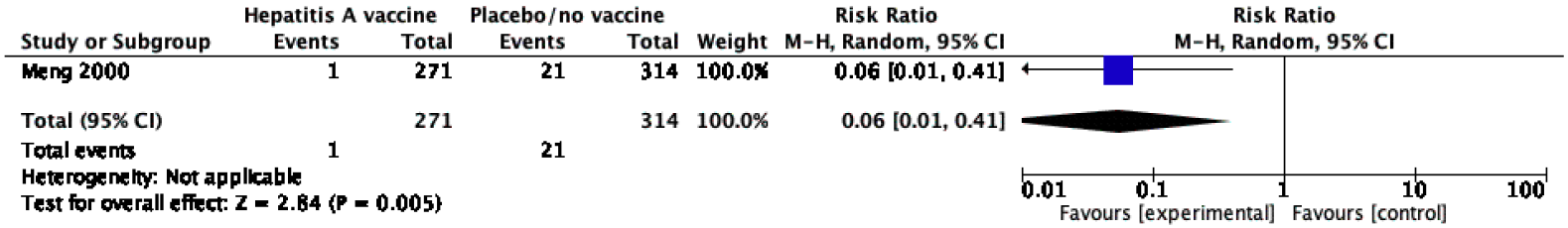


Figure 9. Outcome: Clinical Hepatitis A after 49 to 60 months follow-up

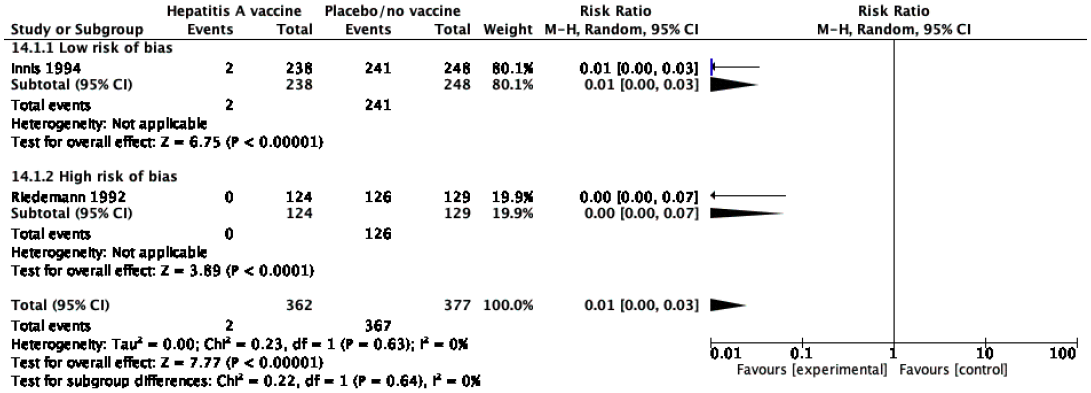


Figure 10. Outcome: Lack of sero-protection

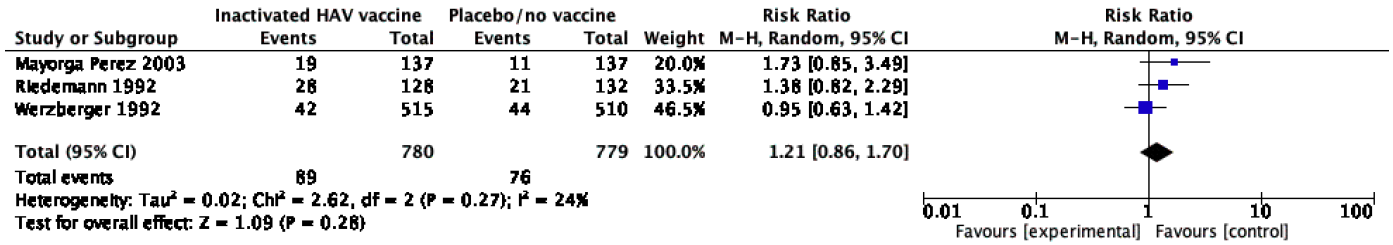


Figure 11. Outcome: Non serious local adverse events

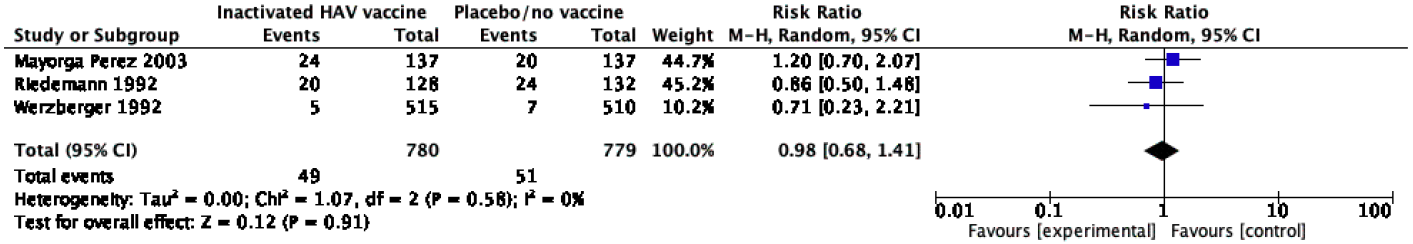


Figure 12. Outcome: Non-serious systemic adverse events

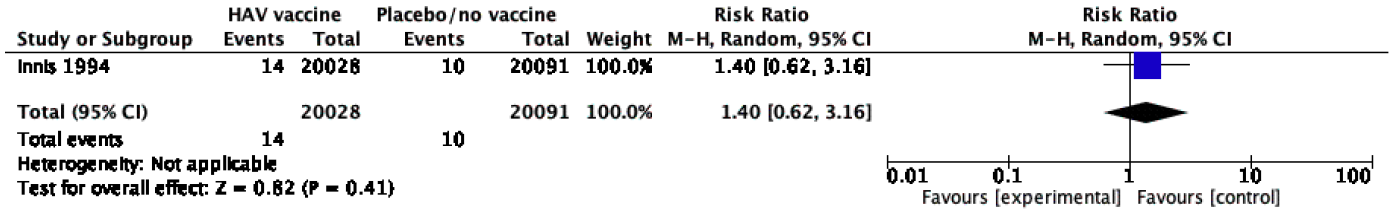
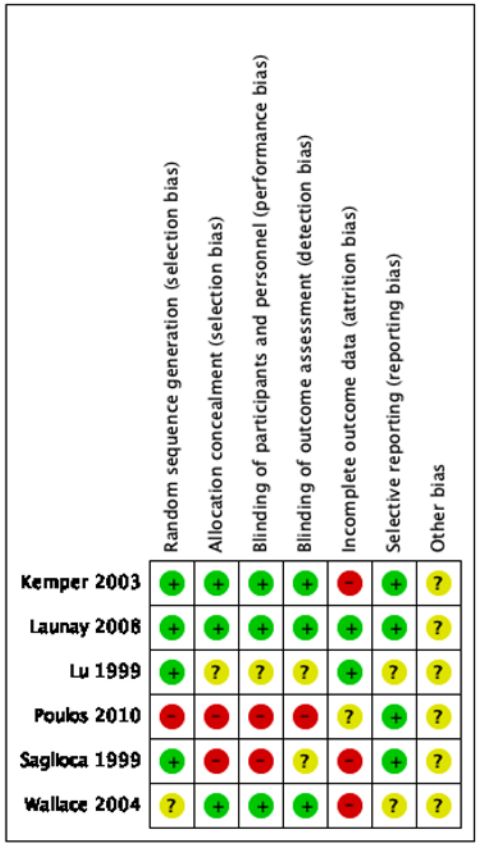
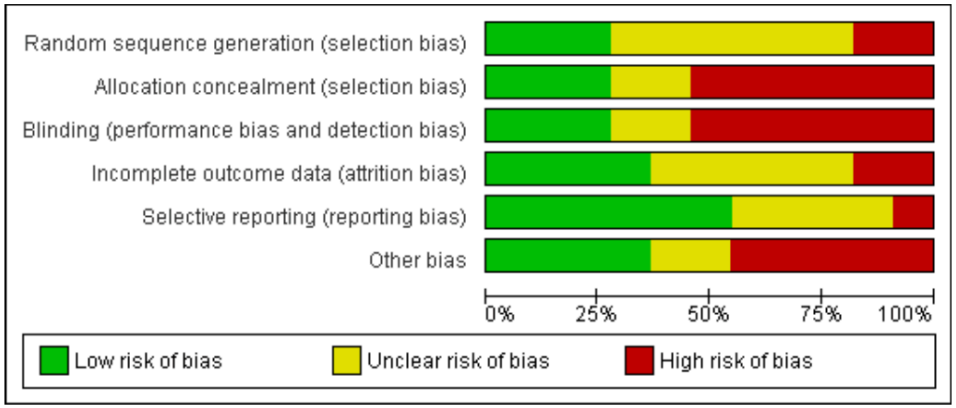


Figure 13. Outcome: All-cause mortality

Appendix 5. Risk of Bias Assessment of Included Studies




Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding (performance bias and detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

Appendix 6. Summary of Sensitivity Analysis by Irving (2012) Systematic Review

Outcome	No. of studies (participants)	Effect Size RR [95% CI]	Interpretation	Certainty of Evidence
Clinical Hepatitis A				
1. All vaccine types	9 (732,380)	0.09 [0.05, 0.17]	Benefit	Low
1.1 Low risk of bias	3 (41,430)	0.09 [0.03, 0.30]	Benefit	
1.2 High risk of bias	6 (690,950)	0.09 [0.04, 0.19]	Benefit	
2. Inactivated HAV vaccines	4 (41,690)	0.12 [0.05, 0.31]	Benefit	
2.1 Low risk of bias	3 (41,430)	0.09 [0.03, 0.30]	Benefit	
2.2 High risk of bias	1 (260)	0.34 [0.04, 3.26]	Inconclusive	
3. Live attenuated HAV*	5 (690,690)	0.07 [0.03, 0.17]	Benefit	
4. High endemicity	8 (731,343)	0.08 [0.04, 0.15]	Benefit	
4.1 Low risk of bias	2 (40,933)	0.05 [0.01, 0.17]	Benefit	
4.2 High risk of bias	6 (690,950)	0.09 [0.04, 0.19]	Benefit	
5. Low endemicity (low risk of bias)	1 (1,037)	0.19 [0.08. 0.42]	Benefit	
6. Follow up duration 1 to 12 months	3 (2,377)	0.20 [0.10, 0.37]	Benefit	
6.1 Low risk of bias	1 (1,037)	0.19 [0.08, 0.42]	Benefit	
6.2 High risk of bias	2 (1,340)	0.21 [0.07, 0.63]	Benefit	
7. Follow up duration 13 to 24 months	4 (164,776)	0.06 [0.02, 0.17]	Benefit	
7.1 Low risk of bias	2 (40,393)	0.05 [0.01, 0.17]	Benefit	
7.2 High risk of bias	2 (124,383)	0.07 [0.01, 0.40]	Benefit	
8. Follow up duration 25 to 36 months*	1 (564,642)	0.05 [0.02, 0.13]	Benefit	
9. Follow up duration 49 to 60 months*	1 (585)	0.06 [0.01, 0.41]	Benefit	
Lack of seroprotection				
1. All studies	2 (739)	0.01 [0.00, 0.03]	Benefit	Low
1.1 Low risk of bias	1 (486)	0.01 [0.00, 0.03]	Benefit	
1.2 High risk of bias	1 (253)	0.00 [0.00, 0.07]	Benefit	
Non serious local AE	3 (1559)	1.21 [0.86, 1.70]	Equivalent	Low
Non serious systemic AE	3 (1559)	0.98 [0.68, 1.41]	Equivalent	Low
All-cause mortality (low risk of bias)	1 (40,119)	1.40 [0.62, 3.16]	Inconclusive	Low

Appendix 7. AMSTAR 2

2012 Irving	Hepatitis A immunization in persons not previously exposed to hepatitis A (review)	Notes: AMSTAR 2: **HIGH** *No new studies after last search

1. Did the research questions and inclusion criteria for the review include the components of PICO?			
For Yes: √ **Population** √ **Intervention** √ **Comparator group** √ **Outcome**	Optional (recommended) ☐ Timeframe for follow-up	☐ **Yes** ☐ No	
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?			
For Yes: The authors state that they had a written protocol or guide that included ALL the following: √ **review question(s)** √ **a search strategy** √ **inclusion/exclusion criteria** √ **a risk of bias assessment**	For Partial Yes: As for partial yes, plus the protocol should be registered and should also have specified: ☐ a meta-analysis/synthesis plan, if appropriate, *and* ☐ a plan for investigating causes of heterogeneity ☐ justification for any deviations from the protocol	☐ ☐ **Yes** Partial Yes No ☐	
3. Did the review authors explain their selection of the study designs for inclusion in the review?			
For Yes, the review should satisfy ONE of the following: √ ***Explanation for* including only RCTs** ☐ OR *Explanation for* including only NRSI ☐ OR *Explanation for* including both RCTs and NRSI		☐ ☐ **Yes** No	
4. Did the review authors use a comprehensive literature search strategy?			
For Partial Yes (all the following):	For Yes, should also have (all the		

☐ searched at least 2 databases (relevant to research question) ☐ provided key word and/or search strategy ☐ justified publication restrictions	following): √ **searched the reference lists / bibliographies of included studies** √ **searched trial/study registries** √ **included/consulted content experts in the field** √ **where relevant, searched for grey literature**	☐ **Yes** ☐ ☐ Partial Yes No	
(e.g., language)	√ **conducted search within 24 months of completion of the review**		

5. Did the review authors perform study selection in duplicate?		
For Yes, either ONE of the following: ☐ **at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include** ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.		☐ **Yes** ☐ No

6. Did the review authors perform data extraction in duplicate?	
For Yes, either ONE of the following: √ **at least two reviewers achieved consensus on which data to extract from included studies** ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.	☐ **Yes** ☐ No

7. Did the review authors provide a list of excluded studies and justify the exclusions?		
For Partial Yes: ☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review	For Yes, must also have: √ **Justified the exclusion from the review of each potentially relevant study**	☐ **Yes** ☐ Partial Yes ☐ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following): ☐ described populations ☐ described interventions ☐ described comparators ☐ described outcomes ☐ described research designs	For Yes, should also have ALL the following: √ **described population in detail** √ **described intervention in detail (including doses where relevant)** √ **described comparator in detail (including doses where relevant)** √ **described study's setting** √ **timeframe for follow-up**	☐ **Yes** ☐ Partial Yes ☐ No
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?		
RCTs For Partial Yes, must have assessed RoB from ☐ unconcealed allocation, *and* ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	For Yes, must also have assessed RoB from: √ **allocation sequence that was not truly random, *and*** √ **selection of the reported result from among multiple measurements or analyses of a specified outcome**	√ **Yes** ☐ Partial Yes ☐ No ☐ Includes only NRSI
NRSI For Partial Yes, must have assessed RoB: ☐ from confounding, *and* ☐ from selection bias	For Yes, must also have assessed RoB: ☐ methods used to ascertain exposures and outcomes, *and* ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☐ Partial Yes ☐ No ☐ Includes only RCTs
10. Did the review authors report on the sources of funding for the studies included in the review?		
For Yes ☐ Must have reported on the sources of funding for individual studies included Reporting that the reviewers looked for this information study authors also qualifies		☐ Yes in the review. Note: ☐ **No** but it was not reported by
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?		

RCTs For Yes: √ **The authors justified combining the data in a meta-analysis** √ **AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.** √ **AND investigated the causes of any heterogeneity**	√ **Yes** ☐ No ☐ No meta-analysis conducted
For NRSI For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	☐ Yes ☐ No ☐ No meta-analysis conducted
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?	
For Yes: ☐ included only low risk of bias RCTs √ **OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect**.	√ **Yes** ☐ No ☐ No meta-analysis conducted
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	
For Yes: ☐ included only low risk of bias RCTs √ **OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results**	☐ **Yes** ☐ No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	

For Yes:

- ☐ There was no significant heterogeneity in the results
- √ **OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review**

☐ **Yes**
☐ 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?

For Yes:

- ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

☐ Yes
☐ **No**
☐ No meta-analysis conducted

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:

- ☐ **The authors reported no competing interests OR**
- ☐ The authors described their funding sources and how they managed potential conflicts of interest

☐ **Yes**
☐ No

Herpes Zoster Vaccine

Appendix 1. Evidence-to-Decision Summary

Burden	No (1)	Probably No	Probably Yes	Yes (3)	Varies	Don't know
Benefits	Trivial	Small (1)	Moderate (2)	Large (1)	Varies	Don't know
Harms	Large	Moderate	Small (4)	Trivial	Varies (1)	Don't know
Certainty of evidence	Very Low	Low (1)	Moderate (2)	High (1)	No included studies	
Balance of effects	Favors no vaccine	Probably favors no vaccine (1)	Equivalent	Probably favors vaccine (1)	Favors vaccine (2)	Varies	Don't know

Resources required	Large costs (4)	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence (resources)	Very Low (2)	Low (1)	Moderate (1)		High	No included studies	
Cost effectiveness	Favors no vaccine (1)	Probably favors no vaccine	Does not favor either	Probably favors vaccine (2)	Favors vaccine (1)	Varies (1)	Don't know/No Studies (1)
Equity	Reduced	Probably reduced	Probably no impact (1)	Probably increased (2)	Increased (1)	Varies	Don't know
Acceptability	No	Probably no (1)	Probably yes (2)		Yes	Varies	Don't know
Feasibility	No (1)	Probably no (1)	Probably yes (2)		Yes	Varies	Don't know
Values	Important variability	Possibly important variability (1)	Probably no important variability (2)		No important variability (1)	Don't know	

Recommendation 1: **Asymptomatic apparently healthy adults**	STRONG against	WEAK against	NO RECOMMENDATION	WEAK in favor (2)	STRONG in favor (1)

Appendix 2. GRADE Summary of Findings Table

Appendix 2.1. Live zoster vaccine versus placebo for preventing herpes zoster in older adults, Adapted from Gagliardi et al., 2019[11]
Patient or population: healthy older adults 60 years old and above
Setting: outpatients
Intervention: live zoster vaccine versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of evidence (GRADE)	Comments
	Assumed risk (Control)	Corresponding risk (Live zoster vaccine versus placebo)				
Incidence of herpes zoster, 3.1 years follow-up Clinical or laboratory criteria Follow-up: mean 3.1 years	**33 per 1000**	**16 per 1000 (14 to 19)**	RR 0.49 (0.43 to 0.56)	38,546 (1 study)	moderate[1]	NNTB=50
Participants with adverse events Clinical or laboratory criteria Follow-up: mean 3.1 years	**344 per 1000**	**584 per 1000 (553 to 615)**	RR 1.71 (1.38 to 2.11)	7119 (5 studies)	moderate[1]	NNTH 4.3
Death Clinical criteria Follow-up: mean 3.1 years	**32 per 1000**	**32 per 1000 (29 to 35)**	RR 1.01 (0.92 to 1.11)	50,820 (5 studies)	moderate[1]	
Participants with adverse events: 1 or more serious adverse events regardless of type of storage of the vaccine Clinical or laboratory criteria Follow-up: mean 3.1 years	**22 per 1000**	**23 per 1000 (21 to 26)**	RR 1.08 (0.95 to 1.21)	51,029 (6 studies)	moderate[1]	
Participants with adverse events - systemic adverse events Clinical or laboratory criteria Follow-up: mean 42 days	**227 per 1000**	**241 per 1000 (222 to 263)**	RR 1.24 (0.82 to 1.87)	7119 (5 studies)	moderate[1]	
Participants with adverse events - injection site adverse events Clinical criteria Follow-up: mean 7 days	**161 per 1000**	**480 per 1000 (441 to 522)**	RR 3.73 (1.93 to 7.21)	7040 (4 studies)	moderate[1]	NNTH 3.6
Dropouts Clinical or laboratory criteria Follow-up: mean 3.1 years	**48 per 1000**	**47 per 1000 (43 to 51)**	RR 0.99 (0.90 to 1.08)	38,916 (3 studies)	moderate[1]	

CI: confidence interval; **NNTB**: number needed to treat for an additional beneficial outcome; **NNTH**: number needed to treat for an additional harmful outcome; **RR**: risk ratio

Explanations
1. Most data came from a large study, and the quality of the evidence was downgraded because the trial did not describe the method used for random sequence generation.

Appendix 2.2. Recombinant zoster vaccine versus placebo for preventing herpes zoster in older adults, Adapted from Gagliardi et al., 2019[11]
Patient or population: healthy older adults 60 years old and above
Setting: outpatients
Intervention: recombinant zoster vaccine versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of evidence (GRADE)	Comments
	Assumed risk (Control)	Corresponding risk (Recombinant zoster vaccine versus placebo)				
Incidence of herpes zoster at least 3.2 years follow-up Clinical or laboratory criteria Follow-up: mean 3.2 years	**34 per 1000**	**3 per 1000 (2 to 4)**	RR 0.08 (0.03 to 0.23)	22,022 (2 studies)	moderate[1]	NNTB=33
Participants with adverse events - death Clinical criteria Follow-up: mean 3.2 years	**43 per 1000**	**41 per 1000 (36 to 45)**	RR 0.94 (0.84 to 1.04)	29,311 (2 studies)	moderate[1]	NNTH 4.3
Participants with adverse events - serious adverse events Clinical or laboratory criteria Follow-up: mean 3.2 years	**130 per 1000**	**126 per 1000 (118 to 133)**	RR 0.97 (0.91 to 1.03)	29,311 (2 studies)	moderate[1]	
Participants with adverse events - any systemic symptom Clinical criteria Follow-up: mean 30 days	**291 per 1000**	**648 per 1000 (617 to 680)**	RR 2.23 (2.12 to 2.34)	9762 (2 studies)	moderate[1]	NNTH=3.0
Participants with adverse events - potential immune-mediated disease Clinical or laboratory criteria Follow-up: mean 3.2 years	**13 per 1000**	**12 per 1000 (9 to 14)**	RR 0.88 (0.71 to 1.08)	29,311 (2 studies)	moderate[1]	
Participants with adverse events - any local symptom Clinical criteria Follow-up: mean 7 days	**117 per 1000**	**807 per 1000 (746 to 873)**	RR 6.89 (6.37 to 7.45)	9769 (2 studies)	moderate[1]	NNTH=1.5
Dropouts - did not receive second dose Clinical or laboratory criteria Follow-up: mean 3.2 years	**40 per 1000**	**50 per 1000 (50 to 50)**	RR 1.25 (1.13 to 1.39)	29,311 (2 studies)	moderate[1]	NNTH=100

CI: confidence interval; **NNTB**: number needed to treat for an additional beneficial outcome; **NNTH**: number needed to treat for an additional harmful outcome; **RR**: risk ratio

Explanations
1. Both studies had limitations in study design or execution (allocation concealment, attrition, or detection bias).

High-dose Inactivated Influenza Vaccine

Appendix 1. Evidence-to-Decision Summary

Burden	No	Probably No	Probably Yes	Yes (6)	Varies	Don't know
Benefits	Trivial	Small	Moderate (5)	Large (1)	Varies	Don't know
Harms	Large	Moderate (2)	Small (3)	Trivial (1)	Varies	Don't know
Certainty of evidence	Very Low (4)	Low (1)	Moderate (1)	High	No included studies	
Balance of effects	Favors no vaccine	Probably favors no vaccine	Equivalent	Probably favors vaccine (5)	Favors vaccine (1)	Varies	Don't know

Resources required	Large costs (5)	Moderate costs	Negligible costs and savings	Moderate savings (1)	Large savings	Varies	Don't know
Certainty of evidence (resources)	Very Low	Low (2)	Moderate (1)	High (1)	No included studies (2)		
Cost effectiveness	Favors no vaccine	Probably favors standard (1)	Does not favor either (1)	Probably favors high dose (2)	Favors high dose (2)	Varies	Don't know
Equity	Reduced	Probably reduced (2)	Probably no impact (1)	Probably increased (2)	Increased (1)	Varies	Don't know
Acceptability	No	Probably no (3)	Probably yes (1)	Yes (1)	Varies (1)	Don't know	
Feasibility	No	Probably no (2)	Probably yes (2)	Yes (1)	Varies (1)	Don't know	
Values	Important variability	Possibly important variability (3)	Probably no important variability (1)	No important variability (2)	Don't know		

Recommendation 1:	STRONG against	WEAK against (2)	NO RECOMMENDATION (1)	WEAK in favor	STRONG in favor (3)

Appendix 2. GRADE Summary of Findings Table

High-dose compared to standard-dose influenza vaccine for the elderly
Author(s): Carol Stephanie C. Tan-Lim, MD, MSc
Question: High-dose compared to standard-dose flu vaccine for the elderly
Setting: Community setting
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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose	Standard dose flu vaccine	Relative (95% CI)	Absolute (95% CI)		
Influenza												
2	randomized trials	not serious	not serious	not serious	not serious	none	242/22097 (1.1%)	309/19044 (1.6%)	**RR 0.76** (0.64 to 0.90)	**4 fewer per 1,000** (from 6 fewer to 2 fewer)	High	CRITICAL
All-cause mortality (follow up: mean 6 months)												
7	randomized trials	serious a	not serious	not serious	not serious	none	4920/52988 (9.3%)	4911/48304 (10.2%)	RR 0.99 (0.95 to 1.03)	1 fewer per 1,000 (from 5 fewer to 3 more)	Moderate	CRITICAL
All-cause hospitalization (follow up: mean 6 months)												
3	randomized trials	serious b	serious c	not serious	not serious	none	6978/44090 (15.8%)	7457/43858 (17.0%)	RR 0.93 (0.90 to 0.96)	12 fewer per 1,000 (from 17 fewer to 7 fewer)	Low	CRITICAL
Serious adverse events (follow up: mean 6 months)												
6	randomized trials	serious d	not serious	not serious	not serious	none	1909/25455 (7.5%)	1763/21036 (8.4%)	RR 0.92 (0.87 to 0.98)	7 fewer per 1,000 (from 11 fewer to 2 fewer)	Moderate	CRITICAL
Systemic reactogenic events												
4	randomized trials	serious e	serious c	not serious	serious f	none	1092/3474 (31.4%)	543/2165 (25.1%)	RR 1.19 (0.91 to 1.55)	48 more per 1,000 (from 23 fewer to 138 more)	Very Low	IMPORTANT
Local reactogenic events												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose	Standard dose flu vaccine	Relative (95% CI)	Absolute (95% CI)		
4	randomized trials	serious e	serious c	not serious	not serious	none	1251/3474 (36.0%)	538/2165 (24.8%)	RR 1.47 (1.26 to 1.71)	117 more per 1,000 (from 65 more to 176 more)	Low	NOT IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Downgraded one level due to serious risk of bias. Two studies had high risk of performance bias and unclear risk of selection bias. One study had unclear risk of selection, performance, and detection bias.

b. Downgraded one level due to serious risk of bias. Two studies had high risk of performance bias and unclear risk of selection bias.

c. Downgraded one level due to serious inconsistency (I^2>50%).

d. Downgraded one level due to serious risk of bias. One study had unclear risk of selection, performance, and detection bias. One study had unclear risk of selection bias. One study had unclear risk of selection, detection, and reporting bias.

e. Downgraded one level due to serious risk of bias. Four studies had unclear risk for selection bias. Three studies had unclear risk of detection bias. Two studies had unclear risk of performance and reporting bias.

f. Downgraded one level due to serious imprecision. Confidence interval is wide.

Appendix 3. Characteristics of Included Studies

Study	Setting	Population	Intervention	Control	Outcome	Secondary Study	Outcome
Diaz Granados 2013 (6)	USA	Elderly medically stable	IIV3 HD	IIV3 SD	Influenza, mortality, serious adverse events	-	-
Diaz Granados 2014 (7)	USA, Canada	Elderly medically stable	IIV3 HD	IIV3 SD	Influenza, mortality, serious adverse events	Diaz Granados 2015a [18]	Hospitalization
						Diaz Granados 2015b [19]	Influenza (stratified by age, comorbidity and frailty)
						Diaz Granados 2016 [20]	Influenza (stratified by previous vaccination type)
Keitel 2006 (8)	USA	Elderly medically stable	IIV3 HD	IIV3 SD	Serious adverse events	-	-
Couch 2007 (9)	USA	Elderly medically stable	IIV3 HD	IIV3 SD	Systemic and local reactogenic events	-	-
Falsey 2009 (10)	USA	Elderly medically stable	IIV3 HD	IIV3 SD	Serious adverse events, mortality, systemic and local reactogenic events	-	-
Tsang 2014 (11)	USA	Elderly medically stable	IIV3 HD	IIV3 SD	Serious adverse event, systemic and local reactogenic events	-	-
Nace 2015 (12)	USA	Frail elderly	IIV3 HD	IIV3 SD	Mortality	-	-
Gravenstein 2017 (13)	USA	Nursing home residents	IIV3 HD	IIV3 SD	Hospitalization, mortality	Saade 2018 [21]	Hospitalization for acute cardiovascular event
Gravenstein 2018 (14)	USA	Nursing home residents	IIV3 HD	IIV3 SD	Hospitalization, mortality	-	-
Cowling 2020 (15)	Hong Kong	Elderly medically stable	IIV3 HD	IIV4 SD	Adverse events	-	-
Sanchez 2020 (16)	Japan	Elderly	IIV4 HD	IIV4 SD	Mortality, serious adverse events	-	-
Schmader 2021 (17)	USA	Elderly	IIV3 HD	aIIV3 SD	Serious adverse event, systemic and local reactogenic events	-	-

Appendix 4. Forest Plots

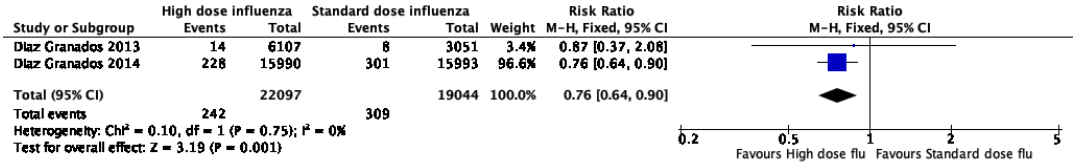

Figure 1. Effect of high-dose influenza vaccine on laboratory-confirmed influenza

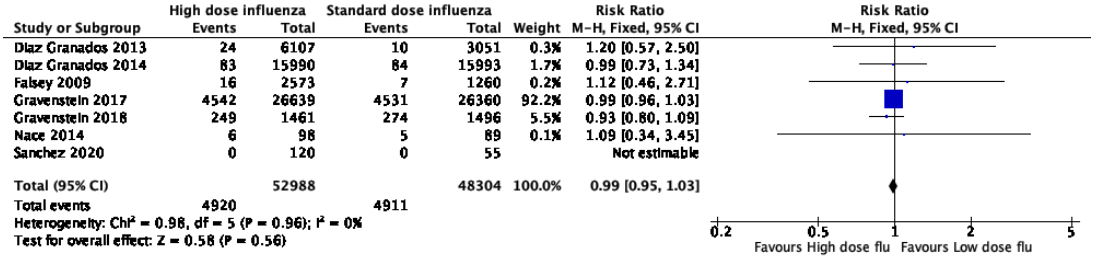

Figure 2. Effect of high-dose influenza vaccine on mortality

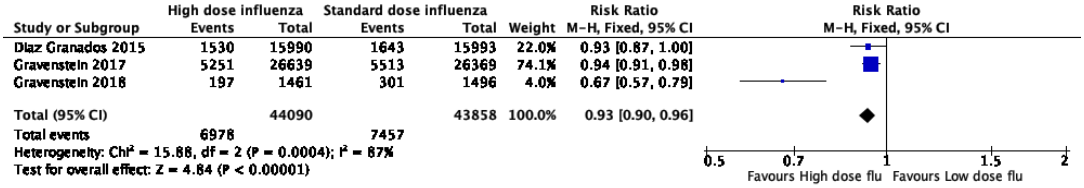

Figure 3. Effect of high-dose influenza vaccine on all-cause hospitalization

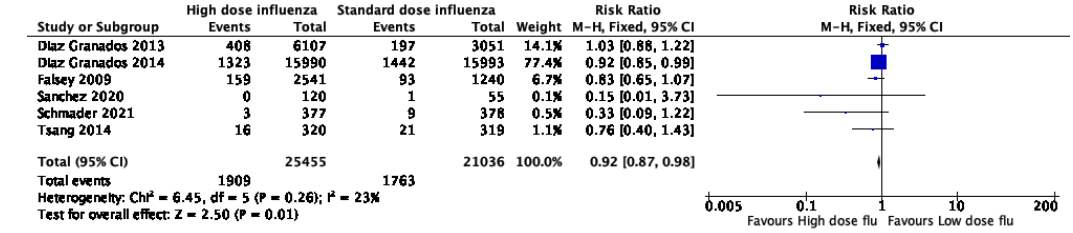

Figure 4. Effect of high-dose influenza vaccine on serious adverse events

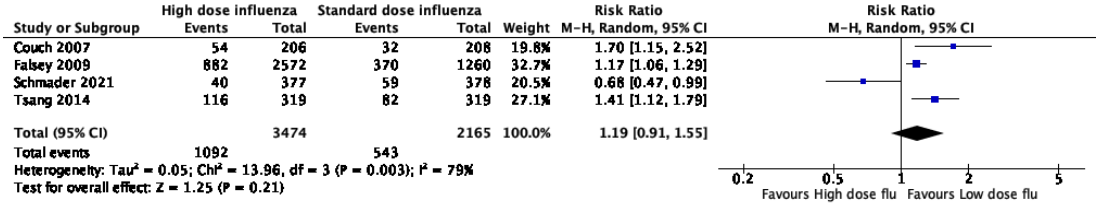

Figure 5. Effect of high-dose influenza vaccine on systemic reactogenic events (combined endpoint)

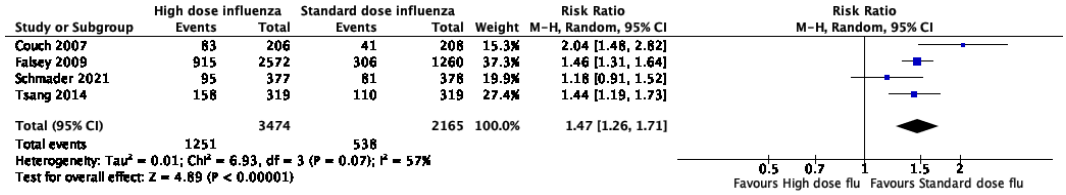

Figure 6. Effect of high-dose influenza vaccine on local reactogenic events (combined endpoint)

Appendix 5. Cost-Effectiveness Studies

	Author	Year	Country	Population	Intervention	Control	Cost-effective? (Y/N)	Reference
1	**Chit et al.**	2015	USA	≥65 years old without moderate or severe illness	High-dose vaccine	Standard-dose vaccine	**Yes**	(23)
2	**Chit et al.**	2015	USA	≥65 years old	High-dose vaccine	Standard-dose vaccine	**Yes**	(24)
3	**Becker et al.**	2016	Canada	≥65 years old without moderate or severe illness	High-dose vaccine	Standard-dose vaccine	**Yes**	(25)
4	**Raviotta et al.**	2016	USA	≥65 years old	High-dose vaccine	Standard-dose vaccine	**Yes**	(26)
5	**France et al.**	2018	USA	≥65 years old	High-dose vaccine	Standard-dose vaccine	**Yes**	(27)
6	**Shireman et al.**	2019	USA	Nursing home residents ≥65 years old	High-dose vaccine	Standard-dose vaccine	**Yes**	(28)
7	**Van Aalst et al.**	2019	USA	Veterans ≥65 years old with ≥1 inpatient or outpatient consult in the previous year	High-dose vaccine	Standard-dose vaccine	**Yes**	(29)
8	**Largeron et al.**	2018	Australia	≥65 years old	High-dose vaccine	Standard-dose vaccine	**Yes**	(30)

Human Papillomavirus Vaccine

Appendix 1. Evidence-to-Decision Summary

Burden	No (1)	Probably No	Probably Yes	Yes (4)	Varies	Don't know (1)
Benefits	Trivial (1)	Small (2)	Moderate (3)	Large	Varies	Don't know
Harms	Large	Moderate (2)	Small (2)	Trivial (3)	Varies (1)	Don't know
Certainty of evidence	Very Low	Low (5)	Moderate (1)	High	No included studies (1)	
Balance of effects	Favors no vaccine	Probably favors no vaccine	Equivalent/Does not favor either (2)	Probably favors vaccine (2)	Favors vaccine (2)	Varies	Don't know

Resources required	Large costs (5)	Moderate costs (1)	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence (resources)	Very Low	Low (2)	Moderate (2)		High (2)	No included studies (1)	
Cost effectiveness	Favors no vaccine (1)	Probably favors no vaccine (2)	Does not favor either	Probably favors vaccine	Favors vaccine	Varies (1)	Don't know/No studies (3)
Equity	Reduced	Probably reduced (2)	Probably no impact (1)	Probably increased (2)	Increased	Varies	Don't know
Acceptability	No (1)	Probably no (3)	Probably yes (1)		Yes	Varies (1)	Don't know
Feasibility	No (1)	Probably no (1)	Probably yes (2)		Yes	Varies (2)	Don't know
Values	Important variability (2)	Possibly important variability (4)	Probably no important variability		No important variability		

Recommendation 1: **Asymptomatic apparently healthy females aged 18-26 years who have not been vaccinated or have not yet completed the vaccine series**	STRONG against	WEAK against	NO RECOMMENDATION	WEAK in favor	STRONG in favor (6)
Recommendation 2: **Asymptomatic apparently healthy males aged 18-26 years who have not been vaccinated or have not yet completed the vaccine series**	STRONG against	WEAK against	NO RECOMMENDATION	WEAK in favor (5)	STRONG in favor
Recommendation 3: **Asymptomatic apparently healthy adults aged 27-45 years**	STRONG against	WEAK against	NO RECOMMENDATION	WEAK in favor (5)	STRONG in favor
Recommendation 4: **Pregnant patients**	STRONG against	WEAK against (6)	NO RECOMMENDATION	WEAK in favor	STRONG in favor
Recommendation 5: **Asymptomatic apparently healthy sex workers**	STRONG against	WEAK against	NO RECOMMENDATION	WEAK in favor	STRONG in favor

Appendix 2. GRADE Summary of Findings Table

Appendix 2.1. 4vHPV vaccine versus placebo on outcome-related HPV type 6, 11, 16, and 18 in apparently healthy female adults aged 16 to 26 years

Author(s): Burog, AILDB
Question: 4vHPV vaccine compared to placebo for apparently female healthy adults (outcome-related HPV type 6, 11, 16, and 18)
Setting: community
Bibliography:

1. Villa LL, Costa RL, Petta CA, Andrade RP, Ault KA, Giuliano AR, Wheeler CM, Koutsky LA, Malm C, Lehtinen M, Skjeldestad FE, Olsson SE, Steinwall M, Brown DR, Kurman RJ, Ronnett BM, Stoler MH, Ferenczy A, Harper DM, Tamms GM, Yu J, Lupinacci L, Railkar R, Taddeo FJ, Jansen KU, Esser MT, Sings HL, Saah AJ, Barr E. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. Lancet Oncol. 2005 May;6(5):271-8. doi: 10.1016/S1470-2045(05)70101-7. PMID: 15863374.
2. Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, Perez G, Brown DR, Koutsky LA, Tay EH, García P, Ault KA, Garland SM, Leodolter S, Olsson SE, Tang GW, Ferris DG, Paavonen J, Lehtinen M, Steben M, Bosch FX, Dillner J, Joura EA, Majewski S, Muñoz N, Myers ER, Villa LL, Taddeo FJ, Roberts C, Tadesse A, Bryan J, Maansson R, Lu S, Vuocolo S, Hesley TM, Saah A, Barr E, Haupt RM. A pooled analysis of continued prophylactic efficacy of quadrivalent human papillomavirus (Types 6/11/16/18) vaccine against high-grade cervical and external genital lesions. Cancer Prev Res (Phila). 2009 Oct;2(10):868-78. doi: 10.1158/1940-6207.CAPR-09-0031. Epub 2009 Sep 29. PMID: 19789295.
3. FUTURE I/II Study Group, Dillner J, Kjaer SK, Wheeler CM, Sigurdsson K, Iversen OE, Hernandez-Avila M, Perez G, Brown DR, Koutsky LA, Tay EH, García P, Ault KA, Garland SM, Leodolter S, Olsson SE, Tang GW, Ferris DG, Paavonen J, Lehtinen M, Steben M, Bosch FX, Joura EA, Majewski S, Muñoz N, Myers ER, Villa LL, Taddeo FJ, Roberts C, Tadesse A, Bryan JT, Maansson R, Lu S, Vuocolo S, Hesley TM, Barr E, Haupt R. Four year efficacy of prophylactic human papillomavirus quadrivalent vaccine against low grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts: randomised controlled trial. BMJ. 2010 Jul 20;341:c3493. doi: 10.1136/bmj.c3493. PMID: 20647284; PMCID: PMC2907480.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	4vHPV vaccine	placebo	Relative (95% CI)	Absolute (95% CI)		
6-month persistent infection (follow-up: mean 35 months)												
1[a]	randomised trials	not serious	not serious	serious[b]	not serious	none	6/276 (2.2%)	48/275 (17.5%)	**RRR 89** (70 to 97)	**-- per 1,000** (from -- to --)	Moderate	CRITICAL
CIN 2/3 or worse												
1[a,c,d]	randomised trials	not serious	not serious	serious[b]	not serious	none	4/276 (1.4%)	35/275 (12.7%)	**RRR 98.2** (93.3 to 99.8)	**-- per 1,000** (from -- to --)	Moderate	CRITICAL
VIN2/3, or VaIN 2/3 or worse												
3[a,c,d]	randomised trials	not serious	not serious	serious[b]	not serious	none	0/7900 (0.0%)	23/7902 (0.3%)	**RRR 100.0** (82.6 to 100.0)	**-- per 1,000** (from -- to --)	Moderate	CRITICAL
Anogenital warts												
2[a,d]	randomised trials	not serious	not serious	not serious	not serious	none	2/7665 (0.0%)	190/7669 (2.5%)	**RRR 100.0** (60.5 to 100.0)	**-- per 1,000** (from -- to --)	High	CRITICAL

CI: confidence interval
Explanations
a. Villa LL, et al. Lancet Oncol. 2005;6:271-8;
b. Downgraded due to indirectness of this outcome to the pre-specified in the review question (i.e., use of clinical surrogate outcome)
c. Kjær SK, et al. Cancer Prev Res. 2009;2:868-78
d. Dillner J, et al. BMJ. 2010;341:c3493

Appendix 2.2. 4vHPV vaccine versus placebo on outcome-related HPV type 6, 11, 16, and 18 in apparently healthy female adults aged 16 to 26 years

Author(s): Burog, AILDB
Question: 9vHPV vaccine compared to 4vHPV vaccine for apparently healthy female adults aged 16 to 26 years (outcome-related HPV type 31, 33, 45, 52, and 58)
Setting: community
Bibliography: Huh WK, Joura EA, Giuliano AR, Iversen OE, de Andrade RP, Ault KA, Bartholomew D, Cestero RM, Fedrizzi EN, Hirschberg AL, Mayrand MH, Ruiz-Sternberg AM, Stapleton JT, Wiley DJ, Ferenczy A, Kurman R, Ronnett BM, Stoler MH, Cuzick J, Garland SM, Kjaer SK, Bautista OM, Haupt R, Moeller E, Ritter M, Roberts CC, Shields C, Luxembourg A. Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16-26 years: a randomised, double-blind trial. Lancet. 2017 Nov 11;390(10108):2143-2159. doi: 10.1016/S0140-6736(17)31821-4. Epub 2017 Sep 5. PMID: 28886907.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	9vHPV vaccine	4vHPV vaccine	Relative (95% CI)	Absolute (95% CI)		
6-month persistent infection												
1[a]	randomised trials	not serious	not serious	serious[b]	not serious	none	41/5941 (0.7%)	946/5955 (15.9%)	**RRR 96.0** (94.6 to 97.1)	**-- per 1,000** (from -- to --)	Moderate	CRITICAL
CIN 2/3 or worse												
1[a]	randomised trials	not serious	not serious	serious[b]	not serious	none	1/5949 (0.0%)	35/5943 (0.6%)	**RRR 97.1** (83.5 to 99.9)	**-- per 1,000** (from -- to --)	Moderate	CRITICAL
CIN 2/3, VIN2/3, or ValN 2/3 or worse												
1[a]	randomised trials	not serious	not serious	serious[b]	not serious	none	0/6009 (0.0%)	3/6012 (0.0%)	**RRR 97.4** (93.3 to 99.4)	**-- per 1,000** (from -- to --)	Moderate	CRITICAL

CI: confidence interval
Explanations
a. Huh WK, et al. Lancet. 2017;390:2143-2159
b. Downgraded due to indirectness of this outcome to the pre-specified in the review question (i.e., use of clinical surrogate outcome)

Appendix 2.3. 4vHPV vaccine versus placebo on outcome-related HPV type 6, 11, 16, and 18 in apparently healthy male adults aged 16 to 26 years

Author(s): Burog, AILDB
Question: 4vHPV vaccine compared to placebo for apparently healthy male adults aged 16 to 26 years
Setting: community
Bibliography: 1. Giuliano AR, Palefsky JM, Goldstone S, Moreira ED Jr, Penny ME, Aranda C, Vardas E, Moi H, Jessen H, Hillman R, Chang YH, Ferris D, Rouleau D, Bryan J, Marshall JB, Vuocolo S, Barr E, Radley D, Haupt RM, Guris D. Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. N Engl J Med. 2011 Feb 3;364(5):401-11. doi: 10.1056/NEJMoa0909537. Erratum in: N Engl J Med. 2011 Apr 14;364(15):1481. PMID: 21288094; PMCID: PMC3495065. 2. Goldstone SE, Jessen H, Palefsky JM, Giuliano AR, Moreira ED Jr, Vardas E, Aranda C, Hillman RJ, Ferris DG, Coutlee F, Marshall JB, Vuocolo S, Haupt RM, Guris D, Garner E. Quadrivalent HPV vaccine efficacy against disease related to vaccine and non-vaccine HPV types in males. Vaccine. 2013 Aug 20;31(37):3849-55. doi: 10.1016/j.vaccine.2013.06.057. Epub 2013 Jul 2. PMID: 23831322.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	4vHPV vaccine	placebo	Relative (95% CI)	Absolute (95% CI)		
6-month persistent infection												
1[a]	randomised trials	not serious	not serious	serious	not serious	none	15/1390 (1.1%)	101/1400 (7.2%)	**RRR 85.6** (73.4 to 92.9)	**-- per 1,000** (from -- to --)	Moderate	CRITICAL
External genital lesion												
1[a]	randomised trials	not serious	not serious	serious[b]	not serious	none	3/1397 (0.2%)	31/1408 (2.2%)	**RRR 90.4** (69.2 to 98.1)	**-- per 1,000** (from -- to --)	Moderate	CRITICAL
Anogenital warts												
1[a]	randomised trials	not serious	not serious	not serious	not serious	none	3/1397 (0.2%)	28/1408 (2.0%)	**RRR 89.4** (65.5 to 97.9)	**-- per 1,000** (from -- to --)	High	CRITICAL
All PeIN lesions												
1[a]	randomised trials	not serious	not serious	serious[b]	very serious[c,d]	none	0/1397 (0.0%)	3/1408 (0.2%)	**RRR 100.0** (-141.1 to 100.0)	**-- per 1,000** (from -- to --)	Very low	CRITICAL
Penile, perianal, or perianal cancer												
1[a]	randomised trials	not serious	not serious	serious[e]	very serious[c,d]	none	0/1397 (0.0%)	0/1408 (0.0%)	not estimatable		Very low	CRITICAL
AIN (any grade) and anal cancer												
1[f]	randomised trials	not serious	not serious	not serious	not serious	none	2/129 (1.6%)	20/126 (15.9%)	**RRR 89.6** (57.2 to 98.8)	**-- per 1,000** (from -- to --)	High	CRITICAL

Explanations
a. Giuliano AR, Palefsky JM, Goldstone S, Moreira ED Jr, Penny ME, Aranda C, Vardas E, Moi H, Jessen H, Hillman R, Chang YH, Ferris D, Rouleau D, Bryan J, Marshall JB, Vuocolo S, Barr E, Radley D, Haupt RM, Guris D. Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. N Engl J Med. 2011 Feb 3;364(5):401-11. doi: 10.1056/NEJMoa0909537. Erratum in: N Engl J Med. 2011 Apr 14;364(15):1481. PMID: 21288094; PMCID: PMC3495065.
b. Downgraded due to indirectness of this outcome to the pre-specified in the review question (i.e., use of clinical surrogate outcome)
c. downgraded one level for imprecision due to low event rate
d. downgraded one level for imprecision due to very wide 95%CI or not estimable.
e. Downgraded for indirectness due to use of AIN2/3 or PeIN2/3 as surrogate markers for anal cancer or penile cancer
f. Goldstone SE, Jessen H, Palefsky JM, Giuliano AR, Moreira ED Jr, Vardas E, Aranda C, Hillman RJ, Ferris DG, Coutlee F, Marshall JB, Vuocolo S, Haupt RM, Guris D, Garner E. Quadrivalent HPV vaccine efficacy against disease related to vaccine and non-vaccine HPV types in males. Vaccine. 2013 Aug 20;31(37):3849-55. doi: 10.1016/j.vaccine.2013.06.057. Epub 2013 Jul 2. PMID: 23831322.

