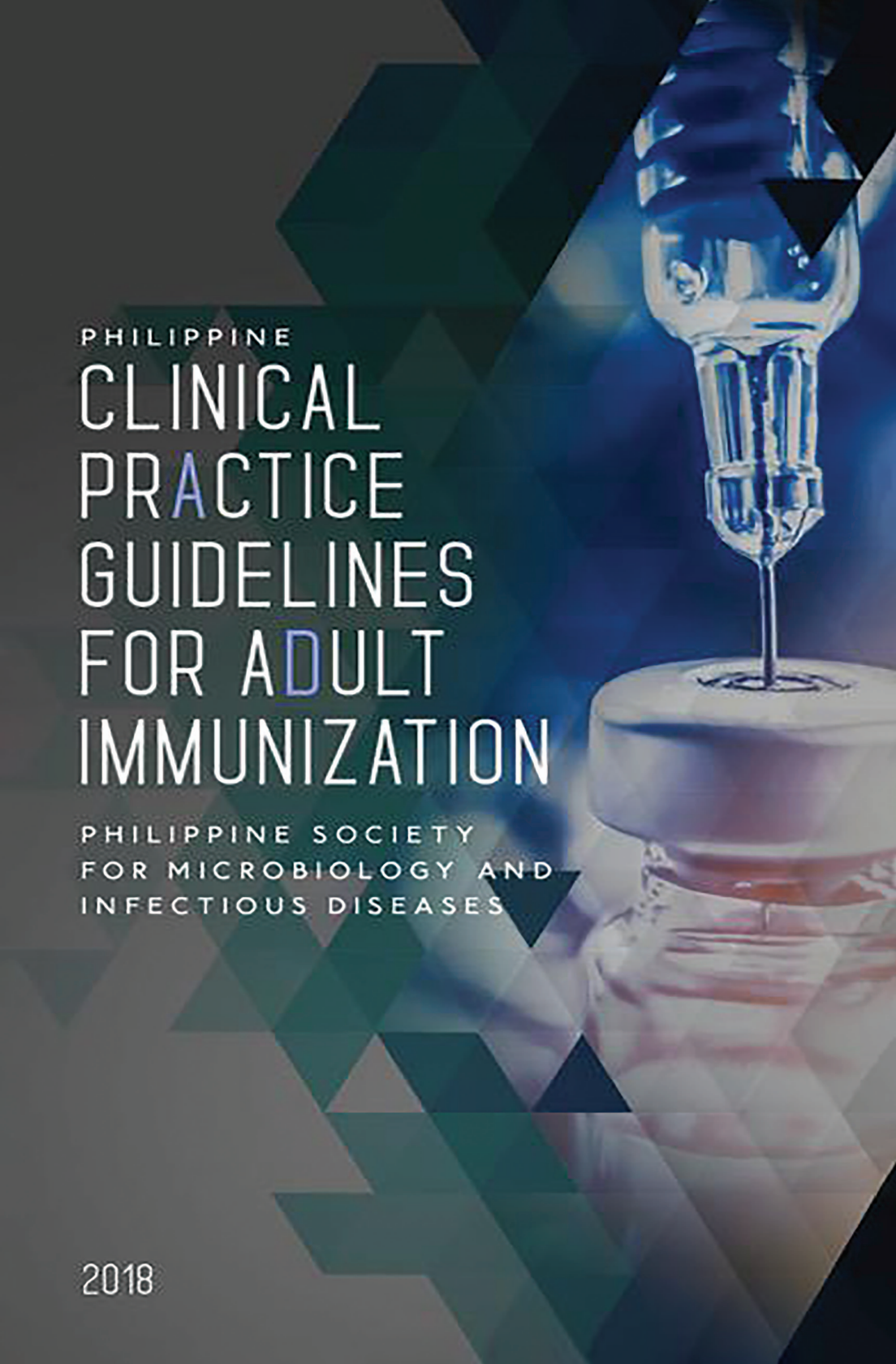

PHILIPPINE

CLINICAL PRACTICE GUIDELINES FOR ADULT IMMUNIZATION

PHILIPPINE SOCIETY FOR MICROBIOLOGY AND INFECTIOUS DISEASES

2018

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ABBREVIATIONS

2vHPV	Bivalent human papilloma virus vaccine
4vHPV	Quadrivalent human papilloma virus vaccine
9vHPV	Nonavalent human papilloma virus vaccine
ACIP	Advisory Committee on Immunization Practices
AEFI	Adverse event following immunization
AGREE II	Appraisal of Guidelines for Research and Evaluation II
AIDS	Acquired immunodeficiency syndrome
AIN	Anal intraepithelial neoplasia
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
BCG	Bacillus Calmette-Guerin
CDC	Center for Disease Control
CFR	Case fatality rate
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
COPD	Chronic obstructive pulmonary disease
CPG	Clinical practice guidelines
CYD	Chimeric yellow fever-dengue virus
DENV	Dengue virus
ELISA	Enzyme-linked immunosorbent assay
ESRD	End-stage renal disease
FDA	Food and Drug Administration
GBS	Guillain-Barre Syndrome
gE	Glycoprotein
GMT	Geometric mean titer

GRADE	**Grading of Recommendations Assessment, Development and Evaluation**
HAI	**Hemagglutination inhibition**
HAV	**Hepatitis A virus**
HBcAb	**Hepatitis B core antibody**
HBsAg	**Hepatitis B surface antigen**
HiB	***Haemophilus influenza b***
HPV	**Human papilloma virus**
HPV	**Human papillomavirus virus**
HZV/HZ	**Herpes zoster virus/herpes zoster**
ID	**Intradermal**
ILI	**Influenza-like illness**
IM	**Intramuscular**
ITT/ITTA	**Intention-to-treat analysis**
JE-CV	**Japanese encephalitis**
JEV	**Japanese encephalitis virus**
LTPS	**Long-term Persistence Study**
MMR	**Measles, mumps, rubella**
MSM	**Men having sex with men**
NAEFI	**National adverse events following immunization**
NNTB	**Number needed to benefit**
NNV	**Number needed to vaccinate**
OCV	**Oral cholera vaccine**
OR	**Odds ratio**
PCV	**Pneumococcal conjugate vaccine**
PDS	**Philippine Dermatologic Society**
PFU	**Plaque-forming units**
PHN	**Post-herpetic neuralgia**
PPSV	**Pneumococcal polysaccharide vaccine**
RCT	**Randomized controlled trials**

RD	**Risk difference**
RR	**Risk ratio**
RZV	**Adjuvanted recombinant zoster virus**
SC	**Subcutaneous**
SPS	**Shingles Prevention Study**
STPS	**Short-term Persistence Study**
TWG	**Technical working group**
VE	**Vaccine efficacy**
VE	**Vaccine efficacy**
VLP	**Virus-like particle**
VZV	**Varicella zoster virus**
WB-BS	**Whole cell B sub-unit**
WC	**Whole cell**
WHO	**World Health Organization**
ZVL	**Live attenuated zoster vaccine**

Executive summary

Through the years, Filipinos have been continually burdened by infectious diseases, including vaccine-preventable diseases, and increasing antibiotic resistance. Thus, immunization should be offered to curb infections that continue to cause a sizeable mortality among the vulnerable adults.

The committee on adult immunizations of the Philippine Society for Microbiology and Infectious Diseases (PSMID) published two handbooks in 2009 and in 2012 to guide physicians and other healthcare workers on the safe and effective administration of vaccines. The committee has upgraded these handbooks to these clinical practice guidelines.

These guidelines incorporate the latest advances and changes in the field of vaccinology and integrate these with expert opinions and evidence-based recommendations using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. It focuses on 16 vaccine-preventable diseases that occur in immunocompetent adult Filipinos and some immunocompromised patients who may benefit with immunization.

These guidelines may be used as a reference while navigating issues regarding vaccines and vaccination. They are intended for the use of physicians, other healthcare workers who vaccinate in different settings, and medical students. These guidelines also serve as a reference for policy makers to guide them in establishing vaccination programs.

For each vaccine included in this document, the technical working group came up with background and foreground questions, while considering the following outcomes: incidence of the disease, clinical progress, microbiological cure, mortality, and hospitalization.

Background questions provide questions that pertain to pathology of the disease, the epidemiology, incidence, and course. The answers to background questions usually introduce the vaccine chapter. Below are some examples of the background questions used in this document:

- What is cholera?
- What are the available vaccines for pneumococcal disease?
- What is the serotype prevalence of human papillomavirus (HPV) in the Philippines?
- What are the common adverse events in the administration of the vaccine?

Foreground questions generally address issues of efficacy, care, and decision making. The members of the technical working group phrase all clinical questions in actionable terms. The questions are in the Population Intervention Comparison Outcome format. Some examples of the foreground questions follow:

- Should hepatitis B vaccine be administered routinely in immunocompetent adults not previously exposed or with unknown exposure status?
- Should influenza vaccine be administered to immunosuppressed adults?
- How effective is the HPV vaccine in preventing cervical cancer and anogenital warts among immunocompetent females?

To facilitate the review of the technical working group, the keywords to be used for searching databases were selected and the relevant articles were retrieved and uploaded. The technical

working group collectively reviewed the evidence profiles for each question, and, using a nominal group technique, determined the overall quality of evidence for both descriptive and actionable questions. The recommendation statements were drafted, and these were presented to an expert panel for comments. Then, a group gave consensus on the recommendations.

In coming up with these clinical practice guidelines, the technical working group used two methods in developing the recommendations: the Appraisal of Guidelines for Research and Evaluation II tool for existing guidelines in other settings; and *de novo* development of statements when there are no available existing published guidelines.

Category	Interpretation
Strength of recommendation	
Strong	We believe that the desirable effects (benefits) clearly outweigh the undesirable effects (risks).
Weak	We believe that the desirable and undesirable effects are closely balanced and uncertain. Thus, evidence may change the balance of risk to benefit.
No recommendation	We believe that further research is required before any recommendation can be made.
Quality of evidence	
High	There is consistent evidence from well-performed randomized control trials (RCTs) or strong evidence from unbiased observational studies. We are confident that further research is very unlikely to change the estimate of the effect.
Moderate	There is evidence from RCTs with important limitations or moderately strong evidence from unbiased observational studies. We are confident that further research is likely to have an important impact on the estimate of the effect.
Low	There is evidence for ≥1 critical outcome from observational studies, from RCTs with serious flaws, or from indirect evidence. Our confidence in the effect estimate is limited. Thus, further research is very likely to change the estimate
Very low	There is evidence for ≥1 or critical outcome from unsystematic clinical observations or very indirect evidence. We are uncertain of the effect estimate.

The recommendations are limited to Filipinos presently residing in the country. They do not cover those who will migrate to other countries or those who will work abroad for a prolonged period of time. Detailed description of each of the vaccine-preventable disease, dosing of vaccines, evidence summaries that support the recommendation, and tables of local disease statistics can be found in the full text of the guideline. The committee acknowledges that this is not the only approach to vaccination, but fully supports the safe delivery of vaccines.

Updates to content

- New information on simultaneous vaccination
- 4-day grace period for multi-dose vaccines
- Live vaccines and antibody-containing products should not be administered simultaneously, otherwise, serologic testing should be done
- Interchangeability of single-component vaccines from different manufacturers
- Enhanced definition of precautions
- Vaccination of hospitalized patients
- Discussion on vaccine safety

Lastly, compared to other and previous PSMID guidelines, the format of these guidelines has been revised. Each vaccine is being discussed in a tabulated form where the evidence is discussed and the strength of recommendations is stated. Where the technical working group deemed it necessary to expound on the findings, further discussion can be found after the initial tables for each vaccine. The technical working group acknowledges that the conceptualization of the format of the Philippine clinical practice guidelines was adapted from the adult immunization guidelines of the Singapore Infectious Diseases Society, which has granted us permission to use such a format.

Chapter 1: General principles of adult vaccination

Immunity

Immunity is the ability of the body to tolerate the presence of material indigenous to the body (self) and to eliminate foreign material (non-self).[1] This ability provides protection from infectious diseases, usually indicated by the presence of an antibody. Immunization is the process of making a person immune or resistant to an infectious disease, usually through vaccination.[2] (See Table 1A for more information.)

An antigen is a live or inactivated substance (e.g., protein, polysaccharide) capable of producing an immune response.

Antibodies are protein molecules produce by B-lymphocytes in response to specific antigens found on the surface of pathogens.

Table 1A. Basic mechanisms for acquiring immunity

	Active immunity	Passive immunity
Acquisition of protection	Produced by the person's own immune system	Transferred from another person or animal
Duration of protection	Permanent	Temporary
Source	Occurs after infection or vaccination through the production of immunologic memory	Transplacental Blood products Homologous pooled human antibody (immunoglobulin) Homologous human hyperimmune globulin Plasma products Heterologous hyperimmune serum (antitoxin)

Types of vaccines[3]

Live attenuated vaccines

- Weakened form of the "wild" virus or bacteria
- Must replicate to be effective
- Immune response similar to natural infection
- Usually effective with one dose
- Severe reactions are possible
- Interference from circulating antibody
- Heat labile

Inactivated vaccines

- Cannot replicate, and not live
- Minimal interference from circulating antibody
- Not as effective as live vaccines
- Require multiple (3 to 5) doses
- Immune response mostly humoral
- Antibody titer falls over time requiring booster doses

Following are the types of inactivated vaccines.

- Whole cell vaccines: from whole organisms that have been inactivated by chemical, thermal, or other means
- Fractional: from components of the whole organism
- Toxoids: inactivated toxins of toxin-producing bacteria
- Polysaccharide vaccines: polysaccharide is linked to proteins to increase effectiveness

Table 1B. Examples of different types of vaccines

Type of vaccine	Examples
Live attenuated	Viral: measles-mumps-rubella, varicella, herpes zoster, yellow fever, oral polio, influenza nasal spray, rotavirus, dengue virus Bacterial: Bacille Calmette-Guérin, oral typhoid
Inactivated whole cell	Viral: influenza, polio, rabies, hepatitis A, Japanese encephalitis Bacterial: pertussis, typhoid, cholera
Fractional	Viral: hepatitis B, influenza, acellular pertussis, human papillomavirus Bacterial: typhoid vaccine
Toxoid	Diphtheria toxoid, tetanus toxoid
Conjugate polysaccharide	Pneumococcal, meningococcal, *Haemophilus influenzae* type b (Hib)

Timing and spacing of vaccines

To optimize maximum benefit from vaccines, the recommended schedules should be followed as closely as possible.[4] Vaccine doses should not be administered at intervals less than these minimum intervals. Doses administered too close together or at too young an age can lead to a suboptimal immune response.[5]

In the case of multi-dose vaccines,[6,7] vaccine doses administered ≤4 days prior to the minimum interval are considered valid. This is known as the "grace period."*

However, this 4-day guideline is not applicable to the rabies vaccine schedule. Doses of any vaccine administered ≥5 days earlier than the minimum interval or age should not be counted as valid doses and should be repeated as age appropriate. The repeat dose should be spaced after the invalid dose by the recommended minimum interval. *(Best Practice Statement)*

Simultaneous administration of vaccines[5] refers to the administration of more than one vaccine on the same clinic day, at different anatomic sites, and not combined in the same syringe. The rationale behind simultaneously administering all vaccines for which a person is eligible at the time of a visit increases the probability that the patient will be fully vaccinated. With some exceptions, same-day administration of widely used vaccines, whether live or inactivated, does not diminish seroconversion rates when vaccines are given separately; rates for adverse reactions are also like those observed when vaccines are administered separately.[8] However, the systematic review did not provide clear evidence on the specific distance between injection sites.

In persons with functional or anatomic asplenia, pneumococcal conjugate vaccine (PCV13) should be given first and then followed by meningococcal conjugate vaccine 4 weeks later.[3] These two vaccines should not be administered simultaneously based on immunogenicity studies that showed reduced antibody concentrations for 3 serotypes of pneumococcus (subtypes 4, 6B, and 18C) when a pneumococcal polyvalent vaccine with antigens from seven common serotypes of *Streptococcus pneumoniae* was administered simultaneously with quadrivalent meningococcal conjugate vaccine.

In non-simultaneous administration, there is no evidence that inactivated vaccines interfere with the immune response to other inactivated vaccines or to live vaccines. Any inactivated vaccine can be administered either simultaneously or at any time before or after a different inactivated or live vaccine. The 2 exceptions are a 4-week interval between PCV13 and quadrivalent polysaccharide-protein conjugate vaccine in a person with anatomic asplenia and the separation of doses between PCV13 and pneumococcal polysaccharide vaccine (PPSV23, 6-12 months recommended for non-high risk; 8 weeks' minimum, if PCV13 is given first, and 1 year minimum in adults if PPSV23 is given first).

Two live vaccines should always be administered on the same day. Otherwise, the live vaccines should be separated by at least 4 weeks to minimize the potential risk for interference.

If 2 such vaccines are separated by <4 weeks, the second vaccine administered should not be counted and the dose should be repeated at least 4 weeks later. The 4-day grace period discussed earlier, which may be used to shorten the minimum interval between doses of the same vaccine, should not be applied to this 4-week interval between 2 different live vaccines.

An exception is yellow fever vaccine, which can be given <4 weeks after measles-mumps-rubella (MMR) or univalent varicella vaccine.

Regarding the timing of administration of vaccines and blood products,[9] inactivated vaccines interfere less with antibody-containing products. The administration of inactivated vaccines and toxoids either simultaneously with or at any interval before or after receipt of an antibody-containing product should not substantially impair development of a protective antibody response. (See Tables 1C and 1D.)

Table 1C. Guidelines for administering antibody-containing products[a] and vaccines[9]

Type of administration	Products administered	Recommended minimum interval between doses

Simultaneous (during the same clinic day)	Antibody-containing products and inactivated antigen		Can be administered simultaneously at different anatomic sites or at any time interval between doses
	Antibody-containing products and live antigen		Should not be administered simultaneously[b] If simultaneous administration of measles-containing vaccine or varicella vaccine is unavoidable, administer at different sites and revaccinate or test for seroconversion after the recommended interval.
Non-simultaneous	Administered first	Administered second	
	Antibody-containing products	Inactivated antigen	No interval necessary
	Inactivated antigen	Antibody-containing products	
	Antibody-containing products	MMR vaccine, varicella vaccine and combined measles-mumps-rubella-varicella (MMRV) vaccine antigens	Dose related[b, c]
	MMR vaccine, varicella vaccine, and combined MMRV vaccine antigens	Antibody-containing products	2 weeks[b]

Reference: Kroger, A. T., Duchin, J., & Vázquez, M. (2017). General best practice guidelines for immunization: Best practices guidance of the advisory committee on immunization practices (ACIP). Retrieved from www.cdc.gov/vaccines/hcp/acip-recs/general-recs/downloads/general-recs.pdf

[a] Blood products that contain substantial amounts of immune globulin include intramuscular, subcutaneous, and intravenous immune globulin, specific hyperimmune globulin (e.g., hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, and rabies immune globulin), whole blood, packed red blood cells, plasma, and platelet products.

[b] Following are the exceptions to these recommendations: yellow fever vaccine; rotavirus vaccine; oral Ty21a typhoid vaccine; live attenuated influenza vaccine; and zoster vaccine. These live attenuated vaccines can be administered at any time before or after or simultaneously with an antibody-containing product.

[c] The duration of interference of antibody-containing products with the immune response to the measles component of a measles-containing vaccine, and possibly a varicella vaccine, is dose related. See Table 1D.

Table 1D. Recommended intervals between administration of antibody-containing products and measles- or varicella-containing vaccine, by product and indication for vaccination[9]

Product/indication	Dose (mg IgG/kg) and route[a]	Recommended interval before measles- or varicella-containing vaccine[b] administration (months)
Blood transfusion		
Red blood cells, washed	10 ml/kg, negligible IgG/kg intravenous	None
Red blood cells, adenine-saline added	10 ml/kg (10 mg IgG/kg) intravenous	3
Packed red blood cells (hematocrit 65%)[c]	10 ml/kg (60 mg IgG/kg) intravenous	6
Whole blood (hematocrit 35%-50%)	10 ml/kg (80-100 mg IgG/kg) intravenous	6
Plasma/platelet products	10 ml/kg (160 mg IgG/kg) intravenous	7
Botulinum Immune Globulin Intravenous (Human)	1.0 ml/kg (50 mg IgG/kg) intravenous	6
Cytomegalovirus immune globulin intravenous	150 mg/kg maximum	6
Hepatitis A immune globulin		
Contact prophylaxis	0.1 ml/kg (3.3 mg IgG/kg) intramuscular	3
International travel, <2-month stay	0.1 ml/kg (3.3 mg IgG/kg) intramuscular	
International travel, ≥2-month stay	0.2 ml/kg (10 mg IgG/kg) intramuscular	
Hepatitis B immune globulin	0.06 ml/kg (10 mg IgG/kg) intramuscular	
Immune globulin intravenous		
Replacement therapy for immune deficiencies[d]	300-400 mg/kg intravenous[d]	8

Immune thrombocytopenic purpura treatment	400 mg/kg intravenous	
Post-exposure varicella prophylaxis		
Post-exposure measles prophylaxis for immunocompromised contacts		
Immune thrombocytopenic purpura treatment	1,000 mg/kg intravenous	10
Kawasaki disease	2 g/kg intravenous	11
Measles prophylaxis IG		
Standard (i.e., non-immunocompromised) contact	0.50 ml/kg (80 mg IgG/kg) intramuscular	6
Monoclonal antibody to respiratory syncytial virus F protein (e.g. Synagis [MedImmune])[e]	15 mg/kg intramuscular	None
Rabies immune globulin	20 IU/kg (22 mg IgG/kg) intramuscular	4
Tetanus immune globulin	250 units (10 mg IgG/kg) intramuscular	3
Varicella immune globulin	125 units/10 kg (60-200 mg IgG/kg) intramuscular, maximum 625 units	5

Reference: Kroger, A. T., Duchin, J., & Vázquez, M. (2017). General best practice guidelines for immunization: Best practices guidance of the advisory committee on immunization practices (ACIP). Retrieved from www.cdc.gov/vaccines/hcp/acip-recs/general-recs/downloads/general-recs.pdf

Abbreviations
IgG: immune globulin G
IGIV: intravenous immune globulin
mg IgG/kg = milligrams of immune globulin G per kilogram of body weight

[a] This table is not intended for determining the correct indications and dosages for using antibody-containing products. Unvaccinated persons might not be protected fully against measles during the entire recommended interval, and additional doses of immune globulin or measles vaccine might be indicated after measles exposure. Concentrations of measles antibody in an immune globulin preparation can vary by manufacturer's lot. Rates of antibody clearance after receipt of an immune globulin preparation might also vary. Recommended intervals are extrapolated from an estimated half-life of 30 days for passively acquired antibody and an observed interference with the immune response to measles vaccine for 5 months after a dose of 80 mg IgG/kg.

[b] Does not include zoster vaccine. Zoster vaccine may be given with antibody-containing blood products.

[c] Assumes a serum immunoglobulin G concentration of 16 mg/ml.

[d] Measles vaccination is recommended for children with mild or moderate immunosuppression from HIV infection, and varicella vaccination may be considered for children with mild or moderate immunosuppression from HIV infection. However, both are contraindicated for persons with severe immunosuppression from HIV or any other immunosuppressive disorder.

[e] Contains antibody only to respiratory syncytial virus.

Single-component vaccines from different manufacturers are interchangeable. Vaccination should not be deferred because the brand used for previous doses is not available or is unknown. Any FDA-approved vaccine brand may be used to continue or complete the series.

It is not necessary to restart the series of any vaccine due to extended intervals between doses. However, for oral typhoid vaccine, the series should be repeated if the four-dose series is extended to more than 3 weeks.[3,9]

Inactivated and live vaccines generally may require multiple doses and may require periodic boosting to maintain immunity, as recommended.[3]

Unless licensed for mixing, individual vaccines should not be mixed in the same syringe.

Contraindications and precautions to vaccination

Please see individual vaccines for their contraindications and precautions. The presence of a moderate or severe acute illness with or without a fever is a precaution to administration of all vaccines.

A contraindication is a condition in a recipient which greatly increases the chance of a serious adverse reaction, hence should not be given.[1,9] For example, MMR should not be administered to severely immunocompromised persons (CD4 ≤200 cells/ul). (See Table 1E for invalid contraindications.)

A precaution is a condition in a recipient which may increase the chance or severity of an adverse event, might cause diagnostic confusion, or might compromise the ability of the vaccine to produce immunity. One example is administering a measles vaccine to a person with passive immunity to measles from a blood transfusion.[1,9]

Certain vaccines may be given to an immunocompromised individual. However, response may be dependent on the severity of immunosuppression.[10] The advice of a specialist should be sought.

Following are the permanent contraindications to vaccination[3]: severe allergic reaction to a vaccine component or following a prior dose; and encephalopathy not due to another identifiable cause occurring within 7 days of pertussis vaccination.

Hospitalization should be an opportunity to provide recommended vaccinations. Efforts should be made to vaccinate patients during their hospitalization or at the time of their discharge.

Table 1E. Invalid contraindications to vaccination[3,9]

Vaccine	Conditions commonly misperceived as contraindications or precautions (i.e., vaccines may be given under these conditions)
General for all vaccines, including DTaP (diphtheria and tetanus toxoids with	Mild acute illness with or without fever

acellular pertussis) vaccine, pediatric diphtheria and tetanus toxoids vaccine, adult Td (tetanus and diphtheria toxoids), adolescent-adult Tdap (tetanus and diphtheria toxoids with acellular pertussis), inactivated polio, MMR, Hib, hepatitis A, hepatitis B, varicella, rotavirus, PCV13, inactivated influenza, PPSV23, MenACWY, meningococcal polysaccharide, HPV, and herpes zoster vaccines	Mild to moderate local reaction (i.e., swelling, redness, soreness); low-grad or moderate fever after previous dose Lack of previous physical examination in well-appearing person Current antimicrobial therapy [a] Convalescent phase of illness Preterm birth (hepatitis B vaccine is an exception in certain circumstances) [b] Recent exposure to an infectious disease History of penicillin allergy, other non-vaccine allergies, relatives with allergies, or receiving allergen extract immunotherapy History of Guillain-Barré syndrome[c]

Abbreviations: DT = diphtheria and tetanus toxoids; DTP = diphtheria toxoid, tetanus toxoid, and pertussis; DTaP = diphtheria and tetanus toxoids and acellular pertussis; GBS = Guillain-Barré syndrome; HBsAg = hepatitis B surface antigen; Hib = *Haemophilus influenzae* type b; HIV = human immunodeficiency virus; HPV = human papillomavirus; IIV = inactivated influenza vaccine; IPV = inactivated poliovirus; LAIV = live, attenuated influenza vaccine; MenACWY = quadrivalent meningococcal conjugate vaccine; MMR = measles, mumps, and rubella; MPSV4 = quadrivalent meningococcal polysaccharide vaccine; PCV = pneumococcal conjugate vaccine; PPSV23= pneumococcal polysaccharide vaccine; Td = tetanus and diphtheria toxoids; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.
(a) Antibacterial drugs might interfere with Ty21a oral typhoid vaccine, and certain antiviral drugs might interfere with varicella-containing vaccines and LAIV4.
(b) Hepatitis B vaccination should be deferred for infants weighing <2,000 g if the mother is documented to be HBsAg negative. Vaccination should commence at chronological age 1 month or at hospital discharge. For infants born to HBsAg-positive women, hepatitis B immune globulin and hepatitis B vaccine should be administered within 12 hours after birth, regardless of weight.
(c) An exception is Guillain-Barré syndrome within 6 weeks of a dose of influenza vaccine or tetanus-toxoid–containing vaccine, which are precautions for influenza vaccines and tetanus-toxoid containing vaccines, respectively.

Reference: Kroger, A. T., Duchin, J., & Vázquez, M. (2017). General best practice guidelines for immunization: Best practices guidance of the advisory committee on immunization practices (ACIP). Retrieved from www.cdc.gov/vaccines/hcp/acip-recs/general-recs/downloads/general-recs.pdf

Screening for contraindications and precautions to vaccination[3]

If the recipient answers "yes" to any one of the following questions, then a more thorough evaluation should be done prior to vaccination.

1. Are you sick today?

2. Do you have allergies to medications, food, or any vaccine?

3. Have you had a serious reaction to a vaccine in the past?

4. Do you have a seizure, brain, or nerve problem?

5. Do you have other co-morbid conditions such as asthma, lung disorder, heart disease, kidney disease, diabetes, or blood disorder?

6. Do you have cancer, leukemia, AIDS, or any other immune system problem?

7. Do you take cortisone, prednisone, other steroids or anticancer drugs, or had x-ray treatments in the past 3 months?

8. Did you receive blood transfusion or other blood products, or been given a medicine called immunoglobulin, in the past year?

9. Are you pregnant, or is there a chance that you could become pregnant during the next month?

10. Have you received any vaccinations in the past 4 weeks?

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Chapter 2: Vaccine safety

The contribution of vaccination to public health is undeniable. But like any other pharmaceutical product, vaccine is not fully safe nor is it completely effective. While most of the adverse events are minor and self-limiting, there are also serious and life-threatening health effects. Keeping vaccines safe is of paramount importance to building public trust and it starts with pharmacovigilance. The Department of Health encourages active surveillance of Adverse Events Following Immunization (AEFI), regardless of causality to vaccines.

AEFI are any untoward medical occurrences which follow immunization and which do not necessarily have a causal relationship with the usage of the vaccine.[1] AEFI could be symptoms, diseases, or abnormal laboratory findings. WHO divides AEFI into vaccine related, immunization related, or coincidental. (See Table 2.)

The difference between a reaction related to the vaccine and an adverse event which can have other causes should be explained to patients. This ensures that they have all information they need to make an informed decision about receiving immunization for themselves. In case of AEFI, vaccine recipients should be advised to report to National Adverse Events Following Immunization (contact number: 651 7800, local 2930) using the appropriate form.

Table 2. Categorization of adverse events following immunization (AEFI)[1]

Cause-specific category of AEFI	Definition	Example
Vaccine		
Product-related reaction	An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product	Extensive limb swelling following vaccination
Quality defect-related reaction	An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product including its administration device as provided by the manufacturer	Failure of the manufacturer to completely inactivate a lot of inactivated polio vaccine leads to cases of paralytic polio.
Immunization		
Error-related reaction	An AEFI that is caused by inappropriate vaccine handling prescribing or administration and thus by its nature is preventable	Non-sterile injection, reconstitution error, vaccine stored or transported incorrectly
Anxiety-related reaction	An AEFI arising from anxiety about the immunization	Vasovagal syncope in an adolescent following immunization

Inconsistent with causal association to immunization		
Coincidental event	An AEFI that is caused by something other than the vaccine product, immunization error or anxiety.	A fever occurs at the time of the vaccination (temporal association), but it is in fact caused by malaria.

Adverse events[2] can be: minor, that which occur within a few hours of injection, resolve after a short period of time, and pose little danger; severe, or that which result in long-term problems; or serious. The third is a regulatory term that refers to events causing a potential risk to the health or life of the recipient, leading to hospitalization, disability or incapacity, congenital abnormalities or birth defects, or death.

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Philippine Integrated Disease Surveillance and Response

Case Investigation Form

(Only for Serious AEFI - Death/ Disability/ Hospitalized/ Cluster of Minor AEFI)

Version 2015

Name of DRU: **Address:**					**Type:** ☐RHU ☐CHO ☐Gov't Hospital ☐Private Hospital ☐Clinic ☐Gov't Laboratory ☐Private Laboratory ☐Airport/Seaport		
I. PATIENT INFORMATION	EPIID Number	Patient's First Name		Middle Name		Last Name	
Complete Address:				District		ILHZ	
Sex: ☐ Male ☐ Female	Date of Birth: *MM/ DD/ YYYY*	Age	☐ Days ☐ Months ☐ Years	Height: _____ cm	Weight: _____ kg	Date Admitted/ Seen/Consult :	*MM DD, YYYY*
Name of hospital/health facility:				Address :		Admitted? ☐ Yes ☐ No ☐ Unknown	
Date onset of AEFI/ present illness	*MM/ DD/ YYYY* TIME *(hh:min:sec)* ___:___:___ AM / PM			Date next higher level notified	____/____/____	Date of Investigation	____/____/____
Name & Designation of Reporter				Institution:		Contact #/email:	
Name & Designation of Investigator				Institution		Contact #/email:	

II. SUSPECTED VACCINE

Suspected Vaccine/s *(Please indicate Generic and Brand Name)*	Date of Vaccination	Time of Vaccination	Dose No. *(e.g.1st, 2nd, 3rd)*	Site of Injection *(Indicate left or right)*	Batch/ Lot No.	Name of Manufacturer	Expiry Date	Name of Vaccinator	Profession of Vaccinator

Diluent	Date of Reconstitution	Time of Reconstitution	Batch/Lot No.	Expiry Date	Name of Vaccinator

Vaccination Center/Facility:

Vaccination Session: ☐ Routine session ☐ Clinic ☐ Mass Campaign ☐ School – based ☐ Others, _____

III. TYPE OF AEFI:

- ☐ Anaphylactoid reaction (acute hypersensitivity reaction)
- ☐ Anaphylaxis
- ☐ Brachial neuritis
- ☐ Disseminated BCG infection
- ☐ Encephalopathy
- ☐ Hypotonic-Hyporesponsive Episode (HHE)
- ☐ Injection site abscess
- ☐ Intussusception
- ☐ Lymphadenitis
- ☐ Osteitis/ Osteomyelitis
- ☐ Persistent (> 3hours) inconsolable crying
- ☐ Seizures
  - ○ Febrile ○ Afebrile
- ☐ Sepsis
- ☐ Severe local reaction
  - ○ Pain, redness and/or swelling of > 3 days
  - ○ Swelling beyond the nearest joint
- ☐ Thrombocytopenia
- ☐ Toxic Shock Syndrome
- ☐ Others (specify)

_____
_____
_____

Case Definition:

- **Adverse event following immunization** is defined as any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.

- **Serious AEFI** is defined as an event that is causing a potential risk to the health/life of a recipient leading to hospitalization, disability/incapacity, congenital abnormalities/birth defects or death.

Philippine Integrated Disease Surveillance and Response

Case Report Form

ADVERSE EVENTS FOLLOWING IMMUNIZATION

Ver. 2015

Name of DRU: _____

Address: _____

Type: ☐RHU ☐CHO ☐Gov't Hospital ☐Private Hospital ☐Clinic ☐Private Laboratory ☐Public Laboratory ☐Seaport/Airport

Patient No.	Patient's Full Name	Age	Sex	Date of Birth	Complete Address	Signs and Symptoms/ Adverse Event	Suspected Vaccine & Dose No. (1st,2nd,3rd)	Lot Batch #/ Expiry date	Date & Time Vaccinated	Name of Vaccinator/ Profession	Date and Time Onset of Illness	Type of AEFI	Outcome
	Indicate First name, Middle name, Last name	*Age*: Indicate D - days M - months Yr. - years *Sex*: F - Female M - Male		mm/dd/yy	Specify Street/Purok/ Subdivision, House #, Barangay, Municipality/ City, Province	Indicate signs and symptoms or adverse event experienced by the case	Indicate suspected vaccine and dose number	Indicate Lot Batch # and expiry date suspected vaccine/s	mm/dd/yy	Indicate full name and profession of the vaccinator	mm/dd/yy	Indicate if Serious or Minor AEFI	A - Alive D - Died (specify date) U - Unknown

Case Definition:

- **Adverse event following immunization** is defined as any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease.

NOTE: *AEFIs to be reported include those that occur within 30 days following vaccination. This form should be completely accomplished by the RHU Nurse/ Hospital staff / DSC of the reporting DRU and submitted to the next higher administrative level every week.*

TYPE of AEFI:

- **Serious AEFI** is defined as an event that is causing a potential risk to the health/life of a recipient leading to hospitalization, disability/incapacity, congenital abnormalities/birth defects or death.
- **Minor AEFI** is an event that is not "serious" and does not pose a potential risk to the health of the recipient. *Cluster of minor AEFIs* should be investigated for causality assessment. A **cluster** of AEFI is defined as two or more cases of the same or similar events related in time, geography, and/ or vaccine administered. *(For Serious AEFI and Cluster of Minor AEFIs, a PIDSR AEFI Case Investigation Form and Guide Questions on Investigation should also be filled-out.)*

LIST OF REPORTABLE SERIOUS AEFIs

Reportable Serious AEFI	Onset time interval*
• Anaphylactoid reaction (acute hypersensitivity reaction) • Anaphylaxis • Persistent (more than 3 hours) inconsolable screaming • HHE • Toxic shock syndrome (TSS)	Within 24 to 48 hours of immunization
• Severe local reaction • Sepsis • Injection site abscess (bacterial/sterile)	Within seven days of immunization
• Seizures, including febrile seizures (6-12 days for measles/MMR; 0-2 days for DTP) • Encephalopathy (6-12 days for measles/MMR; 0-2 days for DTP)	Within 14 days of immunization
• Acute flaccid paralysis (4-30 days for OPV recipient; 4-75 days for contact) • Brachial neuritis (2-28 days after tetanus containing vaccine) • Intussusception (commonly within 21 days after rota vaccines) • Thrombocytopenia (15-35 days after measles/MMR)	Within 3 months of immunization
• Lymphadenitis • Disseminated BCG infection • Osteitis/Osteomyelitis	Between 1 and 12 months after BCG immunization
• Death • Hospitalization • Disability • Any other severe and unusual events that are thought by health workers or the public to be related to immunization	No time limit
*Onset time interval information it is recommended to refer to the Brighton Collaboration case definitions (www.brightoncollaboration.org) and WHO position papers and observed rates information sheets (available at http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/index.html).	

