



**Philippine Obstetrical and Gynecological
Society (Foundation), Inc.**

CLINICAL PRACTICE GUIDELINES
on
IMMUNIZATION FOR WOMEN

November 2017

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Published by:

Philippine Obstetrical and Gynecological Society (Foundation), Inc.
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ISBN 978-971-94651-5-7

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Printed by:

OVT-Graphic Line, Inc.
(Printing & Publishing House)
#23-A Mabini Street, Upper Plaza, West Rembo, Makati City
Tel. Nos.: 882-4119 / 882-4120 • Telefax: 882-4120

MESSAGE FROM THE POGS PRESIDENT



MAYUMI S. BISMARCK, MD

President

Philippine Obstetrical and Gynecological Society (Foundation), Inc., 2017

In behalf of the officers and members of Board of Trustees, I would like to congratulate the laudable efforts and dedication of the IFW committee which has been continuously serving the vulnerable segment of our society, our women, the pregnant, the aging and those with infertility and cancer concern.

Guided by standards based on the best-evidences to help ensure good patient care, CPGs are guidelines aimed to aid practitioners in Obstetrics and Gynecology in screening women in their vaccination requirements as well as recommending safe and support of advocacy on prevention towards quality and patient safety in healthcare. The objective with no intention to replace medical judgement when managing patients.

It is a reality, patient expectations are growing. Patients see themselves as consumers of health services and this has led to the focus to Quality and Patient Safety in Healthcare.

Let me express my sincerest gratitude for the continuous search of the IFW committee and its members for the preventive health services for women. Rest assured that prudent and benevolent advocacy we support this inspiring activity. I pray we all continue to work together for the common cause relevant-patient care.

God bless all of us!

A handwritten signature in black ink, appearing to read "Mayumi S. Bismark".

MAYUMI S. BISMARCK, MD

FOREWORD



BETHA FE M. CASTILLO, MD

Chair, Committee on the Clinical Practice Guidelines, 2017

The Philippine Obstetrical and Gynecological Society, Inc. (POGS) has been an advocate of preventive health services for women. The 2017 POGS Board of Trustees (BOT), through the Committee on Clinical Practice Guidelines (CPG) offer this updated CPG on Immunization for Women (IFW) utilizing the best available evidences.

The development of this CPG was made possible by the dedication and commitment of the Technical Working Group led by the Chair Dr. Susan Pelea-Nagtalon. The CPG on IFW was done with extensive literature search with quality of evidences adapting their recommendations basing on the GRADE system where appropriate. The CPG was then presented to the stakeholders for review in a plenary critiquing session and the relevant issues were considered. This was further reviewed by independent technical team from the committee on CPG using the AGREE II evaluation system.

In behalf of the 2017 POGS BOT and the Committee on CPG, I would like to commend all the members of the Technical Working Group who gave their best efforts in the completion of the CPG on IFW. Our gratitude extends to the stakeholders who gave their valuable inputs in the development of the CPG especially the applicability on the local setting.

We hope to provide the obstetrician-gynecologists and other healthcare providers the foundation in their healthcare delivery for women, to achieve optimal quality in patient primary and preventive care.

A handwritten signature in black ink, appearing to read "Betha Fe M. Castillo, MD".

INTRODUCTION



SUSAN P. NAGTALON, MD

Chair, Immunization for Women (IFW) Working Group

Increasingly, patient expectations are growing. The patients see themselves as consumers of health services and this has led to the focus on Quality and Patient Safety in Healthcare. This practice becomes most important in Obstetrics-Gynecology considering that we deal with the vulnerable segment of women, i.e., the pregnant, the aging, those with infertility, and cancer concerns. Guided by standards based on the best evidences help ensure good patient care.

The following guidelines aim to aid practitioners in Obstetrics-Gynecology in screening women for their vaccination requirements, as well as recommending safe and effective administration of appropriate vaccines. The guidelines are meant to guide clinical practice and not intended to replace medical judgment when managing our patients.

Let me express my sincerest gratitude to the IFW Technical Working Group for this valuable output. Worth acknowledging too, are, Dr. Ricardo M. Manalastas, Jr. for his continued support and inspiration to the Technical Working Group, and Dr. Sybil Lizanne R. Bravo, for coordinating to put the guidelines together. Let me likewise laud the leadership of POGS for its continued commitment to the IFW advocacy (11 years), an integral part of Preventive Health Services for Women.

A handwritten signature in black ink, appearing to read "M Pelea".

SUSAN PELEA-NAGTALON, MD, MSPH

Objectives of the CPG

The objectives of this CPG on Immunization for Women (IFW) are:

1. To elucidate proper administration of appropriate vaccines based on the best available scientific evidence and on extensive agreement among majority of task force members
2. To help encourage every obstetrician-gynecologist to avail of every opportunity to promote vaccination
3. To decrease improper differences in practice
4. To render rational basis for proper administration of recommended vaccines
5. To give continuing education to fellow obstetrician-gynecologists
6. To advocate efficient use of available resources or equipment in administering vaccines
7. To highlight appropriate vaccines that can be administered to pregnant women
8. To educate vaccinators on the right indication, proper dose, correct site, appropriate interval, and dose of these vaccines
9. To educate vaccinators on the storage, reconstitution, proper administration, and handling of these biological products

Description of Target Users

The primary target users of these guidelines are general obstetrician-gynecologists, and secondary target users are healthcare providers involved in the care of pregnant and non-pregnant women including menopausal women (Family Medicine practitioners and general practitioners).

CPG Development Process (Literature Search Strategy)

The GRADE Pro Guideline Development Tool (GDT) software tool was used to assist the individual authors in the creation and evaluation of summary of findings, as applicable, and to assess quality of evidence for these vaccination guidelines.

Overall, for each topic, a research question was formulated; this research question was reformatted into the Population, Intervention, Comparator, and the Outcome (P-I-C-O). Extensive literature search was then performed, and a review of these articles was done to generate evidences.