Appendix 2.4. 4vHPV vaccine versus placebo on adverse events in apparently healthy female adults aged 16 to 26 years

Author(s): Burog, AILDB
Question: 4vHPV vaccine compared to placebo for apparently healthy female adults aged 16 to 26 years
Setting: community
Bibliography: ArbynM, XuL, SimoensC, Martin-HirschPPL. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. Cochrane Database of Systematic Reviews 2018, Issue 5. Art. No.: CD009069. DOI:10.1002/14651858.CD009069.pub3.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	4vHPV vaccine	placebo	Relative (95% CI)	Absolute (95% CI)		
Local/injection site adverse events												
6[a]	randomised trials	not serious	not serious	not serious	not serious	none	4845/5842 (82.9%)	4188/5768 (72.6%)	**RR 1.14** (1.12 to 1.16)	**102 more per 1,000** (from 87 more to 116 more)	High	
Overall systemic event and general symptoms												
6[a]	randomised trials	not serious	not serious	not serious	not serious	none	3577/5880 (60.8%)	3531/5808 (60.8%)	**RR 1.01** (0.98 to 1.04)	**6 more per 1,000** (from 12 fewer to 24 more)	High	
Serious adverse events												
7[a]	randomised trials	not serious	not serious	not serious	not serious	none	154/11548 (1.3%)	187/11431 (1.6%)	**RR 0.81** (0.65 to 1.02)	**3 fewer per 1,000** (from 6 fewer to 0 fewer)	High	
Deaths												
7[a]	randomised trials	not serious	not serious	not serious	not serious	none	18/11379 (0.2%)	11/11286 (0.1%)	**RR 1.54** (0.73 to 3.23)	**1 more per 1,000** (from 0 fewer to 2 more)	High	

CI: confidence interval; **RR:** risk ratio
Explanations
a. ArbynM, XuL, SimoensC, Martin-HirschPPL. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. Cochrane Database of Systematic Reviews 2018, Issue 5. Art.No.: CD009069. DOI: 10.1002/14651858.CD009069.pub3

Appendix 2.5. 9vHPV vaccine versus 4vHPV vaccine on adverse events in apparently healthy female adults aged 16 to 26 years

Author(s): Burog, AILDB

Question: 9vHPV vaccine compared to 4vHPV vaccine for apparently healthy female adults aged 16 to 26 years

Setting: community

Bibliography: a. Huh WK, Joura EA, Giuliano AR, Iversen OE, de Andrade RP, Ault KA, Bartholomew D, Cestero RM, Fedrizzi EN, Hirschberg AL, Mayrand MH, Ruiz-Sternberg AM, Stapleton JT, Wiley DJ, Ferenczy A, Kurman R, Ronnett BM, Stoler MH, Cuzick J, Garland SM, Kjaer SK, Bautista OM, Haupt R, Moeller E, Ritter M, Roberts CC, Shields C, Luxembourg A. Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16-26 years: a randomised, double-blind trial. Lancet. 2017 Nov 11;390(10108):2143-2159. doi: 10.1016/S0140-6736(17)31821-4. Epub 2017 Sep 5. PMID: 28886907.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	9vHPV vaccine	4vHPV vaccine	Relative (95% CI)	Absolute (95% CI)		
Local/injection site adverse events												
1[a]	randomised trials	not serious	not serious	not serious	not serious	none	6961/7686 (90.6%)	6009/7078 (84.9%)	**RR 1.07** (1.05 to 1.08)	**59 more per 1,000** (from 42 more to 68 more)	High	
Overall systemic event and general symptoms												
1[a]	randomised trials	not serious	not serious	not serious	not serious	none	4268/7686 (55.5%)	3886/7078 (54.9%)	**RR 1.01** (0.98 to 1.04)	**5 more per 1,000** (from 11 fewer to 22 more)	High	
Serious adverse events												
1[a]	randomised trials	not serious	not serious	not serious	not serious	none	242/7686 (3.1%)	184/7078 (2.6%)	**OR 1.22** (1.00 to 1.48)	**6 more per 1,000** (from 0 fewer to 12 more)	High	
Deaths												
1[a]	randomised trials	not serious	not serious	not serious	not serious	none	6/7071 (0.1%)	5/7078 (0.1%)	**RR 1.20** (0.37 to 3.94)	**0 fewer per 1,000** (from 0 fewer to 2 more)	High	

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio

Explanations

a. Huh WK, Joura EA, Giuliano AR, Iversen OE, de Andrade RP, Ault KA, Bartholomew D, Cestero RM, Fedrizzi EN, Hirschberg AL, Mayrand MH, Ruiz-Sternberg AM, Stapleton JT, Wiley DJ, Ferenczy A, Kurman R, Ronnett BM, Stoler MH, Cuzick J, Garland SM, Kjaer SK, Bautista OM, Haupt R, Moeller E, Ritter M, Roberts CC, Shields C, Luxembourg A. Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16-26 years: a randomised, double-blind trial. Lancet. 2017 Nov 11;390(10108):2143-2159. doi: 10.1016/S0140-6736(17)31821-4. Epub 2017 Sep 5. PMID: 28886907

Appendix 2.6. 4vHPV vaccine versus placebo on adverse events in apparently healthy male adults aged 16 to 26 years

Author(s): Burog, AILDB
Question: 4vHPV vaccine compared to placebo for apparently healthy male adults aged 16 to 26 years (adverse events)
Setting: community
Bibliography: Giuliano AR, Palefsky JM, Goldstone S, Moreira ED Jr, Penny ME, Aranda C, Vardas E, Moi H, Jessen H, Hillman R, Chang YH, Ferris D, Rouleau D, Bryan J, Marshall JB, Vuocolo S, Barr E, Radley D, Haupt RM, Guris D. Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. N Engl J Med. 2011 Feb 3;364(5):401-11. doi: 10.1056/NEJMoa0909537. Erratum in: N Engl J Med. 2011 Apr 14;364(15):1481. PMID: 21288094; PMCID: PMC3495065.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	4vHPV vaccine	placebo	Relative (95% CI)	Absolute (95% CI)		
Local/injection site adverse events (follow-up: 15 days)												
1[a]	randomised trials	not serious	not serious	not serious	not serious	none	1169/1945 (60.1%)	1047/1950 (53.7%)	**RR 1.12** (1.06 to 1.18)	**64 more per 1,000** (from 32 more to 97 more)	High[b]	
Overall systemic event and general symptoms (follow-up: 15 days)												
2[a,c]	randomised trials	not serious	not serious	serious[d]	not serious	none	696/2499 (27.9%)	708/2509 (28.2%)	**RR 1.01** (0.98 to 1.04)	**3 more per 1,000** (from 6 fewer to 11 more)	Moderate	
Serious adverse events (follow-up: 3 years)												
2[a,c]	randomised trials	not serious	not serious	serious[d]	very serious[e]	none	8/2574 (0.3%)	12/2588 (0.5%)	**OR 0.69** (0.29 to 1.66)	**1 fewer per 1,000** (from 3 fewer to 3 more)	Very low	
Deaths (follow-up: 3 years)												
2[a,c]	randomised trials	not serious	not serious	not serious	very serious[e]	none	3/2582 (0.1%)	11/2591 (0.4%)	**OR 0.30** (0.09 to 1.01)	**3 fewer per 1,000** (from 4 fewer to 0 fewer)	Low	

Explanations
a. Giuliano AR, Palefsky JM, Goldstone S, Moreira ED Jr, Penny ME, Aranda C, Vardas E, Moi H, Jessen H, Hillman R, Chang YH, Ferris D, Rouleau D, Bryan J, Marshall JB, Vuocolo S, Barr E, Radley D, Haupt RM, Guris D. Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. N Engl J Med. 2011 Feb 3;364(5):401-11. doi: 10.1056/NEJMoa0909537. Erratum in: N Engl J Med. 2011 Apr 14;364(15):1481. PMID: 21288094; PMCID: PMC3495065.
b. Evidence for this outcome was not downgraded: the trial was a large multi-national trial with low risk of bias and precise estimates.
c. NCT01862874. E+icacy and tolerability study of V501 in Japanese males (V501-122). clinicaltrials.gov/ct2/show/NCT01862874 (accessed 27 August 2018).
d. Downgraded one level for indirectness: this outcome is a composite measure of events which may or may not be clinically relevant, may or may not be related to the vaccine and may occur outside a biologically plausible time frame relative to vaccine exposure. This outcome is considered to provide indirect evidence about vaccine safety.
e. Downgraded two levels for serious imprecision: few events and a wide 95% confidence interval that incorporates a potential large beneficial e+ect and a potential large harmful effect.

Appendix 2.7. 9vHPV vaccine versus 4vHPV on adverse events in apparently healthy male adults aged 16 to 26 years

Author(s): Burog, AILDB
Question: 9vHPV vaccine compared to 4vHPV vaccine for apparently healthy male adults aged 16 to 26 years (adverse events)
Setting: community
Bibliography: Van Damme P, Meijer CJLM, Kieninger D, Schuyleman A, Thomas S, Luxembourg A, Baudin M. A phase III clinical study to compare the immunogenicity and safety of the 9-valent and quadrivalent HPV vaccines in men. Vaccine. 2016 Jul 29;34(35):4205-4212. doi: 10.1016/j.vaccine.2016.06.056. Epub 2016 Jun 25. PMID: 27354258.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	9vHPV vaccine	4vHPV vaccine	Relative (95% CI)	Absolute (95% CI)		
Local/injection site adverse events (follow-up: 15 days)												
1[a]	randomised trials	not serious	not serious	not serious	not serious	none	196/249 (78.7%)	179/251 (71.3%)	**RR 1.10** (1.00 to 1.22)	**71 more per 1,000** (from 0 fewer to 157 more)	High	
Overall systemic event and general symptoms (follow-up: 15 days)												
1[a]	randomised trials	not serious	not serious	serious[b]	not serious	none	101/249 (40.6%)	100/251 (39.8%)	**RR 1.01** (0.82 to 1.26)	**4 more per 1,000** (from 72 fewer to 104 more)	Moderate	
Serious adverse events (follow-up: 4.5 years)												
1[a]	randomised trials	not serious	not serious	serious[b]	serious[c]	none	0/249 (0.0%)	6/251 (2.4%)	**OR 0.08** (0.00 to 1.35)	**22 fewer per 1,000** (from -- to 8 more)	Low	
Deaths (follow-up: 4.5 years)												
1[a]	randomised trials	not serious	not serious	not serious	very serious[c]	none	0/249 (0.0%)	0/251 (0.0%)	not estimable		Low	

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio
Explanations
a. Van Damme P, Meijer CJLM, Kieninger D, Schuyleman A, Thomas S, Luxembourg A, Baudin M. A phase III clinical study to compare the immunogenicity and safety of the 9-valent and quadrivalent HPV vaccines in men. Vaccine. 2016 Jul 29;34(35):4205-4212. doi: 10.1016/j.vaccine.2016.06.056. Epub 2016 Jun 25. PMID: 27354258.
b. Downgraded one level for indirectness: this outcome is a composite measure of events which may or may not be clinically relevant, may or may not be related to the vaccine and may occur outside a biologically plausible time frame relative to vaccine exposure. This outcome is considered to provide indirect evidence about vaccine safety.
c. Downgraded two levels for serious imprecision: few events and a wide 95% confidence interval that incorporates a potential large beneficial e+ect and a potential large harmful effect.

Appendix 2.8. 4vHPV vaccine versus placebo on outcome-related HPV type 6, 11, 16, and 18 in apparently healthy female adults aged 27 to 54 years

Author(s): Burog, AILDB

Question: 4vHPV vaccine compared to placebo for apparently healthy female adults aged 27 to 45 years (outcome-related HPV types 6, 11, 16, and 18)

Setting: community

Bibliography: Castellsagué X, Giuliano AR, Goldstone S, Guevara A, Mogensen O, Palefsky JM, Group T, Shields C, Liu K, Maansson R, Luxembourg A, Kaplan SS. Immunogenicity and safety of the 9-valent HPV vaccine in men. Vaccine. 2015 Nov 27;33(48):6892-901. doi: 10.1016/j.vaccine.2015.06.088. Epub 2015 Jul 2. PMID: 26144901.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	4vHPV vaccine	placebo	Relative (95% CI)	Absolute (95% CI)		
6-month persistent infection												
1[a]	randomised trials	not serious	not serious	serious[b]	not serious	none	8/1358 (0.6%)	71/1372 (5.2%)	**RRR 88.8** (76.8 to 95.4)	**-- per 1,000** (from -- to --)	Moderate	
CIN2/3 or worse												
1[a]	randomised trials	not serious	not serious	serious[b]	very serious[c,d]	none	1/1358 (0.1%)	6/1370 (0.4%)	**RRR 79.8** (-80.1 to 99.6)	**-- per 1,000** (from -- to --)	Very low	
Anogenital warts												
1	randomised trials	not serious	not serious	not serious	serious[d]	none	0/1376 (0.0%)	5/1384 (0.4%)	**RRR 100.0** (-9.8 to 100.0)	**-- per 1,000** (from -- to --)	Moderate	

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio

Explanations

a. Castellsagué X, Giuliano AR, Goldstone S, Guevara A, Mogensen O, Palefsky JM, Group T, Shields C, Liu K, Maansson R, Luxembourg A, Kaplan SS. Immunogenicity and safety of the 9-valent HPV vaccine in men. Vaccine. 2015 Nov 27;33(48):6892-901. doi: 10.1016/j.vaccine.2015.06.088. Epub 2015 Jul 2. PMID: 26144901.

b. Downgraded due to indirectness of this outcome to the pre-specified in the review question (i.e., use of clinical surrogate outcome)

c. Downgraded one level for imprecision: pooled estimate has a wide 95% confidence interval that incorporates a potential large beneficial effect and a potential large harmful effect.

d. Downgraded by 1 for imprecision due to low event rate

Appendix 2.9. 4vHPV vaccine versus placebo on adverse events in apparently healthy female adults aged 27 to 54 years

Author(s): Burog, AILDB
Question: 4vHPV vaccine compared to placebo for apparently healthy female adults aged 27 to 45 years (Adverse events)
Setting: community
Bibliography: Castellsagué X, Giuliano AR, Goldstone S, Guevara A, Mogensen O, Palefsky JM, Group T, Shields C, Liu K, Maansson R, Luxembourg A, Kaplan SS. Immunogenicity and safety of the 9-valent HPV vaccine in men. Vaccine. 2015 Nov 27;33(48):6892-901. doi: 10.1016/j.vaccine.2015.06.088. Epub 2015 Jul 2. PMID: 26144901.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	4vHPV vaccine	placebo	Relative (95% CI)	Absolute (95% CI)		
Any adverse events												
1[a]	randomised trials	not serious	not serious	not serious	not serious	none	1645/1890 (87.0%)	1535/1888 (81.3%)	**RR 1.07** (1.04 to 1.10)	**57 more per 1,000** (from 33 more to 81 more)	High	
Injection site events (day 1 to 15)												
1[a]	randomised trials	not serious	not serious	not serious	not serious	none	1450/1890 (76.7%)	1213/1890 (64.2%)	**RR 1.19** (1.15 to 1.25)	**122 more per 1,000** (from 96 more to 160 more)	High	
Systemic adverse events (days 1–15)												
1[a]	randomised trials	not serious	not serious	not serious	serious[b]	none	1121/1890 (59.3%)	1135/1888 (60.1%)	**RR 0.99** (0.94 to 1.04)	**6 fewer per 1,000** (from 36 fewer to 24 more)	Moderate	
Discontinuation due to adverse events												
1[a]	randomised trials	not serious	not serious	not serious	serious[b]	none	7/1890 (0.4%)	2/1888 (0.1%)	**RR 3.50** (0.73 to 16.81)	**3 more per 1,000** (from 0 fewer to 17 more)	⊕⊕⊕◯ Moderate	

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio
Explanations
a. Castellsagué X, Giuliano AR, Goldstone S, Guevara A, Mogensen O, Palefsky JM, Group T, Shields C, Liu K, Maansson R, Luxembourg A, Kaplan SS. Immunogenicity and safety of the 9-valent HPV vaccine in men. Vaccine. 2015 Nov 27;33(48):6892-901. doi: 10.1016/j.vaccine.2015.06.088. Epub 2015 Jul 2. PMID: 26144901.
b. Downgraded one level for imprecision: pooled estimate has a wide 95% confidence interval that incorporates a potential large beneficial effect and a potential large harmful effect.

Appendix 3. Characteristics of Included Studies

Study	Study Design	Population	Intervention	Comparator	Outcomes
Dillner 2010[3]	Protocols 013 (NCT00092521) and 015 (NCT00092534): phase III randomised double-blind placebo-controlled clinical trials	Female adolescents and young adults 16–26 years old. All subjects 18 years or older were–have a lifetime history of four or fewer lifetime sex partners. Subjects with prior confirmed HPV disease were excluded from enrolling; however, those with prior or current subclinical HPV infection (through serology and PCR testing, respectively) were not excluded. Enrolled subjects with clinical evidence of external anogenital HPV disease at day 1 were discontinued from the study before randomization. Females 16–26 years old	4-valent HPV (3 doses; 0, 2, 6 months)	Placebo (3 doses; 0, 2, 6 months)	CIN1 VIN1 VaIN1 Condyloma
Villa 2005[10]	Phase IIb randomised double-blind placebo-controlled clinical trial	Healthy women who reported a lifetime history of four or fewer male sex partners. Enrolment of virgins was restricted to women who were 18 years or older and who were seeking contraception. The study did not exclude women with previous HPV infection. Participants were required to use effective contraception during the trial. Females 16–23 years old	4-valent HPV (3 doses; 0, 2, 6 months)	Placebo (3 doses; 0, 2, 6 months)	Persistent infection Persistent infection or disease Disease External genital lesion CIN
Kjaer 2009[11]	Protocol 007 (NCT00365716 and NCT00365378): randomised double-blind placebo-controlled phase IIb clinical trial Protocols 013 (NCT00092521)	Female adolescents and young adults 16–26 years old. All subjects 18 years or older were to have a lifetime history of four or fewer lifetime sex partners. Subjects with prior confirmed HPV disease were excluded from enrolling; however, those with prior or current subclinical	4-valent HPV (3 doses; 0, 2, 6 months)	Placebo (3 doses; 0, 2, 6 months)	CIN2/3+ CIN2 CIN3+ CIN3 AIS VIN2/3+ or VaIN2/3+ VIN2/3 VaIN2/3

Study	Study Design	Population	Intervention	Comparator	Outcomes
	and 015 (NCT00092534): phase III randomised double-blind placebo-controlled clinical trials	HPV infection (through serology and PCR testing, respectively) were not excluded. Enrolled subjects with clinical evidence of external anogenital HPV disease at day 1 were discontinued from the study before randomization. Females 16–26 years old			
NCT01862874 2018[12]	Phase 3, parallel, randomised, controlled trial	Participants: 1124 boys and men (562 received vaccine, 562 received placebo) recruited from Japan Age range:16-26 years	Vaccine: quadrivalent HPV vaccine; 3 doses at day 1, month 2, month 6	Control: aluminium adjuvant placebo (placebo formulated with aluminium hydroxyphosphate sulfate adjuvant); 3 doses at day 1, month 2, month 6	Incidence of persistent HPV-6/11/16/18 infection or disease Adverse events
Huh et al. 2015[13]	Phase II/III, double-blind, randomised, multi-centre trial	Participants: 14215 women (6792 in the nonavalent HPV vaccine group and 6795 in the quadrivalent HPV vaccine group) recruited from 18 countries (Austria, Brazil, Canada, Chile, Colombia, Denmark, Germany, Hong Kong, Japan, Korea, Mexico, New Zealand, Norway, Peru, Sweden, Taiwan, Thailand, and the USA (including Puerto Rico) Age range: 16-26 years	Vaccine 1: nonavalent HPV vaccine; 3 doses: day 1, month 2, month 6	Vaccine 2: quadrivalent HPV vaccine; 3 doses: day 1, month 2, month 6	Clinical: high grade cervical, vulval, and vaginal disease; cervical cancer; persistent HPV infection Harms: adverse events, deaths Immunogenicity: GMT, seroconversion
Giuliano 2011[16]	Phase III, double-blind, parallel, placebo-controlled, randomised and multi-site trial	Participants: 4065 boys and men (2032 to the vaccine group and 2033 to the control group) recruited from 18 countries in five regions (Africa, Asia-Pacific, Europe, Latin America, North America) Age range: 16-26 years	Vaccine: quadrivalent HPV vaccine; 3 doses: day 1, month 2, month 6	Control: aluminium adjuvant placebo (amorphous aluminium hydroxy-phosphate sulphate (AAHS)); 3 doses: day 1, month 2, month 6	Clinical: external genital lesions; penile, perianal, or perineal intraepithelial neoplasia; or penile, perianal, or perineal cancer Harms: adverse events, deaths Immunogenicity: GMT, seroconversion

Study	Study Design	Population	Intervention	Comparator	Outcomes
Goldstone 2013[17]	Randomised placebo-controlled double-blind trial	3463 heterosexual males aged 16–24 years and 602 men who have sex with men (MSM) aged 16–27 years with less than six lifetime sexual partners	4-valent HPV (3 doses; 0,2,6 months)	AAHS containing placebo (3 doses; 0,2,6 months)	Persistent infection ≥6 months External genital lesions Condyloma acuminatum Penile intraepithelial neoplasia (PIN; any grade) PIN1 PIN2/3 Penile, perianal or perineal cáncer Anal intraepithelial neoplasia (AIN) grade 1
Castellsagué 2011[18]	Randomized, placebo-controlled trial in 7 countries (through M48);	Women age 24–45 years (N=3819)	1 : 1 ratio to receive either qHPV (types 6, 11, 16, 18) L1 VLP vaccine	visually indistinguishable adjuvant-containing placebo	Immunogenicity Persistent HPV infection External genital lesions (warts) CIN 1+, CIN 2+ Combined endpoint Harms
van Damme 2016[19]	Phase III, double-blind, controlled, randomised and multicenter trial	Participants: 500 males (249 to the nonavalent HPV vaccine arm, 251 to the quadrivalent HPV vaccine arm) recruited from Belgium, Germany, and the Netherlands Age range: 16-26 years	Vaccine 1: nonavalent HPV vaccine; 3 doses: day 1, month 2, and month 6	Vaccine 2: quadrivalent HPV vaccine; 3 doses: day 1, month 2, and month 6	Harms: adverse events, deaths Immunogenicity: GMT, seroconversion

Influenza Vaccine

Appendix 1. Evidence-to-Decision Summary

Burden	No	Probably No	Probably Yes	Yes (5)	Varies (1)	Don't know
Benefits	Trivial	Small (2)	Moderate (2)	Large (2)	Varies	Don't know
Harms	Large	Moderate (2)	Small (1)	Trivial (3)	Varies	Don't know
Certainty of evidence	Very Low (1)	Low (5)	Moderate	High	No included studies	
Balance of effects	Favors no vaccine	Probably favors no vaccine	Equivalent/Does not favor either (1)	Probably favors vaccine (3)	Favors vaccine (3)	Varies	Don't know

Resources required	Large costs	Moderate costs (5)	Negligible costs and savings (1)	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence (resources)	Very Low	Low (1)	Moderate (2)	High (1)	No included studies (2)		
Cost effectiveness	Favors no vaccine	Probably favors no vaccine (1)	Does not favor either	Probably favors vaccine (4)	Favors vaccine (2)	Varies (1)	Don't know/ No studies (2)
Equity	Reduced	Probably reduced (2)	Probably no impact (1)	Probably increased (2)	Increased (1)	Varies	Don't know
Acceptability	No	Probably no	Probably yes (3)	Yes (2)	Varies (1)	Don't know	
Feasibility	No	Probably no	Probably yes (2)	Yes (3)	Varies (1)	Don't know	
Values	Important variability	Possibly important variability (1)	Probably no important variability (3)	No important variability (2)			

Recommendation 1: **Healthy adults, pregnant women, and elderly (≥65 years old)**	STRONG against	WEAK against	NO RECOMMENDATION	WEAK in favor (6)	STRONG in favor
Recommendation 2: **Healthcare workers**	STRONG against	WEAK against	NO RECOMMENDATION	WEAK in favor (7)	STRONG in favor

Appendix 2. GRADE Summary of Findings Table

Appendix 2.1. Inactivated influenza vaccination compared with no vaccination for healthy adults

Author(s): Carol Stephanie C. Tan-Lim, MD, MSc
Question: Inactivated influenza vaccine compared with no vaccine for healthy adults
Setting: Community setting
Bibliography: Demicheli V, Jefferson T, Ferroni E, Rivetti A, Di Pietrantonj. Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev. 2018;2(2):CD001269.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inactivated influenza vaccine	No vaccine	Relative (95% CI)	Absolute (95% CI)		
Influenza												
22	randomized trials	not serious	not serious	serious [a]	not serious	none	408/37952 (1.1%)	617/23560 (2.6%)	**RR 0.41** (0.36 to 0.47)	**15 fewer per 1,000** (from 17 fewer to 14 fewer)	Moderate	CRITICAL
Influenza-like illness												
14	randomized trials	not serious	serious [b]	not serious	not serious	none	1630/16495 (9.9%)	1438/9207 (15.6%)	**RR 0.84** (0.75 to 0.95)	**25 fewer per 1,000** (from 39 fewer to 8 fewer)	Moderate	CRITICAL
Hospitalization												
2	randomized trials	not serious	not serious	not serious	very serious [c]	none	1/1158 (0.1%)	0/1150 (0.0%)	**RR 2.89** (0.12 to 70.68)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	Low	CRITICAL
Missed working days												
4	randomized trials	serious [d]	serious [e]	not serious	not serious	none	1861	1865	-	MD **0.01 more** (0.08 fewer to 0.09 more)	Low	IMPORTANT
Systemic adverse events (combined endpoints)												
5	randomized trials	serious [f]	not serious	not serious	serious g	none	157/958 (16.4%)	144/934 (15.4%)	**RR 1.08** (0.88 to 1.32)	**12 more per 1,000** (from 19 fewer to 49 more)	Low	CRITICAL

Explanations
a. Downgraded one level due to serious indirectness. Uncertainty over definition, surveillance and testing of influenza in older trials.
b. Downgraded one level for serious inconsistency. There is discordance between the direction and size of effects across the studies. Different definitions of influenza-like illness across the studies could explain why there is variation in the event rates across the control arms.
c. Downgraded one level due to very serious imprecision. Confidence interval includes meaningful reduction and increase in effect, small number of events.
d. Downgraded one level due to serious risk of bias. Effect is influenced by studies judged to be at unclear risk of bias.
e. Downgraded one level due to serious inconsistency. Direction and magnitude of effect differed across the studies (I2 = 82%). Wide confidence interval reflects the range of study effect sizes.
f. Downgraded one level due to serious risk of bias. One study had overall high risk of bias, 3 studies had overall unclear risk of bias
g. Downgraded one level due to serious imprecision. Confidence interval includes meaningful reduction and increase in effect.

Appendix 2.2. Live intranasal influenza vaccination compared with no vaccination for healthy adults

Author(s): Carol Stephanie C. Tan-Lim, MD, MSc
Question: Inactivated influenza vaccine compared with No vaccine for Healthy adults
Setting: Community setting
Bibliography: Demicheli V, Jefferson T, Ferroni E, Rivetti A, Di Pietrantonj. Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev. 2018;2(2):CD001269.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Live intranasal influenza vaccine	No vaccine	Relative (95% CI)	Absolute (95% CI)		
Influenza												
9	randomized trials	serious [a]	not serious	not serious	not serious	none	168/6439 (2.6%)	251/5140 (4.9%)	**RR 0.47** (0.35 to 0.62)	**26 fewer per 1,000** (from 32 fewer to 19 fewer)	Moderate	CRITICAL
Influenza-like illness												
6	randomized trials	serious [b]	not serious	not serious	not serious	none	1467/7032 (20.9%)	1226/5656 (21.7%)	**RR 0.90** (0.84 to 0.96)	**22 fewer per 1,000** (from 35 fewer to 9 fewer)	Moderate	CRITICAL
Local adverse events (combined endpoint)												
3	randomized trials	not serious	not serious	not serious	not serious	none	1386/3233 (42.9%)	439/1688 (26.0%)	**RR 1.56** (1.31 to 1.87)	**146 more per 1,000** (from 81 more to 226 more)	High	IMPORTANT
Systemic adverse events (combined endpoint)												
5	randomized trials	serious [b]	not serious	not serious	serious [c]	none	82/607 (13.5%)	45/411 (10.9%)	**RR 1.40** (0.82 to 2.38)	**44 more per 1,000** (from 20 fewer to 151 more)	Low	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Downgraded one level due to serious risk of bias. All studies had overall unclear risk of bias.
b. Downgraded one level due to serious risk of bias. Four studies had overall unclear risk of bias.
c. Downgraded one level due to serious imprecision. Confidence interval includes meaningful reduction and increase in effect.

Appendix 2.3. Inactivated influenza vaccination compared with no vaccination for pregnant women

Author(s): Carol Stephanie C. Tan-Lim, MD, MSc
Question: Inactivated influenza vaccine compared with no influenza vaccine for pregnant women
Setting: community setting
Bibliography:

1. Demicheli V, Jefferson T, Ferroni E, Rivetti A, Di Pietrantonj. Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev. 2018;2(2):CD001269.
2. Madhi SA, Cutland CL, Kuwanda L, Weinberg A, Hugo A, Jones S, et al. Influenza vaccination of pregnant women and protection of their infants. N Engl J Med. 2014;371(10):918-31.
3. Tapia MD, Sow SO, Tamboura B, Teguete I, Pasetti MF, Kodio M, et al. Maternal immunisation with trivalent inactivated influenza vaccine for prevention of influenza in infants in Mali: a prospective, active-controlled, observer-blind, randomised phase 4 trial. Lancet Infect Dis. 2016;16(9):1026-1035.
4. Steinhoff MC, Katz J, Englund JA, Khatry SK, Shrestha L, Kuypers J, et al. Year-round influenza immunisation during pregnancy in Nepal: a phase 4, randomised, placebo-controlled trial. Lancet Infect Dis. 2017;17(9):981-989.
5. Zaman K, Roy E, Arifeen SE, Rahman M, Raqib R, Wilson E, et al. Effectiveness of maternal influenza immunization in mothers and infants. N Engl J Med. 2008;359(15):1555-64.
6. Nunes MC, Cutland CL, Jones S, Hugo A, Madimabe R, Simoes EAF, et al. Duration of Infant Protection Against Influenza Illness Conferred by Maternal Immunization: Secondary Analysis of a Randomized Clinical Trial. JAMA Pediatr. 2016;170(9):840-7.
7. Nunes MC, Cutland CL, Jones S, Downs S, Weinberg A, Ortiz JR, et al. Efficacy of Maternal Influenza Vaccination Against All-Cause Lower Respiratory Tract Infection Hospitalizations in Young Infants: Results From a Randomized Controlled Trial. Clin Infect Dis. 2017;65(7):1066-1071.
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9. Buchwald AG, Tamboura B, Haidara FC, Coulibaly F, Doumbia M, Diallo F, et al. Maternal Influenza Vaccination and the Risk of Laboratory-Confirmed Influenza Among Household Contacts Under the Age of Five in Mali. Am J Trop Med Hyg. 2019;100(1):159-164.
10. Kozuki N, Katz J, Englund JA, Steinhoff MC, Khatry SK, Shrestha L, et al. Impact of maternal vaccination timing and influenza virus circulation on birth outcomes in rural Nepal. Int J Gynaecol Obstet. 2018;140(1):65-72.
11. Katz J, Englund JA, Steinhoff MC, Khatry SK, Shrestha L, Kuypers J, et al. Impact of Timing of Influenza Vaccination in Pregnancy on Transplacental Antibody Transfer, Influenza Incidence, and Birth Outcomes: A Randomized Trial in Rural Nepal. Clin Infect Dis. 2018;67(3):334-340.
12. Newman KL, Stewart LM, Scott EM, Tielsch JM, Englund JA, Khatry SK, et al. Assessment of indirect protection from maternal influenza immunization among non-vaccinated household family members in a randomized controlled trial in Sarlahi, Nepal. Vaccine. 2020;38(43):6826-6831.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inactivated influenza vaccine	No flu vaccine	Relative (95% CI)	Absolute (95% CI)		
Infant influenza (follow up: 6 months)												
4	randomized trials	not serious	not serious	not serious	not serious	none	156/5157 (3.0%)	241/5113 (4.7%)	**RR 0.64** (0.53 to 0.78)	**17 fewer per 1,000** (from 22 fewer to 10 fewer)	High	CRITICAL
Maternal influenza (follow up: 6 months)												
3	randomized trials	not serious	serious [a]	not serious	not serious	none	68/5081 (1.3%)	138/5042 (2.7%)	**RR 0.47** (0.29 to 0.77)	**15 fewer per 1,000** (from 19 fewer to 6 fewer)	Moderate	CRITICAL
Infant influenza-like illness (follow up: 6 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inactivated influenza vaccine	No flu vaccine	Relative (95% CI)	Absolute (95% CI)		
3	randomized trials	not serious	serious [a]	not serious	serious [b]	none	1481/3093 (47.9%)	1531/3072 (49.8%)	**RR 0.89** (0.73 to 1.08)	**55 fewer per 1,000** (from 135 fewer to 40 more)	Low	CRITICAL
Maternal influenza-like illness (follow up: 6 months)												
3	randomized trials	not serious	serious [a]	not serious	not serious	none	468/3145 (14.9%)	549/3125 (17.6%)	**RR 0.81** (0.67 to 0.99)	**33 fewer per 1,000** (from 58 fewer to 2 fewer)	Moderate	CRITICAL
Infant hospitalization (follow up: 6 months)												
1	randomized trials	not serious	not serious	not serious	serious [b]	none	151/1026 (14.7%)	163/1023 (15.9%)	**RR 0.92** (0.75 to 1.13)	**13 fewer per 1,000** (from 40 fewer to 21 more)	Moderate	CRITICAL
Infant mortality												
2	randomized trials	not serious	not serious	not serious	serious [c]	none	113/3872 (2.9%)	87/3845 (2.3%)	**RR 1.29** (0.98 to 1.70)	**7 more per 1,000** (from 0 fewer to 16 more)	Moderate	CRITICAL
Maternal mortality (follow up: 6 months)												
2	randomized trials	not serious	serious [a]	not serious	serious [b]	none	5/3955 (0.1%)	8/3931 (0.2%)	**RR 0.62** (0.20 to 1.90)	**1 fewer per 1,000** (from 2 fewer to 2 more)	Low	CRITICAL
Infant Serious Adverse Events (follow up: 6 months)												
4	randomized trials	not serious	serious [a]	not serious	serious [c]	none	1460/5108 (28.6%)	1396/5065 (27.6%)	**RR 1.08** (0.92 to 1.28)	**22 more per 1,000** (from 22 fewer to 77 more)	Low	CRITICAL
Maternal Serious Adverse Events (follow up: 6 months)												
2	randomized trials	not serious	not serious	not serious	serious [b]	none	68/2280 (3.0%)	69/2253 (3.1%)	**RR 0.97** (0.70 to 1.35)	**1 fewer per 1,000** (from 9 fewer to 11 more)	Moderate	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Downgraded one level due to significant heterogeneity

b. Downgraded one level due to serious imprecision. Confidence interval includes meaningful reduction and increase in effect.

c. Downgraded one level due to serious imprecision. Confidence interval includes meaningful increase and reduction in effect.

d. Downgraded one level due to serious risk of bias. One study had high risk of attrition bias.

Appendix 2.4. Influenza vaccination compared with no influenza vaccination for healthcare workers

Author(s): Carol Stephanie C. Tan-Lim, MD, MSc
Question: Influenza vaccine compared with no influenza vaccine for healthcare workers
Setting: Hospital setting
Bibliography:

1. Thomas RE, Jefferson T, Lasserson TJ. Influenza vaccination for healthcare workers who work with the elderly. Cochrane Database Syst Rev. 2010;(2):CD005187.
2. Saxen H, Virtanen M. Randomized, placebo-controlled double-blind study on the efficacy of influenza immunization on absenteeism of health care workers. Pediatr Infect Dis J. 1999;18(9):779-83.
3. Weingarten S, Staniloff H, Ault M, Miles P, Bamberger M, Meyer RD. Do hospital employees benefit from the influenza vaccine? A placebo-controlled clinical trial. J Gen Intern Med. 1988;3(1):32-7.
4. Wilde JA, McMillan JA, Serwint J, Butta J, O'Riordan MA, Steinhoff MC. Effectiveness of influenza vaccine in health care professionals: a randomized trial. JAMA. 1999;281(10):908-13.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Influenza vaccine	No flu vaccine	Relative (95% CI)	Absolute (95% CI)		
HCW Influenza												
1	randomized trials	not serious	not serious	not serious	serious [a]	none	3/180 (1.7%)	24/179 (13.4%)	**RR 0.12** (0.04 to 0.41)	**118 fewer per 1,000** (from 129 fewer to 79 fewer)	Moderate	CRITICAL
HCW influenza-like illness												
1	randomized trials	serious [b]	not serious	not serious	serious [c]	none	21/91 (23.1%)	19/88 (21.6%)	**RR 1.07** (0.62 to 1.95)	**15 more per 1,000** (from 82 fewer to 205 more)	Low	CRITICAL
HCW missed working days												
2	randomized trials	serious [b]	not serious	not serious	not serious	none	271	267	-	MD **0.09 days lower** (0.19 lower to 0.02 higher)	Moderate	IMPORTANT
HCW serious adverse events												
1	randomized trials	not serious	not serious	not serious	Very serious [d]	none	0/180 (0.0%)	3/179 (1.7%)	**RR 0.14** (0.01 to 2.73)	**14 fewer per 1,000** (from 17 fewer to 29 more)	Low	CRITICAL
HCW adverse events												
2	randomized trials	serious [e]	serious [f]	not serious	not serious	none	136/307 (44.3%)	28/299 (9.4%)	**RR 5.34** (2.12 to 13.41)	**406 more per 1,000** (from 105 more to 1,000 more)	Low	IMPORTANT
Patient Influenza												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Influenza vaccine	No flu vaccine	Relative (95% CI)	Absolute (95% CI)		
2	randomized trials	serious [g]	not serious	not serious	serious [c]	none	17/376 (4.5%)	20/376 (5.3%)	**Risk difference 0.00** (-0.03 to 0.03)	**-- per 100** (from -- to --)	Low	CRITICAL
Patient hospitalization												
1	randomized trials	serious [g]	not serious	not serious	serious [c]	none	150/1722 (8.7%)	143/1678 (8.5%)	**Risk difference 0.00** (-0.02 to 0.02)	**-- per 1,000** (from -- to --)	Low	CRITICAL
Patient all-cause mortality												
4	randomized trials	serious [h]	very serious [i]	not serious	not serious	none			not pooled	see comment	Very Low	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded one level for serious imprecision. The number of participants did not reach optimal information size.
b. Downgraded one level for serious risk of bias. One study had high risk for performance bias.
c. Downgraded one level due to serious imprecision. Wide confidence interval includes reduction and increase in effect.
d. Downgraded two levels due to very serious imprecision. Wide confidence interval includes reduction and increase in effect, small number of events
e. Downgraded one level due to serious risk of bias. One study had high risk of performance bias, one study had high risk of attrition bias.
f. Downgraded one level due to serious inconsistency (I^2=77%)
g. Downgraded one level due to serious risk of bias. High risk of performance/detection bias.
h. Downgraded one level due to serious risk of bias: High risk of attrition bias.
i. Downgraded due to very serious inconsistency. Meta-analysis was not undertaken for this outcome in view of the high levels of statistical heterogeneity for this outcome and variation in the direction of the effect across the studies.

Appendix 2.5. Inactivated influenza vaccination compared with no influenza vaccination for elderly

Author(s): Carol Stephanie C. Tan-Lim, MD, MSc
Question: Inactivated influenza vaccine compared with no influenza vaccine for elderly
Setting: Community setting
Bibliography:

1. Demicheli V, Jefferson T, Di Pietrantonj C, Ferroni E, Thorning S, Thomas RE, et al. Vaccines for preventing influenza in the elderly. Cochrane Database Syst Rev. 2018;2(2):CD004876,
2. Verhees RAF, Thijs T, Ambergen T, Dinant GJ, Knottnerus JA. Influenza vaccination in the elderly: 25 years follow-up of a randomized controlled trial. No impact on long-term mortality. PLoS ONE. 2019;14(5):e0216983.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inactivated influenza vaccine	No flu vaccine	Relative (95% CI)	Absolute (95% CI)		
Influenza												
2	randomized trials	serious [a]	not serious	serious [b]	not serious	none	22/1020 (2.2%)	52/1020 (5.1%)	RR 0.44 (0.27 to 0.71)	29 fewer per 1,000 (from 37 fewer to 15 fewer)	Low	CRITICAL
Influenza-like illness												
2	randomized trials	serious [a]	not serious	not serious	not serious	none	86/1449 (5.9%)	106/1088 (9.7%)	RR 0.64 (0.49 to 0.84)	35 fewer per 1,000 (from 50 fewer to 16 fewer)	Moderate	CRITICAL
All-cause mortality (follow up: 25 years)												
2	randomized trials	serious [c]	not serious	not serious	not serious	none	714/1449 (49.3%)	708/1088 (65.1%)	RR 0.99 (0.94 to 1.04)	7 fewer per 1,000 (from 39 fewer to 26 more)	Moderate	CRITICAL
Fever												
3	randomized trials	not serious	not serious	not serious	serious [d]	none	33/1270 (2.6%)	20/1249 (1.6%)	RR 1.58 (0.92 to 2.71)	9 more per 1,000 (from 1 fewer to 27 more)	Moderate	IMPORTANT
Nausea												
1	randomized trials	serious [e]	not serious	not serious	serious [d]	none	14/336 (4.2%)	8/336 (2.4%)	RR 1.75 (0.74 to 4.12)	18 more per 1,000 (from 6 fewer to 74 more)	Low	IMPORTANT
General malaise												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inactivated influenza vaccine	No flu vaccine	Relative (95% CI)	Absolute (95% CI)		
3	randomized trials	serious [f]	not serious	not serious	serious [d]	none	85/1270 (6.7%)	70/1249 (5.6%)	RR 1.19 (0.87 to 1.61)	11 more per 1,000 (from 7 fewer to 34 more)	Low	IMPORTANT
Upper respiratory tract symptoms												
2	randomized trials	serious [f]	not serious	not serious	serious [d]	none	55/366 (15.0%)	36/347 (10.4%)	RR 1.35 (0.90 to 2.01)	36 more per 1,000 (from 10 fewer to 105 more)	Low	IMPORTANT
Headache												
2	randomized trials	serious [g]	not serious	not serious	serious [d]	none	66/1240 (5.3%)	61/1238 (4.9%)	RR 1.08 (0.77 to 1.52)	4 more per 1,000 (from 11 fewer to 26 more)	Low	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Downgraded one level due to serious risk of bias. One study had high and unclear risk of bias for more than 1 risk of bias domain
b. Downgraded one level due to indirectness. Uncertainty over the definition, testing and surveillance of influenza in older trials
c. Downgraded one level due to serious risk of bias. One study had high risk of selection bias
d. Downgraded one level due to serious imprecision. Confidence intervals were wide
e. Downgraded one level due to serious risk of bias. One study had unclear risk of selection bias
f. Downgraded one level due to serious risk of bias. Two studies had overall unclear risk of bias
g. Downgraded one level due to serious risk of bias. One study had overall unclear risk of bias

Appendix 2.6. Live influenza vaccination compared with no influenza vaccination for elderly

Author(s): Carol Stephanie C. Tan-Lim, MD, MSc
Question: Live influenza vaccine compared with no influenza vaccine for elderly
Setting: Community setting
Bibliography:

1. Demicheli V, Jefferson T, Di Pietrantonj C, Ferroni E, Thorning S, Thomas RE, et al. Vaccines for preventing influenza in the elderly. Cochrane Database Syst Rev. 2018;2(2):CD004876.
2. Verhees RAF, Thijs T, Ambergen T, Dinant GJ, Knottnerus JA. Influenza vaccination in the elderly: 25 years follow-up of a randomized controlled trial. No impact on long-term mortality. PLoS ONE. 2019;14(5):e0216983.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Live influenza vaccine	No flu vaccine	Relative (95% CI)	Absolute (95% CI)		
Influenza												
1	randomized trials	very serious [a]	not serious	not serious	serious [b]	none	7/111 (6.3%)	14/109 (12.8%)	**RR 0.49** (0.21 to 1.17)	**66 fewer per 1,000** (from 101 fewer to 22 more)	Very Low	CRITICAL
General malaise												
1	randomized trials	serious [c]	not serious	not serious	very serious [d]	none	4/34 (11.8%)	0/11 (0.0%)	**RR 3.09** (0.18 to 53.20)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	Very Low	IMPORTANT
Fever												
1	randomized trials	serious [c]	not serious	not serious	very serious [d]	none	2/34 (5.9%)	0/11 (0.0%)	**RR 1.71** (0.09 to 33.24)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	Very Low	IMPORTANT
Upper respiratory tract symptoms												
1	randomized trials	serious c	not serious	not serious	very serious [d]	none	10/34 (29.4%)	2/11 (18.2%)	**RR 1.62** (0.42 to 6.29)	**113 more per 1,000** (from 105 fewer to 962 more)	Very Low	IMPORTANT
Lower respiratory tract symptoms												
1	randomized trials	serious [c]	not serious	not serious	very serious [d]	none	9/34 (26.5%)	1/11 (9.1%)	**RR 2.91** (0.41 to 20.48)	**174 more per 1,000** (from 54 fewer to 1,000 more)	Very Low	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Downgraded 2 levels due to serious risk of bias. One study had overall high risk of bias.
b. Downgraded 1 level due to serious imprecision. Confidence intervals were wide.
c. Downgraded 1 level due to serious risk of bias. One study had overall unclear risk of bias.
d. Downgraded 2 levels due to very serious imprecision. Confidence intervals were wide and there were very few events in the included study.