Chapter 3: Specific vaccines for adults

Cholera vaccine

Cholera is an acutely dehydrating, watery diarrheal disease caused by ingestion of toxigenic serogroups (O1 and O139) by *Vibrio cholerae.*[1] It results in massive loss of intravascular and extracellular fluids and electrolytes in the small intestine, leading to severe dehydration and shock. Cholera is a disease of poverty and is endemic in developing countries with poor sanitation and lack of clean drinking water. Any age group may be affected, but young children are mostly affected.[1,2]

V. cholerae is a gram-negative, rod-shaped organism that is mainly waterborne. More than 200 serogroups were identified, but serogroups O1 and O39 cause epidemic disease.[1,2] O1 serogroup has two biotypes: Classical and El Tor. Both biotypes can be further classified into Ogawa and Inaba serotypes.[1] There is no proven cross-protection between two serogroups, and immunity to *V. cholerae* infection is group-specific.[1,2]

Cholera causes an estimated 1.4 to 4.3 million cases and 28,000 to 142,000 deaths per year worldwide.[1] Over 1.4 billion persons are at risk globally. While epidemic cholera attracts attention and accounts for most of the cases reported to WHO each year, endemic cholera continues to exact an unacceptable toll primarily in large parts of Africa, South and Southeast Asia, and more recently in the Americas (Haiti). In 2015, a total of 172,454 cases and 1,304 deaths were reported to the World Health Organization (WHO) by 42 countries with an overall case-fatality rate of 0.8%.[1]

Transmission is mainly fecal-oral route by contaminated food and water. In most of the cases, cholera is clinically characterized as acute, profuse watery diarrhea with a duration of 1 or few days. Incubation period may range from several hours to 5 days, average of 2-3 days. In severe cases, patients present with profuse watery diarrhea (rice-water stools), projectile vomiting leading to dehydration, and shock. Death may occur in 18 hours to several days.[1,2]

Table 3. Cholera vaccine for adults

	Killed whole cell monovalent (O1) vaccine with cholera toxin B subunit (WC-BS or WC-rBS)	**Modified killed bivalent whole cell vaccine (WC)**
Description	• Mixture of B subunit of cholera toxin plus formalin and heat killed whole cells strains of *V. cholerae* O1 (monovalent) representing both serotypes Inaba and Ogawa and biotypes El Tor and Classical. It does not contain the cholera subunit A, making it free from toxic effects. • Has short term cross-protection against entero-toxigenic *Escherichia coli* since	• Contains a bivalent preparation of O1 and O139 and lacks the B subunit toxin.

	the heat labile toxin of *E. coli* cross reacts with cholera toxin.	
Recommendations	• Cholera vaccine is effective among adults up to three years after completion of vaccination. *Strong recommendation; moderate quality of evidence* • Oral cholera vaccine may be given as an additional measure to standard epidemic response protocol for cholera. *Strong recommendation; low quality of evidence* • Cholera vaccine is not routinely given. *Strong recommendation; low quality of evidence* • Oral cholera vaccine may be given among pregnant women if there is high risk of exposure (i.e., outbreak, endemic, travel). *Weak recommendation; low quality of evidence*	
Summary of evidence	A meta-analysis involving thirty-two randomized clinical trials and quasi-randomized studies comparing cholera vaccine with placebo showed a translated efficacy of cholera vaccine to 51% (95% CI: 41-59%), which can provide protection to older children and adults for up to three years against cholera.[8]	
	• In the Bangladesh trial (n = 63,498) involving children 2-15 years old and women 16 years old and above, participants were given 3 doses of WC-BS, WC, or placebo, in a randomized double-blind, placebo-controlled trial. • Protective efficacy against classical and El Tor cholera for patients aged 5 years old and above was 78% (95% CI: 61-78) and 63% (95% CI: 41-77), after 1 year and 2 years after vaccination, respectively. • During the first year following vaccination, the recipients showed 33-48% decrease in hospitalization for	• Duration of protection was noted to be two years in adults who received killed whole-cell monovalent vaccine with cholera B subunit toxin.[1] For the modified bivalent WC oral cholera vaccine, the duration of protection is up to 5 years.[1] • A cluster-randomized, double-blind, placebo-controlled study by Bhattacharya et al.[5] showed the protective efficacy among patients aged 15 years old and above was 74% (95% CI: 58-84%) 5 years after vaccination. • A case-cohort study showed the effectiveness of single dose was shown at 80%

	severe diarrhea due to any cause. Women aged 15 years old and above had decreased mortality rate at 23-26% from all causes from the study.[1,4]	(95% CI: 61-100%) over a 4-month period.[6] Another single-dose study done in Bangladesh showed vaccine efficacy of 40% (95% CI: 11-60%) and 63% (95% CI: 24-82%) against all cholera episodes and severe cholera in patients aged more than 1 year old, respectively.[1,7] Due to limited evidence of duration of protection, additional primary vaccination may be considered to provide longer duration of protection if cholera exposure persists.[1]
Indication/Target population	• Vaccination strategies should be tailored based on the assessment of areas with high risk for cholera infection. Targeting specific age groups and people (i.e., travelers visiting to areas with ongoing outbreaks) with high risk for cholera infection may be considered.[1,2]	
Schedule	• 2 liquid doses with 2-6-weeks interval • If the second dose is delayed for more than 6 weeks, the vaccine schedule should be restarted.[1,3]	• 2 liquid doses at 14-days interval
Administration	• Requires co-administration with 3 ml bicarbonate buffer (included in package) in 150 ml of potable water for adults to prevent degradation of B subunit. • Food and drinks should be avoided 1 hour before and after taking the oral vaccine. • Revaccination is recommended where there is continued risk for *V. cholerae* infection.	• Since it lacks the toxin subunit, it does not require bicarbonate buffer when administered. • Revaccination is recommended if it was given more than 3 years from the time of initial vaccination.[1]

	• In adults who were given WC-BS or WC-rBS for more than 2 years, the primary 2-dose vaccination should be repeated.	
Common adverse events	• Adverse events reported include mild abdominal pain, discomfort, or diarrhea.	
Contraindications/precautions	• Not licensed for use in children aged less than 2 years old. • Food and drink should be avoided for one hour before and after vaccination.[1] • Postpone vaccination in case of acute illness (including diarrhea) and avoid if with a history of systemic severe reaction or allergic response after administration of cholera vaccine dose.[2] • Cholera vaccine may be given together with other parenteral or oral vaccines.[1]	
Pregnancy and breastfeeding	• Good safety profile even in patients who are pregnant, immunocompromised, or even with HIV.	

Oral cholera vaccine may be given as an additional measure to standard epidemic response protocol for cholera.

Strong recommendation; low quality of evidence

Summary of evidence

WHO proposed to utilize oral cholera vaccine reactively as supplemental measure to standard cholera epidemic response protocol.[1] A proposed 3-step decision-making tool may provide health authorities regarding the use of cholera vaccine during complex emergencies: (1) a risk assessment for cholera outbreak which should be undertaken first; (2) an assessment of whether key public health priorities are or can be implemented in a timely manner, combined with an analysis of the capacity to contain a possible outbreak; and (3) an assessment of the feasibility of an immunization campaign.[9] Reactive vaccination should be given to as many eligible individuals and should be conducted as quickly as possible.[10] A systematic review and meta-analysis by Bi et al. showed that one-dose oral cholera vaccine provides a similar outcome to two-dose vaccine for short-term protection (1st year after vaccination) and may provide a practical option for outbreaks where reduction of short-term risk at a shorter time is needed.[10]

Oral cholera vaccines are safe among non-pregnant individuals.

Strong recommendation; high quality of evidence

Summary of evidence

A randomized controlled, multicenter, non-inferiority trial was done in the Philippines which involved healthy children and adults aged 1-40 years old where individuals were assigned to receive either two doses of Shanchol or Euvichol. Adverse events rates were observed at 4.4%

and 6.9% between Euvichol and Shanchol, respectively, with no statistical difference between the two vaccines and between age groups. Only mild adverse events—most commonly, headache and fever—were noted; no serious adverse events were reported.[11]

Oral cholera vaccine may be given to patients who are pregnant, immunocompromised, or even those with HIV.

Weak recommendation; low quality of evidence

Summary of evidence

An observational cohort study was done to investigate the safety of oral cholera vaccine (Shanchol) where a 2015 cholera outbreak in Malawi was used. The study assessed the risk of pregnancy loss and neonatal mortality between women who received the vaccine (n=835) and those who were not exposed to vaccine (n = 835). The study showed that there was no associated increased stillbirth outcome or neonatal mortality between the two populations. Also, the findings showed no increased risk for the development of birth defects among pregnant women who received the vaccine. However, there were few enrolled women who received the vaccine during the first trimester which restricts the clinical importance of this outcome in this study.[12] Another retrospective cohort study was done where a face-to-face survey of women was conducted 9 months after vaccination with Dukoral to identify birth outcomes between patients who received the vaccine (n = 196) versus those who did not receive the vaccine (n = 955). Fetal losses were greater in the vaccine group but there was no statistical difference compared with the non-vaccinated group (5.1% versus 2.8%, OR 1.62, p-value = 0.21).[13]

WHO provides that oral cholera vaccines have considerable benefits with very few risks for pregnant women to be included in vaccine campaign.[14]

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Dengue virus vaccine

Note: This vaccine was licensed in the Philippines in December 2015. However, it was withdrawn on December 5, 2017. Once the vaccine becomes available and re-licensed for use, additional data will be provided.

Vaccination is an important component of a comprehensive dengue prevention and control strategy in highly endemic areas, aside from clinical management, surveillance, and vector control. Existing epidemiological data from the Philippines indicate that the country continues to have high endemicity of dengue virus (DENV) infection based on high activity (>150,000 cases/year), multiple serotypes co-circulating, high rates in those <25 years old, and year-round sustained transmission.[1]

Information on the seroprevalence of dengue infections in the Philippines is limited. A recently published 1-year prospective cohort study by Alera et al.[2] focused on an urban community in Cebu City. The study included all patients ≥6 months old. Study participants with a hemagglutination inhibition titer <10 to all four serotypes were dengue-naive. Those with a hemagglutination inhibition titer ≥10 to only one DENV serotype were considered to have monotypic dengue immune status. Those with hemagglutination inhibition titers ≥10 to two or more serotypes were considered to have multitypic immune status. The seroprevalence for all ages was >80%; seroprevalence of multitypic was >98.3% for all ages >15 years old. However, in the age group 6 months to 5 years, more than 50% were seronegative; at 6 to 15 years, 20% were still seronegative. A study by Capeding et al. showed that the incidence rate of inapparent infant DENV infections during 2007 was 103/1,000 person-years (64–155; mean [95% CI]) and 6-fold higher than the incidence rate of symptomatic infant DENV infections (16/1,000 person-years; 11–22; mean [95% CI]).[3] However, no studies were done on the incidence of dengue among adults.

Clinical features of dengue

Dengue fever is a mosquito-borne disease characterized by non-specific signs and symptoms like fever, headache, musculoskeletal pain, rash, abdominal pain, nausea, and vomiting.

In 2009, WHO[4] classified dengue into three levels of severity: dengue without warning signs; dengue with warning signs; and severe dengue. Warning signs may include abdominal pain or tenderness, persistent vomiting, clinical signs of fluid accumulation, mucosal bleeding, lethargy, restlessness, liver enlargement, and increased hematocrit and/or decreasing platelet count. These signs require strict observation and medical intervention.

Severe dengue has any of the clinical manifestations of dengue with or without warning signs plus any of the following: severe plasma leakage leading to shock, or fluid accumulation with respiratory distress; severe bleeding; and severe organ impairment. Severe organ involvement is characterized by liver: aspartate aminotransferase or alanine aminotransferase >1,000; central nervous system: seizures, impaired consciousness; heart: myocarditis; and kidneys: renal failure.

Table 4A. Dengue vaccine for adults

Description	Recombinant live attenuated tetravalent vaccine

Summary of evidence	• The recombinant live attenuated tetravalent vaccine reduces symptomatic dengue, hospitalization, and severe dengue. • Based on 2 phase III clinical trials for chimeric yellow fever virus-DENV (CYD) 14/15,[5] pooled efficacy analyses showed the following efficacy rates: • 65.6% reduction in symptomatic dengue (95% CI: 60.7-69.9) • 80.8% reduction in hospitalized dengue (95% CI: 70.1-87.7) • 93.2% reduction in severe dengue (95% CI: 77.3-98.0) • For serotype-specific vaccine efficacy, vaccine efficacy was as follows: • DENV1: 58.4% (95% CI: 47.7-66.9) • DENV2: 47.1% (95% CI: 31.3-59.2) • DENV3: 73.6% (95% CI: 64.4-80.4) • DENV4: 83.2% (95% CI: 76.2- 88.2) • While there are no efficacy studies done in adults, immunogenicity studies[6-8] among 17-45 years old showed higher geometric mean titer (GMT) in neutralizing antibodies compared to individuals 9-16 years old. Thus, it is possible that levels of protection in adults may be similar or higher compared to that observed in children 9-16 years old. • Serologic testing may be requested prior to vaccination with the first dose.
Indication/Target population	• There are currently no studies and no recommendations for special populations like HIV infection, pregnant women, immunocompromised hosts, travelers, and healthcare workers.
Schedule	• 0, 6, 12 months
Administration	• Subcutaneous
Common adverse events	• The overall safety profile is acceptable 4 years after the 1st dose of the vaccine.
Contraindications	• Known anaphylactic activity to any vaccine component, or documented anaphylaxis with a previous dose of the same dengue vaccine
Precautions	• The live attenuated dengue vaccine may be administered at least 1 month after the receipt of steroids ≥2 weeks of daily ≥20 mg or ≥2 mg/kg body weight of prednisone.

	• Vaccine administration must be postponed in individuals suffering from moderate to severe febrile or acute disease. • Because the risk of immunological interference due to co-administration of live with non-live vaccines is considered small, co administration is permissible with these and other non-live attenuated vaccines.[12]
Pregnancy and breastfeeding	• For theoretical reasons, pregnant women in the 1st trimester should not receive the live attenuated dengue vaccine. If, however, the vaccine was inadvertently administered during the early phase of pregnancy, patients should be reassured that there is no known evidence of risk to the pregnancy. There would be no grounds for termination of the latter.[12,13] If a woman becomes pregnant before all three doses have been administered, the remaining doses should be administered after lactation. The vaccine should not be administered in breastfeeding women.[13]

The most common local reaction noted is pain on injection site. The most common systemic reactions are headache, myalgia, and malaise.

Solicited injection-site reactions after any vaccination were reported for 55% of participants in the tetravalent live attenuated chimeric dengue vaccine in a yellow fever 17D backbone (CYD-TDV) group and 67% of those in the control group.[9] Pain was most frequently reported after each of the three vaccinations, irrespective of vaccine received and the age group of the recipients. In the CYD-TDV group, the incidence of injection-site reactions was comparable after each vaccination (post-dose 1: 31.6%; post-dose 2: 37.8%; post-dose 3: 36.2%). In the adult sub-group, most injection-site reactions were considered Grade 1 to Grade 2 in intensity, and most were present for a maximum of 3 days.

In another study,[10] almost 51% of patients who received the vaccine complained of pain at the injection site followed by erythema (10.5%) and swelling (6%).

Thirteen out of 18 clinical trials in a pooled analysis of data for safety showed that baseline DENV serostatus did not influence the rates of adverse events in those aged 9-60 years old. In the phase IIb and phase III of trials included, 89 and 134 individuals in the CYD-TDV and placebo groups, respectively, were hospitalized during the 25-month period after dose 1, with a risk ratio (RR) of 0.33 (95% CI: 0.25, 0.43) in vaccine recipients. There were 15 and 33 cases of severe dengue disease in the CYD-TDV and placebo groups, respectively, with a RR of 0.23 (95% CI: 0.12; 0.42). The reduced rates of dengue hospitalization and severe dengue was observed until 4 years post dose 1 of the vaccine in individuals aged ≥9 years.[18]

It should be noted that the follow-up of the vaccinated individuals is still ongoing for a subset of patients and that long-term adverse effects of vaccination with CYD-TDV (a live recombinant chimeric vaccine based on a yellow fever 17D backbone) are not yet known.

It has also been argued by some leading dengue researchers that there is theoretical risk of antibody-dependent enhancement of breakthrough dengue infection when the vaccine is administered to seronegative individuals.[15,16] Further studies, including long-term surveillance of vaccinated individuals, are needed to validate this observation.

The manufacturers of the CYD-TDV recommend the vaccine for individuals aged 9-45 years old. The vaccine is recommended as a 3-dose series given 6 months apart. However, the age

to target to optimize impact likely varies by transmission setting. Although only immunogenicity (not vaccine efficacy) has been studied in clinical trials of 17-45-year-olds, in principle these age groups could be targeted for vaccination.[11]

Based on the CYD-TDV trials, it has been recommended that children below 9 years should not receive the vaccine because of safety signals of increased risk of hospitalization for dengue and for developing severe dengue. The trial data also suggest safety signals beyond age 9, with a relative risk of 0.57 (95% CI: 0.18 – 1.86).[5,7] The risk for developing dengue following dengue vaccination is particularly greater in those 2 to 5 years old for which the relative risk of hospitalized dengue in vaccinated individuals was 7.45 (95% CI: 1.15, 313.80) in Year 3, based on 15 cases in the CYD-TDV group and 1 case in the control group.

Immunogenicity studies for CYD-14/15 conducted among those 17-45 years old had GMT levels higher after the 3rd injection, where efficacy was demonstrated. Thus, it is anticipated that these individuals in endemic areas will have higher levels of protection.

In individuals ≥45 years old, although not indicated, the vaccine can be safely given to this age group. Of the 18 clinical trials specified in the article by Gailhardou, et al.,[18] the study in Australia by Torresi et al.[17] was the only study which included individuals >45 years old. They performed a randomized, multi-center, placebo-controlled, observer blind study to evaluate the immunogenicity based on GMTs of CYD-TDV in the dengue-naïve adult population 18-60 years old. An exploratory analysis of antibody response was obtained following GMTs and was compared between those 18-45 years old and those 46-60 years old, respectively. (See Table 4B).

One year of follow-up, beginning 28 days after the third dose of vaccine, showed that CYD-TDV had 56.5% and 60.8% efficacy (with narrow 95% CI) against virologically-confirmed dengue in the 2 phase III studies, respectively.[17]

Table 4B. Analysis of antibody responses

Dengue serotypes	Geometric mean titer (GMT), by age group			
	18-45 years old (n = 447)		46-60 years old (n = 265)	
	GMT	95% confidence interval	GMT	95% confidence interval
1	18.8	16.4-21.7	17.7	15.2-20.7
2	47.2	39.4-56.4	54.2	43.4-67.7
3	63.6	55.1-73.5	83.3	71.2-97.5
4	91.2	75.2-111	144	123-168

Summary of evidence

Vaccine efficacy in terms of reduction of symptomatic dengue among DENV seropositive individuals is higher (81.9%; 95% CI: 67.2-90.0) compared to those who are seronegative (52.5%; 95% CI: 5.9-76.1).[5] Therefore, it is ideal to know the serologic status of an individual prior to vaccination, e.g., a dengue immunoglobulin G ELISA test, particularly among children.

As mentioned earlier, there is a theoretical risk of antibody-dependent enhancement of breakthrough dengue infection when the vaccine is administered to seronegative individuals.[15,16] Further studies, including long-term surveillance of vaccinated individuals, are needed to validate this observation.

In the absence of a nationwide seroprevalence estimate on dengue, it is prudent to check the serologic status of an individual before vaccination. Prior exposure to dengue does not only depend on age but perhaps on socioeconomic exposure and occupational/environmental factors as well. Case reports of severe and fatal dengue in young adults are not uncommon.

Question: CYD-TDV vaccine efficacy (%) depending on serostatus at baseline

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Quality assessment							Number of patients		Effect	Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CYD-TDV DENV	Control group	Relative (95% Confidence Interval)		
Seropositive at baseline											
2	Randomized trials	Not serious	Not serious	Serious[a]	Not serious	None	15/1560 (1.0%)	40/763 (5.2%)	81.9 (67.2 to 90.0)	⊕⊕⊕◯ Moderate	Important
Seronegative at baseline											
2	Randomized trials	Not serious	Not serious	Serious[a]	Not serious	None	16/387 (4.1%)	17/208 (8.2%)	52.5 (5.9 to 76.1)	⊕⊕⊕◯ Moderate	Important

[a] Children included in study

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Haemophilus influenzae type b vaccine

Haemophilus influenzae is a small, non-motile, non-spore forming gram-negative coccobacilli. It is recovered from humans in the upper respiratory tract and, rarely, in the genital tract. It is transmitted via droplet or direct contact with respiratory secretions. Two forms of the bacterium exist, the encapsulated and the non-encapsulated.[1] The non-encapsulated *H. influenzae* is a common cause of otitis media in pediatric population and chronic obstructive pulmonary disease (COPD) exacerbations in adults. Encapsulated strains of *H. influenzae* are the classified based from the polysaccharide composition in the capsule. Six serotypes have been recognized (designated a through f) and serotype b is known to cause around 95% of all invasive disease, commonly seen among infants and children prior to the introduction of vaccine.[2] The capsule of Hib is composed of polymers of ribosyl and ribitol-phosphate (PRP) which is an important virulence factor in the pathogenesis of invasive disease.[3] *H. influenzae* type b (Hib) can cause meningitis, epiglottitis, pneumonia and empyema, and septic arthritis.[4,5]

Generally, healthy unvaccinated adults are protected against invasive Hib disease as 97% have circulating antibodies against Hib (>0.15 ug/ml) ensuring long-term protection.[3,6] Socioeconomic risk factors for invasive Hib infection includes increase exposure to Hib infection from household crowding, large household size, day care attendance, low socioeconomic status, low parental educational levels, and presence school-aged siblings. Host factors that increase Hib infections include sickle cell anemia, antibody deficiency syndromes, patients undergoing chemotherapy, and males.[8]

Infections caused by Hib are established by isolating the organism or detecting capsular antigens from sterile samples (cerebrospinal fluid, blood, etc.). Due to the fastidious nature of the organism, culturing Hib requires special transport and specific media for optimal growth.[7]

The currently available and licensed vaccine against Hib are polysaccharide conjugated vaccines. The vaccine stimulates the development of antibodies to PRP capsule which is bactericidal to the organism.[1] There are no known licensed vaccines available for non-typeable *H. influenzae*. However, partial efficacy against non-typeable *H. influenzae* in otitis media was noted in a randomized clinical trial of PCV13 which contained protein D (surface protein of *H. influenzae*).[7]

Table 5. Hib vaccine for adults

Note: Hib vaccines should be stored between +2 and +8 degrees Celsius.

Description	• Available Hib vaccines are conjugated polysaccharides with any of the following carrier proteins: diphtheria toxoid, tetanus toxoid, non-toxic variant diphtheria toxin CRM 197 (PRP-CRM197) and *Neisseria meningitidis* type b outer membrane protein complex (PRM-OMP).
Indication/Target population	• Hib vaccine is not routinely given to immunocompetent adults because of high titers of Hib antibody. *Strong recommendation; very low quality of evidence*

	• Hib vaccine may be given to adults who are asplenic or scheduled for splenectomy. *Weak recommendation; very low quality of evidence*
Summary of evidence	• There is limited clinical evidence with regards to efficacy of Hib vaccine among asplenic patients. Measurement of antibody response done in a cohort study of adult asplenic patients showed an increase in titers (≥1.0 µg/ml) in 97% of the subjects three weeks after vaccination.[10]
Schedule	• 1 dose of pediatric vaccine (0.5 ml)[4,8]
Administration	• Intramuscular injection (or subcutaneous in individuals with bleeding disorders), preferably in the deltoid area
Common adverse events	• Pain and tenderness at the injection site within 1 day post-vaccination was reported with spontaneous resolution.[11]
Contraindications/precautions	• Anaphylaxis to any vaccine component or a previous dose
Pregnancy and breastfeeding	• Hib vaccine is not recommended for pregnant women. *Strong recommendation; very low quality of evidence*

Hib vaccine is not routinely given to immunocompetent adults.

Strong recommendation; very low quality of evidence

Summary of evidence

Hib disease mostly occurs in unimmunized children under five years old; no trial was conducted among healthy adults. While the disease is not common among adults, certain conditions put adults at risk for Hib disease. A cross-sectional study done in Ontario, Canada detected less than 0.15 ug/ml of protective antibodies in 29% of patients with chronic renal failure, 20% of diabetes, and 55% of myeloma patients, while 70% of myeloma and 58% of chronic renal failure patients have undetectable antibody levels.[9]

Hib vaccine may be given to patients with functional or anatomic asplenia.

Weak recommendation; very low quality of evidence

Summary of evidence

There is limited clinical evidence with regards to efficacy of Hib vaccine among asplenic patients. Measurement of antibody response done in a cohort study of adult asplenic patients showed an increase in titers (≥1.0 µg/ml) in 97% of the subjects three weeks after vaccination.[10] However, 60% (n = 55) of the subjects already had a titer above 1.0 µg/ml prior to vaccination. ACIP guidelines recommend giving single dose of Hib conjugate vaccine to adults who are asplenic or scheduled for splenectomy regardless of immunization status, and experts suggest vaccination at least 14 days before or after the procedure.[6]

Hib vaccine is not recommended in pregnant women.

Strong recommendation; very low quality of evidence

Summary of evidence

An RCT evaluated 213 pregnant women and 213 neonates showed that infants born to mothers who were given the vaccine had significantly higher levels of antibody compared to those who were given placebo.[11] The study showed no difference in preterm delivery outcomes (RR 1.28; 95% CI: 0.12 to 13.86), fetal distress (RR 1.23; 95% CI: 0.67-2.26), intubation (RR 1.03; 95% CI: 0.55 to 1.95), and neonatal jaundice (RR 1.01; 95% CI: 0.52-1.97). Safety profile of the vaccine was not evaluated. The study has high risk for bias due to small sample size and blinding procedures were unclear.

Question: Hib vaccine compared to placebo in pregnant patients

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Certainty assessment							Number of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hib vaccine	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Immunogenicity											
1	RCT	Very serious [a,b]	Not serious	Not serious	Not serious	None	35	40	-	Mean 2.73 ug/ml higher (0 to 0)	⨁⨁◯◯ Low

[a] Blinding not clear

[b] Allocation concealment not stated

Hib vaccine is safe to be given among adult non-pregnant immunocompetent individuals.

Strong recommendation; low quality of evidence

Summary of evidence

Studies on the safety of Hib vaccine were mostly done in pediatric patients. Injection site reactions were reported to be common. Pain and tenderness at the injection site within 1 day post-vaccination was reported with spontaneous resolution.[11] Anaphylaxis was not reported in the pre-licensing clinical trials, as well as not enough evidence to accept or reject causality between anaphylaxis following Hib vaccination.[12]

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Hepatitis A virus vaccine

Hepatitis A is a common vaccine-preventable infection caused by a hepato-tropic picorna virus called hepatitis A virus (HAV). It is endemic in developing countries and is transmitted through direct person-to-person contact usually through fecal-oral route.[1]

Table 6. Hepatitis A virus vaccine for adults

Description	• Formalin-inactivated monovalent vaccine, adsorbed to aluminum hydroxide as adjuvant • Combined inactivated hepatitis A and B vaccines
Recommendation	• Hepatitis A vaccination can prevent hepatitis A infection in immunocompetent individuals. *Strong recommendation; moderate quality of evidence*
Summary of evidence	• In the three randomized trials with low risk of bias (all assessing inactivated vaccine), clinically apparent hepatitis A occurred in 9/20,684 (0.04%) vs 92/20,746 (0.44%) participants in the HAV vaccine and control groups respectively (RR 0.09; 95% CI: 0.03 to 0.30). In all nine randomized trials, clinically apparent hepatitis A occurred in 31/375,726 (0.01%) versus 505/356,654 (0.18%) participants in the HAV vaccine and control groups respectively (RR 0.09; 95% CI: 0.05 to 0.17). These results were supported by trial sequential analyses. Subgroup analyses confirmed the clinical effectiveness of both inactivated hepatitis A vaccines (RR 0.09; 95% CI: 0.03 to 0.30) and live attenuated hepatitis A vaccines (RR 0.07; 95% CI: 0.03 to 0.17) on clinically confirmed hepatitis A. Inactivated hepatitis A vaccines had a significant effect on reducing the lack of seroprotection (less than 20 mIU/L) (RR 0.01; 95% CI: 0.00 to 0.03).[4]
Indication/Target population	• Adult immunocompetent individuals • Other indications • Vaccinate any person seeking protection from HAV infection • Men having sex with men (MSM) • Users of injection drugs • Persons who receive clotting factor concentrates or with clotting factor disorders (e.g. hemophiliacs) • Persons traveling to or working in countries that have high or intermediate endemicity of hepatitis A • Contacts of infected persons • People with chronic liver disease (because of risk of fulminant hepatitis A) • Persons for whom hepatitis A is an occupational hazard (e.g. healthcare workers, some lab workers, food handlers)

	• Persons employed in child care centers, healthcare institutions, institutions for persons with developmental disabilities, schools • Persons exposed to sewage • Armed forces • Persons working with HAV-infected primates or with HAV in a research laboratory setting • Travelers from non-endemic areas which include: tourists, immigrants, and their children returning to their country of origin to visit friends or relatives, military personnel, missionaries, and others who work or study abroad in countries that have high or intermediate endemicity of hepatitis A
Schedule[2]	• The monovalent hepatitis A vaccine is given at a dose of 1440 ELISA units/ml/vial, given as a 2-dose regimen (0 and 6-12 months). • For combined hepatitis A and B vaccines: • 3 doses administered intramuscularly at 0, 1, and 6 months • Dose: 720 ELISA units (hepatitis A) and 20 µg/ml hepatitis B • Booster dose should be given at 1 year. Serologic testing to assess response is not indicated.
Administration	• Intramuscular, deltoid area
Common adverse events	• Local adverse events would include injection site soreness, induration, redness and swelling. • Systemic adverse events on the other hand include headache, malaise, fatigue, nausea, and loss of appetite.[4]
Contraindications	• Known anaphylactic activity to any vaccine component or documented anaphylaxis with a previous dose of the same dengue vaccine
Precautions	• Administered with caution in patients with bleeding disorders since bleeding may occur following an intramuscular injection • History of severe allergic reaction to a previous dose of hepatitis A vaccine or a vaccine component (i.e., 2-phenoxyethanol, yeast) • Any febrile illness
Pregnancy and breastfeeding	• Recommended for susceptible pregnant women who are at increased risk of exposure through lifestyle factors, or where severe outcomes may be expected (e.g. pre-existing liver disease) • The effect of HAV on fetal development has not been assessed. • Effect of the vaccine on breastfed infants through its administration to their nursing mothers has not been evaluated in clinical studies.

Hepatitis A vaccination can prevent hepatitis A infection in immunocompetent individuals.

Strong recommendation; moderate quality of evidence

Summary of evidence

A study done by Barzaga et al.[3] tested anti-HAV positivity in 1,000 Filipinos, male and female, ages 1 to 79 years, belonging to middle- and upper middle-income families. Approximately 40% are students, 20% are employees, most of whom hold supervisory, or junior executive positions. The professionals (health, academe, business, technical) comprise 19% of the study population. Only about 2% belonged to the low-income group. The results of the study showed that hepatitis A infection is highly endemic in our setting. Overall exposure as measured by anti-HAV reactivity is 62% for both males and females, and it increases with age. Whereas most adults after the age of 40 are anti-HAV positive, there are some individuals who, even up to age 62 remain anti-HAV non-reactive. This may reflect real non-exposure to HAV-contaminated food, or it may reflect a subset of population who may have been exposed, produced antibodies, but have lost these antibodies with time. This finding may also be explained in terms of immunologic mechanisms at work in certain individuals that make them more resistant or less susceptible to HAV infection. Overall, of the anti-HAV positive individuals, only 15% had a personal or family history of jaundice. Clinical hepatitis in these anti-HAV positive individuals developed in 2.7% among the 6-10-year old age group, and in 40% in the age group 31-40 years. This finding confirms that most cases of HAV infection are subclinical.[3]

Nine randomized trials with 732,380 participants addressed the primary outcome of clinically confirmed hepatitis A. Of these, four trials assessed the inactivated hepatitis A vaccine (41,690 participants) and five trials assessed the live attenuated hepatitis A vaccine (690,690 participants). In the three randomized trials with low risk of bias (all assessing inactivated vaccine), clinically apparent hepatitis A occurred in 9/20,684 (0.04%) versus 92/20,746 (0.44%) participants in the HAV vaccine and control groups, respectively (RR 0.09; 95% CI: 0.03 to 0.30). In all nine randomized trials, clinically apparent hepatitis A occurred in 31/375,726 (0.01%) versus 505/356,654 (0.18%) participants in the HAV vaccine and control groups, respectively (RR 0.09; 95% CI: 0.05 to 0.17). These results were supported by trial sequential analyses. Subgroup analyses confirmed the clinical effectiveness of both inactivated hepatitis A vaccines (RR 0.09; 95% CI: 0.03 to 0.30) and live attenuated hepatitis A vaccines (RR 0.07; 95% CI: 0.03 to 0.17) on clinically confirmed hepatitis A. Inactivated hepatitis A vaccines had a significant effect on reducing the lack of seroprotection (less than 20 mIU/L) (RR 0.01; 95% CI: 0.00 to 0.03).[4]

Question: Hepatitis A vaccination compared to placebo for prevention of hepatitis A infection

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Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hepatitis A vaccination	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)		
Hepatitis A infection (follow-up: range 2 years to 5 years)												
9	Randomized trials	Not serious	Not serious	Serious [a]	Not serious	None	31/375,726 (0.0%)	505/356,654 (0.1%)	Risk ratio 0.09 (0.05 to 0.17)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⨁⨁⨁◯ Moderate	Critical

[a] Study was done in non-endemic region

Is hepatitis A vaccination recommended in special populations?

According to the Advisory Committee on Immunization Practices (ACIP) formed by the Centers for Disease Control and Prevention, persons with increased risk for hepatitis A virus infection are the travelers, men who have sex with men (MSM), users of injection and non-injection drugs, and those with chronic liver disease.[2]

Travelers would be persons from developed countries who travel to developing countries. Such persons include tourists, immigrants and their children returning to their country of origin to visit friends or relatives, military personnel, missionaries, and others who work or study abroad in countries that have high or intermediate endemicity of hepatitis A. Hepatitis A remains one of the most common vaccine-preventable diseases acquired during travel. One study estimated the risk among persons who did not receive immunoglobulin or vaccine before departure to be 4-30 cases per 100,000 months of stay in developing countries.

Hepatitis A outbreaks among MSM have been reported frequently. Certain studies have identified specific sex practices associated with illness, whereas others have not demonstrated such associations. Seroprevalence surveys have not consistently demonstrated an elevated prevalence of anti-HAV positivity compared with a similarly aged general population. Even if data is lacking and vaccine coverage is low, the ACIP has recommended hepatitis A vaccination of MSM since 1996.

During the preceding 2 decades, outbreaks have been reported with increasing frequency among users of injection and non-injection drugs. Cross-sectional serologic surveys have demonstrated that injection-drug users have a higher prevalence of anti-HAV positivity than the general U.S. population. Transmission among injection-drug users probably occurs through both percutaneous and fecal-oral routes. Since 1996, the ACIP has recommended hepatitis A vaccination of users of illicit drugs, but vaccine coverage data are not available.

Although not at increased risk for HAV infection, persons with chronic liver disease are at increased risk for fulminant hepatitis A. Death certificate data indicate a higher prevalence of chronic liver disease among persons who died of fulminant hepatitis A compared with persons who died of other causes. Thus, hepatitis A vaccination is also recommended for those with chronic liver disease.[2]

How soon can protection be attained after hepatitis A vaccination?

