PHILIPPINE GUIDELINES on PERIODIC HEALTH EXAMINATION

Immunization for Adults

PERIODIC HEALTH EXAMINATION TASK FORCE 2021

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.

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ABBREVIATIONS AND ACRONYMS

AAHS	Amorphous Aluminium Hydroxyphosphate Sulfate
ACIP	Advisory Committee on Immunization Practices
AIN	Anal Intraepithelial Neoplasia
AMHOP	Association of Municipal Health Officers
AMSTAR	A Critical Appraisal Tool for Systematic Reviews
ATAGI	Australian Technical Advisory Group on Immunisation
CAP	Community Acquired Pneumonia
CAPiTA	Community Acquired Pneumonia Immunization Trial in Adults
CDC	Center for Disease Control
CF	Case Fatality Rate
CI	Confidence Interval
CIN	Cervical Intraepithelial Neoplasia
COI	Conflict of Interest
CPG	Clinical Practice Guideline
CP	Consensus Panel
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
FDA	Food and Drug Administration
GMTs	Geometric Mean Titers
GRADE	Grading Of Recommendations, Assessment, Development and Evaluation
HCW	Healthcare Worker
HPV	Human Papillomavirus
ICERs	Incremental Cost-Effectiveness Ratios
ICTRP	International Clinical Trials Registry Platform
ILI	Influenza-Like Illness
IPD	Invasive Pneumococcal Disease
IRR	Incidence Rate Ratio
IQR	Interquartile Range
LMIC	Low to Middle Income Country
MCV	Meningococcal Conjugate Vaccine
MD	Missed Working Days
MNTE	Maternal and Neonatal Tetanus Elimination
NNV	Number Needed to Vaccinate
OPA	Opsonophagocytic Activity
OR	Odds Ratio
PAFP	Philippine Academy Of Philippine Physicians
PCP	Philippine College of Physicians
PCR	Polymerase Chain Reaction
PCV13	Pneumococcal Conjugate Vaccine
PeIN	Penile Intraepithelial Neoplasia
PICO	Population, Intervention, Comparator and Outcome
PFV	Philippine Foundation for Vaccination
PPSV23	Pneumococcal Polysaccharide Vaccine

PSA	Philippine Statistics Authority
PSGIM	Philippine Society of General Internal Medicine
PSMID	Philippine Society of Microbiology and Infectious Diseases
QALD	Quality Adjusted Life Days
QALY	Quality Adjusted Life Years
RCT	Randomized Controlled Trial
RD	Risk Difference
RZV	Recombinant Zoster Vaccine
SAE	Serious Adverse Events
SCR	Seroconversion Rate
SD	Standard Deviation
SRR	Seroresponse Rate
TCV	Typhoid Conjugate Vaccine
Td	Tetanus Toxoid
Tdap	Tetanus, Diphtheria, Pertussis
TIV	Trivalent Inactivated Vaccine
VaIN	Vaginal Intraepithelial Neoplasia
VIN	Vulvar Intraepithelial Neoplasia
VE	Vaccine Efficacy
Vi-rEPA	Vi Polysaccharide Bound To Recombinant *Pseudomonas Aeruginosa* Exoprotein A
Vi-TT	Vi Tetanus Toxoid
WHO	World Health Organization
YLD	Years Lost due to Disability
YLL	Years of Life Lost
ZVL	Zoster Vaccine Live

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

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.

Queries, suggestions, and other concerns regarding this CPG may be directed to the DOH National Practice Guidelines Program office by email (egmd@doh.gov.ph) or to DOH-HPDPB and UP-NIH.

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 twenty (20) 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.

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

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

[2] Schunemann HJ, Mustafa R, Brozek J, Santesso N, Alonso-Coello P, Guyatt G, et al. GRADE Guidelines: 16. GRADE evidence to decision frameworks for tests in clinical practice and public health. J Clin Epidemiol. 2016;76:89-98.

SUMMARY OF RECOMMENDATIONS

Recommendation	Certainty of Evidence	Strength of Panel Recommendation
Question 1: Should influenza vaccine be recommended to apparently healthy adults?		
1.1 Among healthy adults, pregnant women, and elderly (≥65 years old) we suggest annual influenza vaccination using inactivated influenza vaccine.	Low	Weak
1.2 Among healthcare workers, we suggest annual influenza vaccination using inactivated influenza vaccine.	Very Low	Weak
Question 2: 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.		
Question 3: Should pneumococcal vaccine be recommended to apparently adults?		
3.1 Among apparently healthy adults ≥ 65 years of age, we suggest the use of PCV 13.	Moderate	Weak
3.2 Among apparently healthy adults ≥ 65 years of age, we recommend the use of PPSV 23.	Moderate	Strong
3.3 Among apparently healthy adults between 18-64 years of age, we suggest the use of PCV 13.	Low	Weak
3.4 Among apparently healthy adults between 18-64 years of age, there is insufficient evidence to recommend the use of PPSV 23.	Low	N/A

Question 4: Should typhoid vaccine be recommended to apparently healthy adults?		
4.1 Among healthy adults, we suggest the use of Vi polysaccharide intramuscular vaccine for typhoid vaccination.	Low	Weak
4.2 Among healthy adults, there is insufficient evidence to recommend for or against Vi-TT intramuscular vaccines.	Very Low	N/A
4.3 Among healthcare workers, we suggest against the routine use of typhoid vaccines.	Very Low	Weak
Question 5: Should HPV vaccine be recommended to apparently adults?		
5.1 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.	Moderate	Strong
5.2 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.	Very Low	Weak
5.3 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.	Low	Weak
5.4 Among pregnant patients, we suggest against HPV vaccination.	Very Low	Weak
5.5 Among apparently healthy asymptomatic sex workers, there is insufficient evidence to recommend HPV vaccination.	Very Low	N/A
Question 6: Should herpes zoster vaccine be recommended to apparently healthy adults?		
6. Among apparently healthy elderly aged ≥ 60 years old, we suggest herpes zoster vaccine.	Moderate	Weak

Question 7: Should tetanus vaccine be recommended to apparently healthy adults?		
7.1 Among healthy adults with complete primary series, we recommend giving any tetanus-toxoid-containing vaccine every 10 years.	Low	Strong
7.2 Among healthy adults with unknown status or incomplete series, we suggest giving primary series with Tdap followed by any tetanus-toxoid-containing vaccine.	Very Low	Weak
7.3 Among pregnant women with complete primary series, we suggest giving any tetanus toxoid-containing vaccine during each pregnancy.	Low	Weak
7.4 Among pregnant women with unknown status or incomplete series, we suggest giving primary series with Tdap followed by any tetanus-toxoid-containing vaccine.	Low	Weak
Question 8: Should measles-containing vaccine be recommended to apparently healthy adults?		
8. Among healthy adults, we recommend giving measles-containing vaccine.	Very Low	Strong

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 2021 Philippine Guidelines will support the objectives stated in the Universal Health Care Act(2) that all Filipinos are given access to quality and affordable medical services, including primary care benefits.

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 screening tests are used in formulating the recommendations. They can be classified into two: (1) screening for a risk factor and (2) screening for early disease. Screening for the former is directed towards determining the effective management of the condition as a risk factor, and screening for the latter is focused on the performance of the tests that will be used to detect and subsequently treat that early disease and prevent it from progressing.

Health screening also carries potential harm, for example, mislabeling the person as being ill. It can pose a threat to the psychological, social, or physical well-being and even to the individual's financial stability. Because of these probable adverse effects of screening, criteria are set to determine if screening for a particular condition can be beneficial and pragmatic. The voting panel members used these criteria (5) aligned with the EtD framework: (1) burden of illness must be high, (2) screening tests must be accurate enough, (3) early treatment must be more effective than late treatment, (4) confirmatory tests and early management must be safe and available, and (5) costs of screening must be proportional with the potential benefit.

Aside from the regulatory agencies and policymakers in the national government, the target users of this guideline on screening strategies include primary care providers, general physicians, specialists, training institutions, payors, patients, the general public, and industry partners.

Vaccination is one of the most convenient preventive measures against certain 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 eight vaccinations (influenza, pneumococcal, typhoid, human papilloma virus, herpes zoster, tetanus, and measles), taking into consideration the general outcomes of vaccine efficacy, safety, and cost-effectiveness.

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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. SCOPE & PURPOSE

This clinical practice guideline is a systematic synthesis of evidence to address immunization among adults. Recommendations were made on eight vaccinations (influenza, pneumococcal, typhoid, human papilloma virus, herpes zoster, tetanus, and measles), taking into consideration the general outcomes of vaccine efficacy, safety, and cost-effectiveness.

3. GUIDELINE DEVELOPMENT METHODOLOGY

3.1 Organization of the Process

Following the international standards, the DOH (1) 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 consulted different stakeholders in prioritizing and developing the guideline questions. They identified and formed the working groups involved in creating the evidence base and finalizing the recommendations for each clinical question included.

The evidence review experts (ERE) or the technical working group were tasked to review existing CPGs, 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 tasked to review the evidence summaries and develop recommendations during the *en banc* meeting. In the meeting, they prioritized critical and important outcomes; discussed necessary considerations revolving around the recommendations and voted on each recommendation and its strength. They participated 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 ERE searched and appraised international practice guidelines related to periodic health screening, including but not limited to those of the Canadian Task Force on Preventive Health Care, U.S. Preventive Services Task Force, National Institute for Health and Care Excellence. If the CPG were of good quality and done within 5 years (2016-2021), the evidence summaries of the CPG were adopted.

The results of the appraisal of existing CPGs and their evidence summaries determined the need for a systematic search in electronic databases (MEDLINE via PubMed, CENTRAL, Google Scholar) for the need to do de-novo systematic reviews and meta-analysis for each question. All searches were done from May to Nov. of 2021. Details on the time periods were discussed under the specific questions. Please see evidence summaries in Appendices. Relevant local databases and websites of medical societies were also utilized in the search. Keywords were based on PICO (MeSH and free text) set for each question. The ERE also contacted authors of related articles to verify details and identify other research studies for appraisal, if needed.

At least two reviewers worked on each PICO question. The search strategy and inclusion criteria were based on the PICO question and are included in their respective evidence summaries. 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 ERE generated evidence summaries for each of the eight (8) questions. Each evidence summary included evidence on the burden of the problem, benefits, harm, and social and economic impact of the vaccination. Evidence/information that will facilitate in the decision (i.e. cost of vaccine, cost-effectiveness studies, qualitative studies) were also included in the evidence summaries. The Quality of Evidence was assessed using the GRADE approach. (2) See table 1.

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

Certainty of Evidence	Interpretation
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Factors that lower quality of the evidence are:

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

Additional factors that may increase quality are:

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

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, and physicians from different settings (e.g., public primary care settings, private practice, occupational health settings). In the choice of CP, the task force made sure that all stakeholders were part of the target population for the CPGs (See PERIODIC HEALTH EXAMINATION TASK FORCE ON IMMUNIZATION – ADULT 2021).

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, resources and uncertainty due to research gaps. Prior to the series of online consensus panel

meetings, the consensus panel received the draft recommendations together with evidence summaries based on the EtD framework shown in Table 2. These recommendations, together with the evidence summaries, were presented during the *en banc* meeting.

Table 2.Detailed considerations based on the EtD framework (3)

1. Is the problem a priority?
2. How substantial are the desirable anticipated effects?
3. How substantial are the undesirable anticipated effects?
4. What is the certainty of the evidence?
5. Is there important uncertainty about or variability in how much people value the main outcomes, including adverse effects and burden of the vaccine and downstream outcomes of vaccination?
6. Does the balance between desirable and undesirable effects favor the vaccine or the comparison?
7. How large are the resource requirements (costs)?
8. What is the certainty of the evidence of resource requirements (costs)?
9. Does the cost-effectiveness of the vaccine favor the vaccine or the comparison?
10. What would be the impact on health equity?
11. Is the vaccine acceptable to key stakeholders?
12. Is the vaccine feasible to implement?