Appendix 3. Characteristics of Included Studies

Appendix 3.1. Pregnant Women

Study	Setting	Population	Intervention	Control	Outcome	Secondary Study	Outcome
Madhi 2014[11]	South Africa	Pregnant women 20-36 weeks gestation (n=2,116)	IIV3	Placebo	Infant influenza, infant ILI, maternal influenza, maternal ILI (6 months follow-up)	Nunes 2016[15]	Infant influenza stratified by age of infant
						Nunes 2017[16]	Infant Hospitalization
						Simoes 2019[17]	Infant SAE
Tapia 2016[12]	Mali	Pregnant women >28 weeks gestation (n=4,193)	IIV3	MCV	Infant influenza, maternal influenza, infant mortality, maternal mortality, infant SAE, maternal SAE, local and systemic reactogenicity (6 months follow-up)	Buchwald 2019[18]	Household contacts (<5 years old) influenza and ILI
Stein-hoff 2017[13]	Nepal	Pregnant women 17-34 weeks gestation (n=3,693)	IIV3	Placebo	Infant influenza, infant ILI, maternal influenza, maternal ILI, infant mortality, maternal mortality, infant SAE (6 months follow-up)	Kozuki 2017[19]	Infant SAE
						Katz 2018[20]	Infant influenza stratified by gestational age at vaccination
						Newman 2020[21]	Household contact (any age) influenza
Zaman 2008[14]	Banglad esh	Pregnant women on the third trimester	IIV3	PPSV23	Infant influenza, infant ILI, maternal ILI, infant SAE, maternal SAE, local and systemic reactogenicity (6 months follow-up)	-	-

IIV3 trivalent inactivated influenza vaccine; ILI influenza-like illness; MCV meningococcal conjugate vaccine; PPSV23 pneumococcal polysaccharide vaccine; SAE serious adverse events

Appendix 3.2. Healthcare Workers

Study	Setting	Population	Intervention	Control	Outcome
Saxen 1999[23]	Finland	HCW in pediatric tertiary hospital and pediatric community hospital	IIV3	Placebo	HCW missed working days, adverse events
Weingarten 1988[24]	USA	HCW 21-65 years old	IIV3	Placebo	HCW influenza-like illness, missed working days, adverse events
Wilde 1999[25]	USA	HCW in two large teaching hospitals	IIV3	MCV, pneumococcal vaccine, placebo	HCW influenza, missed working days, serious adverse events

IIV3 trivalent inactivated influenza vaccine; MCV meningococcal conjugate vaccine

Appendix 4. Forest Plots

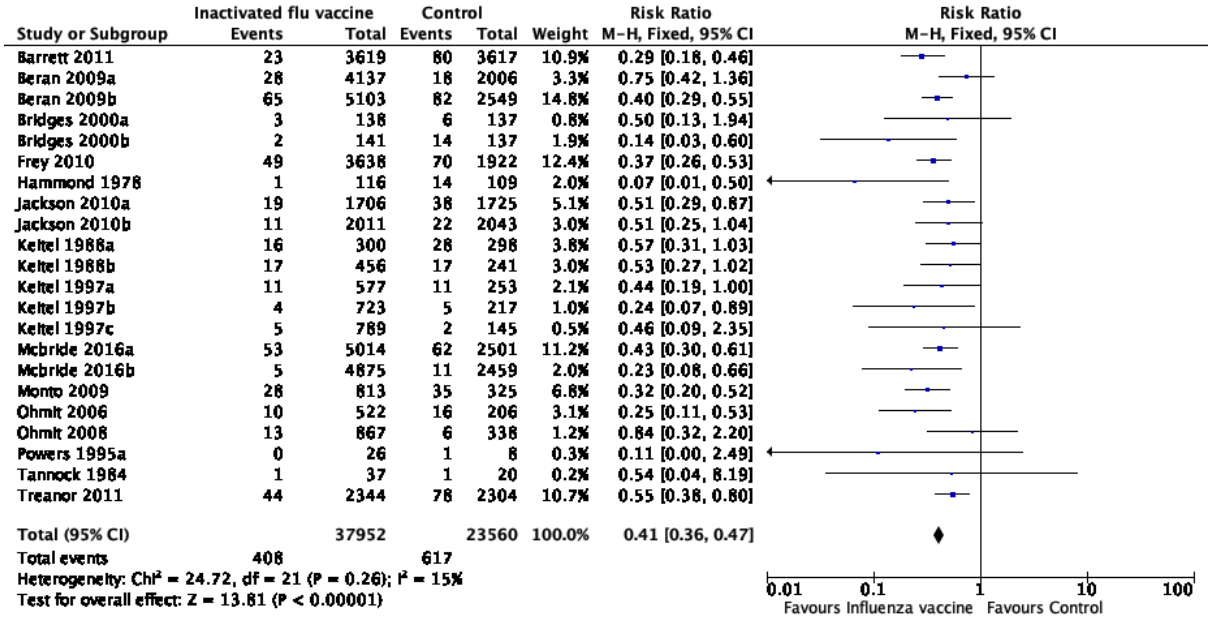

Figure 1. Effect of influenza vaccine among healthy adults on laboratory-confirmed influenza (22 studies)

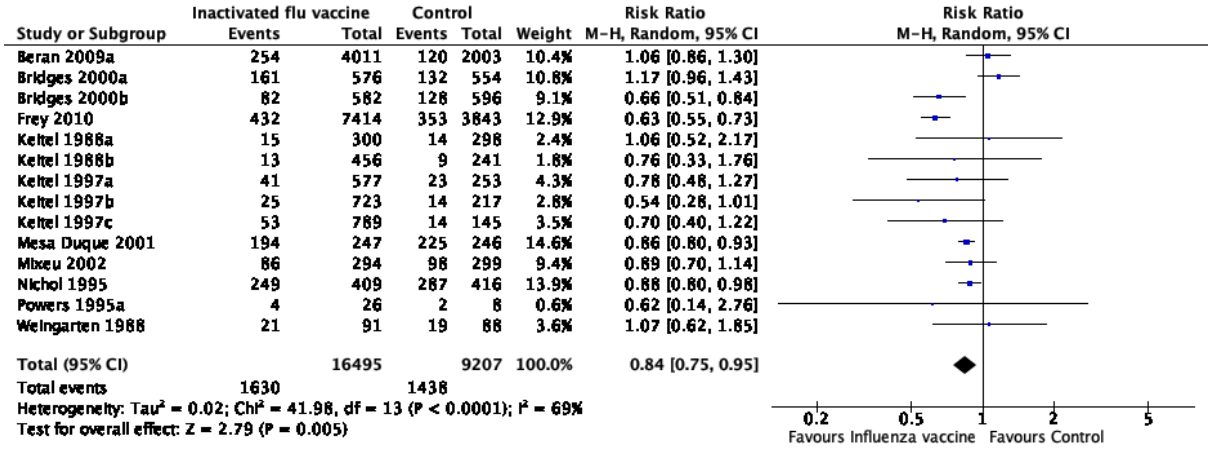

Figure 2. Effect of influenza vaccine among healthy adults on influenza-like illness (14 studies)

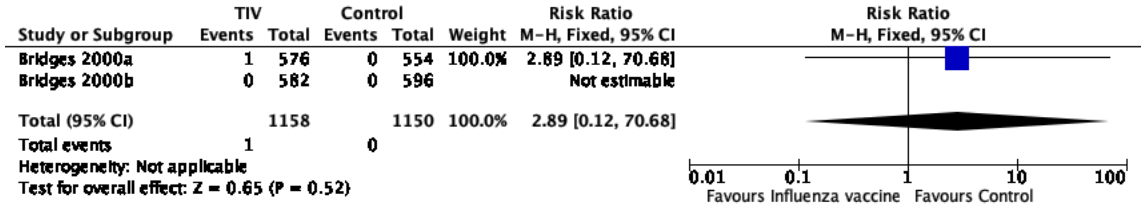

Figure 3. Effect of influenza vaccine among healthy adults on hospitalization (2 studies)

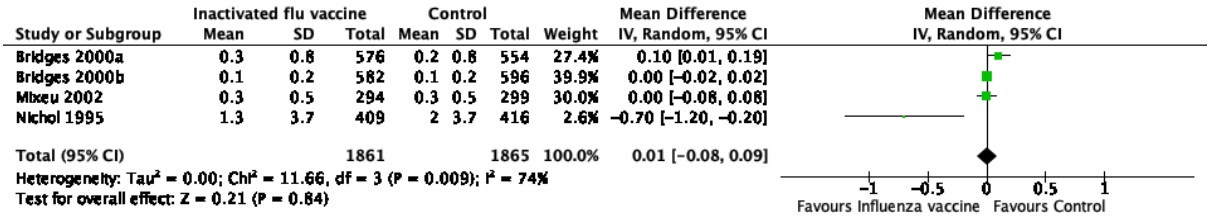

Figure 4. Effect of influenza vaccine among healthy adults on missed working days (4 studies)

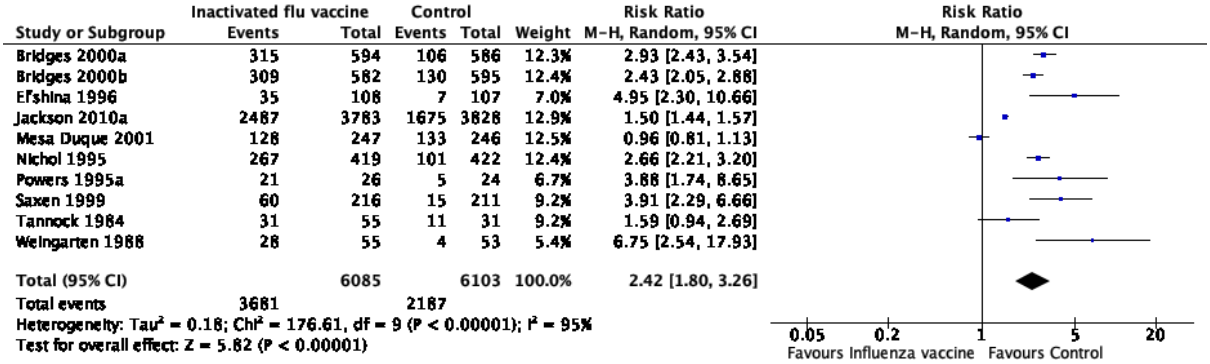

Figure 5. Effect of influenza vaccine among healthy adults on combined local adverse effects (10 studies)

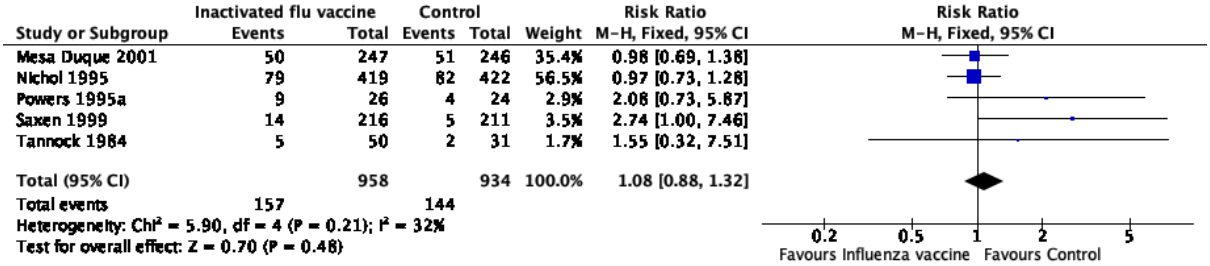

Figure 6. Effect of influenza vaccine among healthy adults on combined systemic adverse effects (5 studies)

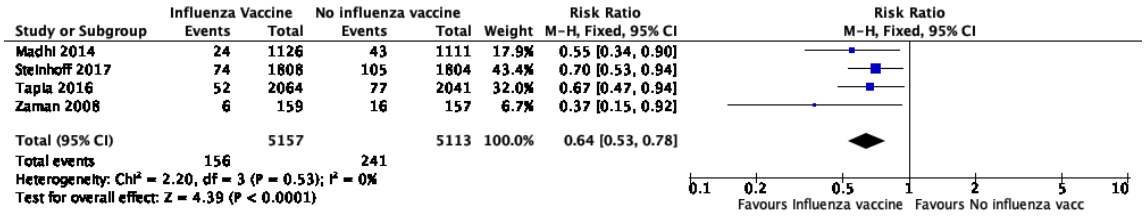

Figure 7. Effect of influenza vaccine among pregnant women on infant influenza (4 studies)

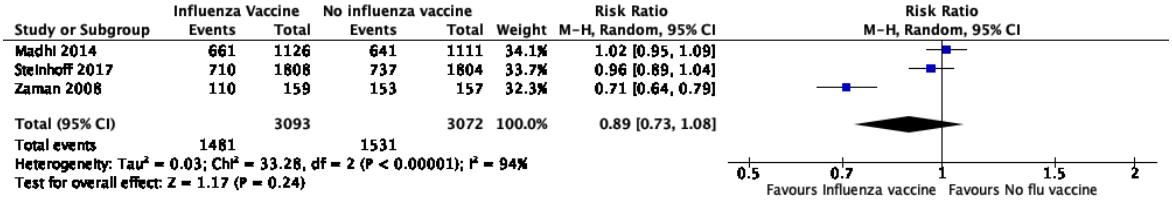

Figure 8. Effect of influenza vaccine among pregnant women on infant influenza-like illness (3 studies)

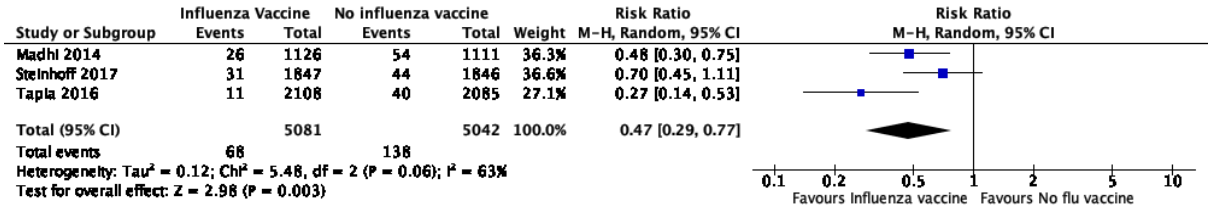

Figure 9. Effect of influenza vaccine among pregnant women on maternal influenza (3 studies)

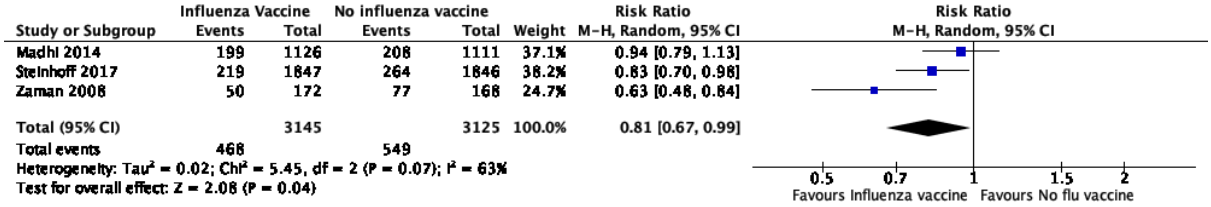

Figure 10. Effect of influenza vaccine among pregnant women on maternal influenza-like illness (3 studies)

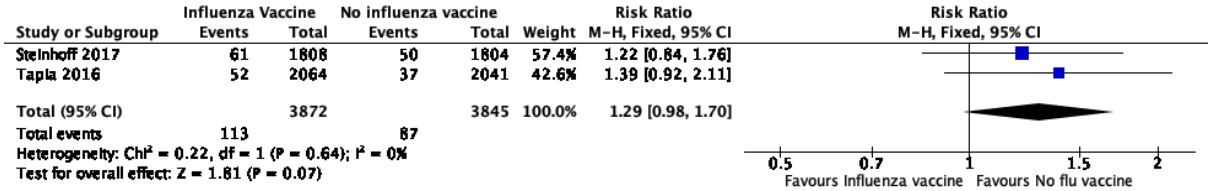

Figure 11. Effect of influenza vaccine among pregnant women on infant mortality (2 studies)

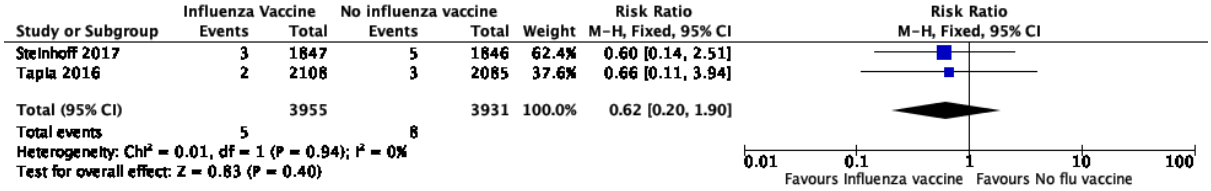

Figure 12. Effect of influenza vaccine among pregnant women on maternal mortality (2 studies)

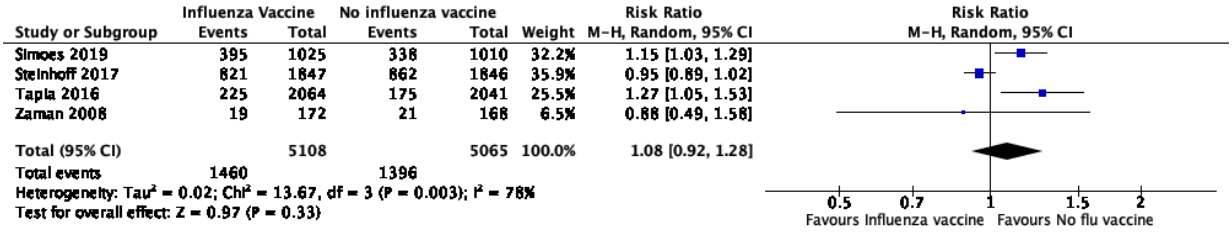

Figure 13. Serious adverse events among infants of pregnant women given influenza vaccine (4 studies)

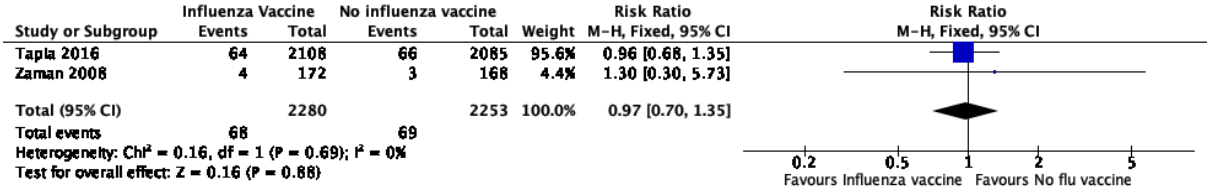

Figure 14. Serious adverse events among pregnant women given influenza vaccine (2 studies)

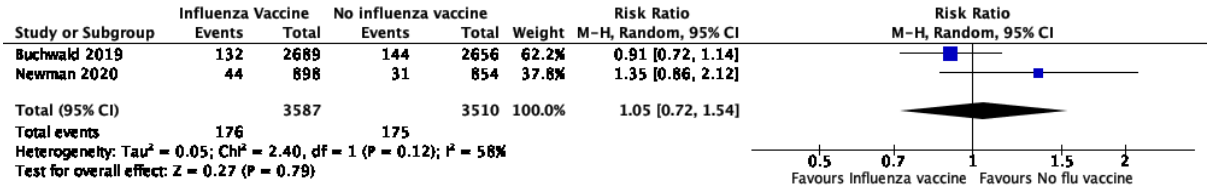

Figure 15. Effect of influenza vaccine among pregnant women on influenza among household contacts (2 studies)

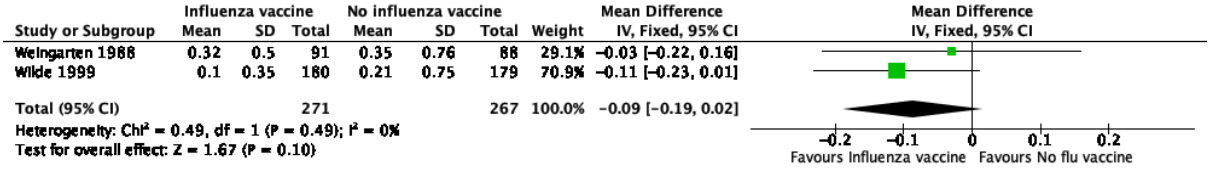

Figure 16. Effect of influenza vaccine among healthcare workers on missed working days (2 studies)

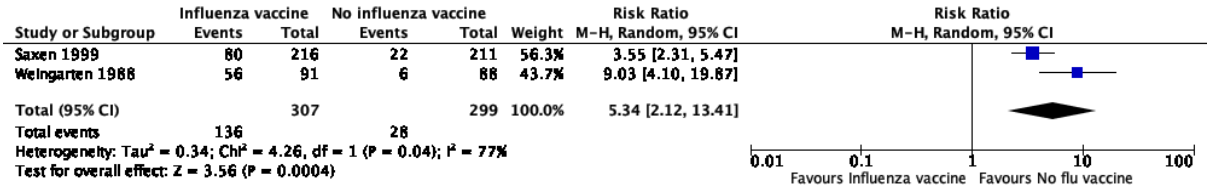

Figure 17. Adverse events of influenza vaccine among healthcare workers (2 studies)

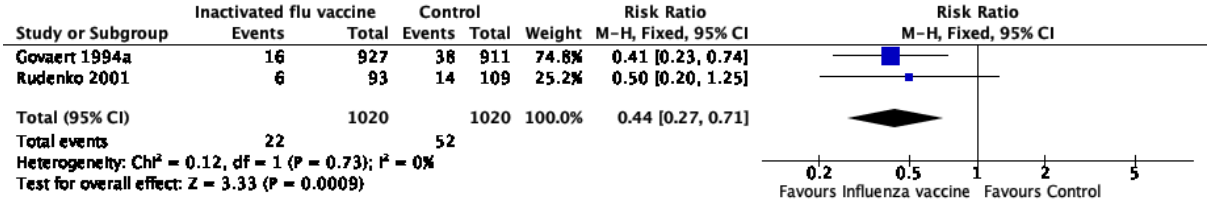

Figure 18. Effect of influenza vaccine among elderly on laboratory-confirmed influenza (2 studies)

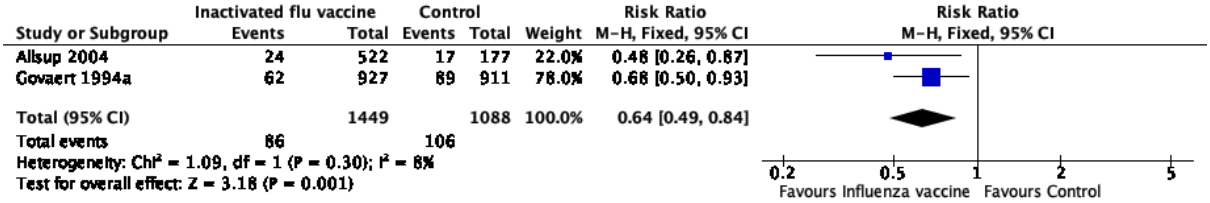

Figure 19. Effect of influenza vaccine among elderly on influenza-like illness (2 studies)

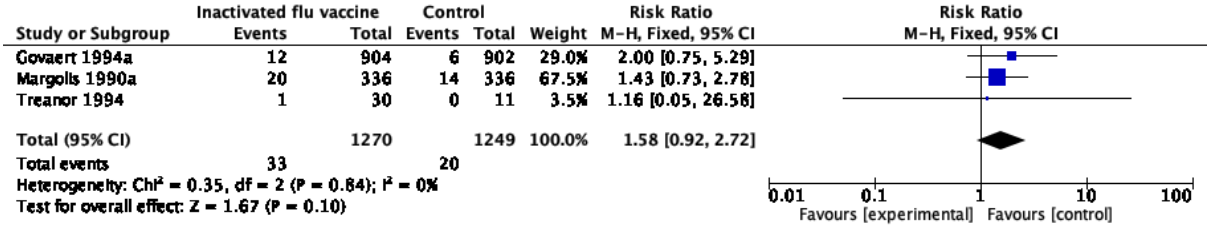

Figure 20. Effect of influenza vaccine among elderly on fever (3 studies)

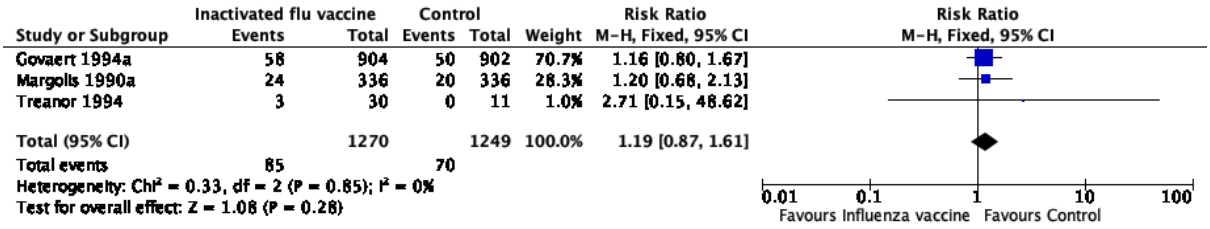

Figure 21. Effect of influenza vaccine among elderly on general malaise (3 studies)

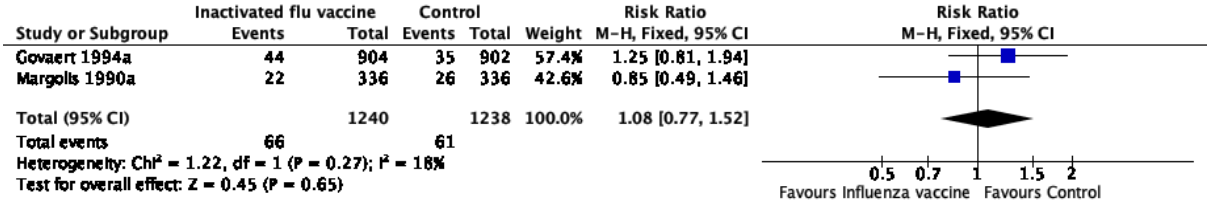

Figure 22. Effect of influenza vaccine among elderly on headache (2 studies)

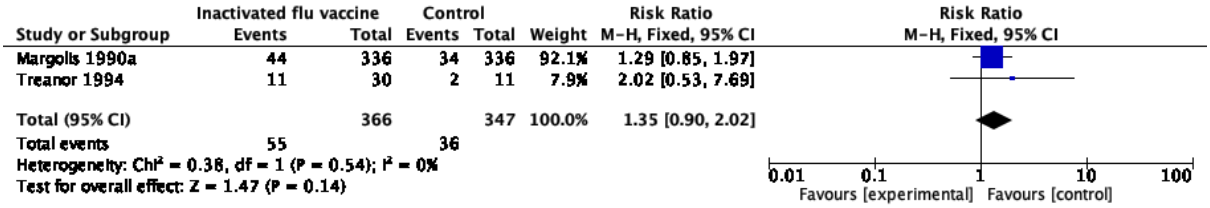

Figure 23. Effect of influenza vaccine among elderly on upper respiratory tract infection (2 studies)

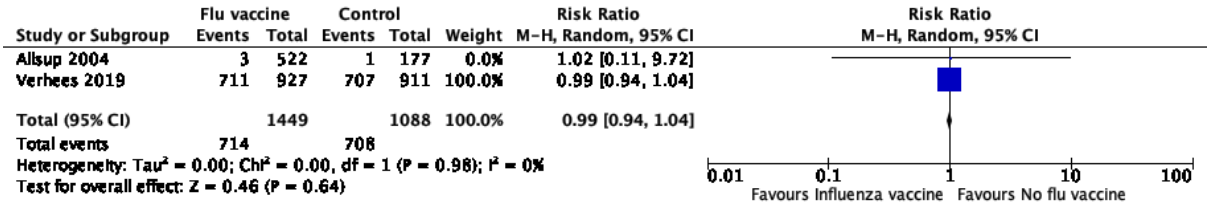

Figure 24. Effect of influenza vaccine among elderly on all-cause mortality (2 studies)

Appendix 5. Cost-Effectiveness Studies

	Author	Year	Country	Population	Intervention	Control	Cost-effective? (Y/N)	Reference
1	**Choi et al.**	2020	Korea	50-64 year old adults	QIV/TIV	No vaccine	**Yes.** The authors recommend quadrivalent vaccine due to greater protection against influenza B.	(28)
2	**Yang KC et al.**	2018	Taiwan	All (universal vaccination)	Influenza vaccine	No vaccine	**Yes.**	(29)
3	**You et al.**	2015	Hong Kong	All age groups	QIV	TIV	**Yes.** QIV cost effective compared with TIV for all age groups except 15-64 years old.	(30)
4	**Yue et al.**	2019	Singapore	All elderly and a proportion from other age groups	Influenza vaccine	No vaccine	**Yes.** The most optimal strategy was vaccination of all the elderly and a proportion of individuals from other age groups	(31)
5	**Yun et al.**	2020	South Korea	Elderly (≥65 years old)	QIV	TIV	**Yes.** QIV is more cost-effective than TIV.	(32)
6	**Jiang et al.**	2020	China	Elderly (69 years old)	QIV	TIV or no vaccine	**Yes.** QIV is more cost-effective than TIV and no influenza vaccine.	(33)
7	**Yang et al.**	2020	China	Elderly (≥60 years old)	Influenza vaccine	No vaccine	**Yes.** Regional analysis showed lower probability (48%) of influenza vaccination being cost-effective in Northeast China where there is low population density, reduced air population, low influenza mortality burden, and possibly poor quality of influenza surveillance. The other regions showed high probability (>80%) that vaccination was cost-effective.	(34)
8	**Boer et al.**	2018	Vietnam, South Africa, Australia	Elderly (≥65 years old), HIV-infected individuals, young children	QIV	TIV	**Yes.** More cost effective in Vietnam and South African than Australia.	(35)
9	**You et al.**	2014	Hong Kong	Elderly (≥65 years old)	QIV	TIV	**Yes.**	(36)
10	**Hoshi et al.**	2020	Japan	Pregnant women	Influenza vaccine	No vaccine	**Yes.**	(37)

Japanese Encephalitis Vaccine

Appendix 1. Evidence-to-Decision Summary

Burden	No	Probably No	Probably Yes	Yes (5)	Varies	Don't know (2)
Benefits	Trivial	Small	Moderate (5)	Large (2)	Varies	Don't know
Harms	Large	Moderate (3)	Small (4)	Trivial	Varies	Don't know
Certainty of evidence	Very Low	Low	Moderate	High	No included studies	
Balance of effects	Favors no vaccine	Probably favors no vaccine	Equivalent	Probably favors vaccine (5)	Favors vaccine (2)	Varies / Don't know

Resources required	Large costs (1)	Moderate costs (6)	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence (resources)	Very Low	Low (1)	Moderate (5)	High	No included studies (1)		
Cost effectiveness	Favors no vaccine	Probably favors no vaccine	Does not favor either	Probably favors vaccine (5)	Favors vaccine (1)	Varies (1)	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased (5)	Increased	Varies	Don't know (2)
Acceptability	No	Probably no (1)	Probably yes (4)	Yes	Varies	Don't know (2)	
Feasibility	No	Probably no (1)	Probably yes (3)	Yes (1)	Varies (1)	Don't know (1)	
Values	Important variability (1)	Possibly important variability (3)	Probably no important variability (2)	No important variability (1)			

Recommendation 1: **Asymptomatic apparently healthy adults**	STRONG against	WEAK against (1)	NO RECOMMENDATION (1)	WEAK in favor (2)	STRONG in favor (3)

Appendix 2. GRADE Summary of Findings Table

Question: Should Japanese encephalitis vaccine be given to asymptomatic apparently healthy adults?
Setting: Primary care/ community
Authors: SBartolo, HHGBayona
Bibliography:

1. Tauber E, Kollaritsch H, von Sonnenburg F, Lademann M, Jilma B, Firbas C, Jelinek T, Beckett C, Knobloch J, McBride WJ, Schuller E, Kaltenböck A, Sun W, Lyons A. Randomized, double-blind, placebo-controlled phase 3 trial of the safety and tolerability of IC51, an inactivated Japanese encephalitis vaccine. J Infect Dis. 2008 Aug 15;198(4):493-9. doi: 10.1086/590116.
2. Torresi J, McCarthy K, Feroldi E, Méric C. Immunogenicity, safety and tolerability in adults of a new single-dose, live-attenuated vaccine against Japanese encephalitis: Randomised controlled phase 3 trials. Vaccine 2010;28:7993–8000
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4. Monath TP, Guirakhoo F, Nichols R, Yoksan S, Schrader R, Murphy C, Blum P, Woodward S, McCarthy K, Mathis D, Johnson C, Bedford P. Chimeric live, attenuated vaccine against Japanese encephalitis (ChimeriVax-JE): phase 2 clinical trials for safety and immunogenicity, effect of vaccine dose and schedule, and memory response to challenge with inactivated Japanese encephalitis antigen. J Infect Dis. 2003 Oct 15;188(8):1213-30. doi: 10.1086/378356. Epub 2003 Oct 3. PMID: 14551893.
5. Nasveld PE, Ebringer A, Elmes N, Bennett S, Yoksan S, Aaskov J, McCarthy K, Kanesa-thasan N, Meric C, Reid M. Long term immunity to live attenuated Japanese encephalitis chimeric virus vaccine: randomized, double-blind, 5-year phase II study in healthy adults. Hum Vaccin. 2010 Dec;6(12):1038-46. doi: 10.4161/hv.6.12.13057. Epub 2010 Dec 1. PMID: 21150279; PMCID: PMC3060383.
6. Nasveld PE, Marjason J, Bennett S, Aaskov J, Elliott S, McCarthy K, et al.Concomitant or sequential administration of live attenuated Japanese Encephalitis chimeric virus vaccine and yellow fever 17D vaccine: randomized double-blind phase II evaluation of safety and immunogenicity. Hum Vaccin. 2010;6:906–14

B. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Japanese Encephalitis Vaccine	Placebo	Relative (95% CI)	Absolute (95% CI)		
Seroconversion rate												
4	randomised trials	not serious	not serious	serious[c]	not serious	none	428/441 (97.1%)	2/109 (1.8%)	**RR 51.87** (44.06 to 53.91)	**933 more per 1,000** (from 790 more to 971 more)	Moderate	CRITICAL
Local Adverse Events												
4	randomised trials	not serious	serious[a]	not serious	serious[b]	none	158/535 (29.5%)	87/340 (25.6%)	**RR 1.11** (0.74 to 1.66)	**28 more per 1,000** (from 67 fewer to 169 more)	Low	IMPORTANT
Systemic Adverse Events												
3	randomised trials	not serious	not serious	serious[c]	serious[b]	none	136/480 (28.3%)	118/318 (37.1%)	**RR 0.81** (0.63 to 1.05)	**71 fewer per 1,000** (from 137 fewer to 19 more)	Low	CRITICAL
Serious Adverse Events												

B. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Japanese Encephalitis Vaccine	Placebo	Relative (95% CI)	Absolute (95% CI)		
6	randomised trials	not serious	not serious	serious[c]	serious[b]	none	56/4064 (1.4%)	14/1400 (0.01%)	**RR 1.04** (0.45 to 2.38)	**0 fewer per 1,000** (from 6 fewer to 14 more)	Low	CRITICAL

CI: confidence interval; **RR:** risk ratio
Explanation
a. i2 is 59%,
b. crossed the line of no effect, c. i2 is 82%
c. Studies involved participants in non-JE-endemic countries

Appendix 3. Characteristics of Included Studies

Appendix 3.1. Asymptomatic, apparently healthy adults

Author/ Year	Study design	Country	Number of patients	Population	Intervention Group(s)	Control	Outcomes	
							Efficacy	Safety
Torresi 2010	RCT	USA Australia	2004	Healthy adults At least 18years of age	Live attenuated JE vaccine, single dose (n=1601)	Placebo (n=403)	None	Local adverse events Systemic adverse events Serious adverse events
Kaltenbock 2009	RCT Phase 3 trial	Austria	192	Healthy adults At least 18years of age	Inactivated Vero Cell derived JE Vaccine (IC51) ± Havrix (n=127)	IC51+ Placebo (n=65)	Immune response up to D56: Seroconversion rate Geometric mean titer	Within 7 days post vaccination: Local adverse events Systemic adverse event Serious adverse events
Tauber 2008	RCT Phase 3 trial	Australia Austria Germany Israel New Zealand Romania USA	2675	Healthy adults At least 18years of age	Inactivated Vero Cell derived JE vaccine or IC51 (n=2010)	Placebo (n=663)	None	Within 2 months post vaccination: Local adverse events Systemic adverse events Serious adverse events
Monath 2003	RCT Phase 2 trial	USA	99	Healthy adults At least 18years of age	Live attenuated JE vaccine or ChimeriVax JE (n=55 JECV) (n=22 JECV +YF)	Placebo (n=22)	Immune response at 30days post vaccination: Seroconversion rate	Within 2 months post vaccination: Local adverse events Systemic adverse events Serious adverse events
Nasveld 2010a	RCT Phase 2 trial	Australia	202	Healthy adults At least 18years of age	Live attenuated JE chimeric virus vaccine (JECV)	Placebo	Immune response at 1mos, 6mos, 7mos, 2yr, 5yr post vaccination: Seroconversion rate with single dose Seroconversion rate with booster	Within 1 month post vaccination: Local adverse events Systemic adverse events Serious adverse events
Nasveld 2010b	RCT	Australia	108	Healthy adults At least 18years of age	Live attenuated JE chimeric virus vaccine + Yellow Fever 17D vaccine	Placebo	Immune response at 30days post vaccination: Seroconversion rate	Within 1 month post vaccination: Local adverse events Systemic adverse events Serious adverse events

Appendix 4. Forest Plots

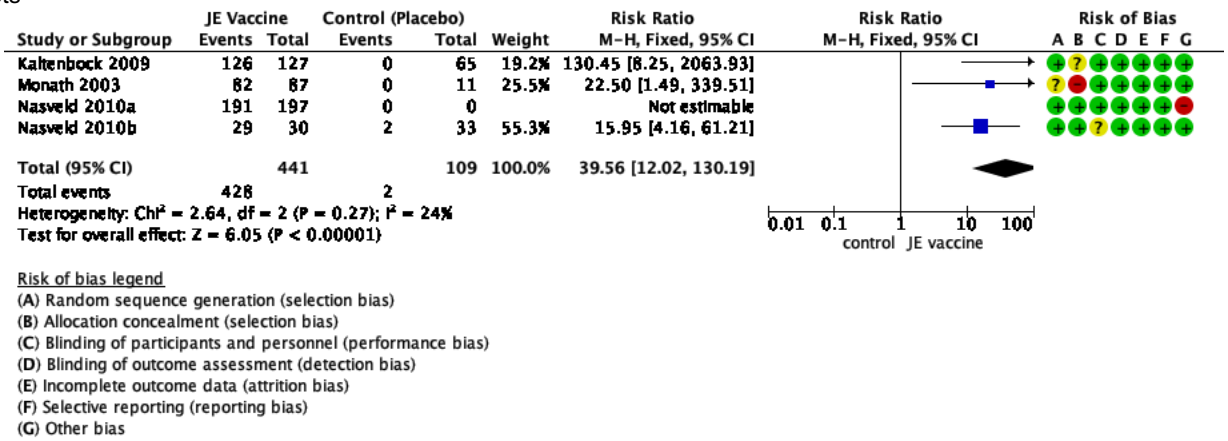
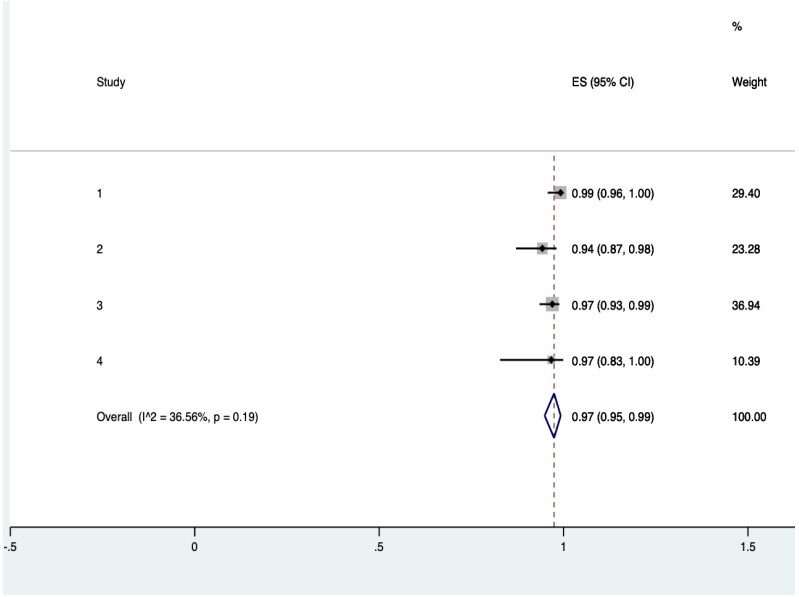


Figure 1. Seroconversion rates 1-month post-vaccination



1-Kaltenbock2009, 2-Monath2003, 3-Nasveld 2010a, 4-Nasveld 2010b

Figure 1.1. Seroconversion rates 1-month post-vaccination (pooled estimate)

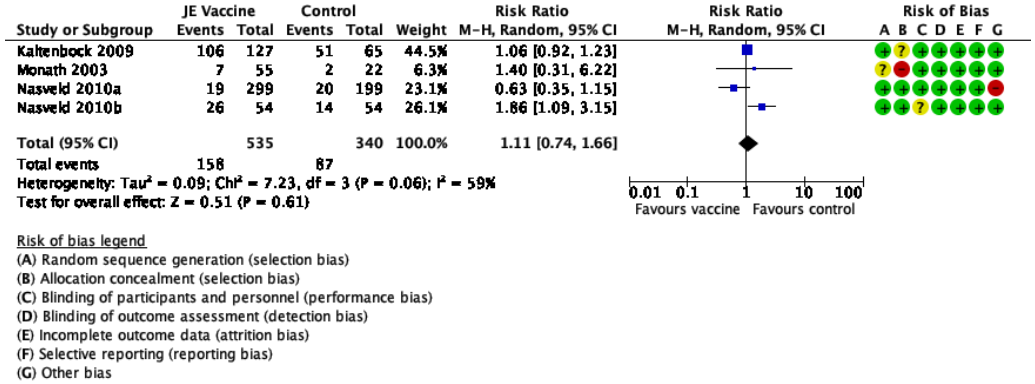


Figure 2. Local adverse events: vaccine vs placebo

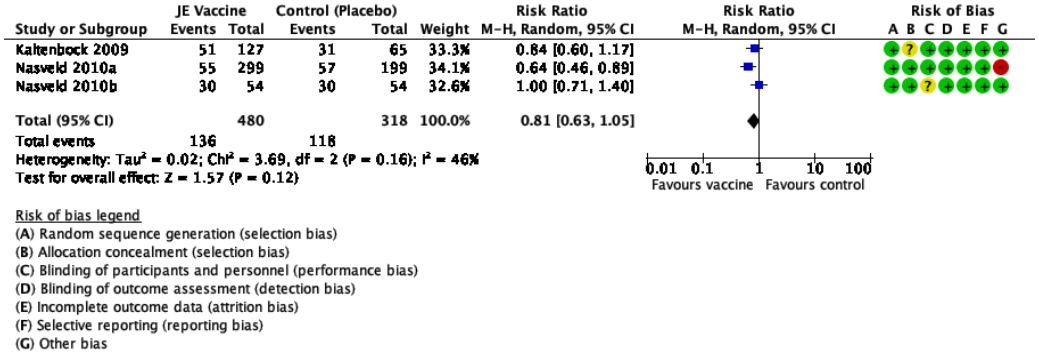


Figure 3. Systemic adverse events: vaccine vs placebo

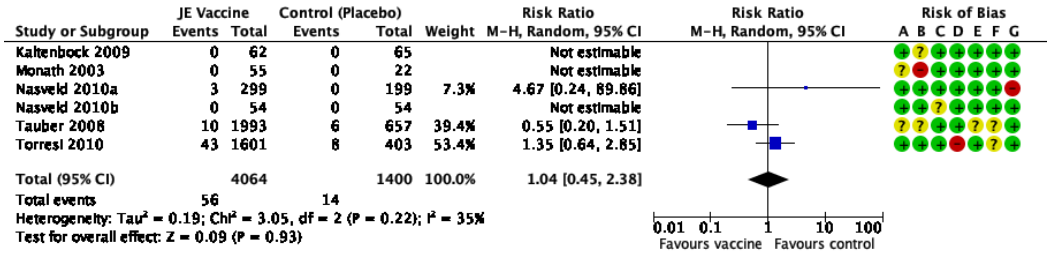
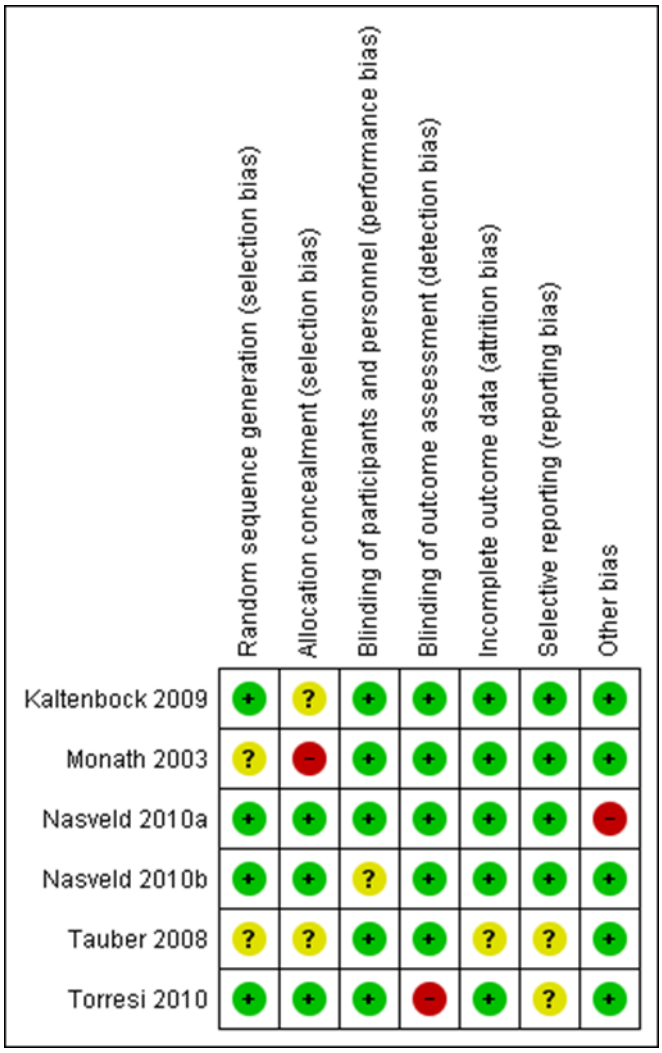