A detailed systematic search was done as applicable and where available per vaccine guideline. Search terms included the vaccine concerned, the preventable disease associated with the biological product, and other relevant terms that are helpful in producing the guideline. Eligible randomized and observational studies that were published in English language were searched for that compared giving and non-administration of the concerned vaccine product to a specified indicated population.

The author of each vaccine guideline is an obstetrician-gynecologist with subspecialty in Infectious Diseases among Women (Reproductive Infectious Disease Specialist).

These practice guidelines were presented in a Plenary Session and Stakeholders were invited. The views and opinions of different obstetrician-gynecologists, pediatric infectious disease specialists, and a representative from geriatric medicine, and lay people were sought for in the development and finalization of the practice guidelines during the Plenary Session.

Guideline Implementation/Utilization and Quality Indicators

These guidelines are created with the main objective of increasing knowledge and awareness and educating obstetrician-gynecologists in the field of immunization. These guidelines will be made available for distribution among members of the Philippine Obstetrical and Gynecological Society, Inc. (POGS). Continuing Medical Educational (CME) activities can also be pursued throughout different regions in the country that will include lectures about principles of vaccination and other related topics including skills in the performance of actual administration of these biological products. Audit and feedback mechanisms will also be performed to assess success of these interventions. These mechanisms will be attended and participated by obstetrician-gynecologists and key opinion leaders.

Reporting of adverse reactions to the POGS will be encouraged through information dissemination and lectures. Management of these reactions will also be included in learning activities.

Strategies to vaccination will be continuously reviewed and implemented. Barriers to vaccination, on one hand, will be constantly monitored and solutions formulated by stakeholders. Improvements will be assessed and disseminated to fellow vaccinators.

Different vaccine manufacturers will be informed of the demand for these products so different regions or areas will be assured of supply.

These immunization guidelines should be updated at least every two years or as needed. The original authors will be invited and informed of the planned revision. With emerging infectious diseases that are affecting the quality of life of our women and their families, and with continuous research into immunology and prevention of infectious diseases, these guidelines should be continuously updated as new knowledge becomes available. This is one of the most reliable ways to protect our women and including their families, from the menace of infectious illnesses.

Funding Source

There is no funding associated with the development of this guideline.

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- The obstetrician-gynecologist, the general practitioner, the patient, the student, the allied medical practitioner, or for that matter, any capacity of the person or individual who may read, quote, cite, refer to, or acknowledge, any, or part, or the entirety of any topic, subject matter, diagnostic condition or idea/s willfully release and waive all the liabilities and responsibilities of the POGS, its officers and general membership, as well as the Committee on the CPG and its Editorial Staff in any or all clinical or other disputes, disagreements, conference audits/controversies, case discussions/critiquing.
- The reader is encouraged to deal with each clinical case as a distinct and unique clinical condition which will never fit into an exact location if reference is made into any or all part/s of this CPG.
- The intention and objective of this CPG is to serve as a guide, to clarify, to make clear the distinction. It is not the intention or objective of this CPG to serve as the exact and precise answer, solution and treatment for clinical conditions and situations. It is always encouraged to refer to the individual clinical case as the one and only answer to the case in question, not this CPG.
- It is hoped that with the CPG at hand, the clinician will find a handy guide that leads to a clue, to a valuable pathway that leads to the discovery of clinical tests leading to clinical treatments and eventually recovery.
- In behalf of the POGS, its Board of Trustees, the Committee on CPG 2017, this CPG is meant to make each one of us a perfect image of Christ, the Healer.

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HEPATITIS A VACCINATION

Patricia M. Kho, MD, FPOGS, IBCLC, FPIDSOG

The hepatitis A infection is primarily transmitted through the fecal-oral route. There is a strong correlation between lack of access to adequate sanitation and clean water to hepatitis A infection. In the Philippines, hepatitis A is described to be moderately endemic, with a seroprevalence of 62% in Metro Manila. Hepatitis A infection is commonly more severe among older children and adults, as compared to infection among children.

The available hepatitis A vaccines are the live attenuated, or the inactivated types. Both are equally effective with long-lasting immunogenicity. However, it is not recommended to administer the live-attenuated vaccine among pregnant women and immunocompromised individuals.

Question:

Should inactivated hepatitis A vaccine vs. no intervention, inactive control or placebo be used for hepatitis A prevention?

Inclusion criteria for the systematic literature review:

Population	Children (1-16 years old)
Intervention	Immunization with inactivated hepatitis A vaccine
Control/comparator intervention	No intervention, inactive control or placebo
Outcomes/endpoints	Hepatitis A infection
Study design	RCT

Recommendations

- Immunization with the inactivated hepatitis A vaccine is recommended to pregnant women who are at risk of getting hepatitis A infection. (Hepatitis A vaccine is recommended for pregnant women by guideline-giving authorities such as the Centers for Disease Control and Prevention [CDC] and the American College of Obstetricians and Gynecologists [ACOG] although there are no studies done on pregnant women. What are stated in the PICO as written by the author are studies among children in the stated age group.)

Women who are at risk of being infected with hepatitis A are the following:

- Travelers to countries where hepatitis A virus is common
- Injection and non-injection illegal drug users
- Women whose sex partners are men who have sex with men
- People with chronic liver disease
- Adults with blood clotting factor disorders
- Adults who are at risk for infection at work, including daycare center staff, personnel in healthcare facilities (e.g. nursing homes), and food handlers

Recommended Schedule

Two doses of the inactivated Hepatitis A vaccine are recommended. The first dose is given at age of one or older, and the booster dose is administered after 6-18 months.

For patients at risk, the first dose is given at least one month before traveling, or immediately to those who are at risk, and the booster dose is administered after 6-18 months.