Nearly 100% of people develop protective levels of antibodies to the virus within 1 month after injection of a single dose of vaccine.[5] All licensed vaccines are highly immunogenic in persons aged >18 years old when administered according to the recommended schedules. Protective antibody levels were identified in 94%-100% of adults 1 month after the first dose. After the second dose, all persons had protective levels of antibody.[2] Even after exposure to the virus, a single dose of the vaccine within 2 weeks of contact with the virus has protective effects. Still, manufacturers recommend 2 vaccine doses to ensure a longer-term protection of about 5 to 8 years after vaccination.[5]

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Hepatitis B virus vaccine

Hepatitis B is a disease that causes a wide spectrum of illness ranging from asymptomatic to icteric including fulminant hepatitis. Chronic carrier state can lead to chronic liver disease, cirrhosis and liver cancer. The etiologic agent is hepatitis B virus from the family Hepadnaviridae, which occurs throughout the world transmitted through unprotected sex, percutaneous transmission in drug abusers, needle stick injuries, maternal-neonatal during labor or delivery, and blood transfusion.[1]

Table 7A. Hepatitis B virus vaccine for adults

Description	• Monovalent recombinant hepatitis B vaccine • Combined inactivated hepatitis A and B vaccines
Recommendation (See text after table.)	• Hepatitis B vaccine is recommended in the prevention of hepatitis B virus infection in high-risk individuals. *Strong recommendation; very low quality of evidence* • Hepatitis B vaccine may be recommended in the prevention of hepatitis B infection in unexposed low-risk individuals. *Weak recommendation; very low quality of evidence* • Hepatitis B vaccine should be routinely administered to patients with chronic renal failure. *Strong recommendation; very low quality of evidence* • A reinforced vaccination schedule should be given to patients with chronic renal failure. *Strong recommendation; very low quality of evidence* • Persons living with HIV should receive hepatitis B vaccination. *Strong recommendation; very low quality of evidence* • A booster dose may be given to healthy individuals 5 years after the primary vaccination schedule for the prevention of hepatitis B virus infection. *Weak recommendation; very low quality of evidence*
Summary of evidence	• Four randomized controlled trials showed that hepatitis B vaccination had an unclear effect on the risk of hepatitis B surface antigen presence (RR 0.96; 95% CI: 0.89 to 1.03, 4 trials with 1,230 participants, I_2 = 0%). Analysis of data of available participants showed RR 0.12; 95% CI: 0.03 to 0.44, 4 trials with 576 participants, I_2 = 0%. Hepatitis B vaccination has an unclear effect on the risk of developing hepatitis B virus markers of infection (hepatitis B surface antigen) in participants without previous knowledge about exposure to hepatitis B infection.[6]
Indication/Target population	• Because of the low quality of evidence among immunocompetent adults, the vaccine is recommended for those >15 years old without previous hepatitis B infections and negative for serum hepatitis B markers, including hepatitis B surface antigen, hepatitis B surface antibody, or

	hepatitis B core antibody who are classified as high risk to develop the infection (those who are always in contact with blood or blood products, blood-contaminated instruments, stained body fluids, or tissues, including medical students, health-care workers, prisoners, and drug users).[5a]
Schedule[b]	• Monovalent: two doses separated by no less than 4 weeks, and a third dose 4 to 6 months after the second dose (0, 1, and 6 months)[1] • The standard hepatitis B vaccination schedule of 0-1-6 months should be used to confer long term protection among high-risk groups who do not need immediate protection against hepatitis B. *Strong recommendation; moderate quality of evidence* • The accelerated hepatitis B vaccination schedule of 0-2-6 weeks (0-14-42 days) plus booster dose (see below) may be used for high-risk groups who need immediate protection and rapid seroconversion. *Weak recommendation; moderate quality of evidence* • Patients who received the accelerated schedule of 0-2-6 weeks (0-14-42 days) should receive a booster dose 1 year after the 1st dose, if hepatitis B surface antibody titer is below 10 mIU/ml. *Strong recommendation; very low quality of evidence* • Combined • 3 doses administered intramuscularly at 0, 1 and 6 months • Dose: 720 ELISA units (hepatitis A) and 20µg/ml hepatitis B • Booster dose should be given at 1 year
Administration	• Intramuscular, deltoid area
Common adverse events	• Pain, redness and soreness at the injection site and fever
Contraindications and precautions	• Hypersensitivity to any component of the vaccine, including baker's yeast • Should not be administered to subjects with moderate or severe acute illness with or without fever
Pregnancy and breastfeeding	• The effect on breastfed infants of the administration of the vaccine to their mother has not been evaluated in clinical studies.

[a] Does not include men who have sex with men (MSM)

[b] For high-risk individuals: Serologic testing (hepatitis B surface antibody titer) should be done 3 months after the last dose of the primary course and yearly thereafter.

Question: Hepatitis B vaccination compared to placebo for prevention of Hepatitis B infection in persons not previously exposed or with unknown exposure status

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Mathew, J. L., El Dib, R., Mathew, P. J., Boxall, E. H., & Brok, J. (2008). Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status. *Cochrane Database of Systematic Reviews, 3*, Art. No.: CD006481.

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hepatitis B vaccination	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)		
Hepatitis B infection [follow-up: range 1 months to 15 years; assessed with detection of HBsAg, HBe antigen (HBeAg), HBV DNA, or antibody to HBc antigen in serum (anti-HBc)]												
4	Randomized trials	Serious [a]	Serious [b]	Serious	Not serious	Publication bias strongly suspected [c]	316/594 (53.2%)	362/636 (56.9%)	Risk ratio 0.96 (0.89 to 1.03)	23 fewer per 1,000(from 17 more to 63 fewer)	⨁◯◯◯ Very low	

[a] All included trials had low methodological quality.

[b] There was significant heterogeneity because hepatitis B vaccination showed an unclear effect on the risk of presence of anti-HBc antibodies.

[c] Many of the included trials did not report outcomes that seemed highly relevant to report on.

Vaccination schedule for hepatitis B virus vaccine

Among high-risk groups, should the accelerated hepatitis B vaccination schedule be used rather than the standard vaccination schedule to confer immunity against hepatitis B?

The standard hepatitis B vaccination schedule of 0-1-6 months should be used to confer long term protection among high-risk groups who do not need immediate protection against hepatitis B.

Strong recommendation; moderate quality of evidence

The accelerated hepatitis B vaccination schedule of 0-2-6 weeks (0-14-42 days) plus booster dose may be used for high-risk groups who need immediate protection and rapid seroconversion. (See Table 7B.)

Weak recommendation; moderate quality of evidence

Patients who received the accelerated schedule of 0-2-6 weeks (0-14-42 days) should receive a booster dose 1 year after the 1st dose, if hepatitis B surface antibody titer is below 10 mIU/ml.

Strong recommendation; very low quality of evidence

Summary of evidence

In the study by Jin et al., high-risk healthy subjects were defined as those who are more than 15 years old without previous hepatitis B infections and who are negative for serum hepatitis B markers, including hepatitis B surface antigen, hepatitis B surface antibody, or hepatitis B core antibody who are always in contact with blood or blood products, blood-contaminated instruments, stained body fluids, or tissues, including medical students, healthcare workers, prisoners, and drug users. It was elucidated in the study that higher seroprotection rates were detected in the accelerated group (0-14-42 days) compared with the standard group at the first or third month after the initial dose. However, there were no statistically significant differences in seroprotection rates between the accelerated and standard groups at 7 months after the initial dose. (See Table 7B.) There was note of rapidly declining antibody levels in the accelerated hepatitis B vaccination schedule. Some studies recommend a fourth booster dose to address this issue.[5]

Table 7B. Relative benefit of accelerated schedules months after 1st hepatitis B virus vaccine dose

Number of months after 1st hepatitis B virus vaccine dose	Relative benefit of recommended accelerated schedule				
	0-14-42 days (0-2-6 weeks)	0-7-21 days (0-1-3 weeks)	0-7-28-56 days (0-1-4-8 weeks)	0-1-2 months (0-4-8 weeks)	0-1-2-12 months (0-4-8-48 weeks)
1	12.52 (1.76-88.99)	2.88 (2.28-3.64)	4.69 (1.67-13.22)	-	1.36 (0.84-2.19)

3	2.01 (1.25-3.24)	1.03 (0.82-1.29)	-	1.28 (1.11-1.46)	1.16 (1.02-1.32)
7	1.04 (0.94-1.15)	0.98 (0.91-1.06)	0.93 (0.81-1.08)	0.93 (0.84-1.02)	0.92 (0.82-1.03)
12	-	0.97 (0.89-1.07)	-	-	0.95 (0.89-1.01)

The standard vaccination program (0-1-6 months) appears to be more efficient in terms of sustained antibody levels compared to accelerated schedules without booster doses. However, when the standard vaccination program was compared with the accelerated hepatitis B vaccination schedule plus the 4th booster dose after 12 months, there was no significant difference in the level of protection against hepatitis B (RR 0.97; CI: 0.89-1.07).[4] Therefore, for those who are not requiring rapid seroconversion and immediate protection, the standard hepatitis B vaccination schedule is recommended. Rapid seroconversion and immediate protection in the short term can make it possible for high-risk groups to use accelerated schedules, but the long-term protection and effectiveness of the primary accelerated schedule doses should be recognized in the future.

Question: Accelerated hepatitis B vaccine schedule compared to standard hepatitis B vaccination schedule for protection against hepatitis B infection in high-risk healthy adults

Bibliography:

Jin, H., Tan, Z., Zhang, X., Wang, B., Zhao, Y., & Liu, B. (2015). Comparison of accelerated and standard hepatitis B vaccination schedules in high-risk healthy adults: A meta-analysis of randomized controlled trials. *PLoS One 10*(7), e0133464.

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Accelerated hepatitis B vaccine schedule	Standard hepatitis B vaccination schedule	Relative (95% confidence interval)	Absolute (95% confidence interval)		
Prevention of hepatitis B infection 1 month after initial dose of hepatitis B vaccine (follow-up: range 1 months to 36 months; assessed with two or more consecutive patient blood specimens positive for anti-HB levels above 10 IU/L, 1 month after initial vaccine dose)												
10	Randomized trials	Not serious	Serious [a]	Not serious	Not serious	None	432/753 (57.4%)	197/758 (26.0%)	Not estimable		⨁⨁⨁◯ Moderate	
Prevention of hepatitis B infection 3 months after initial dose of hepatitis B vaccine (follow-up: range 1 months to 36 months; assessed with two or more consecutive patient blood specimens positive for anti-HB levels above 10 IU/L, 1 month after initial vaccine dose)												
10	Randomized trials	Not serious	Serious [a]	Not serious	Not serious	None	311/361 (86.1%)	255/367 (69.5%)	Not estimable		⨁⨁⨁◯ Moderate	

Question: Accelerated hepatitis B vaccine schedule compared to standard hepatitis B vaccination schedule for protection against hepatitis B infection in high-risk healthy adults

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Jin, H., Tan, Z., Zhang, X., Wang, B., Zhao, Y., & Liu, B. (2015). Comparison of accelerated and standard hepatitis B vaccination schedules in high-risk healthy adults: A meta-analysis of randomized controlled trials. *PLoS One 10*(7), e0133464.

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Accelerated hepatitis B vaccine schedule	Standard hepatitis B vaccination schedule	Relative (95% confidence interval)	Absolute (95% confidence interval)		
Prevention of hepatitis B infection 7 months after initial dose of hepatitis B vaccine (follow-up: range 1 months to 36 months; assessed with two or more consecutive patient blood specimens positive for anti-HB levels above 10 IU/L, 1 month after initial vaccine dose)												
10	Randomized trials	Not serious	Serious [a]	Not serious	Not serious	None	523/585 (89.4%)	563/589 (95.6%)	Not estimable		⨁⨁⨁◯ Moderate	
Prevention of hepatitis B infection 12 months after initial dose of hepatitis B vaccine (follow-up: range 1 months to 36 months; assessed with two or more consecutive patient blood specimens positive for anti-HB levels above 10 IU/L, 1 month after initial vaccine dose)												

Question: Accelerated hepatitis B vaccine schedule compared to standard hepatitis B vaccination schedule for protection against hepatitis B infection in high-risk healthy adults

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Jin, H., Tan, Z., Zhang, X., Wang, B., Zhao, Y., & Liu, B. (2015). Comparison of accelerated and standard hepatitis B vaccination schedules in high-risk healthy adults: A meta-analysis of randomized controlled trials. *PLoS One 10*(7), e0133464.

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Accelerated hepatitis B vaccine schedule	Standard hepatitis B vaccination schedule	Relative (95% confidence interval)	Absolute (95% confidence interval)		
10	Randomized trials	Not serious	Serious [a]	Not serious	Not serious	None	157/200 (78.5%)	162/200 (81.0%)	Risk ratio 0.97 (0.89 to 1.07)	24 fewer per 1,000 (from 57 more to 89 fewer)	⨁⨁⨁◯ Moderate	
Prevention of hepatitis B infection 22 months after initial dose of hepatitis B vaccine (follow-up: range 1 months to 36 months; assessed with two or more consecutive patient blood specimens positive for anti-HB levels above 10 IU/L, 1 month after initial vaccine dose)												
10	Randomized trials	Not serious	Serious [a]	Not serious	Not serious	None	70/96 (72.9%)	75/95 (78.9%)	Not estimable		⨁⨁⨁◯ Moderate	

Question: Accelerated hepatitis B vaccine schedule compared to standard hepatitis B vaccination schedule for protection against hepatitis B infection in high-risk healthy adults

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Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Accelerated hepatitis B vaccine schedule	Standard hepatitis B vaccination schedule	Relative (95% confidence interval)	Absolute (95% confidence interval)		
Prevention of hepatitis B infection 36 months after initial dose of hepatitis B vaccine (follow-up: range 1 months to 36 months; assessed with two or more consecutive patient blood specimens positive for anti-HB levels above 10 IU/L, 1 month after initial vaccine dose)												
10	Randomized trials	Not serious	Serious [a]	Not serious	Not serious	None	86/139 (61.9%)	94/141 (66.7%)	Not estimable		⨁⨁⨁◯ Moderate	

[a] The variety of accelerated schedules could have impacted heterogeneity. Some factors, such as male dominance (57.03%, 1,026/1,799), limit the generalizability of the results.

Hepatitis B vaccine should be routinely administered to patients with chronic renal failure.

Strong recommendation; very low quality of evidence

Summary of evidence

In the study by Schroth et al.,[11] chronic renal failure was defined as serum creatinine greater than 200 µmol/L for a period of more than six months or individuals receiving dialysis (hemodialysis or peritoneal dialysis).

Hepatitis B vaccines available in the Philippines are of the recombinant form. No plasma-derived vaccines are available in the market in the Philippines. There were studies comparing plasma-derived hepatitis B vaccine and placebo, as well as plasma-derived vaccine and recombinant vaccine. However, there were no trials comparing recombinant hepatitis B vaccine with placebo.

Despite the lack of trials regarding recombinant hepatitis B vaccine, it is a well-known fact that patients with chronic renal failure are at risk for hepatitis B virus infection due to their increased exposure to blood products, hemodialysis and an impaired immune response. Therefore, based on expert opinion hepatitis B vaccine should be routinely administered to patients with chronic renal failure regardless of dialysis.

A reinforced vaccination schedule should be given to patients with chronic renal failure.

Strong recommendation; very low quality of evidence

Summary of evidence

The ACIP recommends a 4-dose schedule of recombinant (40 µg) vaccine in renal patients over 20 years old. The current Centers for Disease Control and Prevention recommendations for vaccination of renal patients over 20 years old also specifies a four-dose recombinant vaccine schedule of 40 µg at 0, 1, 2, and 6 months.[12]

The initial analysis comparing the reinforced vaccination schedule with the standard 3 inoculation vaccination schedule yielded a RR 1.36, 95% CI: 0.85 to 2.16 and indicated that the reinforced series was not significantly more effective in achieving seroconversion compared to three inoculations. Therefore, the recommendation is based on a very low quality of evidence.

Question: Reinforced recombinant hepatitis B vaccination compared to 3 recombinant hepatitis B inoculations in patients with chronic renal failure

Bibliography:

Kim, D. K., Bridges, C. B., & Harriman, K. H. (2016). Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older. *Morbidity and Mortality Weekly Report*, *65*.

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reinforced recombinant hepatitis B vaccination	Three recombinant hepatitis B inoculations	Relative (95% confidence interval)	Absolute (95% confidence interval)		
Achieving seroconversion [follow up: range 12 months to 24 months; assessed with adequate anti-HBs response (> 10 IU/L or SRU)]												
2	Randomized trials	Serious [a]	Very serious [b]	Not serious	Not serious	None	37/63 (58.7%)	17/43 (39.5%)	Risk ratio 1.36 (0.85 to 2.16)	142 more per 1,000 (from 59 fewer to 459 more)	⨁◯◯◯ Very low	

[a] Low methodologic quality, i.e., unclear generation of allocation sequence and allocation concealment; no double blinding, small sample size

[b] The use of two differing doses of vaccine (20 µg and 40 µg) in a reinforced vaccination series (Jilg 1986a) may have affected the outcome.

Persons living with HIV should receive hepatitis B vaccination.

Strong recommendation; very low quality of evidence

Summary of evidence

One randomized controlled trial by Okwen et al.,[13] published in two papers revealed that hepatitis B vaccine increased antibody titers to protective levels over the short term (one year). This protection was not sustained in the absence of antiretroviral therapy. No adverse events were noted. Other outcomes such as hepatitis B infection, morbidity, and mortality due to hepatitis B were not addressed, hence the very low quality of evidence.

Question: Hepatitis B vaccination compared to placebo for reducing morbidity and mortality in persons with HIV infection

Setting: Spain

Bibliography: Okwen MP, Reid S, Njei B, Mbuagbaw L. Hepatitis B vaccination for reducing morbidity and mortality in persons with HIV infection. *Cochrane Database of Systematic Reviews 2014*, Issue 10. Art. No.: CD009886.

Outcomes	Illustrative comparative risks[a] (95% confidence interval)		Relative effect (95% confidence interval)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Hepatitis B vaccination compared to placebo				
Hepatitis B antibody titer (IgG), follow-up: 12 months	The median IgG titer in the control group was 2.14 (interquartile range 695.55) mIU/mL.	The median IgG titer in the intervention group was 321.00 (interquartile range 970.31) mIU/mL.	Not estimable	25 (1 study)	⊕◯◯◯Very low[1,2]	Authors report "Statistically significant (P < 0.05) difference between the groups using the Mann-Whitney U-test for comparison."

[1,2] The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% confidence interval).

A booster dose may be given to healthy individuals 5 years after the primary vaccination schedule for the prevention of hepatitis B virus infection.

Weak recommendation; very low quality of evidence

Summary of evidence

Based on the study by Poorolajal and Hooshmand,[15] there were no eligible randomized clinical trials to support or refute the need for a booster dose of hepatitis B vaccine in healthy individuals, with normal immune status, who had fully responded to a complete course of the vaccine.

There were non-randomized clinical trials obtained; however, there was no comparison done with a control group. The clinical consequences of offering a booster dose to healthy people with hepatitis B surface antibody levels below 10 mIU/ml more than five years after initial hepatitis B vaccination are not known. In principle, therefore, there is a need to conduct such randomized clinical trials

Common adverse events in the administration of hepatitis B vaccine

In a meta-analysis by Mathew et al., adverse events were analyzed in three groups: systemic, local, and other. The denominator for these was calculated based on the number of potential events (calculated as number of participants multiplied by the number of doses). The risk of developing fever with hepatitis B vaccine was not significantly affected (RR 1.42; 95% CI: 0.60 to 3.38, 2 trials with 14,169 potential events, I_2 = 92.3%, random-effects model). The fixed-effect model showed RR 1.03, 95% CI: 0.90 to 1.18. The two trials compared hepatitis B vaccine co-administered with other childhood vaccines versus routine childhood vaccines alone.[7,8] Local reactions included pain, redness, and soreness, singly or in combination. The risk of developing local reactions was significantly increased among hepatitis B vaccine recipients (RR 2.93; 95% CI: 1.72 to 4.99; 2 trials with 1,904 potential events; I_2 = 36.9%). The two trials compared hepatitis B vaccine either alone or co-administered with other childhood vaccine versus routine childhood vaccine.[7,9]

One trial reported headache,[10] and the risk of developing this event was unclear (RR 2.33; 95% CI: 0.64 to 8.56; 1 trial with 110 participants). The comparator group received hepatitis A vaccine.

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Herpes zoster vaccine

Herpes zoster (HZ), or shingles, is the clinical manifestation of the reactivation of latent varicella zoster virus (VZV), which as a primary infection causes varicella or chickenpox. It is transmitted via airborne route or direct contact or inhalation of aerosols from vesicular fluid of skin lesions.[1] Primary infection with VZV induces the production of specific memory T cells in sufficient numbers to keep the virus in its latent form. Host factors such as aging, or other conditions that affect cellular immunity, may reduce T cells to levels that no longer inhibit viral replication, therefore increasing the likelihood of clinical manifestations of the disease.[2]

Clinically, HZ consists of three distinct stages. The prodromal phase lasts for two to three weeks and patients experience neuritic pain, paresthesias, or pruritus, generally localized to one dermatome. After the prodrome, acute vesiculation occurs over a period of three to five days and then subsides with the formation of crusts, which may take up to three weeks to occur. The third clinical stage, if it occurs, is the development of post-herpetic neuralgia, which is defined as neuritic pain that persists around the affected dermatome after the rash has healed, or pain that lasts at least 30 days from the onset of lesions. It is the leading cause of long-lasting morbidity after resolution of the acute outbreak. Its likelihood of developing increases with the age of the patient.[3]

Involvement of the eyelid (herpes zoster ophthalmicus) is a sight-threatening condition and is usually signaled by lesions at the tip of the nose.[1] In addition to post-herpetic neuralgia, infection with VZV may lead to other serious, but rare, complications. These include bacterial superinfection, viral dissemination, myelitis, encephalitis, and peripheral and cranial nerve palsies. Reactivation in the ophthalmic region of the trigeminal nerve may lead to blindness, and infection of the geniculate ganglion to facial weakness and occasional hearing disorders. Much of these complications have very limited treatment options. With our current technologies, the most effective way to combat them is preventing both initial infection and reactivation of VZV.[3]

Table 8A. Herpes zoster vaccine for adults

Note: Care should be taken not to confuse ZVL, which is stored in the freezer and administered subcutaneously, with RZV, which is stored in the refrigerator and administered intramuscularly.

Type	Live attenuated zoster vaccine (ZVL)	Adjuvanted recombinant zoster virus[20] (RZV)*
Description	• Neomycin-containing recombinant live attenuated tetravalent vaccine; contains the same live attenuated virus used in the chickenpox vaccine, but it has over 14-fold more plaque-forming units of the attenuated virus per dose. Therefore, the two vaccines are not interchangeable. This vaccine activates specific T cell production, thus increasing existing immunity	• 50 ug of recombinant VZV glycoprotein E formulated with AS01B adjuvant which is a proprietary adjuvant system containing MPL (3-O-desacyl-40-monophosphoryl lipid A[21]

	and avoiding reactivation of viral replication.[1,2]	
Recommendations and summary of evidence	• For immunocompetent adults ≥60 years old without prior history of herpes zoster to prevent the disease • The vaccinated group had a reduced incidence of herpes zoster as early as 30-days post-vaccination: RR 0.33, 95% CI: 0.13 to 0.84. At 42-days post-vaccination, the benefits of vaccination are clear, with a RR of 0.29 (95% CI: 0.13 to 0.68).[2] *Strong recommendation; moderate quality of evidence* • For immunocompetent adults (>60 years old) with prior history of herpes zoster infection to prevent the recurrence of the disease. Persons of the appropriate age should be vaccinated whether or not they report a prior episode of herpes zoster.[18] *Weak recommendation; low quality of evidence*	• For adults aged ≥50 years, for the prevention of herpes zoster and related complications, irrespective of prior receipt of varicella vaccine or ZVL • For the prevention of herpes zoster and related complications for immunocompetent adults who previously received ZVL • RZV is preferred over ZVL for the prevention of herpes zoster and related complications. *Strong recommendation; high quality of evidence*
Indication/Target population	• Immunocompetent adults age 60 and above without prior history of herpes zoster to prevent the disease • May be given to immunocompetent adults (>60 years old) with prior history of herpes zoster infection to prevent disease recurrence	• Prevention of herpes zoster in immunocompetent adults aged ≥50 years • Immunocompetent adults previously vaccinated with ZVL
Schedule	• Single dose	• 2 doses (0.5 ml each)
Administration	• Fully reconstituted dose of 0.65 ml, subcutaneous in deltoid area[1]	• Administered intramuscularly, 2–6 months apart

		• The vaccine series need not be restarted if more than 6 months have elapsed since the first dose. However, the efficacy of alternative dosing regimens has not been evaluated, data regarding the safety of alternative regimens are limited, and individuals might remain at risk for herpes zoster during a longer than recommended interval between doses 1 and 2. ◦ If the second dose of RZV is given <4 weeks after the 1st, the 2nd dose should be repeated. ◦ Two doses of the vaccine are necessary regardless of prior history of herpes zoster or prior receipt of ZVL.
Common adverse events	• Erythema, pain or tenderness, swelling, pruritus or warmth, occurred more commonly in zoster vaccine than placebo recipients, but these reactions were generally mild.[12]	• Pain, myalgia, and fatigue as most common adverse events; redness and swelling, shivering, fever, and gastrointestinal symptoms may also occur.
Contraindications	• Known anaphylactic reaction to any vaccine component or a previous dose, including to neomycin	• Known anaphylactic reaction to any component of the vaccine
Precautions	• Postponed in acute severe illness	• Postponed in acute severe illness • No safety data presently available for pregnant or lactating women; consider delaying vaccination.

* Formerly referred to as herpes zoster subunit vaccine or HZ/su)

Herpes zoster live attenuated vaccine should be given to immunocompetent adults age 60 and above without prior history of herpes zoster to prevent the disease.

Strong recommendation; moderate quality of evidence

Summary of evidence

There was a total of 13 included trials, which enrolled 69,916 participants comparing the VZV vaccine with placebo. Ten (53,381 participants) of the 13 trials studied the currently available live attenuated VZV vaccine, whereas the other 3 trials studied the adjuvanted recombinant VZV subunit zoster vaccine, which is not yet available in the market. Out of the 10 trials on the live attenuated VZV vaccine, only one trial namely the Shingles Prevention Study by Oxman et al., which was published in 2005 evaluated the incidence of herpes zoster virus infection.[2]

Participants in the study include older adults (mean age $\geq$60 years) who have had history of varicella without any immunosuppressive disorders.[4] The study evaluated the effectiveness of zoster vaccine versus placebo in reducing the incidence of herpes zoster with a median surveillance of 3.1 years and reported a significant reduction for this outcome in the vaccinated group: RR 0.49, 95% CI: 0.43 to 0.56. Although this was a significant difference in favor of the intervention, the magnitude of this effect was a risk difference of 2%, and the number needed to treat for an additional beneficial outcome was 50. The quality of the evidence was moderate due to one downgrade because of risk of bias (no description of the randomization process). The vaccinated group had a reduced incidence of herpes zoster as early as 30-days post-vaccination: RR 0.33, 95% CI: 0.13 to 0.84. These cases were excluded from the final intention-to-treat analysis. At 42-days post-vaccination, the benefits of vaccination are clear, with an RR of 0.29 (95% CI: 0.13 to 0.68).[2]

Question: Herpes zoster live attenuated vaccine compared to placebo for preventing herpes zoster infection among older adults

Bibliography: Gagliardi, A. M., Andriolo, B. N., Torloni, M. R., & Soares, B. G. O. (2016). Vaccines for preventing herpes zoster in older adults. *Cochrane Database of Systematic Reviews*, *3*(3), Art. No.: CD008858.

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Herpes zoster live attenuated vaccine	Placebo	Relative (95% CI)	Absolute (95% CI)		
Incidence of herpes zoster (follow up: mean 3.1 years; assessed with clinical and laboratory criteria)												
1	Randomized trial	Serious [a]	Not serious	Not serious	Not serious	None	315/19,270 (1.6%)	642/19,276 (3.3%)	Risk ratio 0.49 (0.43 to 0.56)	17 fewer per 1,000 (from 15 fewer to 19 fewer)	⨁⨁⨁◯ Moderate	Critical
One or more serious adverse event regardless of storage of the vaccine (follow up: median 3.1 years; assessed with clinical and laboratory criteria)												

Question: Herpes zoster live attenuated vaccine compared to placebo for preventing herpes zoster infection among older adults

Bibliography: Gagliardi, A. M., Andriolo, B. N., Torloni, M. R., & Soares, B. G. O. (2016). Vaccines for preventing herpes zoster in older adults. *Cochrane Database of Systematic Reviews*, *3*(3), Art. No.: CD008858.

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Herpes zoster live attenuated vaccine	Placebo	Relative (95% CI)	Absolute (95% CI)		
4	Randomized trials	Serious [a]	Serious [a,b]	Not serious	Not serious	None	595/25,437 (2.3%)	554/25,459 (2.2%)	Risk ratio 1.08 (0.96 to 1.20)	2 more per 1,000 (from 1 fewer to 4 more)	⨁⨁◯◯ Low	Critical
Adverse event: hospitalization (follow up: median 3.1 years; assessed with number of hospitalized subjects)												
1	Randomized trial	Serious [a]	Not serious	Not serious	Not serious	None	1,137/3,345 (34.0%)	1,115/3,271 (34.1%)	Risk ratio 1.00 (0.93 to 1.07)	0 fewer per 1,000 (from 24 fewer to 24 more)	⨁⨁⨁◯ Moderate	Critical
Adverse event: injection site adverse reaction (follow up: median 3.1 years)												

Question: Herpes zoster live attenuated vaccine compared to placebo for preventing herpes zoster infection among older adults

Bibliography: Gagliardi, A. M., Andriolo, B. N., Torloni, M. R., & Soares, B. G. O. (2016). Vaccines for preventing herpes zoster in older adults. *Cochrane Database of Systematic Reviews*, *3*(3), Art. No.: CD008858.

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Herpes zoster live attenuated vaccine	Placebo	Relative (95% CI)	Absolute (95% CI)		
3	Randomized trials	Serious [a]	Not serious	Not serious	Not serious	None	1,691/3,529 (47.9%)	580/3,457 (16.8%)	Risk ratio 2.99 (2.75 to 3.26)	334 more per 1,000 (from 294 more to 379 more)	⊕⊕⊕◯ Moderate	Critical
Drop-outs: death (follow up: median 3.1 years; assessed with number of deaths)												
3	Randomized trials	Serious [a]	Not serious	Not serious	Not serious	None	817/25,333 (3.2%)	809/25,354 (3.2%)	Risk ratio 1.01 (0.92 to 1.11)	0 fewer per 1,000 (from 3 fewer to 4 more)	⊕⊕⊕◯ Moderate	Critical

[a] No information about randomization; [b] Allocation concealment not stated

Although ZVL is FDA-approved for people aged 50 years and older, the ACIP declined to recommend the use of herpes zoster vaccine among adults aged 50 through 59, unless vaccine providers are anticipating that patients will have a poor tolerance of herpes zoster or post-herpetic neuralgia symptoms. Although the vaccine has short-term efficacy, there have been no long-term studies of vaccine protection in this age group.[19]

Table 8B. GRADE of live attenuated zoster vaccine (ZVL) studies: included data, by outcome[20]

Outcome	Number of subjects (number of studies)	Comparison groups	Findings
Prevention of herpes zoster	50-59y: 22,439 (1) ≥60y: ~4.7 million (8)	One dose ZVL vs placebo or no vaccine	Vaccine efficacy against herpes zoster, clinical trial data: [95% CI] • 50-59y: 70% [54-81] • 60-69y: 64% [56-71] • 70-79y: 41% [28-52] • ≥80y: 18% [-29-48] Vaccine efficacy from observational studies in adults ≥60y ranged from 33% to 51% (within 4 years post vaccination).
Prevention of post-herpetic neuralgia	≥60y: ~4 million (8)	One dose ZVL vs placebo or no vaccine	Vaccine efficacy against herpes zoster, clinical trial data: [95% CI] • 60-69y: 65.7% [20.4-86.7] • ≥70y: 66.8% [43.3-81.3] Vaccine efficacy from observational studies in adults ≥60y ranged from 41% to 69% (within 4 years post vaccination).
Duration of protection against herpes zoster (up to 4 years post vaccination)	≥60y: ~3.9 million (5)	One dose ZVL vs placebo or no vaccine	RCT (SPS, STPS, LTPS) vaccine efficacy ≥60y, by year post vaccination: • 1y: 62.0 [49.6–71.6] • 2y: 48.9 [34.7–60.1] • 3y: 46.8 [31.1–59.2] • 4y: 44.6 [20.5–61.8] • 5y: 43.1 [5.1–66.5] • 6y: 30.6 [−6.0 to 54.6] • 7y: 46.0 [28.4–60.2]

			• 8y: 31.1 [11.2–47.6] •9y: 6.8 [−16.5 to 26.4] •10y: 14.1 [−11.3 to 34.9] •11y: −1.7 [−57.1 to 37.9] Observational studies: ZVL wanes year by year. Beyond 4 years, all studies estimate vaccine efficacy ≤40% after 4 years post vaccination.
Serious adverse events	≥50y: ~712,000 (28)	One dose ZVL vs placebo or no vaccine	No differences in serious adverse events between vaccinated and placebo groups in RCTs. Overall found no serious adverse events associated with ZVL In clinical trials 2 subjects with varicella-like rashes and zoster like rashes had polymerase chain reaction confirmed Oka/Merck strain varicella.
Reactogenicity	≥50y: ~310,000 (25)	One dose ZVL vs placebo	Injection-site reactions were the most common adverse reaction related to vaccination. 4 studies reported moderate/severe (Grade 3) injection-site reactions that ranged between 0%-4% of vaccine recipients
Abbreviations y: Years old RCT: Randomized controlled trial SPS: Shingles Prevention Study STPS: Short-term Persistence Study LTPS: Long-term Persistence Study			

Table 8C. Summary of the evidence for select outcomes with the use of live attenuated zoster vaccine (ZVL) in immunocompetent adults aged 50 years and older[20]

Outcomes	Design (number of studies)	Initial evidence	Risk of bias	Inconsistency	Indirectness	Imprecision	Others	Evidence type	Outcome evidence type	Overall evidence type
Benefits										
Prevent herpes zoster	2 RCT	1	Not serious	Not serious	Not serious	Not serious	None	1		
	7 Observational studies	3	Serious [a] (-1)	Not serious	Not serious	Not serious	None	4	1	1
Prevent post-herpetic neuralgia	1 RCT	1	Not serious	N/A	Not serious	Not serious	None	1		
	2 RCT with limitations[c]	2	Not serious	Not serious	Not Serious	Serious (-1)	None	3	1	
	3 Observational studies	3	Serious [b] (-1)	Not serious	Not serious	Not serious	None	4		1
Duration of protection against herpes zoster (up to	2 RCT with limitations[c]	2	Not serious	Not serious	Not serious	Not serious	None	2		
	3 Observational studies	3	Serious [a]	Not serious	Not serious	Not serious	None	4	1	1

4 years post vaccination)			(-1)							
Harms										
Serious adverse events (after any dose)	8 RCT	1	Not serious	Not serious	Not serious	Not serious	None	1	1	1
	13 RCT with limitations	2	Serious [d] (-1)	Not serious	Not serious	Not serious	None	3		
	7 Observational studies	3	Serious [a] (-1)	Not serious	Not serious	Not serious	None	4		
Reactogenecity (Grade 3 reaction)	15 RCT	1	Not serious	Not serious	Not serious	Not serious	None	1	1	
	5 Non-RCT	2	Serious [d] (-1)	Not serious	Not serious	Not serious	None	3		
	5 Observational studies	3	Serious [a] (-1)	Not serious	Not serious	Not serious	None	4		

Abbreviations
ZVL: Live attenuated zoster vaccine
RCT: Randomized controlled trial

[a] Outcome assessors were likely aware of intervention received by participants.

[b] Outcome assessors were likely aware of intervention received by participants. Post-herpetic neuralgia may have been underreported. The diagnosis of the disease is based on healthcare encounters, not self-reports.

[c] Limitations due to comparison groups. During the Short-term Persistence Study, placebo participants could receive ZVL and censoring due to vaccination may have introduced bias that increased incidence of HZ among remaining placebo recipients. During the Long-term Persistence Study, there were no unvaccinated controls so comparison group was modeled.

[d] Studies were non-blinded, open-label trials with no comparison group.

Herpes zoster vaccine may be given to immunocompetent adults (>60 years old) with prior history of herpes zoster infection to prevent the recurrence of the disease.

Weak recommendation; low quality of evidence

Summary of evidence

While repeated zoster has been confirmed in immunocompetent persons after a previous episode, the actual risk of recurrence has not been firmly established. Moreover, the benefit of vaccinating immunocompetent patients who have had shingles has not been systematically examined.