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

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

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 Panelists (CP) and make recommendations on how to manage the COI. For TF members with potential significant COIs, the member of 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 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 were not allowed to join the roster of consensus panel members. See Conflict of Interest Declaration at the end of the document.

3.6 External Review Process

The CPGs were reviewed by independent stakeholders, who were not members of the Task Force. They were also presented in conferences and to relevant societies for their comments and suggestions.

3.7 Planning for Dissemination and Implementation

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

conferences, social media sites, professional society conventions, and journal publications.

References

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4. RECOMMENDATIONS AND PANEL DISCUSSION

4.1 Influenza Vaccine for Adults

RECOMMENDATIONS

1. Among healthy adults, pregnant women, and elderly (≥65 years old), we suggest annual influenza vaccination using inactivated influenza vaccine. *(Low certainty of evidence; Weak recommendation)*

2. Among healthcare workers, we suggest annual influenza vaccination using inactivated influenza vaccine. *(Very low certainty of evidence; Weak recommendation)*

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 decision of the panel of not making 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.

4.1.1 Burden of 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 most number of cases were reported in the 40 to 64 year-old (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 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) ages 65 years old and above, and I pregnant women.(8) 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)

4.1.2 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

Outcomes	No. of Studies (no. of participants)	Effect Estimate (95% CI)	Interpretation	Certainty of Evidence
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

4.1.2.1 Healthy Adults

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.

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 December 31, 2016.

WHO international clinical trials registry platform (ICTRP) and ClinicalTrials.gov were searched until July 1, 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.

4.1.2.2 Pregnant Women

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.

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)

4.1.2.3 Healthcare Workers

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.

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 along, 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).

4.1.2.3 Elderly

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.

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.

4.1.3 Cost Implication

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.(27)

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.(28-37)

In the Philippines, no local cost-effectiveness study on influenza vaccines has been published. The cost of each type of influenza vaccine are listed in Table 2.

Table 2. Unit cost of influenza vaccine

Parameter	Type of influenza vaccine		
	Inactivated quadrivalent	Inactivated trivalent	Live intranasal
Unit cost of vaccine	Php 600-800 (38)	Php 450-500[a]	Php 821.91 to 1,184.30[b] (39)

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

4.1.4 Equity, Acceptability, and Feasibility

A local study published in 2020 evaluated the perceptions and attitudes of Filipinos towards influenza vaccination using focus group discussions.(40) 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.

4.1.5 Recommendations from Other Groups

One local and six international guidelines recommend annual influenza vaccination among adults.(41-47) Five guidelines specified prioritization of high-risk adults.(43,45-48) Table 3 summarizes the recommendations on influenza vaccination from other groups.

Table 3. Recommendations on influenza vaccination from other groups

Group	AGREE Rigor Domain Score	Recommendation	Basis for recommendation
ACIP 2020 (41)	78.1	Routine annual influenza vaccination is recommended for all persons aged ≥6months who do not have contraindications.	Not indicated
WHO 2020 (42)	72.9	For countries considering the initiation or expansion of programs for seasonal 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.	Not indicated
PSMID 2018 (43)	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 (44)	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

Group	AGREE Rigor Domain Score	Recommendation	Basis for recommendation
Singapore guidelines 2016 (45)	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 immu-nization handbook 2021 (46)	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 complications are strongly recommended to receive influenza vaccine every year.	Not indicated Strong recommendation
Indian CPG 2019 (47)	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, EUGMS – European Geriatric Medicine, EVASCG – Escmid Vaccine Study Group, PSMID – Philippine Society of Microbiology and Infectious Diseases, WHO – World Health Organization

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3.1.1 Priority of the Problem

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4.2 High-dose Influenza Vaccine for the Elderly

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.

4.2.1 Burden of 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)

4.2.2 Benefits and Harms of High-dose Influenza Vaccine

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.

The summary table of all critical outcomes of high-dose influenza vaccination among apparently healthy elderly 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

The forest plots are shown in Appendix 3. The summary of findings table and reasons for downgrading are found in Appendix 4.

Twelve primary randomized controlled trials (RCTs) and four secondary studies evaluate 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 2.

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.

4.2.3 Cost Implication

A systematic review on the cost-effectiveness of high-dose influenza vaccine among ages 65 years old and above was published in March 2021.(22) 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 and all similarly reported that high-dose influenza vaccine was cost-effective compared to standard-dose influenza vaccine.(23-29) Another study done in Australia likewise reported that high-dose trivalent inactivated influenza vaccine was cost-effective compared to standard-dose.(30) 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. In addition, high-dose influenza vaccines are not yet available locally. The unit cost of standard-dose and high-dose influenza vaccines are shown in Table 2.

Table 2. Unit cost of influenza vaccine

Parameter	Type of influenza vaccine	
	High-dose	Standard-dose
Unit cost of vaccine	Php 3,063.05[a] (31)	Php 600-800 (32)

[a] *Converted from USD (not locally available)*

4.2.4 Equity, Acceptability, and Feasibility

A Philippine study published in 2020 evaluated the perceptions and attitudes of Filipinos towards influenza vaccination using focus group discussions.(33) 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.

4.2.5 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 ages 65 years old and above.(34)

Table 3. Recommendation on high-dose influenza vaccination from other groups

Group	Recommendation	Basis for recommendation
ACIP 2020 (34)	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

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4.3 Pneumococcal Vaccine for Adults

RECOMMENDATIONS

1. **Among apparently healthy adults ≥65 years of age, we suggest the use of PCV13.** ***(Moderate certainty of evidence; Weak recommendation)***

2. **Among apparently healthy adults ≥65 years of age, we recommend the use of PPSV23.** ***(Moderate certainty of evidence; Strong recommendation)***

3. **Among apparently healthy adults between 18-64 years of age, we suggest the use of PCV13.** ***(Low certainty of evidence; Weak recommendation)***

4. **Among apparently healthy adults between 18-64 years of age, there is insufficient evidence to recommend the use of PPSV23.** ***(Low certainty of 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.
- There are no studies on the sequential use of PCV13 and PPSV23 among immunocompetent adults without comorbidities, precluding the panel from making recommendations on this vaccination strategy.

4.3.1 Burden of 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.

4.3.2 Benefits and Harms of Pneumococcal Vaccine

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)

The summary of all 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)	PCV 13 was non-inferior to PPSV 23 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

4.3.2.1 Immunocompetent Adults Aged ≥65 Years Old

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 has 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).

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 PPSV3 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, vaccilive 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 4 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)

4.3.2.2 Immunocompetent Adults Aged 18 to 64 Years Old

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 were 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).

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 were statistically significantly greater for nine serotypes (see Appendix 4 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, and 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)

4.3.3 Cost Implication

A 2015 local cost-analysis study on the economic burden of community acquired pneumonia among adult patients admitted in a tertiary private hospital found that hospitalization costs ranged from Php 36,153 to 113,633, with one week post-discharge cost that ranged from Php 1,450 to 8,800.(23) Patients admitted for high-risk pneumonia

had higher estimated health care costs, ranging from Php 104,544 to 249,685, with one week post-discharge cost ranging from Php 24,403 to 89,433. Economic burden of pneumonia in 2012 was also estimated at Php 8.48 billion for CAP-MR and Php 643.76 million for CAP-HR. Currently, PPSV23 is priced at Php 2,400 while PCV13 is Php 3,545.

Evidence on the cost-effectiveness of pneumococcal vaccine among adults in different countries have mixed results.(24-28) More recent studies showed that pneumococcal vaccination is not a cost-effective strategy especially in the healthy adult population.

Table 2 summarizes the results of cost-effectiveness studies on pneumococcal vaccine.

Table 2. Cost-effectiveness studies of pneumococcal vaccines among healthy adults

Setting	Cost-effective?				Conclusion
	PCV13	PPSV23	Sequential PCV13-PPSV 23	PCV13 vs. PPSV23	
IMMUNOCOMPETENT ADULTS ≥65 YEARS OLD					
Korea, 2017 (24)	**YES** ($4,529 per QALY)	**YES** ($25,786 per QALY)	**YES** ($1,228 per QALY)	**YES, PCV13 > PPSV23** ($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 (25)	**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 f*or ≥ 65 y/o*	**NO** for ≥ 65 y/o	[a]	[a]	
Japan, 2016 (26)	**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 (27)	**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 (24)	**NO**	**NO**	[a]	[a]	Neither PCV13 nor PPSV 23 is cost-effective in the low-risk group.

Setting	Cost-effective?				Conclusion
	PCV13	PPSV23	Sequential PCV13-PPSV 23	PCV13 vs PPSV23	
IMMUNOCOMPETENT ADULTS 18-65 YEARS OLD					
South Africa, 2020 (28)	[a]	[a]	[a]	**YES, PCV13 > PPSV23** ($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)*

4.3.4 Equity, Acceptability, and Feasibility

A 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).(29)

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.(29) This reflects that treatment rather than prevention is prioritized especially in limited settings.(30)

4.3.5 Recommendations from Other Groups

There are one local (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 3 summarizes the recommendations on pneumococcal vaccines from other groups.

Table 3. 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.(12,29)	Strong	Moderate
		PPSV23[a] can be administered routinely to immunocompetent adults, especially the elderly, to prevent pneumococcal disease.(12,29)	Strong	Low
		PCV13 can be administered routinely to immunocompetent adults in preventing pneumococcal pneumonia.(12,29)	Strong	Moderate
		PPSV23 and PCV13 may be recommended to immunocompetent adults, especially the elderly, in preventing mortality.(12,29)	Strong	Low
Indian CPG 2019 (8)	79.1	PPSV23 vaccination is recommended in all adults above age 65.(30)	Grade 2A	
ACIP 2021 (9)	78.1	PPSV23 vaccination (1 dose) is recommended in all adults aged ≥65 years.(31)	Grade 2A	
		PCV13 vaccination is recommended based on shared clinical decision-making for adults aged ≥65 years who do not 51mmunocompromised51romizing 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. (32,33)	Evidence Category A	
Immunocompetent elderly				
Aus51mmunon immuni-zation 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.		

Group	GRADE Rigor Score	Recommendation for immunocompetent adults	Basis for recommendation/s	
			Strength	Quality of evidence
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	
Aus52mmunon immuni-zation 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

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3.3.1 Priority of the Problem

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3.3.2 Benefits and Harms of Pneumococcal Vaccine

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3.3.4 Equity, Acceptability, and Feasibility

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4.4 Typhoid Vaccine for Adults

RECOMMENDATIONS

1. **Among healthy adults, we suggest the use of Vi polysaccharide intramuscular vaccine for typhoid vaccination.** ***(Low certainty of evidence; Weak recommendation)***

2. **Among healthy adults, there is insufficient to recommend for or against Vi-TT intramuscular vaccines for typhoid vaccination.** ***(Very low certainty of evidence)***

3. **Among healthcare workers, we suggest against the routine use of typhoid vaccines.** ***(Very low certainty of evidence; Weak recommendation)***

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.

4.4.1 Burden of 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.

4.4.2 Benefits and Harms of Typhoid Vaccine

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 in children to adult populations, while the RCTs on the newer Vi-rEPA and Vi-TT vaccines were57mmhildren.

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

Outcomes	No. of Studies (no. of participants)	Effect Estimate (95% CI)	Interpretation	Certainty of Evidence
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

[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.*

4.4.2.1 Immunocompetent Adults

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.

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)

4.4.2.2 Healthcare Workers

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.

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)

4.4.3 Cost Implication

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.(27) 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 $671,000 in government investment would avert $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.(28)

4.4.4 Equity, Acceptability, and Feasibility

There are no international and local studies on the equity, acceptability, and feasibility of typhoid vaccination.