Supporting Statements

Outcome	Study	Hepatitis A vaccine		Control	
		Events	Total	Events	Total
Hepatitis A occurrence	Innis 1994	2	38157	38	33586
	Pérez 2003	4	137	22	137
	Riedemann 1992		128		132
	Werzberger 1992	0	519	25	518

Cost information

BRAND	DESCRIPTION	COST
Avaxim 160 (adult)	Inactivated Hepatitis A vaccine containing 160 antigen units per 0.5 mL for intramuscular injection	P2249/ syringe
Havrix 1440 (adult)	Inactivated Hepatitis A vaccine containing 1440 Elisa Units per 1 mL for intramuscular injection	P170/vial

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HEPATITIS B VACCINATION

Patricia M. Kho, MD, FPOGS, IBCLC, FPIDSOG

The Hepatitis B virus causes Hepatitis B infection, which is a known carcinogen of the liver. It is the predominant risk factor for the development of liver cirrhosis and hepatocellular cancer in the Philippines. Hepatitis B infection is hyperendemic in our country, and 16.7% of the adult Philippine population is chronically infected with Hepatitis B. Since 2011, The Philippine Department of Health (DOH) has been promoting universal hepatitis B vaccination of all infants soon after birth. It is important to continue universal Hepatitis B vaccination in order to reduce the burden of liver cirrhosis and hepatocellular carcinoma.

Question:

Does routine immunization with the hepatitis B vaccine, compared to no immunization, reduce the incidence of liver cirrhosis and liver cancer?

Inclusion criteria for the systematic literature review:

Population	Newborn babies Children
Intervention	Immunization with hepatitis B vaccine right after delivery
Control/comparator intervention	No immunization, or immunization with placebo
Outcomes/endpoints	Hepatitis B infection
Study design	RCT Meta analysis

Recommendations

- Immunizing newborns prevents hepatitis B infection and will help prevent liver cirrhosis and liver cancer during adulthood.
- All newborn infants should be immunized with the hepatitis B vaccine at birth. A 3 or 4 dose schedule should be followed.
- Infants whose mothers are hepatitis B positive should receive hepatitis B immunoglobulin within 12 hours after birth, to be followed by hepatitis B immunization.

- All adults who have no documented proof of having completed the hepatitis B vaccine series should get a hepatitis B panel. Individuals who are hepatitis B negative and who are anti-HBs negative, should be immunized against hepatitis B.

Recommended Schedule

Age group	Volume	Number of Doses	Schedule
0 to 19 years	0.5 ml	3	Age: birth, 1-2, 4, 6-18 months For older children who did not start hepatitis B series at birth: 0, 1-2, 4-6 months
20 years and older	1.0 ml	3	0, 1-2, 4-6 months
Pregnant women (if without proof of immunity)	1.0 ml	3	0, 1-2, 4-6 months

Supporting Statements

Outcome	Study	Hepatitis B vaccine		Control (no immunization or placebo)		Relative Risk
		Events	Total	Events	Total	
Hepatitis B occurrence	Ip 1989	7	35	23	34	0.30 (0.15, 0.60)
	Liu 1987	3	27	2	26	0.14 (0.05, 0.41)
	Xu 1995	7	60	12	30	0.29 (0.13, 0.66)
	Khuklovich 1996	2	70	9	31	0.01 (0.02, 0.43)

Cost information

BRAND	COST
Engerix B 20 mcg/dose	P525/vial
Hepabig 20 mcg/dose	P1450/vial

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INFLUENZA VACCINATION

Valiant L. See, MD, FPOGS, FPIDSOG

Influenza, commonly known as “the flu”, is an infectious disease caused by an influenza virus. The most common symptoms include: a high fever, runny nose, sore throat, muscle pains, headache, coughing, and feeling tired. Untreated cases of influenza may lead to viral pneumonia, secondary bacterial pneumonia, sinus infections, and exacerbation of underlying medical disorders such as asthma or heart failure. There are three types of influenza viruses affecting people, Type A, Type B, and Type C.

The influenza vaccine is recommended by the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) for high-risk groups such as children, the senior citizen group, health care personnel, and patients with chronic medical illnesses such as asthma, diabetes mellitus, cardiac disease, or are immunocompromised among others. In healthy adults it is modestly effective in decreasing the amount of influenza-like symptoms in a population.

Every year, the WHO gauges which strains of the virus will highly be circulating in the following year, allowing drug companies to form vaccines that will provide the best immunity against these strains.

Question:

Does routine immunization with the influenza vaccine, compared to no immunization, reduce the incidence hospitalization among adults?

Inclusion criteria for the systematic literature review:

Population	Adult patients with co-morbid disease like cardiac disease, diabetes mellitus Infants whose mothers were vaccination
Intervention	Immunization with influenza vaccine right
Control/comparator intervention	No immunization
Outcomes/endpoints	Influenza infection
Study design	RCT Case control

Recommendations

- Flu vaccination can diminish the chance of flu-related admission in infants and older adults.
- Flu vaccination is an important preventive measure for patients with chronic medical illness.
- Flu vaccination helps safeguard pregnant women from getting infected and also protect the infant from contracting the disease after birth.

Recommended Schedule

Annual vaccination with the current influenza vaccine preparation starting at 6 months of age and above

Supporting Statements

A randomized, double-blind, placebo controlled study included 658 optimally treated coronary artery disease (CAD) patients. Three hundred and twenty-five patients received the influenza vaccine, and 333 patients received placebo. Median follow-up was 298 days. Primary endpoint was the cardiovascular death. In optimally treated CAD patients, influenza vaccination improves the clinical course of CAD and reduces the frequency of coronary ischemic events.¹

A case control study evaluated 80 patients who were admitted and discharged from hospital with pneumonia, bronchitis, influenza, diabetic ketoacidosis, coma and diabetes during the influenza epidemics. One hundred and sixty controls, who were not admitted to hospital during this period, were randomly selected. Immunization against influenza was assessed in 37 cases and 77 controls. Significant association was detected between reduction in hospitalization and influenza vaccination during the period immediately preceding an epidemic. Multiple logistic regression analysis estimated that influenza vaccination reduced hospital admissions by 79% (95% confidence interval [CI] 19-95%) during the two epidemics, after adjustment for potential confounders.²