A cohort study in Kaiser Permanente Southern California was conducted by Tseng et al. to compare the incidence of recurrent herpes zoster between the vaccinated and the unvaccinated matched cohorts. All members age ≥60 years who were vaccinated with zoster vaccine between 1 January 2007 and 31 December 2010 were identified through electronic health records and served as the vaccinated cohort. Subjects selected for this study needed to meet the following criteria: (1) they had not received a diagnosis of HZ during the 180-day period prior to the date of vaccination, which eliminated the possibility of HZ having been diagnosed during the period being carried forward into the follow-up period; (2) they had had at least 1 visit with a HZ diagnosis that included a prescription of anti-viral medication on the same day 180–730 days prior to vaccination (defined as the "reference period"), and (3) they had not received a diagnosis of HZ ≤1 year prior to the index HZ case (defined as the first HZ case diagnosed in the reference period), which ensured that the index HZ case was an incident episode rather than a carry-forward diagnosis from an earlier episode. An unvaccinated cohort that consisted of randomly sampled members who were matched 5:1 to the vaccinated cohort based on birth date (±1 year) was identified. Each unvaccinated person was assigned an index date that matched the vaccination date of the matched vaccinated member and was required to meet the 3 criteria listed for the vaccinated cohort. As the zoster vaccine is not recommended for immunocompromised patients, the researchers excluded them from both cohorts to increase their comparability in terms of underlying risk of HZ. Immunocompromised patients were defined as those with human immunodeficiency virus infection, leukemia, or lymphoma diagnoses or those having immunosuppressive agents prescribed during the period from ≤1 year before the index date until the end of follow-up.[11]

There were 1,036 vaccinated and 5,180 unvaccinated members included in the study. There were 97 incident HZ cases identified electronically during the follow-up period; 20 were in the vaccinated cohort, and 77 were in the unvaccinated cohort (RR 1.29; 95% CI: 0.79-2.11). This data supports the observation that recurrences of HZ are relatively uncommon in immunocompetent persons. Although there was a trend toward the incidence being lower in the vaccinated group, the scarcity of events precludes the ability to confirm a meaningful difference between groups.[11]

It is hypothesized that the occurrence of HZ is associated with a decline in host-specific, threshold level of VZV-specific cell-mediated immunity. Exogenous and endogenous exposures to infectious VZV may promote the maintenance of robust VZV memory immunity. The protection of high-potency Oka vaccine likely results from restoration of VZV-specific T cells to a level above the threshold, either by reversing a gradual decline from the original expansion of VZV-specific memory T cells or by substituting immunization for exogenous or endogenous re-exposure that boosts immunity. Data from this cohort study suggest that the short-term risk of HZ recurrence following a recent initial episode is low among immunocompetent adults, regardless of vaccination status.[11]

Question: Herpes zoster vaccination compared to unvaccinated cohorts for the prevention of recurrent episodes of herpes zoster in immunocompetent older adults

Setting: Kaiser Permanente Southern California

Bibliography: Tseng, H. F., Chi, M., Smith, N., Marcy, S. M., Sy, L. S., & Jacobsen, S. J. (2012). Herpes zoster vaccine and the incidence of recurrent herpes zoster in an immunocompetent elderly population. *Journal of Infectious Diseases*, *206*(2), 190–6.

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Herpes zoster vaccination	Unvaccinated cohorts	Relative (95% confidence interval)	Absolute (95% confidence interval)		
Incidence of recurrence of herpes zoster (follow-up: mean 3 years)												
1	Observational study	Not serious	Not serious	Not serious	Not serious	None	20/1,036 (1.9%)	77/5,180 (1.5%)	Risk ratio 1.29 (0.79 to 2.11)	4 more per 1,000 (from 3 fewer to 17 more)	⨁⨁◯◯ Low	

Herpes zoster adjuvanted recombinant vaccine (RZV) should be given to immunocompetent adults age 50 and above without prior history of herpes zoster to prevent the disease.

Strong recommendation; high quality of evidence

Summary of evidence

In January 2018, the ACIP released GRADE recommendations for the use of RZV. The report is considered a supplement to the 2008 Prevention of Herpes Zoster Recommendations of the ACIP, for the use of ZVL in adults age 60 years and older. Key outcomes considered critical in the GRADE process included prevention of herpes zoster, post-herpetic neuralgia, and serious adverse events following vaccination; outcomes considered important were that for duration of protection and reactogenecity. All outcomes were considered for both RZV and ZVL compared with no vaccination. There were no clinical studies that compared the vaccines directly with one another.[20] Tables 8D and 8E show the GRADE data of RZV studies.

Table 8D. Included data, by outcome, of RZV[20]

Outcome	Number of subjects (number of studies)	Comparison groups	Findings
Prevention of herpes zoster	50-59y: 7,017 (1) 60-69y: 4,307 (1) ≥70y: 16,596 (1)	2 dose RZV vs placebo	Vaccine efficacy [95% CI] • 50-59y: 96.6% [89.6-99.3] • 60-69y: 97.4% [90.1-99.7] • ≥70y: 91.3% [86.8-94.5]
Prevention of post-herpetic neuralgia	≥50y: 27,916 (1) ≥70y: 16,596 (1)	2 dose RZV vs placebo	Vaccine efficacy [95% CI] • ≥50y: 91.2% [75.9-97.7] • ≥70y: 88.8% [68.7-97.1]
Duration of protection against herpes zoster (up to 4 years post vaccination)	14,693 (1)	2 dose RZV vs placebo	Vaccine efficacy remained about 85% in the first 4 years following vaccination.
Serious adverse events	29,965 (8)	2 dose RZV vs placebo	No differences in serious adverse events between vaccinated and placebo groups. No serious adverse events related to vaccination found.
Reactogenicity (Grade 3 reaction)	10,590[a] (8)	2 dose RZV vs placebo	Grade 3 reactions[b] more commonly reported in vaccinated populations compared to placebo. In phase III clinical trials (n = 9,936): • 16.5% of vaccine recipients reported any Grade 3

			reaction compared to 3.1% of placebo recipients. • 9.4% of vaccine recipients reported Grade 3 injection-site reactions, compared to 0.3% of placebo recipients. • 10.8% of vaccine recipients reported Grade 3 systemic reactions, compared to 2.4% of placebo recipients. Safety and immunogenicity studies reported similar reactogenicity rates among participants receiving RZV.

Abbreviations
y: Years old
RZV: Recombinant zoster vaccine

[a] In the Zoster Efficacy Studies in Adults 50 years/70 years of Age or Older (ZOE 50/70) Phase III clinical trials, reactogenicity data was only collected from a randomly selected sub-set of participants (n = 9,936).

[b] Grade 3 solicited adverse events are those reactions related to vaccination which were severe enough to prevent normal activities. These may include injection-site reactions (i.e., pain, redness, and swelling), or systemic events (i.e., myalgia, fatigue, headache, fever, shivering, or gastrointestinal symptoms).

Table 8E. Summary of the evidence for select outcomes with use of RZV in immunocompetent adults aged 50 years and older[20]

Outcomes	Design (number of studies)	Initial evidence	Risk of bias	Inconsistency	Indirectness	Imprecision	Others	Evidence type	Outcome evidence type	Overall evidence type
Benefits										
Prevent herpes zoster	1 RCT	1	Not serious	Not serious	Not serious	Not serious	None	1	1	1
Prevent post-herpetic neuralgia	1 RCT	1	Not serious	Not serious	Not serious	Not serious	None	1	1	1
Duration of protection against herpes zoster (up to 4 years post vaccination)	1 RCT	1	Not serious	Not serious	Not serious	Not serious	None	1	1	1
Harms										
Serious adverse events	2 RCT	1	Not serious	Not serious	Not serious	Not serious	None	1	1	1
	4 RCT	1	Serious[a] (-1)	Not serious	Serious[b]	Not serious	None	3		

(after any dose)	with no placebo				(-1)					
	2 Non-RCT	2	Serious [a] (-1)	Not serious	Serious [b] (-1)	Not serious	None	4		
Reactogenecity (Grade 3 reaction)	2 RCT	1	Not serious	Not serious	Not serious	Not serious	None	1	1	
	4 RCT with no placebo	1	Serious [a] (-1)	Not serious	Serious [b] (-1)	Not serious	None	3		
	2 Non-RCT	2	Serious [a] (-1)	Not serious	Serious [b] (-1)	Not serious	None	4		

Abbreviations
RZV: Recombinant zoster vaccine
RCT: Randomized controlled trial

[a] Studies were non-blinded, open-label trials.

[b] No placebo comparison group. Did not directly meet our policy question of comparing outcomes between vaccine and placebo recipients

Based on the ACIP GRADE findings, vaccinating adults starting at age 50 will prevent disease incidence in midlife, and the vaccine will likely continue to provide substantial protection beyond 4 years as recipients age. RZV may be used in adults aged ≥50 years, irrespective of prior receipt of varicella vaccine or ZVL, and does not require screening for a history of chickenpox (varicella). ZVL, meanwhile, remains a recommended vaccine for prevention of herpes zoster in immunocompetent adults aged ≥60 years.

The ACIP report also recommends the use of RZV in immunocompetent adults who have previously received ZVL: in all age categories, especially those ≥70 years old, RZV estimates of efficacy against herpes zoster were higher than ZVL estimates. Studies have shown that ZVL effectiveness wanes substantially over time, leaving recipients with reduced protection against herpes zoster. RZV elicited similar safety, reactogenicity, and immunogenicity profiles regardless of prior ZVL receipt.

As to the timing of RZV for persons previously vaccinated with ZVL, there are no data or theoretical concerns to indicate that RZV would be less safe or less effective when administered at an interval of <5 years. Clinical trials indicated lower efficacy of ZVL in adults aged ≥70 years; therefore, a shorter interval may be considered based on the recipient's age when ZVL is administered. Based on expert opinion, RZV should not be given <2 months after receipt of ZVL.

Adverse events from herpes zoster vaccine

Zoster vaccine was generally well tolerated in adults >50 years. Non-serious injection-site reactions, including erythema, pain or tenderness, swelling, pruritus or warmth, occurred more commonly in zoster vaccine than placebo recipients, but these reactions were generally mild.[12]

In the Shingles Prevention Study, all adverse events that occurred within 42 days of vaccination were recorded, and an adverse event sub-study was carried out, which involved 3,345 participants who received the vaccine and 3,271 who received placebo. Overall, in the 42 days post injection, similar types and low numbers (both 1.4%) of serious adverse events occurred in both groups. During the whole study, a similar number of deaths occurred in vaccine and placebo groups (both 4.1%). Varicella-like rash, a non-serious adverse event, was more common in the vaccine group than in the placebo group. For rashes at the injection site, the difference in risk was significant (0.1% versus 0.04%, $p < 0.05$) while insignificant at other sites (0.1% versus 0.1%, $p > 0.05$).[4] In the safety sub-study, however, rates of all kinds of adverse events and serious adverse events were both significantly higher in the vaccine group (RR 1.69; 95% CI: 1.60 to 1.79) than the placebo group (RR 1.53; 95% CI: 1.03 to 2.25). The incidence of serious adverse events was low (1.91% and 1.25% for each group), and the authors claimed that no clinically meaningful differences were found between groups according to a subject-to-subject review of serious adverse events.[4] Adverse events at the injection site were more common among vaccine recipients than placebo recipients ($p < 0.05$) as well as among the total subjects, but they were mild and resolved in a few days. The same pattern of adverse events was reported when zoster vaccine was administered in patients with chronic illnesses,[13] with or without influenza vaccine,[14] or as a refrigerator-stable or frozen formulation.[15] There were significantly more local injection-site adverse effects when zoster vaccine was administered concomitantly with pneumococcal vaccine over sequential administration,[16] providing further justification for not administering the two vaccines concomitantly.

Furthermore, over the entire study period no Merck/Oka vaccine DNA strain was detected in any participants with confirmed herpes zoster, which indicated that vaccination did not cause or induce herpes zoster. Zoster vaccine used in the Shingles Prevention Study was considered safe for its recipients.[5]

Although the primary studies did not assess adverse events associated with autoimmune diseases, a matched case-control study that collected data from May 2006 to November 2014 was conducted by the Vaccine Adverse Event Reporting System (a national vaccine safety surveillance database maintained jointly by the United States Centers for Disease Control and Prevention and the Food and Drug Administration) to clarify severe autoimmune adverse events post live attenuated herpes zoster vaccine. The adverse events assessed were arthritis, vasculitis, systemic lupus erythematosus, thrombocytopenia, alopecia, Guillain-Barré syndrome, optic neuritis, and multiple sclerosis. That study reported a higher incidence of arthritis and alopecia, after vaccination. Compared to the unexposed, patients with zoster vaccination had 2.2 and 2.7 times the odds of developing arthritis and alopecia, respectively (p value < 0.001 and p value = 0.015, respectively).[17]

For RZV, in 8 studies involving almost 11,000 subjects, Grade 3 injection-site reactions (pain, redness, and swelling) were reported by 9.4% of vaccine recipients (vs 0.3% of placebo recipients), and Grade 3 solicited systemic events (myalgia, fatigue, headache, shivering, fever, and gastrointestinal symptoms) was noted in ~11% of vaccine recipients (vs 2.4% of placebo recipients). Overall, the most common solicited adverse reactions were pain (78%), myalgia (45%), and fatigue (45%).[20,22]

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Human papillomavirus vaccine

Forty types of the human papillomavirus have been consistently associated with genital warts and cancer of the cervix, vulva, vagina, penis, anus, head, neck and respiratory tract, with the types categorized according to their epidemiologic association with cervical cancer. Types 6 and 11 (low-risk or non-oncogenic types) cause 90% of benign or low-grade cervical cell abnormalities, anogenital warts, and laryngeal papillomas. High-risk or oncogenic types (i.e., 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69, 73, and 82) cause 99.7% of low-grade cervical cell abnormalities, high-grade cervical cell abnormalities that are precursors to cancer, and ano-genital cancers.

Humans are the only reservoir. The risk of acquiring HPV infection is 50% during one's lifetime. More than 80% of sexually active women will have been infected by age 50. Risk factors include cigarette smoking, high parity, increased age, immune suppression, long-term oral contraceptive use, co-infection with other sexually transmitted diseases (e.g. HIV, gonorrhea), other host factors (diet, genetics), and endogenous hormones.[1]

Table 9A. Available vaccines against human papillomavirus (HPV)

	Vaccine type		
	Bivalent	**Quadrivalent**	**Nonavalent**
Brand name	Cervarix	Gardasil	Gardasil 9
Virus-like particles	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58
Manufacturer	GlaxoSmithKline	Merck and Co., Inc.	Merck and Co., Inc.
Volume per dose	0.5 ml	0.5 ml	0.5 ml

A case-control study by Ngelangel et al.[2] showed that HPV type 16 was the most common HPV type in women with cervical squamous cell carcinoma followed by HPV types 18, 45, 52, and 51 (Table 9-1). On the other hand, HPV type 18 was the most common in women with cervical adenocarcinoma/adenosquamous carcinoma, followed by types 16 and 45. A recent report by Institut Catala d'Oncologia presented the prevelance of HPV types that cause cervical cancer in the Philippines, in decreasing order of frequency: 16, 18, 45, 52, 58, 59, 51, 66, 31, and 56.[3]

In anal cancer, HPV 16 is the most common type detected, followed by HPV 18 representing 78% and 5% of HPV-positive tumors, respectively.[4] However there are no local data on the prevalence of HPV among cases of anal cancer.[3]

Meanwhile, from 2011 to 2015, 11 Philippine Dermatologic Society institutions diagnosed 952 cases of anogenital warts, most of which were found in men (Figure 1).

Table 9B. Vaccine serotypes comparison to most common human papillomavirus (HPV) serotypes in the Philippines

Available vaccines against HPV				Most common HPV serotypes in the Philippines[a]	Most common HPV serotypes in the Philippines in women with cervical squamous cell carcinoma[a]	Most common HPV serotypes in the Philippines in women with cervical adenocarcinoma/ adenosquamous carcinoma[a]
Characteristic	Vaccine type			16, 18, 45, 52, 58, 59, 51, 66, 31, 56	16, 18, 45, 52, 51	18, 16, 45
	Bivalent	Quadrivalent	Nonavalent			
Brand name	Cervarix	Gardasil	Gardasil 9			
Virus-like particles	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58			
Manufacturer	Glaxo Smith Kline	Merck and Co., Inc.	Merck and Co., Inc.			
Volume per dose	0.5 ml	0.5 ml	0.5 ml			

[a] In decreasing order of frequency

Figure 1. Anogenital HPV cases in 11 Philippine Dermatologic Society institutions, 2011-2015

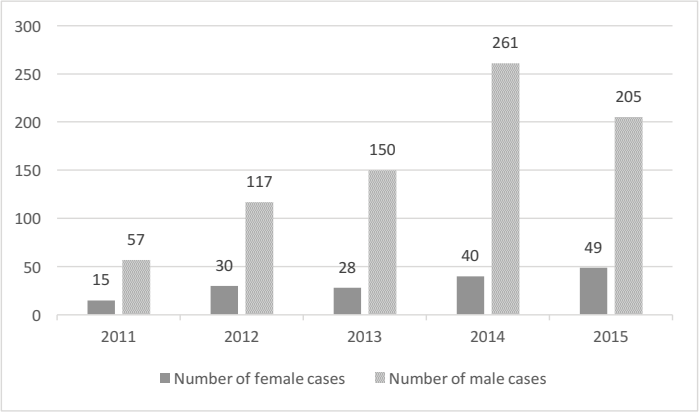

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Table 9C. Human papillomavirus vaccine for adults

	Bivalent	Quadrivalent	Nonavalent
Description	• Contains 20 mcg each of types 16 and 18 L1 major capsid protein, self-assembled as intact, non-infectious virus-like particles[9]	• Contains types 6 (20 mcg), 11 (40 mcg), 16 (40 mcg), 18 (20 mcg) L1 major capsid protein, self- assembled as intact, non-infectious virus-like particles[9]	• Each 0.5-mL dose contains type 6 (30 mcg), type 11 (40 mcg), type 16 (60 mcg), type 18 (40 mcg), type 31 (20 mcg), type 33 (20 mcg), type 45 (20 mcg), type 52 (20 mcg), and type 58 (20 mcg) L1 major capsid protein, self- assembled as

			intact, non-infectious virus-like particles.[10]
Recommendation Indication*/ Target population (See text below table for summary of evidence)	• Effective in preventing cervical cancer associated with HPV 16/18 among immunocompetent adult females and can be given until 26 years old. *Strong recommendation; high quality of evidence*	• 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*	
		• May be given to adult immunocompetent males from ages 16-26 for the prevention of anal cancer and genital warts *Strong recommendation; moderate to high quality of evidence*	
	Bivalent	Quadrivalent	Nonavalent
Schedule	0, 1, 6 months	0, 2, 6 months	
	• If the dose schedule is interrupted, no need to restart the dosing regimen. If the regimen is interrupted after the first dose, the second dose should be administered and give the third dose at least after 12 weeks. • Nonavalent HPV vaccine may be given to continue or complete a three-dose schedule series that started with bivalent or quadrivalent vaccine.		• If vaccination providers do not know or do not have the HPV vaccine product previously administered, or are in settings transitioning to nonavalent vaccine, any available HPV vaccine product may be used to continue or complete the series for females and males for protection against HPV 16 and 18.
Administration	• Intramuscular, deltoid area • Observe patients for 15 minutes after administration.		
Common adverse events	• Mostly injection site-related pain, swelling, and erythema that were mild to moderate in intensity • Systemic symptoms were dizziness, nausea, headache, and urticaria.		
Contraindications	• History of immediate hypersensitivity to yeast or to any vaccine component or following a prior dose		
Precautions	• Moderate or severe acute illness		

Pregnancy	• Pregnant women are not recommended to receive HPV vaccine, although there is no evidence that the vaccine poses harm. If a woman is found to be pregnant after initiating the HPV vaccination series, delay the remaining doses until after the pregnancy. No other intervention is needed. Pregnancy testing is not needed before administering HPV vaccine.[8]

* Before potential exposure to HPV through sexual activity, females who are sexually active, sexually active females who have not been infected with any of the four HPV vaccine types

Summary of evidence

Bivalent HPV vaccine

A study on Asian population was identified where a phase II/III randomized, double-blind, placebo-controlled trial among 6,000 Chinese women aged 18-25 years old to determine the efficacy of bivalent HPV vaccine. Result of vaccine efficacy for the prevention of ≥CIN1 and/or 6-months persistent infection (CIN1+/6M PI) associated with HPV 16/18 is 94.2% (95% CI: 62.7, 99.99) as per according-to-protocol cohort for efficacy.[1] A multicenter, randomized, double-blind, controlled, and extended 72-month post-vaccine follow-up study was done to evaluate vaccine efficacy against development of ≥CIN2 among subjects from previous trial with successful vaccine efficacy against CIN1+/6M PI from HPV 16/18. As per according-to-protocol cohort for efficacy, vaccine efficacy showed 87.3% (95% CI: 5.3–99.7) in women who are HPV DNA-negative and seronegative at baseline pre-vaccination.[2]

A meta-analysis of randomized clinical trials of HPV vaccine among Asian women aged 18-25 years old reported a significant seroconversion of HPV 16 and 18 antibodies. In the sub-analysis of vaccine types, the pooled relative risk of bivalent HPV vaccine's immunogenicity on HPV 16 and 18 were 44.86 (95% CI: 11.90–169.15) and 43.22 (95% CI: 25.35–73.68), respectively, showing a significant increase in seroconversion due to vaccination.[3]

Quadrivalent and nonavalent HPV vaccines

Both vaccines protect against HPV 16 and 18 that causes the majority (around 66%) of cervical cancers and other HPV-associated malignancies. The nonavalent vaccine covers additional five HPV types, which account for about 15% of cervical cancers.[4] In a randomized, international, double-blind, phase IIb–phase III study comparing quadrivalent and nonavalent among 14,000 females aged 16-26 years old, nonavalent efficacy for the prevention of ≥CIN2 caused by HPV 31, 33, 45, 52, or 58 was 96.3% in the per protocol population. Efficacy for the prevention of high-grade cervical neoplasia, adenocarcinoma in situ, and cervical cancer caused by HPV 31, 33, 45, 52, 58 was 96.3% (95% CI: 79.8, 99.8). There were a few cases of ≥CIN2 caused by HPV 6, 11, 16, or 18 in both vaccines with no statistical difference. Both the quadrivalent and nonavalent vaccines also protected against HPV 6 and 11 types that cause anogenital warts, with no statistical significance between two groups.[5] Non-inferior immunogenicity of nonavalent vaccine compared with quadrivalent vaccine was used to infer efficacy for HPV 6, 11, 16, and 18.[6]

The ACIP recommends that vaccination series can be started at age 9. Vaccination for females can be given at ages 13 to 26 who have not been previously vaccinated or who have not completed the 3-dose regimen.[7]

Question: Should HPV bivalent vaccine be used for the prevention of cervical cancer?

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Quality assessment							Summary of findings				
Participants, (number of studies), follow-up period	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% confidence interval)**	**Anticipated absolute effects**	
							With control	**With HPV bivalent vaccine**		**Risk with Control**	**Risk difference with HPV bivalent vaccine (95% confidence interval)**
Cervical intraepithelial neoplasia (CIN)2+ associated with HPV types 16, 18 (2) (assessed with: cytology/histopathology)											
5,059 (1 study) 72 months	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⨁⨁⨁⨁ High	8/2535 (0.32%)	1/2524 (0.04%)	Vaccine efficacy (%) 87.3 (5.3 to 99.7)	Study population	
										3 per 1,000	272 more per 1,000 (from 14 more to 311 more)

										Moderate	
											-
CIN1+/6M PI associated with HPV types 16, 18 (1) (assessed with: cytology/histopathology)											
4,999 (1 study) 48 months	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⨁⨁⨁⨁ High	17/2502 (0.68%)	1/2497 (0.04%)	Vaccine efficacy (%) 94.2 (62.7 to 99.99)	Study population	
										7 per 1,000	633 more per 1,000 (from 419 more to 673 more)
										Moderate	
											-

Question: Should quadrivalent and nonavalent HPV vaccine be used for cervical cancer and anogenital warts among immunocompetent females aged 16-26 years old?

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Quality assessment	Summary of findings

Participants, (number of studies), follow-up period	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% confidence interval)	Anticipated absolute effects	
							With control	With quadrivalent and nonavalent HPV vaccine		Risk with control	Risk difference with quadrivalent and nonavalent HPV vaccine (95% confidence interval)
High-grade cervical neoplasia, adenocarcinoma in situ, and cervical cancer for HPV types 6, 11, 16, 18 (1)											
11,655 (1 study)	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⨁⨁⨁⨁ High	1/5,832 (0.02%)	1/5,823 (0.02%)	-	Study population	
											0 fewer per 1,000 (from 0 fewer to 0 fewer)
High-grade cervical neoplasia, adenocarcinoma in situ, and cervical cancer for HPV types 31, 33, 45, 56, 58 (1)											
11,891 (1 study)	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⨁⨁⨁⨁ High	27/5,943 (0.45%)	1/5,948 (0.02%)	Risk reduction 96.3 (79.8 to 99.8)	Study population	
										5 per 1,000	433 more per 1,000 (from 358 more to 449 more)

Anogenital warts HPV types 6, 11 (1)											
11,752 (1 study)	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⨁⨁⨁⨁ High	1/5,876 (0.02%)	5/5,876 (0.09%)	-	Study population	
											0 fewer per 1,000 (from 0 fewer to 0 fewer)

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Summary of evidence

Quadrivalent HPV vaccine for males

Studies on quadrivalent HPV vaccine were done among males with primary outcomes on vaccine efficacy against external genital warts and anal intraepithelial neoplasia for anal cancer. A study by Palefsky et al.[1] performed a randomized, placebo-controlled, double-blind trial of quadrivalent HPV vaccine among 602 MSM aged 16-26 years old who were HIV-negative at the start of the trial. Vaccine efficacy against anal intra-epithelial neoplasm from HPV 6, 11, 16, and 18 in the intention-to-treat population showed a reduction of 50.3% (95% CI: 25.7, 67.2) while 77.5% in the per-protocol efficacy population (95% CI: 39, 6, 93.3). Similarly, another trial was done observing vaccine efficacy of quadrivalent HPV vaccine to reduce external genital warts among males 18-26 years old. In the intention-to-treat population, observed efficacy was noted at 50.3% (95% CI: 25.7, 67.2) against genital warts associated with HPV types 6, 11, 16, and 18. Per-protocol population showed 90.4% reduction (95% CI: 69.2, 98.1).[2]

Nonavalent HPV vaccine for males

There are no studies on nonavalent HPV vaccines that measured clinical outcomes in men. A randomized, double-blind, controlled trial in 500 males aged 16-26 years old were evaluated for immunogenicity following vaccination between quadrivalent and nonavalent HPV vaccine. Antibody levels against HPV 6, 11, 16, and 18 at month 7 after three-dose regimen with nonavalent HPV vaccine showed to be non-inferior compared to quadrivalent group. Anti-HPV 31/33/45/52/58 GMTs were at least 2-fold up to 15-fold higher in the nonavalent vaccine group versus quadrivalent group.[3] Another multi-center study involving 1,106 heterosexual men, 1,101 women, and 313 MSM aged 16-26 years old were evaluated for immunogenicity after 3-dose regimen of nonavalent vaccine. Results showed that more than 99% of subjects showed an increase in GMT titers after 7 months of 3-dose regimen in all groups. The GMT for 9 HPV type strains were non-inferior between HM and women.[4]

The ACIP recommends quadrivalent or nonavalent HPV vaccine can be administered to males aged 13 to 21 years old who were not previously immunized or who failed to complete 3-dose regimen. Males aged 22 to 26 may also be vaccinated.[5]

There are no available recommendations for bivalent HPV vaccine in males.

Question: Should quadrivalent HPV vaccine be used for the prevention of genital warts and anal cancer among immunocompetent males?

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Quality assessment							Summary of findings				
Participants, (number of studies), follow-up period	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% confidence interval)**	**Anticipated absolute effects**	
							With control	**With quadrivalent HPV vaccine**		**Risk with control**	**Risk difference with quadrivalent HPV vaccine (95% confidence interval)**
Genital warts types 6, 11, 16, 18 as per-protocol population (1)											
2,805 (1 study)	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⨁⨁⨁⨁ High	31/1,408 (2.2%)	3/1,397 (0.21%)	Vaccine efficacy (%) 90.4 (69.2 to 98.1)	Study population 22 per 1,000	1,000 more per 1,000 (from

											1,000 more to 1,000 more)
Genital warts types 6, 11, 16, 18 as per intention-to-treat analysis (1)											
4,065 (1 study)	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⨁⨁⨁⨁ High	77/2,033 (3.8%)	27/2,032 (1.3%)	-	Study population	
										38 per 1,000	38 fewer per 1,000 (from 38 fewer to 38 fewer)
Anal intra-epithelial neoplasm associated with HPV types 6, 11, 16, 18 as per intention-to-treat analysis (2)											
551 (1 study)	No serious risk of bias	No serious inconsistency	Serious [a]	No serious imprecision	Undetected	⨁⨁⨁ Moderate	77/276 (27.9%)	38/275 (13.8%)	Vaccine efficacy (%) 50.3 (25.7 to 67.2)	Study population	
										279 per 1,000	1,000 more per 1,000 (from 1,000 more to 1,000 more)

Outcome: anal intra-epithelial neoplasm associated with HPV types 6, 11, 16, 18 as PPA (2)											
402 (1 study)	No serious risk of bias	No serious inconsistency	Serious [a]	No serious imprecision	Undetected	⨁⨁⨁ Moderate	24/208 (11.5%)	5/194 (2.6%)	Vaccine efficacy (%) 77.5 (39.6 to 93.3)	Study population	
										115 per 1,000	1,000 more per 1,000 (from 1,000 more to 1,000 more)

[a] Mostly Caucasians

Question: Should HPV vaccine be used for the prevention of genital warts and anal cancer in immunocompetent adult males?

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Quality assessment							
Participants, number of studies, follow-up period	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**
Van Damme et al.[1] (outcome assessed: non-inferiority GMT antibody levels per HPV type between quadrivalent and nonavalent HPV vaccine)							
500 males, 1 study, 7 months	Randomized trial	Not serious	Not serious	Serious[a]	Not serious	Not detected	⨁⨁⨁ Moderate
Castellsagué et al.[2] (outcome assessed: non-inferiority GMT antibody levels per HPV type between men and women aged 16-26 years old)							
1,106 heterosexual men, 313 men who have sex with men, and 1,101 women; 1 study; 7 months	Randomized trial	Not serious	Not serious	Serious[a]	Not serious	Not detected	⨁⨁⨁ Moderate

[a] Outcome measures assessed were GMT antibody levels

Table 9D. Summary of month 7 GMT ratio between nonavalent and quadrivalent vaccine groups of males aged 16-26; HPV-specific per-protocol immunogenicity[a]

HPV type antibody	Nonavalent (*N = 249)*			Quadrivalent (*N = 251)*			Estimated GMT ratio nonavalent/quadrivalent (95% confidence interval)[c]
	n	GMT (mMu/ml)	95% confidence interval	n	GMT (mMu/ml)[b]	95% confidence interval[b]	
Anti-HPV 6	228	758.3	665.9; 863.4	226	618.4	554.0; 690.3	1.23 (1.04; 1.45)
Anti-HPV 11	228	681.7	608.9; 763.4	226	769.1	683.5; 865.3	0.89 (0.76; 1.04)
Anti-HPV 16	234	3924.1	3513.8; 4382.3	237	3787.9	3378.4; 4247.0	1.04 (0.89; 1.21)
Anti-HPV 18	234	884.3	766.4; 1020.4	236	790.9	683.0; 915.7	1.12 (0.91; 1.37)

Abbreviations
mMu: milli-Merck unit
N: number of randomized participants in the respective vaccination group
n: number of participants contributing to the analysis

[a] Van Damme, P., Meijer, C. J., Kieninger, D., Schuyleman, A., Thomas, S., Luxembourg, A., & Baudin, M. (2016). A phase III clinical study to compare the immunogenicity and safety of the 9-valent and quadrivalent HPV vaccines in men. *Vaccine*, *34*(35), 4205-4212.

[b] The estimated GMT ratio and associated CI are based on an analysis of variance model including group and age strata as independent variables.

[c] Non-inferiority was achieved if the lower bound of the two-sided 95% CI for the GMT ratio was greater than 0.50.

Table 9E. Per-protocol analysis of non-inferiority anti-HPV geometric mean titers at month 7 between heterosexual males and women aged 16-26[a]

HPV type anti	Heterosexual males (*N = 1,103)*		Women (*N = 1,099)*		Heterosexual males/women	
	n	GMT (mMu/ml)	*n*	GMT (mMu/ml)	GMT Ratio	95% confidence
Anti-HPV 6	847	782.0	708	703.9	1.11	(1.02, 1.21)
Anti-HPV 11	851	616.7	712	564.9	1.09	(1.00, 1.19)
Anti-HPV 16	899	33460.0	781	2788.3	1.20	(1.10, 1.30)
Anti-HPV 18	906	808.2	831	679.8	1.19	(1.08, 1.31)

Anti-HPV 31	908	708.5	826	570.1	1.24	(1.13, 1.37)
Anti-HPV 33	901	384.8	853	322.0	1.19	(1.10, 1.30)
Anti-HPV 45	909	235.6	871	185.7	1.27	(1.14, 1.41)
Anti-HPV 52	907	386.8	849	335.2	1.15	(1.05, 1.26)
Anti-HPV 58	897	509.8	839	409.3	1.25	(1.14, 1.36)

Abbreviations
mMu: milli-Merck unit
N: number of individuals randomized to the respective vaccination group
n: number of individuals contributing to the analysis

[a] Castellsagué, X., Giuliano, A. R., Goldstone, S., Guevara, A., Mogensen, O., Palefsky, J. M., …Kaplan, S. S. (2015). Immunogenicity and safety of the 9-valent HPV vaccine in men. *Vaccine*, *33*(48), 6892-6901.

[b] 95% CI was computed from an analysis of variance model with log of antibody titers as the response and vaccination group as fixed effect. Non-inferiority was established when the lower bound of the two-sided 95% CI of GMT ratio between HM and women was greater than 0.67 for each HPV type.

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[5] Petrosky, E., Bocchini, J. A. Jr., Hariri, S., Chesson, H., Robinette Curtis, C., Saraiya, M., …Markowitz, L. E. (2015). Use of 9-valent human papillomavirus (HPV) vaccine: Updated HPV vaccination recommendations of the Advisory Committee on Immunization Practices. *Morbidity and Mortality Weekly Report, 64*(11), 300-304.

Dosing schedule recommendations

Bivalent and quadrivalent HPV vaccines are given in a 3-dose schedule (0, 1, 6 months). If the vaccine schedule is interrupted, the vaccination series does not need to be restarted. The ACIP recommends that in cases of inadequate doses or doses received at an earlier recommended dosing interval should be re-administered. If the dose schedule is interrupted both for bivalent and quadrivalent, no need to restart the dosing regimen. If the regimen is interrupted after the first dose, the second dose should be administered and give the third dose at least after 12 weeks.[1]

Nonavalent HPV vaccine is also given as a 3-dose schedule (0, 1, 6 months). If vaccination providers do not know or do not have the HPV vaccine product previously administered, or are in settings transitioning to nonavalent vaccine, any available HPV vaccine product may be used to continue or complete the series for females for protection against HPV 16 and 18;

nonavalent or quadrivalent vaccine may be used to continue or complete the series for males. There are no data on efficacy of fewer than 3 doses of nonavalent vaccine.[2]

Nonavalent HPV vaccine may be given to continue or complete a three-dose schedule series that started with bivalent or quadrivalent vaccine. However, there is no ACIP recommendation regarding giving additional doses of nonavalent HPV vaccine for individuals who started the dosing series with bivalent or quadrivalent HPV vaccine and completed with one or two doses of nonavalent HPV vaccine. Similarly, there are no current recommendations for additional nonavalent HPV vaccine doses for those who have previously completed bivalent or quadrivalent HPV vaccine, since majority of HPV-related cancers are caused by HPV 16 or 18. The benefit of protection against the five additional serotypes by nonavalent HPV vaccine would be mostly limited to females, since there is only a small percentage of HPV-associated cancers in males from the five-additional serotypes addressed by nonavalent HPV vaccine.[3]

References

[1] Centers for Disease Control and Prevention. (2014). Human papillomavirus vaccination: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Report*, *63*(5), 3-36. Retrieved from https://www.cdc.gov/mmwr/pdf/rr/rr6305.pdf

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[3] Centers for Disease Control and Prevention. Supplemental information and guidance for vaccination providers regarding use of 9-valent HPV. Retrieved from https://www.cdc.gov/hpv/downloads/9vhpv-guidance.pdf

Influenza virus vaccine

Influenza A and B viruses are important human respiratory pathogens which are transmitted mainly by droplets and aerosols originating from the respiratory secretions of infected people and, occasionally, also through contact with virus-contaminated fomites. Both A and B viruses cause seasonal influenza epidemics and out-of-season sporadic cases and outbreaks. Complications of influenza include otitis media, pneumonia, secondary bacterial pneumonia, and exacerbations of chronic respiratory disease.