4.4.5 Recommendations from Other Groups

Three international guidelines recommend typhoid vaccine for healthy adults and HCWs within endemic countries.(29-31) 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 (29)	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 (30)	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 (11,14,32), 1 RCT including adults (33), 2 case control (34,35), 1 cohort (36), 1 Descriptive (37)
		Typhoid vaccine is recommended for laboratory workers who routinely work with *Salmonella typhi.*	Not indicated	
ACIP 2015 (31)	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 (38,39), 2 RCTs (13,15)
		Typhoid vaccine is recommended for healthcare workers or those who routinely work with *Salmonella typhi*	Strong	

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

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4.5 HPV Vaccine for Adults

RECOMMENDATIONS

1. **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.** ***(Moderate certainty of evidence; Strong recommendation)***

2. **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.** ***(Very low certainty of evidence; Weak recommendation)***

3. **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.** ***(Low certainty of evidence; Weak recommendation)***

4. **Among pregnant patients, we suggest against HPV vaccination.** ***(Very low certainty of evidence; Weak recommendation)***

5. **Among apparently healthy asymptomatic sex workers, there is insufficient evidence to recommend HPV vaccination.** ***(Very low certainty of 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.

4.5.1 Burden of 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

4.5.2 Benefits and Harms of HPV Vaccine

Nine randomized controlled trials were included in this review. Appendix 1 shows a summary of the characteristics of these studies.

4.5.2.1 Immunocompetent Females Aged 16 to 26 Years Old

The summary of all critical outcomes of HPV vaccination among immunocompetent females aged 16 to 26 years old is shown in Table 2.

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]

Outcomes	No. of Studies *(no. of participants)*	Effect Estimate	Interpretation	Certainty of Evidence
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

CIN – Cervical intraepithelial neoplasia, VaIN – Vaginal intraepithelial neoplasia, VE – Vaccine effic–cy 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)

4.5.2.2 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

Outcomes	No. of Studies *(no. of participants)*	Effect Estimate	Interpretation	Certainty of Evidence
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

AIN – Anal intraepithelial neoplasia, PeIN – Penile intraepithelial neoplasia, VE – Vaccine effic–cy defined as (1 − relative risk) × 100%

[a] 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=2,790; high certainty of evidence)

Vaccination with 4vHPV decreased the incidence of HPV infection and related diseases for ≥6 months with a vaccine efficacy of 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 were 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 were 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 either 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 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)

4.5.2.3 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

Outcomes	No. of Studies *(no. of participants)*	Effect Estimate	Interpretation	Certainty of Evidence
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

CIN – Cervical intraepithelial neoplasia, VE – Vaccine effic–cy 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.

4.5.2.4 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.

4.5.2.5 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 of spontaneous abortions, late fetal deaths, and congenital anomaly cases out of the total number of known pregnancy outcomes, and 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)

4.5.2.6 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)

4.5.2.7 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.

4.5.3 Cost Implication

Table 5 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 5. Unit cost of HPV vaccination

Parameter	Vaccination	
	Quadrivalent (4v-) HPV vaccine	Nonavalent (9v-) HPV vaccine
Unit cost of vaccine (22,23)	Php 562.50 to Php 4,800 per dose	Php 6,750 to Php 10,125 per dose

4.5.4 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.(25)

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).(26)

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 decrease significantly.(27)

4.5.5 Recommendations from Other Groups

Table 6 summarizes the recommendations on HPV vaccination from other groups.

Table 6. Recommendations on HPV vaccination from other groups

Group	Recommendation for immunocompetent adults	Basis for recommendation/s	
		Strength	Quality of evidence
PSMID 2018 (28)	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 (29)	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 (30)	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 (31)	We suggest to vaccI HPV vaccine-naive adolescents aged 18 to 26 years against HPV, Irrespective of their gender.	Weak recommendation for a procedure	Low
	We suggest to Inate 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 (32)	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

Group	Recommendation for immunocompetent adults	Basis for recommendation/s	
		Strength	Quality of evidence
ACIP 2019 (33)	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, PSMID – Philippine Society of Microbiology and Infectious Diseases

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3.5.1 Priority of the Problem

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4.6 Herpes Zoster Vaccine for Adults

RECOMMENDATION

Among apparently healthy elderly aged ≥60 years old, we suggest herpes zoster vaccine. ***(Moderate certainty of evidence; Weak recommendation)***

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: (a) live attenuated vaccine (ZVL) and (b) recombinant vaccine (RZV). Evidence showed higher vaccine efficacy rates with RZV. Additionally, the recombina84mmunocompromisedferred for immunocompromized patients. 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 two doses.
- Evidence on the cost-effectiveness of herpes zoster vaccine included studies conducted abroad, posing applicability issues.

4.6.1 Burden of 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, cervical nerves, while 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 are shown in Table 1.

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

Age	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

In a review of data from Asia-Pacific countries including the Philippines, herpes zoster incidence is comparable to the Western population where lifetime risk is approximately one-third and with an incidence of 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, 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 noted higher rates among women, immunocompromised individuals, individuals aged 50 to 70 years old, and those with postherpetic neuralgia. In that 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% in those older than 50 years and 33% in those older than 80 years of age.(7)
Its diagnosis in the Philippines remains clinical. Management options include antivirals, analgesics, with 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.

4.6.2 Benefits and Harms of Herpes Zoster Vaccine

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

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

Outcomes	No. of Studies *(no. of participants)*	Effect Estimate	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

Outcomes	No. of Studies *(no. of participants)*	Effect Estimate	Interpretation	Certainty of Evidence
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** (95% CI 3.26, 5.81)	Favors placebo	Moderate

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 study14 (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 trial14 (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).

4.6.3 Cost Implication

In the Philippines, ZVL costs around 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.(23) Fifteen out of 25 (60%) studies concluded that ZVL was cost-effective compared with no vaccine at a vaccine price ranging from $93 to $236 (2018 values). In the single RZV study (24) 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 was 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.(25) Another study was done in Canada whose model predicted that RZV is likely cost-effective in Canada for adults 60 years.(26)

4.6.4 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 (27) and this has been partially attributed to a financial barrier because out-of-pocket cost is incurred for herpes zoster vaccine via copayments.(28,29)

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.(30)

4.6.5 Recommendations from Other Groups

The Australian Technical Advisory Group on Immunisation (ATAGI) recommends shingles vaccination for immunocompetent elderly aged 60 years and above.(31) However, vaccination from age 50 years can be considered if they are at a higher risk of disease.

Meanwhile, both the ATAGI (31) and the Advisory Committee on Immunization Practices (ACIP) of the US CDC (32) 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 (33) recommendations are for use at the individual level and 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 with the former having a stronger recommendation and a higher quality of evidence than the latter. Further, PSMID

recommends the use of RZV in immunocompetent adults age 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 (34) 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.(35)

All the aforementioned groups did not include zoster vaccine in their recommended vaccines for healthcare workers.(33,36-38)

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, WHO – World Health Organization

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4.7 Tetanus Vaccine for Adults

RECOMMENDATION

1. **Among healthy adults with complete primary series, we recommend giving any tetanus toxoid-containing vaccine every 10 years.** ***(Low certainty of evidence; Strong recommendation)***

2. **Among healthy adults with unknown status or incomplete series, we suggest giving primary series with Tdap followed by any tetanus toxoid-containing vaccine.** ***(Very low certainty of evidence; Weak recommendation)***

3. **Among pregnant women with complete primary series, we suggest giving any tetanus toxoid-containing vaccine during each pregnancy.** ***(Low certainty of evidence; Weak recommendation)***

4. **Among pregnant women with unknown status or incomplete series, we suggest giving primary series with Tdap followed by any tetanus toxoid-containing vaccine.** ***(Low certainty of evidence; Weak recommendation)***

Remarks

For pregnant women, administer the first dose of Tdap any time during pregnancy, but ideally at 27 to 36 weeks age of gestation (AOG). Administer the second dose four weeks after the first dose and at least two weeks before giving birth. Administer the third dose six months after the first dose and provide additional Td doses for each subsequent pregnancy.

Considerations

The consensus panel considered the following when formulating this recommendation:

- 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 base 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.

4.7.1 Burden of 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)

4.7.2 Benefits and Harms of Tetanus Vaccine

Evidence for this review was obtained from eight studies. Appendix 2 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)

4.7.2.1 Healthy Adults

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.

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

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)[a] and study design limitations as estimates came from intervention arms across studies.

[a] 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;

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.

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)

4.7.2.2 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 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.

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.

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

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 was 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).(14)

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.(14) 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.[a] 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.(14)

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.

4.7.3 Cost Implication

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 (16,17) and have different conclusions.(16-19) 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 3.

[a] 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. Summary of cost-effectiveness studies on tetanus vaccination

Study	Population	Method	Cost-Effectiveness of Tetanus Vaccination
Fernandes et al., 2019 (16)	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 US$ 8,459)
Havers et al.,2019 (17)	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 US$81,678)
Griffiths et al.,2004 (18)	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 US$3.61)
Abu-Raya et al., 2020 (19)	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 < US$10)

Ding et al. (20) 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 US$ 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. (18) 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 US$117.00, and the cost per discounted DALY averted was US$3.61. On the other hand, Abu-Raya et al. (19) 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$14 in the next ten years. Computing the amount in US dollars using the average exchange rate in 2020 of 0.75, Tdap vaccination was cost-effective if the acquisition price was below US$ 10. However, it should be noted that the study focused more on pertussis infections instead of tetanus that Tdap vaccination prevents.

Fernandes et al. (16) likewise found that introducing universal adult vaccination with Tdap (US$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 US$8,459. However, this recommendation was largely driven by the burden of pertussis instead of

tetanus infections. In a similar vein, Havers et al. (17) 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 US$ 984 and QALY saved at US$ 81,678, at an incidence of 250 cases per 100,000 person years.

The local cost of tetanus vaccine is shown in Table 4.

Table 4. Unit cost of tetanus vaccination

Parameter	Vaccination
Unit cost of tetanus toxoid vaccine	Public Price: Php 28-108 (21) Private Price: Php 400 (22)

4.7.4 Equity, Acceptability, and Feasibility

Vaccine hesitancy was listed by the WHO as one of the top ten global health threats.(23) 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.(24)

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).(25) 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.(25)

4.7.5 Recommendations from Other Groups

Three international (ACIP 2020, WHO 2018, Australian Immunisation Handbook) and one local (PSMID 2018) guidelines (26-29) recommend giving the tetanus vaccine to healthy adults with incomplete or unknown series. Table 5 shows a summary of the recommendation on tetanus vaccination from other groups.

Table 5. Recommendations from other groups

Group	AGREE Rigor Domain Score	Recommendation	Strength	Quality
ACIP 2020 (26)	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 (27)	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 (28)	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 pregn[an]cy, ideally early in the 3rd trimester	Not indicated	

Group	AGREE Rigor Domain Score	Recommendation	Strength	Quality
PSMID 2018 (29)	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 2011)
		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, incl[ud]ing 3-[pr]imary 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 w[ee]ks before birth, and the 3rd do[se] 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 pregn[an]cy, 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

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4.8 Measles-Containing Vaccine for Adults

RECOMMENDATION

Among healthy adults, we recommend giving measles-containing vaccine. ***(Very low certainty of evidence; Strong recommendation)***

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 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 the airborne transmission of measles thereby having a highly infectious nature, the high morbidity and mortality rates associated with it, and the expected increase of adult population susceptible to measles secondary to currently low vaccination rates.

4.8.1 Burden of 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)

4.8.2 Benefits and Harms of Measles-Containing Vaccine

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)

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*

4.8.2.1 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%

SCR – seroconversion rate, SRR – seroresponse rate, ELISA – Enzyme-linked immunosorbent assay, EIA – enzyme immunoassay, Td – Tetanus, diphtheria, MMR – Measles, Mumps, Rubella.
[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)

4.8.2.2 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.

4.8.3 Cost Implication

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.(19,20) Appendix 5 shows the detailed characteristics of these studies.