A case-control study of vaccine effectiveness in preventing laboratory-confirmed influenza hospitalizations in older adults showed that influenza vaccination was associated with a significant reduction of hospitalization among adults.³

In a case-control study, the mothers of 2 (2.2%) of 91 case subjects and 31 (19.9%) of 156 control subjects aged < 6 months, and 1 (4.6%) of 22 case

subjects and 2 (5.6%) of 36 control subjects aged \geq 6 months, had received influenza vaccine during pregnancy. The effectiveness of influenza vaccine given to mothers during pregnancy in preventing hospitalization among their infants, adjusted for potential confounders, was 91.5% (95% CI, 61.7%-98.1%; P = .001) for infants aged < 6 months.⁴

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TETANUS, DIPHTHERIA AND PERTUSSIS (TDAP) VACCINATION

Valiant L. See, MD, FPOGS, FPIDSOG

TETANUS (Lockjaw) causes painful muscle tightening and stiffness, usually all over the body. DIPHTHERIA can cause nasopharyngeal and skil infection with pseudomembrane formation due to a protein toxin that causes systemic toxicity, myocarditis and polyneuropathy. PERTUSSIS (Whooping Cough) causes persistent and paroxysmal coughing lasting for more than 21 days; post-tussive vomiting cases are also seen in adults. These are all bacterial infections. Diphtheria and pertussis are transmitted by aerosol droplet. Tetanus spread by direct contact of spores to traumatized sites of the body like cuts, punctures, bites or wounds.

Question:

Does routine immunization with the tetanus, diphtheria, pertussis vaccine, compared to no immunization, reduce the incidence hospitalization among adults for complications of tetanus, diphtheria, and pertussis?

Inclusion criteria for the systematic literature review:

Population	Infants whose mother was vaccinated
Intervention	Immunization with TDap vaccine
Control/comparator intervention	No immunization
Outcomes/endpoints	Safety of vaccine, antibodies and protection of the infant
Study design	RCT Case control

Recommendations

- Tdap vaccine can protect adolescents, adults, health care professionals and persons who have close contact with infants from tetanus, diphtheria, and pertussis.
- Pregnant women should get a dose of Tdap during every pregnancy, to protect the unborn from developing pertussis after birth.
- A Td booster should be given every 10 years. Tdap may be given as one of these boosters

Recommended Schedule

Pregnant women should get a dose of Tdap during every pregnancy, to protect the newborn from pertussis. Infants are most at risk for severe, life-threatening complications from pertussis.

- Overview of the Center for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices recommends a dose of Tdap for pregnant women during each pregnancy, irrespective of prior Tdap vaccination history.
- The American College of Obstetricians and Gynaecologists (ACOG) support the revised recommendations.¹

Another vaccine, called Td, protects against tetanus and diphtheria, but not pertussis. A Td booster should be given every 10 years. Tdap may be given as one of these boosters if you have never gotten Tdap before. Tdap may also be given after a severe cut or burn to prevent tetanus infection.

Supporting Statements

A prospective observational study evaluated the safety of Tdap vaccine for infants exposed during pregnancy. Infants were followed for between 6 and 12 months after birth. There were no significant differences in birth weight, gestational age at birth, congenital anomalies or infant growth as compared with population. No cases of pertussis occurred in this cohort despite high rates of disease in the community. These data add to the growing pool of evidence that the administration of Tdap vaccine during pregnancy is an appropriate strategy for reducing pertussis in infants.²

An observational study on the safety of pertussis vaccination 20,074 pregnant women vaccinated found no evidence of an increased risk of stillbirth and adverse events related to pregnancy.³

A case-control study evaluated infants aged < 8 weeks with pertussis infection. The study found that maternal pertussis vaccination is effective in preventing pertussis infection in infants aged < 8 weeks and may be considered in other countries experiencing high levels of pertussis.⁴

A clinical trial of 48 pregnant women aged 18 to 45 years who received Tdap ($n=33$) or placebo ($n=15$) at 30 to 32 weeks' gestation, sought to evaluate the safety and immunogenicity of Tdap immunization during pregnancy and its effect on infant responses to the DtaP vaccine. Outcomes showed maternal immunization with Tdap resulted in high concentrations of pertussis antibodies in infants during the first 2 months of life and did not substantially alter infant responses to DTaP.⁵

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PNEUMOCOCCAL VACCINATION

Christine D. Dizon, MD, MBA-H, FPOGS, FIFEPAG, FPIDSOG

Streptococcus pneumoniae is a gram-positive bacterium known to cause a range of illnesses – from otitis media to invasive disease such as sepsis, meningitis and pneumonia. Symptoms depend on the site of infection. Serious or life-threatening infection is seen more commonly in children, the elderly, asplenic patients and those who are immunocompromised. Two forms of pneumococcal vaccine are currently available for administration in adults---a conjugated vaccine (PCV13) and a polysaccharide vaccine (PPV23).

Question:

Is pneumococcal vaccination effective in preventing pneumococcal disease in adults?

Inclusion criteria for the systematic literature review:

Population	Persons \geq 50 years old, healthy or with age-typical underlying diseases High risk adults < 50 years old
Intervention	Vaccination with PPV23 Vaccination with PCV13 (For meta-analysis: vaccination with older pneumococcal vaccine formulations)
Control/comparator intervention	No vaccination or placebo OR Direct comparison of PPV23 vs. PCV13
Outcomes/endpoints	Invasive pneumococcal disease (IPD) Pneumonia, all causes Mortality, all causes Pneumococcal pneumonia Mortality due to pneumonia
Study design	RCT

Recommendation

- Pneumococcal vaccination is recommended for use in susceptible adults \geq 50 years old and those at high-risk who are < 50 years old. Both PPV23 and PCV13 are recommended for the prevention of invasive pneumococcal disease.

Recommended Schedule

A *single dose* of PCV13 is administered first prior to PPV23. It is recommended that the dosing interval between the vaccines in healthy adults be 1 year and in high-risk individuals, 8 weeks apart.