Table 10A. Influenza vaccine in adults [a]

	Trivalent influenza vaccine [b]	**Quadrivalent influenza vaccine**
Description	Contains 2 influenza A strains covering AH1N1 and AH3N2, and 1 influenza B virus, depending on prevailing WHO recommendation	Contains 4 influenza surface antigens covering for AH1N1 and AH3N2 viruses, and both B viruses (Victoria and Yamagata)
Recommendation, summary of evidence, indication/target population (See text below table.)	• Inactivated influenza vaccine is routinely recommended in preventing influenza and influenza-like illness in immunocompetent adults. • Efficacy of inactivated vaccines in preventing confirmed influenza is 60% (95% CI: 53% to 66%) with a number needed to vaccinate of 71 (95% CI: 64 to 80). When the vaccine content matches the circulating strain, the efficacy is 62% (95% CI: 52% to 69%) and the number needed to vaccinate is 58 (95% CI: 52 to 69). *Strong recommendation; moderate quality of evidence*	
	• The use of the inactivated influenza vaccine versus placebo is effective in preventing the occurrence of influenza or influenza-like illness. However, there is no benefit as to preventing mortality for the elderly population. *Strong recommendation; moderate quality of evidence*	
	• Influenza vaccine may be given to patients with cancer to prevent all-cause mortality and pneumonia. *Weak recommendation; low to moderate quality of evidence*	
	• Influenza vaccine should be administered to patients with HIV with CD4 count >100 cells/ul to prevent laboratory-confirmed influenza. *Strong recommendation; moderate quality of evidence*	
	• To prevent influenza-related respiratory infections and hospitalizations, influenza vaccine should be given to patients with bronchial asthma, COPD and cardiovascular disease. *Strong recommendation; moderate to high quality of evidence*	

	• Influenza vaccine may be given to patients with end-stage renal disease. *Weak recommendation; very low quality of evidence*
Schedule	• Yearly
Administration	• Intramuscular, deltoid area
Common adverse events	• Local tenderness and soreness • Safety profile of the vaccines is acceptable
Contraindications	• Severe allergic reaction to vaccine component[c] or following prior dose of the vaccine
Precautions	• Moderate to severe acute illness • Guillain-Barré syndrome
Pregnancy and breastfeeding	• No evidence that inactivated influenza vaccine causes damage to the fetus. • Inactivated influenza vaccine can be administered to those who are pregnant in the 2nd or 3rd trimester or planning to be pregnant during the influenza season

[a] All influenza vaccines are only good for 1 year. The vaccines are available in the Philippines from February-June.

[b] Will soon be replaced completely by the quadrivalent vaccine

[c] Some inactivated influenza vaccines: traces of eggs (such as ovalbumin, chicken proteins), formaldehyde, gentamicin sulphate and sodium deoxycholate which are used during the manufacturing process. Excipients include sodium chloride, disodium phosphate dodecahydrate, potassium dihydrogen phosphate, potassium chloride, magnesium chloride hexahydrate, α-tocopheryl hydrogen succinate, polysorbate 80, octoxinol 10 and water for injections. Other inactivated vaccines may also contain excipients such as cetyltrimethylammonium bromide and magnesium chloride hexahydrate.[15]

Summary of evidence

Immunocompetent adults

A meta-analysis containing 116 studies of healthy adults aged 16-65 years old[1] showed the use of the inactivated influenza vaccine is more effective in preventing the occurrence of influenza or influenza-like illness versus placebo or no intervention, but it has no benefit in preventing hospitalization. Influenza vaccine is 16% effective in preventing influenza-like illness and 60% effective in preventing confirmed influenza in antigenically matched strains. The vaccine is 10% effective in preventing influenza-like illness and 55% effective in preventing confirmed influenza in unmatched or unknown strains.

Data from RCTs showed that inactivated vaccines reduced influenza-like illness episodes compared to placebo or no intervention (RR 0.83; 95% CI: 0.78, 0.87), however heterogeneity is high. In a subgroup analysis, WHO recommended-matching vaccine is effective in preventing influenza-like illness (RR 0.83; 95% CI: 0.77, 0.89) as well as WHO-recommended vaccines where the strains were unknown or absent (RR 0.82; 95% CI: 0.75, 0.90).

The efficacy of inactivated vaccines in preventing confirmed influenza is 60% (95% CI: 53% to 66%) with a number needed to vaccinate of 71 (95% CI: 64 to 80).[1] When the vaccine content matches the circulating strain, the efficacy is 62% (95% CI: 52% to 69%) and the number needed to vaccinate is 58 (95% CI: 52 to 69). The results are very similar when matching is absent or unknown (vaccine efficacy 55%; 95% CI: 41%to 66%) and number needed to vaccinate of 60 (95% CI: 50 to 80).

These paradoxical results, showing an apparently higher specific effectiveness and a lower specific efficacy, are mainly because influenza-like illness and confirmed influenza have a very different incidence among the study population: 15.6% of unvaccinated participants versus 9.9% of vaccinated participants developed influenza-like illness symptoms, while the corresponding figures for participants who developed laboratory-confirmed influenza are 2.4% and 1.1% for unvaccinated and vaccinated people, respectively.

In an RCT composed of healthy working adults, vaccination with unknown matching shows no appreciable effect on working days lost or hospitalization (RR 2.89; 95% CI: 0.12, 70.68).[2]

Question: Should influenza vaccine (compared to placebo) be used in healthy adults?

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Quality assessment							Summary of findings				
Participants, (number of studies), follow-up period	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% confidence interval)**	**Anticipated absolute effects**	
							With no vaccination	**With influenza vaccination**		**Risk with no vaccination**	**Risk difference with influenza vaccination (95% confidence interval)**
Influenza-like illness											
20,942 (7 studies)	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⨁⨁⨁⨁ High	675/7,184 (9.4%)	977/13,758 (7.1%)	Risk ratio 0.82 (0.75 to 0.90)	Study population	
										94 per 1,000	17 fewer per 1,000 (from 9 fewer to 23 fewer)

										Moderate	
											-
Influenza											
15,068 (7 studies)	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⨁⨁⨁⨁ High	151/4,967 (3%)	150/1,0,101 (1.5%)	Risk ratio 0.44 (0.35 to 0.56)	Study population	
										30 per 1,000	17 fewer per 1,000 (from 13 fewer to 20 fewer)
										Moderate	
											-
Hospitalization											
1,130 (1 study)	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	Undetected	⨁⨁⨁⨀ Moderate	0/554 (0%)	1/576 (0.17%)	Risk ratio 2.89 (0.12 to 70.68)	Study population	
											-
										Moderate	
											-

[a] Wide confidence interval

Elderly

The use of the inactivated influenza vaccine versus placebo is effective in preventing the occurrence of influenza or influenza-like illness. However, there is no benefit as to preventing mortality for the elderly population.

In a systematic review[3] there was noted relative scarcity of RCTs. Given the heterogeneous nature of the setting, follow-up, and outcome definition, no firm conclusions can be drawn from this body of evidence. Based on the results of meta-analysis, inactivated vaccines were more effective than placebo against influenza-like illness in conditions of high viral circulation among elderly individuals (RR 0.59; 95% CI: 0.47, 0.73). The vaccines were also effective against influenza (RR 0.42; 95% CI: 0.27, 0.66). However, one RCT showed no benefit in preventing mortality (RR 1.02; 95% CI: 0.11, 9.72).

Question: Should influenza vaccination vs no vaccination be used in the elderly?

Bibliography:

Jefferson, T., Di Pietrantonj, C., Al-Ansary, L. A., Ferroni, E., Thorning, S., & Thomas, R. E. (2010). Vaccines for preventing influenza in the elderly. *Cochrane Database of Systematic Reviews*, 2:CD004876.

Quality assessment							Summary of findings				
Participants, (number of studies), follow-up period	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% confidence interval)	Anticipated absolute effects	
							With no vaccination	With influenza vaccination		Risk with no vaccination	Risk difference with influenza vaccination (95% confidence interval)
Influenza											
2,217 (3 studies)	No serious risk of bias	Serious [a]	No serious indirectness	No serious imprecision	Undetected	⨁⨁⨁⊖ Moderate	63/1107 (5.7%)	26/1110 (2.3%)	Risk ratio 0.42 (0.27 to 0.66)	Study population	
										57 per 1,000	33 fewer per 1,000 (from 19 fewer to 42 fewer)
										Moderate	
											-

Mortality											
699 (1 study)	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious [b]	Undetected	⨁⨁⨁⊖ Moderate	1/177 (0.56%)	3/522 (0.57%)	Risk ratio 1.02 (0.11 to 9.72)	Study population	
										6 per 1,000	0 more per 1,000 (from 5 fewer to 49 more)
										Moderate	
											-

[a] Heterogenous population
[b] Wide confidence interval

Patients with malignancies

Influenza vaccine effectiveness among cancer patients is unclear, as the immune dysfunction that accompanies cancer and because chemotherapy might lower immune response to the vaccine. For cancer patients, therefore, there is no clear information on the importance, need, and safety of the vaccine. In a retrospective study of Stage 4 adenocarcinoma patients who underwent chemotherapy,[4] the hazard ratio for death was 0.88 (95% CI: 0.77 to 0.99), and there was significantly less episodes of pneumonia among patients who were given vaccine compared to those unvaccinated, but no difference in the length of hospitalization. In a prospective cohort study of patients with solid and hematologic malignancies, all-cause mortality was significant among those who were not given the vaccine vs those who were vaccinated (19.1% vs 11.9%, *p* value = 0.005), and in the multivariate analysis the odds ratio for death among those who were vaccinated was 0.43 (95% CI: 0.23,0.75).[5] In an open-label RCT of patients with multiple myeloma, vaccination reduced the influenza-like illness among those given the vaccine (RR 0.18; 95% CI) but no difference in pneumonia events.[6] No life-threatening or persistent adverse effects from vaccination were reported.[7]

Question: Should influenza vaccination vs no vaccination be given to patients who underwent chemotherapy?

Setting: Stage 4 colorectal adenocarcinoma with active chemotherapy

Bibliography: Earle, C. C. (2003). Influenza vaccination in elderly patients with advanced colorectal cancer. *Journal of Clinical Oncology*, *21*(6), 1161–6.

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Influenza vaccine	No vaccine	Relative (95% confidence interval)	Absolute (95% confidence interval)		
All-cause mortality												
1	Observational study	Not serious	Not serious	Not serious	Not serious	None	Vaccinated 626 (39.7%) and unvaccinated 951 (60.3%). One-year survival rated for vaccinated group 60.2% and in those unvaccinated 55.3%. Hazard ratio for death was 0.88 (95% CI: 0.77 to 0.99). Vaccinated adults had less pneumonia (7/626 vs 33/951 person years). Mean days of hospitalization was 15.6, 95% CI: 13.3 to 17.8 in the vaccinated group versus 16.4, 95% CI: 14.3 to 18.4 among unvaccinated adults.				⊕⊕◯◯ Low	Critical
Pneumonia												

Question: Should influenza vaccination vs no vaccination be given to patients who underwent chemotherapy?

Setting: Stage 4 colorectal adenocarcinoma with active chemotherapy

Bibliography: Earle, C. C. (2003). Influenza vaccination in elderly patients with advanced colorectal cancer. *Journal of Clinical Oncology*, *21*(6), 1161–6.

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Influenza vaccine**	**No vaccine**	**Relative (95% confidence interval)**	**Absolute (95% confidence interval)**		
1	Observational study	Not serious	Not serious	Not serious	Not serious	None	Vaccinated adults had less pneumonia (7/626 vs 33/951 person years).				⊕⊕◯◯ Low	Critical
Hospitalization												
1	Observational study	Not serious	Not serious	Not serious	Not serious	None	Mean days of hospitalization was 15.6, 95% CI: 13.3 to 17.8 in the vaccinated group versus 16.4, 95% CI: 14.3 to 18.4 among unvaccinated adults.				⊕⊕◯◯ Low	Important

Question: Should influenza vaccination vs no vaccination be given to immunosuppressed patients?

Setting: Multiple myeloma

Bibliography: Musto, P. & Carotenuto, M. (1997). Vaccination against influenza in multiple myeloma. *British Journal of Haematology*, *97*(2), 505-6.

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Influenza vaccine	No vaccine	Relative (95% confidence interval)	Absolute (95% confidence interval)		
Influenza-like illness												
1	Randomized trials	Serious[a]	Not serious	Not serious	Not serious	None	8/25 (32.0%)	18/25 (72.0%)	Risk ratio 0.18 (0.05 to 0.61)	590 fewer per 1,000 (from 281 fewer to 684 fewer)	⊕⊕⊕◯ Moderate	Critical
Pneumonia												
1	Randomized trials	Serious[a]	Not serious	Not serious	Not serious	None	0/25 (0.0%)	4/25 (16.0%)	Odds ratio 0.09 (0.00 to 1.84)	143 fewer per 1,000(from -- to 100 more)	⊕⊕⊕◯ Moderate	Important

[a] Includes children and adult population

Patients living with HIV

In a systematic review of 1,562 HIV-infected individuals with a CD4 count of >100 cells/ul,[8] influenza vaccine is 85% effective in preventing laboratory-confirmed influenza. However, it is not effective in preventing influenza-like illness, mortality, and hospitalization for antigenically matched strains.

In the observational studies, one cohort study showed an effectiveness of 71% (95% CI: 44–85%) for prevention of laboratory-confirmed influenza, while 2 cohort studies showed a pooled efficacy of 60% (95% CI: -9 to 38).[8] No significant effect of influenza vaccination on risk of all-cause hospitalization and pneumonia was observed. Effects on mortality and respiratory illness were not reported. However, evidence on these outcomes is of low quality, mostly due to small numbers of events and due to high risk of bias in the observational studies.

All RCTs included in the review reported that the predominantly circulating virus strains during the study periods were the same as included in the respective vaccine. Belongia et al. found that influenza vaccine efficacy/effectiveness varied substantially across different seasons and was highest when antigenic match was optimal.[9]

Vaccine safety in adults was assessed in one RCT. Frequency of any adverse events (pain, redness, swelling, limp formation, bruising, itching, rigors, fatigue, headache, fits, myalgia, arthralgia, and fever) did not differ between vaccine and placebo recipients in the four days following vaccination (RR 1.46, 95% CI: 0.66–3.21). No severe adverse events following influenza vaccination were observed.

Question: Should influenza vaccine be used in patients with HIV?

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3. Yamanaka, H., Teruya, K., Tanaka, M., Kikuchi, Y., Takahashi, T., Kimura, S., …HIV/Influenza Vaccine Study Team. (2005). Efficacy and immunologic responses to influenza vaccine in HIV-1-infected patients. *Journal of Acquired Immune Deficiency Syndromes*, *39*(2), 167–73.

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Influenza vaccine**	**No vaccine**	**Relative (95% confidence interval)**	**Absolute**		
Laboratory-confirmed influenza												
2	RCT	None	None	None	Serious [a]	None	3/310 (0.97%)	22/298 (7.4%)	Risk ratio 0.15 (0.03 to 0.78)	63 fewer per 1,000 (from 16 fewer to 72 fewer)	⊕⊕⊕◯ Moderate	

								0%		-		
None												
1	Observational study	Serious [b]	None	None	None	none	31/132 (23.5%)	52/84 (61.9%)	Risk ratio 0.40 (0.12 to 1.29)	371 fewer per 1,000 (from 545 fewer to 180 more)	⨁◯◯◯ Very low	
								0%		-		

[a] Wide confidence interval

[b] Confounders

Patients with end-stage renal disease

Evidence on the protective effects of influenza vaccination in patients with end-stage renal disease is limited. In a systematic review of observational studies,[10] a statistically significant 32% protective efficacy of vaccination were found for all-cause mortality (95% CI: 24–39%) and for cardiac death, 16% efficacy (95% CI: 1–29%), but not for death due to infection (vaccine efficacy 17%; 95% CI: −5%–35%). Moreover, a significant 14% protective efficacy of influenza vaccination was also observed for hospitalization due to influenza or pneumonia (95% CI: 7–20%). For the prevention of influenza-like illness, influenza vaccination was also found to have a protective efficacy of 12% (95% CI: 10-14%).

There is only very low quality of evidence that influenza vaccination of patients with end-stage renal disease can prevent mortality, hospitalization, or other clinical outcomes. Although pooled estimates showed small to moderate protective effects against all-cause mortality and hospitalization due to influenza or pneumonia in this patient sub-group, vaccine efficacy measured outside influenza seasons showed even greater protective effects. However, given the high rates of health-endangering events in these patients, even a low vaccine efficacy is enough to recommend annual influenza vaccination to them. Serious adverse events were not seen.

Question: Should influenza vaccine be used in patients with end-stage renal disease?

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Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Influenza vaccine	No vaccine	Relative (95% confidence interval)	Absolute		
All-cause mortality for end-stage renal disease												
4	Observational studies	Serious [a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	1,798/8,759 (20.5%)	Risk ratio 0.68 (0.61 to 0.76)	66 fewer per 1,000 (from 49 fewer to 80 fewer)	⊕◯◯◯ Very low	
								0%		-		

Cardiac death												
1	Observational study	Serious [a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	- 0%	Risk ratio 0.84 (0.71 to 0.98)	- -	⊕◯◯◯ Very low	
Hospitalization due to influenza/pneumonia												
4	Observational studies	Serious [a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	4,445/2,584 (172%) 0%	Risk ratio 0.86 (0.80 to 0.93)	241 fewer per 1,000 (from 120 fewer to 344 fewer) -	⊕◯◯◯ Very low	
Influenza-like illness												
1	Observational study	Serious [a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	- 0%	Risk ratio 0.88 (0.85 to 0.90)	- -	⊕◯◯◯ Very low	

[a] Confounders

Patients with asthma

In a randomized controlled trial of patients aged 6-18 years old with bronchial asthma,[11] there is significant reduction in the number of influenza-related asthma exacerbations as well as any asthma exacerbations. The duration of asthma exacerbation in patients given the influenza vaccine was shorter by two days compared to those who were given placebo. In a systematic review, the adverse effects of inactivated influenza vaccine were not significant in all treatment arms.[12]

Question: Should influenza vaccine be used for patients with asthma?

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van der Wouden, J. C., Bueving, H. J., Bersen, R. M. D., de Jongste, J. C., van Suiklekom-Smit, L. W. A., Rimmelzwaan, G. F., et al. (2003). Influenza vaccination in asthmatic children: Randomized double-blind placebo-controlled trial. Proceedings of the American Thoracic Society 99th International Conference: C108.

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Influenza vaccine**	**Placebo**	**Relative** (95% confidence interval)	**Absolute** (95% confidence interval)		
Influenza-related asthma exacerbations												
1	Randomized trial	Not serious	Not serious	Serious [a]	Not serious	None	20/347 (5.8%)	17/349 (4.9%)	Risk ratio 0.001 (0.002 to 0.004)	49 fewer per 1,000 (from 49 fewer to 49 fewer)	⊕⊕⊕◯ Moderate	Critical
Duration of influenza-related asthma exacerbation (days)												

Question: Should influenza vaccine be used for patients with asthma?

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van der Wouden, J. C., Bueving, H. J., Bersen, R. M. D., de Jongste, J. C., van Suiklekom-Smit, L. W. A., Rimmelzwaan, G. F., et al. (2003). Influenza vaccination in asthmatic children: Randomized double-blind placebo-controlled trial. Proceedings of the American Thoracic Society 99th International Conference: C108.

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Influenza vaccine**	**Placebo**	**Relative** (95% confidence interval)	**Absolute** (95% confidence interval)		
1	Randomized trial	Not serious	Not serious	Serious [a]	Serious [b]	None	24	18	-	Mean difference 2 days fewer (4.84 fewer to 0.84 more)	⊕⊕◯◯ Low	Important
Any asthma exacerbation												
1	Randomized trial	Not serious	Not serious	Serious [a]	Not serious	None	297/347 (85.6%)	314/349 (90.0%)	Risk ratio 0.04 (0.09 to 0.00)	864 fewer per 1,000 (from -- to 819 fewer)	⊕⊕⊕◯ Moderate	Critical

[a] Trial involved children 6-18 years old; [b] Wide confidence interval

Patients with COPD

In a 2006, a systematic review on inactivated influenza vaccine in COPD patients resulted in a significant reduction in the total number of exacerbations in vaccinated subjects compared with those who received placebo (vaccine efficacy 73%; 95% CI: -0.64 to -0.11; p = 0.006). While there was no statistically significant effect of vaccination on early exacerbation rates (vaccine efficacy 0.01; 95% CI: -0.11 to 0.13; p = 0.87), inactivated influenza vaccination significantly reduced late (i.e., occurring more than three to four weeks after vaccination) exacerbation rates (vaccine efficacy -0.39; 95% CI: -0.61 to -0.18; p =0.0004).[13]

It was also shown that inactivated influenza vaccination reduced influenza-related respiratory infections (vaccine efficacy 19%; 95% CI: 0.07-0.48; p = 0.0005). However, there was no significant effect for hospitalization (OR 0.33; 95% CI: 0.09, 1.24; p = 0.52) or mortality (RR 0.87; 95% CI: 0.28, 2.70).

In both COPD patients and in elderly patients (only a minority of whom had COPD), there was a significant increase in the occurrence of local adverse reactions in vaccines, but the effects were generally mild and transient.

Influenza vaccinations were generally well tolerated. A large, well conducted RCT showed that influenza vaccination in healthy adults showed no significant side effects, except for arm soreness.

Question: Should influenza vaccine be used in patients with COPD?

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Quality assessment							Summary of findings				
Participants, (studies), follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% confidence interval)**	**Anticipated absolute effects**	
							With placebo	**With influenza vaccination**		**Risk with placebo**	**Risk difference with influenza vaccination (95% confidence interval)**
Influenza-related respiratory illness, chronic obstructive pulmonary disease											
180 (2 studies) 1 year	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⨁⨁⨁⨁ High	26/92 (28.3%)	6/88 (6.8%)	Risk ratio 0.19 (0.07 to 0.48)	Study population	
										283 per 1,000	229 fewer per 1,000 (from 147 fewer to 263 fewer)

Hospitalization due to influenza-related exacerbations											
180 (2 studies)	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	Undetected	⨁⨁⨁⊖ Moderate	7/92 (7.6%)	2/88 (2.3%)	Risk ratio 0.33 (0.09 to 1.24)	Study population	
										76 per 1,000	51 fewer per 1,000 (from 69 fewer to 18 more)
Mortality related to acute respiratory infection											
180 (2 studies)	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	Undetected	⨁⨁⨁⊖ Moderate	7/92 (7.6%)	6/88 (6.8%)	Risk ratio 0.87 (0.28 to 2.70)	Study population	
										76 per 1,000	10 fewer per 1,000 (from 55 fewer to 129 more)
Exacerbations											
180 (2 studies)	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⨁⨁⨁⨁ High	24/92 (26.1%)	24/88 (27.3%)	Risk ratio 0.34 (-0.67 to -0.11)	Moderate	
											261 fewer per 1,000 (from 261 more to 300 more)

[1] Wide confidence interval

Patients with cardiovascular disease

In two secondary prevention trials, influenza vaccine with standard of care was shown to be protective than placebo with standard of care among patients with cardiac diseases (RR 0.45; 95% CI: 0.26-0.76), $p < 0.003$) with no significant heterogeneity.[14] Cardiovascular deaths occurred in 2.3% of participants in the vaccine groups and in 5.1% of those in the control groups.

Question: Should influenza vaccine be used in patients with cardiovascular disease?

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Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Influenza vaccine**	**No vaccination**	**Relative (95% confidence interval)**	**Absolute**		
Cardiovascular death												
4	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	832/0 (0%)	835/0 (0%)	Risk ratio 0.45 (0.26 to 0.76)	-	⨁⨁⨁⨁ High	
								0%		-		

Table 10B. Summary of evidence for patients with specific medical illnesses and related vaccine efficacies

Medical condition	Efficacy	Outcomes	Recommendation and quality of evidence
End-stage renal disease	12% (95% CI: 0.10, 0.14)	Influenza-like illness	*Weak recommendation; very low quality of evidence*
	14% (95% CI: 0.07, 0.20)	Hospitalization due to influenza and pneumonia	*Weak recommendation; very low quality of evidence*
	31% (95% CI: 0.24, 0.39)	All-cause mortality	*Weak recommendation; very low quality of evidence*
Bronchial asthma	98% (95% CI: -0.01, 0.05)	Influenza-related asthma exacerbations and any asthma exacerbation	*Strong recommendation; moderate quality of evidence*
COPD	19% (95% CI: 0.07, 0.48)	Influenza-related respiratory illnesses	*Strong recommendation; moderate quality of evidence*
	67% (95% CI: 0.09, 1.24)	Hospitalization due to influenza-related exacerbations	*Strong recommendation; moderate quality of evidence*
	73% (95% CI: -0.64, -0.11)	Exacerbations	*Strong recommendation; moderate quality of evidence*
Cardiovascular disease	55% (95% CI: 0.26, 0.76)	Cardiovascular death	*Strong recommendation; high quality of evidence*

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Japanese encephalitis virus vaccine

Japanese encephalitis (JE) is a vector-borne viral disease. The JE virus is the leading cause of viral encephalitis in Asia. It is estimated that 67,900 severe clinical cases of JE occur annually despite widespread availability of vaccine, causing about 13,000-20,000 deaths. Most JE virus infections are asymptomatic, and severe disease is estimated to occur in about 1 per 250 JE virus infections. The disease can occur at all ages.[1]

Existing epidemiological data from the Philippines (i.e., 1-4 cases in Pampanga, Laguna, Mindoro; 5-19 cases in Bulacan, Camarines Norte, Camarines Sur, Iloilo, Negros Oriental and North Cotabato; 20-50 cases in Tarlac and Metro Manila; and >50 cases in Nueva Ecija) indicate that JE is endemic with a year-round transmission with peak season from July to September.[2] The Department of Health Epidemiology Bureau recorded a decrease of 61% confirmed JE cases from January 1-August 12, 2017 compared to the same period in 2016 (85 cases vs 218 cases), respectively.[3]

The JE virus is the most common vaccine-preventable cause of encephalitis in Asia. Vaccination is the most effective strategy to prevent and control JE.[1]

According to WHO, JE vaccination should be integrated into national immunization schedules in all areas where JE is recognized as a public health priority. Even if the number of JE-confirmed cases is low, vaccination should be considered where there is a suitable environment for JE virus transmission, such as the presence of animal reservoirs, ecological conditions supportive of virus transmission, and proximity to other countries or regions with known JE virus transmission.[1] The JE virus is responsible for 7.4% to 40% of acute meningitis-encephalitis syndrome, and it affects predominantly children <15 years old. Fifteen percent of cases in adults had a case fatality ratio of 8.1%-15.3%.

Aside from vector control, surveillance, and clinical management, vaccination is recommended as part of a comprehensive JE virus prevention and control strategy.

Table 11. Japanese encephalitis virus vaccine in adults

Description	• Four broad classes of JE vaccines are currently in use: inactivated Vero cell-derived vaccines, live attenuated vaccine, live recombinant vaccines, and inactivated mouse brain-derived vaccines.[1] • In the Philippines, the only vaccine available and approved by the FDA against JE is the JE live attenuated recombinant, chimeric vaccine.
Recommendation	• The vaccine can be given at any time if without contraindications. *Weak recommendation; high quality of evidence*
Summary of evidence	• In a randomized controlled phase III immunogenicity study, seroconversion after a single JE live attenuated recombinant, chimeric vaccine was 99.1% (compared with mouse-derived vaccine) after 60 days and induced a rapid immune response with 93.6% of the participants developing protective neutralizing antibodies to the JE

	virus as early as 14 days post-vaccination, underlining the potent immunogenicity of this live attenuated flaviviral vaccine.[4] • In a randomized, double-blind, five-year phase II study in healthy adults, live attenuated JE chimeric vaccine provides 84% of seroprotection 5 years after injection with just a single dose.[5] • In a modeling data analysis, one dose of the live attenuated JE chimeric virus vaccine confers to most adults a high level of protection for at least 10 years.[6] • The vaccine is not an effective strategy in reducing cases during an outbreak because the primary prevention strategy is vector control. • According to WHO, the value of reactive vaccination campaigns during outbreaks of JE has not been studied in countries where JE vaccination has not been introduced. Thus, an assessment needs to be made of whether it is appropriate to implement an immediate vaccine response, including considerations such as size of the outbreak, timeliness of the response, population affected, and programmatic capacity.[1]
Indication/Target population	• Children 9 months and above, including adults • Travelers going to the following countries[6] • Bangladesh, Bhutan, Brunei, Burma • Cambodia, China, India, Indonesia • Japan, Korea, Laos, Malaysia, Nepal • Papua New Guinea, Philippines, Singapore • Taiwan, Thailand, Timor Leste, Vietnam
Schedule	• Single-dose administration • No booster dose needed in immunocompetent adults
Administration	• Subcutaneous injection
Common adverse events	• The most common adverse events were injection site reaction (12.4%), fatigue (22.8%), headache (26%), myalgia (16.6%), respiratory, and gastrointestinal. There was no significant difference in the incidence of injection site reactions between live attenuated JE chimeric vaccine and placebo groups in this study.[3]
Contraindications	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose

	• Hypersensitivity to any vaccine component (e.g., protamine sulfate)
Precautions	• History of previous allergic reactions or urticaria to the JE vaccine or any ingredient in the vaccine[8]
Pregnancy and breastfeeding[8]	• Vaccination should be deferred because of theoretical risk to the developing fetus. • If pregnant women must travel to a high-risk area, they should be vaccinated if the benefits outweigh the risks of vaccination to the mother and the developing fetus. • Breastfeeding is not a contraindication to vaccination. • Whether JE vaccines are excreted in human milk is not known; caution should be used when considering JE vaccine.

Question: Should Japanese encephalitis vaccine be used in healthy adults?

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Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Live recombinant JE vaccine	Inactivated vaccine	Relative (95% confidence interval)	Absolute		
Seroconversion after 60 days												
1	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	343/346 (99.1%)	347/365 (95.1%)	Risk ratio 0.09 (97.5 to 99.8)	865 fewer per 1,000 (from 1,000 more to 1,000 more)	⊕⊕⊕⊕ High	
Safety												

1	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	833/1,601 (52%)	204/403 (50.6%)	Risk ratio 0.48 (0 to 0)	263 fewer per 1,000 (from 506 fewer to 506 fewer)	⨁⨁⨁⨁ High	

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Measles-mumps-rubella (MMR) vaccine

The measles virus is an enveloped, ribonucleic acid virus of the genus *Morbillivirus*. Although at least 20 different genotypes have been isolated in various parts of the world, there is only one serotype. Measles is highly contagious, and an infected person will often transmit the virus to over 90% of unprotected close contacts.[1] Measles is an exanthematous disease presenting with fever, coryza, conjunctivitis, and maculopapular rash that is transmitted from person to person by direct contact with respiratory droplets or airborne spread. It is associated with a high morbidity and mortality in children which can also affect young adults.[2] While most persons recover from measles without lasting effects, severe forms of the disease with bleeding from skin and mucosa may occur. Among children less than 5 years of age, measles complications frequently include otitis media and pneumonia. Persons with malnutrition, especially vitamin A deficiency, or with severe immunological disorders such as advanced HIV infection are at increased risk of developing severe or even fatal measles.[1]

Mumps is an acute febrile illness caused by a paramyxovirus of which there is only one serotype. Humans are the only known host for the mumps virus, which is spread via direct contact or by airborne droplets from the upper respiratory tract of infected individuals. It is often characterized by non-specific symptoms such as myalgia, headache, malaise, and low-grade fever followed by unilateral or bilateral swelling of the parotid and other salivary glands, most common among school-aged children and young adults. Normally, mumps is a mild, self-limiting disease that disappears without sequelae. However, complications such as encephalitis or sensorineural deafness may occur. Orchitis (a painful inflammation of the testes) occurs in 20% of young adult males who develop mumps.

Meanwhile, the rubella virus, a togavirus of the genus *Rubivirus*, is an enveloped single-stranded RNA virus with a single serotype that does not cross-react with other togaviruses. Humans are the only known host, with seasonal epidemics occurring every 5-9 years over a worldwide distribution. Rubella is an acute febrile exanthematous disease transmitted through direct or droplet contact from nasopharyngeal secretions and is characterized by cervical lymphadenopathy.[2] In pregnant women, the virus infects the placenta and the developing fetus. Infection by the rubella virus is characterized by a transient rash. Joint pain and arthritis rarely occur in children, but may affect up to 70% of adults. Rubella virus can be found in nose and throat secretions and urine from 1 week before to 2 weeks after rash onset, although infants with congenital rubella may excrete the virus for a year or more in pharyngeal secretions and urine. Congenital rubella syndrome is caused by infection in early pregnancy; from just before conception and during the first 8-10 weeks of gestation rubella infection may result in multiple fetal defects in up to 90% of cases, affecting many organs and often results in miscarriage or stillbirth, and some serious developmental disabilities.[1]

Table 12. Measles-mumps-rubella vaccine in adults

Description	• Live attenuated strains of measles, mumps, rubella
Recommendations	• One dose of the MMR vaccine is routinely recommended for immunocompetent adults. *Strong recommendation; low quality of evidence* • One dose of the MMR vaccine within 72 hours is recommended as post-exposure prophylaxis.