4.8.4 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.(21) 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.(22) Although safe and effective vaccine has been available over six decades, vaccine hesitancy and social and political unrest globally have led to under-vaccination.(21) Vaccine hesitancy is one of the contributors to low vaccination coverage in both developed and developing countries.(21,23,24)

Determinants of measles vaccine hesitancy were identified in a qualitative study in Sudan (23) 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.(24)

4.8.5 Recommendations from Other Groups

There are one local and three international guidelines that recommend influenza vaccination among adults. 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.(25)

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.(29) 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.(30) 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.(26) International guidelines also recommend two doses of measles-containing vaccines for adults at high risk of transmission among healthcare workers.(2,25,27,28)

Table 3 summarizes the recommendations on measles-containing vaccination from other groups.

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

Recommendations for Measles vaccine	Guideline 1: PSMID 2018	Guideline 2: Australian Immunization Handbook 2021	Guideline 3: WHO Routine Immunization 2020	Guideline 4: USA ACIP 2013
AGREE Rigor Domain Score Overall quality assessment–	56.3	93.75	72.9	78.1
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: ACI–	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: MMAWR
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 have received for catch-up vaccination / unknown history - 4 weeks apart Basis for recommendation: not indicated	**STRONG RECOMMENDATION; HIGH LEVEL OF SCIENTIFIC EVIDENCE** 2 doses of measles containing vaccine are more effective than one dose in protecting against measles Basis for recommendation: not indicated	**NO RATING** 1-2 doses for those with unknown history of prior infection Basis for recommendation: not indic–ted
Population Subgroup 3 - healthcare workers single dose	a	a	a	a

Recommen-dations for Measles vaccine	Guideline 1: PSMID 2018	Guideline 2: Australian Immunization Handbook 2021	Guideline 3: WHO Routine Immunization 2020	Guideline 4: USA ACIP –013
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: MMAWR

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

[a] *No recommendations*

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3.8.1 Priority of the Problem

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5. RESEARCH IMPLICATIONS

Many research questions from the identified clinical questions in this CPG were unanswered in terms of cost-effectiveness, equity, applicability, and feasibility.

The lack of local data on vaccines was highlighted in the evidence base. Specifically, there is paucity of local studies on vaccine efficacy and safety. Local vaccine surveillance studies would help identify the uptake of specific vaccines and their associated adverse events among Filipinos.

Direct evidence also remains lacking on the efficacy of measles-containing vaccines and typhoid vaccines among adults, whereas most existing studies have been conducted among the pediatric population. Considering the COVID-19 pandemic, studies are also needed on the impact of the pandemic on vaccine uptakes, as well as the effect of vaccination for other diseases on COVID-19-related outcomes. This is especially true for influenza vaccine since COVID-19 can present as influenza-like illness.

The lack of local data on the burden of disease was also highlighted by the evidence base. Ideally, estimates of burden of disease could help in identifying which vaccine-preventable diseases need prioritization in terms of vaccine administration. The value of vaccines may be underappreciated if there is insufficient relevant data on disease burden. Furthermore, surveillance systems must be in place not only to identify disease burden, but also to monitor the decline of disease rates with vaccine introduction. Currently, majority of the diseases targeted by the vaccines in this CPG have no robust surveillance in place.

Local serotype surveillance studies are likewise needed to guide recommendations on the specific types of vaccines. For instance, locally prevailing serotypes of pneumococcal infection per subgroup (e.g., by age group) will allow the identification of appropriate vaccine type (i.e., PPSV23 or PCV13).

Moreover, none of the eight vaccines tackled in this CPG had local evidence on cost-effectiveness. Generating data on this is necessary especially since the provision of vaccines is more challenging in many low- and middle-income countries like the Philippines. Studies on economic impact of vaccines should look beyond just averted healthcare costs. Apart from the common cost-effectiveness or cost-benefit analyses, research should look into less well-considered economic savings such as prevention of long-term morbidity following acute infections from vaccine-preventable diseases. Considering the noticeable social stratification in the country, equity studies that look into the impact of vaccines across social strata are also needed to allow targeting of the most vulnerable in the society.

Lastly, acceptability studies on specific vaccines are sparse. Only two of the vaccines tackled, namely HPV and influenza vaccine, had acceptability studies among Filipinos in the evidence base. Both of which focused on the acceptability of these vaccines among

consumers. Acceptability among providers and healthcare workers, as well as adequacy of infrastructures for vaccine handling and storage should also be identified as these will affect the feasibility of vaccine administration.

Indeed, many research questions emerged from collating the evidence for this CPG and can be explored further. Local studies on vaccine efficacy, disease and vaccine surveillance, and economic and social effects of vaccines are among the identified research gaps. Filling in these gaps can provide a clearer picture of the impact of vaccination and may influence the recommendations for updating this guideline.

6. DISSEMINATION AND IMPLEMENTATION

A full copy of this document will be sent to the Department of Health for transmittal and publication. The Disease Prevention and Control Bureau will transmit copies of this CPG to the Philippine Health Insurance Corporation (PHIC) and health maintenance organizations (HMOs) and NGOs involved in a periodic health examination. The recommendations and the evidence summaries will be posted in the PHEX web based application.

All strong recommendations in this guideline can be used for monitoring and auditing practices in institutions. These can be converted to key performance indicators and it can also be used in creating clinical pathways.

The DOH planned to develop a simplified version of this CPG and made it available in the format that will be ready for reproduction and dissemination to the patients in different health care settings. It will also be available for interested parties who might visit the DOH website.

7. APPLICABILITY ISSUES

The PHEX Task Force accentuates some caveats of this CPG using equity and applicability lenses. Evaluating risk factors for a disease and the probability of developing diseases, history of serious adverse events towards vaccines, and financial accessibility are essential factors when considering vaccination. This CPG does not necessarily supersede the consumers' (i.e., health professionals, hospital administrators, employers, payors, patients) values, settings, and circumstances.

Although this CPG intends to influence the direction of health policies for the general population, it should not be the sole basis for recreating or abolishing practices that aim to improve the health conditions of many Filipinos, particularly those part of the workforce.

8. UPDATING OF THE GUIDELINES

The recommendations herein shall hold until such time that new evidence on screening, diagnosing or managing various risk factors and diseases emerges and contingencies dictate updating this Philippine Guidelines on Periodic Health Examination. The CPGs will be updated every 3-5 years or earlier if new significant evidence becomes available.

9. APPENDICES

Search Strategy, Characteristics of Included Studies, Forest Plots, GRADE Evidence, and Cost-effectiveness Studies for the Research Questions

1. Influenza Vaccine for Adults

Appendix 1. Search Strategy

A. 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

B. 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

Appendix 2. Characteristics of Included Studies

A. 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
Steinhoff 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)	Bangladesh	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, SAE – serious adverse events, MCV - meningococcal conjugate vaccine, PPSV23 – pneumococcal polysaccharide vaccine

B. 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 3. Forest Plots

A. Effects of Influenza Vaccine in Healthy Adults

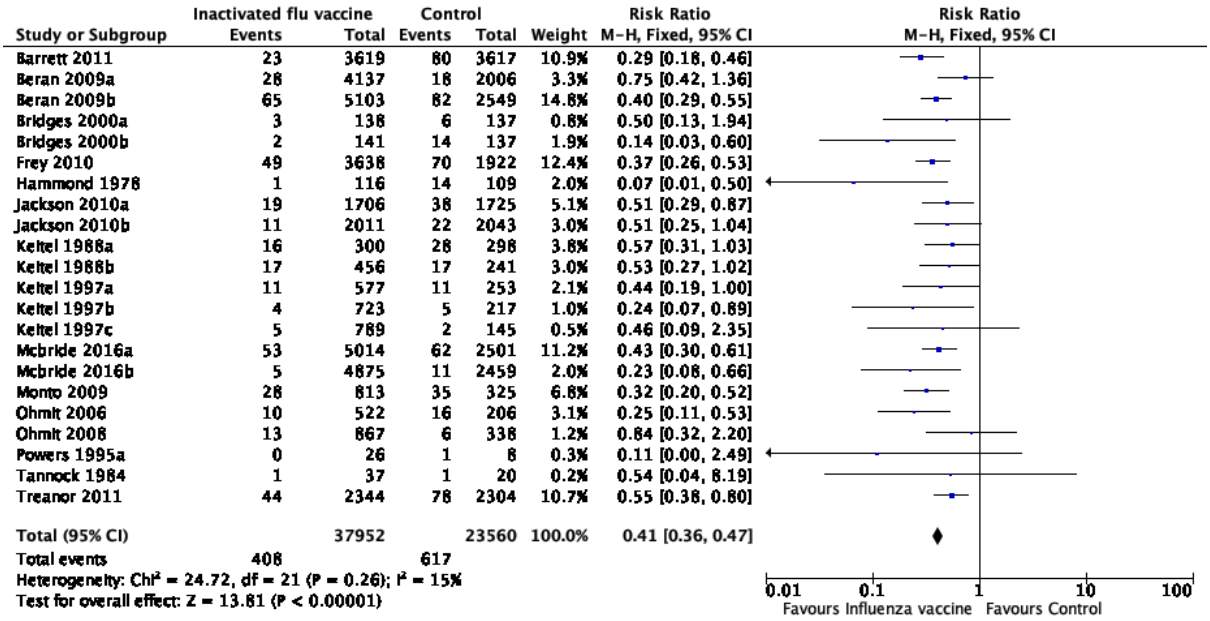

Figure 1. Effect of influenza vaccine among healthy adults on laboratory-confirmed influenza (22 studies)

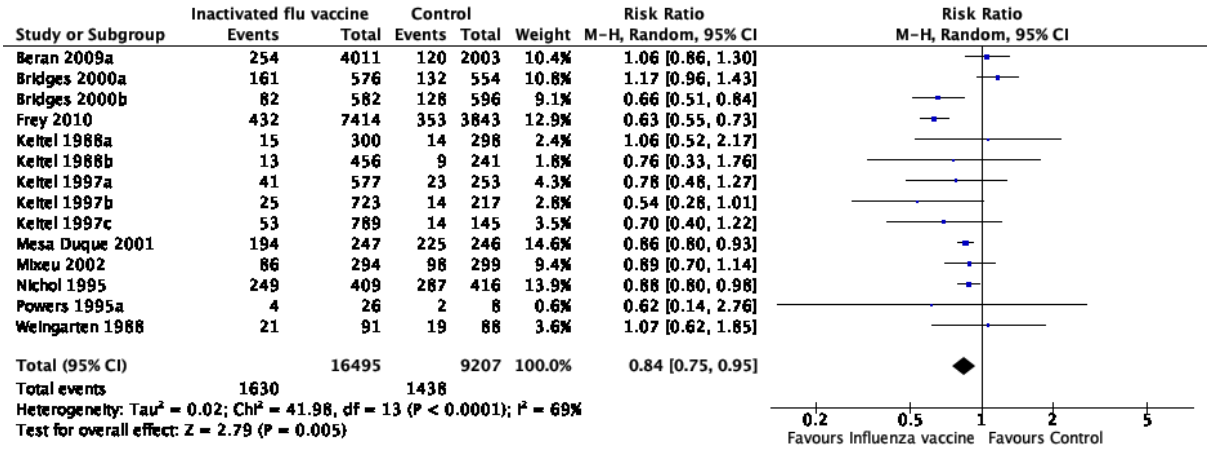

Figure 2. Effect of influenza vaccine among healthy adults on influenza-like illness (14 studies)

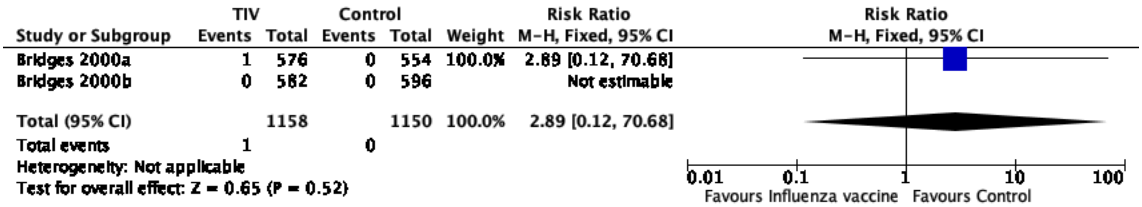

Figure 3. Effect of influenza vaccine among healthy adults on hospitalization (2 studies)