Revaccination with PPV23 is recommended for adults < 65 years after 5 years.

Supporting Statements

A systematic literature search was performed to identify randomized controlled trials (RCTs) and meta-analyses investigating the efficacy of pneumococcal vaccines in the prevention of pneumococcal disease in adults. Only those articles published in English with available full-texts were included. Four (4) systematic reviews and meta-analysis were identified that addressed the question of PPV efficacy in adults.¹⁻⁴ Three of these studies analyzed explicitly the PPV23 efficacy. While there were differences in the trials included, overall, the meta-analyses demonstrated clear efficacy of PPV vaccine to prevent invasive pneumococcal disease in adults. The table below summarizes the findings of the 4 meta-analyses reviewed.

OUTCOME	STUDY	PPV VACCINE		CONTROL		ODDS RATIO 95% CI
		Events	Total	Events	Total	
Invasive Pneumococcal Disease (IPD)	Moberly et al 2013	15	18634	63	17855	0.23 [0.13, 0.40]
	Falkenhorst et al 2017	3	22282	13	21308	0.22 [0.06, 0.77]
Pneumonia, all causes	Moberly et al 2013	978	22643	1547	25091	0.69 [0.63, 0.75]
	Diao et al 2016	422	77899	480	78111	0.88 [0.77, 1.00]
	Schiffner-Rohe et al 2015	366	15597	373	14566	0.91 [0.79, 1.06]
Mortality, all causes	Moberly et al 2013	1018	24018	1039	23542	0.96 [0.88, 1.05]
	Diao et al 2016	205	1617	198	1621	1.04 [0.85, 1.29]
Pneumococcal pneumonia	Moberly et al 2013	15	18132	60	17531	0.24 [0.14, 0.42]
	Diao et al 2016	33	1139	58	1154	0.56 [0.36, 0.87]
	Falkenhorst et al 2017	85	22282	98	21308	0.83 [0.62, 1.11]
	Schiffner-Rohe et al 2015	85	15119	98	14099	0.81 [0.60, 1.08]
Mortality due to pneumonia	Moberly et al 2013	135	15592	221	15131	0.59 [0.48, 0.73]
	Diao et al 2016	32	1530	48	1541	0.66 [0.42, 1.05]

The results above were consistent with the analysis of 4 RCTs specifically investigating either PCV13 or PPV23; the 2 currently available formats of the pneumococcal vaccines.

There are no clinical studies evaluating efficacy of the 2 vaccines given in series. Immunogenicity studies of PCV - PPSV23 sequence among immunocompetent adults suggest that 1) shorter intervals (e.g. 8 weeks),

may be associated with increased local reactogenicity when compared with longer intervals, and 2) longer intervals (e.g. \geq 1 year) may lead to an improved immune response against serotypes in both vaccines compared with a single dose of PCV13 or PPSV23. The recommended interval between PCV13 and PPV23 for adults aged \geq 19 years with certain underlying medical conditions (including adults aged \geq 65 years with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid [CSF] leaks, or cochlear implants) is \geq 8 weeks, minimizing the risk window for invasive pneumococcal disease caused by serotypes unique to PPV23 in these highly vulnerable groups. Moreover, adults who received PPSV23 before age 65 years for any indication should receive another dose of the vaccine after 5 years.

There were no studies identified that included participants similar to the Philippines setting. There were also no RCTs on PPV23 or PCV 13 alone identified that involved adults 18-50 y/o with underlying disease.

Cost information

TYPE	BRAND	COST
PCV13	Prevenar 13	P3,670
PPV23	Pneumovax 23	P1,130.50
	Pneumo23	P1,200

*based on MIMS online [Accessed on June 25, 2017]

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MEASLES, MUMPS AND RUBELLA (MMR) VACCINATION

Katherine Angelo-Dela Cruz, MD, FPOGS, FPIDSOG

Measles, or rubeola, is a highly contagious viral disease. The measles virus, which belongs to the paromyxovirus, is transmitted by direct contact or through air droplets from the nose, mouth, or throat of infected persons.¹ Initial symptoms usually appear 10-12 days after infection, presenting with fever, runny nose, cough and sore throat. After several days, a rash appears that spreads all over the body.^{1,2}

Mumps is another contagious disease caused by a virus that presents with a few days of fever, headache, muscle aches, tiredness, loss of appetite, and later followed by swollen salivary glands.³ Mumps is generally a childhood disease. However, it can also infect adults and may cause more serious complications. These include meningitis, orchitis, and deafness.⁴

Rubella, or German measles, is another contagious viral infection that is also spread by airborne droplets. It often affects children causing a mild disease with symptoms that include a low-grade fever, sore throat and rash. The rash in rubella has a classic presentation, which starts on the face and spreads to the rest of the body. In pregnant women, acquiring the infection early in pregnancy can cause miscarriage, stillbirth or serious birth defects known as congenital rubella syndrome.¹

Question:

Is MMR vaccination effective in the prevention of MMR infection?

Inclusion criteria for the systematic literature review:

Population	Children and/or adults
Intervention	MMR vaccination
Control/comparator intervention	No MMR vaccination or placebo
Outcomes/endpoints	Measles Mumps Rubella
Study design	Review

Recommendations

- Adults born in 1957 or later without acceptable evidence of immunity to measles, mumps, or rubella should receive 1 dose of MMR vaccine unless they have a medical contraindication to the vaccine, e.g. pregnancy or severe immunodeficiency.⁵
- Pregnant women who do not have evidence of immunity to rubella should receive 1 dose of MMR upon completion or termination of pregnancy and before discharge from the healthcare facility; non-pregnant women of childbearing age without evidence of rubella immunity should receive 1 dose of MMR.⁵

Supporting Statements

A systematic literature search was done, where reviews written in English with available full-text were collated. There were no randomized controlled trials (RCTs) found on MMR vaccination in the adult populations comparing efficacy in disease prevention among vaccinated and non-vaccinated groups.⁶