Summary of evidence	• Antibodies develop among approximately 96% of children vaccinated at age 12 months with a single strain of the measles vaccine strain. Almost all persons who do not respond to the measles component of the first MMR vaccine at age ≥12 months respond to the 2nd vaccine dose. • One dose of measles-containing vaccine administered at age ≥12 months was approximately 94% effective in preventing measles in studies conducted in the WHO Region America. Meanwhile the effectiveness of 2 doses of measles-containing vaccine was ≥99% in 2 studies conducted in the United States and 100% in 3 studies in Canada. Similar results of vaccine effectiveness have been reported from Australia and Europe. • Both serologic and epidemiologic evidence indicate that measles-containing vaccine induce long-lasting immunity in most persons. Approximately 95% of vaccinated persons examined 11 years after initial vaccination and 15 years after the second dose of MMR vaccine had detectable antibodies to measles. • Studies indicate that 1 dose of MMR vaccine can provide persistent antibodies to mumps. Most persons (70%-99%) examined approximately 10 years after initial vaccination had detectable mumps antibodies. Few studies assessing the effectiveness of 2 doses of mumps-containing vaccine showed 80%-92% effectiveness in outbreak populations particularly in the U.S. Studies in Europe and Canada estimate an effectiveness of 66%-95% of 2 doses of mumps-containing vaccine. • In addition, 70% of adults who were vaccinated in childhood had T-lymphocyte immunity to mumps compared with 80% of adults who acquired natural infection in childhood. • Among persons who received a second dose of MMR vaccine, most mounted a secondary immune response, approximately 50% had a fourfold increase in antibody titers, and the proportion with low or undetectable titers was significantly reduced from 20% before vaccination with a second dose to 4% at 6 months post vaccination. • Rubella vaccination induces both humoral and cellular immunity. Approximately 95% of susceptible persons aged ≥12 months developed serologic evidence of immunity to rubella after vaccination with a single dose of rubella vaccine containing the RA 27/3 strain. After a second dose of MMR vaccine, approximately 99% had detectable rubella

	antibody, and approximately 60% had a fourfold increase in titer. • Outbreaks of rubella in populations vaccinated with the rubella RA 27/3 vaccine strains are rare. Studies show that vaccines containing rubella RA 27/3 strain are estimably 97% effective in preventing clinical disease after a single dose. • Majority of persons had detectable rubella antibodies up to 16 years after 1 dose of rubella-containing vaccine, but antibody levels decreased over time. However, date from surveillance of rubella and congenital rubella syndrome suggest that waning immunity with increased susceptibility to rubella disease does not occur. Among those with 2 doses, approximately 91%-100% had detectable antibodies 12-15 years after receiving the 2nd dose. • MMR vaccine may be given as post-exposure prophylaxis on a case-to-case basis. • For measles, evidence of the effectiveness of MMR or measles vaccine administered as post-exposure prophylaxis is limited and mixed. Effectiveness may depend on the timing of vaccination and the nature of the exposure. If given within 72 hours of initial measles exposure, MMR vaccine might provide some protection against infection or modify the clinical course of the disease. Post-exposure prophylaxis does not appear to be effective in settings with intense, prolonged, close contact such as households and small childcare facilities, even when dose is administered within 72 hours of rash onset. This is because persons in this setting are often exposed for long durations during the prodromal period when the index patient is infectious. • Post-exposure MMR vaccination has not been shown to prevent or alter the clinical severity of mumps and rubella.
Indication/Target population[2,5]	• Prevention of measles, mumps and rubella[2-4] • According to the ACIP, it is recommended that for the prevention of measles and mumps, 1 dose is recommended for adults not at high risk for exposure and transmission. • On the other hand, for adults at high risk of transmission (e.g., students attending colleges or other post-high school educational institutions, healthcare personnel, and international travelers),

	2 doses are recommended. For prevention of rubella, 1 dose of MMR vaccine is recommended for persons aged ≥12 months. • Among adults, vaccination may be recommended to all adults who have not received complete vaccination for measles, mumps, or rubella during childhood. • Immunocompetent adults with prior history of the disease during outbreaks • Evidence of adequate vaccination for school-age children, college students, and students in other postsecondary educational institutions who are at risk for exposure and infection during measles and mumps outbreaks consists of 2 doses of measles- or mumps-containing vaccine separated by at least 28 days, respectively. If the outbreak affects preschool-aged children or adults, with community-wide transmission, a second dose should be considered for children aged 1-4 years or adults who have received 1 dose.[2] • Vaccination is recommended among adults who are at higher risk of infection (i.e., those in educational institutions, healthcare personnel, and international travelers to areas with possible suboptimal vaccination coverage). • Unvaccinated women planning to become pregnant should be vaccinated 3 months before conceiving. Pregnancy status should be confirmed prior to vaccine administration. They should be advised not to get pregnant until 3 months after.
Schedule	• 1-2 doses, given at least 28 days apart
Administration	• Subcutaneous injection
Common adverse events	• Fever, transient rashes, and lymphadenopathy, or parotitis • Febrile reactions usually occur 7-12 days after vaccination and generally last 1-2 days. Majority of persons are otherwise asymptomatic. Coryza, cough, pharyngitis, and headache after revaccination were found to be significantly lower with a second dose of MMR vaccine, while conjunctivitis, nausea, vomiting and lymphadenopathy and joint pains had no significant change compared with the pre-vaccination baseline (but data are in school-aged children). • With regards to serious adverse events, expert committees determined a causal relation of MMR vaccine and anaphylaxis, febrile seizures, thrombocytopenic purpura,

	transient arthralgia, and measles inclusion body encephalitis in persons with demonstrated immune-deficiencies. • Immune thrombocytopenic purpura after receipt of live attenuated measles vaccine is usually self-limited and not life threatening. However, complications may include severe bleeding requiring transfusion. The risk for immune thrombocytopenic purpura increases during the 6 weeks after vaccination. On the basis of case reports, the risk for MMR vaccine-associated thrombocytopenia might be increased for persons who previously have had immune thrombocytopenic purpura. • Joint symptoms are associated with the rubella component of MMR vaccine. The symptoms generally begin 1-3 weeks after vaccination, are usually mild and not incapacitating, last about 2 days, and rarely recur. Among persons without rubella immunity who receive rubella-containing vaccine, arthralgia and transient arthritis occur more frequently among adults than children.
Contraindications	• Concurrent moderate or severe illness including untreated active tuberculosis should be deferred until they have recovered. Consequently, before administering MMR vaccine to persons with untreated active TB, initiating anti-tuberculous therapy is advisable. The decision to postpone vaccination depends largely on the cause of the illness and the severity of symptoms. • Pregnancy • Severely immunocompromised persons
Precautions	• Precautions for MMR vaccines include recent (≤11 months) receipt of an antibody-containing blood product, concurrent moderate or severe illness with or without fever, history of thrombocytopenia or thrombocytopenic purpura, and tuberculin skin testing. • MMR vaccine might interfere with the response to a tuberculin skin test, resulting in a temporary depression of tuberculin skin sensitivity. Therefore, it should be administered either any time before, simultaneously with, or at least 4-6 weeks after MMR vaccine.
Pregnancy and breastfeeding	• Because of the theoretical risk to the fetus when a mother receives a live vaccine, women should be counseled to avoid becoming pregnant for 28 days after receipt of the MMR vaccine. • If the vaccine is inadvertently administered to a pregnant woman or a pregnancy occurs within 28

	days of vaccination, she should be counseled about the risk to the fetus. Reports have documented no cases of congenital rubella syndrome among 1,000 live-born infants of susceptible women who were vaccinated inadvertently with rubella 27/3 vaccine while pregnant or just before conception. This data is considerably lower than the ≥20% risk associated with wild rubella virus infection of mothers during the first trimester of pregnancy with wild rubella virus. • Postpartum administration of MMR vaccine to women should be given immediately after delivery and tested at least 3 months later to ensure that they have presumptive evidence of immunity. This is because pregnant women receive blood products during the last trimester of pregnancy or at delivery. • Avoided in breast-feeding women

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Meningococcal vaccine

Neisseria meningitidis, an aerobic gram-negative diplococcus, causes severe disease in humans and can present in one of three syndromes. Approximately 50% of meningococcal disease present as meningitis, followed by around 37% with bacteremia or meningococcemia, and with 9% presenting as pneumonia. Symptoms may rapidly progress, leading to fatal outcomes in 24 to 48 hours even with appropriate treatment.[1,2]

The organism resides in the nasopharyngeal mucosal surface and is transmitted by large droplet from asymptomatic carriers. Patients may continue to be infectious up to 24 hours after initiation of appropriate treatment.[1,2]

There are 13 serogroups of the bacteria based on the polysaccharide structure. Serogroups A, B, C, X, W135, and Y account for most of the invasive meningococcal infections.[1]

Table 13. Meningococcal vaccine in adults

	Quadrivalent polysaccharide vaccine	**Quadrivalent polysaccharide-protein conjugate vaccine**
Description	• Derived from *N. meningitides* polysaccharide serotypes A, C, Y, W135, with 50 ug of each serotype incorporated into the vaccine[1,2]	Contains 4 mcg of each of the of *N. meningitides* polysaccharide serotypes A, C, Y and W-135, conjugated to diphtheria toxoid[1]
Recommendation, indication/target population	• Routine vaccination is not recommended in immunocompetent adults. Should the elderly, 65 years old and older, choose to have meningococcal vaccination, the quadrivalent polysaccharide vaccine is the recommended vaccine and found to be immunogenic in older adults. There is limited data on the use of the quadrivalent polysaccharide-protein conjugate vaccine for immunocompetent elderly individuals. *Weak recommendation; low quality of evidence* • Adults who will travel to endemic and hyper-endemic areas for meningococcal disease. This is especially recommended if a traveler is coming from low-endemic regions.[1,7] *Strong recommendation; moderate quality of evidence* • Travelers to the African meningitis belt: Benin, Burkina Faso, Burundi, Cameroon, Chad, Cote d'Ivoire, Central African Republic, Democratic Republic of Congo, Eritrea, Ethiopia, Gambia, Ghana, Guinea, Guinea Bissau, Kenya, Mali, Mauritania, Niger, Nigeria, Rwanda, Senegal, South Sudan, Sudan, Tanzania, Togo, and Uganda *Strong recommendation; moderate quality of evidence* • High-risk groups	

	• Patients with anatomic or functional asplenia • Immunocompromised patients including persons living with HIV • Patients with complement component or properdin deficiencies • Personnel handling *N. meningitidis* isolates, such as microbiologists, medical technologists, or pathologists • Close contacts of meningococcal disease patients *Strong recommendation; moderate quality of evidence* • Outbreak control *Strong recommendation; moderate quality of evidence* • Considered in the following groups • Students living in dormitories • Unvaccinated students • Military personnel *Weak recommendation; low quality of evidence*	
Summary of evidence	• A Cochrane review on the polysaccharide vaccine by Patel et al.[3] in 2005 has documented efficacy levels against meningococcal disease caused by serogroups A and C at 85% to 100% in children 2 years old and older and adults. The vaccine induces production of immunogenic antibodies against serogroups Y and W135 for both adults and children more than 2 years old. However, clinical efficacy has not yet been documented for these serogroups. • Hyporesponsiveness leading to decrease in antibody production to serogroups A and C can occur with repeated doses of the polysaccharide vaccine. This decrease in	• More recent studies of the conjugate vaccine showed effectiveness of 80 to 85% within 3 to 4 years after vaccination.[7] • The advantage proposed by using conjugate vaccine over the polysaccharide vaccine is its ability to elicit immunologic memory. This immunologic memory is primed by the vaccine and occurs even in the absence of bactericidal antibodies.[7]

	antibody production has not however established reduction in clinical efficacy.[4,5]	
	• A randomized controlled trial by Bilukha et al. in 2005 compared meningococcal quadrivalent vaccine and meningococcal polysaccharide vaccine among participants aged 11 to 18 years old.[8] For both vaccines, >97% of the participants reached serum bactericidal antibody assay with rabbit complement geometric mean of more than 128 observed 28 days after vaccination. The study also revealed the same immunogenicity result among participants aged 19 to 55 years old. • Meningococcal vaccination is not proven to be effective in eradication of mucosal carriage.	
Schedule	• 0.5 ml as a single dose 10 days before travel. For high-risk groups, it is recommended to give two doses, 2 months apart.[4,7] • If risk is continuous, re-vaccinate with 2 doses (2 months apart) every 5 years.	
Administration	• Subcutaneous or IM	• Intramuscular (IM)
Common adverse events	• Pain and redness at the injection site • Although rare, fever, headache, fatigue, malaise, irritability, diarrhea, or anorexia can also occur within 7 days of vaccination.[2,7]	
Contraindications	• Anaphylaxis to any vaccine component or a previous dose	
Precautions	• Vaccination should be deferred for persons with acute severe illness until the illness is resolved.[5] • Meningococcal polysaccharide vaccine is an inactivated vaccine and can be administered to the immunocompromised, but response may be impaired.[5] • If an individual, such as those with functional or anatomic asplenia, was given a pneumococcal conjugate vaccine (PCV13), quadrivalent polysaccharide-protein conjugate vaccine should only be given 4-weeks after the PCV13[a].[5]	
Pregnancy and breastfeeding	• Both vaccines are classified under Category C[b], since data is lacking on pregnant and breastfeeding women. However, they can be given if the benefits outweigh the risks.[7]	

[a] There is limited data on the interval of polysaccharide meningococcal and conjugate pneumococcal vaccine.

[b] Animal reproduction studies have shown an adverse effect on the fetus. There are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.[8]

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Pneumococcal vaccine

Streptococcus pneumoniae can cause infections affecting the upper respiratory tract (otitis media, sinusitis), the lower respiratory tract (pneumonia), or can cause serious infections (meningitis, bacteremia, endocarditis, peritonitis, arthritis). It has a widespread distribution, often affecting the elderly and young children. This organism is transmitted through droplet inhalation from patients with active disease or healthy carriers.

There are two types of pneumococcal vaccines available in the Philippines.[1] (See Table 14B.) These vaccines are serotype-specific to cover for those frequently associated with severe illnesses.[2]

Table 14A. *Streptococcus pneumoniae* serotypes in the Philippines vs available vaccine serotypes

Most common *S. pneumoniae* serotypes in the Philippines*	Serotypes in pneumococcal polysaccharide vaccine (PPSV23)	Serotypes in pneumococcal conjugate vaccine (PCV13)
1 5 14 4 6B	1, 3, 5, 6B, 14, 19A, 19F, 23F	
	2, 4, 7F, 8, 9N, 9V, 10A, 11A, 12F, 15B, 17F, 18C, 20, 22F, 33F	4V, 6A 7, 9F 18

* In descending order of frequencies: Strain 1 (~16%), 5 (~14%), 14 (6%), 4 (6%), and 6B (~4%)

A local passive laboratory-based surveillance study from June 2010 to September 2012 determined the serotype distribution of pneumococcal isolates in the Philippines.[3] This study included 301 isolates from blood, cerebrospinal fluid, pleural fluid, and peritoneal fluid, with 56.4% isolates coming from the adult age group.

References

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Table 14B. Pneumococcal vaccine for adults

	23-valent polysaccharide vaccine (PPSV23)	13-valent conjugate vaccine (PCV13)
Description	• Each dose contains 25 mcg each of pneumococcal polysaccharides from 23 serotypes.	• Each dose contains pneumococcal polysaccharides from 13 serotypes conjugated to carrier proteins.

<table>
<tr><td rowspan="3">Recommendation, indication/target population

(See text after table for summary of evidence.)</td><td colspan="2">• PPSV23 and PCV13 can be administered routinely to immunocompetent elderly patients to prevent invasive pneumococcal disease.

Strong recommendation; moderate quality of evidence</td></tr>
<tr><td>• PPSV23 can be administered routinely to immunocompetent adults, especially the elderly, in preventing pneumococcal pneumonia.

Strong recommendation; low quality of evidence</td><td>• PCV13 can be administered routinely to immunocompetent adults in preventing pneumococcal pneumonia.

Strong recommendation; moderate quality of evidence</td></tr>
<tr><td colspan="2">• PPSV23 and PCV13 may be recommended to immunocompetent adults, especially the elderly, in preventing mortality.

Strong recommendation; low quality of evidence</td></tr>
<tr><td>Schedule</td><td colspan="2">• PCV13 may be given first, followed by PPSV23 at least 1 year after the PCV13 dose. No revaccination with PPSV23 nor PCV13 is needed.

Strong recommendation; very low quality of evidence

• Adult Filipinos more than 50 years of age who were previously given PPSV23, may be given PCV13 vaccination at least 1 year after.

Strong recommendation; very low quality of evidence

• Adult Filipinos who were previously vaccinated with PPSV23 at less than 50 years old, but who are now 50 years old or more may receive 1 dose of PCV13 at least 1 year after, then another dose of PPSV23 after 1 year of the PCV13 dose.

Strong recommendation; very low quality of evidence

• Adult Filipinos more than 50 year of age who were previously given PPSV23, WITHOUT previous PCV13, may opt to be given another dose of PPSV23 after 5 years. No re-vaccination thereafter.

Weak recommendation; very low quality of evidence</td></tr>
<tr><td>Administration</td><td>• Subcutaneous or intramuscular</td><td>• Intramuscular</td></tr>
<tr><td>Common adverse events</td><td colspan="2">• Redness, swelling and soreness at injection site

• Fever, malaise and muscle pain can also occur, although this is infrequent.

• Allergic reactions may also occur due to the vaccine or vaccine components.</td></tr>
<tr><td>Contraindications</td><td colspan="2">• Anaphylaxis to any vaccine component or a previous dose</td></tr>
<tr><td>Precautions</td><td colspan="2">• Moderate to severe illness with or without fever</td></tr>
</table>

Pregnancy and breastfeeding	• Immunization with PPSV23 can be given during pregnancy, although its safety during the first trimester of pregnancy has not been evaluated. No adverse consequences have been reported among newborns whose mothers were inadvertently vaccinated during pregnancy. • There is no data on PCV13 in pregnancy.

Summary of evidence

There is no head to head comparison of PPSV23 and PCV13 for all-cause and vaccine-type invasive pneumococcal disease, pneumonia, and mortality. Thus, individual studies were assessed as to their efficacy.

Outcome examined: Invasive pneumococcal disease

PPSV23

Pooled results of 11 randomized trials[1] assessing the efficacy of PPSV23 vs placebo among 36, 489 patients showed that there is an odds ratio of 0.26 (CI 0.14 to 0.45) in preventing invasive pneumococcal disease from all pneumococcal strains after administration of PPSV.

Moderate quality of evidence

For vaccine type strains, the pooled results of 5 studies[1] with 31,223 participants, showed that PPSV23 has an odds ratio of 0.18 (CI 0.10 to 0.31) for invasive pneumococcal disease.

Moderate quality of evidence

PCV13

A large randomized trial[2] of 84,496 participants comparing the efficacy of PCV13 to placebo showed an odds ratio of 0.51 (CI 0.34 to 0.78) in reducing invasive pneumococcal disease from any pneumococcal strain.

Moderate quality of evidence

In the same study,[2] an odds ratio of 0.24 (CI 0.11 to 0.52) was shown for PCV13 in preventing vaccine-type strains of Invasive pneumococcal disease.

Moderate quality of evidence

Outcome examined: Pneumonia

PPSV23

Pooled results of 16 randomized trials[1] with a total of 47,734 patients studied showed an odds ratio of 0.72 (range 0.56 to 0.93) of acquiring pneumonia from any cause after administration of PPSV23. However, this meta-analysis showed significant heterogeneity with $I_2 = 85\%$ and Chi^2 $p < 0.0001$.

Low quality of evidence

This was analyzed further into subgroups of bacteremic and non-bacteremic pneumonia. There were ten studies[1] for bacteremic pneumonia with a total of 35,483 participants showed that PPSV23 has an odds ratio of 0.26 (CI 0.15 to 0.46).

Moderate quality of evidence

For non-bacteremic pneumonia that included 9 studies[1] and 20,355 participants, PPSV23 has an odds ratio of 0.46 (CI 0.25 to 0.84). But for this analysis, there is significant heterogeneity with I_2 = 75% and Chi^2 p = 0.0001.

Low quality of evidence

For vaccine-type strains, pooled results of 7 studies[1] with 37,550 participants, showed an odds ratio of 0.14 (CI 0.09 to 0.23) for PPSV23 in preventing pneumonia. This analysis, however, has significant heterogeneity with I_2 = 59% and Chi^2 p = 0.02.

This was further sub-analyzed to bacteremic (4 studies, 30,561) and non-bacteremic (5 studies,[4] 18,568 participants) pneumonia, with an odds ratio of 0.13 (CI 0.05 to 0.38) (*Moderate quality of evidence*), and 0.27 (CI 0.08 to 0.87) (*Low quality of evidence*), respectively. There was significant heterogeneity for non-bacteremic pneumonia with I_2 = 0% and Chi^2 p = 0.01.

PCV13

In a large randomized trial,[2] an odds ratio of 0.95 (CI 0.86 to 1.05) was shown among participants who received PCV13 compared to placebo in preventing any strain of pneumococcal pneumonia. The odds ratio may be insignificant, but it shows a trend towards benefit of the vaccine.

This was analyzed further into subgroups of bacteremic and non-bacteremic pneumonia for all strains. For preventing bacteremic pneumonia, PCV13 had an odds ratio of 0.78 (CI 0.62 to 0.97). While for non-bacteremic pneumonia, PCV13 had an odds ratio of 0.83 (CI 0.62 to 1.09). This shows that the vaccine is more protective for bacteremic pneumonia, although there is a trend towards benefit for non-bacteremic pneumonia.

In the same study,[2] in preventing vaccine strains of pneumonia, PCV13 had an odds ratio of 0.61 (0.48 to 0.77). Subgrouping these cases to bacteremic and non-bacteremic pneumonia, the odds ratios were 0.62 (CI 0.46 to 0.85) and 0.45 (0.30 to 0.68) respectively. This further strengthens the benefit of PCV13 in preventing pneumonia, especially those caused by vaccine type strains.

Outcome examined: Mortality

PPSV23

Pooled results of 14 randomized trials,[1] with a total of 47, 560 patients, assessing the efficacy of PPSV23 in preventing all-cause mortality showed an odds ratio of 0.90 (range 0.74 to 1.09) (*Low quality of evidence*). But there was significant heterogeneity with I_2 = 69% and Chi^2 p = 0.0007.

Sub-group analysis of prevention of mortality due to pneumonia or pneumococcal disease by PPSV23 from the pooled results of 9 studies[1] with 30,723 participants showed an odds ratio of 0.61 (CI 0.50 to 0.76). There is still significant heterogeneity with this analysis with I_2 = 74% and Chi^2 p = 0.0001.

PCV13

The result of a randomized trial[2] with 84,492 participants showed an odds ratio of 1.00 (CI 0.95 to 1.05) among those who received PCV13 in preventing all-cause mortality.

Mortality from pneumonia or pneumococcal disease with PPSV23 has an odds ratio of 0.61 (CI 0.50 to 0.76), while that of PCV13 showed an odds ratio of 0.86 (CI 0.29 to 2.55). However, a meaningful analysis of this data could not be done because of the small number of events.

There is no significant difference in all-cause mortality between PCV13 and PPSV23.

Although there were participants from low-income countries, there is relative indirectness of the studies because the Philippines was not represented in the studies included in the meta-analysis. There is also a predominance of males among the study participants. The mean age of participants in the study on PCV13 was 72 years old.[2]

The heterogeneity of studies may be due to the presence of selection bias and detection bias of some of the studies, with inadequate concealment of allocation and inadequate blinding. This is especially true for the older studies, probably due to inadequate reporting and varied vaccine formulations.

Table 14C. Outcome-based comparison of odds ratios of pneumococcal conjugate vaccine (PCV13) and pneumococcal polysaccharide vaccine (PPSV23)

Outcome	PCV13 (single RCT of 84,492 participants)	PPSV23 (meta)	Number of studies (for PPSV23)	Total patients	Events in vaccine group	Events in placebo group	Heterogeneity
All-cause mortality	1 (0.95, 1.05)	0.90 (0.74, 1.09)	14	47,560	15/24,018	63/23,542	I_2 = 69%; p = 0.00007
Mortality due to pneumonia or invasive pneumococcal disease	0.86 (0.29, 2.55)	0.61 (0.50, 0.76)	9	30,723	140/15,592	222/15,131	I_2 = 74%; p = 0.0001
All pneumococcal strains							
Invasive pneumococcal disease	0.51 (0.34, 0.78)	0.26 (0.14, 0.45)	11	36,489	978/18,634	1,547/17,855	I_2 = 0%; p = 0.56
Pneumonia	0.95 (0.86, 1.05)	0.72 (0.56, 0.93)	16	47,734	1,018/2,4018	1,039/3,542	I_2 = 85%; p < 0.0001
Bacteremic pneumonia	0.78 (0.62, 0.97)	0.26 (0.15, 0.46)	10	35,483	15/18,132	60/17,351	I_2 = 0%; p = 0.48
Non-bacteremic pneumonia	0.83 (0.62, 1.09)	0.46 (0.25, 0.84)	9	20,335	100/9,633	276/10,702	I_2 = 75%; p = 0.0001

Vaccine-type strains							
Invasive pneumococcal disease	0.24 (0.11, 0.52)	0.18 (0.10, 0.31)	5	31,223	14/13,889	140/17,334	I_2 = 0%; p = 0.70
Pneumonia	0.61 (0.48, 0.77)	0.20 (0.13, 0.32)	7	37,550	22/18,251	160/19,299	I_2 = 59%; p = 0.02
Bacteremic pneumonia	0.62 (0.46, 0.85)	0.13 (0.05, 0.38)	4	3,0561	3/15,583	30/14,978	I_2 = 0%; p = 0.92
Non-bacteremic pneumonia	0.45 (0.30, 0.68)	0.27 (0.08, 0.87)	5	18,568	19/8,755	130/9,813	I_2 = 70%; p = 0.01

Question: Pneumococcal polysaccharide vaccine compared to placebo for immunocompetent adults

Setting: Philippines

Bibliography: Moberley, S., Holden, J., Tatham, D. P., & Andrews, R. M. (2013). Vaccines for preventing pneumococcal infection in adults. *Cochrane Database of Systematic Reviews*, Issue 1. Art. No.: CD000422. doi: 10.1002/14651858.CD000422.pub3

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pneumococcal polysaccharide vaccine	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)		
Invasive pneumococcal disease												
11	Randomized trials	Not serious	Serious [a,b]	Serious [a,b]	Not serious	Strong association	15/18,634 (0.1%)	63/17,855 (0.4%)	Odds ratio 0.26 (0.14 to 0.45)	3 fewer per 1,000 (from 2 fewer to 3 fewer)	⊕⊕⊕◯ Moderate	Critical
Pneumonia												

Question: Pneumococcal polysaccharide vaccine compared to placebo for immunocompetent adults

Setting: Philippines

Bibliography: Moberley, S., Holden, J., Tatham, D. P., & Andrews, R. M. (2013). Vaccines for preventing pneumococcal infection in adults. *Cochrane Database of Systematic Reviews*, Issue 1. Art. No.: CD000422. doi: 10.1002/14651858.CD000422.pub3

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pneumococcal polysaccharide vaccine**	**Placebo**	**Relative** (95% confidence interval)	**Absolute** (95% confidence interval)		
16	Randomized trials	Serious [c,d]	Serious [a,b]	Serious [a,b]	Not serious	Strong association	978/22,643 (4.3%)	1,547/25,091 (6.2%)	Odds ratio 0.72 (0.56 to 0.93)	16 fewer per 1,000 (from 4 fewer to 26 fewer)	⨁⨁◯◯ Low	Critical

All-cause mortality

Question: Pneumococcal polysaccharide vaccine compared to placebo for immunocompetent adults

Setting: Philippines

Bibliography: Moberley, S., Holden, J., Tatham, D. P., & Andrews, R. M. (2013). Vaccines for preventing pneumococcal infection in adults. *Cochrane Database of Systematic Reviews*, Issue 1. Art. No.: CD000422. doi: 10.1002/14651858.CD000422.pub3

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pneumococcal polysaccharide vaccine	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)		
14	Randomized trials	Serious [c,d]	Serious [a,b]	Serious [a,b]	Not serious	Strong association	1,018/24,018 (4.2%)	1,039/23,542 (4.4%)	Odds ratio 0.90 (0.74 to 1.09)	4 fewer per 1,000 (from 4 more to 11 fewer)	⊕⊕◯◯ Low	Critical
Mortality due to pneumonia or invasive pneumococcal disease												
9	Randomized trials	Serious [c,d]	Serious [a,b]	Serious [a,b]	Not serious	Strong association	140/15,592 (0.9%)	222/15,131 (1.5%)	Odds ratio 0.61 (0.50 to 0.76)	6 fewer per 1,000 (from 3 fewer to 7 fewer)	⊕⊕◯◯ Low	Critical

Question: Pneumococcal polysaccharide vaccine compared to placebo for immunocompetent adults

Setting: Philippines

Bibliography: Moberley, S., Holden, J., Tatham, D. P., & Andrews, R. M. (2013). Vaccines for preventing pneumococcal infection in adults. *Cochrane Database of Systematic Reviews*, Issue 1. Art. No.: CD000422. doi: 10.1002/14651858.CD000422.pub3

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pneumococcal polysaccharide vaccine**	**Placebo**	**Relative** (95% confidence interval)	**Absolute** (95% confidence interval)		
Invasive pneumococcal disease-vaccine type strains												
5	Randomized trials	Not serious	Serious [a,b]	Serious [a,b]	Not serious	Strong association	14/13,889 (0.1%)	140/17,334 (0.8%)	Odds ratio 0.18 (0.10 to 0.31)	7 fewer per 1,000 (from 6 fewer to 7 fewer)	⨁⨁⨁◯ Moderate	Critical
Pneumonia-vaccine type strains												

Question: Pneumococcal polysaccharide vaccine compared to placebo for immunocompetent adults

Setting: Philippines

Bibliography: Moberley, S., Holden, J., Tatham, D. P., & Andrews, R. M. (2013). Vaccines for preventing pneumococcal infection in adults. *Cochrane Database of Systematic Reviews*, Issue 1. Art. No.: CD000422. doi: 10.1002/14651858.CD000422.pub3

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pneumococcal polysaccharide vaccine	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)		
7	Randomized trials	Serious [c,d]	Serious [a,b]	Serious [a,b]	Not serious	Strong association	22/18,251 (0.1%)	160/19,299 (0.8%)	Odds ratio 0.20 (0.13 to 0.32)	7 fewer per 1,000 (from 6 fewer to 7 fewer)	⨁⨁◯◯ Low	Critical

[a] Different population

[b] Includes different age groups

[c] Selection bias

[d] Detection bias

Question: PCV13 compared to placebo for immunocompetent adults

Setting: Philippines

Bibliography: Bonten, M. J. M., Huijts, S. M., Bolkenbaas, M., Webber, C., Patterson, S., Gault, S., …Grobbee, D. E. (2015). Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *New England Journal of Medicine*, 372, 1114-25.

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV13	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)		
Invasive pneumococcal disease												
1	Randomized trial	Not serious	Serious [a,b]	Serious [a,b]	Not serious	Strong association	34/42,240 (0.1%)	66/42,256 (0.2%)	Odds ratio 0.51 (0.34 to 0.78)	1 fewer per 1,000 (from 0 fewer to 1 fewer)	⨁⨁⨁◯ Moderate	Critical
Pneumonia												

Question: PCV13 compared to placebo for immunocompetent adults

Setting: Philippines

Bibliography: Bonten, M. J. M., Huijts, S. M., Bolkenbaas, M., Webber, C., Patterson, S., Gault, S., …Grobbee, D. E. (2015). Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *New England Journal of Medicine*, 372, 1114-25.

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV13	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)		
1	Randomized trial	Not serious	Serious [a,b]	Serious [a,b]	Not serious	Strong association	747/42,240 (1.8%)	787/42,256 (1.9%)	Odds ratio 0.95 (0.86 to 1.05)	1 fewer per 1,000 (from 1 more to 3 fewer)	⊕⊕⊕◯ Moderate	Critical
All-cause mortality												

Question: PCV13 compared to placebo for immunocompetent adults

Setting: Philippines

Bibliography: Bonten, M. J. M., Huijts, S. M., Bolkenbaas, M., Webber, C., Patterson, S., Gault, S., …Grobbee, D. E. (2015). Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *New England Journal of Medicine*, 372, 1114-25.

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV13	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)		
1	Randomized trial	Not serious	Serious [a,b]	Serious [a,b]	Not serious	Strong association	3006/42,237 (7.1%)	3005/42,255 (7.1%)	Odds ratio 1.00 (0.95 to 1.05)	0 fewer per 1,000 (from 3 fewer to 3 more)	⨁⨁⨁◯ Moderate	Critical
Mortality due to pneumonia or invasive pneumococcal disease												

Question: PCV13 compared to placebo for immunocompetent adults

Setting: Philippines

Bibliography: Bonten, M. J. M., Huijts, S. M., Bolkenbaas, M., Webber, C., Patterson, S., Gault, S., …Grobbee, D. E. (2015). Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *New England Journal of Medicine*, 372, 1114-25.

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV13	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)		
1	Randomized trial	Not serious	Serious [a,b]	Serious [a,b]	Not serious	Strong association	6/42,240 (0.0%)	7/42,256 (0.0%)	Odds ratio 0.86 (0.29 to 2.55)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕◯ Moderate	Critical
Invasive pneumococcal disease-vaccine type strains												

Question: PCV13 compared to placebo for immunocompetent adults

Setting: Philippines

Bibliography: Bonten, M. J. M., Huijts, S. M., Bolkenbaas, M., Webber, C., Patterson, S., Gault, S., …Grobbee, D. E. (2015). Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *New England Journal of Medicine*, 372, 1114-25.

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV13	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)		
1	Randomized trial	Not serious	Serious [a,b]	Serious [a,b]	Not serious	Strong association	8/42,240 (0.0%)	33/42,256 (0.1%)	Odds ratio 0.24 (0.11 to 0.52)	1 fewer per 1,000 (from 0 fewer to 1 fewer)	⨁⨁⨁◯ Moderate	Critical
Pneumonia-vaccine type strains												

Question: PCV13 compared to placebo for immunocompetent adults

Setting: Philippines

Bibliography: Bonten, M. J. M., Huijts, S. M., Bolkenbaas, M., Webber, C., Patterson, S., Gault, S., …Grobbee, D. E. (2015). Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *New England Journal of Medicine*, 372, 1114-25.

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV13	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)		
1	Randomized trial	Not serious	Serious [a,b]	Serious [a,b]	Not serious	Strong association	109/42,240 (0.3%)	179/42,256 (0.4%)	Odds ratio 0.61 (0.48 to 0.77)	2 fewer per 1,000 (from 1 fewer to 2 fewer)	⊕⊕⊕◯ Moderate	Critical

[a] Filipinos not represented

[b] Mean age of participants is 72.

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[2] Bonten, M. J. M., Huijts, S. M., Bolkenbaas, M., Webber, C., Patterson, S., Gault, S., …Grobbee, D. E. (2015). Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *New England Journal of Medicine*, 372, 1114-25.

Schedule of administration of pneumococcal vaccine in adults

Summary of evidence

The ACIP[1] recommends a series of vaccination of adults ≥65 years old with both PCV13 and PPSV23 (Kobayashi, 2015). However, pneumococcal vaccination is recommended among adult Filipinos aged 50 years old and above because of lower life expectancy.[2]

In an in-vitro study by Jackson et al.,[3] opsonophagocytic activity was compared among those who received PCV13 and PPSV23. This study showed that PCV13 induced a higher immune response compared to PPSV23 for much of serotypes covered by PCV13, with a significantly higher opsonophagocytic activity GMT after 1 month of vaccination. However, there was a decrease in opsonophagocytic activity titer 1 year after.

PCV13 should be given first before PPSV23 because the functional response is better, with better opsonophagocytic activity, compared to those who received an initial PPSV23 only or PPSV13 as the initial vaccine before PCV13. Subjects who initially received PPSV23 had lower opsonophagocytic activity responses after subsequent administration of PCV13, compared to those who received PCV13 first followed by PPSV23. This is regardless of the level of the initial opsonophagocytic activity response to PPSV23 (Greenberg et al., 2014).[4]

Revaccination with PPSV23 after 5 years of previous PPSV23 vaccination is supported by the systematic review of 12 articles by Caya et al.[5] An increase in antibody response was documented by the review following PPSV23 revaccination. However, the data was lacking for multiple revaccinations or booster doses of PPSV23.

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[1] Kobayashi, M., Bennet, N. M., Gierke, R., Almendares, O., Moore, M. R., Whitney, C. G., …Pilishvili, T. (2015). Intervals between PCV13 and PPSV23 vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Report*, *64*(34), 944-947.

[2] Philippine Society for Microbiology and Infectious Diseases. (2012). *Handbook on adult immunization for Filipinos* (2nd ed.). Quezon City: PSMID.

[3] Jackson, L. A., Gurtman, A., van Cleeff, M., Jansen, K. U., Jayawardene, D., Devlin, C., ...Schmoele-Thoma, B. (2013). Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine compared to a 23-valent pneumococcal polysaccharide vaccine in pneumococcal vaccine-naïve adults. *Vaccine*, *31*(35), 3577-3584.

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Rabies vaccine

Rabies is a preventable, zoonotic disease caused by the Lyssavirus (Rhabdoviridae family), a genus of viruses that includes the rabies virus group. It affects the central nervous system leading to fatal acute encephalomyelitis that is not treatable.[1-3]

The incubation period lasts 20 to 90 days with no symptoms. This is followed by the prodrome with non-specific symptoms of headache, malaise, body aches, pain, itching, or paresthesia at the bite site which happens within 2 to 10 days. The third stage is the acute neurologic phase, which lasts for 2-7 days, wherein the patient manifests with furious rabies encephalitis, with inspiratory spasms, autonomic disability, hydrophobia, and aerophobia. Once these neurologic symptoms appear, rabies is nearly fatal due to respiratory paralysis.

Rabies virus is endemic in the Philippines.[1,3] Domestic dogs transmit the virus in more than 80% of cases, followed by cats and other domestic animals. Rats do not carry rabies in the Philippines. The virus is primarily transmitted through the bite or scratch of an infected animal. It may also occur when a victim's infected saliva encounters the mucosa or open lesions. Rarely, rabies can be transmitted by inhalation of aerosol droplets and infected organ transplants.

Table 15A. Rabies vaccine for adults

	Purified Vero cell rabies vaccine (PVRV)	**Purified chick embryo cell (PCEC) vaccine**
Description[a]	• Each dose contains at least 2.5 IU of inactivated rabies virus.[2]	
Recommendation, summary of evidence	• For post-exposure prophylaxis, follow Department of Health recommendations. (See Table 15C.) *Best Practice Statement*	
	• Pre-exposure prophylaxis • In a meta-analysis of 11 studies,[4] pre-exposure prophylaxis with rabies vaccine in children aged 2 months to 15 years old was safe and immunogenic. • Three doses of pre-exposure vaccination of PCEC vaccine shows immunogenicity in 100% by Day 28. *Strong recommendation; moderate quality of evidence* • Post-exposure prophylaxis • 98% and 100% immunogenicity are achieved on Day 14 and Day 30, respectively.[2] *Strong recommendation; moderate quality of evidence*	
Indication/Target population	• Pre-exposure prophylaxis[3] • Healthcare workers directly caring for rabies patients • Individuals directly involved in rabies control • Personnel in rabies diagnostic laboratories	

	• Pet owners and household members • Animal handlers • Field workers such as dog vaccinators/catchers • Veterinarians and veterinary students • Children 5 to 14 years old living in areas where there is high incidence of rabies • Spelunkers • Post-exposure prophylaxis
Schedule [b]	• Pre-exposure prophylaxis • Day 0, 7, 21/28 • Post-exposure prophylaxis • Day 0, 3, 7, 14, 28
Administration	• Intradermal, 0.1 ml ○ The Department of Health recommends giving rabies vaccine through the intradermal route due to limited resources.[3] • Intramuscular: 0.5 ml PVRV, 1 ml for PCEC vaccine • Patients with contraindication to intramuscular injections, such as patients with hematologic conditions, should also receive the vaccine through the intradermal route. • Immunocompromised patients (e.g. persons living with HIV and patients with cancers, autoimmune diseases, chronic liver disease, or are on chronic immunosuppressant) should receive the vaccine via the intramuscular route. • There is suboptimal response of the vaccine when given via the intradermal route among these patients. • Avoid intravascular administration as this can lead to severe adverse reactions.
Common adverse events[1,5]	• Most common are soreness, swelling, and an itching induration at the injection site. • Fever, rash, flu-like symptoms, headache, nausea, dizziness, and abdominal pain can also happen. • Rarely, neurologic reactions have also been reported.
Contraindications	• Severe hypersensitivity reaction to the vaccine or any vaccine component[1]
Precautions	• Moderate to severe acute illness with or without fever[2]

Pregnancy and breastfeeding	• Data on the vaccine among pregnant and lactating mothers is insufficient and is classified as Category C.[c] It is not contraindicated in this group of patients.[3]

[a] The gold standard human diploid cell vaccine is not available in the Philippines.[1]

[b] Refer to Department of Health manual operations.

[c] Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans. However, potential benefits may warrant use of the drug in pregnant women despite potential risks.[5]

Based on the Department of Health manual of operations,[3] pre-exposure prophylaxis is given based on Table 15C.