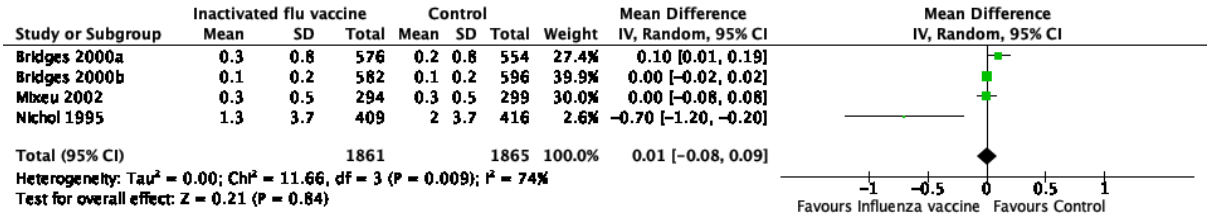

Figure 4. Effect of influenza vaccine among healthy adults on missed working days (4 studies)

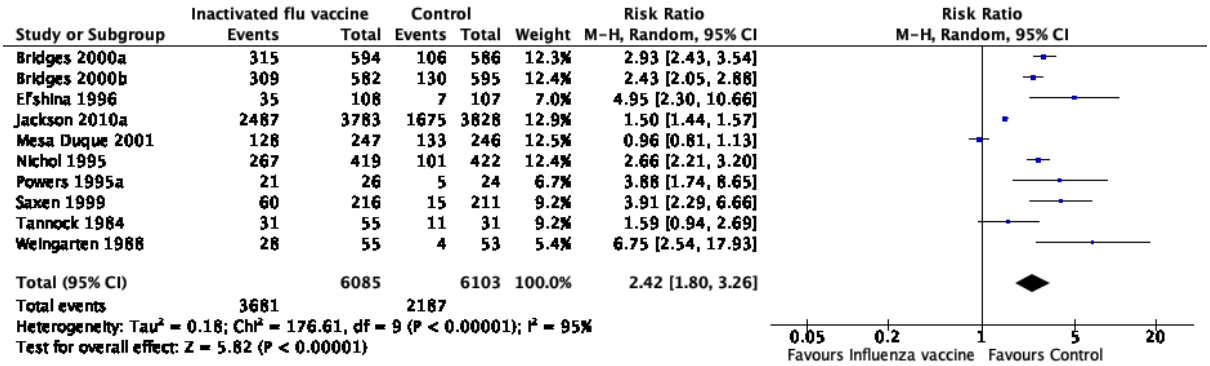

Figure 5. Effect of influenza vaccine among healthy adults on combined local adverse effects (10 studies)

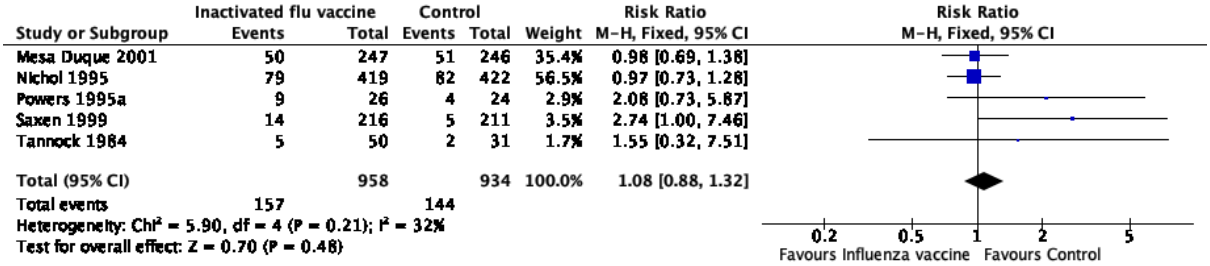

Figure 6. Effect of influenza vaccine among healthy adults on combined systemic adverse effects (5 studies)

B. Effects of Influenza Vaccine in Pregnant Women

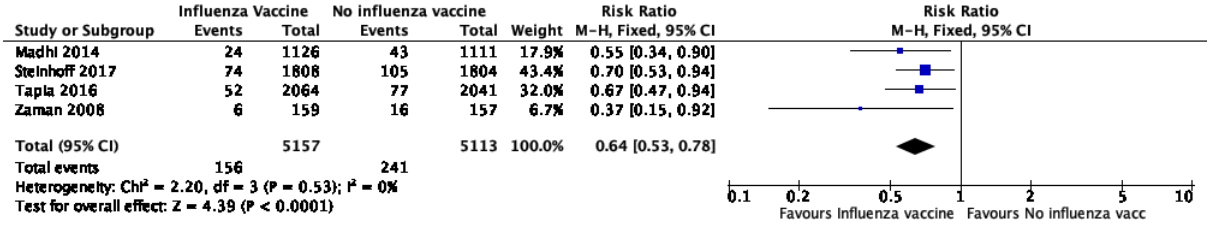

Figure 7. Effect of influenza vaccine among pregnant women on infant influenza (4 studies)

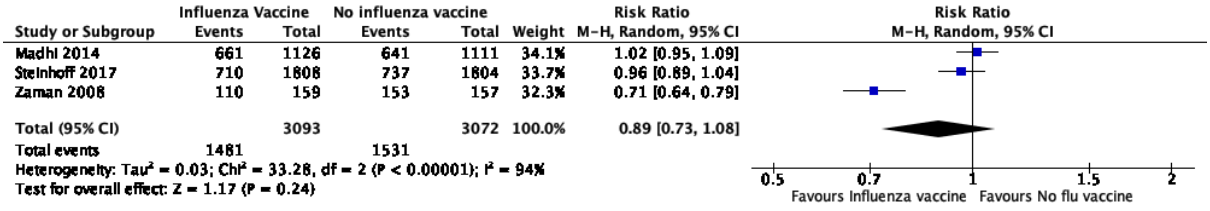

Figure 8. Effect of influenza vaccine among pregnant women on infant influenza-like illness (3 studies)

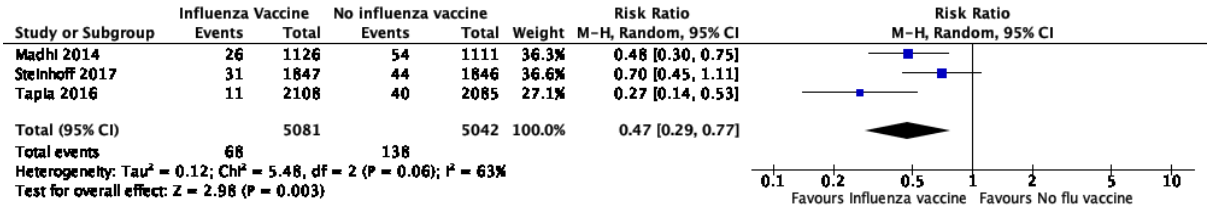

Figure 9. Effect of influenza vaccine among pregnant women on maternal influenza (3 studies)

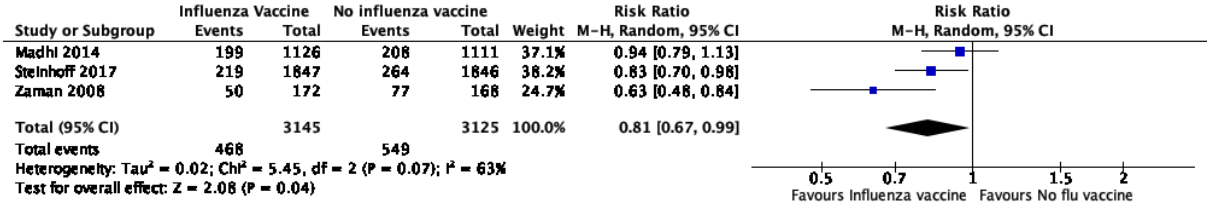

Figure 10. Effect of influenza vaccine among pregnant women on maternal influenza-like illness (3 studies)

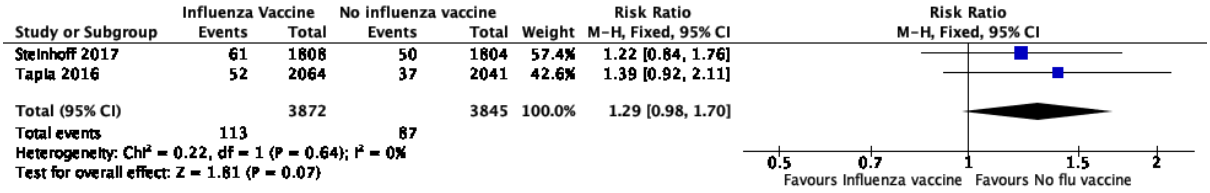

Figure 11. Effect of influenza vaccine among pregnant women on infant mortality (2 studies)

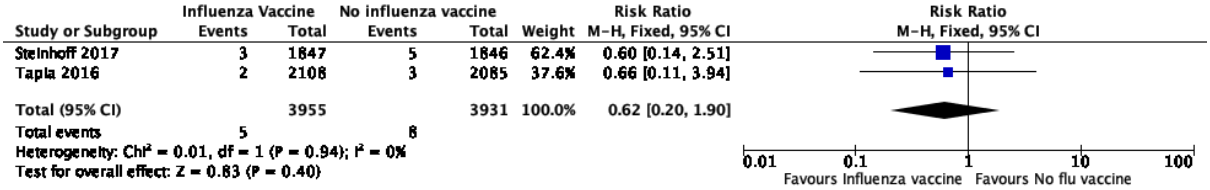

Figure 12. Effect of influenza vaccine among pregnant women on maternal mortality (2 studies)

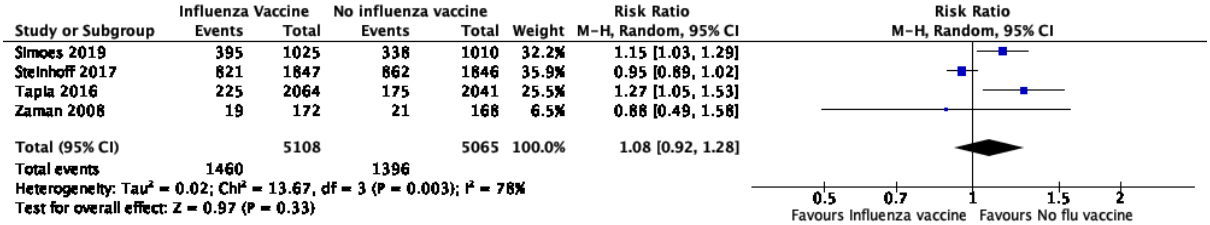

Figure 13. Serious adverse events among infants of pregnant women given influenza vaccine (4 studies)

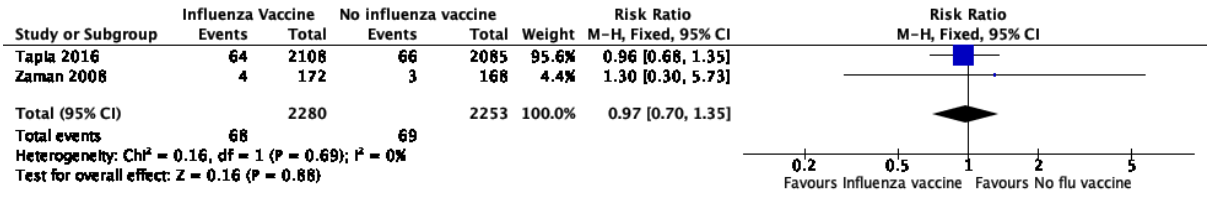

Figure 14. Serious adverse events among pregnant women given influenza vaccine (2 studies)