A study was conducted by Moon, et al. among adult Korean military recruits on MMR vaccination. The study showed that prior to vaccination of MMR, the standardized incidence ratio of mumps in the military was 7.06. After vaccination, there was a decline in the incidence to 0.96. Overall vaccine effectiveness was estimated at 86.4%. The results of this study provide evidence to suggest the use of the MMR vaccination in the prevention of mumps in high-risk adults.⁷

In 2003, Morice, et al. presented the results of the Costa Rica National Plan of Action of 2000. This plan had the following goals: eradication of measles, control of rubella acceleration and prevention of congenital rubella syndrome, and improve surveillance. The national plan included the following: (1) A national mass vaccination campaign targeting a single dose of MR vaccine to men and women aged 15-39 years old; (2) Routine postpartum MR vaccination of all previously unvaccinated women; (3) Maintenance of high coverage among children with 2 doses of MMR; (4) Strengthened the integrated measles and rubella surveillance system; and (5) Development of a congenital rubella syndrome surveillance system. The study showed a reduction in the number of confirmed cases of measles and rubella after implementing the vaccination program.⁸

Cost information

Brand	COST
MMR II	P649.40/vial
Trimovax	P520/vial
Priorix	P684.10/vial

*based on MIMS online [Accessed on June 25, 2017]

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HUMAN PAPILLOMAVIRUS VACCINATION

Lorina Quimio-Esteban, MD, FPOGS, FPIDSOG

Human papillomavirus (HPV) is related with anogenital cancer (cervical, vaginal, vulvar, penile, and anal), oropharyngeal cancer, and genital warts. There are more than 150 HPV genotypes; among these, 13 genotypes have been shown to cause cervical cancer.¹ Most cases of HPV-associated cancer are caused by HPV genotypes 16 and 18.² In the United States, HPV genotypes 16 and 18 are reported to cause 66% of cervical cancer cases, while HPV genotypes 31, 33, 45, 52, and 58 account for 15% of cases of cervical cancer.³ For cervical intraepithelial neoplasia (CIN) 2+, 50-60% of cases are caused by HPV genotypes 16 and 18, and 25% of cases are caused by HPV genotypes 31, 33, 45, 52, and 58.¹ Nearly 90% of cases of genital warts are caused by HPV genotypes 6 and 11.²

The HPV vaccines are recommended for persons who would like to significantly reduce the risk of infection and disease. The bivalent (HPV2) vaccine prevents infection with HPV types 16 and 18; the quadrivalent (HPV4) prevents infection with HPV types 6, 11, 16 and 18; and the nonavalent (HPV9) vaccine prevents infection with HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58. These vaccines can protect women from persistent HPV infection and from intraepithelial neoplasia of the cervix, vagina and vulva.⁴ The HPV4 and HPV9 vaccines may be given to males for the prevention of genital warts and HPV 16 and 18-associated anal intraepithelial lesions (AIN) and anal cancer.

Question 1:

Is HPV2 vaccination effective in preventing HPV genotypes 16 and 18 related-cervical cancer, CIN 1, CIN 2/3 and adenocarcinoma in-situ in females?

Inclusion criteria for the systematic literature review:

Population	Females \geq 9 years old
Intervention	Vaccination with HPV2
Control/comparator intervention	No vaccination or placebo
Outcomes/endpoints	Cervical cancer CIN 1 CIN 2/3 Adenocarcinoma in-situ, cervix
Study design	RCT

Recommendation

- HPV2 vaccination is recommended for use in females \geq 9 year old.

Supporting Statements

The HPV2 vaccine was 92.9% (96.1% confidence interval [CI] 79.9-98.3) effective in preventing CIN 2+ associated with HPV-16/18 in the 4-year end-of-study analysis of the randomized double blind PATRICIA (PApillaMoma TRIal against Cancer In young Adults) trial. The efficacy of HPV2 vaccine against CIN 2+ related with 12 non-vaccine oncogenic types was 54.0%. Individual cross-protection against CIN 2+ associated with HPV 31, HPV 33, and HPV 45 was seen.⁵ HPV2 vaccine was 100% effective (95% CI 85.5-100) against CIN 3+ in the cohort of women who were HPV negative at baseline/women before sexual debut (TVC-naive) and 45.7% (95% CI 22.9-62.2) in the total vaccinated cohort (TVC) which included women who received 1 vaccine dose regardless of HPV status/women who are sexually active. The effectiveness of the HPV2 against all adenocarcinoma in-situ was 100% (95% CI 31-100) and 76.9% (95% CI 16-95.8) in the TVC-naive and TVC, respectively.⁶

Cross-protective efficacy of the HPV2 vaccine against 4 oncogenic non-vaccine HPV types was demonstrated in different trial cohorts in the end-of-study analysis of PATRICIA. Consistent vaccine efficacy against persistent infection and CIN 2+ associated HPV 33, 31, 45, and 51 (with or without HPV 16/18 co-infection) was seen. The effectiveness of HPV2 vaccine against CIN 2+ associated with the 12 non-vaccine HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), with or without HPV 16/18 co-infection was 34.2 to 56.2%.⁷

Question 2:

Is HPV4 vaccination effective in preventing HPV genotypes 6, 11, 16, and 18-related cervical, vulvar, vaginal cancer; CIN 1; CIN 2/3; adenocarcinoma in situ; vulvar intraepithelial neoplasia (VIN) 2/3; and vaginal intraepithelial neoplasia (VAIN) 2/3 in females; penile intraepithelial neoplasia 1/2/3 and penile cancer in males; warts, anal intraepithelial neoplasia (AIN) and anal cancer in males and females?