Figure 4. Serious adverse events: vaccine vs placebo

Appendix 5. Risk of Bias Assessment of Included Studies



Measles Vaccine

Appendix 1. Evidence-to-Decision Summary

Burden	No	Probably No	Probably Yes	Yes (5)	Varies (1)	Don't know
Benefits	Trivial	Small (1)	Moderate (2)	Large (3)	Varies	Don't know
Harms	Large	Moderate	Small (3)	Trivial (3)	Varies	Don't know
Certainty of evidence	Very Low (1)	Low (2)	Moderate	High (2)	No included studies	
Balance of effects	Favors no vaccine	Probably favors no vaccine	Equivalent/Does not favor either (1)	Probably favors vaccine (1)	Favors vaccine (4)	Varies / Don't know

Resources required	Large costs	Moderate costs	Negligible costs and savings (2)	Moderate savings (2)	Large savings (2)	Varies	Don't know
Certainty of evidence (resources)	Very Low	Low (1)	Moderate (3)	High (2)	No included studies		
Cost effectiveness	Favors no vaccine	Probably favors no vaccine	Does not favor either	Probably favors vaccine (2)	Favors vaccine (4)	Varies	Don't know
Equity	Reduced	Probably reduced	Probably no impact (2)	Probably increased (3)	Increased (1)	Varies	Don't know
Acceptability	No	Probably no	Probably yes (4)	Yes (2)	Varies	Don't know	
Feasibility	No	Probably no	Probably yes (3)	Yes (3)	Varies	Don't know	
Values	Important variability	Possibly important variability (4)	Probably no important variability	No important variability			

Recommendation 1: **Healthy adults (non-pregnant or unvaccinated)**	STRONG against	WEAK against	NO RECOMMENDATION	WEAK in favor (3)	STRONG in favor (3)

Appendix 2. GRADE Summary of Findings Table

Appendix 2.1. MCV vs. placebo in apparently healthy adults

Author(s): Renee Anne Karmela L. Feliciano, MD, Howell Henrian G. Bayona, MSc , Jeriel De Silos, MD
Setting: Non-healthcare setting
Bibliography:

1. Schmid D, Holzmann H, Schwarz K, et al. Measles outbreak linked to a minority group in Austria, 2008. Epidemiol Infect 2010; 138: 415–425.
2. Vitek C, Aduddel M, Brinton M, et al. Increased protections during a measles outbreak of children... : The Pediatric Infectious Disease Journal. Pediatr Infect Dis J 1999; 18: 620–623.
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5. Marin M, Nguyen HQ, Langidrik JR, et al. Measles Transmission and Vaccine Effectiveness during a Large Outbreak on a Densely Populated Island: Implications for Vaccination Policy. Clin Infect Dis 2006; 42: 315–319.
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8. Sutcliffe PA, Rea E. Outbreak of measles in a highly vaccinated secondary school population. C Can Med Assoc J 1996; 155: 1407.
9. Serres G De, Boulianne N, Meyer F, et al. Measles vaccine efficacy during an outbreak in a highly vaccinated population: incremental increase in protection with age at vaccination up to 18 months. Epidemiol Infect 1995; 115: 315.
10. Pawaskar M, Schmidt E, Marshall GS, et al. Use of M-M-R II outside of the routinely recommended age range - a systematic literature review [published online ahead of print, 2021 Jun 15]. Hum Vaccin Immunother. 2021;1-7. doi:10.1080/21645515.2021.1933874.
11. Nyaku M, Richardson E, Martinon-Torres F, et al. Evaluation of the Safety and Immunogenicity of M-M-RII (Combination Measles-mumps-rubella Vaccine) Clinical Trials of Healthy Children and Adults Published Between 2010 and 2019. Pediatr Infect Dis J 2021; 40: 1046–1054.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Measles-Containing Vaccine Effectiveness	placebo	Relative (95% CI)	Absolute (95% CI)		
2 Doses vs 0												
9	observational studies	not serious	not serious	serious[a]	serious[b]	none	23/2218 (1.0%)	289/500 (57.8%)	RR 0.03 (0.02 to 0.06)	**561 fewer per 1,000** (from 566 fewer to 543 fewer)	Very low	IMPORTANT
Immunogenicity												
8	randomised trials	not serious	serious[c]	not serious	serious[d]	none	In the Pawaskar et al review, 8 studies were included in the review, with 7 studies done in persons ≥7 years old. Five of the 7 studies gave the MMR vaccine as a second dose, 1 gave it as a single dose, and the remaining study was unspecified in another study. In the Nyaku et al review, 2 out of the 15 studies were done in individuals ≥7 years old. One study is already included in the Pawaskar et al review, while the other study is unique				Low	IMPORTANT
Adverse events												
7	randomised trials	not serious	serious[e]	not serious	serious[d]	none	Reported adverse reactions to MMR vaccine include fever, rash, lymphadenopathy, joint complaints, hypersensitivity reactions, development of immune thrombocytopenia (ITP), and seizures. Pawaskar et al investigated the safety data in the included 7 studies on people ≥7 years of age. The rates of adverse events in these studies consisted of fever ≥ 38˚C (5.2%-8.7%), injection site reactions (2%-33.3%), and measles/rubella-like rash after the 2nd dose (0.4%). Overall, this study suggests that the MMR vaccine is safe and well-tolerated by recipients ≥ 7 years old. No serious adverse events were documented in the studies included in the review.				Low	IMPORTANT

Explanations
a. The studies were not conducted in persons who were vaccinated with an MCV as an adult (1-level downgrade)
b. Moderate to substantial heterogeneity of the generated forest plot was noted (I2 = 60%)
c. Measurement of immunogenicity is not similar in all included studies.
d. Adolescent age groups are part of the study population in some of the included studies.
e. Some of the adverse events are not measured in some of the included studies.

Appendix 2.2. MCV vs placebo in preventing all-cause mortality in healthcare workers

Bibliography: Higgins JPT, Soares-Weiser K, López-López JA, et al. Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. BMJ 2016; 355: 5170.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	All-cause mortality	Alive	Relative (95% CI)	Absolute (95% CI)		
All-Cause Mortality												
4	randomised trials	not serious	not serious	serious[a]	serious[b]	none	169/17190 (1.0%)	17021/17190 (99.0%)	RR 0.74 (0.51 to 1.07)	**257 fewer per 1,000** (from 485 fewer to 69 more)	Low	IMPORTANT

CI: confidence interval; **RR**: risk rati

Explanations

a. The study is conducted on children (not healthcare workers).

b. The CI crossed 1.0 (inconclusive)

Appendix 3. Characteristics of Included Studies

Study ID	Study Design	Setting	Population	Intervention	Comparator	Outcomes
Vaccine Effectiveness (2 Doses vs 0 Dose)						
Uzicanin and Zimmerman et al., 2011[14]	Systematic Review	Community outbreak setting (multiple countries)	9 to 11-months of age and ≥ 12 months of age (either vaccinated or unvaccinated)	History of MCV immunization	No history of MCV immunization	Vaccine effectiveness
Seroconversion and/ or Immunogenicity						
Pawaskar et al., 2021[2]	Systematic Review	Community outbreak setting (multiple countries)	Recipients of M-M-R-II vaccines (6 to 11-month old and persons ≥7 years of age.)	Recipients of M-M-R-II vaccine	Different MCV	Seroconversion rate
Nyaku et al., 2021[13]	Systematic Review	Community outbreak setting (multiple countries)	Recipients of M-M-R-II vaccines (12-13 months old, 4-7 years old, and persons ≥7 years of age.)	Recipients of M-M-R-II vaccine	Investigational MMR (non-inferiority)	Seroconversion rate
Healthcare Workers						
Higgins et al, 2016[15]	Systematic Review	Effect on mortality of standard titer MCV in children under 5.	Children under 5 (n=17,190)			
Jia et al, 2018[16]	Cohort Study	Hospital outbreak among healthcare workers in a hospital in Xinjiang Uighur Autonomous Region of the People's Republic of China	19 healthcare workers (18 to 45 years of age)	Had received MCV before the outbreak	Not vaccinated and unknown vaccine status	Proportion of infected who are either vaccinated or not vaccinated
Barbadoro et al., 2012[17]	Cohort Study	Outbreak in a teaching hospital in Central Italy	72 Healthcare workers in a teaching hospital in central Italy (4 are positive)	Had received MCV before the outbreak	Not vaccinated	Proportion of infected who are either vaccinated or not vaccinated
Shakoor et al., 2015[18]	Narrative review	Hospital readiness during community measles outbreak in low-resource settings	n/a	PPE, environmental control, administrative control (including MCVs)	n/a	Measles containment in hospitals
Resource Implication						
Zeng et al., 2019[19]		East China	Simulated birth cohort in 2014	With Measles vaccination	No measles vaccination	Cost-effectiveness of vaccine
Zhou et al., 2004[20]		USA	Hypothetical US birth cohort of infants born in 2001	With MMR Vaccination Program	No MMR vaccination program	Cost-effectiveness of vaccine

Appendix 3.2. Results of Included Studies

Table 1. Immunogenicity of M-M-R II in individuals 6–11 months and ≥7 years of age, Adapted from Pawaskar et al., 2021[12]

Author, Year	Study Country (Study period)	Population, N receiving M-M-R II	Age	Time-frame post-vaccination	Immunogenicity (Measles)
6–11 months of age					
Redd	US (1992–1994)	285	9.6 months (mean)	1 month	87.4% SCR defined as detectable antibody post-vaccination but not pre-vaccination (indirect EIA)
≥7 years of age					
Abu-Elyazeed	US, Estonia and Slovakia (2014–2015)	457, with at least one previous dose of a MMR vaccine	25.6 years (mean)	42 days	99.1% SRR defined as ≥200 mIU/mL (ELISA)
Gothefors	Sweden (1997)	150, who had a first dose of M-M-R II in their 2nd year	11–12 years (range)	40 days	5.7% immune response defined as ≥4-fold increase in pre-vaccination antibody activity in initially seropositive subjects (ELISA) 100% SCR defined as appearance of detectable antibody activity in initially seronegative subjects (ELISA)
Diaz-Ortega	Mexico (2010–2011)	62 (M-M-R II via injection) All received one dose of a M-M-R II at 1–2 years	6.72 (mean)	1 month	100% SCR defined as ≥120 mIU/mL (PRN)
				1 year	100%
Diaz-Ortega	Mexico	100 (not specified if prevaccinated or unvaccinated)	18–25 years (range enrolled)	2 months	96% SCR defined as ≥120 mIU/mL (PRN)
				1 year	95%
Sarno	Mexico (1999–2000)	40 (standard syringe); 12/40 had received prior measles vaccine, 1/40 MMR at 12 months of age	11.1 years (mean)	12 weeks	100% above baseline
Dos Santos	Brazil (1996)	219, previously vaccinated and unvaccinated	8.92 years (mean)	21–30 days	99.5% SPR, threshold not defined (ELISA)
Cassidy*	US (1996–1997)	97 (all vaccines at visit 1), 100 (HB at visit 1, Td and M-M-R II at 4.5 months) [dose 2]	11–12 years (range)	6 weeks	100% [HB, M-M-R II and Td at visit 1] 100% [HB at visit 1, M-M-R II and Td at 4.5 months] SP defined as ≥120 IU/ml (EIA)

EIA enzyme immunoassay; ELISA enzyme-linked immunosorbent assay; HB Hepatitis B; NR not reported; PRN plaque reduction neutralization; SCR seroconversion rate; SPR seropositivity rate; SP seroprotection; SRR seroresponse rate; Td Tetanus-diphtheria

*All other antigens also 100% in both groups with the exception of 98.8% for tetanus and diphtheria in the group receiving HB at visit 1 while M-M-R II and Td at visit 4.5 months.

Table 2. Safety of M-M-R II in individuals ≥7 years of age, Adapted from Pawaskar et al., 2021 (12)

Author, Year	Study Arm	N	Timeframe (AE)	Fever	Injection site reactions	Measles/rubella like rash
Abu-Elyazeed	M-M-R II	457	0-42 days	5.2% (defined as temperature ≥38°C)	11.7% injection site redness; 11.5% injection site pain (day 0–3)	NR
Diaz-Ortega	M-M-R II injection	62	12 months	6.45% (not defined)	NR	NR
Diaz-Ortega	NA	100	NR	NR	NR	NR
Gothefors	NA	150	40 days	8.7% (defined as temperature ≥38.1°C)	33.3% injection site pain; 25.3% redness; 12.7% swelling (day 0–3)	NR
Sarno	M-M-R II delivered by standard syringe (either before or after reconstitutional buffer delivered by injection)	40	NR	2.5% mild fever at 15 days (not defined)	12.5% injection site soreness (within 15 days)	NR
Dos Santos	NA	NR	NR	NR	NR	NR
Dos Santos	NA	2216	30 days	4.7% (not defined)	2% injection site pain (within 30 days)	NR
Cassidy	HB (visit 1) M-M-R® II (visit 1) Td (visit 1)	97	0-4 days	2.2% (not defined)	NR	NR
	HB (visit 1) M-M-R® II (at 4.5 months) Td (at 4.5 months)	100	0-4 days	0	NR	NR

HB Hepatitis B; NR not reported; Td Tetanus-diphtheria

Appendix 4. Forest Plots

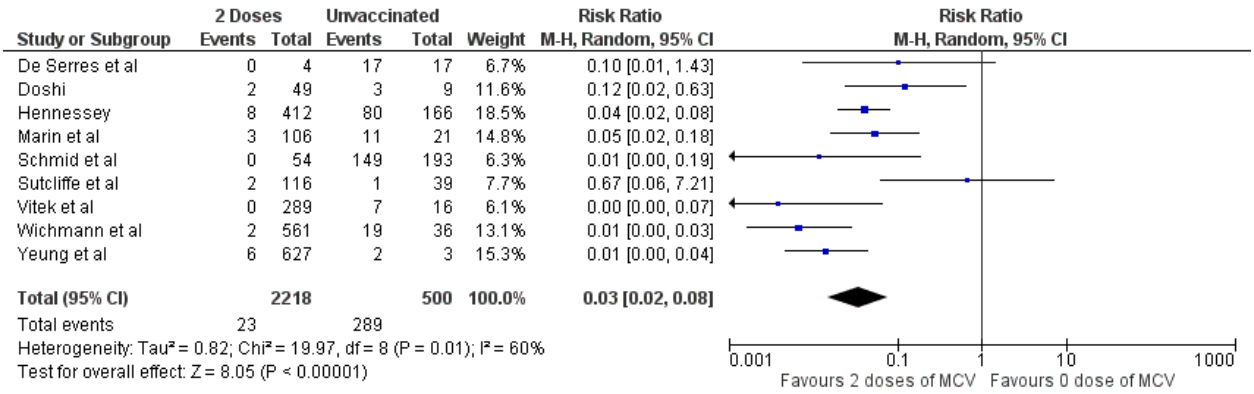


Figure 1. 2-dose MCV vs no vaccine in preventing measles infection

Birth cohort	Deaths/ children*	Prior BCG†	Prior DTP‡	Age at first dose	Observation period§	Effect measure	Adjustment	Relative risk (95% CI)	Relative risk (95% CI)	Mortality reduction¶	Assessment of risk of bias
Clinical trials											
Guinea-Bissau 1989-2001[a56]	(3+3)/300	NR	Many	6 months	Age 6-9 months	RR	None		1.00 (0.20 to 4.91)	0% (-392% to 80%)	Moderate risk
Guinea-Bissau 1989-2001[a35]	(42+40)/8511	NR	Many	6 months	Age 6-9 months	MRR	None		0.94 (0.53 to 1.67)	6% (-67% to 47%)	Moderate risk
Guinea-Bissau 2002-08[a61]	(16+48)/6417	NR	All	4.5 months	Age 4.5-9 months	HR	Age		0.67 (0.38 to 1.19)	33% (-19% to 62%)	Moderate risk
Nigeria c.1961[a66]	(5+12)/1962	NR	NR	6-24 months	6-20 months follow-up	RR	None		0.41 (0.14 to 1.15)	59% (-15% to 86%)	Moderate risk
FE subtotal: P=0.55, I^2=0%									0.74 (0.51 to 1.07)		
RE subtotal									0.74 (0.51 to 1.07)		
with estimated predictive interval									(0.33 to 1.66)		
Observational studies											
Case-control											
Benin 1983-87[a2]	(12+49)/252	Many	Many	NR	Age 4-36 months	OR	Age, sex, others		0.36 (0.16 to 0.81)	64% (19% to 84%)	High risk
India 1991-98[a65]	(252+66)/636	Most	Most	NR (before 12 months)	Age 12-60 months	OR	None		0.36 (0.23 to 0.56)	64% (44% to 77%)	High risk
Cohort											
Bangladesh 1977-85[a45]	(170+321)/16 268	Some	Some	NR (from 9 months)	Age 9-60 months	HR	Age, sex, others		0.51 (0.42 to 0.62)	49% (38% to 58%)	High risk
Bangladesh 1986-2001[a1]	NR/36650	Many	Many	NR (from 9 months)	Age 9-60 months	HR	Age, sex, BCG, DTP, others		0.93 (0.65 to 1.34)	7% (-34% to 35%)	High risk
DR Congo 1973-75[a50]	(3+21)/c.600	NR	NR	Mean 8.8 months	Age 7-21 months	MRR	None		0.29 (0.09 to 0.98)	71% (2% to 91%)	High risk
Guinea-Bissau 1978-83[a52]	(7+5)/c.210	NR	NR	NR (6-35 months)	13 months follow-up	RR	Age		0.62 (0.20 to 1.88)	38% (-88% to 80%)	High risk
Guinea-Bissau 1978-83[a51]	(3+8)/99	NR	NR	NR (6-35 months)	12 months follow-up	RR	None		0.51 (0.15 to 1.81)	49% (-81% to 86%)	High risk
Guinea-Bissau 1984-87[a55]	NR/722	NR	NR	Median 11.1; 15 months	Age 17.5 months or more	HR	Age, sex, others		0.34 (0.17 to 0.68)	66% (32% to 83%)	High risk
Guinea-Bissau 1990-96[a13]	(19+94)/4230	Many	Many	Median 10.6 months	Age 7-19 months	HR	Age, BCG		0.48 (0.27 to 0.87)	52% (13% to 73%)	High risk
Guinea-Bissau 1999-2006[a60]	(103+358)/12 119	Many	Many	NR (by 12 months in 53%)	Age 9-35 months	HR	Age, others		0.71 (0.56 to 0.90)	29% (10% to 44%)	High risk
Haiti 1981-82[a63]	NR/1381	NR	NR	Median 9 months	Age 9-39 months	OR	None		0.10 (0.02 to 0.42)	90% (58% to 98%)	High risk
India 1986-91[a64]	(94+37)/12 034	Most	Most	NR (at 6-8 [8-11] months 85% [15%])	Age 12-60 months	MRR	Age, sex		0.34 (0.23 to 0.51)	66% (49% to 77%)	High risk
India 1987-89[a19]	NR/3883	Many	Many	Median 9.4 months	Age 12-60 months	MRR	None		0.31 (0.12 to 0.80)	69% (20% to 88%)	High risk
Malawi 1995-97[a22]	NR/669	Most	Most	Median 10.8 months	Age 9-18 months	HR	Age, others		0.42 (0.16 to 1.14)	58% (-14% to 84%)	High risk
Papua New Guinea 1989-94[a23]	NR/4048	All	Many	NR (by 12 months in 74%)	Age 6-11 months	HR	Age, DTP, others		0.48 (0.18 to 1.26)	52% (-26% to 82%)	High risk
Senegal 1985-87[a67]	(53+124)/2030	NR		Mean 15.8 months	Age 9-24 months	MRR	None		0.99 (0.72 to 1.37)	1% (-37% to 28%)	High risk
Senegal 1987-89[a67]	(31+34)/1159	NR		Mean 11.6 months	Age 9-24 months	MRR	None		0.68 (0.42 to 1.10)	32% (-10% to 58%)	High risk
Senegal 1996-99[a24]	(13+372)/4133	Some		NR (by 12 [24] months in 9% [20%])	Age 24 months	HR	Age, sex, others		0.55 (0.31 to 0.98)	45% (2% to 69%)	High risk
FE subtotal: P<0.001, I^2=64%									0.57 (0.52 to 0.63)		
RE subtotal									0.51 (0.42 to 0.63)		
with estimated predictive interval									(0.25 to 1.04)		
Excluded (very high risk of bias)											
Burundi 1984-88[a49]	(16+66)/1899	NR	NR	NR (at 9-11 months in 59%)	6 months follow-up	MRR	None		0.30 (0.17 to 0.52)		Very high risk
Ghana 1984-91[a32]	(17+27)/1793	Many	All (OS)	NR (6-35 months)	4 months follow-up	HR	Age, others		0.51 (0.29 to 0.97)		Very high risk
Ghana 1994-99[a28]	NR/17 701	All	All	Median 9.1 months	Age 9-11 months	HR	None		0.78 (0.43 to 1.41)		Very high risk
Ghana 1998-2004[a5]	NR/17 967	Many	Many	NR (by 12 [24] mo in 5% [64%])	Age 60 months	HR	Age, others		0.14 (0.13 to 0.16)		Very high risk
Guinea-Bissau 2004-09[a43]	(18+29)/3764	NR	NR	NR (6-23 months)	12 months follow-up	MRR	None		0.42 (0.23 to 0.76)		Very high risk
India 2006-11[a21]	(58+17)/11 390	Many	Many	Mean 9.4 months	Age 9-15 months	MRR	None		0.41 (0.24 to 0.70)		Very high risk
Senegal 1989-96[a25]	(20+35)/7796	Many	Many	Median 9.7 months	Age up to 24 months	HR	None		0.98 (0.75 to 1.27)		Very high risk

Figure 2. MCV and all-cause mortality, adapted from Higgins et al, 2016[15]

Appendix 5. Cost-Effectiveness Studies

Author	Year	Country	Population	Intervention	Control	Bcr	Savings	Cost-effective? (y or n)
Zeng, et al.[19]	2019	East China	Simulated birth cohort in 2014	With Measles vaccination	No measles vaccination	BCR = 6.06	NPV = $73.38M	Y current measles vaccination program appeared to be cost-effective and to offer substantial benefits
Zhou, et al.[20]	2004	USA	Hypothetical US birth cohort of infants born in 2001	With MMR Vaccination Program	No MMR vaccination program	Direct benefit-cost ratio = 14.2 Societal benefit-cost ratio = 26.0)	NPV = direct cost $3.5 billion societal perspective $7.6billion)	Y national 2-dose MMR vaccination program is highly cost-beneficial and results in substantial cost savings

Meningococcal Vaccine

Appendix 1. Evidence-to-Decision Summary

Burden	No (1)	Probably No	Probably Yes	Yes (3)	Varies (1)	Don't know (1)
Benefits	Trivial	Small (1)	Moderate (6)	Large	Varies	Don't know
Harms	Large	Moderate (2)	Small (5)	Trivial	Varies	Don't know
Certainty of evidence	Very Low	Low	Moderate	High	No included studies	
Balance of effects	Favors no vaccine	Probably favors no vaccine	Equivalent	Probably favors vaccine (2)	Favors vaccine (4)	Varies (1)	Don't know

Resources required	Large costs (2)	Moderate costs (2)	Negligible costs and savings	Moderate savings	Large savings	Varies (2)	Don't know (1)
Certainty of evidence (resources)	Very Low (2)	Low	Moderate (2)	High (1)	No included studies (2)		
Cost effectiveness	Favors no vaccine	Probably favors no vaccine	Does not favor either	Probably favors vaccine (2)	Favors vaccine	Varies (2)	No included studies (3)
Equity	Reduced	Probably reduced (2)	Probably no impact (1)	Probably increased	Increased (1)	Varies (1)	Don't know (2)
Acceptability	No	Probably no (3)	Probably yes (1)	Yes (1)	Varies (1)	Don't know (1)	
Feasibility	No (1)	Probably no (2)	Probably yes (4)	Yes	Varies	Don't know	

Recommendation 1: **Asymptomatic apparently healthy adults**	STRONG against	WEAK against (2)	NO RECOMMENDATION	WEAK in favor (5)	STRONG in favor

Appendix 2. GRADE Summary of Findings Table

Table 1. GRADE Evidence Profile: MenACWY versus control for healthy adults aged 18 to 55 years

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MenACWY-DT	control	Relative (95% CI)‡	Absolute (95% CI)		
Serious adverse events (all healthy adults)												
1	randomised trials	not serious	not serious	not serious	not serious	none	0/199 (0.0%)	0/99 (0.0%)	not estimable		High	CRITICAL
Serious adverse events (pregnant women)												
4	observational studies	serious[a]	not serious	serious[a]	not serious	none	Zheteyeva and colleagues found that among 103 pregnant women (median age is 17 years) exposed inadvertedly, 17 had spontaneous abortions (16.5%), 1 congenital anomaly (1% aqueductal stenosis and severe ventriculomegaly). Becerra-Culqui 2020 identified 92 women who were vaccinated during the pregnancy period. Two spontaneous abortions (16.7%) and one induced abortion (5.3%).Myers 2017 identified 14 pregnant women exposed to MenACWY-CRM, 3 reports included limited information on birth outcomes that were in all cases normal. In a study by Hansen and research team, MenACWY-D safety in large integrated health care system was examined. They identified 25 pregnancy exposures with 12 live births (1 infant with dermoid cyst), 5 elective abortions, 1 fetal death; authors reported no unusual pattern of adverse events, but very few exposed pregnancies only.				Very Low	CRITICAL
Vaccine response - MenA (assessed with: Proportion of subjects exhibiting seroconversion)												
1	randomised trials	not serious	not serious	not serious	not serious	none	154/198 (77.8%)	9/97 (9.3%)	**RR 8.38** (4.48 to 15.69)	**685 more per 1,000** (from 323 more to 1,000 more)	High	CRITICAL
Seroconversion rate - MenC (assessed with: Proportion of subjects exhibiting seroconversion)												
1	randomised trials	not serious	not serious	not serious	not serious	none	174/197 (88.3%)	8/99 (8.1%)	**RR 10.93** (5.61 to 21.28)	**802 more per 1,000** (from 373 more to 1,000 more)	High	CRITICAL
Vaccine response - MenW (assessed with: Proportion of subjects exhibiting seroconversion)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MenACWY-DT	control	Relative (95% CI)‡	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	not serious	none	182/197 (92.4%)	12/98 (12.2%)	**RR 7.54** (4.43 to 12.84)	**801 more per 1,000** (from 420 more to 1,000 more)	High	CRITICAL
Vaccine response - MenY (assessed with: Proportion of subjects exhibiting seroconversion)												
1	randomised trials	not serious	not serious	not serious	not serious	none	97/197 (49.2%)	8/98 (8.2%)	**RR 6.03** (3.06 to 11.89)	**411 more per 1,000** (from 168 more to 889 more)	High	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. there were no control groups to compare the effects among those who were pregnant and unvaccinated. only pregnancies and inadvertent exposures to vaccination were reported

‡ Efficacy (higher relative effect means higher efficacy) and safety outcomes (lower relative effect means safer use)

Table 2. GRADE Evidence Profile: MenACWY versus control for high-risk adults aged 18 to 55 years

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MenACWY-DT	control	Relative (95% CI)‡	Absolute (95% CI)		
Serious adverse events												
1	randomised trials	not serious	not serious	serious[b]	not serious[c]	none	0/199 (0.0%)	0/99 (0.0%)	not estimable		Moderate	CRITICAL
Serious adverse events (pregnant women)												
4	observational studies	serious[a]	not serious	serious[a]	not serious	none	Zheteyeva and colleagues found that among 103 pregnant women (median age is 17 years) exposed inadvertedly, 17 had spontaneous abortions (16.5%), 1 congenital anomaly (1% aqueductal stenosis and severe ventriculomegaly). Becerra-Culqui 2020 identified 92 women who were vaccinated during the pregnancy period. Two spontaneous abortions (16.7%) and one induced abortion (5.3%).Myers 2017 identified 14 pregnant women exposed to MenACWY-CRM, 3 reports included limited information on birth outcomes that were in all cases normal. In a study by Hansen and research team, MenACWY-D safety in large integrated health care system was examined. They identified 25 pregnancy exposures with 12 live births (1 infant with dermoid cyst), 5 elective abortions, 1 fetal death; authors reported no unusual pattern of adverse events, but very few exposed pregnancies only.				Very Low	CRITICAL
Vaccine response - MenA (assessed with: Proportion of subjects exhibiting seroconversion)												
1	randomised trials	not serious	not serious	serious[b]	not serious	none	154/198 (77.8%)	9/97 (9.3%)	**RR 8.38** (4.48 to 15.69)	**685 more per 1,000** (from 323 more to 1,000 more)	Moderate	CRITICAL
Seroconversion rate - MenC (assessed with: Proportion of subjects exhibiting seroconversion)												
1	randomised trials	not serious	not serious	serious[b]	not serious	none	174/197 (88.3%)	8/99 (8.1%)	**RR 10.93** (5.61 to 21.28)	**802 more per 1,000** (from 373 more to 1,000 more)	Moderate	CRITICAL
Vaccine response - MenW (assessed with: Proportion of subjects exhibiting seroconversion)												
1	randomised trials	not serious	not serious	serious[b]	not serious	none	182/197 (92.4%)	12/98 (12.2%)	**RR 7.54** (4.43 to 12.84)	**801 more per 1,000** (from 420 more to 1,000 more)	Moderate	CRITICAL
Vaccine response - MenY (assessed with: Proportion of subjects exhibiting seroconversion)												
1	randomised trials	not serious	not serious	serious[b]	not serious	none	97/197 (49.2%)	8/98 (8.2%)	**RR 6.03** (3.06 to 11.89)	**411 more per 1,000** (from 168 more to 889 more)	Moderate	CRITICAL

Table 3. GRADE Evidence Profile: MenB vaccines vs. Control group (HAV vaccine or saline for young adults 18-25 years old)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MenB vaccines	Control	Relative (95% CI) ‡	Absolute (95% CI)		
Vaccine response (MenB-4c) (follow-up: range 2 months)												
1	randomised trial	serious[a]	not serious	not serious	serious	none	191/192 (99%)	129/197 (65.0%)	**RR 1.52** (1.37 to 1.68)	**341 more per 1,000** (from 242 fewer to 445 more)	Moderate	CRITICAL
Vaccine response (MenfHBP) (follow-up: mean 28 days)												
1	randomised trial	serious[a]	not serious	not serious	not serious	none	2217/2471 (89.7%)	87/822 (10.6%)	**RR 8.48** (6.95 to 10.35)	**792 more per 1,000** (from 630 more to 990 more)	Moderate	CRITICAL
Vaccine response (follow-up: 1 year)												
1	randomised trial	serious[a]	not serious[a]	not serious	not serious	none	163/192 (84.9%)	89/197 (45.2%)	**RR 1.88** (1.59 to 2.22)	**398 more per 1,000** (from 267 more to 551 more)	Moderate	CRITICAL
Serious adverse event (MenfHBP) (follow-up: 6 months)												
1	randomised trial	serious[a]	not serious	not serious	serious[b]	none	33/2471 (1.3%)	11/822 (1.3%)	**RR 1.00** (0.50 to 1.95)	**0 fewer per 1,000** (from 7 fewer to 13 more)	Low	CRITICAL
Serious adverse event (MenB4C) (follow-up: 6 months)												
1	randomised trial	serious[a]	not serious	not serious	not serious	none	One participant had a serious AE (fractured patella) unrelated to vaccination.				Moderate	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Read 2017 had unclear risk of selection bias and high attrition; Ostergaard 2017 - failure to blind participants

b. wide confidence interval

‡ Efficacy (higher relative effect means higher efficacy) and safety outcomes (lower relative effect means safer use)

Table 4. GRADE Evidence Profile: MenB vaccines vs. Control group (HAV vaccine or saline for high-risk adults)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MenB vaccines	Control	Relative (95% CI) ‡	Absolute (95% CI)		
Case of serogroup B meningococcal Infection (MenB-4c) (follow-up: 2 academic years)												
1	observational study	serious[a]	not serious	not serious	serious[c]	Plausible confounding would suggest spurious effect	0/5502 (0%)	0	-	-	Very Low	CRITICAL
Vaccine response (MenB-4c) (follow-up: range 2 months)												
1	randomised trials	serious[a]	not serious	serious	serious	none	191/192 (99%)	129/197 (65.0%)	**RR 1.52** (1.37 to 1.68)	**341 more per 1,000** (from 242 fewer to 445 more)	Very Low	CRITICAL
Vaccine response (MenfHBP) (follow-up: mean 28 days)												
1	randomised trials	serious[a]	not serious	serious	not serious	none	2217/2471 (89.7%)	87/822 (10.6%)	**RR 8.48** (6.95 to 10.35)	**792 more per 1,000** (from 630 more to 990 more)	Very Low	CRITICAL
Vaccine response (follow-up: 1 year)												
1	randomised trials	serious[a]	not serious[a]	serious	not serious	none	163/192 (84.9%)	89/197 (45.2%)	**RR 1.88** (1.59 to 2.22)	**398 more per 1,000** (from 267 more to 551 more)	Very Low	CRITICAL
Serious adverse event (MenfHBP) (follow-up: 6 months)												
1	randomised trials	serious[a]	not serious	serious	serious[b]	none	33/2471 (1.3%)	11/822 (1.3%)	**RR 1.00** (0.50 to 1.95)	**0 fewer per 1,000** (from 7 fewer to 13 more)	Very Low	CRITICAL
Serious adverse event (MenB4C) (follow-up: 6 months)												
1	randomised trials	serious[a]	not serious	serious	not serious	none	One participant had a serious AE (fractured patella) unrelated to vaccination.				Very Low	CRITICAL
Serious adverse event (MenB4C) (follow-up: 24 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MenB vaccines	Control	Relative (95% CI) ‡	Absolute (95% CI)		
1	Observational study	serious[a]	not serious	not serious	not serious	Plausible confounding would suggest spurious effect	report of rhabdomyolysis 1 day after the MenB-4C vaccination				Very Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Read 2017 had unclear risk of selection bias and high attrition; Ostergaard 2017 - failure to blind participants; McNamara 2015 (observational study had only one outbreak setting despite multiple cities with outbreaks, no description of a non-exposed cohort, and no clear description of outcome ascertainment after vaccination, although they probably did gold standard testing as multiple institutions collaborated for the vaccination program)

b. wide confidence interval

c. Without the data on control group or nonexposure group, the result is inconclusive.

‡ Efficacy (higher relative effect means higher efficacy) and safety outcomes (lower relative effect means safer use)

Appendix 3. Characteristics of Included Studies

Appendix 3.1. MenACWY vaccines

Study Author, Year	Method	Setting	Population	Intervention	Comparator	Outcome
Kim 2016[11]	Phase III RCT	Korea	Healthy adults 11-55 years	MenACWY-DT (Menactra®; 0.5 mL dose)	Tdap (Adacel; 0.5 mL)	Immunogenicity (28 days), safety data including SAEs (28 days)
Añez 2010[6]	Phase III RCT	USA, Puerto Rico	At least 15 years	MenACWY-TT (Nimenrix®)	MenACWY-DT (Menactra®)	Immunogenicity, reactogenicity, safety
Baxter 2011, 2015[14]	Phase II RCT	USA	19-55 years	MenACWY-TT (Nimenrix®)	MenACWY-DT (Menactra®)	Immunogencity, reactogenicity, safety, persistence
Borja-Tabora 2015[10]	Phase II RCT	Philippines & Saudi Arabia	19-65 years	MenACWY-TT (Nimenrix®)	MenACWY-PS (Mencevax®)	Immunogencity, safety, persistence
Dhingra 2020[9]	Phase III RCT	USA	10-55 years	MenACWY-TT (Nimenrix®)	MenACWY-DT (Menactra®)	Immunogenicity, reactogenicity, safety
Reisinger 2009[15]	Phase III RCT	USA	19-55 years	MenACWY-CRM (no brand; Novartis)	MenACWY-DT (Menactra®)	Immunogenicity, reactogenicity, safety
Stamboulian 2010[13]	Phase III RCT	Argentina, Colombia	19-65 years	MenACWY-CRM (no brand; Novartis)	MenACWY-DT (Menactra®)	Immunogenicity, reactogenicity, safety
Dbaibo 2013[7]	RCT	Lebanon	At least 56 years	MenACWY TT (Nimenrix®)	MenACWY PS (Mencevax®)	Immunogenicity, reactogenicity, safety
Shao 2009[12]	Phase III RCT	USA	19-55 years	MenACWY-PS (Mencevax®)		Immunogenicity, reactogenicity, safety

Appendix 3.2. MenB vaccines

Study Author, Year	Method	Setting	Population	Intervention	Comparator	Outcome
Ostergaard 2017[18]	RCT	Canada, Denmark, Finland, Poland, Spain, US	Healthy 18-25 years (study also included adolescents)	MenB-FHbp (Trumenba; Pfizer) at 2, 6 months, intramuscular (n=2471)	HAV vaccine (Havrix, GSK) or saline 0.5mL (n=822)	Immunogenicity (% of participants with hSBA titer > 4) safety (solicited and unsolicited adverse events within 7 days)
Read 2017[17]	RCT	UK	Healthy 18-24 years (n=581)	MenB-4C 0.5 mL, intramuscular (n=192)	Saline (n=197) MenACWY-CRM (n=192) Both 0.5 mL, intramuscular	Immunogenicity (1, 2, 4, 6, 12 months) – expressed as % of subjects with hSBA titers ≥ 4, antibody persistence at 3 years
McNamara 2015	Prospective cohort	US	University students and staff living in a dormitory, faculty and staff with medical condition that increases risk of meningococcal disease	Vaccination MenB-4C	none	Case of serogroupB meningococcal disease, serious AE

Appendix 4. Forest Plots

Appendix 4.1. Outcome 1: Vaccine Response

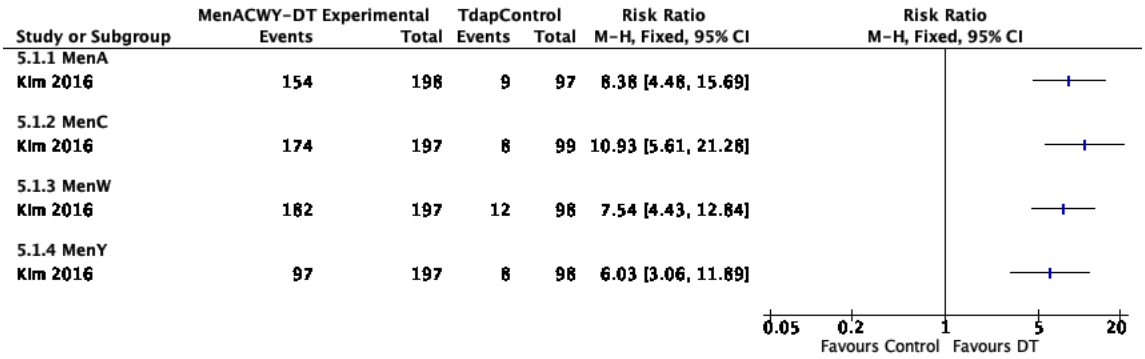


Figure 1. Comparison of vaccine response of healthy adults vaccinated with MenACWY-DT and an active control (Tdap)

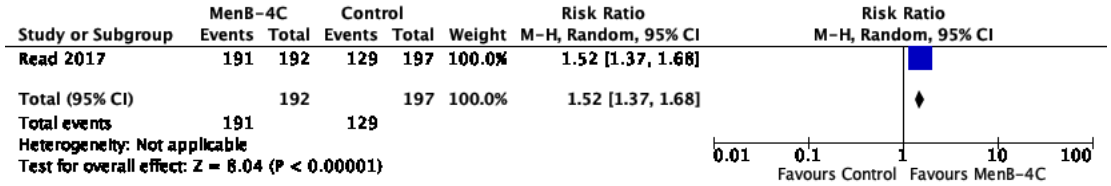


Figure 2. Comparison of vaccine response of young adults vaccinated with MenB-4C (Bexsero) and saline/HAV vaccine

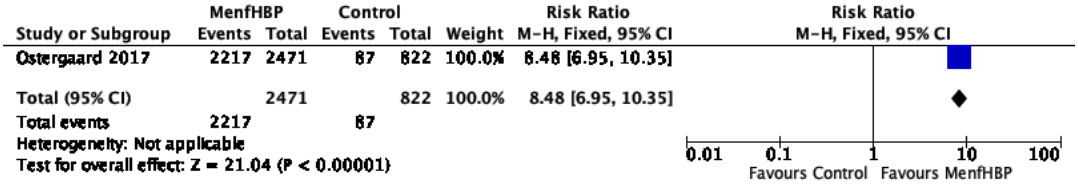


Figure 3. Comparison of vaccine response of young adults vaccinated with MenfHBP (Trumenba) and saline/HAV vaccine

Appendix 4.2. Outcome 2: Persistence of Immunity

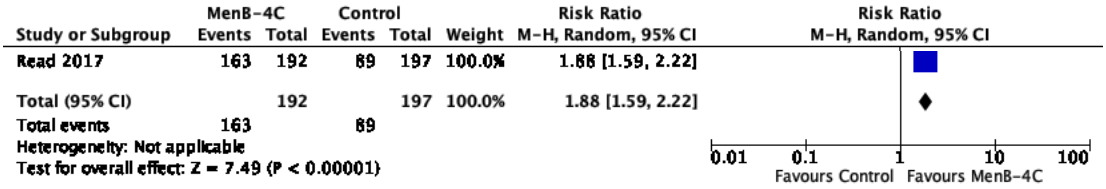


Figure 4. Comparison of persistence of increase in hSBA titers (>/1:4) of those vaccinated with MenB-4C

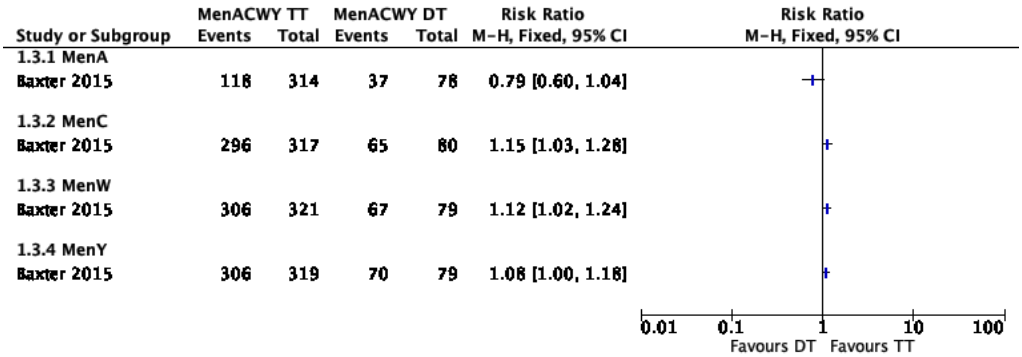


Figure 5. Comparison of persistence of increase in hSBA titers (>/1:4) of those vaccinated with MenACWY TT and MenACWY DT measured at Year 3

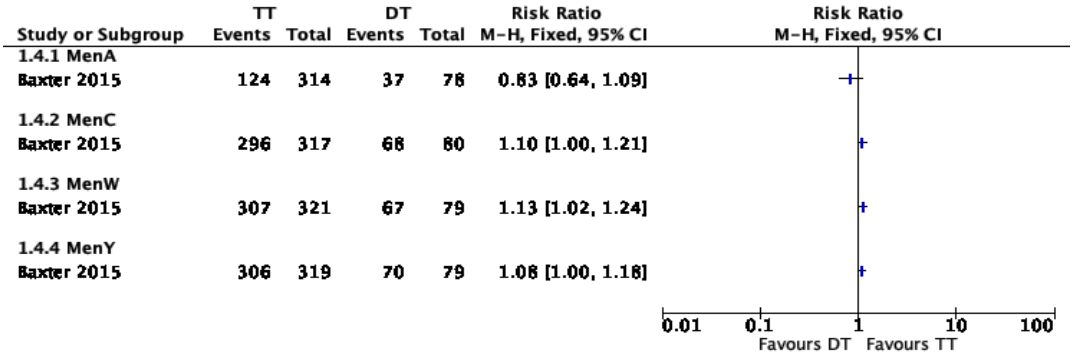


Figure 6. Comparison of persistence of increase in hSBA titers (>/1:8) of those vaccinated with MenACWY TT and MenACWY DT measured at Year 3