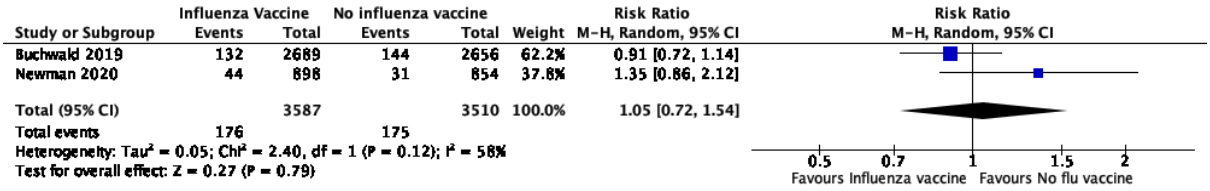

Figure 15. Effect of influenza vaccine among pregnant women on influenza among household contacts (2 studies)

C. Effects of Influenza Vaccine in Healthcare Workers

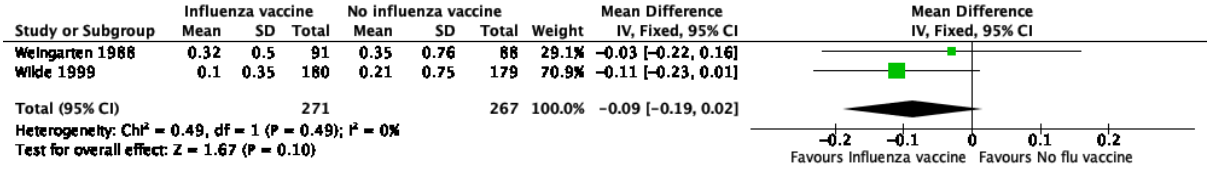

Figure 16. Effect of influenza vaccine among healthcare workers on missed working days (2 studies)

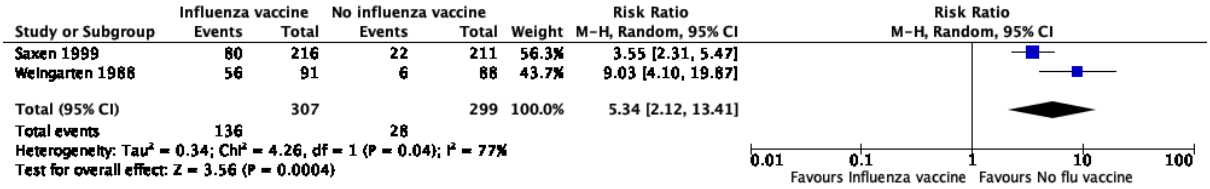

Figure 17. Adverse events of influenza vaccine among healthcare workers (2 studies)

D. Effects of Influenza Vaccine Among Elderly

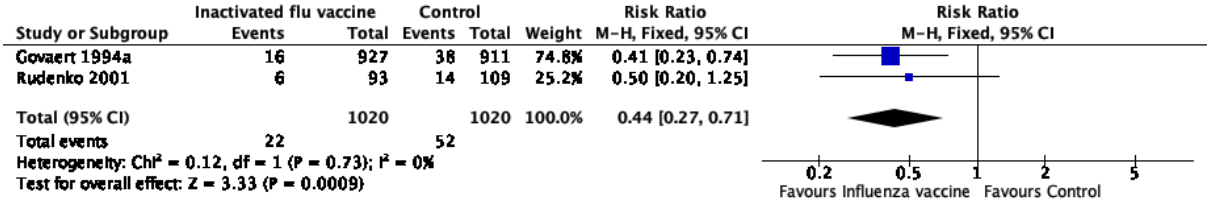

Figure 18. Effect of influenza vaccine among elderly on laboratory-confirmed influenza (2 studies)

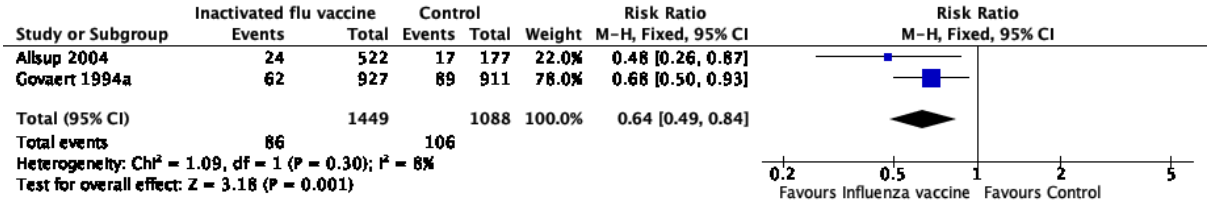

Figure 19. Effect of influenza vaccine among elderly on influenza-like illness (2 studies)

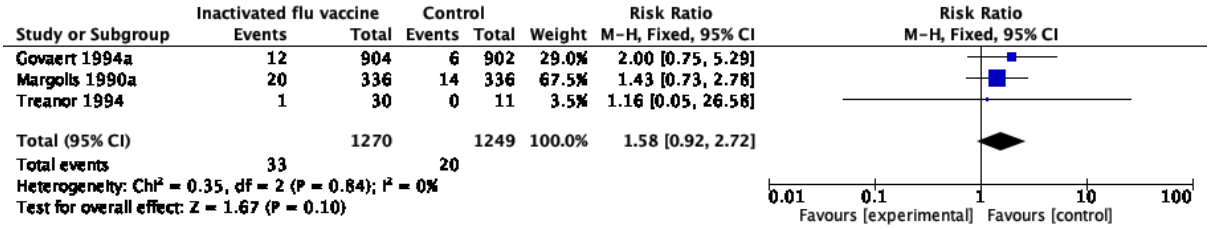

Figure 20. Effect of influenza vaccine among elderly on fever (3 studies)

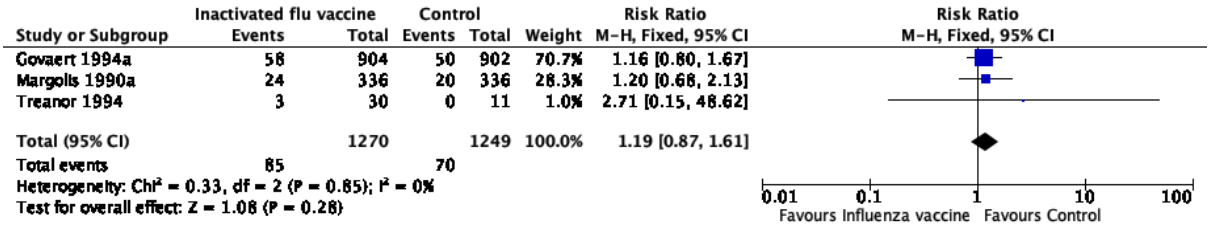

Figure 21. Effect of influenza vaccine among elderly on general malaise (3 studies)

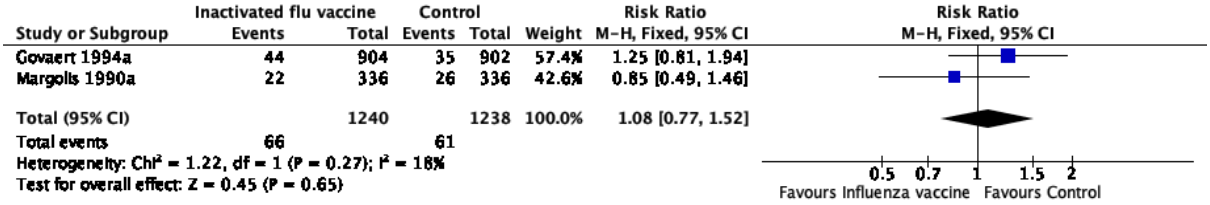

Figure 22. Effect of influenza vaccine among elderly on headache (2 studies)

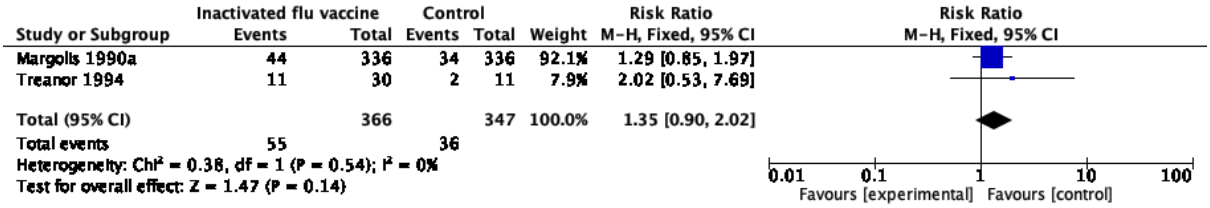

Figure 23. Effect of influenza vaccine among elderly on upper respiratory tract infection (2 studies)

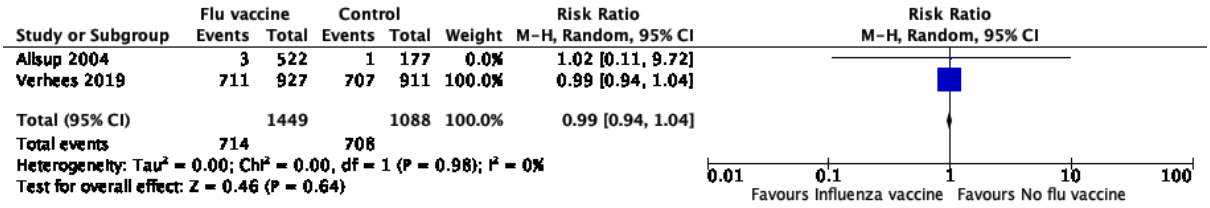

Figure 24. Effect of influenza vaccine among elderly on all-cause mortality (2 studies)

Appendix 4. GRADE Evidence Profile

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

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

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.

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.

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.
8. SImoes EAF, Nunes MC, Carosone-Link P, Madimabe R, Ortiz JR, Neuzil KM, et al. Trivalent influenza vaccination randomized control trial of pregnant women and adverse fetal outcomes. Vaccine. 2019; 37(36): 5397–5403.
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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)												
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

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)		
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.

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												
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

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)		
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.

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												
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												

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)		
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

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 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)

2. High-dose Influenza Vaccine for the Elderly

Appendix 1. Search Strategy

1. 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

2. 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

Appendix 2. Characteristics of Included Studies

Study	Setting	Population	Interven-tion	Con-trol	Outcome	Secondary Study	Outcome
Diaz Grana-dos 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	-	-
Gravens tein 2017 (13)	USA	Nursing home residents	IIV3 HD	IIV3 SD	Hospitalization, mortality	Saade 2018 [21]	Hospitalization for acute cardiovascular event
Gravens tein 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	-	-
Schmad er 2021 (17)	USA	Elderly	IIV3 HD	aIIV3 SD	Serious adverse event, systemic and local reactogenic events	-	-

IIV3 – Inactivated trivalent influenza vaccine, aIIV3 – adjuvanted inactivated trivalent influenza vaccine, IIV4 - Inactivated quadrivalent influenza vaccine, HD – high dose, SD – standard dose

Appendix 3. Forest Plots

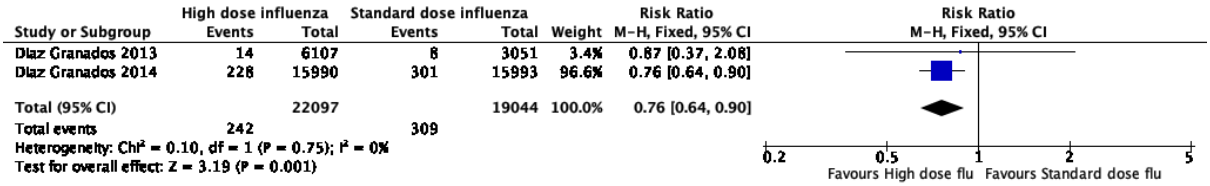

Figure 1. Effect of high-dose influenza vaccine on laboratory-confirmed influenza