Table 15B. Department of Health (DOH) recommendations: Pre-exposure prophylaxis

	Purified Vero cell rabies vaccine (PVRV)			Purified chick embryo cell (PCEC) vaccine		
Schedule/route	Day 0	Day 7	Day 21/28	Day 0	Day 7	Day 21/28
Intradermal	0.1 ml	0.1 ml	0.1 ml	0.1 ml	0.1 ml	0.1 ml
Intramuscular	0.5 ml	0.5 ml	0.5 ml	1 ml	1 ml	1 ml

Rabies post-exposure can be categorized in one of three categories. (See Table 15C.) Appropriate management is detailed in the table.[3]

Table 15C. DOH recommendations: Post-exposure prophylaxis

Category of exposure	Type of exposure	Management
Category 1	• Feeding or touching an animal • Licking of intact skin (with reliable history and thorough physical examination) • Exposure to patient with signs and symptoms of rabies by sharing of eating or drinking utensils • Casual contact (talking to, visiting, and feeding suspected rabies cases) and routine delivery of health care to patient with signs and symptoms of rabies	1. Wash exposed skin immediately with soap and water. 2. No vaccine or rabies immune globulin (RIG) needed. Pre-exposure prophylaxis may be considered for high-risk persons.
Category 2	• Nibbling of uncovered skin with or without bruising or hematoma	1. Wash wound with soap and water. 2. Start vaccine immediately:

	• Minor or superficial scratches or abrasions without bleeding, including those induced to bleed • All Category 2 exposures on the head and neck area are considered Category 3 and should be managed as such.	A. Complete vaccination regimen until Day 28 if: • Biting animal is laboratory proven to be rabid. Or • Biting animal is killed, or it died without laboratory testing. Or • Biting animal has signs and symptoms of rabies. Or • Biting animal is not available for observation for 14 days. B. May omit Day 28 dose if: • Biting animal is alive and remains healthy after the 14-day observation period. Or • Biting animal died within the 14-day observation period, was confirmed by veterinarian to have no signs and symptoms of rabies, and was fluorescent antibody test negative. RIG is not indicated.
Category 3	• Transdermal bites (puncture wounds, lacerations, avulsions) or scratches or abrasions with spontaneous bleeding • Licks on broken skin or mucous membrane • Exposure to a rabies patient through bites, contamination of mucous membranes (eyes, oral/nasal mucosa, genital or anal mucous membrane) or open skin lesions with body	1. Wash wound with soap and water. 2. Start vaccine and RIG immediately: A. Complete vaccination regimen until Day 28 if: • Biting animal is laboratory proven to be rabid. Or • Biting animal is killed or died without laboratory

	fluids through splattering and mouth-to-mouth resuscitation • Unprotected handling of infected carcass • Ingestion of raw infected meat • Exposure to bats All Category 2 exposures on head and neck areas	testing. Or • Biting animal has signs and symptoms of rabies. Or • Biting animal is not available for observation for 14 days. b. May omit Day 28 dose if: • Biting animal is alive and remains healthy after the 14-day observation period. Or • Biting animal died within the 14 days observation period, was confirmed by veterinarian to have no signs and symptoms of rabies, and was fluorescent antibody test-negative.

Post-exposure prophylaxis using the updated 2-site intradermal route is recommended by the Department of Health[9] on Days 0, 3, 7, and 28. The vaccine is given at a dose of 0.1 ml on the left and right deltoids or anterolateral thighs in infants.

If the vaccine will be given through the intramuscular route, the department[3] recommends the WHO standard regimen of PVRV 0.5 ml or PCEC vaccine of 1 ml on one deltoid or anterolateral thigh in infants.

Table 15D. DOH recommendations: Post-exposure prophylaxis for infants

Day of immunization	Purified Vero cell rabies vaccine (PVRV)	Purified chick embryo cell (PCEC) vaccine	Site of injection
Day 0	0.5 ml	1 ml	One deltoid or anterolateral thigh in infants
Day 3	0.5 ml	1 ml	One deltoid or anterolateral thigh in infants
Day 7	0.5 ml	1 ml	One deltoid or anterolateral thigh in infants

Day 14	0.5 ml	1 ml	One deltoid or anterolateral thigh in infants
Day 28	0.5 ml	1 ml	One deltoid or anterolateral thigh in infants

For individuals with Category 3 exposures and where RIG is indicated:[6]

- RIG is administered only once, and immediately as soon as possible after initiation of post-exposure prophylaxis.
- Administration of RIG should not exceed Day 7 after the first dose of vaccine has been given.
- Regardless of availability of RIG, vaccines should never be withheld.
- The proper administration of RIG will neutralize the virus at the wound site within a few hours.
- Equine RIG shows similar clinical outcomes as that of human RIG in preventing rabies. In addition, equine RIG is less costly. As equine RIG products are now highly purified, skin testing before its administration is unnecessary and should be abandoned.
    - Maximum dose for equine RIG is 40 IU/kg body weight; for human RIG, it is 20 IU/kg body weight. There is no minimum dose.
    - Infiltrate RIG as much as possible into the wound. The remainder of the calculated dose of RIG does not need to be injected intramuscular at a distance from the wound, but it can be fractionated in smaller, individual syringes to be used for other patients, aseptic retention given.
- If RIG is unavailable, thorough and prompt wound washing, in addition to immediate administration of the 1st vaccine dose, followed by a complete course of rabies vaccine, will save up to 99% of lives.
- If a limited amount of RIG is available, RIG allocation should be prioritized for exposed patients based on the following criteria (from most to least urgent):
    - Multiple bites;
    - Deep wounds;
    - Bites to highly innervated parts of the body, such as head, neck, hands and genitals;
    - Patients with severe immunodeficiency;
    - History of biting animal indicative of confirmed or probable rabies; and
    - A bite, scratch, or exposure of a mucous membrane by a bat that can be ascertained for rabies testing.

References

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Tetanus, diphtheria, and pertussis vaccine

Diphtheria is a systemic intoxication caused by the exotoxin produced by *Corynebacterium diphtheriae*. Humans are carriers of this bacteria. It can be acquired through direct contact or by sneezing or coughing. The incubation period is generally between 2-5 days.[1] Clinical presentation is an upper respiratory tract infection and is distinguished by a thick membrane in the mucosa, caused by the damage of the cells.

The exotoxin consists of two polypeptides: Fragment B, which is responsible for binding to surface receptors and penetration into cells; and Fragment A, which is responsible for the manifestation by interfering with protein synthesis.[1] Transmission can occur through droplets and close physical contact.

Pertussis is a highly communicable disease caused by *Bordetella pertussis*. The incubation period is commonly 1-10 days with a range of 4-21 days, and is most infectious during first two weeks of illness.[2] It presents as a classic acute infectious respiratory illness that is commonly seen in children.

Pertussis evolves into three clinical stages. The highly contagious catarrhal stage is characterized by coryza, sneezing, low-grade fever, and occasional cough. The second stage, the paroxysmal stage, is the diagnostic stage and is characterized by bursts of paroxysms of numerous rapid coughs, which occur frequently at night, due to difficulty of expelling thick mucus from the tracheobronchial tree. The convalescent stage is the recovery stage where the cough lessens and disappears in two to three weeks.

In adults, the clinical presentation is less classic and may be asymptomatic. Though the illness is typically mild, adults can transmit the disease through droplets to unimmunized children or immunocompromised individuals. According to WHO, pooled analysis indicates that the sources of pertussis in households are from mothers (39% 95% CI: 33%-45%), fathers (16% 95% CI: 12%-21%), and grandparents (5% 95% CI: 2%-10%).[3]

Tetanus is a neuromuscular dysfunction caused by a potent exotoxin, tetanospasmin, elaborated by *Clostridium tetani*. The disease occurs after the entry of the bacteria through breaks in the skin, after an incubation period of about 3-21 days. Three clinical features of tetanus are identified: the localized tetanus, usually involving muscles of the same anatomic area; the cephalic tetanus occurring in the facial area; and the generalized tetanus, which is the most severe type.[4] Generalized tetanus occurs in a descending manner, starting from trismus, stiffness of the neck, difficulty in swallowing, and rigidity of the abdomen. Patients may also have generalized tonic clonic seizures and autonomic instability. Tetanus is not transmitted from person to person.

Table 16A. Tetanus, diphtheria, and pertussis vaccine for adults

Description	• Almost exclusively available in fixed combinations as tetanus toxoid and adult diphtheria toxoid (Td) or tetanus toxoid and acellular pertussis (Tdap). Active vaccines of tetanus and diphtheria are derived by inactivating the toxins of *C. tetani* and *C. diphtheria*. The toxoids are adsorbed on to an aluminum phosphate adjuvant with thimerosal as preservative. • The combination vaccines, Tdap or Td, for adults and adolescents are composed of the same amount of tetanus toxoid (at least 20 IU)

	relative to pediatric dose but a reduced amount of diphtheria toxoid (at least 2 IU), lesser or same amount of acellular pertussis cells (at least 8 mcg), depending on the brand.[6] • Immunity against pertussis wanes approximately 5-10 years after completion of childhood vaccination, leaving adolescents and adults susceptible to the disease.[5] The acellular vaccine composed of inactivated components of *B. pertussis* cells is the recommended vaccine for adults. • The passive vaccine of tetanus is the tetanus immune globulin derived by cold-ethanol fractionation of the plasma of hyper-immune adults. There are two types: human immunoglobulin available in 250-5000 IU and equine immunoglobulin available in 1500-5000 IU.
Recommendation, indication/target population	• Adults who have not been vaccinated or are incompletely vaccinated with tetanus-diphtheria combination 3-dose primary series should receive the complete primary series that includes 1 dose of Tdap to prevent tetanus, diphtheria, and pertussis. *Strong recommendation; low to moderate quality of evidence*
	• Td vaccination every 10 years may be given to adults aged 19-64 years old, if the last vaccination was at least 10 years ago. *Weak recommendation; low quality of evidence*
	• Adults who anticipate to have close contact with an infant <12 months old may receive one dose of Tdap to prevent transmission of pertussis. *Weak recommendation; very low quality of evidence*
	• Adults who sustained wounds assessed to be tetanus-prone should be given Td with or without tetanus immunoglobulin to prevent tetanus infection. *Strong recommendation; low quality of evidence*
Schedule	• Td of 0.5 ml each should be given intramuscularly with the second dose given 4-8 weeks after the first dose, and the third dose given at 6-12 months after the second dose. • Adults of all ages who have never received Tdap as an adolescent or adult, or for whom vaccine status is unknown, should receive Tdap as their first dose, followed by Td to complete their primary series.[20]
Administration	• Intramuscular
Common adverse events	• Rare
Contraindications	• Anaphylactic reaction to a prior dose of the vaccine or any of its components

	• History of encephalopathy and prolonged seizures not attributable to another identifiable cause within 7 days of administration of prior dose of vaccine[2]
Precautions	• Moderate to severe acute illness • Guillain-Barré syndrome within 6 weeks after a previous dose of tetanus toxoid-containing vaccine • History of Arthus-type hypersensitivity reactions after a previous dose of tetanus or diphtheria toxoid-containing vaccine • History of seizure or unstable neurologic disorder for pertussis-containing vaccine[2]
Pregnancy and breastfeeding	• Pregnant women should receive at least two doses of tetanus toxoid-containing vaccine with an interval of at least 4 weeks between doses and the second dose at least 2 weeks before birth and a third dose should be given at least 6 months after the first dose. *Strong recommendation; moderate quality of evidence* • Pregnant women should receive the vaccine at any time during pregnancy, but the optimal timing of Tdap administration is at 27 to 36 weeks gestation to maximize maternal antibody response and passive antibody transfer to the infant. *Strong recommendation; low quality of evidence* • In subsequent pregnancies, pregnant women should receive at least 1 dose of Td for lifelong protection against tetanus. *Strong recommendation; moderate quality of evidence* • Women with documented evidence of receiving 5 doses of vaccine, including 3-primary series and 4th and 5th doses spaced at least 1 year, should not be further vaccinated during pregnancy in order to avoid the risk of increased local reactions. *Strong recommendation; low quality of evidence*

Summary of evidence

The 3-dose primary series of the combination vaccines is the foundation for building lifelong immunity against tetanus, diphtheria, and pertussis. No controlled clinical trials examining the efficacy of the vaccines has ever been conducted. According to WHO, there is evidence of effectiveness against diphtheria from observational studies, although effectiveness against diphtheria did not reach 100%. However, the studies cited were mostly from pediatric population and observational studies.[4]

The ACIP reported that there was no significant difference in the number of patients who developed protective levels of anti-diphtheria one month after giving Td or Tdap.[7] After the third dose of the tetanus toxoid vaccine, adults had high levels of antibodies, but were found to have lesser antibody response compared to children.[8]

Tdap/Td vaccine in pregnant women

Summary of evidence

Only WHO has a statement on the giving of the vaccine to pregnant women, and the evidence is based on two randomized controlled trials. According to WHO, "pregnant women should receive at least two doses of tetanus toxoid-containing vaccine with an interval of at least 4 weeks between doses and the second dose at least 2 weeks before birth. To ensure protection for a minimum of 5 years, a third dose should be given at least 6 months after the 2nd dose. A fourth and fifth dose should be given at intervals of at least 1 year or in subsequent pregnancies, in order to ensure lifelong protection."[8] Women who have documented evidence that they received all of the doses for protection, i.e., either 6 doses of tetanus toxoid-containing vaccine in childhood or 5 doses if first vaccinated during adulthood, should not be given further vaccinated during pregnancy in order to avoid the risk of increased local reactions.[8]

ACIP guidelines state that the highest concentration of maternal antibodies to be transferred to the child is close to birth.[9] Women who received Tdap during the first and second trimester were noted to have low levels of antibodies at term.[10] WHO reported that the point estimate for vaccine effectiveness of maternal vaccination more than 7 days before birth was 91% (95% CI: 84%-95%) using the screening method with adjusted vaccine effectiveness estimated at 93% (95% CI: 81%-97%) seen in case control; thus Tdap during pregnancy is effective in protecting infants from pertussis and may impact morbidity and mortality of infants against pertussis who are too young to be vaccinated.[11]

Td vaccine as booster for adults

Summary of evidence

Booster vaccination is given to reduce morbidity of tetanus, diphtheria, and pertussis. However, most of the studies reviewing the benefits of booster vaccination are on children who completed the primary dose of vaccine series with 3 booster shots before 18 years old. The available data, as reported by WHO, do not support the recommendation of decennial booster doses beyond the 6-dose schedule, as immunity can be extended up to mid-adulthood. If tetanus vaccination is started during adulthood, a total of 5 appropriately spaced doses are required to obtain lifelong protection.[8] According to the review done by WHO, no data in observational studies showed clinical effectiveness of booster in preventing diphtheria among adults, and there is limited data on the levels of protective immunogenicity.[12] Further study on the efficacy of the booster vaccine is needed.

Healthcare workers and adults who anticipate contact with infants <12 months old

Summary of evidence

Cocooning is a strategy implemented in various countries to protect infants who are too young to be vaccinated by vaccinating their close contacts who may be sources of pertussis infection.[11] The ACIP and WHO both agree that there is no evidence on the effectiveness of vaccinating healthcare workers and adults as a strategy to prevent nosocomial transmission to infants within healthcare settings.[13,14] WHO guidelines state that there is not sufficient substantial data to say that vaccinating adults could prevent pertussis in infants. Immunity against pertussis after acellular pertussis-containing vaccine rapidly declines as compared to whole cell pertussis vaccine.[15]

Tetanus vaccine as part of wound management

Summary of evidence

There is no change in the recommendation from the 2012 handbook. Provision of tetanus vaccine has been a standard of care to prevent infections in contaminated wounds for years, based on Infectious Diseases Society of America guidelines on combat-related injuries.[16] Despite shortage of tetanus immunoglobulin in combat zones, no cases of tetanus were reported, and this was attributed to the success of primary immunization series. Wounds are considered tetanus prone if they are sustained more than 6 hours before surgical treatment of the wound, wounds or burns that show a significant degree of devitalized tissue or a puncture-type wound, particularly where there has been contamination with soil/manure, wounds with foreign bodies, compound fractures, wounds or burns in patients who have evidence of sepsis, frostbite, and high-velocity missile injuries.[17,18]

Table 16B. Tetanus immunotherapy for management of wound in immunocompetent individuals[19]

Characteristic	Clean, minor wounds		All other wounds	
History of tetanus toxoid/doses	Tdap or Td	Tetanus immunoglobulin[a,b,c,]	Tdap or Td	Tetanus immunoglobulin[a,b,c,]
Unknown or <3 doses	Yes	No	Yes	Yes
3 or more doses	No (yes, if >10 years since last Td)	No	No (yes, if >10 years since last Td)	No

[a] The recommended prophylactic dose of tetanus immunoglobulin is 250 units.

[b] When tetanus toxoid and tetanus immunoglobulin are administered concurrently, separate syringes should be used.

[c] People with HIV infection or severe immunodeficiency who have contaminated wounds (including minor wounds) should also receive tetanus immunoglobulin, regardless of their history of immunization.

Adverse events with Tdap

Summary of evidence

According to WHO guideline, reactions such as pain and erythema are reported by those who receive booster doses, but mild systemic reactions, including fever malaise and aches, occur in 0.5-1.0% of vaccines. Serious adverse events are rare. Guillain-Barré syndrome has been reported rarely, but population levels do not support association between tetanus toxoid and Guillain-Barré syndrome.

The ACIP also reviewed the safety of repeat Tdap administration to pregnant women. Reported events showed that a second dose of Tdap was tolerated by pregnant women, and fever was reported in 2.4%-6.5% of recipients of booster.[9] The ACIP believes that the benefit of the vaccine outweighs more than the theoretical concerns of severe adverse events.

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Typhoid vaccine

Typhoid fever is caused by *Salmonella enterica* serovar Typhi and remains an important cause of enteric disease in the Philippines. It is transmitted through the fecal-oral route and is most common in areas with poor water and sanitation systems and practices.[1]

The emergence of drug-resistant strains of *S. typhi* in the 1980s has led to the widespread use of fluoroquinolones such as ciprofloxacin and ofloxacin in countries where multidrug resistance is a problem. In the Philippines, there is an increasing trend of resistance to ciprofloxacin, nalidixic acid, and chloramphenicol.[2]

Table 17. Typhoid vaccine in adults

Description	• Each dose contains 25 mcg of purified Vi capsular polysaccharides of *S. typhi* (Ty2 strain).
Recommendation, indication/target population	• Typhoid fever Vi polysaccharide vaccine may be given to immunocompetent adults living in an endemic area. Sanitation is still recommended to prevent typhoid fever. *Strong recommendation; moderate quality of evidence* • Typhoid vaccine should not be routinely administered to laboratory workers, intimate contacts of carriers, and during outbreaks. *Strong recommendation; very low quality of evidence*
Summary of evidence	• The vaccine was able to decrease the risk of typhoid fever with RR 0.31 (95% CI: 026, 0.37) on the first year, with an RR 0.41 (95% CI: 0.31, 0.55) on the second year and RR 0.50 (0.32, 0.78) on the third year, though there was noted heterogeneity on year 2. Among the studies included in the meta-analysis, the RCT done in Pakistan showed no benefit of vaccine over the placebo, and this study was noted to have caused the heterogeneity. The cumulative incidence of typhoid fever vaccine had RR of 0.45 (95% CI: 0.30, 0.70).[4]
Schedule	• Single dose • Re-vaccination every 3 years for travelers • One dose should be given ≥2 weeks prior to expected exposure.
Administration	• Subcutaneous • Intramuscular
Common adverse events[5]	• Swelling and pain over the injection site • Fever, erythema
Contraindications	• Intradermal administration • History of any adverse reaction to a previous dose

Precautions	• Sanitation is still recommended to prevent typhoid fever. • Moderate or severe acute illness • Bleeding disorders and taking anticoagulants[1]
Pregnancy and breastfeeding	• Given with precaution in breastfeeding patients • Pregnant women may receive the vaccine[6] • Category C[a]

[a] Animal reproduction studies have shown an adverse effect on the fetus. There are no adequate and well-controlled studies in humans, but potential benefits may warrant the use of the drug in pregnant women despite potential risks.[7]

Question: How effective is typhoid fever vaccine vs placebo in preventing typhoid fever?

Setting: Endemic country

Bibliography: Anwar, E., Goldberg, E., Fraser, A., Acosta, C. J., Paul, M., & Leibovici, L. (2014). Vaccines for preventing typhoid fever. *Cochrane Database of Systematic Reviews*, (1), CD001261.

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	vi capsular polysaccharide vaccine	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)		
Incidence of typhoid fever after 1 year												
6	Randomized trials	Not serious	Not serious	Serious [a]	Not serious	None	-/50672	-/49530	Risk ratio 0.31 (0.26 to 0.37)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕◯ Moderate	Critical
Incidence of typhoid fever year 2												

Question: How effective is typhoid fever vaccine vs placebo in preventing typhoid fever?

Setting: Endemic country

Bibliography: Anwar, E., Goldberg, E., Fraser, A., Acosta, C. J., Paul, M., & Leibovici, L. (2014). Vaccines for preventing typhoid fever. *Cochrane Database of Systematic Reviews*, (1), CD001261.

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	vi capsular polysaccharide vaccine	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)		
4	Randomized trials	Not serious	Not serious	Serious [a]	Not serious	None	30/5,209 (0.6%)	41/5122 (0.8%)	Risk ratio 0.41 (0.31 to 0.55)	5 fewer per 1,000 (from 4 fewer to 6 fewer)	⊕⊕⊕◯ Moderate	Critical
Year 3												
1	Randomized trials	Not serious	Not serious	Serious [a]	Not serious	None			Risk ratio 0.50 (0.32 to 0.78)	1 fewer per 1,000 (from 0 fewer to 1 fewer)	⊕⊕⊕◯ Moderate	

Question: How effective is typhoid fever vaccine vs placebo in preventing typhoid fever?

Setting: Endemic country

Bibliography: Anwar, E., Goldberg, E., Fraser, A., Acosta, C. J., Paul, M., & Leibovici, L. (2014). Vaccines for preventing typhoid fever. *Cochrane Database of Systematic Reviews*, (1), CD001261.

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	vi capsular polysaccharide vaccine	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)		
Cumulative incidence of typhoid fever at 2.5 to 3 years												
1	Randomized trials	Not serious	Not serious	Serious[a]	Not serious	None	30/5692 (0.5%)	66/5692 (1.2%)	Risk ratio 0.45(0.30 to 0.70)	6 fewer per 1,000 (from 3 fewer to 8 fewer)	⊕⊕⊕◯ Moderate	
Adverse event: fever												

Question: How effective is typhoid fever vaccine vs placebo in preventing typhoid fever?

Setting: Endemic country

Bibliography: Anwar, E., Goldberg, E., Fraser, A., Acosta, C. J., Paul, M., & Leibovici, L. (2014). Vaccines for preventing typhoid fever. *Cochrane Database of Systematic Reviews*, (1), CD001261.

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	vi capsular polysaccharide vaccine	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)		
4	Randomized trials	Not serious	Not serious	Serious [a]	Not serious	None	343/66242 (0.5%)	349/66796 (0.5%)	Risk ratio 0.98 (0.85 to 1.14)	0 fewer per 1,000 (from 1 fewer to 1 more)	⊕⊕⊕◯ Moderate	
Adverse event: erythema												
3	Randomized trials	Not serious	Not serious	Serious [a]	Serious [b]	None	345/65858 (0.5%)	336/66403 (0.5%)	Risk ratio 3.04 (0.45 to 20.30)	10 more per 1,000 (from 3 fewer to 98 more)	⊕⊕◯◯ Low	

Question: How effective is typhoid fever vaccine vs placebo in preventing typhoid fever?

Setting: Endemic country

Bibliography: Anwar, E., Goldberg, E., Fraser, A., Acosta, C. J., Paul, M., & Leibovici, L. (2014). Vaccines for preventing typhoid fever. *Cochrane Database of Systematic Reviews*, (1), CD001261.

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	vi capsular polysaccharide vaccine	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)		
Swelling at injection site												
3	Randomized trials	Not serious	Not serious	Serious [a]	Not serious	None	19/955 (2.0%)	0/812 (0.0%)	Risk ratio 6.06 (1.07 to 34.22)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕◯ Moderate	
Pain at injection site												

Question: How effective is typhoid fever vaccine vs placebo in preventing typhoid fever?

Setting: Endemic country

Bibliography: Anwar, E., Goldberg, E., Fraser, A., Acosta, C. J., Paul, M., & Leibovici, L. (2014). Vaccines for preventing typhoid fever. *Cochrane Database of Systematic Reviews*, (1), CD001261.

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	vi capsular polysaccharide vaccine	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)		
1	Randomized trials	Not serious	Not serious	Serious [a]	Not serious	None	56/334 (16.8%)	7/333 (2.1%)	Risk ratio 7.98 (3.69 to 17.24)	147 more per 1,000 (from 57 more to 341 more)	⊕⊕⊕◯ Moderate	
Serious adverse events												
4	Randomized trials								Not estimable		-	

[a] Population studied included children.

[b] Wide confidence interval

Summary of evidence

Microbiologists and laboratory workers

No controlled trials examined the efficacy of typhoid vaccine in laboratory workers. A case series of 4 laboratory workers who worked on *S. typhi* received typhoid fever vaccine and developed atypical case of typhoid fever. The study did not mention the type of vaccine that the workers received.[3] The most common presenting symptoms were anorexia, generalized aching, chills and fever, headache, malaise, excessive perspiration, and abdominal pain. In all patients, the onset of the disease was insidious.

Intimate contact with carriers

No trials or observational studies were done on intimate contacts with carriers.

Outbreaks

No trials or observational studies examined the efficacy of typhoid fever vaccine during outbreaks.

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Varicella virus vaccine

Varicella is a highly contagious disease caused by the varicella zoster virus. It causes vesicles, itching, tiredness, and fever. The virus is transmitted via airborne and enters the system through the respiratory tract and conjunctiva. Incubation period is 14 to 16 days before the onset of rash until the lesions have crusted.[1-2] Recovery from primary varicella infection usually results in lifetime immunity.

Table 18. Varicella vaccine in adults

Description	• 0.5 ml dose contains a minimum of 1350 plaque-forming units of the live attenuated strains of VZV Oka varicella virus.[3] • The vaccine has undergone sequential passages, and the reconstituted form contains small amounts of sucrose, processed porcine gelatin, sodium chloride, ethylenediaminetetraacetic acid, neomycin, and trace quantities of DNA and protein. • There are two vaccines available against varicella: the varicella vaccine, and combination measles-mumps-rubella-varicella vaccine. Only the former can be given to adults.
Recommendation, indication/target population	• The vaccine should not be given routinely to immunocompetent adults. *Strong recommendation; very low quality of evidence* • Healthcare workers without history of varicella infection should be given varicella vaccine. *Strong recommendation; very low quality of evidence* • Varicella vaccine may be given as post-exposure prophylaxis within 72 hours after exposure. *Weak recommendation; very low quality of evidence* • The vaccine is safe to be given to patients but is poorly immunogenic to those who underwent hematopoietic stem cell transplant. *Weak recommendation; low quality of evidence* • Varicella vaccine should not be given to HIV-infected adults regardless of their immunogenicity. *Strong recommendation; very low quality of evidence*
Summary of evidence	See text below table.
Schedule	• 2 doses, given 4 weeks apart[1]
Administration	• Subcutaneous
Common adverse events[10,11]	• Mild local reaction at the injection site was the most common (10%) during first vaccine, and after the second dose (8%).

	• Vaccine-associated rashes varied from one to 100 lesions with a mean of 14; the onset varied between two and 35 days mean 17 after immunization. • Other reported side effects after the first dose of vaccine included upper respiratory tract symptoms, such as sore throat in 15(8%) of 187and fever >37.8 C (100F) in 4 (2%) of 187. • Side effects after second doses of vaccine (including rash, upper respiratory tract infection, and fever) were reported by <1% of subjects during first vaccine, 13/150 after the second dose.
Contraindications[1]	• History of anaphylactic reaction to any vaccine component, including neomycin and gelatin • Pregnancy • Malignant condition affecting bone marrow or lymphatic system • Primary or acquired immunodeficiency including HIV+ (if combination MMR) • Family history of congenital or hereditary immunodeficiency in first-degree relatives • Untreated active tuberculosis
Precautions[1]	• Acute severe illness • Untreated tuberculosis • Thrombocytopenia • Recent administration of blood, plasma, or immune globulin • Use of salicylates
Pregnancy and breastfeeding[1]	• If given, avoid pregnancy for 4 weeks. • Not safe for pregnant patients • Give vaccine post-partum, if susceptible

Summary of evidence

No studies were conducted on the effectiveness of varicella vaccine among adults comparing it with placebo. Most pre-licensure studies on varicella vaccine are for children.

In a survey conducted by the National Health and Nutrition Examination Survey prior to the introduction of varicella vaccine in the United States, the prevalence of VZV-specific immunoglobulin G antibody was 96.3% (95.7-96.9), with antibody titers rising from 86% (83.0-88.6) from ages 6-11 years old to individuals 20 years old and above. [4] Among those who were born outside the United States, the prevalence for varicella antibody was 96.4% (95.8-97.0). The study concluded that the antibodies were from naturally acquired varicella. In other temperate countries, seroprevalence conversion was noted as individuals reach adolescent stage. This is in contrast to tropical countries where seroprevalence is different. In the Philippines, from 1992-1994, the seroprevalence of the general community (0-69 years old) was 76%, with 57% prevalence in children under 5 years old and increasing rate up to 30 years old, with 92-95% found in individuals above 30 years old.[5] Another seroprevalence study among children revealed that adolescents had the highest rate at 81.33%.[6]

Question: Varicella vaccine 867 Oka-Merck compared to placebo for post-exposure prophylaxis

Setting: Community setting, exposed siblings, 867 Oka-Merck Vaccine

Bibliography: Arbeter, A. M., Starr, S. E., & Plotkin, S. A. (1986). Varicella vaccine trials in healthy children and adults. *Pediatrics*, 78(4 Pt 2), 748-56.

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Varicella vaccine 867 Oka-Merck**	**Placebo**	**Relative (95% confidence interval)**	**Absolute (95% confidence interval)**		
Mild varicella disease (assessed with: cases)												
1	Randomized trials	Very serious [a]	Not serious	Serious [b]	Not serious	None	4/13 (30.8%)	0/13 (0.0%)	Not estimable	[c]	⨁◯◯◯ Very low	
Moderate to severe disease												
1	Randomized trials	Very serious [a]	Not serious	Serious [b]	Not serious	None	0/13 (0.0%)	12/13 (92.3%)	Not estimable		⨁◯◯◯ Very low	

[a] Randomization and allocation were not clear. No information about double blinding

[b] Population included individuals 18 months to 16 years old of healthy exposed siblings

[c] No explanation was provided

Summary of evidence

Post-exposure prophylaxis

Two trials studied the utility of varicella vaccine as post-exposure prophylaxis. In one trial that evaluated the efficacy of the varicella vaccine among children and adults, it showed that the vaccine Oka-Merck strain was 70% effective in preventing mild varicella infection and was 100% effective in preventing moderate to severe disease. In another study, there was no significant difference among children who were given the single-dose varicella vaccine (Oka/RIT) 2000 compared to those who received placebo (RR 0.90, 95% CI: 0.95-2.21).[7]

Question: Single-dose varicella vaccine (Oka/RIT) 2000 plaque-forming units compared to placebo for post-exposure prophylaxis

Setting: Hospital setting; healthy exposed siblings aged 1-13 years with negative history of varicella

Bibliography: Mor, M., Harel, L., Kahan, E., & Amir, J. (2004). Efficacy of postexposure immunization with live attenuated varicella vaccine in the household setting - a pilot study. *Vaccine*, *23*, 325-8.

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Single-dose varicella vaccine (Oka/RIT) 2000 plaque-forming units**	**Placebo**	**Relative (95% confidence interval)**	**Absolute (95% confidence interval)**		
Clinical varicella												
1	Randomized trials	Not serious	Not serious	Serious [a]	Serious [b]	None	9/22 (40.9%)	9/20 (45.0%)	Risk ratio 0.90 (0.55 to 2.21)	45 fewer per 1,000 (from 202 fewer to 545 more)	⊕⊕◯◯ Low	
Moderate to severe varicella disease												

Question: Single-dose varicella vaccine (Oka/RIT) 2000 plaque-forming units compared to placebo for post-exposure prophylaxis

Setting: Hospital setting; healthy exposed siblings aged 1-13 years with negative history of varicella

Bibliography: Mor, M., Harel, L., Kahan, E., & Amir, J. (2004). Efficacy of postexposure immunization with live attenuated varicella vaccine in the household setting - a pilot study. *Vaccine*, *23*, 325-8.

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single-dose varicella vaccine (Oka/RIT) 2000 plaque-forming units	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)		
1	Randomized trials	Not serious	Not serious	Serious[a]	Serious[b]	None	1/22 (4.5%)	8/20 (40.0%)	Risk ratio 0.11 (-- to --)	356 fewer per 1,000 (from -- to --)	⨁⨁◯◯ Low	

[a] Study population included children 1 to 13 years old.

[b] Imprecise due to small sample size

Summary of evidence

Hemotopoietic stem cell transplant and HIV patients

In a cohort of adult autologous hemotopoietic stem cell transplant recipients,[8] the vaccine was given on the 4th month after the transplant and another dose after 4 weeks. Two months after the first dose, two out of the 10 patients with pre- and post-vaccination results elicited a vaccine response; one of 15 patients mounted a vaccine response 1.5 months after a second dose of vaccine. The respective GMTs were 675.6 (95% CI: 179.3–2545.2) and 707.5 (95% CI: 308.0–1625.5). In the vaccinated group, 44.8% (95% CI: 26.4–64.3; *n* = 13/29) of patients reported any adverse events, and 10.3% (95% CI: 2.2–27.4; *n* = 3/29) reported Grade 3 adverse events that were causally related to varicella vaccination. The following adverse events were observed: pain 24% (10.3-43.5); redness 20.7% (8-39.7); swelling 3.4% (0.1-17.8); fever 20.7% (8-39.7); and rash 17.2 (5.8-35.8).

No randomized trials or observational studies were done on adults living with HIV. In a small non-randomized trial of 112 children infected with HIV ages 1-8 years old given 2 doses of varicella vaccine,[9] symptomatic patients with CD4 count of less than 500 had the lowest immunologic response 3 years after the vaccine administration, but the least infected children had higher immunologic response 3 years post vaccination compared to those who had natural immunity. Adverse events were equal among all the HIV-infected children given the vaccine. No efficacy trials were also done on both adult and children infected with HIV.

Question: Safety and immunogenicity of varicella vaccine compared to natural immunity for children with HIV

Setting: US children infected with HIV aged 1-8 years old

Bibliography: Levin, M. J., Gershon, A. A., Weinberg, A., Song, L. Y., Fentin, T., Nowak, B., & Pediatric AIDS Clinical Trials Group 265 Team. (2006). Administration of live varicella vaccine to HIV-infected children with current or past significant depression of CD4(+) T cells. *Journal of Infectious Diseases*, *194*, 247-55.

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Varicella vaccine**	**Placebo or other vaccines**	**Relative (95% confidence interval)**	**Absolute (95% confidence interval)**		
Adverse events: local reaction												
1	Observational study	Not serious	Not serious	Serious [a]	Serious [b]	None	No significant difference in local site reaction among the different of HIV in the population. After the first injection, 6%–21% of subjects in each group developed local reactions, of these 25% had Grade 3 reactions (defined as 25–50 mm of induration/erythema or crying with touch).				⊕◯◯◯ Very low	Critical
Systemic adverse event												
1	Observational study	Not serious	Not serious	Serious [a]	Serious [b]	None	After the first dose, 12-28% of subjects reported systemic adverse events.				⊕◯◯◯ Very low	Critical

Question: Safety and immunogenicity of varicella vaccine compared to natural immunity for children with HIV

Setting: US children infected with HIV aged 1-8 years old

Bibliography: Levin, M. J., Gershon, A. A., Weinberg, A., Song, L. Y., Fentin, T., Nowak, B., & Pediatric AIDS Clinical Trials Group 265 Team. (2006). Administration of live varicella vaccine to HIV-infected children with current or past significant depression of CD4(+) T cells. *Journal of Infectious Diseases*, *194*, 247-55.

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Varicella vaccine**	**Placebo or other vaccines**	**Relative (95% confidence interval)**	**Absolute (95% confidence interval)**		
Immunogenicity												
1	Observational study	Not serious	Not serious	Serious [a]	Serious [c]	None	The antibody response of the groups 1 year after the second dose of vaccine ranged from 43-65% compared to patients with natural infection of 73%. Three years after the vaccine the antibody response of the vaccinated patients ranged from 29-52% compared to 30% of patients with natural immunity.				⊕◯◯◯ Very low	Important

[a] Population involved children 1-8 years old with HIV

[b] Confidence interval not stated for dichotomous outcomes.

[c] Confidence interval not stated for continuous outcome.

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[3] VARIVAX® III (varicella virus vaccine, live attenuated [Oka/Merck]) [package insert]. Merck Canada Inc. 2016. Retrieved on April 12, 2017 from http://www.merck.ca/assets/en/pdf/products/VARIVAX_III-PM_E.pdf

[4] Kilgore, P. E., Kruszon-Moran, D., Seward, J. F., Jumaan, A., Van Loon, F. P. L., Forghani, B., …Hadler, S. C. (2003). Varicella in Americans from NHANES III: Implications for control through routine immunization. *Journal of Medical Virology 70*, S111-118.

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[8] Sasadeusz, J., Prince, H. M., Schwarer, A. Szer, J., Stork, A., Bock, H. L., …Innis, B. L. (2014). Immunogenicity and safety of a two-dose live attenuated varicella vaccine given to adults following autologous hematopoietic stem cell transplantation. *Transplant Infectious Disease*, *16*, 1024–1031.