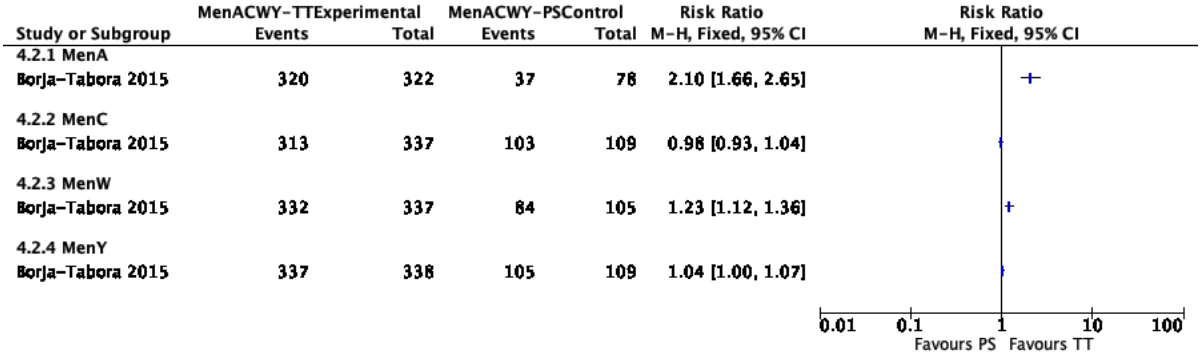


Figure 7. Comparison of persistence of increase in rSBA titers (>/1:8) of those vaccinated with MenACWY TT and MenACWY PS measured at Year 3

Appendix 4.3. Indirect Evidence: Comparison of Different Meningococcal Vaccines

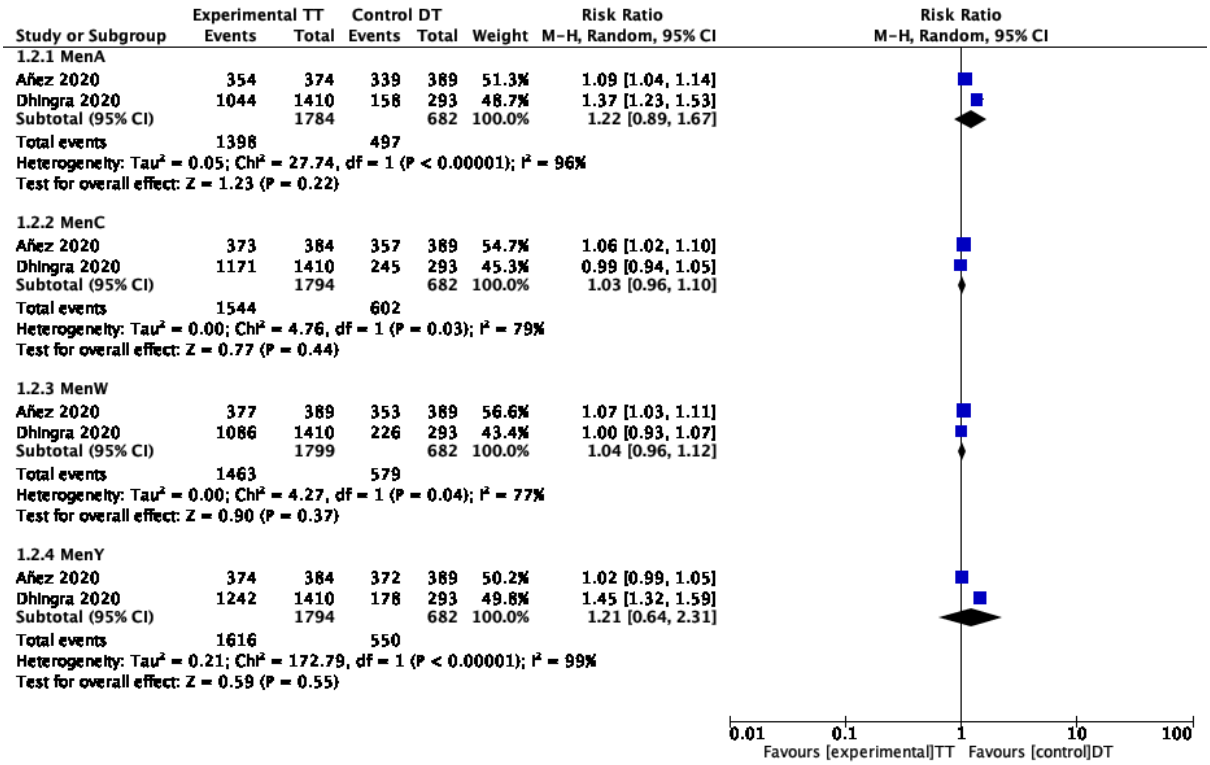


Figure 8. Comparison of vaccine response of healthy adults vaccinated with MenACWY-TT and DT

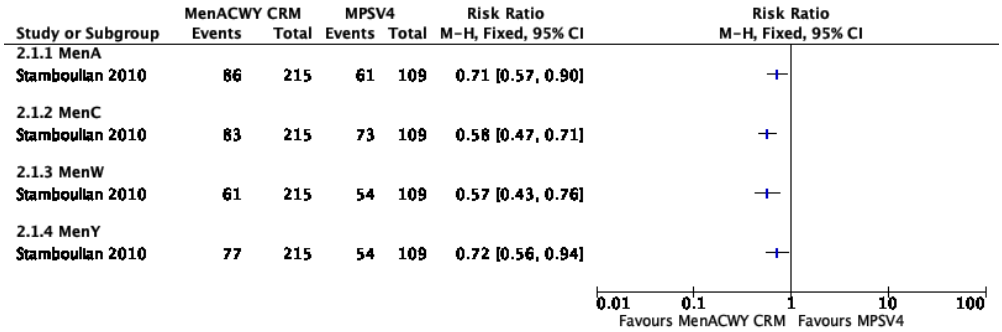


Figure 9. Comparison of vaccine response of healthy adults vaccinated with MenACWY CRM and MPSV4

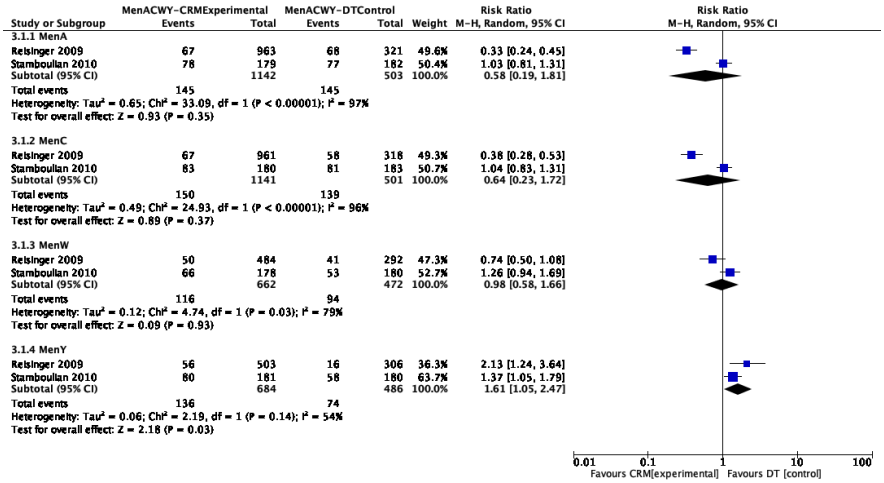


Figure 10. Comparison of overall vaccine response of healthy adults vaccinated with MenACWY-CRM and MenACWY-DT

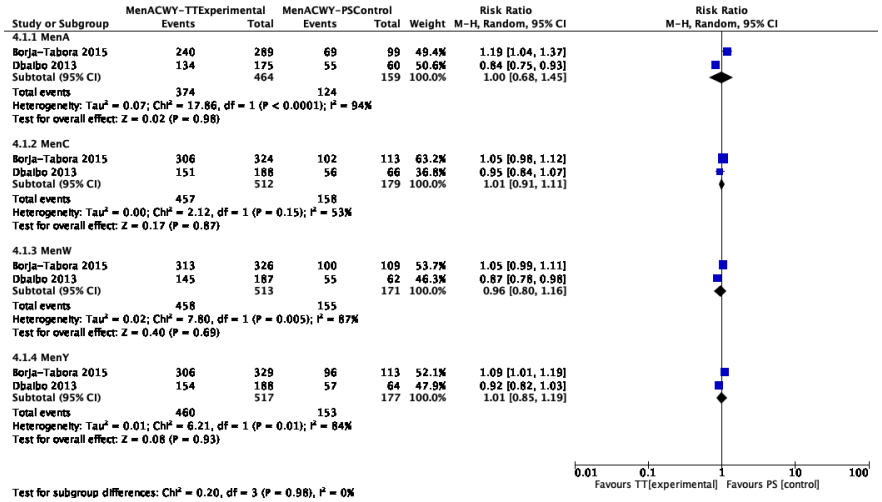


Figure 11. Comparison of vaccine response of healthy adults vaccinated with MenACWY-TT and MenACWY PS

Appendix 5. Risk of Bias Assessment of Included Studies

Appendix 5.1. Clinical Practice Guidelines (AGREE II)

Domains	Score (%)		
	Australian Immunisation Handbook 2021	ACIP 2020	PSMID 2018
1. Scope and Purpose	77.8	100	88.9
2. Stakeholder Involvement	83.3	72.2	44.4
3. Rigor of Development	87.5	85.4	56.3
4. Clarity of Presentation	88.9	100	77.8
5. Applicability	77.8	50	20.8
6. Editorial Independence	91.7	75	16.7
Average	**84.5**	**80.4**	**50.8**

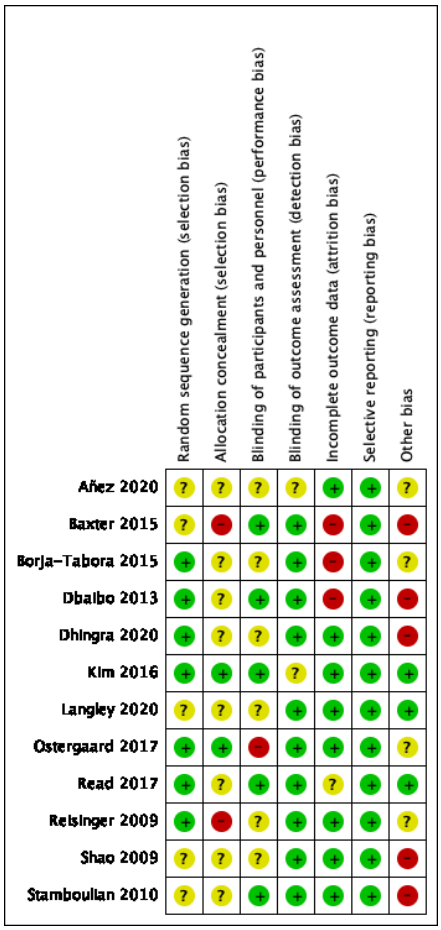
Appendix 5.2. Systematic Reviews (AMSTAR 2)

	Becerra-Culqui, 2021	Htar 2020
1. RQ and Inclusion criteria	Yes	Yes
2. Protocol	No	Yes
3. Justification for inclusion a particular study design	No	Yes
4. Comprehensive literature search	No	Partial Yes
5. Independent study selection	Yes	Yes
6. Independent data extraction	No	Yes
7. Excluded studies & justification	Partial Yes	Partial Yes
8. Detailed description of included studies	Partial Yes	Yes
9. RoB assessment	No	No
10. Reporting of funding of each study	No	No
11. Appropriate statistical methods in meta-analysis	N/A	N/A
12. Assess potential impact of RoB in individual studies	N/A	N/A
13. Included RoB in discussing results	No	No
14. Satisfactory explanation of heterogeneity	No	No
15. Investigation of publication bias	N/A	N/A
16. Reported no/conflict of interest	Yes	Yes
AMSTAR 2 Verdict	Critically Low	Critically Low

There are 2 types of meningococcal vaccines available in the United States:

- MenACWY (conjugate) vaccines (Menactra®, Menveo®, and MenQuadfi®)
- MenB (recombinant protein) vaccines (Bexsero® and Trumenba®)

Appendix 5.3. Randomized Controlled Trials



Appendix 5.4. Observational Study (Newcastle-Ottawa Scale)

	McNamara 2015
Selection	
1. Representativeness of the exposed cohort	Selected group of users
2. Selection of the non-exposed cohort	No description of non-exposed cohort
3. Ascertainment of exposure	Secure record, structured interview
4. Demonstration that outcome of interest was not present at start of study	Yes
Comparability	
1. Comparability of cases and controls	No
Outcome	
1. Assessment of outcome	Record linkage, self-report
2. Was follow-up long enough for outcomes to occur	Yes (2 academic years)
3. Adequacy of follow up cohorts	No statement

Monkeypox Vaccine

Appendix 1. Evidence-to-Decision Summary

Burden	No (2)	Probably No	Probably Yes	Yes	Varies (1)	Don't know (3)
Benefits	Trivial	Small (4)	Moderate (1)	Large	Varies	Don't know (1)
Harms	Large	Moderate (4)	Small (2)	Trivial	Varies	Don't know
Certainty of evidence	Very Low	Low	Moderate	High	No included studies	
Balance of effects	Favors no vaccine	Probably favors no vaccine (1)	Equivalent (2)	Probably favors vaccine (2)	Favors vaccine	Varies (1)	Don't know

Resources required	Large costs (5)	Moderate costs (1)	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence (resources)	Very Low	Low (2)	Moderate (1)		High (2)	No included studies (1)	
Cost effectiveness	Favors no vaccine	Probably favors no vaccine (1)	Does not favor either (2)	Probably favors vaccine (2)	Favors vaccine (1)	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact (2)	Probably increased (2)	Increased (1)	Varies (1)	Don't know
Acceptability	No (1)	Probably no (1)	Probably yes (3)		Yes	Varies (1)	Don't know
Feasibility	No	Probably no (3)	Probably yes (1)		Yes	Varies (1)	Don't know (1)
Values	Important variability (1)		Possibly important variability (4)	Probably no important variability (1)	No important variability		

Recommendation 1: **Asymptomatic apparently healthy adults**	STRONG against	WEAK against (3)	NO RECOMMENDATION	WEAK in favor (3)	STRONG in favor

Appendix 2. GRADE Summary of Findings Table

Appendix 2.1. Primary preventive vaccination with MVA-BN for healthy adults with low-risk of exposure to monkeypox.
Question: Monkeypox vaccination compared to no vaccination for asymptomatic apparently healthy adults
Setting: Primary care / community

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	monkeypox vaccination	no vaccination	Relative (95% CI)	Absolute (95% CI)		
Immunogenicity (follow-up: range 2 weeks to 2 years; assessed with: seroconversion rates, antibody titer levels)												
1[a]	randomised trials	not serious[b]	not serious	serious[c]	not serious	none	Vaccine-naive: 1-dose - RR 22.4 (95%CI 9.4 to 53.6) 2-dose - RR 26.9 (95%CI 12.2 to 59.1) With prior smallpox vaccination - RR 28.4 (95%CI 11.9 to 67.7). Approximately half of all participants seroconverted for neutralizing antibodies (nAb) at week 2. By the 4th week, seroconversion rate was highest at 62.4% for the 1-dose group. The 2-dose group exhibited peak seroconversion (89.2%) by week 6. In subjects with prior smallpox vaccination, 78.5% were seroconverted by week 2. In the placebo group, seroconversion rates remained low throughout the duration of the study (1.1 to 3.4%).				Moderate	CRITICAL
Local and systemic adverse events (follow-up: 6 months)												
1[d]	randomised trials	not serious	not serious	serious[c]	not serious	none	Ilchmann 2022 - RR 2.64 (1,75, 3.97) *Other data: Ilchmann 2022 - 718 / 753 (95.4%) - (injection site reactions, chills, urticaria) Overton 2023 - 1030/1129 (91.2%) - local AEs Overton 2023 - 754/1129 (66.8%) - systemic AEs				Moderate	IMPORTANT
Serious adverse events (follow-up: 6 months)												
1	randomised trials	not serious	not serious	serious[c]	serious[d]	none	Ilchmann 2022 - RR 3.49 [95%CI 0.18, 67.21] *Other data: Overton 2023 - 0 SAEs (out of 1129 participants) Duffy 2022 - 2 myocarditis, 3 anaphylaxis (out of 987,209 doses of JYNNEOS)				Low	CRITICAL

CI: confidence interval
Explanations
a. Ilchmann 2022 (with data from Zitzmann-Roth 2015)
b. 93% adhered to the intervention, although results were not analyzed using intention-to-treat analysis
c. Study was performed before the onset of the 2022 monkeypox outbreak; not done on MPXV-neutralizing antibodies
d. Ilchmann 2022, Overton 2023, Duffy 2022 also provided AE estimates for mpox vaccination (MVA-BN)
e. Wide confidence intervals
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3. Overton E, Schmidt D, Vidojkovic S, et al. A randomized phase 3 trial to assess the immunogenicity and safety of 3 consecutively produced lots of freeze-dried MVA-BN® vaccine in healthy adults. Vaccine. 2023;41(2):397-406. doi:10.1016/j.vaccine.2022.10.0564
4. Ilchmann H, Samy N, Reichhardt D, et al. Single and 2-dose vaccinations with modified vaccinia Ankara-Bavarian Nordic® induce durable B cell memory responses comparable to replicating smallpox vaccines [published online ahead of print, 2022 Nov 21]. J Infect Dis. 2022;jiac455. doi:10.1093/infdis/jiac455

Appendix 2.2.1. Primary preventive vaccination with ACAM2000 compared to no vaccination for persons with a high risk of exposure to monkeypox (from WHO November 16, 2022 Guidelines).

Certainty assessment								Summary of findings
Outcomes	**Participants (studies) Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Impact**
Immunogenicity: % of vaccinees with seroconversion	317 (4 studies) [u]	very serious [b]	not serious	serious [v]	not serious [e]	none	Very low	• The proportion of ACAM2000 vaccinees reaching seroconversion with MPXV neutralizing antibodies may be high, but the evidence is very uncertain. • We found no studies addressing seroconversion with MPXV neutralizing antibodies, but the proportion of ACAM2000 vaccinees that reached seroconversion (nonMPXV specific) ranged from 76% to 97%.
Immunogenicity: vaccination take rate	2268 (6 studies) [t]	very serious [b]	not serious	not serious	not serious [e]	none	Low	• The proportion of ACAM2000 vaccinees with vaccination take may be high, but the evidence is uncertain. • The proportion of ACAM2000 vaccinees with a take ranged from 84% to 100%.
Clinical effectiveness/ efficacy against monkeypox infection	-	-	-	-	-		-	• We found no clinical study assessing this outcome. • The clinical effectiveness/efficacy of primary preventive vaccination with ACAM2000 versus no vaccination against monkeypox is unknown. • ACAM2000 clinical effectiveness/efficacy against MPX is inferred from indirect evidence, such as efficacy data from animal challenge studies, immunogenicity data of ACAM2000 compared to Dryvax, and indirect surveillance data in Democratic Republic of the Congo
Myopericarditis	1743620 (8 studies)	very serious [b]	serious [i]	serious [g]	serious [j]	none	Very low	• Myopericarditis may be very rare in ACAM2000 vaccinees, but the evidence is very uncertain. • A random-effects model metaanalysis found an overall incidence of myopericarditis of 131 cases per 100,000 ACAM2000 vaccinees, 95% CI 28 to 607. • A total of 269 cases of myopericarditis were reported across eight studies with a total of 1,743,620 vaccinees.
Serious adverse events: Neurological serious adverse events [k]	843744 (4 studies) [l]	very serious [b]	not serious	serious [g]	not serious [m]	none	Very low	• Neurological serious adverse events may not occur in ACAM2000 vaccinees, but the evidence is very uncertain. • No neurological adverse events were reported in the four

								studies explicitly informing this outcome.
Serious adverse events: eczema vaccinatum or erythema multiforme, progressive vaccinia or generalized vaccinia	843744 (4 studies) [l]	very serious [b]	not serious	serious [g]	not serious [m]	none	Very low	• Eczema vaccinatum or erythema multiforme, progressive vaccinia or generalized vaccinia may be very rare in ACAM2000 vaccinees, but the evidence is very uncertain. • We found five cases of generalized vaccinia (McNeil 2014), one case of eczema vaccinatum (McNeil 2014), one case of progressive vaccinia (McNeil 2014) in the studies explicitly informing these outcomes. • Beachkofsky 2010 (excluded from this review as it was a case study) described another case of ACAM2000 generalized vaccinia.
Serious adverse events: autoinoculation	843714 (3 studies) [n]	very serious [b]	not serious	serious [g]	not serious [m]	none	Very low	• Autoinoculation may be very rare in ACAM2000 vaccinees, but the evidence is very uncertain. • A total of five cases of autoinoculation were described in the studies informing this outcome. • No case of ocular vaccinia was reported.
Serious adverse events: vaccine-related deaths	1732264 (6 studies) [j,o]	very serious [b]	not serious	serious [g]	not serious [m]	none	Very low	• Vaccine-related deaths may not occur in ACAM2000 vaccinees, but the evidence is very uncertain. • In the six studies reporting this information, two out of 1,732,264 vaccinees died (not confirmed if vaccine-related). [p]
Serious adverse events: adverse events requiring hospitalization	834465 (1 observational study) [q]	not serious	not serious	serious [g,r]	not serious [s]	none	Very low	• Adverse events requiring hospitalization may be very rare in ACAM2000 vaccinees, but the evidence is very uncertain. • 143 out of 834,465 vaccinees (17 per 100,000) were hospitalized. However, it was not specified if the hospitalizations were vaccine-related.
Local adverse events	13952 (8 studies) [a]	very serious [b]	not serious [c]	not serious [d]	not serious [e]	none	Low	• Local adverse events may be very frequent in ACAM2000 vaccines, but the evidence is uncertain. • ACAM2000 vaccination leaves a permanent scar (known as "take") at the injection site following successful inoculation. • Examples of local adverse events commonly reported were injection site pain (up to 77%), redness (up to 74%), pruritus (up to 97%), injection site swelling (up to 48%), and rash (up to 20%)
Systemic adverse events	848417 (9 studies) [f]	not serious [b]	not serious [c]	serious [g]	not serious [e]	none	Very low	• Systemic adverse events may be frequent in ACAM2000 vaccinees, but the evidence is very uncertain. • Constitutional symptoms were frequent, such as muscle pain (up to 60%), fatigue (up to 49%), malaise (up to 37%), feeling hot (up to 37%), fever (up to 11%), chills (up to 17%), rigors (up to 21%), exercise tolerance decreased (up to 11%)

								• Dyspnea (up to 4%), lymph node pain (up to 73%), headache (up to 60%), nausea (up to 23%), vomiting (up to 7%), diarrhoea (up to 23%), and constipation (up to 6%)

Explanations

a. Six RCTs (H-400-002; H-400-003; H-400-005; H-400-009; H-400-012; POX-MVA-006); one uncontrolled trial (VA-006); one observational study (H-406-004).
b. Uncontrolled designs, lack of blinding, inconsistent measurement and reporting of outcomes, and unclear risk of selective outcome reporting.
c. We did not downgrade for inconsistency as the findings pointed consistently to a high frequency of the outcome.
d. We did not downgrade for indirectness. Although safety data from large population-based programs is limited, we consider that the safety profile captured in the included evidence can reflect the local AEs in most populations.
e. We did not downgrade for imprecision as the study samples were usually powered to detect this outcome, which was frequent.
f. Six RCTs (H-400-002; H-400-003; H-400-005; H-400-009; H-400-012; POX-MVA-006); one uncontrolled trial (VA-006) and two observational studies (H-406-004; McNeil 2014).
g. Studies were performed with selected populations in controlled contexts, such as trials with healthy subjects and military personnel. General use of the vaccine may reveal effects not observed in these situations.
h. Four RCTs (H-400-002; H-400-009; H-400-012; H-400-005); four observational studies (McNeil 2014; H-406-005; H-406-004; Engler 2015).
i. I2=99% showed substantial statistical heterogeneity.
j. Although the metanalysis pointed to a low incidence of myopericarditis, its 95% CI was wide enough to reduce the certainty of the evidence.
k. Post-vaccinial encephalitis (PVE), post-vaccinial encephalomyelitis (PVEM)
l. Two RCTs (H-400-002; H-400-005); 2 observational studies (H-406-004; McNeil 2014).
m. At least one study sample was powered to detect the outcome.
n. One RCT (H-400-005); two observational studies (McNeil 2014; H-406-004).
o. Three RCTs (H-400-005; POX-MVA-006; H-400-002); one uncontrolled trial (VA-006); two observational studies (McNeil 2014; H406-005).
p. One subject showed myocarditis (dilated cardiomyopathy), infarction/necrosis of the liver and hemorrhage/necrosis of the right adrenal gland (McNeil 2014). The other death was attributed to rhabdomyolysis without myocarditis evidence at autopsy (H-406- 005). It was not confirmed if the vaccine caused the deaths.
q. Only McNeil 2014 reported this outcome.
r. It was not specified if the hospitalizations were vaccine-related.
s. We did not downgrade for imprecision as the study sample was powered to detect this outcome.
t. Five RCTs (ACAM2000_FDA_Study1; ACAM2000_FDA_Study2; H-400-002; POX-MVA-006; H-400-005); one observational study (Pugh 2014)

Appendix 2.2.2. Primary preventive vaccination with MVA-BN compared to no vaccination for persons with a high risk of exposure to monkeypox (from WHO November 16, 2022 Guidelines)

Certainty assessment								Summary of findings
	Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Impact
Immunogenicity: % of vaccines with seroconversion	1222 (8 studies)[o]	very serious[b]	not serious	serious[p]	not serious[e]	none	Very low	• The proportion of MVA-BN vaccinees reaching seroconversion with MPXV neutralizing antibodies may be high, but the evidence is very uncertain. • We found no studies addressing seroconversion with MPXV neutralizing antibodies, but the proportion of MVA-BN vaccinees that reached seroconversion (nonMPXV specific) was always over 98%.[q]
Immunogenicity: vaccination take rate - not reported	-	-	-	-	-	-	-	• Not applicable for MVA-BN: it is a replication-deficient vaccine, thus vaccination with MVA-BN does not produce a take.
Clinical effectiveness/ efficacy against monkeypox infection - not reported	-	-	-	-	-	-	-	• We found no peer-reviewed clinical studies assessing this outcome. • The clinical effectiveness/efficacy of primary preventive vaccination with MVA-BN versus no vaccination against monkeypox is unknown.[r]
Myopericarditis	9713 (19 studies) [h]	very serious [b]	not serious [i]	serious [g]	very serious [j]	none	Very low	• Myopericarditis may not occur in MVA-BN vaccinees, but the evidence is very uncertain. • The included studies did not find any case of myopericarditis. • POX-MVA-013 reported that one out of its 2,798 MVA-BN vaccinees presented a potential myocarditis (but the case did not meet the CDC definition).
Serious adverse events:	9713 (19 studies) [l]	very serious [b]	not serious [i]	serious [g]	very serious [j]	none	Very low	• Neurological serious adverse events may not occur in MVA-BN vaccinees,

Neurological serious adverse events								but the evidence is very uncertain. • No neurological serious adverse events were reported.
Serious adverse events: eczema vaccinatum or erythema multiforme, progressive vaccinia or generalized vaccinia	9713 (19 studies) [l]	very serious [b]	not serious [i]	serious [g]	very serious [j]	none	Very low	• Eczema vaccinatum or erythema multiforme, progressive vaccinia or generalized vaccinia may not occur in MVA-BN vaccinees, but the evidence is very uncertain. • No cases were reported.
Serious adverse events: autoinoculation	9713 (19 studies) [l]	very serious [b]	not serious [i]	serious [g]	very serious [j]	none	Very low	• Autoinoculation may not occur in MVA-BN vaccinees, but the evidence is very uncertain. • No cases of autoinoculation were described. • No case of ocular vaccinia was reported.
Serious adverse events: vaccine-related deaths	9713 (19 studies) [l]	very serious [b]	not serious [i]	serious [g]	very serious [j]	none	Very low	• Vaccine-related deaths may not occur in MVA-BN vaccinees, but the evidence is very uncertain. • No cases of MVA-BN vaccine related deaths were reported.[m]
Serious adverse events: adverse events requiring hospitalization	9713 (19 studies)[l]	very serious[b]	not serious[i]	serious[g]	very serious[j]	none	Very low	• Adverse events requiring hospitalization may not occur in MVA-BN vaccinees, but the evidence is very uncertain. • No AEs requiring hospitalization were reported.
Systemic adverse events	5457 (6 studies) [f]	very serious [b]	not serious [c]	serious [g]	not serious [e]	none	Very low	• Systemic adverse events may be frequent in MVA-BN vaccinees, but the evidence is very uncertain. • Constitutional symptoms were frequent, such as muscle pain (up to

								43%), fatigue (up to 30%), malaise (up to 17%), fever (up to 2%), chills (up to 10.4%), headache (up to 34.8%) and nausea (up to 17.3%).
Local adverse events	5921 (6 studies)[f]	very serious[b]	not serious[c]	not serious[d]	not serious[e]	none	Low	• Local adverse events may be very frequent in MVA-BN vaccines, but the evidence is uncertain. • Local adverse events commonly reported were injection site pain (up to 85%), including movement limitation, redness (up to 61%), pruritus (up to 18%), swelling (up to 52%), induration and itching (up to 43%)

Explanations

a. Five RCTs (POX-MVA-006; POX-MVA-013; POX-MVA-029; POX-MVA-031; MVA_07-0042) and one uncontrolled trial (POX-MVA03x).
b. Uncontrolled designs, lack of blinding, inconsistent measurement and reporting of outcomes, and unclear risk of selective outcome reporting.
c. We did not downgrade for inconsistency as the findings pointed consistently to a high frequency of the outcome.
d. We did not downgrade for indirectness. Although safety data from large population-based programs is limited, we consider that the safety profile captured in the included evidence can reflect the local AEs in most populations.
e. We did not downgrade for imprecision as the study samples were usually powered to detect this outcome, which was frequent.
f. Four RCTs (POX-MVA-006; POX-MVA-013; POX-MVA-031; MVA_07-0042); one non-randomized trial (POX-MVA-010); one uncontrolled trial (POX-MVA-03x).
g. Studies were performed with selected populations in controlled contexts, such as trials with healthy subjects and military personnel. General use of the vaccine may reveal effects not observed in these situations.
h. 15 RCTs (MVA_05-0010; MVA_11-0021; Vollmar 2006; POX-MVA-002; POX-MVA-004; POX-MVA-005; POX-MVA-006; POX-MVA008; POX-MVA-009; POX-MVA-013; POX-MVA-027; POX-MVA-028; POX-MVA-029; POX-MVA-031; POX-MVA-037); 3 nonrandomized trials (POX-MVA-007; POX-MVA-010; POX-MVA-011); 1 uncontrolled trial: (POX-MVA-03x).
i. All the studies presented zero cases.
j. The study samples were not powered to detect rare adverse events.
k. Post-vaccinial encephalitis (PVE), post-vaccinial encephalomyelitis (PVEM)
l. 15 RCTs: MVA_05-0010; MVA_11-0021; POX-MVA-002; POX-MVA-004; POX-MVA-005; POX-MVA-006; POX-MVA-008; POX-MVA009; POX-MVA-013; POX-MVA-027; POX-MVA-028; POX-MVA-029; POX-MVA-031; POX-MVA-037; Vollmar 2006; 3 non-randomized trial: POX-MVA-007; POX-MVA-010; POX-MVA-011; 1 uncontrolled trial POX-MVA-03x).
m. Only three studies reported explicitly all-cause mortality. Two out 1129 vaccinees died in POX-MVA-031 (unknown cases). No death occurred among the 22 vaccinees in POX-MVA-03x and the 221 vaccinees in POX-MVA-006.
n. Five RCTs (ACAM2000_FDA_Study1; ACAM2000_FDA_Study2; H-400-002; POX-MVA-006; H-400-005); one observational study (Pugh 2014). o. Seven RCTs (POX-MVA-008; POX-MVA-009; MVA_11-0021; POX-MVA-027; POX-MVA-028; POX-MVA-029; POX-MVA-031); one uncontrolled trial (POX-MVA-03x).
p. We found no studies demonstrating MPXV-neutralizing antibodies in vaccinated individuals.
q. One preprint (Zaeck 2022) concluded that primary MVA-BN immunization in subjects not previously exposed to MPXV or historic vaccination yielded relatively low levels of MPXV neutralizing antibodies.
r. One preprint (Arbel 2022) posted on August 22, 2022 indicated that one dose MVA-BN was effective in preventing MPX infections at the short term (vaccine effectiveness 100%; 95% CI: 100%-100%; 8,168 subjects of which 626 (7%) were vaccinated; followup: between 7 and 15 days from the first dose).

Appendix 2.3. Primary preventive vaccination with LC16m8 compared to no vaccination for persons with a high risk of exposure to monkeypox (from WHO November 16, 2022 Guidelines)

Certainty assessment								Summary of findings
	Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Impact
Immunogenicity: % of vaccines with seroconversion	3614 (3 studies)	very serious[b]	not serious	not serious	not eerious[e]	none	Low	• The proportion of LC16m8 vaccinees with vaccination take may be high, but the evidence is uncertain. • The proportion of vaccinees with a take ranged from 90% to 100%.
Immunogenicity: vaccination take rate	3614 (3 studies) [a]	very serious [b]	not serious	not serious	not serious [e]	none	Low	• The proportion of LC16m8 vaccinees with vaccination take may be high, but the evidence is uncertain. • The proportion of vaccinees with a take ranged from 90% to 100%.
Myopericarditis	3346 (2 studies) [g]	very serious [b]	not serious [h]	serious [f]	very serious [i]	none	Very low	• Myopericarditis may not occur in LC16m8 vaccinees, but the evidence is very uncertain. • Studies reporting on cardiac events found no symptomatic myocarditis, pericarditis or myopericarditis among LC16m8 vaccinees.
Serious adverse events: Neurological serious adverse events[j]	3488 (2 studies) [k]	very serious [b]	not serious [h]	serious [f]	very serious [i]	none	Very low	• Neurological serious adverse events may not occur in LC16m8 vaccinees, but the evidence is very uncertain. • No neurological serious adverse events were reported.
Serious adverse events: eczema vaccinatum or erythema multiforme, progressive vaccinia or generalized	3614 (3 studies) [a]	very serious [b]	not serious [h]	serious [f]	very serious [i]	none	Very low	• Eczema vaccinatum or erythema multiforme, progressive vaccinia or generalized vaccinia may not occur in LC16m8 vaccinees, but the evidence is very uncertain. • No cases were reported.

vaccinia								
Serious adverse events: autoinoculation	3489 (2 studies) [k]	very serious [b]	not serious [h]	serious [f]	very serious [i]	none	Very low	• Autoinoculation may be rare in LC16m8 vaccinees, but the evidence is very uncertain. • Autoinoculation was not frequent (up to 0.4%) among LC16m8 vaccinees.
Serious adverse events: vaccine-related deaths	268 (1 study) [l]	very serious [m]	not serious [h]	serious [f]	very serious [i]	none	Very low	• Vaccine-related deaths may not occur in LC16m8 vaccinees, but the evidence is very uncertain. • No cases of LC16m8 vaccine related deaths were reported.
Serious adverse events: adverse events requiring hospitalization	3221 (1 study)[n]	very serious[o]	not serious	serious[f]	very serious[i]	none	Very low	• AEs requiring hospitalization may be very rare in LC16m8 vaccinees, but the evidence is very uncertain. • One study reported one case (0.03%) requiring hospitalisation due to a vaccine-related adverse event. The hospitalisation took place during the study twenty days after immunisation due to a rash onset (at day three post vaccination) that spread to the patient's extremities and trunk (Saito 2009).
Systemic adverse events	3614 (3 studies)[a]	very serious [b]	not serious[c]	serious[f]	not serious[e]	none	Very low	• Systemic adverse events may be frequent in LC16m8 vaccinees, but the evidence is very uncertain. • Systemic adverse events reported included constitutional symptoms such as fatigue (up to 0.7%) and fever (up to 7%) among LC16m8 vaccinees (one cohort study: n = 268 vaccinees; Nishiyama 2015). • Another study reported that at least one instance of systemic reactogenicity was present in 75% of vaccinees participating, but the range of events included in this category was unclear (n = 125; VAX012). • Information on common systemic adverse in other studies such as headache, malaise, chills, nausea and muscle pain for the overall populations examined in the included studies was not provided.
Local adverse events	3614 (3 studies)[a]	very serious[b]	very serious[c]	very serious[d]	not serious[e]	none	Low	• Local adverse events may be very frequent in LC16m8 vaccines, but the evidence is uncertain.

								• Local AEs commonly reported were rash (up to 2.4%), movement limitation (up to 12%), lymphadenopathy (up to 36.8%), local erythema (up to 78.0%) and induration (up to 100%). • Severe local AEs (such as those intense enough to prevent routine daily activities) were inconsistently reported. Rash of severe onset in the extremities to trunk, or trunk only was not frequent (up to 0.1%) in one cohort study (n = 3221 vaccinees; Saito 2009).

CI: confidence interval

Explanations

a. One RCT (VAX012) and two observational cohort studies (Nishiyama 2015; Saito 2009)
b. Uncontrolled designs, lack of blinding, inconsistent measurement and reporting of outcomes, and unclear risk of selective outcome reporting.
c. We did not downgrade for inconsistency as the findings pointed consistently to a high frequency of the outcome.
d. We did not downgrade for indirectness. Although safety data from large population-based programs is limited, we consider that the safety profile captured in the included evidence can reflect the local AEs in most populations.
e. We did not downgrade for imprecision as the study samples were usually powered to detect this outcome, which was frequent.
f. Studies were performed with selected populations in controlled contexts, such as trials with healthy subjects and military personnel. General use of the vaccine may reveal effects not observed in these situations.
g. One uncontrolled trial (VAX012) and one cohort study (Saito 2009).
h. All the studies presented zero cases.
i. The study samples were not powered to detect rare adverse events.
j. Post-vaccinial encephalitis (PVE), post-vaccinial encephalomyelitis (PVEM)
k. Two observational cohort studies (Nishiyama 2015; Saito 2009)
l. One cohort study (Nishiyama 2015).
m. Uncontrolled design.
n. One cohort study (Saito 2009).
o. Uncontrolled design.
p. We found no studies demonstrating MPXV-neutralizing antibodies in vaccinated individuals.
q. Analysed subsamples of vaccinees in some cases significantly younger than the overall population.
r. Serum samples from small subsamples of vaccinees

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Appendix 3. Characteristics of Included Studies

Author / Year	Study Design	Country	Total participants	Population	Intervention	Control	Outcomes	Duration of follow-up
Ilchmann 2022	RCT, phase 2, double-blind, placebo-controlled, non-inferiority trial (2006-2009)	Germany	753	**Study 1: No vaccination history** Healthy adults (men and nonpregnant women) 18-55 years old with or without prior smallpox vaccination, no detectable vaccinia scar n=549 (73%) **Study 2: With prior smallpox vaccination** Healthy adults with prior smallpox vaccination (with vaccinia scar) n=204 (27%)	**Arm 1:** MVA-BN 1 dose + placebo 1 dose (1xMVA), 4 wks apart n=181 **Arm 2:** MVA-BN 2 doses (2xMVA), 4 wks apart n=183 *MVA-BN provided in liquid frozen 0.5-mL aliquots of ≥0.5 x 10^8 50% tissue culture infectious dose ($TCID_{50}$); subcutaneous administration	**Arm 3:** Tris buffer placebo (PBO; IDT Biologika GmbH, Germany) 2 dose, 4 wks apart n=181	**1. Immunogenicity** by ELISA and PRNT assays (for those receiving primary series and booster doses) - Seroconversion rate (antibody titers ≥ 6 for PRNT and ≥50 for ELISA) - Geometric mean titer (GMT levels) **2. Safety and reactogenicity by** memory aid/self-report - solicited local AEs - solicited systemic AEs - unsolicited AEs - serious AEs - AEs of special interest (cardiac symptoms, ECG changes, cardiac enzymes above normal limits)	Immunogenicity: 2, 4, 6, 8 wks, 6 months, 2 years Safety: 8 days, 2 wks; by memory aid
Overton 2023	RCT, phase 3, double-blind, multicenter, lot-to-lot consistency trial (end: 2020)	USA	1129	Healthy men and women 18-45 years, no history of autoimmune or coronary heart disease, no prior smallpox vaccination	**Arm 1:** MVA-BN 2 doses, Lot Group 1, C00020 n=377 **Arm 2:** MVA-BN 2 doses, Lot Group 2, C00021 n=375 **Arm 3:** MVA-BN 2 doses, Lot Group 3, C00022 n=377 MVA-BN *MVA-BN was freeze-dried provided as lyophilized aliquots with nominal virus titer of 1 x 10^8 Inf.U/0.5mL dose; subcutaneous administration	No control group	**1. Immunogenicity** by ELISA and PRNT - Total serum antibodies / GMT titers (by ELISA) - Total neutralizing antibodies (by PRNT) - Seroconversion (antibody titers ≥ 200 ELISA or ≥ 20 PRNT) **2. Safety and reactogenicity** assessed using memory aid - Solicited local AEs (erythema, swelling, pruritus, induration, pain) - Solicited systemic AEs (elevated body temperature, headache, chills, myalgia, nausea, fatigue) - Unsolicited AEs - AESIs (cardiac symptoms, ECG changes, troponin I values > ULN)	Immunogenicity: 2 wks after 2nd dose; Safety: 8 days (for solicited AEs), 1-6 months (for unsolicitedAEs)
Kennedy	Phase 1-2,	USA	154	Healthy, vaccinia-naive	**LC16m8 vaccine**	No placebo	**1. Immunogenicity**	Immunogenicit

2011	Randomized, multicenter, double-blind comparative study (2004-2005)			adults	1 dose, 10^8 plaque-forming units/mL, 0.02 µL, subcutaneous n=125 **Dryvax vaccine** n=29	control group	- neutralizing antibody titer to intracellular mature virus by PRNT - extracellular enveloped virus (EEV) neutralizing antibody (30% or 50% reduction in EEV plaque count by PRNT) - cell-mediated immune (CMI) responses by IFN-γ-ELISPOT lymphoproliferation assays **2. Vaccine skin take rates** **3. Size of lesion at vaccination site** **4. Viral persistence** **5. Viremia after vaccination** **6. Safety and reactogenicity** by diary card / self-report	y:3, 7, 10, 13, 22 days; 1, 2, 6, 12 months Safety: 2x daily until 21 days Take rate: 6-12 days

Appendix 4. Forest Plots

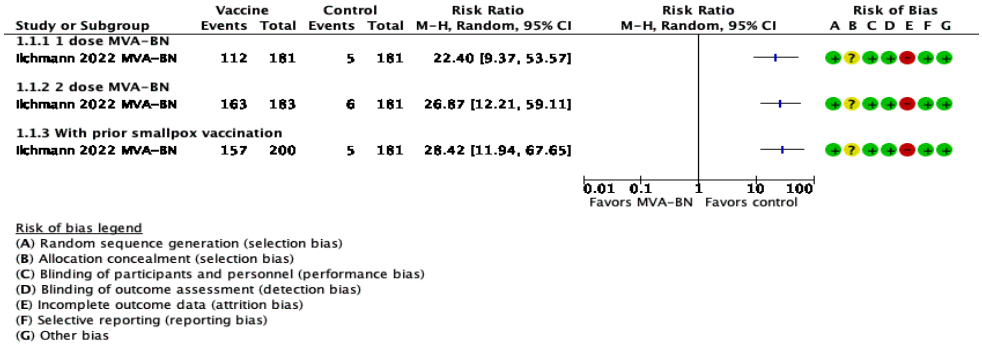


Figure 1. Seroconversion rate at 4-6 weeks post-vaccination with MVA-BN.

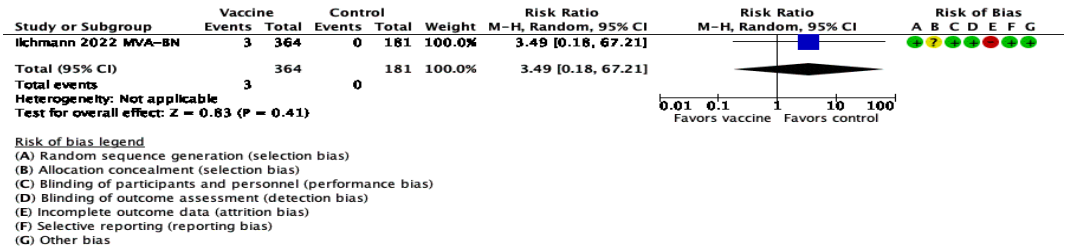


Figure 2. Serious adverse events and AEs of special interest (cardiac events) within 6 months post-vaccination with MVA-BN.