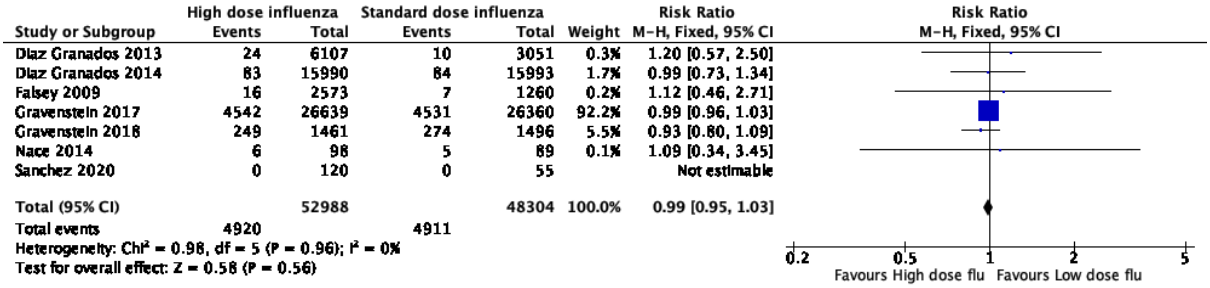

Figure 2. Effect of high-dose influenza vaccine on mortality

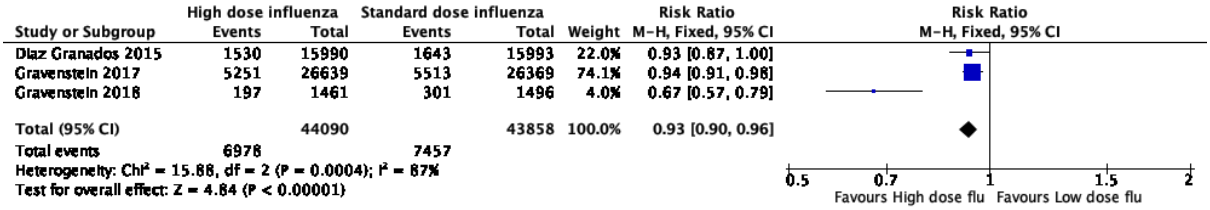

Figure 3. Effect of high-dose influenza vaccine on all-cause hospitalization

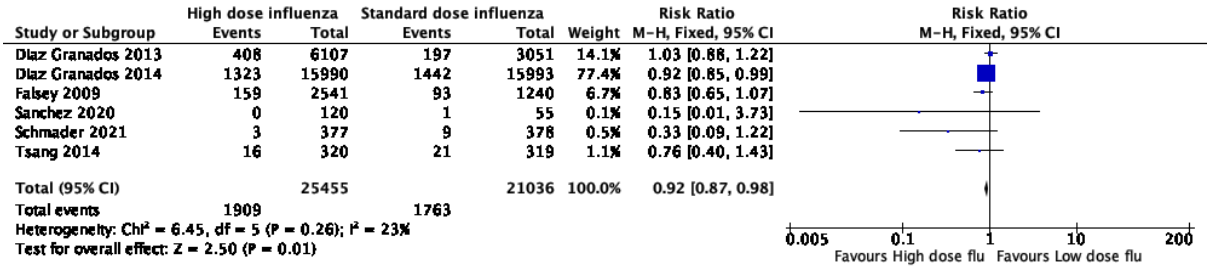

Figure 4. Effect of high-dose influenza vaccine on serious adverse events

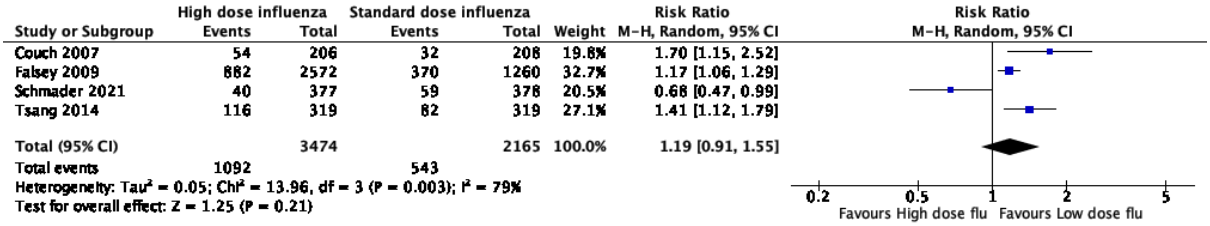

Figure 5. Effect of high-dose influenza vaccine on systemic reactogenic events (combined endpoint)

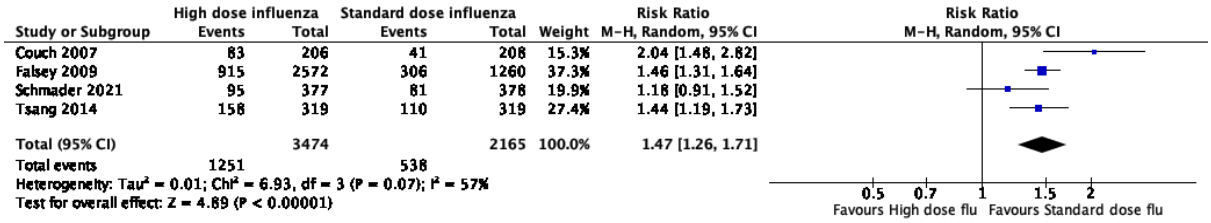

Figure 6. Effect of high-dose influenza vaccine on local reactogenic events (combined endpoint)

Appendix 4. GRADE Evidence Profile

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
Bibliography:

1. Diaz Granados CA, Dunning AJ, Jordanov E, Landolfi V, Denis M, Talbot HK. High-dose trivalent influenza vaccine compared to standard dose vaccine in elderly adults: Safety, immunogenicity and relative efficacy during the 2009–2010 season. Vaccine. 2013;31(6):861-6.
2. Diaz Granados CA, Dunning AJ, Kimmel M, Kirby D, Treanor J, Collins A, et al. Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults. N Engl J Med. 2014;371:635-645.
3. Keitel WA, Atmar RL, Cate TR, Petersen NJ, Greenberg SB, Ruben F, et al. Safety of high doses of influenza vaccine and effect on antibody responses in elderly persons. Arch Intern Med. 2006;166(10):1121-7.
4. Couch RB, Winokur P, Brady R, Belshe R, Chen WH, Cate TR, et al. Safety and Immunogenicity of a High Dosage Trivalent Influenza Vaccine among Elderly Subjects. Vaccine. 2007; 25(44): 7656–7663.
5. Falsey AR, Treanor JJ, Torniporth N, Capellan J, Gorse GJ. Randomized, Double-Blind Controlled Phase 3 Trial Comparing the Immunogenicity of High-Dose and Standard-Dose Influenza Vaccine in Adults 65 Years of Age and Older. J Infect Dis. 2009;200(2):172-80
6. Tsang P, Gorse GJ, Strout CB, Sperling M, Greenberg DP, Ozol-Godfrey A, et al. Immunogenicity and safety of Fluzone® intradermal and high-dose influenza vaccines in older adults ≥65 years of age: A randomized, controlled, phase II trial. Vaccine. 2014;32(21):2507-17.
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8. Gravenstein S, Davidson HE, Taljaard M, Ogarek J, Gozalo P, Han L, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccination on numbers of US nursing home residents admitted to hospital: a cluster-randomised trial. Lancet Respir Med. 2017 Sep;5(9):738-746.
9. Gravenstein S, Davidson HE, Han LF, Ogarek JA, Dahal R, Gozalo PL, et al. Feasibility of a cluster-randomized influenza vaccination trial in U.S. nursing homes: Lessons learned. Hum Vaccin Immunother. 2018; 14(3): 736–743.
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11. Sanchez L, Matsuoka O, Inoue S, Inoue T, Meng Y, Nakama T, et al. Immunogenicity and safety of high-dose quadrivalent influenza vaccine in Japanese adults ≥65 years of age: a randomized controlled clinical trial. Hum Vaccin Immunother. 2020;16(4):858-866.
12. Schmader KE, Liu CK, Harrington T, Rountree W, Auerbach H, Walter EB, et al. Safety, Reactogenicity, and Health-Related Quality of Life After Trivalent Adjuvanted vs Trivalent High-Dose Inactivated Influenza Vaccines in Older Adults: A Randomized Clinical Trial. JAMA Netw Open. 2021;4(1):e2031266.
13. Diaz Granados CA, Robertson CA, Talbot HK, Landolfi V, Dunning AJ, Greenberg DP. Prevention of serious events in adults 65 years of age or older: A comparison between high-dose and standard-dose inactivated influenza vaccines. Vaccine. 2015;33(38):4988-93.
14. Diaz Granados CA, Dunning AJ, Robertson CA, Talbot HK, Landolfi V, Greenberg DP. Efficacy and immunogenicity of high-dose influenza vaccine in older adults by age, comorbidities, and frailty. Vaccine. 2015;33(36):4565-71.
15. Diaz Granados CA, Dunning AJ, Robertson CA, Talbot HK, Landolfi V, Greenberg DP. Effect of Previous-Year Vaccination on the Efficacy, Immunogenicity, and Safety of High-Dose Inactivated Influenza Vaccine in Older Adults. Clin Infect Dis. 2016;62(9):1092-1099.
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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

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)		
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												
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 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)

3. Pneumococcal Vaccine for Adults

Appendix 1. Search Strategy

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

Appendix 2. Study Appraisal

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

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 152mmunocompromising 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. GRADE Evidence Profile

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)

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

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).

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.

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 1. GRADE Evidence Profile

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)				

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	**High-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
	59 per 10,000	**26 per 10,000** (15 to 45)				
	Medium-risk population					
	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.

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 typhoid fever at 2.5 to 3 years	**Moderate**[a]		**RR 0.45** (0.30 to 0.70)	11,384 (1 study)	⊕⊕⊖⊖ **LOW**[g,h] Due to imprecision and indirectness	May reduce incidence of typhoid fever
	4 per 10,000	**1.8 per 10,000** (1.2 to 2.8)				
	High[a]					

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)				
	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%).

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 typhoid fever at 2.5 to 3 years	**Moderate[a]**		**RR 0.11** (0.05 to 0.23)	12,008 (1 study)	⨁⨁⨀⨀ **LOW[c]**	May have little to no reduction incidence of typhoid fever in the adult population
	4 per 10,000	**0.44 per 10,000** (0.2 to 0.92)				
	High[a]					

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)				
	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.

5. HPV Vaccine for Adults

Appendix 1. Search Strategy

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

Appendix 2. 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 lesión CIN
Kjaer 2009 (11)	Protocol 007 (NCT00365716 and NCT00365378): randomised double-blind placebo-controlled phase IIb clinical trial	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	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
	Protocols 013 (NCT00092521) and 015 (NCT00092534): phase III randomised double-blind placebo-controlled clinical trials	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			
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

Appendix 3. GRADE Evidence Profile

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

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 VaIN 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)

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

CI: confidence interval

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.

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.

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.

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	

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio

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.

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.

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

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.

6. Herpes Zoster Vaccine for Adults

Appendix 1. Summary of Findings

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.

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).