[9] Levin, M. J., Gershon, A. A., Weinberg, A., Song, L. Y., Fentin, T., Nowak, B., & Pediatric AIDS Clinical Trials Group 265 Team. (2006). Administration of live varicella vaccine to HIV-infected children with current or past significant depression of CD4(+) T cells. *Journal of Infectious Diseases*, *194*, 247-55.

[10] World Health Organization (20 June 2014). Varicella and herpes zoster vaccines: WHO position paper, June 2014. *Weekly Epidemiological Record, 89*(25), 265-288.

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Appendix

Vaccine-preventable Diseases, 2008-2017

Data from the Epidemiology Bureau
Public Health Surveillance Division

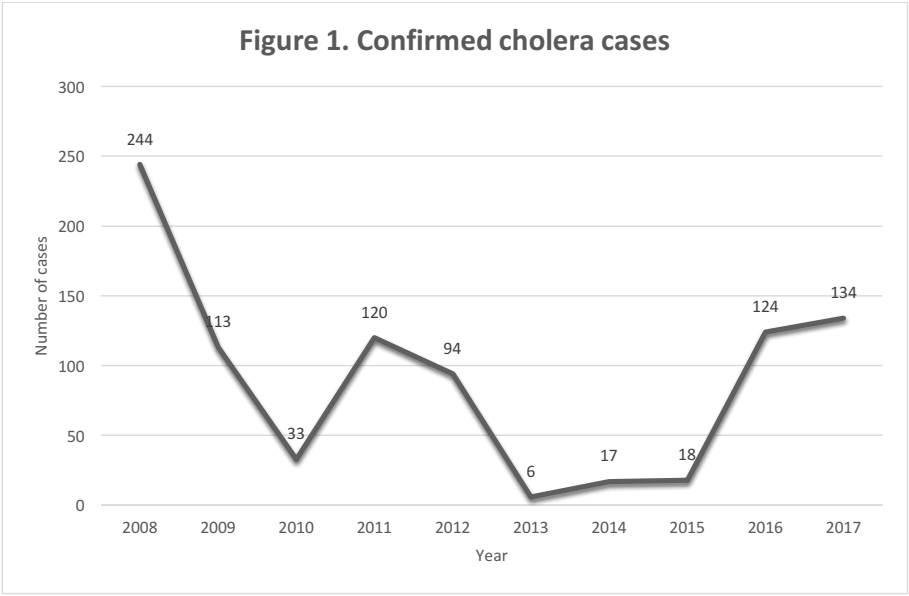
Figure 1. Confirmed cholera cases
300
250
200
150
100
50
0
Number of cases
244
113
33
120
94
6
17
18
124
134
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
Year

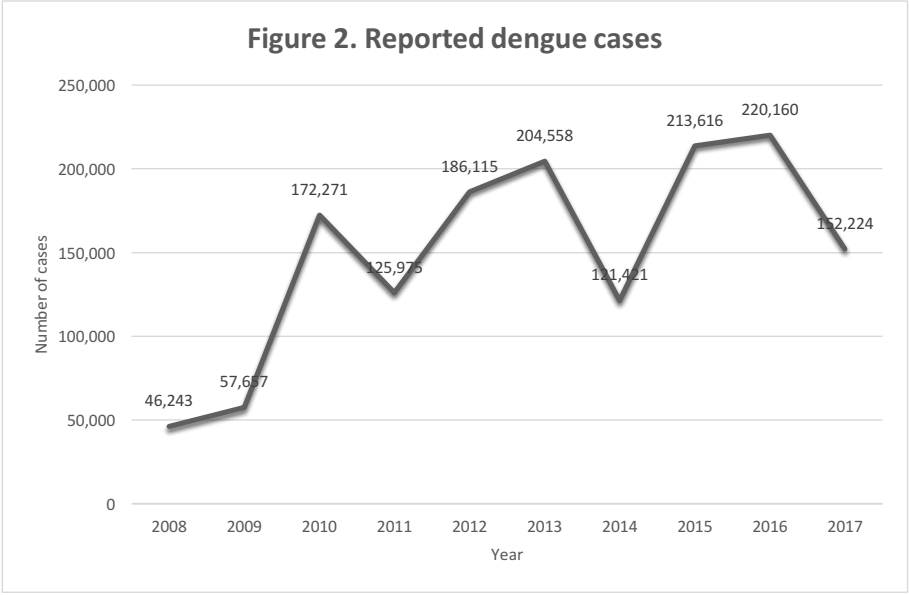
Figure 2. Reported dengue cases
250,000
200,000
150,000
100,000
50,000
0
Number of cases
46,243
57,617
172,271
125,975
186,115
204,558
121,421
213,616
220,160
152,224
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
Year

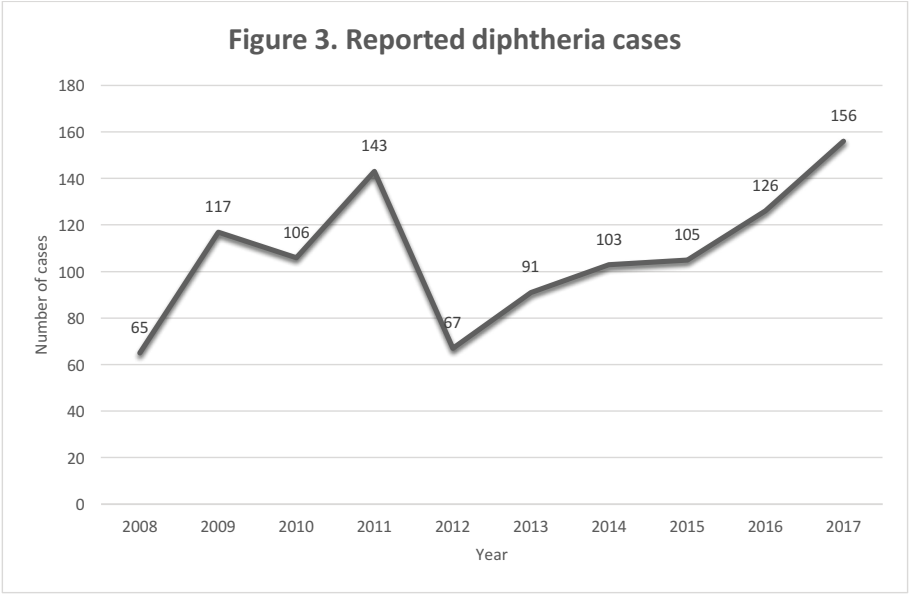
Figure 3. Reported diphtheria cases
180
160
140
120
100
80
60
40
20
0
Number of cases
65
117
106
143
67
91
103
105
126
156
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
Year

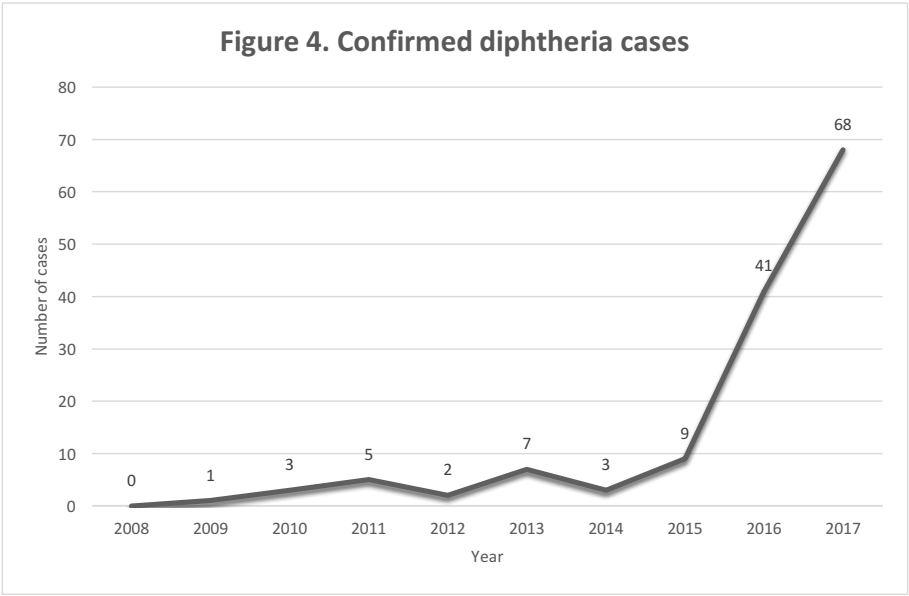
Figure 4. Confirmed diphtheria cases
80
70
60
50
40
30
20
10
0
Number of cases
0
1
3
5
2
7
3
9
41
68
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
Year

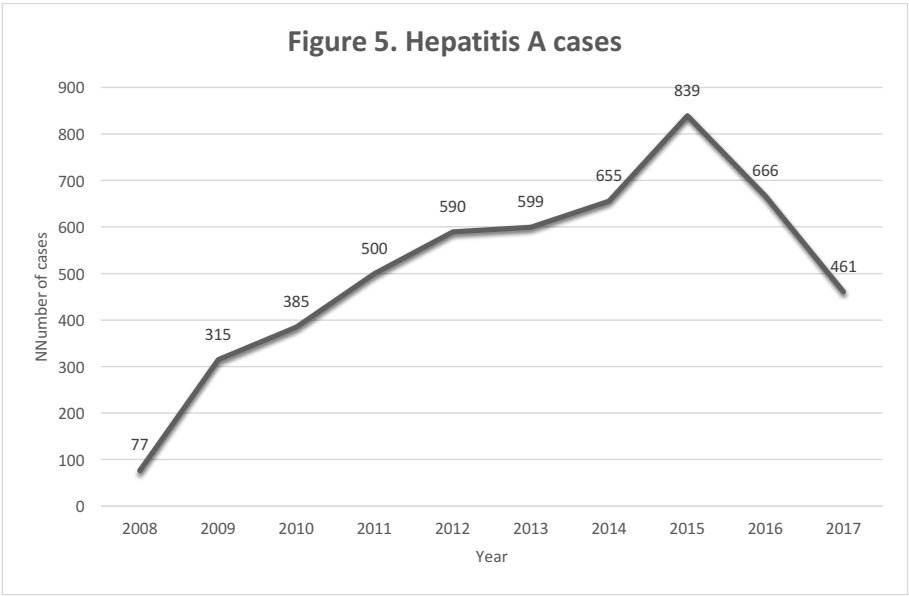
Figure 5. Hepatitis A cases
NNumber of cases
900
800
700
600
500
400
300
200
100
0
77
315
385
500
590
599
655
839
666
461
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
Year

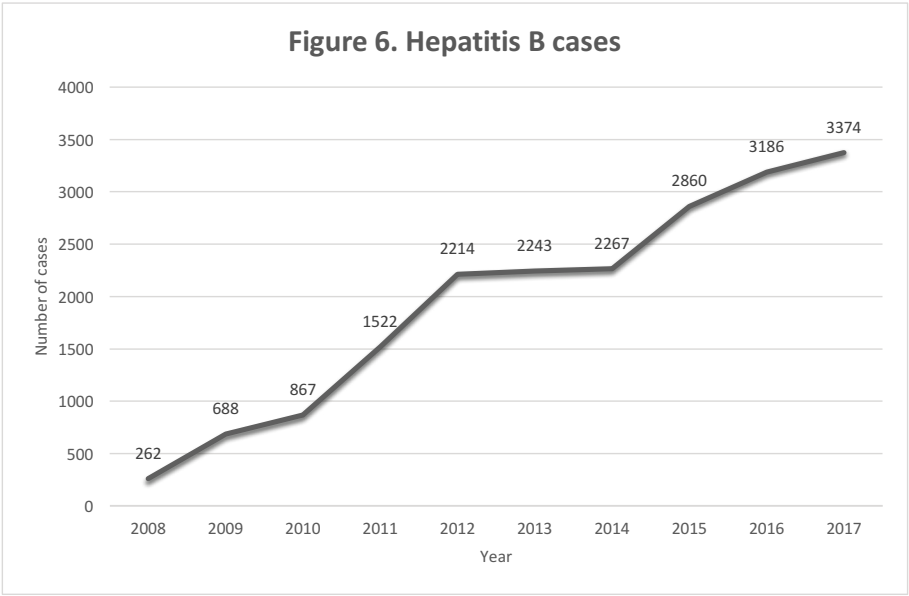
Figure 6. Hepatitis B cases
Number of cases
4000
3500
3000
2500
2000
1500
1000
500
0
262
688
867
1522
2214
2243
2267
2860
3186
3374
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
Year

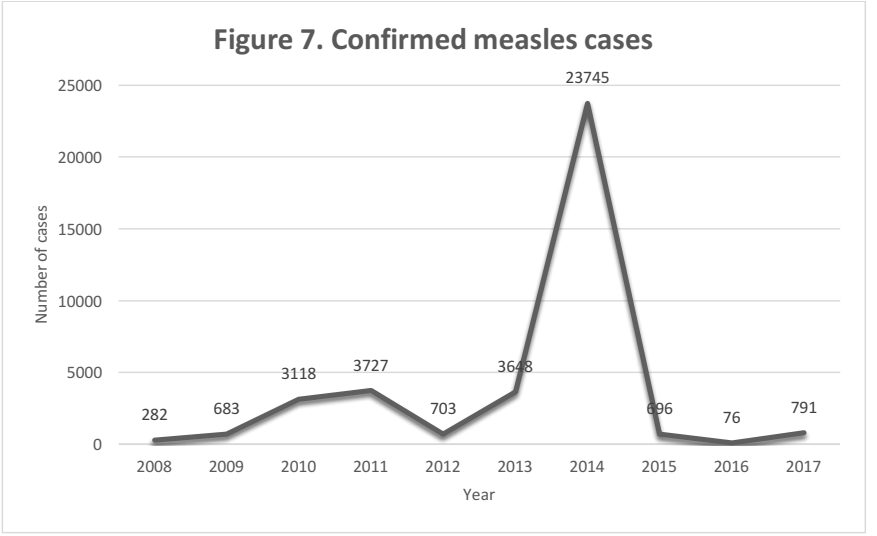
Figure 7. Confirmed measles cases
25000
20000
15000
10000
5000
0
Number of cases
282
683
3118
3727
703
3648
23745
696
76
791
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
Year

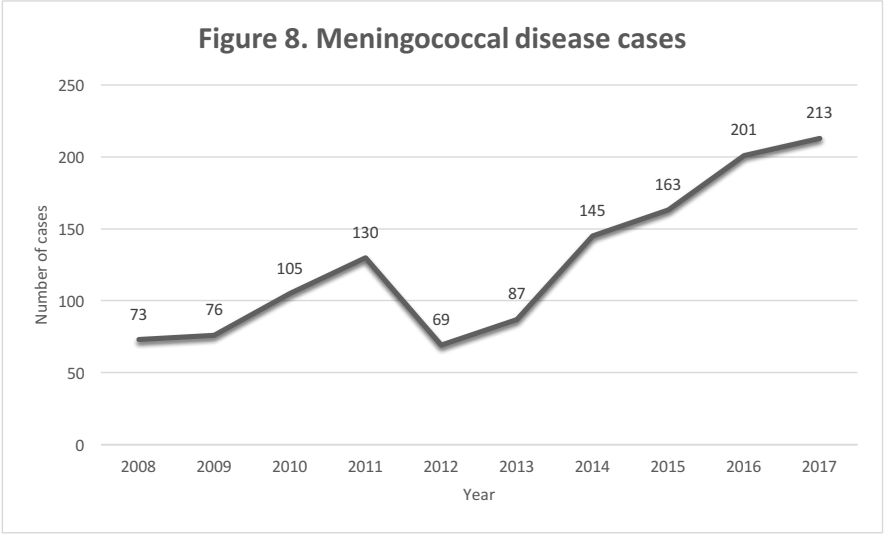
Figure 8. Meningococcal disease cases
250
200
150
100
50
0
Number of cases
73
76
105
130
69
87
145
163
201
213
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
Year

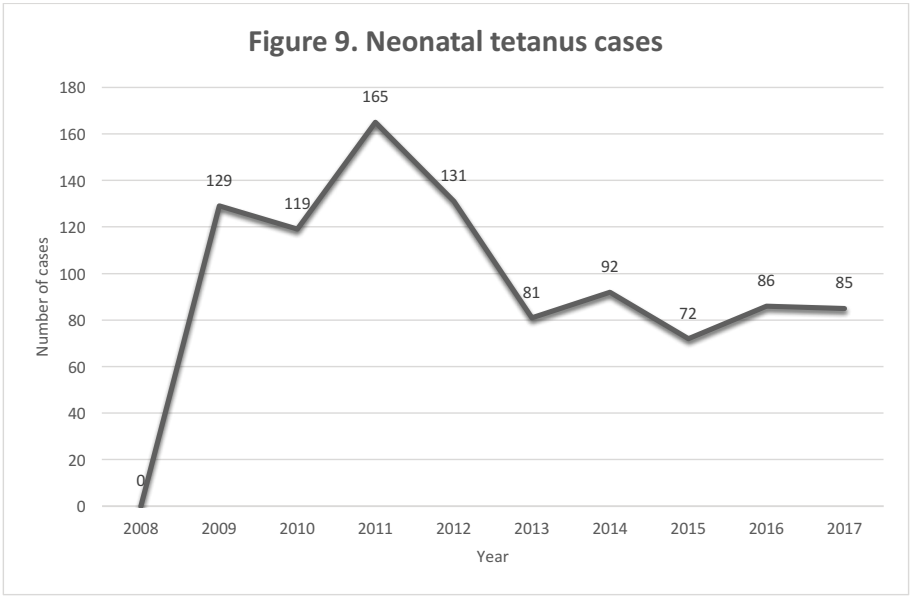
Figure 9. Neonatal tetanus cases
Number of cases
Year
0
129
119
165
131
81
92
72
86
85
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017

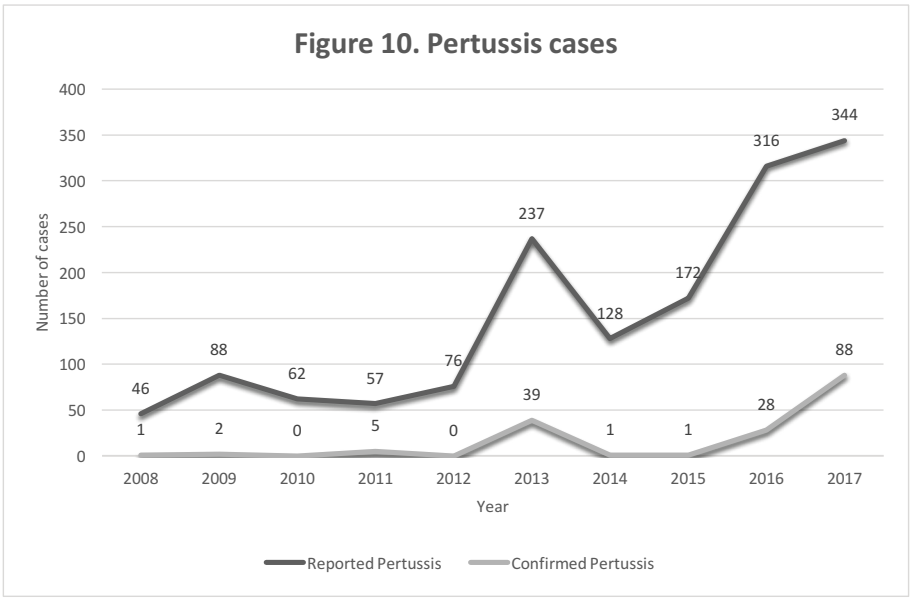
Figure 10. Pertussis cases
Number of cases
Year
46
88
62
57
76
237
128
172
316
344
1
2
0
5
0
39
1
1
28
88
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
Reported Pertussis
Confirmed Pertussis

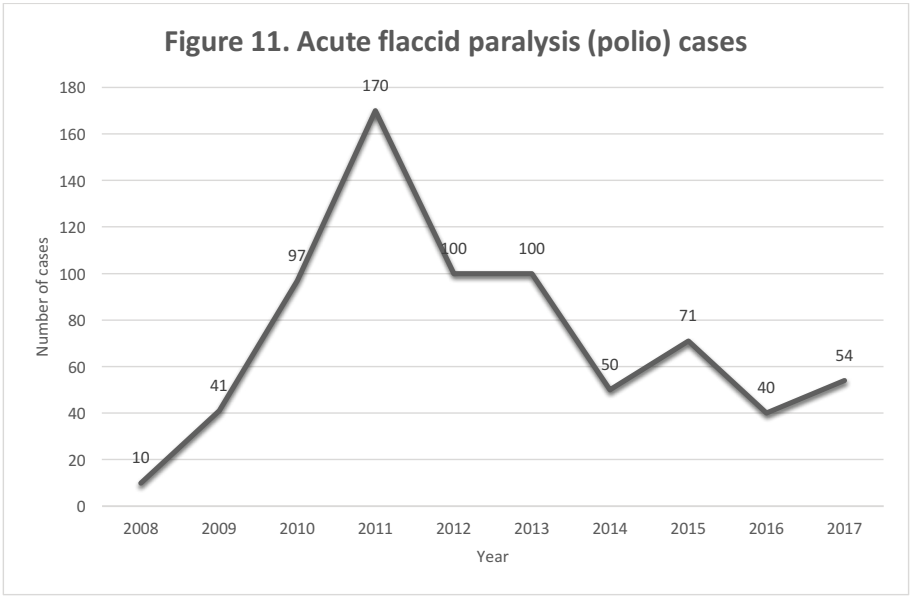
Figure 11. Acute flaccid paralysis (polio) cases
Number of cases
Year
180
160
140
120
100
80
60
40
20
0
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
10
41
97
170
100
100
50
71
40
54

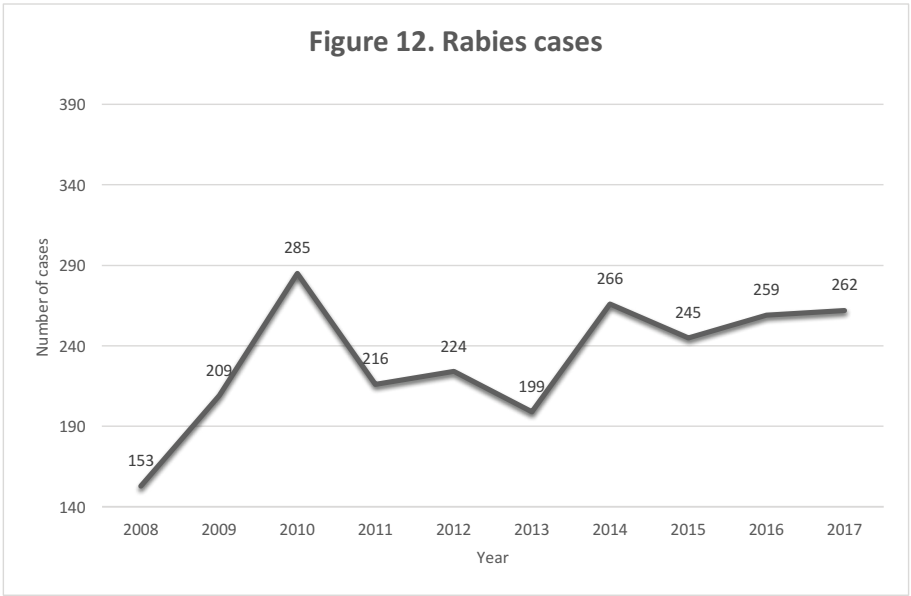
Figure 12. Rabies cases
Number of cases
Year
390
340
290
240
190
140
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
153
209
285
216
224
199
266
245
259
262

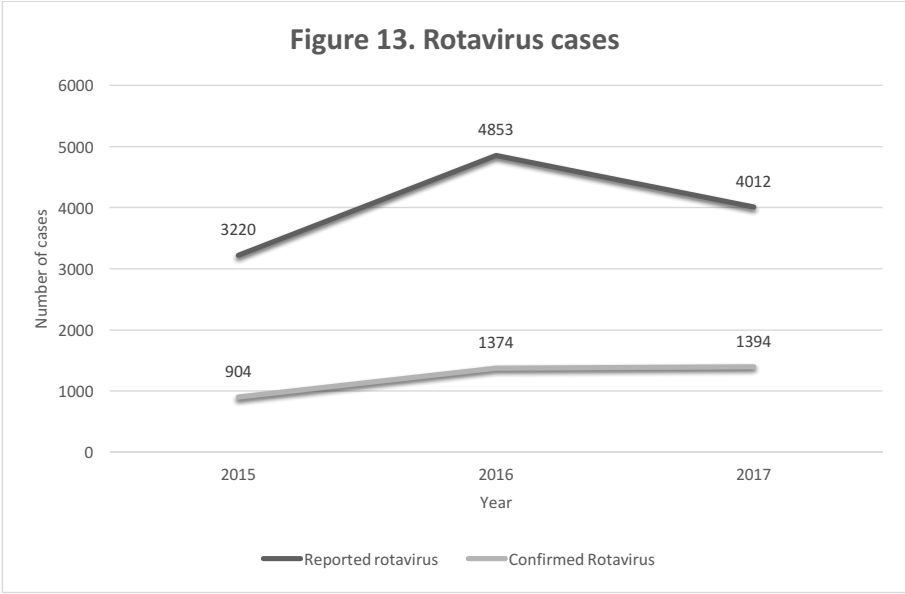
Figure 13. Rotavirus cases
6000
5000
4000
3000
2000
1000
0
Number of cases
4853
4012
3220
1374
1394
904
2015
2016
2017
Year
Reported rotavirus
Confirmed Rotavirus

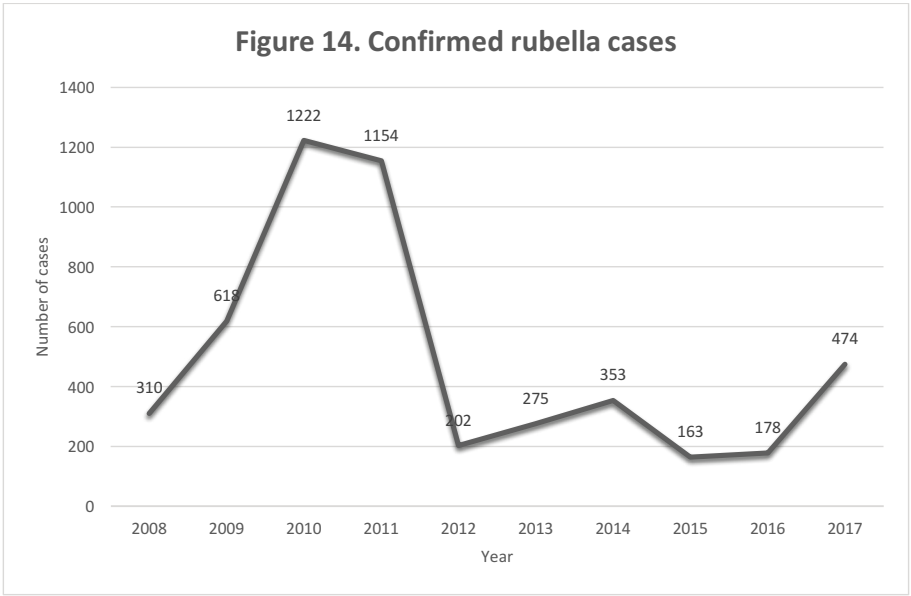
Figure 14. Confirmed rubella cases
1400
1200
1000
800
600
400
200
0
Number of cases
1222
1154
618
474
353
310
275
202
178
163
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
Year

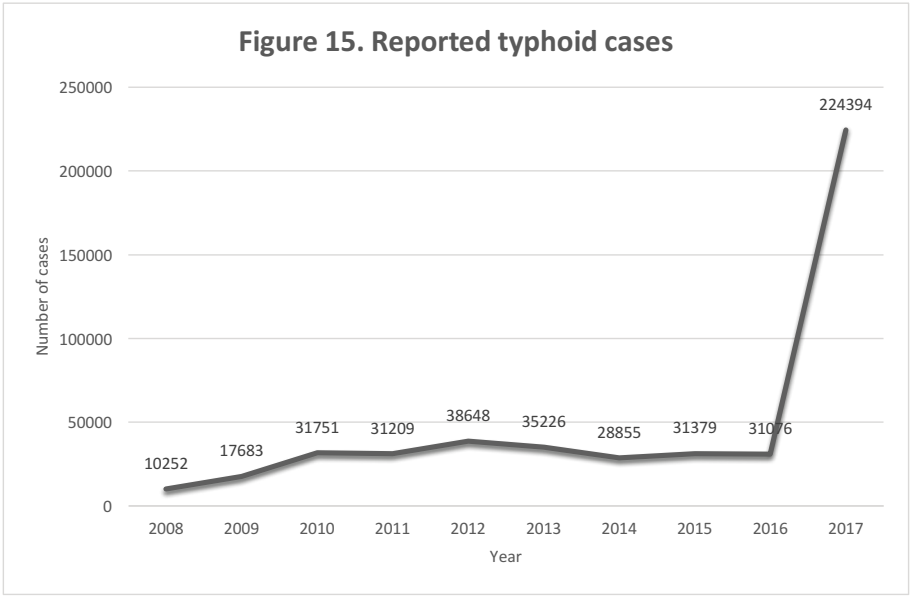
Figure 15. Reported typhoid cases
250000
200000
150000
100000
50000
0
Number of cases
224394
38648
35226
31751
31209
31379
31076
28855
17683
10252
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
Year

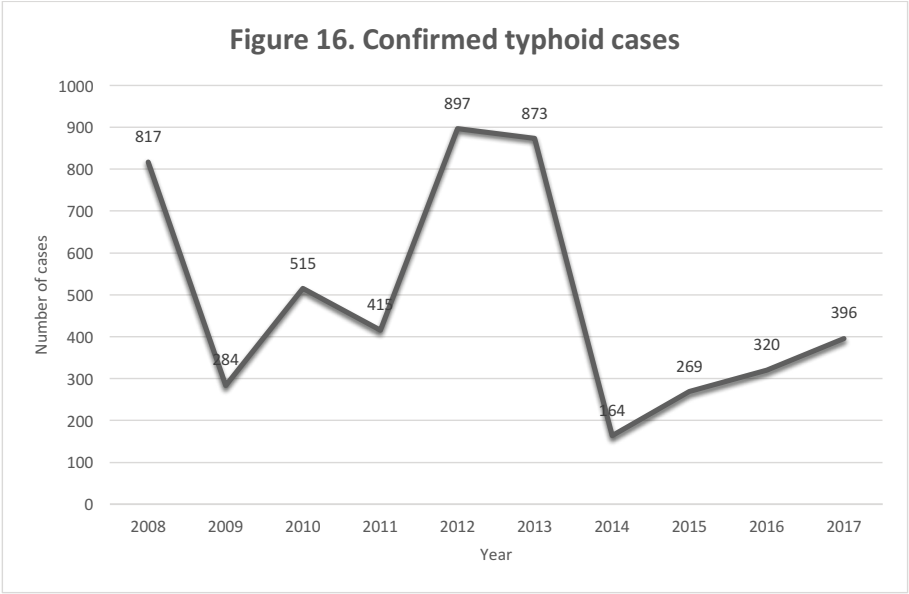
Figure 16. Confirmed typhoid cases
1000
900
800
700
600
500
400
300
200
100
0
Number of cases
817
284
515
415
897
873
164
269
320
396
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
Year

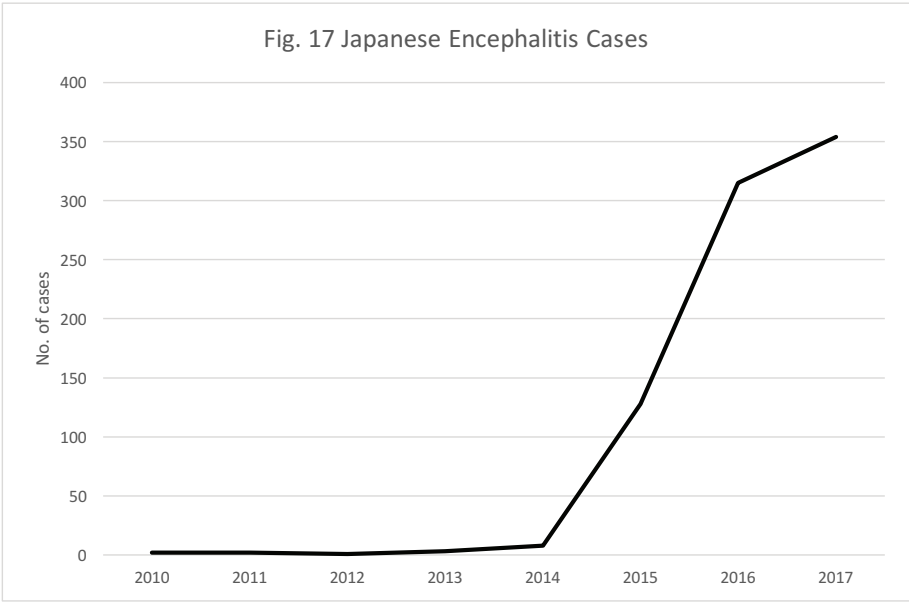
Fig. 17 Japanese Encephalitis Cases
400
350
300
250
200
150
100
50
0
No. of cases
2010
2011
2012
2013
2014
2015
2016
2017

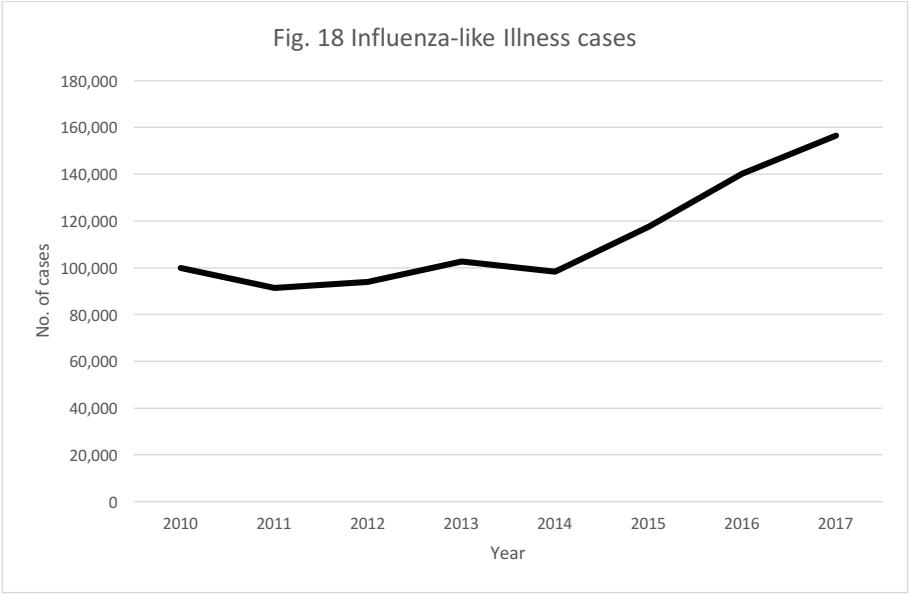
Fig. 18 Influenza-like Illness cases
180,000
160,000
140,000
120,000
100,000
80,000
60,000
40,000
20,000
0
No. of cases
2010
2011
2012
2013
2014
2015
2016
2017
Year

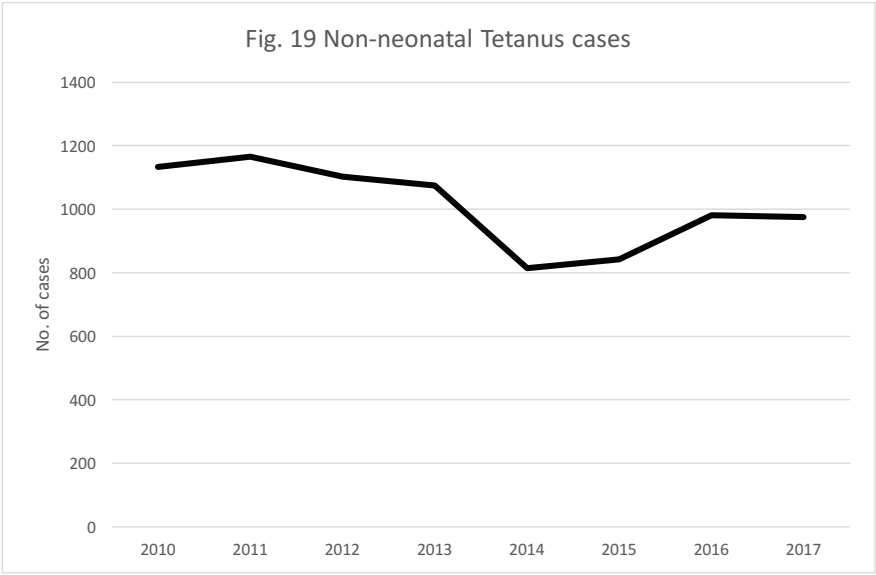
Fig. 19 Non-neonatal Tetanus cases
1400
1200
1000
800
600
400
200
0
No. of cases
2010
2011
2012
2013
2014
2015
2016
2017