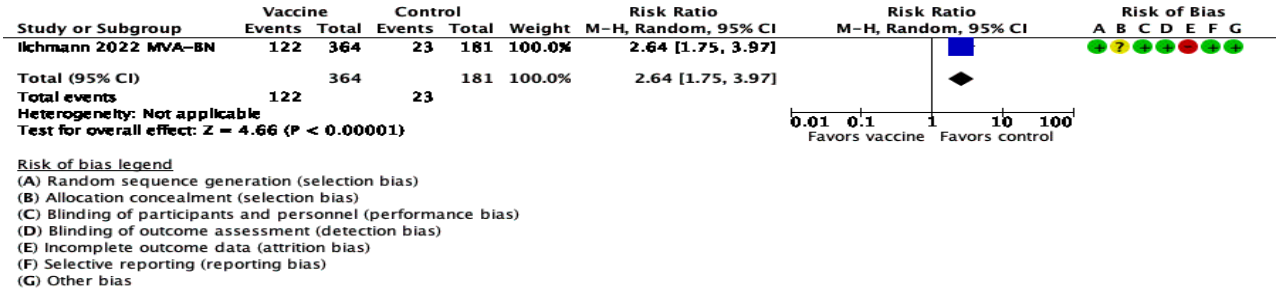
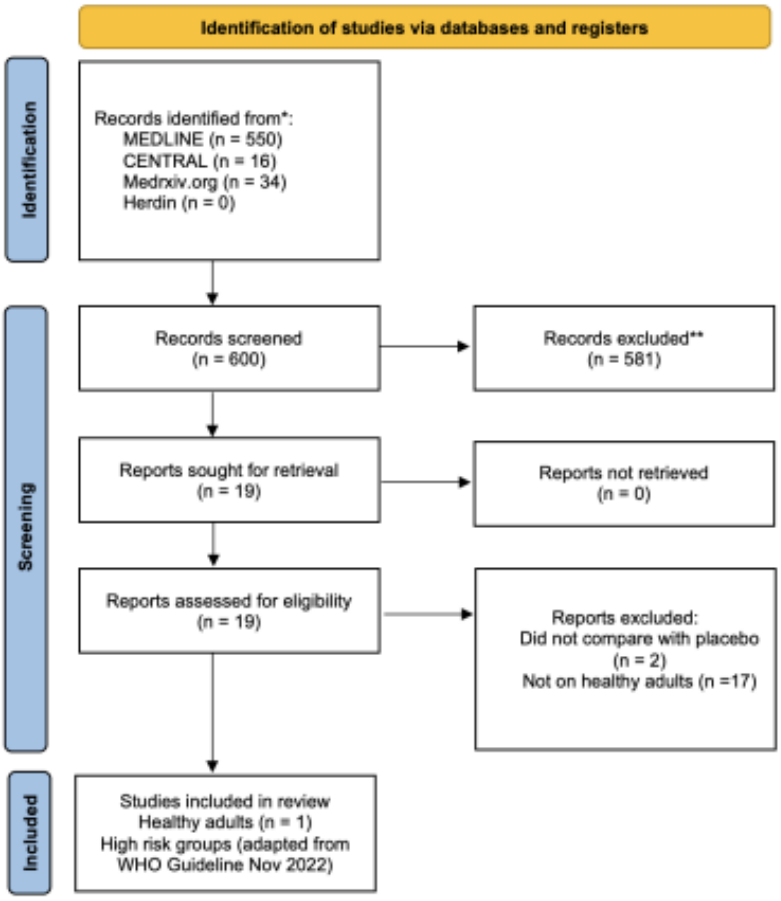


Figure 3. Local and systemic adverse events (at least one unsolicited AE)

Appendix 5. PRISMA Flow Diagram



Pneumococcal Vaccine

Appendix 1. Evidence-to-Decision Summary

Burden	No	Probably No	Probably Yes	**Yes (6)**	Varies	Don't know
Benefits	Trivial	Small	**Moderate (5)**	Large	Varies (1)	Don't know
Harms	Large (1)	Moderate (4)	**Small (1)**	Trivial	Varies	Don't know
Certainty of evidence	Very Low	Low	**Moderate (5)**	High	No included studies	
Balance of effects	Favors no vaccine	Probably favors no vaccine	Equivalent	**Probably favors vaccine (4)**	Favors vaccine (2)	Varies	Don't know

Resources required	Large costs (2)	Moderate costs (2)	Negligible costs and savings	**Moderate savings (2)**	Large savings	Varies	Don't know
Certainty of evidence (resources)	Very Low (1)	Low (1)	Moderate (2)	High	No included studies (2)		
Cost effectiveness	Favors no vaccine	Probably favors no vaccine	Does not favor either	**Probably favors vaccine (3)**	Favors vaccine (2)	Varies (1)	Don't know
Equity	Reduced (1)	Probably reduced	Probably no impact	**Probably increased (4)**	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes (4)**	Yes (1)	Varies	Don't know	
Feasibility	No	Probably no	**Probably yes (4)**	Yes (2)	Varies	Don't know	
Values	Important variability	Possibly important variability (3)	**Probably no important variability (3)**	No important variability (1)			

Recommendations 1: **Asymptomatic apparently healthy adults**	STRONG against	WEAK against (1)	NO RECOMMENDATION	WEAK in favor	**STRONG in favor (5)**

Appendix 2. GRADE Summary of Findings Table

Appendix 2.1. PCV13 compared to placebo for healthy adults ≥65 years old

Setting: Community

Bibliography:

1. Bonten MJM, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Gault S, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med. 2015;372(12):1114–25.2.
2. Webber C, Patton M, Patterson S, Schmoele-Thoma B, Huijts SM, Bonten MJM. Exploratory efficacy endpoints in the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA). Vaccine. 2017;35(9):1266–72.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV13	placebo	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow-up: 4 years)												
1[1]	randomized trials	not serious	not serious	not serious	serious[a]	none	8/42240 (0.0%)	9/42256 (0.0%)	**RR 0.89** (0.34 to 2.30)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	Moderate	CRITICAL
Community-acquired pneumonia (follow-up: 4 years; assessed with: culture of S. pneumonia from blood, pleural fluid, and/or other sterile site)												
1	randomized trials	not serious	serious[b]	not serious	not serious	none	144/42240 (0.3%) [b]	185/42256 (0.4%)	**RR 0.78** (0.63 to 0.97)	**1 fewer per 1,000** (from 2 fewer to 0 fewer)	High	CRITICAL
Adverse events (follow-up: 1 months)												
1[1]	randomized trials	not serious	not serious	not serious	not serious	none	188/1006 (18.7%)	144/1005 (14.3%)	**RR 1.37** (1.08 to 1.74)	**53 more per 1,000** (from 11 more to 106 more)	High	CRITICAL
Invasive pneumococcal disease (IPD) (follow-up: 4 years)												
1[2]	randomized trials	not serious	not serious	not serious	not serious	none	34/42240 (0.1%) [b]	67/42256 (0.2%)	**RR 0.51** (0.34 to 0.77)	**1 fewer per 1,000** (from 1 fewer to 0 fewer)	High	CRITICAL
Serious adverse events (follow-up: 6 months)												
1[1]	randomized trials	not serious	not serious	not serious	not serious	none	70/1006 (7.0%)	60/1005 (6.0%)	**RR 1.18** (0.82 to 1.68)	**11 more per 1,000** (from 11 fewer to 41 more)	High	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Number of deaths associated with vaccine does not permit meaningful analysis of vaccine efficacy

b. Modified intention-to-treat population (mITT)

Appendix 2.2. PPSV23 compared to placebo for healthy adults ≥65 years old

Setting: Community

Bibliography: Falkenhorst G, Remschmidt C, Harder T, Hummers-Pradier E, Wichmann O, Bogdan C (2017) Effectiveness of the 23-Valent Pneumococcal Polysaccharide Vaccine (PPV23) against Pneumococcal Disease in the Elderly: Systematic Review and Meta-Analysis. PLoS ONE 12(1): e0169368. doi:10.1371/journal. pone.0169368

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV13	placebo	Relative (95% CI)	Absolute (95% CI)		
Pneumococcal pneumonia												
4	randomized trials	not serious	serious[a]	not serious	not serious	none	85/22282 (0.4%) [b]	98/21308 (0.5%)	**RR 0.75** (0.35 to 1.62)	**1 fewer per 1,000** (from 3 fewer to 3 more)	Moderate	CRITICAL
Invasive pneumococcal disease (IPD) (follow-up: 4 years)												
4[2]	randomized trials	not serious	not serious	not serious	not serious	none	3/22282 (0.0%) [b]	13/21308 (0.0%)	**RR 0.27** (0.08 to 0.90)	**0 fewer per 1,000** (from 1 fewer to 0 fewer)	Moderate	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Substantial heterogeneity (I^2=58%)

b. Imprecision from wide confidence intervals

Appendix 2.3. PPSV23 compared to PCV13 for healthy adults ≥65 years old

Setting: Community

Bibliography: Shiramoto M, Hanada R, Juergens C, Shoji Y, Yoshida M, Ballan B, et al. Immunogenicity and safety of the 13-valent pneumococcal conjugate vaccine compared to the 23-valent pneumococcal polysaccharide vaccine in elderly Japanese adults. Hum Vaccin Immunother. 2015;11(9):2198–206.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PPSV23	PCV13	Relative (95% CI)	Absolute (95% CI)		
Immunogenicity (follow-up: 1 months; assessed with: opsonophagocytic assays (OPA) geometric mean titers (GMTs))												
1	randomized trials	not serious	not serious	not serious	not serious	none	The obtained functional antibody response for PCV13 were non-inferior to that of PPSV23 for all 12 serotypes, but statistically higher for 9 of the 12 serotypes common between vaccines: serotype 4 [ratio 2.6 (95% CI 1.96, 3.44)], serotype 5 [ratio 2.9 (95% CI 2.22, 3.86)], serotype 6B [ratio 1.4 (95% CI 1.10, 1.75)], serotype 7F [ratio 1.4 (95% CI 1.12, 1.74)] serotype 9V [ratio 2.3 (95% CI 1.59, 3.24)], serotype 18C [ratio 2.1 (95% 1.61, 2.86)], serotype 19A [ratio 2.3 (95% CI 1.91, 2.92)], serptype 19F [ratio 2.0 (95% CI 1.42, 2.79)], serotype 23F [ratio 2.5 (95% CI 1.84, 3.49)] serotype 6A which is unique to PCV 13 [ratio 3.1 (95% CI 2.38, 4.14)].[a]				High	IMPORTANT
Adverse events (follow-up: 14 days)												
1	randomized trials	not serious	not serious	not serious	not serious	none	166/370 (44.9%)	211/367 (57.5%)	**RR 0.60** (0.45 to 0.80)	**230 fewer per 1,000** (from 316 fewer to 115 fewer)	High	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Ratio of GMTs (PCV13 / PPSV23) is calculated by back transforming the mean difference between vaccines on the logarithmic scale. CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV13–PPSV23).

Appendix 2.4. PPSV23 compared to placebo or PCV13 for healthy adults 18-64 years old

Setting: Community

Bibliography:

1. Jackson LA, Gurtman A, van Cleeff M, Jansen KU, Jayawardene D, Devlin C, et al. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine compared to a 23-valent pneumococcal polysaccharide vaccine in pneumococcal vacnaïvenaive adults. Vaccine. 2013;31(35):3577–84.
2. Russell KL, Baker CI, Hansen C, Poland GA, Ryan MAK, Merrill MM, et al. Lack of effectiveness of the 23-valent polysaccharide pneumococcal vaccine in reducing all-cause pneumonias among healthy young military recruits: a randomized, double-blind, placebo-controlled trial. Vaccine. 2015;33(9):1182–7.

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Immunogenicity (PPSV23 vs PCV13) (follow-up: 1 months; assessed with: proportion of subjects with 4-fold increase in OPA geometric mean titers (GMTs))									
1[1]	randomized trials	not serious	not serious	not serious	not serious	none	PCV13 OPA GMTs were noninferior to PPSV23 for all 12 common serotypes and statistically significantly greater in PCV13 recipients for 8 of the 12 common serotypes (1, 4, 6B, 7F, 9V, 18C, 19A, 23F). For serotype 6A, contained only in PCV13, the OPA GMT was sub-stantially greater in PCV13 recipients than in PPSV23 recipients	High	CRITICAL
Pneumonia incidence (PPSV23 to placebo) (follow-up: 9-12 weeks; assessed with: radiography)									
1[2]	randomized trials	serious[a]	not serious	not serious	not serious	none	HR 1.136 (0.92 – 1.40)	Moderate	CRITICAL

CI: confidence interval

Explanations

a. Reporting bias: unclear outcome data in each study arm.

Appendix 2.5. PCV13 compared to placebo for healthy adults 18-64 years old

Setting: Community

Bibliography:

1. Ahmed SS, Pondo T, Xing W, McGee L, Farley M, Schaffner W, et al. Early impact of 13-Valent pneumococcal conjugate vaccine use on invasive pneumococcal disease among adults with and without underlying medical conditions-United States. Clin Infect Dis. 2020;70(12):2484–92.
2. Bryant KA, Frenck R, Gurtman A, Rubino J, Treanor J, Thompson A, et al. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine in adults 18–49 yearnaïveage, naive to 23-valent pneumococcal polysaccharide vaccine. Vaccine. 2015;33(43):5854–60
3. Zhu F, Hu Y, Liang Q, Young M Jr, Zhou X, Chen Z, et al. Safety and tolerability of 13-valent pneumococcal conjugate vaccine in healthy Chinese adults, children and infants. Ther Adv Drug Saf. 2015;6(6):206–11.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV13	placebo	Relative (95% CI)	Absolute (95% CI)		
Invasive pneumococcal disease (assessed with: isolation of a pneumococcus from a sterile site (blood, CSF))												
1[1]	observational studies	not serious	not serious	not serious	not serious	none	PCV13-type IPD incidence decreased by 74% (95% CI -78, -70) with an incidence difference of -3.1/100,000 in healthy persons.				Low	CRITICAL
Adverse events (follow-up: 7 days)												
2[2,3]	observational studies	not serious	not serious	not serious	not serious	none	Zhu et al: Out of 24 adults, 6 (25%) experienced any systemic event, 1 (4.2%) had fever. Pain in the injection site was most common (n=23 [95.8%], none of which were severe. Local reactions lasted for a mean of 3.3 days for injection site pain. Bryant et al: PCV13 was well tolerated in 18-49 y/o and 60-64 y/o. Redness, swelling, pain, and limitation of arm movement were more frequent among subjects 18–49 years of age (779/801 [97.3%]) compared with those 60–64 years of age. (277/337 [82.2%]). Pain at the injection site was the most frequently reported local reaction, occurring in >80% of subjects in each age group. Severe pain, categorized as an inability to move the arm above the shoulder, occurred in 15.6% and 1.7% of subjects 18–49 and 60–64 years of age, respectively. The mean duration of local reactions was ≤3 days in both age groups. At least 1 systemic event was reported by 96% and 83% of adults in the 18-49 and 60-64 y/o groups, respectively (most common: generalized muscle pain, headache, fatigue). Events lasted <6 days.				Low	CRITICAL
Immunogenicity (follow-up: 1 months; assessed with: opsonophagocytic activity (OPA) geometric mean titers (GMTs) and IgG geometric mean concentrations (GMCs))												
1[3]	observational studies	not serious	not serious	not serious	not serious	none	OPA responses in adults 18-49 y/o were statistically significantly higher compared to adults 60-64 y/o for all serotypes except for serotype 3. Immune responses most robust in young adults (18-29 years).				Low	

CI: confidence interval

Appendix 3. Characteristics of Included Studies

Study ID	Study Design	Setting	Population	Intervention	Comparator	Outcomes
Population with adults ≥65 years (4 RCTs)						
Bonten M et al. 2015[12]	RCT	Netherlands	adults ≥ 65 years of age	PCV 13	placebo	• Prevention of first episode of vaccine type strains of pneumococcal CAP • Non-bacteremic and noninvasive pneumococcal CAP • Invasive pneumococcal disease
Webber C. et al. 2017 CAPiTA trial[13]	RCT parallel group, double blind trial	Multi-center (USA, UK, Netherlands)	immunocompetent adults ≥ 65 years of age with no prior pneumococcal vaccination history	PCV 13	placebo	• Primary Endpoint: prevent first episode of VT –CAP • Secondary endpoints: prevention of NB/NI VT-CAP and VT-IPD
van Deursen A. et al. 2017[14]	RCT parallel group, double blind trial	Multi-center (USA, UK, Netherlands)	immunocompetent adults ≥ 65 years of age with no prior pneumococcal vaccination history	PCV 13	placebo	• Immune response (before and at 1, 12 and 24 months after vaccination; with 3 age-stratified study participant cohorts)
Shiramoto M et al. 2015[15]	RCT modified double blind	Japan (multi-center)	immunocompetent adults ≥ 65 years of age without *S. pneumoniae* infection within last 5 years	PCV 13	PPSV 23	• Immune responses elicited by PCV 13 compared with PPSV23 (non-inferiority) • Immune response of PCV 13 for serotype 6A, a serotype unique to PCV 13 • Safety profile of PCV 13

Study ID	Study Design	Setting	Population	Intervention	Comparator	Outcomes
Population with Patients Between 18-64 years(2 RCTs, 1 case control, 2 cohort)						
Bryant KA et al. 2015[16]	Cohort	USA (multi-center)	Adults age 18-64 years	PCV 13	No comparator	• Immune responses (1 month after vaccination) • Non-inferiority of immune responses in subjects 18-49 years old versus subjects 60-64 years old
Ahmed S et al. 2019[17]	Case control	USA	Adults 19-64 years with 334mmunocompromising conditions, chronic stable medical conditions, and immunocompetent adults with comorbidities	PCV 13	No comparator	• Invasive pneumococcal disease (IPD) among adults with and without PCV 13 indications
Zhu F et al. 2015[18]	Cohort (open-label)	China	Three cohorts: healthy adults (18-55 years), children (3-5 years) and infants (42 – 98 days)	PCV 13	No comparator	• Local and systemic adverse events
Rusell K et al. 2015[19]	RCT	USA	Healthy US military trainees (17-20 years old) without history of PPSV23 vaccination in the last 5 years	PPSV 23	Placebo	• *S. pneumonia* infections • Any-cause pneumonia, • Any-cause respiratory disease
Jackson L. et al. 2013[20]	RCT	USA	Pneumococcal vaccine naïve adults 60–64 years of age Third arm: 50–59 years of age received open-label PCV13	PCV 13	PPSV 23	• Immunogenicity of PCV13 vs. PPSV23 for the 12 serotypes common to the 2 vaccines among subjects 60-64 (non-inferiority) • Immunogenicity of PCV13 for 50-59 years old compared 60-64 years old

Appendix 4. Risk of Bias Assessment of Included Studies

Figure 1. Risk of bias assessment of included randomized controlled trials

Table 1. Newcastle-Ottawa Assessment of Study Quality

Parameters	Bryant 2015[16]	Ahmed 2019[17]
Selection		
Representativeness of exposed cohort	1	1
Selection of non-exposed cohort	1	1
Ascertainment of exposure	1	1
Demonstration that outcome of interest was not present at start of study	1	1
Comparability		
Comparability of cohorts on the basis of the design or analysis controlled for confounders	1	1
Outcome		
Assessment of outcome	1	1
Was follow-up long enough for outcomes to occur	1	1
Adequacy of follow-up of cohorts	1	1
Total	8	8
Quality	Good	Good

Rabies Vaccine

Appendix 1. Evidence-to-Decision Summary

Burden	No	Probably No	Probably Yes	Yes (7)	Varies	Don't know (1)
Benefits	Trivial (1)	Small (3)	Moderate (2)	Large	Varies	Don't know (2)
Harms	Large	Moderate (3)	Small (3)	Trivial (2)	Varies	Don't know
Certainty of evidence	Very Low (4)	Low (3)	Moderate	High	No included studies (1)	
Balance of effects	Favors no vaccine	Probably favors no vaccine	Equivalent (2)	Probably favors vaccine (2)	Favors vaccine (2)	Varies (1)	Don't know (1)

Resources required	Large costs	Moderate costs (7)	Negligible costs and savings	Moderate savings (1)	Large savings	Varies	Don't know
Certainty of evidence (resources)	Very Low	Low (3)	Moderate (5)	High	No included studies		
Cost effectiveness	Favors no vaccine	Probably favors no vaccine (1)	Does not favor either	Probably favors vaccine (3)	Favors vaccine (3)	Varies	No included studies (1)
Equity	Reduced	Probably reduced	Probably no impact (1)	Probably increased (1)	Increased (2)	Varies (1)	Don't know (3)
Acceptability	No	Probably no	Probably yes (4)	Yes (2)	Varies	Don't know (2)	
Feasibility	No	Probably no (1)	Probably yes (6)	Yes (1)	Varies	Don't know	
Values	Important variability (2)	Possibly important variability (6)	Probably no important variability	No important variability			

Recommendation 1: **Asymptomatic apparently healthy adults**	STRONG against	WEAK against	NO RECOMMENDATION (1)	WEAK in favor (6)	STRONG in favor (1)
Recommendation 2: **High-risk populations**	STRONG against	WEAK against	NO RECOMMENDATION	WEAK in favor (3)	STRONG in favor (5)

Appendix 2. GRADE Summary of Findings Table

Appendix 2.1. Abbreviated PVRV regimen versus standard PVRV regimen among apparently healthy asymptomatic adults
Question: Abbreviated PVRV regimen compared to standard PVRV regimen for pre-exposure rabies vaccine among healthy students at risk for rabies

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	abbreviated PVRV regimen	standard PVRV regimen	Relative (95% CI)	Absolute (95% CI)		
Geometric Mean Titer (IU/mL) (follow-up: 45 days)												
1	randomised trials	not serious	not serious	serious[b]	serious[c]	none	73	100	-	MD **0.39 IU/mL higher** (1.93 lower to 2.71 higher)	Low	CRITICAL
Geometric Mean Titer (IU/mL) (follow-up: 360 days)												
1	randomised trials	not serious	not serious	serious[b]	serious[c]	none	66	20	-	MD **1.14 IU/mL higher** (0.71 lower to 2.99 higher)	Low	CRITICAL
Seroconversion Proportion (0.5IU/mL or higher) (follow-up: 45 days)												
2	randomised trials	not serious	not serious	serious[b]	not serious	none	94/94 (100.0%)	123/123 (100.0%)	**RR 1.00** (0.98 to 1.02)	**0 fewer per 1,000** (from 20 fewer to 20 more)	Moderate	CRITICAL
Seroconversion Proportion (0.5IU/mL or higher) (follow-up: 360 days)												
1	randomised trials	not serious	not serious	serious[b]	not serious	none	62/66 (93.9%)	20/20 (100.0%)	**RR 0.96** (0.87 to 1.05)	**40 fewer per 1,000** (from 130 fewer to 50 more)	Moderate	CRITICAL
Local and Systemic Adverse Events												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	25/158 (15.8%)	70/510 (13.7%)	**RR 1.15** (0.76 to 1.76)	**21 more per 1,000** (from 33 fewer to 104 more)	Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; Explanation: a) high risk for detection bias, b) active comparator, c) wide confidence interval

Appendix 2.2. Abbreviated PCECV regimen versus standard PCECV regimen among apparently healthy asymptomatic adults
Question: Abbreviated PCECV regimen compared to standard PCECV regimen for pre-exposure rabies vaccine among healthy adults

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	abbreviated PCECV regimen	standard PCECV regimen	Relative (95% CI)	Absolute (95% CI)		
Geometric Mean Titer (IU/mL) (follow-up: 45 days)												
2	randomised trials	not serious	not serious	serious[b]	serious[c]	none	265	265	-	MD **0.99 IU/mL lower** (4.01 lower to 2.03 higher)	Low	CRITICAL
Geometric Mean Titer (IU/mL) (follow-up: 13 months)												
1	randomised trials	not serious	not serious	serious[b]	serious[c]	none	104	96	-	MD **0.1 IU/mL higher** (0.82 lower to 1.02 higher)	Low	CRITICAL
Seroconversion Proportion (0.5IU/mL or higher) (follow-up: range 45 days to 90 days)												
3	randomised trials	not serious	not serious	serious[b]	not serious	none	288/289 (99.7%)	288/288 (100.0%)	**RR 1.00** (0.99 to 1.01)	**0 fewer per 1,000** (from 10 fewer to 10 more)	Moderate	CRITICAL
Seroconversion Proportion (0.5IU/mL or higher) (follow-up: 13 months)												
1	randomised trials	not serious	not serious	serious[b]	not serious	none	94/104 (90.4%)	91/96 (94.8%)	**RR 0.95** (0.88 to 1.03)	**47 fewer per 1,000** (from 114 fewer to 28 more)	Moderate	CRITICAL
Local Adverse Events												
2	randomised trials	serious[a]	not serious	serious[b]	not serious	none	503/746 (67.4%)	267/475 (56.2%)	**RR 0.99** (0.89 to 1.11)	**6 fewer per 1,000** (from 62 fewer to 62 more)	Low	CRITICAL
Systemic Adverse Events												
2	randomised trials	serious[a]	not serious	serious[b]	not serious	none	203/746 (27.2%)	132/475 (27.8%)	**RR 0.87** (0.72 to 1.04)	**36 fewer per 1,000** (from 78 fewer to 11 more)	Low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; Explanation: a) high risk for detection bias, b) active comparator, c) wide confidence interval

Appendix 2.3. Intradermal PVRV route versus intramuscular PVRV route among apparently healthy asymptomatic adults
Question: Intradermal PVRV compared to intramuscular PVRV for pre-exposure rabies vaccine among healthy adults

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intradermal PVRV	intramuscular PVRV	Relative (95% CI)	Absolute (95% CI)		
Geometric Mean Titer (IU/mL) (follow-up: 21 days)												
1	randomised trials	not serious	not serious	serious[b]	serious[c]	none	36	37	-	MD **1.67 IU/mL higher** (1.47 lower to 4.81 higher)	Low	CRITICAL
Geometric Mean Titer (IU/mL) (follow-up: 365 days)												
1	randomised trials	not serious	not serious	serious[b]	serious[c]	none	35	36	-	MD **0.06 IU/mL higher** (0.33 lower to 0.45 higher)	Low	CRITICAL
Seroconversion Proportion (0.5IU/mL or higher) (follow-up: range 21 days to 90 days)												
2	randomised trials	not serious	not serious	serious[b]	not serious	none	73/75 (97.3%)	52/53 (98.1%)	**RR 0.99** (0.92 to 1.05)	**10 fewer per 1,000** (from 78 fewer to 49 more)	Moderate	CRITICAL
Seroconversion Proportion (0.5IU/mL or higher) (follow-up: 365 days)												
1	randomised trials	not serious	not serious	serious[b]	serious[c]	none	21/35 (60.0%)	19/36 (52.8%)	**RR 1.14** (0.75 to 1.71)	**74 more per 1,000** (from 132 fewer to 375 more)	Low	CRITICAL
Local Adverse Events												
4	randomised trials	serious[a]	not serious	serious[b,d]	serious[c]	none	119/479 (24.8%)	89/453 (19.6%)	**RR 1.18** (0.85 to 1.64)	**35 more per 1,000** (from 29 fewer to 126 more)	Very low	CRITICAL
Systemic Adverse Events												
4	randomised trials	serious[a]	not serious	serious[b,d]	serious[c]	none	60/479 (12.5%)	69/453 (15.2%)	**RR 0.81** (0.54 to 1.23)	**29 fewer per 1,000** (from 70 fewer to 35 more)	Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio Explanation: a) high risk for detection bias, b) active comparator, c) wide confidence interval, d) pediatric population included

Appendix 2.4. Intradermal PCECV route versus intramuscular PCECV route among apparently healthy asymptomatic adults
Question: Intradermal PCECV compared to intramuscular PCECV for pre-exposure rabies vaccine among healthy adults

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intradermal PCECV	intramuscular PCECV	Relative (95% CI)	Absolute (95% CI)		
Geometric Mean Titer (IU/mL) (follow-up: 77 days)												
1	randomised trials	not serious	not serious	serious[b]	serious[c]	none	12	12	-	MD **1.08 IU/mL higher** (2.33 lower to 4.49 higher)	Low	CRITICAL
Geometric Mean Titer (IU/mL) (follow-up: 365 days)												
1	randomised trials	not serious	not serious	serious[b]	serious[c]	none	11	11	-	MD **0.02 IU/mL lower** (0.43 lower to 0.39 higher)	Low	CRITICAL
Seroconversion Proportion (0.5IU/mL or higher) (follow-up: range 21 days to 90 days)												
2	randomised trials	not serious	not serious	serious[b]	not serious	none	31/31 (100.0%)	31/31 (100.0%)	**RR 1.00** (0.92 to 1.09)	**0 fewer per 1,000** (from 80 fewer to 90 more)	Moderate	CRITICAL
Seroconversion Proportion (0.5IU/mL or higher) (follow-up: range 365 days to 756 days)												
2	randomised trials	not serious	not serious	serious[b]	not serious	none	23/30 (76.7%)	26/30 (86.7%)	**RR 0.92** (0.72 to 1.18)	**69 fewer per 1,000** (from 243 fewer to 156 more)	Moderate	CRITICAL
Local and Systemic Adverse Events												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	11/12 (91.7%)	8/12 (66.7%)	**RR 1.38** (0.89 to 2.12)	**253 more per 1,000** (from 73 fewer to 747 more)	Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; Explanation: a) high risk for detection bias, b) active comparator, c) wide confidence interval

Appendix 2.5. PVRV versus PCECV among apparently healthy asymptomatic adults
Question: PVRV compared to PCECV for pre-exposure rabies vaccine among healthy adults

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PVRV	PCECV	Relative (95% CI)	Absolute (95% CI)		
Geometric Mean Titer (IU/mL) (follow-up: 90 days)												
1	randomised trials	not serious	not serious	serious[b]	serious[c]	none	56	63	-	MD **1.05 IU/mL lower** (2.46 lower to 0.36 lower)	Low	CRITICAL
Seroconversion Proportion (0.5IU/mL or higher) (follow-up: 90 days)												
2	randomised trials	not serious	not serious	serious[b]	not serious	none	79/79 (100.0%)	86/86 (100.0%)	**RR 1.00** (0.97 to 1.03)	**0 fewer per 1,000** (from 30 fewer to 30 more)	Moderate	CRITICAL
Local Adverse Events												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	1/56 (1.8%)	1/63 (1.6%)	**RR 1.13** (0.07 to 17.57)	**2 more per 1,000** (from 15 fewer to 263 more)	Very low	CRITICAL
Systemic Adverse Events												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	0/56 (0.0%)	6/63 (9.5%)	**RR 0.09** (0.00 to 1.50)	**87 fewer per 1,000** (from -- to 48 more)	Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; Explanation: a) high risk for detection bias, b) active comparator, c) wide confidence interval

Appendix 3. Characteristics of Included Studies

Author/Year	Study design	Country	Number of patients	Population	Intervention Group(s)	Control	Outcomes	
							Efficacy	Safety
Cunha 2010	RCT	Brazil	127	Professionals at risk of exposure to rabies virus (aged 18 years or older) who require pre-exposure rabies vaccine Mean age (years): Intervention: 33.2 Control: 31.8	n=65 Type: PVRV (Verorab) Regimen: 1-1-1 (days 0, 7, 28) Dose: 0.1 mL Route: ID	n=62 Type: PVRV (Verorab) Regimen: 1-1-1 (days 0, 7, 28) Dose: 0.5 mL Route: IM	GMT (RFFIT) Seroconversion (≥0.5 IU/mL, RFFIT) Follow-up: 10, 90, 180 days	Local AE (erythema, stiffening, pain, itching) Systemic AE (headache, nausea)
Dreesen 1989	RCT	USA	38	Volunteers (aged 21–37 years) with no prior history of rabies vaccination Mean age (years): not reported	n=19 Type: PCECV (Behringwerke AG) Regimen: 1-1-1 (days 0, 7, 28) Dose: 0.1 mL Route: ID	n=19 Type: PCECV (Behringwerke AG) Regimen: 1-1-1 (days 0, 7, 28) Dose: 1.0 mL Route: IM	GMT (RFFIT) Follow-up: 28, 52, 92, 365, 756 days	Local AE (redness, pain, swelling, warmth, itching) Systemic AE (fever, myalgia, malaise, headaches, dizziness, nausea, hives, and rash)
Endy 2020	Open-label RCT	USA	24	Adults (aged 18–60 years) with no prior history of rabies vaccination Mean age (years): 32.4	n=12 Type: PCECV (RabAvert) Regimen: 1-1-1 (days 0, 7, 28) Dose: 0.1 mL Route: ID	n=12 Type: PCECV (RabAvert) Regimen: 1-1-1 (days 0, 7, 28) Dose: 1.0 mL Route: IM	GMT (RFFIT) Seroconversion (≥0.5 IU/mL, RFFIT) Follow-up: 7, 14, 28, 77, 365, 372 days	Local and systemic AE (pain, itching, and swelling at the injection site, fatigue, low-grade fever, and muscle aches) SAE

Author/Year	Study design	Country	Number of patients	Population	Intervention Group(s)	Control	Outcomes	
							Efficacy	Safety
Huang 2013	Open-label RCT	China	181	Healthy veterinary school students (aged 18–26 years) with no prior history of rabies vaccination Mean age (years): Intervention: 20.81 Control: 22.80	n=79 Type: PVRV (Liaoning Cheng Da) Regimen: 2-1 (days 0, 7) Dose: not reported Route: IM	n=102 Type: PVRV (Liaoning Cheng Da) Regimen: 1-1-1-1-1 (Essen; days 0, 3, 7, 14, 28) Dose: not reported Route: IM	GMT (RFFIT) Seroconversion (≥0.5 IU/mL, RFFIT) Follow-up: 7, 14, 45, 180, 360 days	Local AE (pain, pruritus, edema, erythema) Systemic AE (headache, fever, myalgia, malaise, sleepiness)
Jaiiaroensup 1998	RCT	Thailand	600	Veterinary and nursing students, and animal bite clinic staff Mean age (years): not reported	n=300 Type: PVRV (Merieux) Regimen: 1-1-1 (days 0, 7, 28) Dose: 0.1 mL Route: ID	n=300 Type: PVRV (Merieux) Regimen: 1-1-1 (days 0, 7, 28) Dose: 0.5 mL Route: IM	Follow-up: 7, 28, 35 days	Safety: Local AE (edema, urticarial eruption, pustule, erythema, induration, pain, pruritus, rash) Systemic AE (asthenia, fever, headache, malaise, myalgia, nausea)
Li 2015	Open-label RCT	China	397	Healthy adults (aged ≥51 years) with no prior history of vaccination Mean age (years): Intervention: 62.1 Control: 61.9	n=197 Type: PCECV (Rabipur) Regimen: 2-1-1 (Zagreb; days 0, 7, 21) Dose: 1.0 mL Route: IM	n=200 Type: PCECV (Rabipur) Regimen: 1-1-1-1-1 (Essen; days 0, 3, 7, 14, 28) Dose: 1.0 mL Route: IM	GMT (RFFIT) Seroconversion (≥0.5 IU/mL, RFFIT) Follow-up: 14, 42 days	Local AE (erythema, induration, pain) Systemic AE (loss of appetite, nausea, headache, myalgia, fatigue, fever) Mortality
Ma 2014	Open-label RCT	China	824	Healthy adults (aged 18–50 years) with no prior history of rabies vaccination Mean age (years): Intervention: 38.2 Control: 39.3	n=549 Type: PCECV (Rabipur) Regimen: 2-1-1 (Zagreb; days 0, 7, 21) Dose: not reported Route: IM	n=275 Type: PCECV (Rabipur) Regimen: 1-1-1-1-1 (Essen; days 0, 3, 7, 14, 28) Dose: not reported Route: IM	GMT (RFFIT) Seroconversion (≥0.5 IU/mL, RFFIT) Follow-up: 7, 14, 42 days, 13 months	Local AE (erythema, swelling, pain) Systemic AE (fever, malaise, headache, nausea, myalgia, fatigue, rash)

Author/Year	Study design	Country	Number of patients	Population	Intervention Group(s)	Control	Outcomes	
							Efficacy	Safety
Miranda 2014	Open-label RCT	Philippines	189	Healthy adults (aged 18–65 years) with no prior history of rabies vaccination Mean age (years): Intervention: 30.39 (standard); 27.46 (modified) Control: 24.45	n=112 Type: PVRV (Speeda) Regimen: 2-2-2-2 (days 0, 3, 7, 30) Dose: 0.1 mL Route: ID	n=62 Type: PCECV (Rabipur) Regimen: 2-2-2-2 (days 0, 3, 7, 30) Dose: 0.1 mL Route: ID	GMT (RFFIT) Seroconversion (≥0.5 IU/mL, RFFIT) Follow-up: 14, 30, 90 days	Local AE (erythema, itching, pain) Systemic AE (fever, dizziness, headache)
Quiambao 2022	Open-label RCT	Philippines	73	Healthy adults (aged 18–64 years) with no prior history of rabies vaccination Mean age (years): Intervention: 23.8 Control: 22.6	n=36 Type: PVRV (Verorab) Regimen: 2-2 (days 0, 7) Dose: 0.1 mL Route: ID	n=37 Type: PVRV (Verorab) Regimen: 1-1 (days 0, 7) Dose: 0.5 mL Route: IM	GMT (RFFIT) Seroconversion (≥0.5 IU/mL, RFFIT) Follow-up: 21 days, 6 months	Local AE Systemic AE SAE Mortality
Vodopija 1986	Double-blind RCT	Yugoslavia (Croatia)	46	Healthy male adults (aged 19–25 years) with no prior history of rabies vaccination Mean age (years): not reported	n=21 Type: PVRV (Merieux) Regimen: 1-1-1 (days 0, 7, 21) Dose: 5.14 IU Route: IM	n=25 Type: PCECV (Behringwerke) Regimen: 1-1-1 (days 0, 7, 21) Dose: 7.18 IU Route: IM	Efficacy: GMT (RFFIT) Seroconversion (≥0.5 IU/mL, RFFIT) Follow-up: 7, 14, 21, 28, 90 days	-
Wongsaroj 2013	RCT	Thailand	55	Healthy adults (aged 18–24 years) Mean age (years): not reported	n=39 Type: PVRV (Sanofi Pasteur) Regimen: 2-2 (days 0, 21) Dose: 0.1 mL Route: ID	n=16 Type: PVRV (Sanofi Pasteur) Regimen: 1-1-1 (days 0, 7, 21) Dose: 0.5 mL Route: IM	GMT (RFFIT) Seroconversion (≥0.5 IU/mL, RFFIT) Follow-up: 35, 365 days	Local AE (pain, pruritus, erythema) Systemic AE (fever)

AE adverse events; GMT geometric mean titer; ID intradermal; IM intramuscular; PCECV purified chick embryo cell vaccine; PrEP pre-exposure prophylaxis; PVRV purified Vero-cell rabies vaccine; RCT randomized controlled trial; RFFIT rapid fluorescent focus inhibition test; SAE serious adverse events

Appendix 4. Forest Plots

Appendix 4.1. Abbreviated vs. Standard Regimen

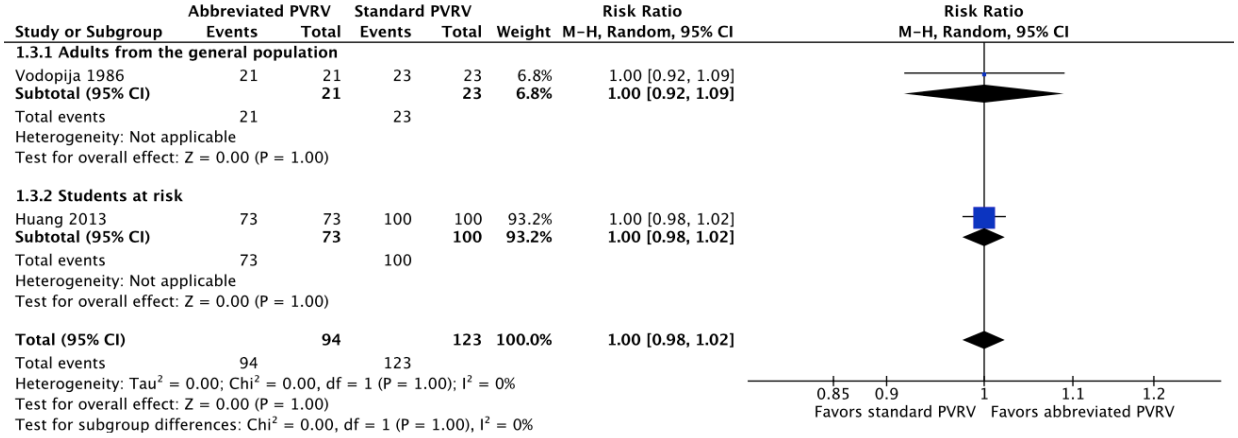


Figure 1. Effects of abbreviated PVRV versus standard PVRV on the proportion of seroconverted healthy adults (45–90 days)

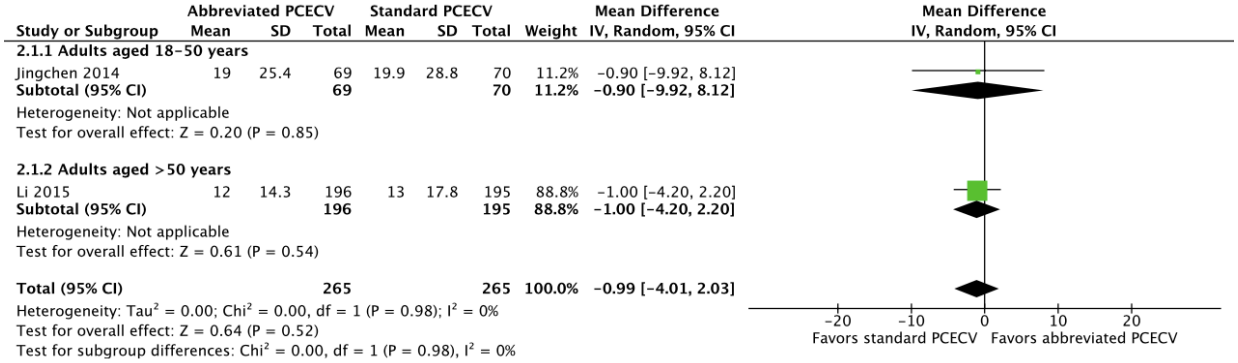


Figure 2. Effects of abbreviated PCECV versus standard PVRV on the RVNA GMT of healthy adults (42-90 days)

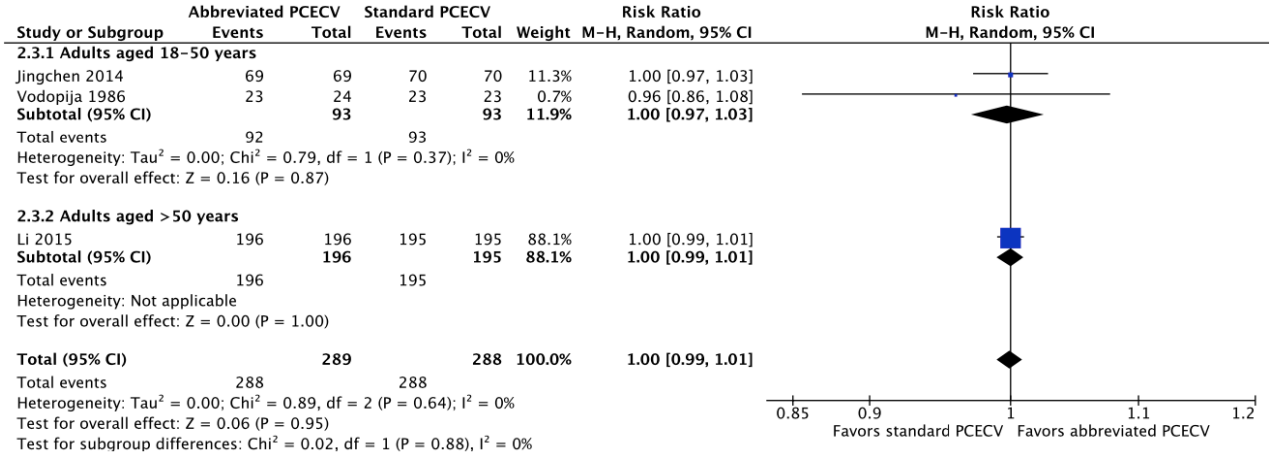


Figure 3. Effects of abbreviated PCECV versus standard PCECV on the proportion of seroconverted healthy adults (42–90 days)

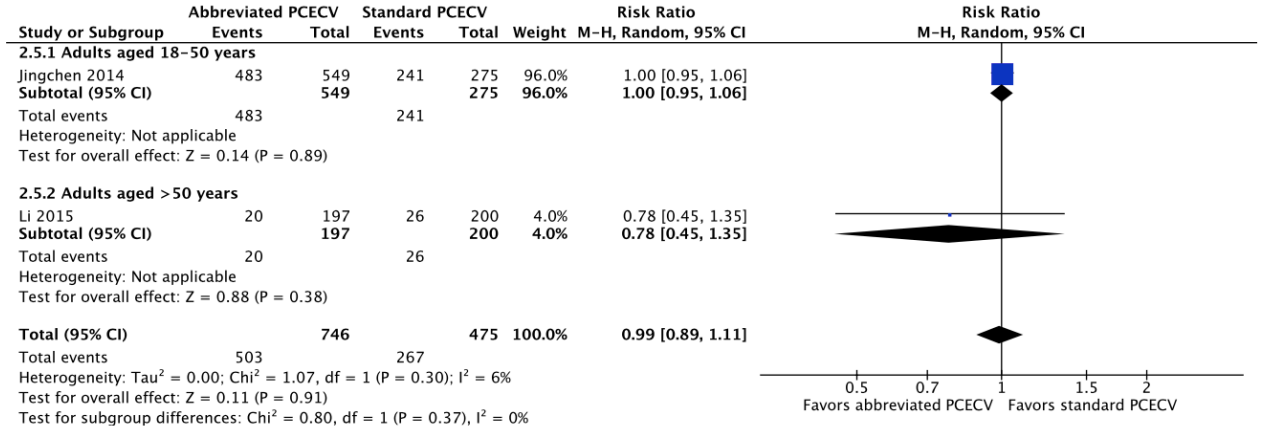


Figure 4. Effects of standard PCECV versus abbreviated PCECV on local adverse events of healthy adults

Appendix 4.2. Intradermal vs. Intramuscular Route

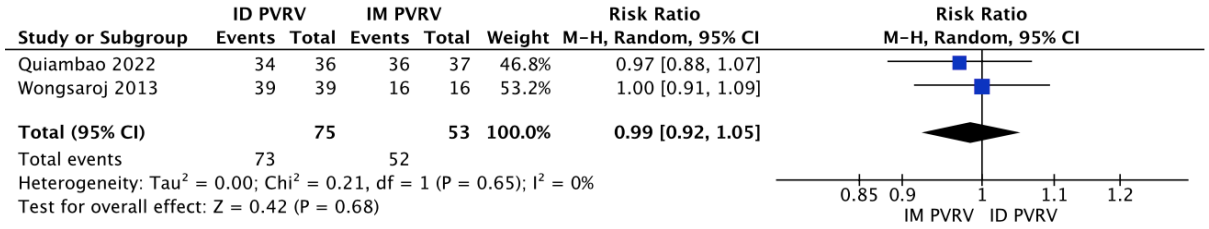


Figure 5. Effects of intradermal PVRV versus intramuscular PVRV on the proportion of seroconverted healthy adults (21–90 days)

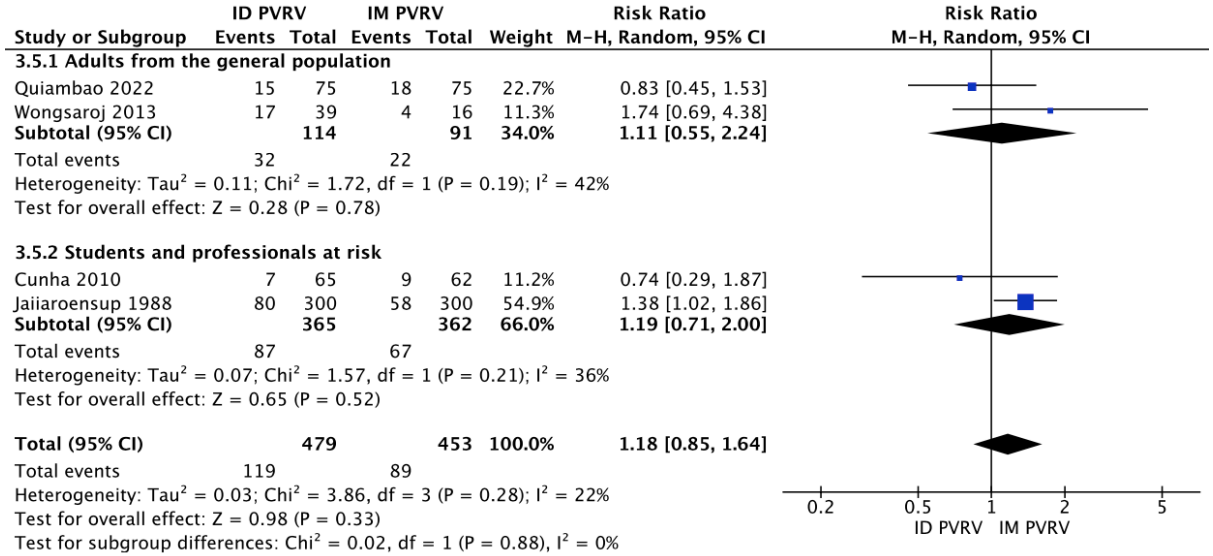


Figure 6. Effects of intradermal PVRV versus intramuscular PVRV on local adverse events of healthy adults

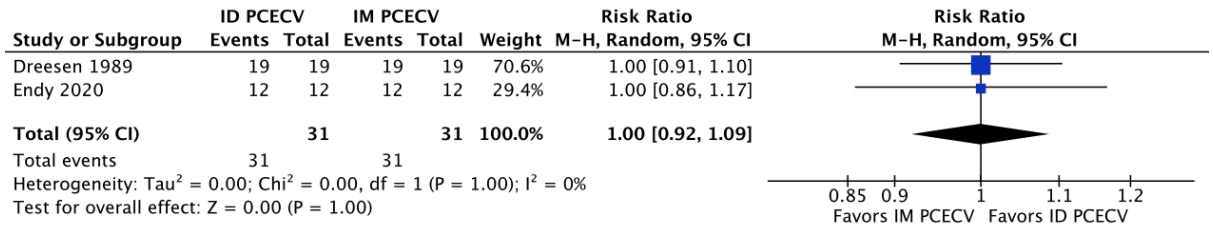


Figure 7. Effects of intradermal PCECV versus intramuscular PCECV on the proportion of seroconverted healthy adults (21–90 days)

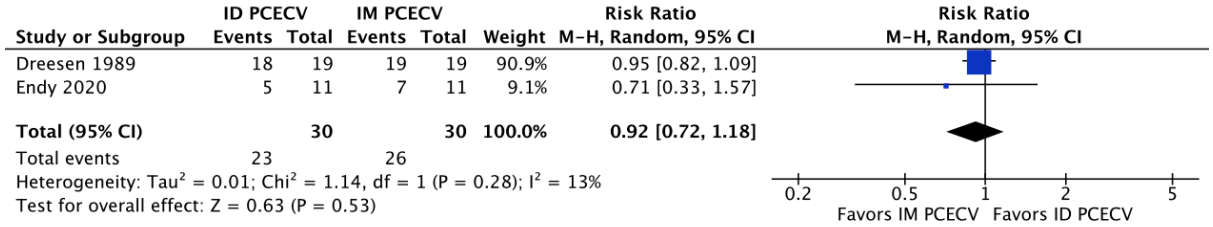


Figure 8. Effects of intradermal PCECV versus intramuscular PCECV on the proportion of seroconverted healthy adults (365–756 days)

Appendix 4.3. PCECV vs. PVRV

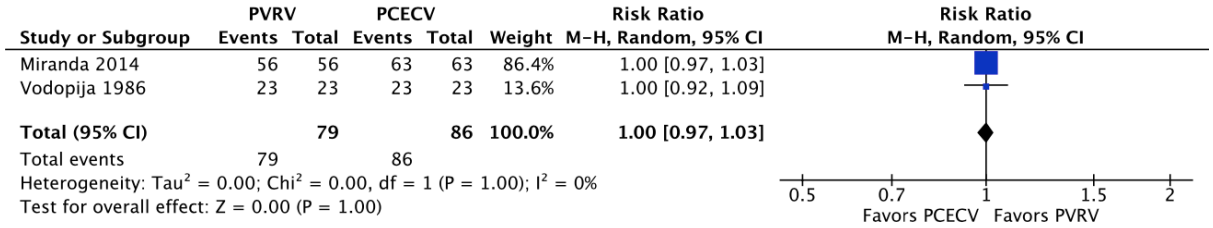
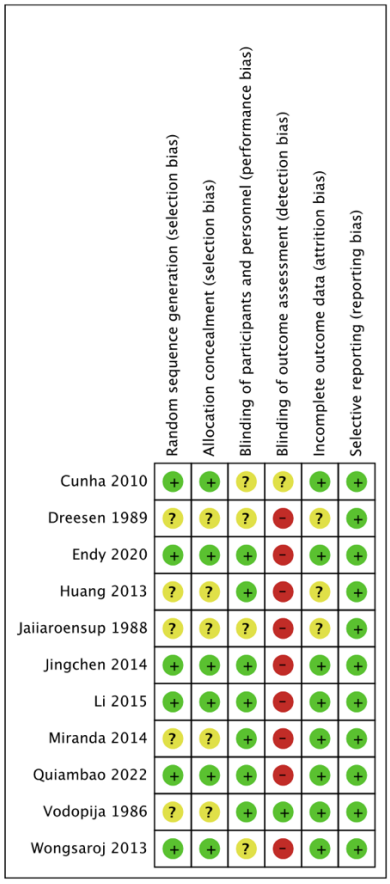
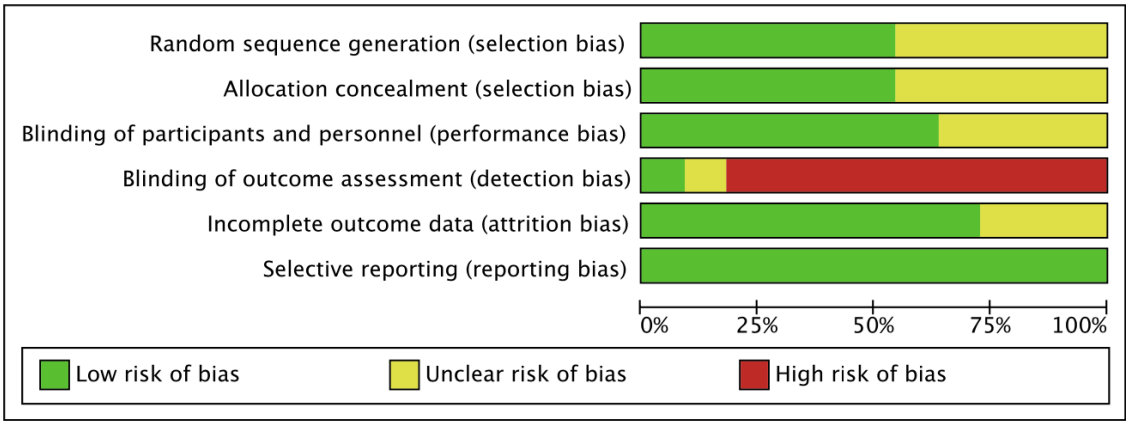


Figure 9. Effects of PVRV versus PCECV on the proportion of seroconverted health adults (90 days)

Appendix 5. Risk of Bias Assessment of Included Studies





*Studies were rated as having high risk for detection bias only for safety outcomes. For efficacy outcomes, risk of bias for this component was rated low or not serious.