7. Tetanus Vaccine for Adults

Appendix 1. 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 2. GRADE Evidence Profile

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. Forest Plots

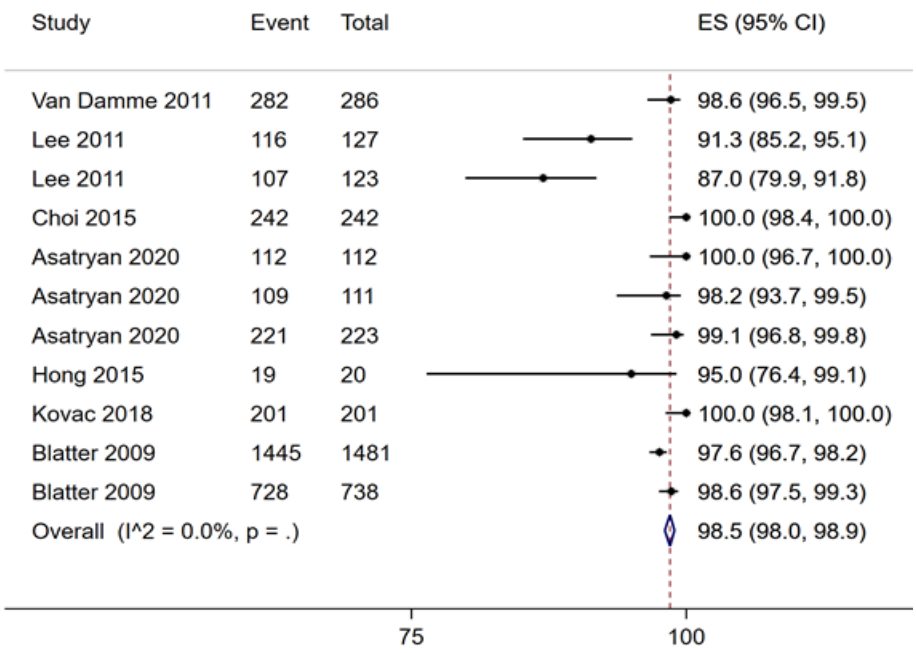

Figure 1. Immune response rates after tetanus vaccination

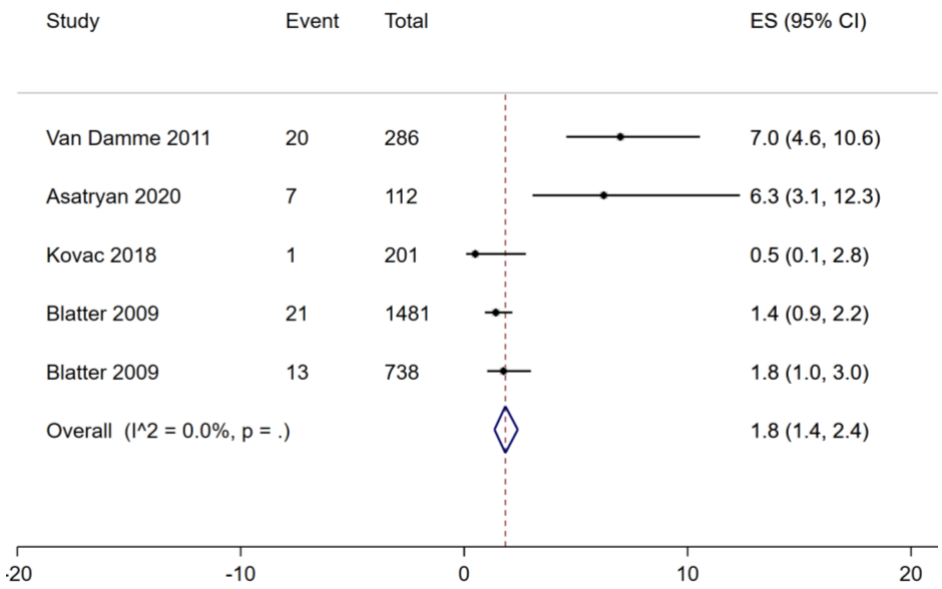

Figure 2. Grade 3 adverse events after tetanus vaccination

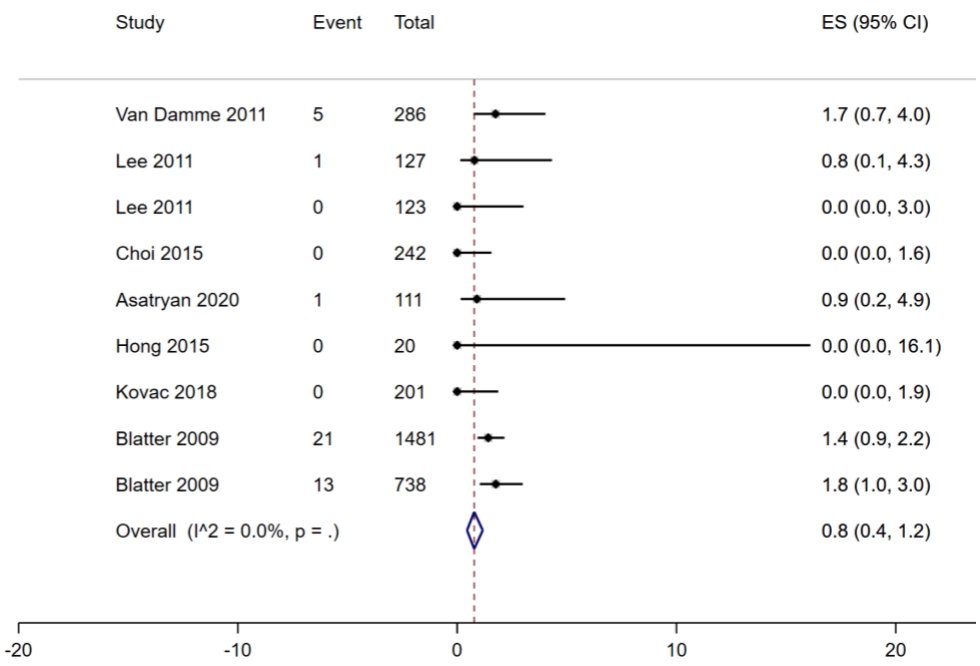

Figure 3. Serious adverse events after tetanus vaccination

8. Measles-Containing Vaccine for Adults

Appendix 1. Search Strategy

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

Appendix 2. 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 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 1 year	100% SCR defined as ≥120 mIU/mL (PRN) 100%
Diaz-Ortega	Mexico	100 (not specified if prevaccinated or unvaccinated)	18–25 years (range enrolled)	2 months 1 year	96% SCR defined as ≥120 mIU/mL (PRN) 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 3. Forest Plots

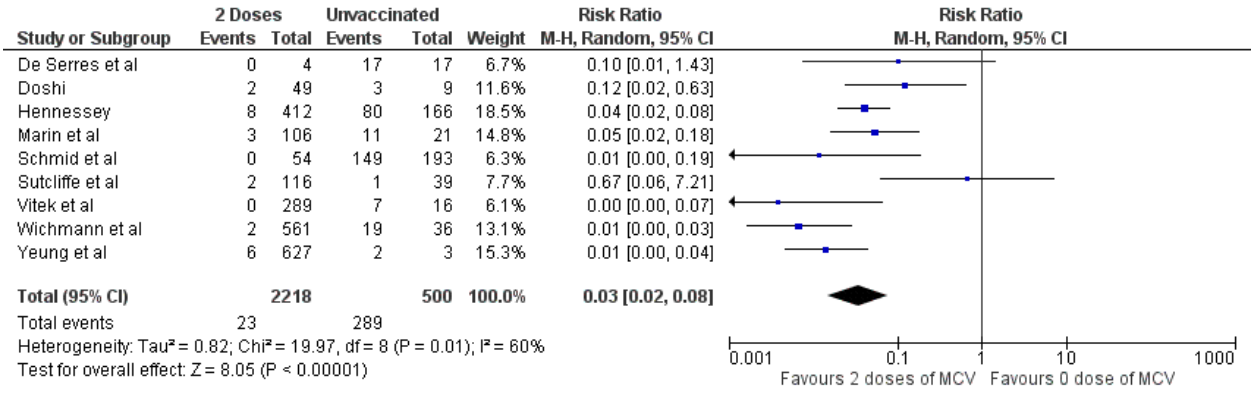

Figure 1. 2-dose MCV vs no vaccine in preventing measles infection

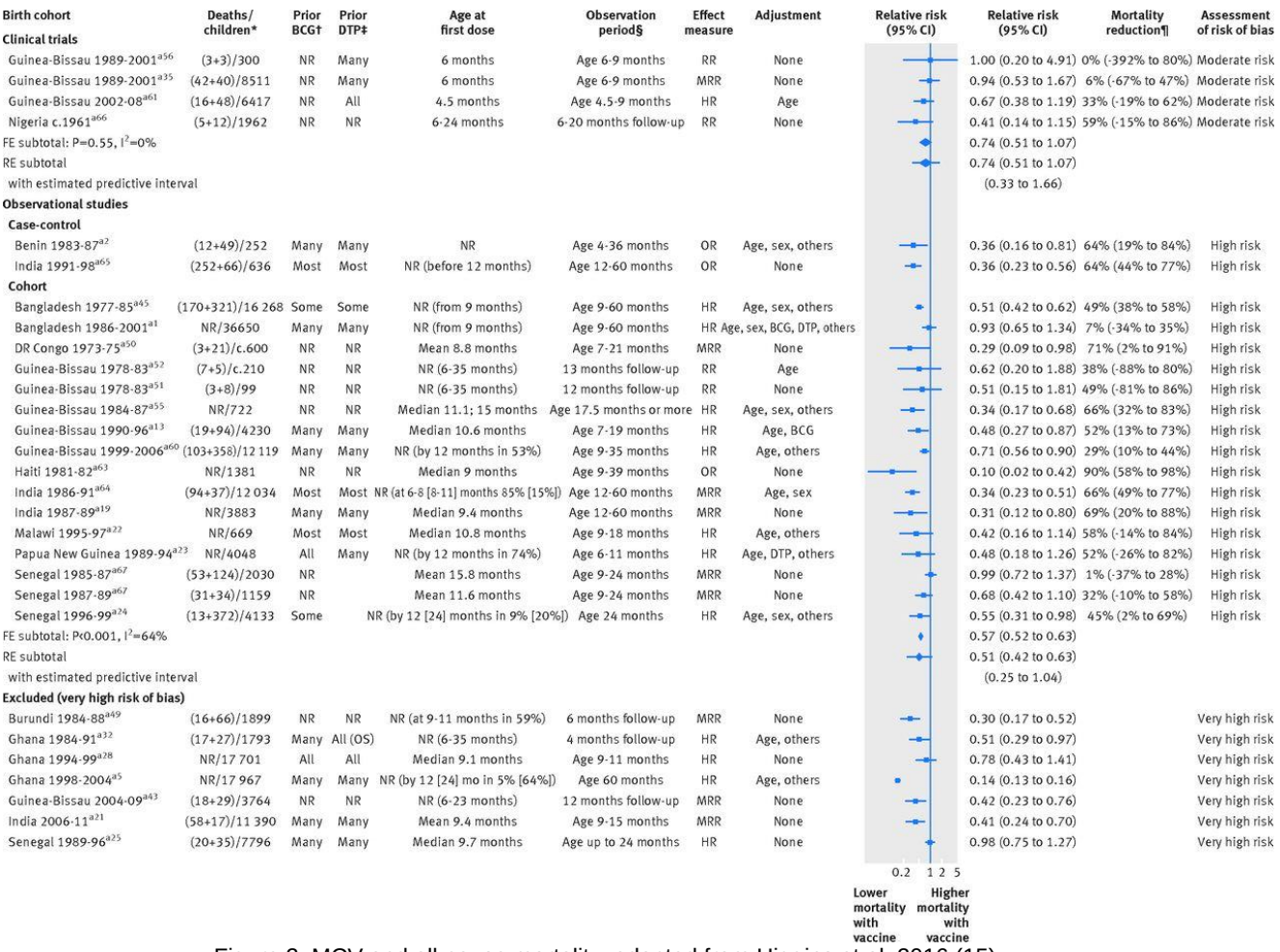

Figure 2. MCV and all-cause mortality, adapted from Higgins et al, 2016 (15)

Appendix 4. GRADE Evidence Profile

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:

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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

CI: confidence interval; **RR**: risk rati

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

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 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

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CONFLICT OF INTEREST DECLARATION

Panelist	COI based on Oversight Committee	Remarks
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Imelda Astre Luna, MD (PFV)	Manageable A for questions 1 to 7 Manageable B for question 8	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)
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