Inclusion criteria for the systematic literature review:

Population	Females ≥ 9-45 years old, males 2-26 years old
Intervention	Vaccination with HPV 4
Control/comparator intervention	No vaccination or placebo
Outcomes/endpoints	Cervical, vulvar, vaginal cancer CIN 1 CIN 2/3 Adenocarcinoma in-situ, cervix VIN 2/3 VAIN 2/3 Penile intraepithelial neoplasia Penile cancer Warts, AIN and anal cancer in males and females
Study design	RCT

Recommendation

- HPV4 vaccination is recommended for use in females 9-45 years old and in males 9-26 years old.

Supporting Statements

The usefulness of the HPV4 vaccine was assessed in 6 AAHS-controlled, double-blind, randomized phase II and III clinical studies that enrolled 28,413 individuals (20,541 girls and women 16-26 years old, 4,055 boys and men 16-26 years old, 3,817 women 24-45 years old). The HPV4 demonstrated that it is 98% effective in reducing the incidence of CIN (any grade including CIN 2/3) or AIS; 99% efficacious in reducing cases of genital warts; 100% effective in reducing VIN 2/3 and VAIN 2/3 related to vaccine HPV types 6, 11, 16, or 18 in those girls and women who were polymerase chain reaction (PCR) negative and seronegative at baseline. In addition, girls and women who were already infected with 1 or more vaccine-related HPV types prior to vaccination were protected from precancerous cervical lesions and external genital lesions caused by the other vaccine HPV types. Moreover, it is 89% efficacious in reducing the incidence of genital warts related to vaccine HPV types 6 and 11 in boys and men who were PCR negative and seronegative at baseline. It showed 73-75.5% efficacy in reducing the incidence of AIN grades 1 (both condyloma and non-acuminata), 2 and 3 related to vaccine HPV types 6, 11, 16, and 18 in boys and men who were PCR negative and seronegative at baseline.

Table 1. Analysis of Efficacy of HPV4 in the Per Protocol Efficacy (PPE) Population for Vaccine HPV Types*

Population	Gardasil		AAHS Control		% Efficacy (95% CI)
	N	Number of cases	N	Number of cases	
HPV 16- or 18-related CIN 2/3 or AIS					
Study 1 [‡]	755	0	750	12	100.0 (65.1, 100.0)
Study 2	231	0	230	1	100.0 (-3744.9, 100.0)
Study 3	2201	0	2222	36	100.0 (89.2, 100.0)
Study 4	5306	2	5262	63	96.9 (88.2, 99.6)
Combined Protocols [§]	8493	2	8464	112	98.2 (93.5, 99.8)
HPV 16-related CIN 2/3 or AIS					
Combined Protocols [§]	7402	2	7205	93	97.9 (92.3, 99.8)

HPV 16- or 18-related VIN 2/3

Study 2	231	0	230	0	Not calculated
Study 3	2219	0	2239	6	100.0 (14.4, 100.0)
Study 4	5322	0	5275	4	100.0 (-50.3, 100.0)
Combined Protocols [§]	7772	0	7744	10	100.0 (55.5, 100.0)

HPV 16- or 18-related VIN 2/3

Study 2	231	0	230	0	Not calculated
Study 3	2219	0	2239	5	100.0 (-10.1, 100.0)
Study 4	5322	0	5275	4	100.0 (-50.3, 100.0)
Combined Protocols [§]	7772	0	7744	9	100.0 (49.5, 100.0)

HPV 6-, 11-, 16-, or 18-related CIN (CIN 1, CIN 2/3) or AIS

Study 2	235	0	233	3	100.0 (-138.4, 100.0)
Study 3	2241	0	2258	77	100.0 (95.1, 100.0)
Study 4	5388	9	5374	145	93.8 (88.0, 97.2)
Combined Protocols [§]	7864	9	7865	225	96.0 (92.3, 98.2)

HPV 6-, 11-, 16-, or 18-related Genital Warts

Study 2	235	0	233	3	100.0 (-139.5, 100.0)
Study 3	2261	0	2279	58	100.0 (93.5, 100.0)
Study 4	5404	2	5390	132	98.5 (94.5, 99.8)
Combined Protocols [§]	7900	2	7902	193	99.0 (96.2, 99.9)

HPV 6- and 11-related Genital Warts

Combined Protocols [§]	6932	2	6856	189	99.0 (96.2, 99.9)
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N = Number of individuals with at least 1 follow-up visit after Month 7

CI = Confidence Interval

Note 1: Point estimates and confidence intervals are adjusted for person-time of follow-up.

Note 2: The first analysis in the table (i.e., HPV 16- or 18-related CIN 2/3, AIS or worse) was the primary endpoint of the vaccine development plan.

Note 3: Table 11 does not include cases due to non-vaccine HPV types.

AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

- * The PPE population consisted of individuals who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and through 1 month postdose 3 (Month 7).

† See Table 14 for analysis of vaccine impact in the general population.

‡ Evaluated only the HPV 16 L1 VLP vaccine component of Gardasil

§ Analyses of the combined trials were prospectively planned and included the use of similar study entry criteria.

Table 12: Analysis of Efficacy of Gardasil in the PPE^{*} Population of 16- Through 26-Year-Old Boys and Men for Vaccine HPV Types

Endpoint	Gardasil		AAHS Control		% Efficacy (95% CI)
	N [†]	Number of cases	N	Number of cases	
External Genital Lesions HPV 6-, 11-, 16-, or 18- related					
External Genital Lesions	1394	3	1404	32	90.6 (70.1, 98.2)
Condyloma	1394	3	1404	28	89.3 (65.3, 97.9)
PIN 1/2/3	1394	0	1404	4	100.0 (-52.1, 100.0)
CI = Confidence Interval AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate					
* The PPE population consisted of individuals who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and through 1 month postdose 3 (Month 7).					
† N = Number of individuals with at least 1 follow-up visit after Month 7					

Table 13: Analysis of Efficacy of Gardasil for Anal Disease in the PPE^{*} Population of 16- Through 26-Year-Old Boys and Men in the MSM Sub-study for Vaccine HPV Types