Tetanus Vaccine

Appendix 1. Evidence-to-Decision Summary

Burden	No	Probably No	Probably Yes	Yes (4)	Varies (2)	Don't know
Benefits	Trivial (2)	Small (1)	Moderate (1)	Large (2)	Varies	Don't know
Harms	Large	Moderate	Small (4)	Trivial (1)	Varies (1)	Don't know
Certainty of evidence	Very Low	Low (5)	Moderate (1)	High	No included studies	
Balance of effects	Favors no vaccine (1)	Probably favors no vaccine	Equivalent/ Does not favor either (1)	Probably favors vaccine (1)	Favors vaccine (3)	Varies	Don't know

Resources required	Large costs	Moderate costs	Negligible costs and savings (4)	Moderate savings	Large savings	Varies (2)	Don't know
Certainty of evidence (resources)	Very Low	Low (3)	Moderate (2)	High	No included studies (1)		
Cost effectiveness	Favors no vaccine	Probably favors no vaccine (2)	Does not favor either (1)	Probably favors vaccine (1)	Favors vaccine (1)	Varies (1)	No included studies (1)
Equity	Reduced	Probably reduced	Probably no impact (5)	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no (1)	Probably yes (2)	Yes (2)	Varies	Don't know	
Feasibility	No	Probably no	Probably yes (5)	Yes (1)	Varies	Don't know	
Values	Important variability (1)	Possibly important variability (2)	Probably no important variability (2)	No important variability (1)			

Recommendation 1: **Asymptomatic apparently healthy adults**	STRONG against	WEAK against (2)	NO RECOMMENDATION	WEAK in favor (2)	STRONG in favor (2)

Appendix 2. GRADE Summary of Findings Table

Appendix 2.1. Pooled immune response rates, adverse events, and serious adverse events after tetanus vaccination versus placebo

Patient or population: healthy adults
Setting: any
Intervention: any tetanus toxoid-containing vaccine
Comparison: placebo

Outcomes	Effect size (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
Immune response rate	ES 98.5% (98.0 to 98.9%)	3,664 (1 sub-analysis of 4 RCTs; 4 RCT, 6 arms; 2 open-label trials)	Moderate[a,b] Due to indirectness and study design limitations. Upgraded due to high effect size.	Immune response rates are increased with tetanus vaccination versus placebo or any tetanus toxoid containing vaccine or no comparator
Grade 3 adverse events	ES 1.8 (1.4 to 2.4)	2,818 (1 sub-analysis of 4 RCTs; 1 RCT, 2 arms; 2 open-label trials)	Low Due to indirectness and study design limitations[c,d]	Grade 3 adverse events probably have increased risk with tetanus toxoid vaccination versus placebo
Serious adverse events	ES 0.8 (0.4 to 1.2)	3,329 (1 sub-analysis of 4 RCTs; 3 RCT, 5 arms; 3 open-label trials, 3 arms)	Low Due to indirectness and study design limitations[e, f]	Serious adverse events probably increased risk with tetanus toxoid vaccination versus placebo

CI: confidence interval; **RR**: risk ratio
Explanations
a. No serious risk of bias detected.
b. Indirectness due to use of another typhoid vaccine as comparator or no comparator used.
c. Indirectness due to nonstandard definitions of “Grade 3 Adverse Events” between trials. No serious risk of bias detected. No serious inconsistency, and although there is visual heterogeneity, there is no statistical heterogeneity, I2 = 0%. No serious risk of publication bias.
d. For the purposes of this meta-analysis, Grade 3 adverse events are defined as any symptom that would cause difficulty or impairment in daily activities.
e. Indirectness due to nonstandard definitions of “Severe Adverse Events” between trials. No serious risk of bias detected. No serious inconsistency, no statistical heterogeneity, I2 = 0%. No serious risk of publication bias.
f. For the purposes of this meta-analysis, “Severe Adverse Events” are defined as any symptom directly caused by the vaccination that would cause hospitalization, mortality, prolonging in-patient hospitalization, or cause impairment or disability in daily activities.

Appendix 3. Characteristics of Included Studies

Study	Population	Intervention	Comparison	Outcome
Blatter et al., 2009[6]	Healthy adults 19-64 years old	Tdap3v or Tdap5v	None	• Anti-tetanus toxoid antibody levels ≥0.1IU/mL after 1 month • Grade 3 adverse events • Serious adverse events
Hong et al., 2015[7]	Adults 20 years and older who did not receive a Tdap vaccine within 5 years of the trial	Td	Placebo and standard Td	• Anti-tetanus toxoid antibody levels ≥0.1IU/mL after 2 and 4 weeks • Serious adverse events
Lee et al., 2019[8]	Adults ≥ 18 years old who were not injected with Td or TdaP within the recent 5 years	Td	Standard Td	• Anti-tetanus toxoid antibody levels ≥0.1IU/mL after 28 days • Serious adverse events
Van Damme et al., 2011[9]	Adults > 55 years old who had participated in a clinical trial of dTpa (Boostrix), and have not received diphtheria or tetanus-containing vaccines within the past 5 years	dTpa	dTpa-IPV	• Anti-tetanus toxoid antibody levels ≥0.1IU/mL after 1 month • Grade 3 adverse events • Serious adverse events
Perrett et al., 2020[10]	Pregnant women	Tdap at 27–36 weeks' gestation and placebo at <72-hour-postpartum immunization	Placebo at 27–36 weeks' gestation and Tdap at <72-hour-postpartum immunization	• Adverse events • Grade 3 adverse events • Serious adverse events
Kovac et al., 2018[11]	Healthy adults 19–30 years with previous booster (either Tdap or Td) 10 years (±300 days) before	Tdap booster for those who received Tdap 10 years ago	Tdap booster for those who received Td 10 years ago	• Anti-tetanus toxoid antibody levels ≥0.1IU/mL after 1 month • Grade 3 adverse events • Serious adverse events
Asatryan et al., 2020[12]	≥4 years of age with completed series (4-7 years old with primary series + booster; >8 years old with last diphtheria, tetanus vaccination (with or without pertussis) more than 5 years prior to the study)	dTpa with reduced antigen content	None	• Anti-tetanus toxoid antibody levels ≥0.1IU/mL after 1 month • Grade 3 adverse events • Serious adverse events
Choi et al., 2010[13]	Adults 40 years or older who had not received DPT or Td vaccination	Td	None	• Anti-tetanus toxoid antibody levels ≥0.1IU/mL 4 weeks after the 1st dose and 4 weeks after the 3rd dose • Serious adverse events

Appendix 4. Forest Plots

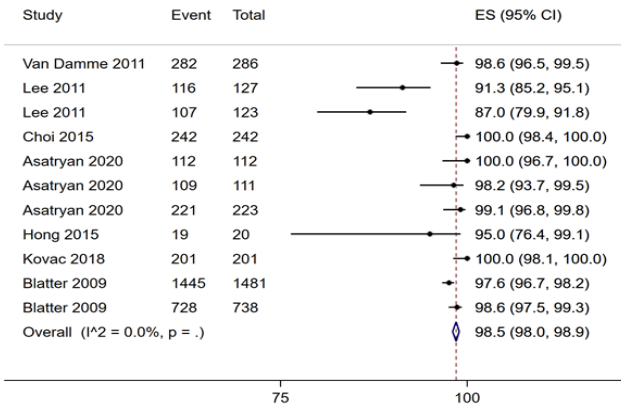


Figure 1. Immune response rates after tetanus vaccination

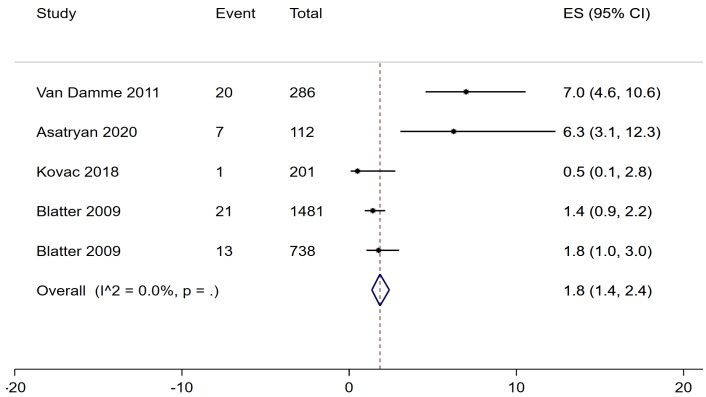


Figure 2. Grade 3 adverse events after tetanus vaccination

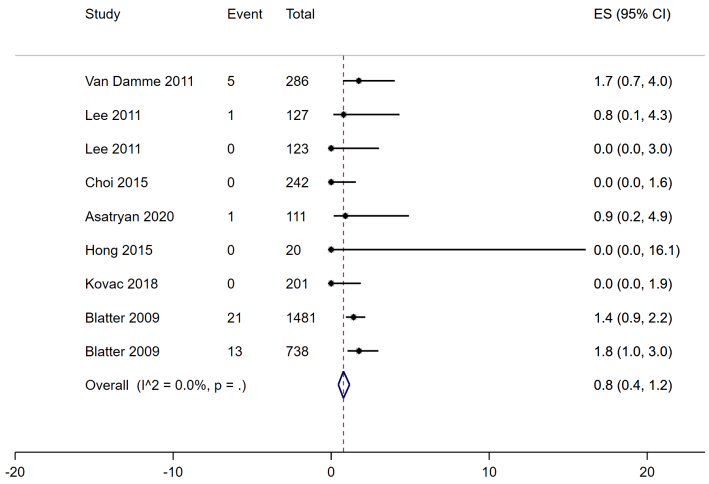


Figure 3. Serious adverse events after tetanus vaccination

Typhoid Vaccine

Appendix 1. Evidence-to-Decision Summary

Burden	No	Probably No	Probably Yes	Yes (4)	Varies (2)	Don't know
Benefits	Trivial	Small (2)	Moderate (4)	Large	Varies	Don't know
Harms	Large	Moderate (2)	Small (2)	Trivial (2)	Varies	Don't know
Certainty of evidence	Very Low	Low (3)	Moderate (3)	High	No included studies	
Balance of effects	Favors no vaccine	Probably favors no vaccine (1)	Equivalent	Probably favors vaccine (5)	Favors vaccine	Varies	Don't know

Resources required	Large costs (5)	Moderate costs (1)	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence (resources)	Very Low	Low (2)	Moderate	High	No included studies (4)		
Cost effectiveness	Favors no vaccine	Probably favors no vaccine (1)	Does not favor either	Probably favors vaccine	Favors vaccine (1)	Varies (1)	Don't know/No studies (2)
Equity	Reduced	Probably reduced	Probably no impact (1)	Probably increased (2)	Increased	Varies (1)	Don't know
Acceptability	No (1)	Probably no (1)	Probably yes (1)	Yes	Varies (2)	Don't know	
Feasibility	No (2)	Probably no (1)	Probably yes (1)	Yes	Varies (1)	Don't know	
Values	Important variability	Possibly important variability (3)	Probably no important variability (1)	No important variability (2)			

Recommendation 1: **Asymptomatic apparently healthy adults**	STRONG against	WEAK against (1)	NO RECOMMENDATION (4)	WEAK in favor	STRONG in favor (1)

Appendix 2. GRADE Summary of Findings Table

Appendix 2.1. Ty21a vaccination (three doses) versus placebo for typhoid fever

Patient or population: adults and children aged 5 years of age and older
Settings: any
Intervention: oral Ty21a (3 doses) - liquid, enteric capsule, or gelatin capsule
Comparison: placebo
Bibliography:

1. Yang HH, Wu CG, Xie GZ, Gu QW, Wang BR, Wang LY, et al. Efficacy trial of Vi polysaccharide vaccine against typhoid fever in south-western China. Bulletin of the World Health Organization. 2001;79(7):625–31.
2. Sur D, Ochiai RL, Bhattacharya SK, Ganguly NK, Ali M, Manna B, et al. A Cluster-Randomized Effectiveness Trial of Vi Typhoid Vaccine in India. New England Journal of Medicine. 2009 Jul 23;361(4):335–44

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Ty21a (3 doses)				
Incidence of typhoid fever, year 1 post-vaccination	**Medium-risk population**		**RR 0.55** (0.35 to 0.86)	76,296 (3 studies)	**Low**[a,b,c]	Cases of typhoid fever are probably reduced with vaccination
	4 per 10,000	**2 per 10,000** (1 to 3)				
	High-risk population					
	59 per 10,000	**32 per 10,000** (21 to 51)				
Incidence of typhoid fever, year 2 post-vaccination	**Medium-risk population**		**RR 0.41** (0.29 to 0.57)	76,296 (3 studies)	**Low**[a,b,c]	Cases of typhoid fever are probably reduced with vaccination
	4 per 10,000	**2 per 10,000** (1 to 2)				
	High-risk population					
	59 per 10,000	**24 per 10,000** (17 to 34)				
Incidence of typhoid fever, year 3 post-vaccination	**Medium-risk population**		**RR 0.44** (0.25 to 0.76)	76,296 (3 studies)	**Low**[a,b,c]	Cases of typhoid fever are probably reduced with vaccination
	4 per 10,000	**2 per 10,000** (1 to 3)				
	High-risk population					
	59 per 10,000	**26 per 10,000** (15 to 45)				

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Ty21a (3 doses)				
Cumulative cases of typhoid fever at 2.5 to 3 years	**Medium-risk population**		**RR 0.50** (0.39 to 0.65)	235,239 (4 studies)	**Low**[a,b,c]	Cases of typhoid fever are probably reduced with vaccination
	4 per 10,000	**2 per 10,000** (2 to 3)				
	High- risk population					
	59 per 10,000	**30 per 10,000** (23 to 38)				

CI: confidence interval; **RR:** risk ratio

*The incidence of typhoid in a medium-risk setting was taken from the control group in a study from China (12) while the incidence in a high-risk setting was taken from a study in India (11). This is consistent with the incidence levels described by a global epidemiological study (Crump 2004).

Explanations

a. No serious risk of bias detected.

b. No serious inconsistency I^2 = 33%.

c. Downgraded for directness and imprecision: cluster-adjusted trials added, estimated ICC = 0.0015 (from Sur 2009 IND).

d. No serious inconsistency, no heterogeneity I^2 = 0%.

f. There is moderate heterogeneity (I^2 = 50%), which is not explained by stratifying into type of preparation. However, the CIs fall within a clinically important threshold, meaning the heterogeneity is unlikely be clinically significant, so we have not downgraded for this.

Appendix 2.2. Vi polysaccharide vaccine (1 dose) versus control for preventing typhoid fever

Patient or population: adults and children of 2 years of age and older
Settings: any
Intervention: Vi polysaccharide vaccine (1 dose)
Comparison: control; efficacy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Vi polysaccharide vaccine (1 dose)				
Incidence of typhoid fever, year 1 post-vaccination	**Moderate**[a]		**RR 0.31** (0.26 to 0.37)	99,797 (3 studies)	**Moderate**[b,c,d]	Probably reduces incidence of typhoid fever
	4 per 10,000	**1.2 per 10,000** (1.0 to 1.5)				
	High[a]					
	59 per 10,000	**18.29 per 10,000** (15.34 to 21.83)				
Incidence of typhoid fever, year 2 post-vaccination	**Moderate**[a]		**RR 0.41** (0.29 to 0.57	194,969 (4 studies)	**Low**[b,d,e,f]	May reduce incidence of typhoid fever
	4 per 10,000	**1.6 per 10,000** (1.2 to 2.2)				
	High[a]					
	59 per 10,000	**24.19 per 10,000** (18.29 to 32.45)				
Incidence of typhoid fever, year 3 post-vaccination	**Moderate**[a]		**RR 0.5** (0.32 to 0.78)	11,384 (1 study)	**Low**[g,h]	May reduce incidence of typhoid fever
	4 per 10,000	**2 per 10,000** (1.28 to 3.12)				
	High[a]					
	59 per 10,000	**29.5 per 10,000** (18.88 to 46.02)				
Cumulative cases of	**Moderate**[a]		**RR 0.45**	11,384	**Low**[g,h]	May reduce incidence of

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Vi polysaccharide vaccine (1 dose)				
typhoid fever at 2.5 to 3 years	**4 per 10,000**	**1.8 per 10,000** (1.2 to 2.8)	(0.30 to 0.70)	(1 study)	Due to imprecision and indirectness	typhoid fever
	High[a]					
	59 per 10,000	**26.55 per 10,000** (17.7 to 41.3)				
Serious adverse events	No serious adverse events reported					
Fever	**5 per 1000**	**5 per 1000** (4.2 to 5.7)	**RR 0.98** (0.84 to 1.13)	132,261 (3 studies)	**Low**[b,c,j,k]	May have little or no association with erythema
Erythema	**5 per 1000**	**6 per 1000** (2 to 22)	**RR 1.15** (0.33 to 4.03)	132,261 (3 studies)	**Very Low**[b,i,k]	May have little or no association with erythema

CI: confidence interval; **RR:** risk ratio

*The basis for the **assumed risk** (for example, the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Explanations

a. The incidence of typhoid in a medium-risk setting is taken from the control group in a study from China (Yang 2001 CHN).The incidence of typhoid in a high-risk setting is taken from a study in India (Sur 2009 IND). This is consistent with the incidence levels described by a global epidemiological study (Crump 2004).

b. No serious risk of bias detected.

c. No serious inconsistency: The result was consistent across all 3 trials (I^2 = 0%).

d. No serious imprecision: the result is statistically significant with a narrow 95% CI. The meta-analysis is adequately powered to detect this effect.

e. Downgraded by 1 level for inconsistency: the magnitude of the protective effect varied between trials from 34% to 69% (I^2 = 72%). The reasons for this are not clear; one potential factor may be the different age groups included in the trials, with Khan 2012 PAK suggesting lower protective effect in children < 5 years of age.

f. No serious indirectness: the vaccine has been evaluated in trials from endemic settings (India, Pakistan, China and South Africa).

g. Downgraded by 1 level for imprecision: wide CIs.

h. Downgraded by 1 level for indirectness - only assessed in one trial in South Africa in children aged 5 to 15 years.

i. No serious indirectness: the vaccine has been evaluated in trials from endemic settings (China) and in one trial conducted in a non-endemic setting (USA).

j. Downgraded by 1 level for serious imprecision: The result is not statistically significant.

k. Downgraded by 1 level for inconsistency (I^2 = 63%)

Appendix 2.3. Vi-rEPA vaccine (2 doses) versus control for preventing typhoid fever

Patient or population: children 2 years of age and older
Settings: any
Intervention: Vi-rEPA vaccine (2 doses)
Comparison: control; efficacy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Vi-rEPA vaccine (2 doses)				
Incidence of typhoid fever, year 1 post-vaccination	**Moderate**[a]		**RR 0.06** (0.01 to 0.25)	12,008 (1 study)	**Low**[b,c]	May have little to no reduction incidence of typhoid fever in the adult population
	4 per 10,000	**0.24 per 10,000** (0.04 to 1)				
	High[a]					
	59 per 10,000	**3.5 per 10,000** (0.6 to 14.8)				
Incidence of typhoid fever, year 2 post-vaccination	**Moderate**[a]		**RR 0.13** (0.04 to 0.44)	12,008 (1 study)	**Low**[c]	May have little to no reduction incidence of typhoid fever in the adult population
	4 per 10,000	**0.52 per 10,000** (0.16 to 1.8)				
	High[a]					
	59 per 10,000	**7.7 per 10,000** (2.4 to 26.0)				
Incidence of typhoid fever, year 3 post-vaccination	**Moderate**[a]		**RR 0.09** (0.04 to 0.22)	12,008 (1 study)	**Low**[c]	May have little to no reduction incidence of typhoid fever in the adult population
	4 per 10,000	**0.36 per 10,000** (0.16 to 0.88)				
	High[a]					
	59 per 10,000	**5.31 per 10,000** (2.36 to 12.98)				
Cumulative cases of	**Moderate**[a]		**RR 0.11**	12,008	**Low**[c]	May have little to no

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Vi-rEPA vaccine (2 doses)				
typhoid fever at 2.5 to 3 years	**4 per 10,000**	**0.44 per 10,000** (0.2 to 0.92)	(0.05 to 0.23)	(1 study)		reduction incidence of typhoid fever in the adult population
	High[a]					
	59 per 10,000	**6.49 per 10,000** (2.95 to 13.57)				
Serious adverse events	**See comment**	**See comment**	**Not estimable**	12,008 (1 study)	See comment	No serious adverse events were reported
Fever after Vi-rEPA (dose 1)	**5 per 1000**	**13 per 1000 (8 to 18)**	**RR 2.54** (1.69 to 3.62)	12,008 (1 study)	**Low[d]**	Probably associated with fever following vaccination
Fever after Vi-rEPA (dose 2)	**4 per 1000**	**18 per 1000 (11 to 27)**	**RR 4.39** (2.85 to 6.77)	11,091 (1 study)	**Low[d]**	Probably associated with fever following vaccination
Erythema after Vi-rEPA (dose 2)	**0.2 per 1000**	**0.4 per 1000 (0.04 to 4.4)**	**RR 2.01** (0.19 to 22.21)	11,091 (1 study)	**Very Low[d,e]**	May have little or no association with erythema
Swelling at injection site after Vi-rEPA (dose 2)	**0.2 per 1000**	**4 per 1000 (0.5 to 30)**	**RR 20.15** (2.71 to 150.08)	11,091 (1 study)	**Low[d]**	Probably associated with swelling at injection site

CI: confidence interval; **RR:** risk ratio

*The basis for the **assumed risk** (for example, the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Explanations

a. The incidence of typhoid in a medium-risk setting is taken from the control group in a study from China (Yang 2001 CHN). The incidence of typhoid in a high-risk setting is taken from a study in India (Sur 2009 IND). This is consistent with the incidence levels described by a global epidemiological study (Crump 2004).

b. No serious risk of bias detected.

c. Downgraded by 1 level for indirectness: the vaccine has been evaluated by only one trial in children 2 to 5 years of age in a high-incidence setting (Vietnam).

d. Downgraded by 1 level for imprecision: wide 95% CIs.

e. Downgraded by 1 level for serious imprecision: the result is not statistically significant.

Varicella Vaccine

Appendix 1. Evidence-to-Decision Summary

Burden	No (1)	Probably No	Probably Yes	Yes (5)	Varies (1)	Don't know (1)
Benefits	Trivial (1)	Small (1)	Moderate (3)	Large (1)	Varies (1)	Don't know (1)
Harms	Large	Moderate	Small (6)	Trivial (1)	Varies (1)	Don't know
Certainty of evidence	Very Low	Low	Moderate	High	No included studies	
Balance of effects	Favors no vaccine	Probably favors no vaccine	Equivalent (1)	Probably favors vaccine (5)	Favors vaccine (1)	Varies (1)	Don't know

Resources required	Large costs (5)	Moderate costs (2)	Negligible costs and savings	Moderate savings	Large savings	Varies (1)	Don't know
Certainty of evidence (resources)	Very Low	Low	Moderate	High	No included studies		
Cost effectiveness	Favors no vaccine	Probably favors no vaccine	Does not favor either (1)	Probably favors vaccine (2)	Favors vaccine (1)	Varies (2)	No included studies (2)
Equity	Reduced	Probably reduced	Probably no impact	Probably increased (2)	Increased	Varies (2)	Don't know (4)
Acceptability	No (1)	Probably no (2)	Probably yes (2)	Yes (1)	Varies (1)	Don't know (!)	
Feasibility	No (3)	Probably no (1)	Probably yes (3)	Yes	Varies (1)	Don't know	
Values	Important variability (2)	Possibly important variability (4)	Probably no important variability (2)	No important variability			

Recommendation 1: **Asymptomatic apparently healthy adults**	STRONG against	WEAK against (4)	NO RECOMMENDATION	WEAK in favor (3)	STRONG in favor (1)

Appendix 2. GRADE Summary of Findings Table

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Seroconversion rate (follow-up: range 1.5 months to 6 years; assessed with: VZV antibody responses by FAMA titers ≥1;2 or gpELISA ≥ 1.25 units /mL)									
5[a]	observational studies	not serious	serious[b]	not serious	not serious	none	Pooled seroconversion rate = 96% (95%CI 92 to 99%)	Very low	CRITICAL
Incidence of breakthrough infections (follow-up: range 2 months to 11.8 years)									
3[c]	observational studies	serious[d]	not serious	not serious	not serious	none	Pooled incidence rate = 7% (95%CI 5 to 10%)	Very low	CRITICAL
Varicella attack rates (follow-up: range 2 months to 11.8 years)									
2[e]	observational studies	serious[f]	not serious	not serious	not serious	none	Pooled attack rate = 14% (95%CI 9 to 21%)	Very low	CRITICAL
Local adverse reactions (follow-up: range 5 days to 1.5 months; assessed with: vaccine report card/ subjective report)									
4[g]	observational studies	not serious	serious[h]	not serious	not serious	none	Pooled local adverse reactions rate = 25% (13 to 39%)	Very low	CRITICAL
Systemic adverse events (follow-up: range 1 months to 1.5 months; assessed with: vaccine report card / subjective report)									
2[i]	observational studies	not serious	not serious	not serious	not serious	none	Pooled systemic adverse event rate = 11% (95%CI 8 to 16%)	Low	CRITICAL
Varicella-like rash (follow-up: range 1 months to 1.5 months; assessed with: vaccine report card / subjective report)									
4[j]	observational studies	not serious	not serious	not serious	not serious	none	Pooled varicella-like rash rate = 4% (95%CI 3 to 5%) All were mild to moderate in severity according to study authors	Low	CRITICAL
Systemic adverse event: fever (follow-up: range 1 months to 1.5 months; assessed with: vaccine report card/ subjective report)									
3[k]	observational studies	not serious	not serious	serious[l]	not serious	none	Pooled fever rate = 7% (95%CI 3 to 13%)	Very low	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Serious adverse events									
2	Observational studies	not serious	not serious	not serious	not serious	none	No SAEs reported in all studies	Low	CRITICAL

Explanations:
(a) Zerboni 1998, Paradis 2021, Kuter 1995, Gershon 1998, Nader 1995
(b) I 2 = 80.84%
(c) Ampofo 2002, Zerboni 1998, Gershon 1988
(d) Gershon 1988 and Ampofo 2002 included mostly healthcare workers in their participants
(e) Kuter 1995, Ampofo 2002
(f) Ampofo 2002 included mostly healthcare workers in their participants; higher exposure rates to varicella cases
(g) Paradis 2021, Levin 1992, Gershon 1988, Kuter 1995
(h) I 2 = 97.47%
(i) Paradis 2021, Gershon 1988
(j) Paradis 2021, Levin 1992, Gershon 1988, Kuter 1995
(k) Paradis 2021, Gershon 1988, Kuter 1995
(l) I 2 = 91.14%

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7. Zerboni L, Nader S, Aoki K, Arvin A. Analysis of the Persistence of Humoral and Cellular Immunity in Children and Adults Immunized with Varicella vaccine. The Journal of Infectious Diseases 1998;177:1701-4

Author(s): HJLimos, HHGBayona
Question: Varicella vaccines compared to no vaccines for healthcare workers
Setting: Primary care / community
Bibliography: (1) Burgess M, Cossart Y, Wilkins D, Botham S, Fearns G, Chitour K. Varicella vaccination of health-care workers. Vaccine 17 (1999) 765-769; (2) Ndumbe PM, MacQueen S, Holzel H, Davies EG, Cradock-Watson JE, Dunn H, et al. Immunization of nurses with a live varicella vaccine. The Lancet (1985) 1144-1146; (3) Saiman L, LaRussa P, Steinberg S, Zhuo J, Baron K, Whittier S. Persistence of Immunity to Varicella-zoster virus after Vaccination of Healthcare Workers. Infection Control and Hospital Epidemiology (2001) 279-283

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Seroconversion rate (follow-up: range 1 months to 4 years; assessed with: VZV antibody responses by FAMA titers ≥1;2 or gpELISA ≥ 1.25 units /mL)									
3[a]	observational studies	not serious[b]	serious[c]	not serious	not serious	none	Pooled seroconversion rates Short term (1-2 months): 95% (95%CI 91 to 98%) Medium term (5-6 months): 94% (95%CI 89 to 97%) Long term (> 6 months): 81% (95%CI 58 to 97%)	Very low	CRITICAL
Incidence of breakthrough infections (follow-up: range 2 months to 3 months)									
2[d]	observational studies	not serious	not serious	not serious	not serious	none	Pooled incidence rate = 9% (95%CI 5 to 14%)	Low	CRITICAL
Varicella attack rates (follow-up: range 2 months to 11.8 years)									
1[e]	observational studies	not serious	not serious	not serious	not serious	none	8% (95%CI 3 to 17%)	Low	CRITICAL
Local adverse events (follow-up: 1.5 months; assessed with: injection site rash)									
1[f]	observational studies	not serious	serious[g]	not serious	not serious	none	47% (95%CI 37 to 57%)	Very low	CRITICAL
Varicella-like rash (follow-up: 1.5 months; assessed with: vaccine report card / subjective report)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
2[h]	observational studies	not serious	not serious	not serious	not serious	none	Pooled varicella-like rash rate = 7% (95%CI 3 to 12%)	Low	CRITICAL
Systemic adverse event: fever (follow-up: 1.5 months; assessed with: vaccine report card/ subjective report)									
2[h]	observational studies	not serious	not serious	not serious	not serious	none	Pooled fever rate = 1% (0 to 4%)	Low	CRITICAL
Other systemic adverse events (follow-up: 1.5 months; assessed with: vaccine report card / subjective report)									
1[f]	observational studies	not serious	not serious	not serious	not serious	none	2% (95%CI 0 to 7%)	Low	CRITICAL

2. **CI:** confidence interval
3. Explanations
4. a. Burgess 1998, Saiman 2001, Ndumbe 1985
5. b. Low risk of bias for Burgess 1998 and Ndumbe 1985. Saiman 2001 et al had unclear risk of bias for one aspect (vaccinees were enrolled in several different protocols with a 3rd dose not being standardized)
6. c. Heterogeneity was significant when all studies for long term effetct were pooled (I2 = 92.48%)
7. d. Saiman 2001 and Ndumbe 1985
8. e. Saiman 2001
9. f. Burgess 1998
10. g. I2 = 97.47%
11. h. Burgess 1998, Ndumbe 1985

Appendix 3. Characteristics of Included Studies

Appendix 3.1. Asymptomatic, apparently healthy adults

Author/ Year	Study design	Country	Number of patients	Population	Intervention Group(s)	Control	Outcomes	
							Efficacy	Safety
Ampofo 2002	Observational	USA	461	Asymptomatic apparently health adults aged 22-41 years old without history of chickenpox and negative serologic test	Live attenuated varicella (Oka) vaccine by Merck Sharp and Dohme or SmithKlineBeecham	None	Breakthrough varicella infection Varicella attack rate	None
Zerboni 1997	Observational	USA	40	Healthy children and adult 13-45 years old who seroconverted and did not develop breakthrough varicella	Live attenuated varicella (Oka) by Merck	None	Breakthrough varicella infection Seroconversion rate	None
Gershon 1988	Observational	USA	187	Healthy adults aged 17-57 years old with no history of chickenpox and no serologic evidence of prior varicella	Live attenuated varicella (Oka) vaccine by Merck Sharp and Dohme	None	Breakthrough varicella infection Seroconversion rate	Local reaction or injection site-related reactions Rash Fever Systemic adverse reactions
Kuter 1995	RCT	USA	757	Healthy adolescents and adults 13-54 years old serologically susceptible to varicella	Live attenuated varicella (Oka) by Merck Sharp and Dohme	None	Varicella attack rate Seroconversion rate	Local reactions or injection site-related reactions Varicella-like rashes Fever Systemic adverse reactions
Paradis 2021	Observational	USA	50	Healthy adults with negative history of varicella and herpes zoster infection	Live attenuated varicella (Oka) by Merck Sharp and Dohme	None	Seroconversion rate	Local reactions or injection site-related reactions Varicella-like rashes Fever Systemic adverse reactions

Author/ Year	Study design	Country	Number of patients	Population	Intervention Group(s)	Control	Outcomes	
							Efficacy	Safety
Levin 1992	Observational	USA	202	Healthy adults aged 55->87 years old with history of varicella confirmed by serologic testing but never had herpes zoster	Live attenuated varicella (Oka) vaccine by Merck Sharp and Dohme	None	None	Local reactions or injection site-related reactions Varicella-like rashes Fever Systemic adverse reactions
Nader 1995	Observational	USA	40	Healthy adolescent and adults with no previous history of varicella	Live attenuated varicella (Oka) vaccine by Merck Sharp and Dohme	None	Seroconversion rate	None

Appendix 3.2. Healthcare workers

Author/ Year	Study design	Country	Number of patients	Population	Intervention Group(s)	Control	Outcomes	
							Efficacy	Safety
Burgess 1998	Observational	Australia	110	Healthy non-immune healthcare workers with past history of varicella	Live attenuated varicella (Oka) vaccine by Smithkline Beecham	None	Seroconversion rate	Local reactions or injection site-related reactions Fever Rash Systemic reactions
Saiman 2001	Observational	USA	120	Health adult healthcare workers aged 19-45 years old with no history of chickenpox and negative varicella serology	Live attenuated varicella (Oka) vaccine by Merck Sharp and Dohme or by Smithkline Beecham	None	Breakthrough varicella infection Varicella attack rate Seroconversion rate	None
Ndumbe 1985	Observational	London	34	Student nurses with no previous history of chickenpox and seronegative to VZV	Live attenuated varicella (Oka) vaccine by Smithkline Beecham	None	Breakthrough varicella infection Seroconversion rate	Local reactions or injection site-related reactions Fever Rash Systemic reactions

Appendix 4. Forest Plots

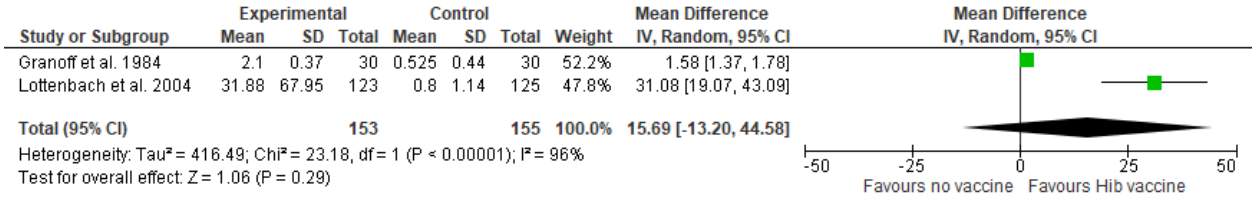


Figure 1. Total change in serum anti-PRP Antibody concentrations, 1-month post-vaccination

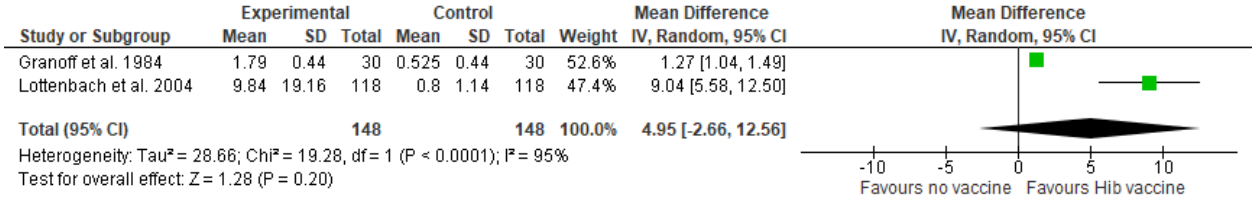


Figure 2. Total change in serum anti-PRP Antibody concentrations, 12-months post-vaccination

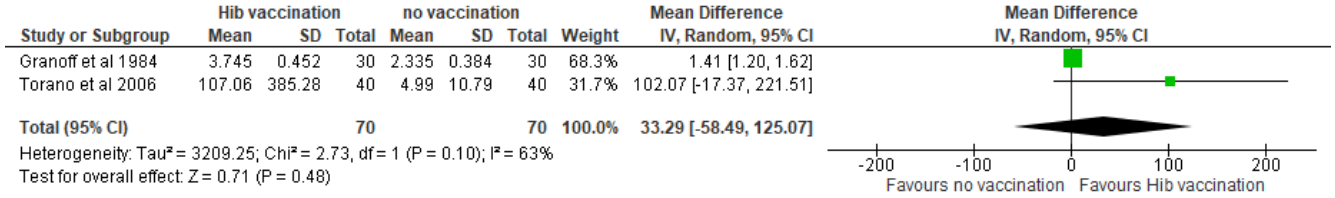
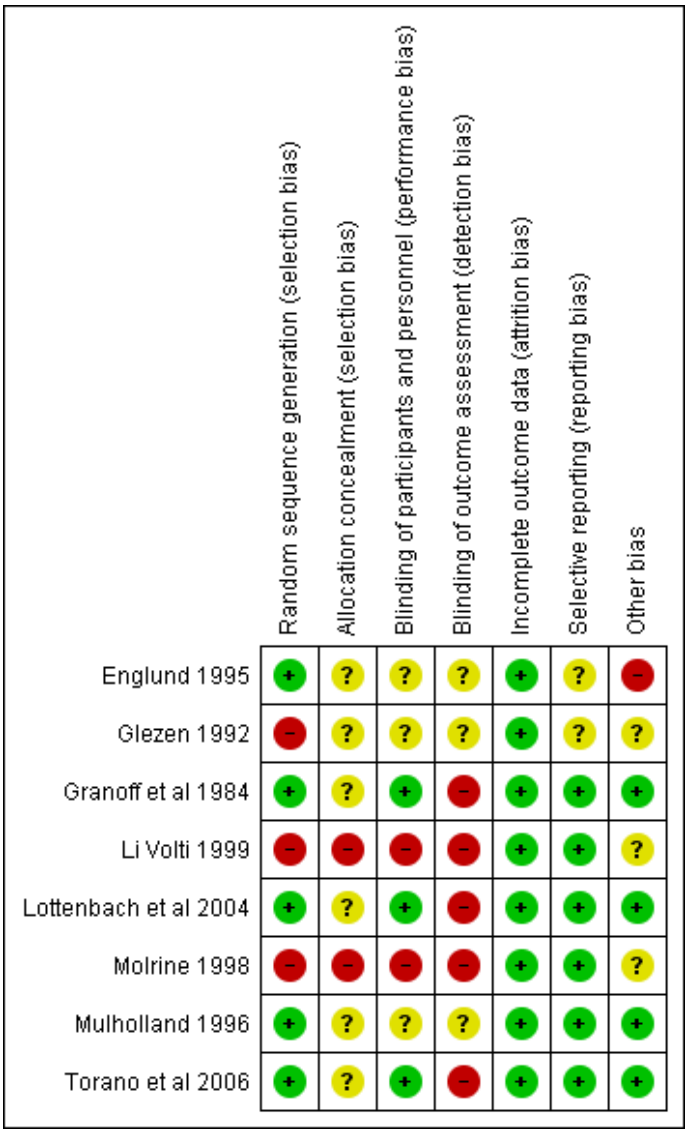


Figure 3. Total change in serum IgG Antibody concentrations, 1-month post-vaccination

Appendix 5. Risk of Bias Assessment of Included Studies



Search Strategy

CHOLERA

Search date: October 2022
Publication date: 2017 – 2022
Filters: Randomized Controlled Trials
Hand searching, Google Scholar, Cochrane and PUBMED

SEARCH	QUERY	RESULTS
#5	("adult"[MeSH Terms] AND (("cholera vaccines"[MeSH Terms] OR ("cholera"[All Fields] AND "vaccines"[All Fields]) OR "cholera vaccines"[All Fields] OR ("cholera"[All Fields] AND "vaccine"[All Fields]) OR "cholera vaccine"[All Fields] OR ((((("live"[All Fields] AND "OT"[All Fields] AND ("attenuate"[All Fields] OR "attenuated"[All Fields] OR "attenuates"[All Fields] OR "attenuating"[All Fields] OR "attenuation"[All Fields] OR "attenuations"[All Fields] OR "attenuator"[All Fields] OR "attenuators"[All Fields])) OR ("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields])) AND ("cholera"[MeSH Terms] OR "cholera"[All Fields] OR "choleras"[All Fields] OR "cholera s"[All Fields] OR "cholerae"[All Fields] OR "cholerae s"[All Fields] OR "choleraic"[All Fields])) OR ("cholera vaccine cvd 103 hgr"[Supplementary Concept] OR "cholera vaccine cvd 103 hgr"[All Fields] OR "cvd 103 hgr"[All Fields]))) AND "randomized controlled trial"[Publication Type])) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])	172
#4	("cholera vaccines"[MeSH Terms] OR ("cholera"[All Fields] AND "vaccines"[All Fields]) OR "cholera vaccines"[All Fields] OR ("cholera"[All Fields] AND "vaccine"[All Fields]) OR "cholera vaccine"[All Fields] OR ((((("live"[All Fields] AND "OT"[All Fields] AND ("attenuate"[All Fields] OR "attenuated"[All Fields] OR "attenuates"[All Fields] OR "attenuating"[All Fields] OR "attenuation"[All Fields] OR "attenuations"[All Fields] OR "attenuator"[All Fields] OR "attenuators"[All Fields])) OR ("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields])) AND ("cholera"[MeSH Terms] OR "cholera"[All Fields] OR "choleras"[All Fields] OR "cholera s"[All Fields] OR "cholerae"[All Fields] OR "cholerae s"[All Fields] OR "choleraic"[All Fields])) OR ("cholera vaccine cvd 103 hgr"[Supplementary Concept] OR "cholera vaccine cvd 103 hgr"[All Fields] OR "cvd 103 hgr"[All Fields]))) AND (randomizedcontrolledtrial[Filter])	267
# 3	#2 OR #6	5,960
# 2	((“cholera vaccine”[MeSH Terms]) OR ((live OT attenuated OR oral) AND cholera)) OR (CVD 103-HgR)	2,970
#1	"cholera vaccines"[MeSH Terms] OR ("cholera"[All Fields] AND "vaccines"[All Fields]) OR "cholera vaccines"[All Fields] OR ("cholera"[All Fields] AND "vaccine"[All Fields]) OR "cholera vaccine"[All Fields]	4,592

HAEMOPHILUS INFLUENZAE B (HIB)

Search strategy and yield: 29 September 2022, EMBASE

SEARCH STRATEGY/SEARCH TERMS	RESULTS	
	YIELD	ELIGIBLE
haemophilus influenzae type b':ab,ti AND vaccin*:ab,ti AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR 'controlled clinical trial'/de) AND [article]/lim AND [humans]/lim AND [abstracts]/lim AND [clinical study]/lim AND ([embase]/lim OR [preprint]/lim)	357	6

Search strategy and yield: 28 October 2022, MEDLINE (PubMed)

SEARCH STRATEGY/SEARCH TERMS	RESULTS	
	YIELD	ELIGIBLE
'haemophilus influenzae type b' AND vaccin* AND adult Filters applied: Meta-Analysis, Randomized Controlled Trial, Systematic Review	59	6
'haemophilus influenzae type b' AND vaccin* AND (healthcare workers OR physicians OR doctors OR nurses OR hospital staff)	10	0
'haemophilus influenzae type b' AND vaccin* AND aspleni* AND adult Filters applied: Meta-Analysis, Randomized Controlled Trial, Systematic Review.	0	0
'haemophilus influenzae type b' AND vaccin* AND pregnan* Filters applied: Meta-Analysis, Randomized Controlled Trial, Systematic Review.	20	4

Search strategy and yield: 28 October 2022, CENTRAL

SEARCH STRATEGY/SEARCH TERMS	RESULTS	
	YIELD	ELIGIBLE
'haemophilus influenzae type b' AND vaccin* AND adult	42	1
'haemophilus influenzae type b' AND vaccin* AND aspleni* AND adult	3	1
'haemophilus influenzae type b' AND vaccin* AND pregnan*	18	1
'haemophilus influenzae type b' AND vaccin* AND (healthcare workers OR physicians OR doctors OR nurses OR hospital staff)	39	0

Search strategy and yield: 28 October 2022, HERDINPlus

SEARCH STRATEGY/SEARCH TERMS	RESULTS	
	YIELD	ELIGIBLE
haemophilus influenzae type b	12	0

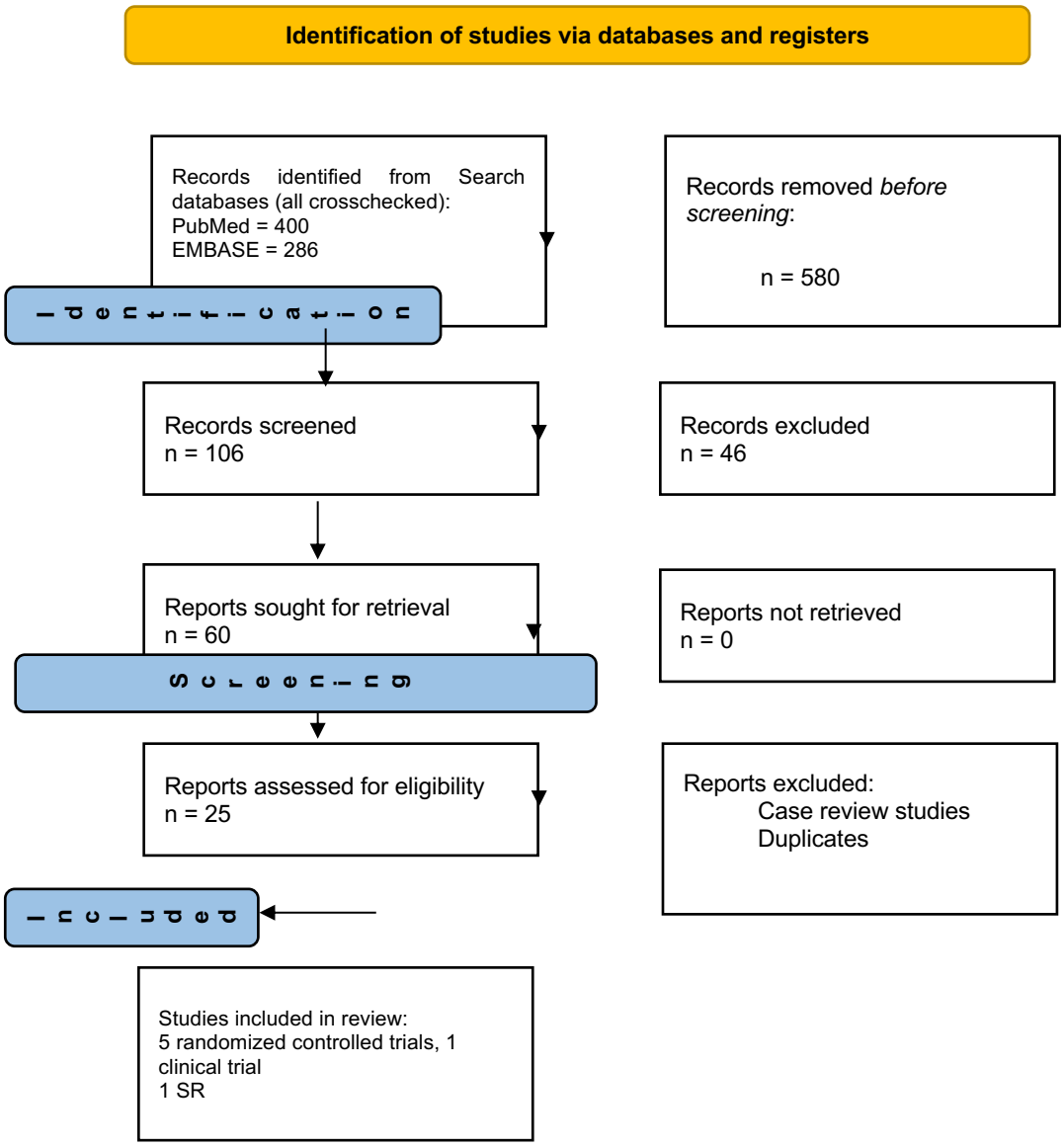
HEPATITIS A

Search strategy and yield: 26 October 2022, MEDLINE (PubMed)

QUERY	RESULTS
Search: **Hepatitis A vaccine** Filters: **Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Systematic Review** ("hepatitis a vaccines"[MeSH Terms] OR "hepatitis a vaccines"[All Fields] OR "hepatitis a vaccine"[All Fields]) AND (clinicaltrial[Filter] OR meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]) **Translations** **Hepatitis A vaccine:** "hepatitis a vaccines"[MeSH Terms] OR "hepatitis a vaccines"[All Fields] OR "hepatitis a vaccine"[All Fields]	400
Search: **Hepatitis A vaccine** Filters: **Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Systematic Review, from 2017 – 2022** ("hepatitis a vaccines"[MeSH Terms] OR "hepatitis a vaccines"[All Fields] OR "hepatitis a vaccine"[All Fields]) AND ((clinicaltrial[Filter] OR meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]) AND (2017:2022[pdat])) **Translations** **Hepatitis A vaccine:** "hepatitis a vaccines"[MeSH Terms] OR "hepatitis a vaccines"[All Fields] OR "hepatitis a vaccine"[All Fields]	37

Search strategy and yield: 29 September 2022, EMBASE

QUERY	RESULTS
hepatitis a':ab,ti AND **vaccin***:ab,ti AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR **'controlled clinical trial'**/de) AND [article]/lim AND [humans]/lim AND [abstracts]/lim AND [clinical study]/lim AND ([embase]/lim OR [preprint]/lim)	286


Identification of studies via databases and registers
Identification
Records identified from Search databases (all crosschecked):
PubMed = 400
EMBASE = 286
Records removed *before screening*:
n = 580
Records screened
n = 106
Records excluded
n = 46
Reports sought for retrieval
n = 60
Reports not retrieved
n = 0
Screening
Reports assessed for eligibility
n = 25
Reports excluded:
Case review studies
Duplicates
Included
Studies included in review:
5 randomized controlled trials, 1 clinical trial
1 SR

HERPES ZOSTER

HIGH-DOSE INACTIVATED INFLUENZA VACCINE

MEDLINE (August 1, 2021, 12:00 am)

Step	Query	Results
1	Randomized controlled trial[Publication Type]	540,225
2	Controlled clinical trial[Publication Type]	629.663
3	Randomized[Title/Abstract]	574,570
4	Placebo[Title/Abstract]	226,299
5	Clinical trial as topic[MeSH Terms]	361,263
6	Randomly[Title/Abstract]	363,387
7	Trial[Title]	244,422
8	#1 or #2 or #3 or #4 or #5 or #6 or #7	1,473,465
9	Animals[MeSH Terms]	24,415,701
10	Humans[MeSH Terms]	19,547,398
11	#9 and #10	19,547,398
12	#9 not #11	4,868,303
13	#8 not #12	1,362,651
14	Influenza vaccine	36,889
15	Flu vaccine	32,663
16	#14 or #15	37,323
17	#13 and #16	3,473
18	#13 and #16 Filters: from 2017-2021	747
19	High-dose	109299
20	High dose	307048
21	#19 or #20	307048
22	#18 and #21	214

Cochrane (August 1, 2021, 1:00 pm)

Step	Query	Results
1	(influenza vaccine):ti,ab,kw	5686
2	(High dose): ti,ab,kw	24211
3	(high-dose):ti,ab,kw	24211
4	#2 or #3	24211
5	#1 and #4	209

HUMAN PAPILLOMAVIRUS (HPV)

Search date: October 3, 2021 (Last search)
Publication date: 10 years
Hand searching, Google Scholar, PUBMED, CENTRAL

Search	Query	Results
1	human papillomavirus	45,706
2	((((vaccine) OR (vaccination)) OR (tetravalent)) OR (quadrivalent)) OR ("nonavalent"[All Fields])	430,156
3	(("clinical study"[All Fields]) OR ("randomized controlled trial"[Publication Type])) OR ("clinical trial"[Publication Type])	959,061
4	((human papillomavirus) AND (((((vaccine) OR (vaccination)) OR (tetravalent)) OR (quadrivalent)) OR ("nonavalent"[All Fields]))) AND ((("clinical study"[All Fields]) OR ("randomized controlled trial"[Publication Type])) OR ("clinical trial"[Publication Type]))	560
5	((human papillomavirus) AND (((((vaccine) OR (vaccination)) OR (tetravalent)) OR (quadrivalent)) OR ("nonavalent"[All Fields]))) AND ((("clinical study"[All Fields]) OR ("randomized controlled trial"[Publication Type])) OR ("clinical trial"[Publication Type]))	83

INFLUENZA

MEDLINE (July 31, 2021, 3:00 pm)

Step	Query	Results
1	Randomized controlled trial[Publication Type]	540,225
2	Controlled clinical trial[Publication Type]	629.663
3	Randomized[Title/Abstract]	574,570
4	Placebo[Title/Abstract]	226,299
5	Clinical trial as topic[MeSH Terms]	361,263
6	Randomly[Title/Abstract]	363,387
7	Trial[Title]	244,422
8	#1 or #2 or #3 or #4 or #5 or #6 or #7	1,473,465
9	Animals{MeSH Terms]	24,415,701
10	Humans[MeSH Terms]	19,547,398
11	#9 and #10	19,547,398
12	#9 not #11	4,868,303
13	#8 not #12	1,362,651
14	Influenza vaccine	36,889
15	Flu vaccine	32,663
16	#14 or #15	37,323
17	#13 and #16	3,473
18	#13 and #16 Filters: from 2017-2021	747
19	adults	8,208,115
20	Elderly	5,696,562
21	Pregnant	201,296
22	Healthcare worker	684,574
23	#19 or #20 or #21 or #22	9,085,481
24	#18 and #23	512

Cochrane (August 1, 2021, 1:00 pm)

Step	Query	Results
1	(influenza vaccine):ti,ab,kw	5,686
2	Flu vaccine	754
3	MeSH descriptor: [Influenza Vaccines] explode all trees	1,588
4	#1 or #2 or #3	5,887
5	Adult	659,277
6	Elderly	53,346
7	Healthcare worker	938
8	Healthcare personnel	5,165
9	Pregnant	24,182
10	#5 or #6 or #7 or #8 or #9	717,365
11	#10 and #4	2,761
12	#11 with publication date from Jan 2017 to Jul 2021	1,432
13	Mortality	101,813
14	Hospitalization	45,530
15	Hospitalization	45,556
16	Flu-like symptoms	804
17	Influenza symptoms	2,079
18	Adverse events	126,766
19	Safety	261,295
20	Missed working days	1,160
21	Opportunity cost	1,882
22	Cost-effectiveness	23,456
23	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22	42,8385
24	#23 and #12	1,019

JAPANESE ENCEPHALITIS

Search strategy and yield: 29 September 2022, EMBASE

SEARCH STRATEGY / SEARCH TERMS	RESULTS	
	Yield	Eligible
'japanese encephalitis':ab,ti AND vaccin*:ab,ti AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR 'controlled clinical trial'/de) AND [article]/lim AND [humans]/lim AND [abstracts]/lim AND [clinical study]/lim AND ([embase]/lim OR [preprint]/lim)	60	2

Search strategy and yield: 6 February 2023, MEDLINE (PubMed)

SEARCH STRATEGY / SEARCH TERMS	RESULTS	
	Yield	Eligible
(("japanese encephalitis vaccines"[MeSH Terms] OR "vaccin*"[Title/Abstract] OR ("immunisation"[Title/Abstract] OR "immunization"[Title/Abstract])) AND ("japanese encephalitis"[Title/Abstract] AND "encephalitis, japanese"[MeSH Terms])) AND (randomizedcontrolledtrial[Filter])	45	17
(("japanese encephalitis vaccines"[MeSH Terms] OR "vaccin*"[Title/Abstract] OR ("immunisation"[Title/Abstract] OR "immunization"[Title/Abstract])) AND ("japanese encephalitis"[Title/Abstract] AND "encephalitis, japanese"[MeSH Terms])) AND (systematicreview[Filter])	14	1
(("japanese encephalitis vaccines"[MeSH Terms] OR "vaccin*"[Title/Abstract] OR ("immunisation"[Title/Abstract] OR "immunization"[Title/Abstract])) AND ("japanese encephalitis"[Title/Abstract] AND "encephalitis, japanese"[MeSH Terms])) AND (clinicaltrial[Filter] OR observationalstudy[Filter] OR randomizedcontrolledtrial[Filter])	73	17

MEASLES

Database: PubMed Outcomes and filters	Search strategy/search terms	Date and time	Results	
			Yield	**Eligible**
INCIDENCE				
CT, MA, RCT, SR, 10 years	((Measles vaccine OR MMR) AND (ADULTS)) AND (incidence OR vaccine efficacy)	9/16/2021 2:55pm	98	1
Hand searched/suggested studies				
MORTALITY				
CT, MA, RCT, SR, 10 years	((Measles vaccine OR MMR) AND (Adults)) AND (death OR mortality)	9/16/21 2:49PM	62	0
Hand searched/suggested studies		9/14/21	1	1
HOSPITALIZATION				
CT, MA, RCT, SR, 10 years	((Measles vaccine OR MMR) AND (ADULTS)) AND (hospitalization OR admission)	9/16/2021 2:51pm	126	2
ADVERSE EVENTS				
CT, MA, RCT, SR, 10 years	((Measles vaccine OR MMR) AND (ADULTS)) AND (adverse effects OR adverse events)	9/16/2021 2:53pm	94	1
Hand searched/suggested studies		9/16/2021	1	1
COST EFFECTIVENESS				
CT, MA, RCT, SR, 10 years	(Measles vaccine OR MMR) AND (cost)	9/17/2021 9am	33	0

MENINGOCOCCAL

Search strategy and yield: MEDLINE (PubMed)

KEYWORDS	STRATEGY	YIELDS	HITS
meningococcal vaccine	((meningococcal vaccine[Title/Abstract]) OR (meningococcal vaccine[MeSH Terms])) OR (meningoco*[MeSH Terms])	13,335	-
asymptomatic apparently healthy adults, health workers, travelers, military recruits, pregnant, breastfeeding, adults aged >65 yo	((((((((((adult[MeSH Terms]) OR (children[MeSH Terms])) OR (healthcare worker[MeSH Terms])) OR (pregnant woman[MeSH Terms])) OR (pregnant women[MeSH Terms])) OR (adult[Title/Abstract])) OR (children[Title/Abstract])) OR (healthcare worker[Title/Abstract])) OR (healthcare pro*[Title/Abstract])) OR (healthcare provider[MeSH Terms])) OR (older adult[MeSH Terms])	10,347,952	-
	(((meningococcal vaccine[Title/Abstract]) OR (meningococcal vaccine[MeSH Terms])) OR (meningoco*[MeSH Terms])) AND ((((((((((adult[MeSH Terms]) OR (children[MeSH Terms])) OR (healthcare worker[MeSH Terms])) OR (pregnant woman[MeSH Terms])) OR (pregnant women[MeSH Terms])) OR (adult[Title/Abstract])) OR (children[Title/Abstract])) OR (healthcare worker[Title/Abstract])) OR (healthcare pro*[Title/Abstract])) OR (healthcare provider[MeSH Terms])) OR (older adult[MeSH Terms]))	7,657	-
Systematic review	systematic review[Publication Type]	37	2 (Htar, 2020; Culqui 2021)

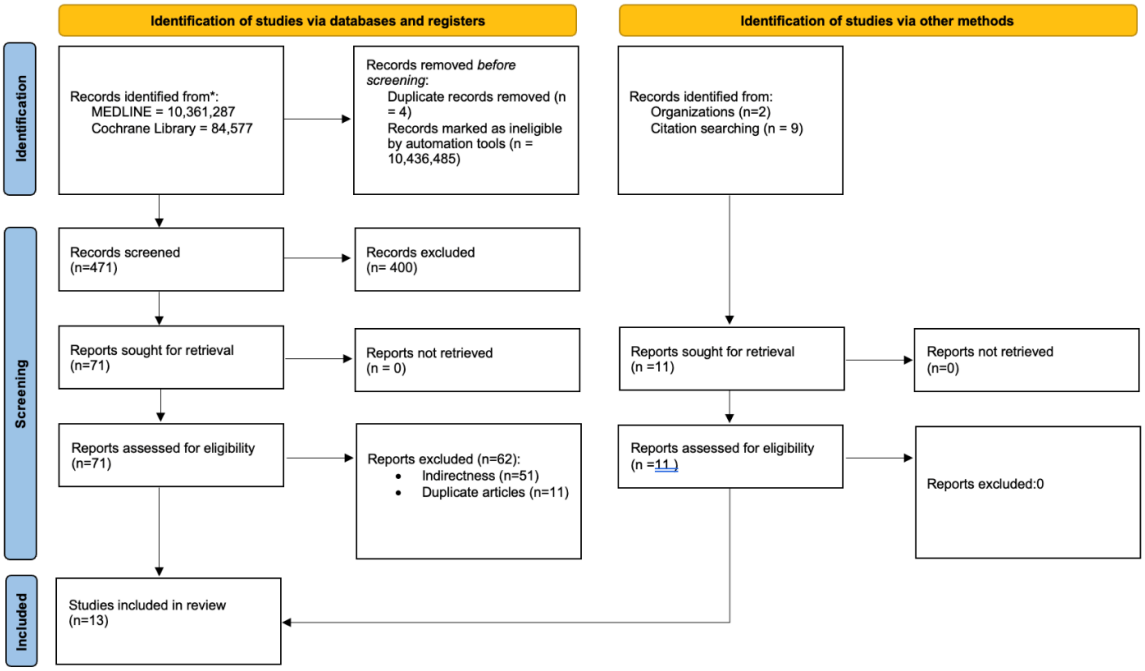
Search strategy and yield: Cochrane Library (CENTRAL & Database of Systematic Reviews)

KEYWORDS	STRATEGY	YIELDS	HITS
meningococcal vaccine	MenACWY, MenB, conjugate vaccines, routine vaccination, meningococcal vaccination (both MeSH and free text)	1,288	1 (Patel, 2005)
asymptomatic apparently healthy adults, health workers, travelers, military recruits, pregnant, breastfeeding, adults aged >65 yo	Adult*[MeSH], adult, healthy adults*	83,289	-
	Meningococcal vaccine and adult keywords	434	1

Notes:

- Excluded due to indirectness:
  - Population = 45 (infants, toddlers, adolescents)
  - Method (not phase II or III RCTs) = Phase I (Gonzales-Lopez, 2019; Chen 2018; Sheldon 2012; Richmond 2012; Perez 2007; EUCTR2004-000767-10-IT;
- Duplicate articles = 11

PRISMA Flow Diagram



MONKEYPOX

Search strategy and yield: 15 February 2023, MEDLINE (PubMed)

SEARCH STRATEGY / SEARCH TERMS	RESULTS	
	Yield	Eligible
((vaccine[Title/Abstract] OR vaccination[Title/Abstract] OR immunization[Title/Abstract] OR immunisation[Title/Abstract]) or ("Vaccination"[Mesh]) or ("Smallpox Vaccine"[Mesh])) and ((monkeypox[Title/Abstract]) or ("Monkeypox"[Mesh]))	550	19

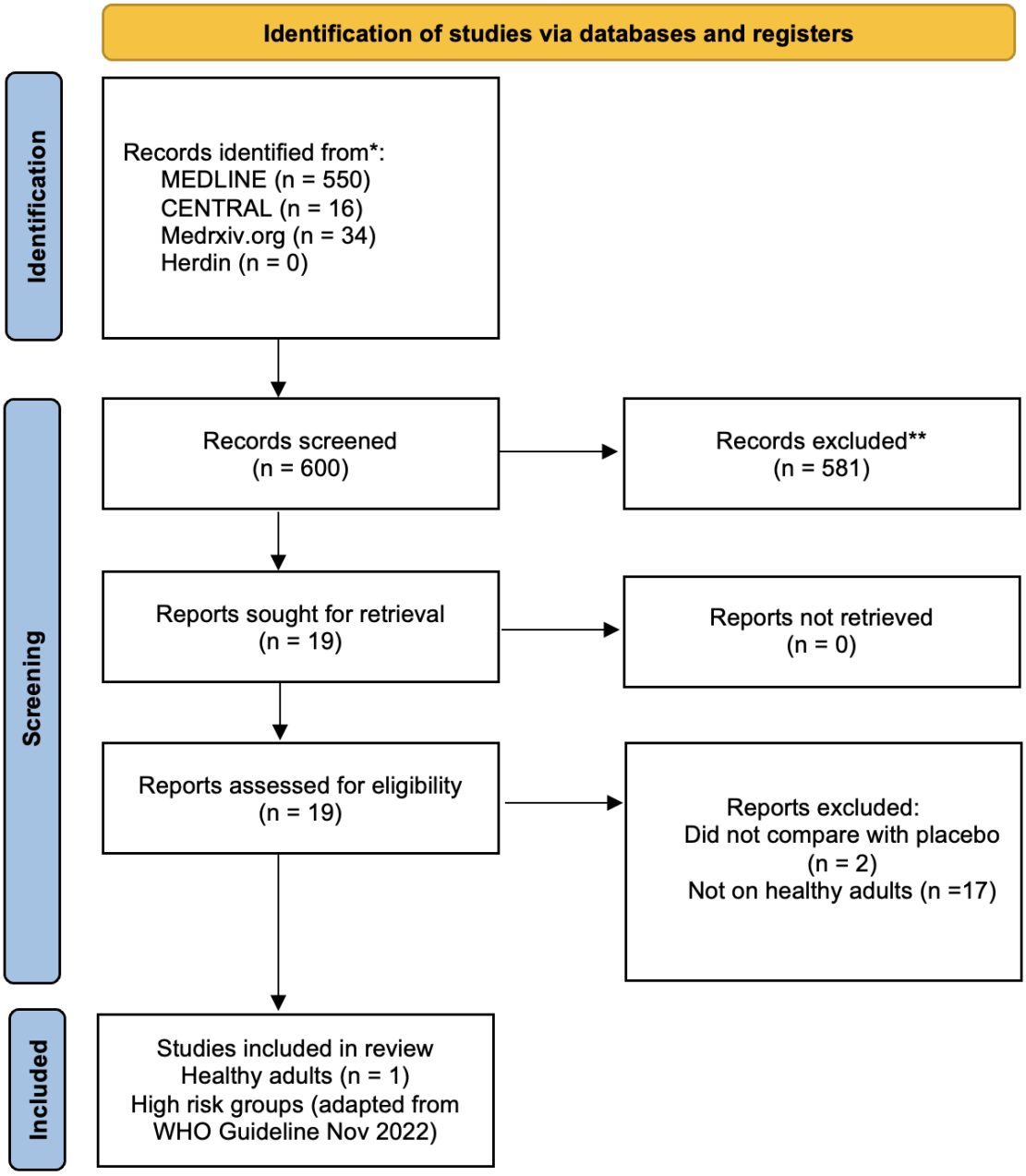
Search strategy and yield: 15 February 2023, Cochrane Library (CENTRAL)

SEARCH STRATEGY / SEARCH TERMS	RESULTS	
	Yield	Eligible
Monkeypox" "vaccine" "immunization"	9 (2 reviews, 7 RCTs)	6

Search strategy and yield: Medrxiv.org

SEARCH STRATEGY / SEARCH TERMS	RESULTS	
	Yield	Eligible
Recently posted papers posted from May 1, 2022 to March 1, 2023 with the following search terms "monkeypox" OR "vaccine" OR "immunization	34	1

For HerdinPlus no study was available for the following search terms: "monkeypox" AND "vaccine" AND "immunization"


Identification of studies via databases and registers
Identification
Records identified from*:
MEDLINE (n = 550)
CENTRAL (n = 16)
Medrxiv.org (n = 34)
Herdin (n = 0)
Screening
Records screened
(n = 600)
Records excluded**
(n = 581)
Reports sought for retrieval
(n = 19)
Reports not retrieved
(n = 0)
Reports assessed for eligibility
(n = 19)
Reports excluded:
Did not compare with placebo
(n = 2)
Not on healthy adults (n =17)
Included
Studies included in review
Healthy adults (n = 1)
High risk groups (adapted from
WHO Guideline Nov 2022)

PNEUMOCOCCAL

Search date: September 11, 2021
Publication date: 10 years
Hand searching, Google Scholar, and PUBMED

Search	Query	Results
# 7	#5 AND #6 AND #1	160
# 6	vaccine immunogenicity	22,188
# 5	#2 OR #4	538,880
# 4	adult immunization [MeSH] (“adult”[MeSH Terms] OR “adult”[All Fields] OR “adults”[All Fields] OR “adult s”[All Fields]) AND (“vaccination”[MeSH Terms] OR “immunization”[MeSH Terms])	
# 3	“pneumococcal pneumonia” “pneumococcal pneumonia”[All Fields]	6.104
# 2	healthy adults [MeSH] (“healthies”[All Fields] OR “healthy”[All Fields]) AND “adult”[MeSH Terms]	504,890
# 1	“pneumococcal vaccine” OR “polysaccharide vaccine” “pneumococcal vaccine”[All Fields] OR “polysaccharide vaccine”[All Fields]	4,809

RABIES

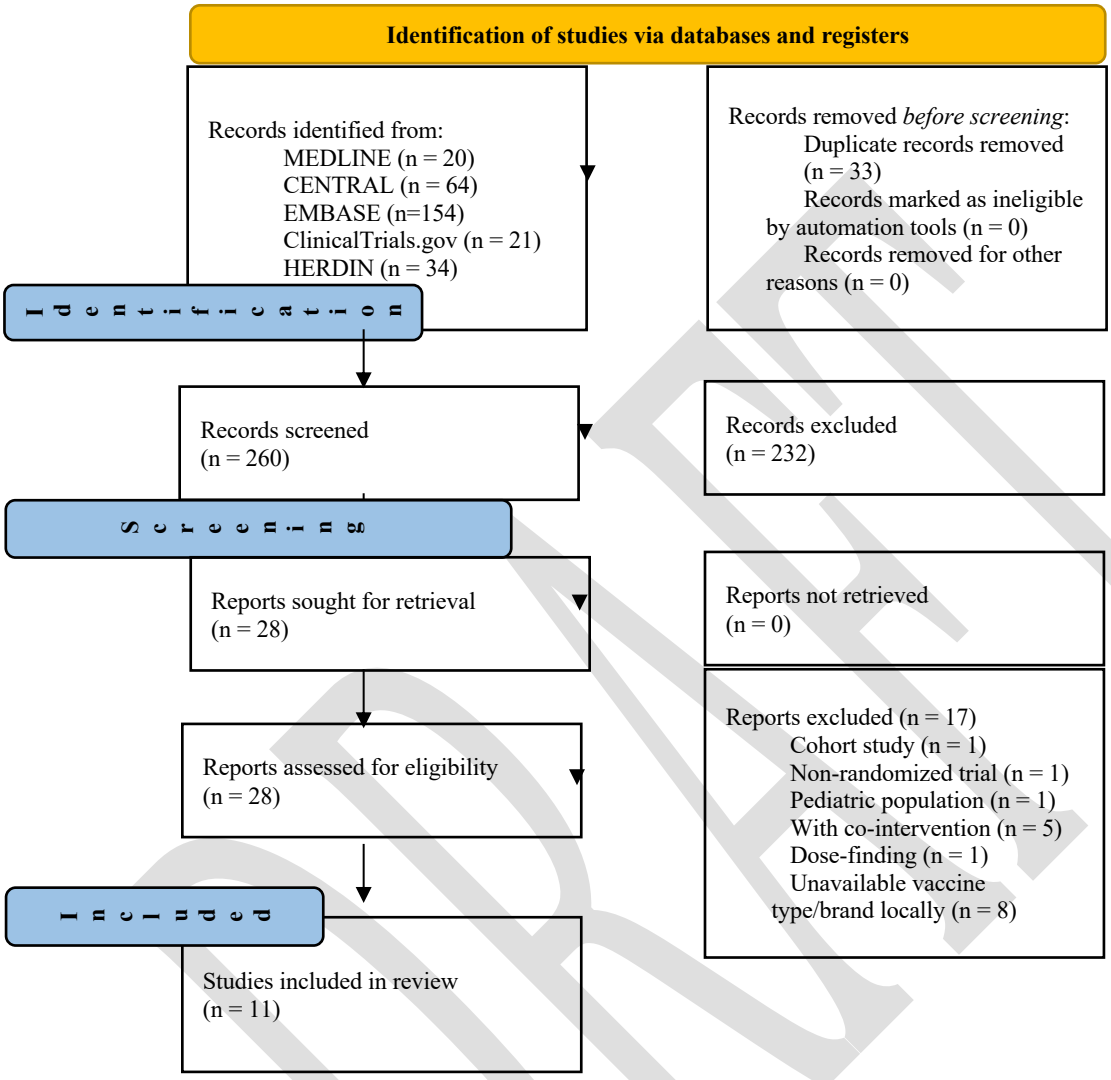
A comprehensive and systematic search of local and international databases was done (with date of last search: September 16, 2022) from database inception until September 16, 2022, through MEDLINE, Cochrane CENTRAL, HERDIN, and clinicaltrials.gov using a combination of medical subject headings (MeSH) and keywords search on rabies, pre-exposure vaccine, and prophylaxis. Only studies with the outcome of interest were included. The references of included studies were also hand searched to identify additional studies that may not have appeared in the database search. No language restrictions were applied. Additional search was done for unpublished studies through communications with authors or known researchers.

Search strategy and yield: 16 September 2022, MEDLINE (PubMed)

#	QUERY	RESULTS
1	"rabies"[MeSH Terms]	10,738
2	"lyssavirus"[MeSH Terms]	5,647
3	rabies[Title/Abstract]	15,362
4	#1 or #2 or #3	16,649
5	vaccin*[Title/Abstract]	388,547
6	prophyla*[Title/Abstract]	186,336
7	#5 or #6	560,557
8	pre-exposure[Title/Abstract]	9,144
9	#4 and #7 and #8 Filters: Randomized Controlled Trial, Humans, Adult: 19+ years	**20**

Search strategy and yield: 16 September 2022, Cochrane Library (CENTRAL)

#	QUERY	RESULTS
1	MeSH descriptor: [Rabies] explode all trees	188
2	MeSH descriptor: [Lyssavirus] explode all trees	76
3	(rabies):ti,ab,kw	471
4	#1 or #2 or #3	472
5	(vaccin*):ti,ab,kw	29,181
6	(prophyla*):ti,ab,kw	40,413
7	#5 or #6	68,411
8	(pre-exposure):ti,ab,kw	1,219
9	#4 and #7 and #8	**64**


Identification of studies via databases and registers
Records identified from:
MEDLINE (n = 20)
CENTRAL (n = 64)
EMBASE (n=154)
ClinicalTrials.gov (n = 21)
HERDIN (n = 34)
Records removed *before screening*:
Duplicate records removed (n = 33)
Records marked as ineligible by automation tools (n = 0)
Records removed for other reasons (n = 0)
Identification
Records screened
(n = 260)
Records excluded
(n = 232)
Screening
Reports sought for retrieval
(n = 28)
Reports not retrieved
(n = 0)
Reports assessed for eligibility
(n = 28)
Reports excluded (n = 17)
Cohort study (n = 1)
Non-randomized trial (n = 1)
Pediatric population (n = 1)
With co-intervention (n = 5)
Dose-finding (n = 1)
Unavailable vaccine type/brand locally (n = 8)
Included
Studies included in review
(n = 11)

DRAFT

TETANUS

TYPHOID

VARICELLA

Search strategy and yield: MEDLINE Systematic Reviews (SRs)

STEP	QUERY	RESULTS
1	Systematic review[Publication Type]	209,187
2	Meta-analysis[Publication Type]	168,685
3	"review"[Publication Type]	3,055,674
4	(Review[Title/Abstract]) OR ("Systematic review"[Title/Abstract])	2,024,224
5	(Meta-analysis[Title/Abstract]) OR ("Meta analysis"[Title/Abstract]) OR (Metaanalysis[Title/Abstract])	217,566
6	#1 OR #2 OR #3 OR #4 OR #5	3,889,355
7	"Chickenpox Vaccine"[Mesh]	3,203
8	"Varicella vaccine" OR "Varicella vaccination"	2,080
9	("Chickenpox vaccine") OR ("Chickenpox vaccination")	2,248
10	#7 OR #8 OR #9	3,867
11	"Adult"[Mesh] OR adults OR adult	8,547,921
12	Elderly OR "Aged"[Mesh]	5,938,842
13	"Healthcare worker" OR "Health worker" OR "Health Personnel"[Mesh]	597,110
14	#11 OR #12 OR #13	9,291,574
15	#6 AND #10 AND #14	439
16	Filter	112

Search strategy and yield: MEDLINE Randomized Control Trials (RCTs)

STEP	QUERY	RESULTS
1	Randomized controlled trial[Publication Type]	579,852
2	Controlled clinical trial[Publication Type]	670,017
3	(Randomized[Title/Abstract]) OR (Randomised[Title/Abstract])	750,605
4	Randomly[Title/Abstract]	394,290
5	Clinical trial as topic[MeSH Terms]	377,441
6	Trial[Title]	271,803
7	#1 or #2 or #3 or #4 or #5 or #6	1,564,821
8	Animals[MeSH Terms]	25,850,232
9	Humans[MeSH Terms]	20,796,553
10	#8 and #9	20,796,553
11	#8 not #10	5,053,679
12	#7 not #11	1,452,382
13	"Chickenpox Vaccine"[Mesh]	3,203
14	"Varicella vaccine" OR "Varicella vaccination"	2,080
15	("Chickenpox vaccine") OR ("Chickenpox vaccination")	2,248
16	#13 or #14 or #15	3,867
17	"Adult"[Mesh] OR adults OR adult	8,547,980
18	Elderly OR "Aged"[Mesh]	5,938,886
19	"Healthcare worker" OR "Health worker" OR "Health Personnel"[Mesh]	597,110
20	#17 OR #18 OR #19	9,291,669
21	("letter"[Publication Type]) OR ("editorial"[Publication Type]) OR ("comment"[Publication Type]	2,101,504
22	#20 NOT #21	8,898,792
23	#12 AND #16 AND #20	265

Search strategy and yield: Cochrane Library (CENTRAL)

STEP	QUERY	RESULTS
1	(“randomized controlled trial”):pt OR (“controlled clinical trial”):pt OR (Randomized):ti,ab,kw OR (Randomised):ti,ab,kw OR (Randomly):ti,ab,kw	1,132,586
2	MeSH descriptor: [Clinical Trials as Topic] explode all trees	48,686
3	(“trial”):ti	374,347
4	#1 OR #2 OR #3	1,202,650
5	MeSH descriptor: [Chickenpox Vaccine] explode all trees	210
6	(“Varicella vaccine”) OR (“varicella vaccination”) OR (“chickenpox vaccine”) OR (“chickenpox vaccination")	288
7	#5 OR #6	359
8	MeSH descriptor: [Adult] explode all trees	495,015
9	adults OR adult	765,481
10	elderly	57,350
11	MeSH descriptor: [Aged] explode all trees	221,243
12	"Healthcare worker" OR "Health worker"	1,570
13	MeSH descriptor: [Health Personnel] explode all trees	10,525
14	#8 OR #9 OR #10 OR #11 OR #12 OR #13	892,315
15	#4 AND #7 AND #14	107

Search strategy and yield: EMBASE

QUERY	RESULTS
varicella':ab,ti AND vaccin*:ab,ti AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR 'controlled clinical trial'/de) AND [article]/lim AND [humans]/lim AND [abstracts]/lim AND [clinical study]/lim AND ([embase]/lim OR [preprint]/lim) PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only	190

AGREE REPORTING CHECKLIST (SELF EVALUATION)

Fillable forms may be downloaded here: http://www.agreetrust.org/resource-centre/agree-reporting-checklist/

AGREE TABLES

AGREE Reporting Checklist (Self Evaluation)

Fillable forms may be downloaded here: http://www.agreetrust.org/resource-centre/agree-reporting-checklist/

Sample from LCPG Manuscript

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

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
DOMAIN 1: SCOPE AND PURPOSE		
1. OBJECTIVES *Report the overall objective(s) of the guideline. The expected health benefits from the guideline are to be specific to the clinical problem or health topic.*	☒ Health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) ☐ Expected benefit(s) or outcome(s) ☒ Target(s) (e.g., patient population, society)	3, 20
2. QUESTIONS *Report the health question(s) covered by the guideline, particularly for the key recommendations.*	☒ Target population ☒ Intervention(s) or exposure(s) ☒ Comparisons (if appropriate) ☒ Outcome(s) ☒ Health care setting or context	See relevant sections
3. POPULATION *Describe the population (i.e., patients, public, etc.) to whom the guideline is meant to apply.*	☒ Target population, sex and age ☒ Clinical condition (if relevant) ☒ Severity/stage of disease (if relevant) ☒ Comorbidities (if relevant) ☐ Excluded populations (if relevant)	3-4, 20
DOMAIN 2: STAKEHOLDER INVOLVEMENT		
4. GROUP MEMBERSHIP *Report all individuals who were involved in the development process. This may include members of the steering group, the research team involved in selecting and reviewing/rating the evidence and individuals involved in formulating the final recommendations.*	☒ Name of participant ☐ Discipline/content expertise (e.g., neurosurgeon, methodologist) ☒ Institution (e.g., St. Peter's hospital) ☐ Geographical location (e.g., Seattle, WA) ☒ A description of the member's role in the guideline development group	190-197
5. TARGET POPULATION PREFERENCES AND VIEWS *Report how the views and preferences of the target population were sought/considered and what the resulting outcomes were.*	☒ Statement of type of strategy used to capture patients'/publics' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences)	19-20

	☒ Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups) ☐ Outcomes/information gathered on patient/public information ☒ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	
6. TARGET USERS *Report the target (or intended) users of the guideline.*	☒ The intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators) ☒ How the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)	3, 20
DOMAIN 3: RIGOUR OF DEVELOPMENT		
7. SEARCH METHODS *Report details of the strategy used to search for evidence.*	☒ Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL) ☒ Time periods searched (e.g., January 1, 2004 to March 31, 2008) ☒ Search terms used (e.g., text words, indexing terms, subheadings) ☒ Full search strategy included (e.g., possibly located in appendix)	16, 370-391
8. EVIDENCE SELECTION CRITERIA *Report the criteria used to select (i.e., include and exclude) the evidence. Provide rationale, where appropriate.*	☒ Target population (patient, public, etc.) characteristics ☒ Study design ☒ Comparisons (if relevant) ☒ Outcomes ☒ Language (if relevant) ☐ Context (if relevant)	211-369
9. STRENGTHS & LIMITATIONS OF THE EVIDENCE *Describe the strengths and limitations of the evidence. Consider from the perspective of the individual studies and the body of evidence aggregated across all the studies. Tools exist that can facilitate the reporting of this concept.*	☒ Study design(s) included in body of evidence ☒ Study methodology limitations (sampling, blinding, allocation concealment, analytical methods) ☒ Appropriateness/relevance of primary and secondary outcomes considered ☒ Consistency of results across studies ☒ Direction of results across studies ☒ Magnitude of benefit versus magnitude of harm ☒ Applicability to practice context	211-369
10. FORMULATION OF RECOMMENDATIONS *Describe the methods used to formulate the recommendations and*	☒ Recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered)	22

how final decisions were reached. Specify any areas of disagreement and the methods used to resolve them.	☒ Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures) ☒ How the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote)	
11. CONSIDERATION OF BENEFITS AND HARMS *Report the health benefits, side effects, and risks that were considered when formulating the recommendations.*	☒ Supporting data and report of benefits ☒ Supporting data and report of harms/side effects/risks ☒ Reporting of the balance/trade-off between benefits and harms/side effects/risks ☒ Recommendations reflect considerations of both benefits and harms/side effects/risks	See relevant sections
12. LINK BETWEEN RECOMMENDATIONS AND EVIDENCE *Describe the explicit link between the recommendations and the evidence on which they are based.*	☒ How the guideline development group linked and used the evidence to inform recommendations ☒ Link between each recommendation and key evidence (text description and/or reference list) ☒ Link between recommendations and evidence summaries and/or evidence tables in the results section of the guideline	See relevant sections
13. EXTERNAL REVIEW *Report the methodology used to conduct the external review.*	☒ Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence) ☒ Methods taken to undertake the external review (e.g., rating scale, open-ended questions) ☒ Description of the external reviewers (e.g., number, type of reviewers, affiliations) ☒ Outcomes/information gathered from the external review (e.g., summary of key findings) ☒ How the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations)	23
14. UPDATING PROCEDURE *Describe the procedure for updating the guideline.*	☒ A statement that the guideline will be updated ☒ Explicit time interval or explicit criteria to guide decisions about when an update will occur ☒ Methodology for the updating procedure	189
DOMAIN 4: CLARITY OF PRESENTATION		

15. SPECIFIC AND UNAMBIGUOUS RECOMMENDATIONS *Describe which options are appropriate in which situations and in which population groups, as informed by the body of evidence.*	☒ A statement of the recommended action ☒ Intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) ☒ Relevant population (e.g., patients, public) ☒ Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply) ☒ If there is uncertainty about the best care option(s), the uncertainty should be stated in the guideline	See relevant sections
16. MANAGEMENT OPTIONS *Describe the different options for managing the condition or health issue.*	☒ Description of management options ☒ Population or clinical situation most appropriate to each option	See relevant sections
17. IDENTIFIABLE KEY RECOMMENDATIONS *Present the key recommendations so that they are easy to identify.*	☒ Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms ☒ Specific recommendations grouped together in one section	See relevant sections and Executive Summary (9)
DOMAIN 5: APPLICABILITY		
18. FACILITATORS AND BARRIERS TO APPLICATION *Describe the facilitators and barriers to the guideline's application.*	☒ Types of facilitators and barriers that were considered ☒ Methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation) ☒ Information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography) ☒ How the information influenced the guideline development process and/or formation of the recommendations	189
19. IMPLEMENTATION ADVICE/TOOLS *Provide advice and/or tools on how the recommendations can be applied in practice.*	☒ Additional materials to support the implementation of the guideline in practice. For example: o Guideline summary documents o Links to check lists, algorithms o Links to how-to manuals	211-369

	○ Solutions linked to barrier analysis (see Item 18) ○ Tools to capitalize on guideline facilitators (see Item 18) ○ Outcome of pilot test and lessons learned	
20. RESOURCE IMPLICATIONS *Describe any potential resource implications of applying the recommendations.*	☒ Types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) ☒ Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.) ☒ Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course) ☒ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	188-189 and other relevant sections
21. MONITORING/ AUDITING CRITERIA *Provide monitoring and/or auditing criteria to measure the application of guideline recommendations.*	☒ Criteria to assess guideline implementation or adherence to recommendations ☒ Criteria for assessing impact of implementing the recommendations ☒ Advice on the frequency and interval of measurement ☒ Operational definitions of how the criteria should be measured	188
DOMAIN 6: EDITORIAL INDEPENDENCE		
22. FUNDING BODY *Report the funding body's influence on the content of the guideline.*	☒ The name of the funding body or source of funding (or explicit statement of no funding) ☒ A statement that the funding body did not influence the content of the guideline	4
23. COMPETING INTERESTS *Provide an explicit statement that all group members have declared whether they have any competing interests.*	☒ Types of competing interests considered ☒ Methods by which potential competing interests were sought ☒ A description of the competing interests ☒ How the competing interests influenced the guideline process and development of recommendations	23, 194-196