HPV 6-, 11-, 16-, or 18- related Endpoint	Gardasil		AAHS Control		% Efficacy (95% CI)
	N [†]	Number of cases	N	Number of cases	
AIN 1/2/3	194	5	208	24	77.5 (39.6, 93.3)
AIN 2/3	194	3	208	13	74.9 (8.8, 95.4)
AIN 1	194	4	208	16	73.0 (16.3, 93.4)
Condyloma Acuminatum	194	0	208	6	100.0 (8.2, 100.0)
Non-acuminate	194	4	208	11	60.4 (-33.5, 90.8)
CI = Confidence Interval AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate					
* The PPE population consisted of individuals who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and through 1 month postdose 3 (month 7).					
† N = Number of individuals with at least 1 follow-up visit after Month 7					

Question 3:

Is HPV9 vaccination effective in preventing HPV genotypes 6, 11, 16, 18, 31, 33, 45, 52, and 58-related cervical, vulvar and vaginal cancer; CIN 2/3; adenocarcinoma in-situ; VIN 2/3; and VAIN 2/3 in females; penile intraepithelial neoplasia 1/2/3 and penile cancer in males; warts, AIN and anal cancer in males and females?

Inclusion criteria for the systematic literature review:

Population	Females and males \geq 9 years old
Intervention	Vaccination with HPV 9
Control/comparator intervention	No vaccination or placebo
Outcomes/endpoints	Cervical, vulvar, vaginal cancer CIN 2/3 Adenocarcinoma in-situ, cervix VIN 2/3 VAIN 2/3 Penile intraepithelial neoplasia Penile cancer Warts, AIN and anal cancer in males and females
Study design	RCT

Recommendation

- HPV9 vaccination is recommended for use in females and males \geq 9 years old.

Supporting Statements

In a phase II efficacy trial, the HPV9 vaccine demonstrated 96.7% efficacy for the prevention of CIN 2+, VIN 2/3 caused by HPV 31, 33, 45, 52 or 58. The immunogenicity from the HPV9 vaccine was comparable with HPV4 vaccine and this is used to extrapolate efficacy for HPV 6, 11, 16 and 18. Geometric mean titers (GMT) 1 month after the 3rd dose were non-inferior for HPV 6, 11, 16 and 18. Among those in the HPV9 group, > 99% seroconverted to all 9 HPV vaccine types. Noted also was the fact that the GMTs were higher in adolescents aged 9-15 years compared with females 16-26 years old. The GMT in males aged 16-26 years were non-inferior to those in females.⁸

In a randomized, international, double-blind, phase 2b-3 study on the efficacy and immunogenicity of the HPV9 vaccine in 14,215 women aged 16-26 years, the rate of high-grade cervical, vulvar, or vaginal disease irrespective of HPV type in the population which included participants with and those without prevalent infection or disease was 14.0 per 1000 person-years in both vaccine groups. The rate of high-grade cervical, vulvar, or vaginal disease related to HPV 31, 33, 45, 52, and 58 in the susceptible population was 0.1 per 1000 person-years in the HPV9 group and 1.6 per 1000 person-years in the HPV4 group. The HPV9 vaccine demonstrated a 96.7% efficacy (95% CI 80.9-99.8). Antibody responses to HPV 6, 11, 16, and 18 were comparable to those generated by the HPV4 vaccine. Injection site adverse events were more common in the HPV9 group than in the HPV4 group.⁹

The results from 7 clinical studies support that the HPV9 vaccine was efficacious against HPV disease and persistent infection caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The efficacy for cervical, vulvar, vaginal, and anal diseases, genital warts and persistent infection that was demonstrated in the original clinical studies for the HPV4 vaccine can be extended to HPV9 vaccine. In clinical studies, protective efficacy has been shown to last up to 5.6 years after the 3rd dose for HPV9 vaccine. (Table 2)

In the analysis of HPV9 vaccine safety and immunogenicity in young men 16-26 years of age, seroconversion was noted for each of the 9 vaccine HPV types in > 99% of participants. Antibody response was evaluated separately in heterosexual men and men having sex with men (MSM). The antibody response to HPV9 vaccine in heterosexual men 16-26 years of age was shown to be non-inferior to those observed in young women 16-26 years of age (the population used to establish HPV9 vaccine efficacy).¹⁰

Table 2. Analysis of Efficacy of HPV9 Vaccine Against HPV Types 31, 33, 45, 52, and 58 in the PPE Population 16- 26 Year Old Women*

Disease Endpoint	HUMAN PAPILLOMAVIRUS 9- VALENT (TYPES 6, 11, 16, 18, 31, 33, 45, 52, 58) RECOMBINANT VACCINE (GARDASIL™ 9) N† =7099		GARDASIL N† =7105		%Efficacy (95% CI)‡
	n‡	Number of cases§	n‡	Number of cases§	
HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer	6016	1	6017	38	97.4 (85.0, 99.9)
HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3 or AIS*	5949	1	5943	35	97.1 (83.5, 99.9) 96.9
CIN2	5949	1	5943	32	(81.5, 99.8) 100
CIN3	5949	0	5943	7	(39.4, 100)
HPV 31-, 33-, 45-, 52-, 58-related CIN 1	5949	1	5943	87	98.9 (94.1, 99.9)
HPV 31-, 33-, 45-, 52-, 58-related Vulvar or Vaginal Disease ^b	6009	1	6012	18	94.4 (67.7, 99.7)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥ 6 Months ^a	5941	41	5955	946	96.0 (94.6, 97.1)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥ 12 Months ^a	5941	23	5955	657	96.7 (95.1, 97.9)
HPV 31-, 33-, 45-, 52-, 58-related ASC-US HR-HPV Positive or Worse Pap ^b Abnormality	5883	37	5882	506	92.9 (90.2, 95.1)
HPV 31-, 33-, 45-, 52-, 58-related Cervical Biopsy	6013	6	6014	253	97.7 (95.1, 99.0)

HPV 31-, 33-, 45-, 52-, 58-related Cervical Definitive Therapy Procedure^a	6013	4	6014	41	90.2 (75.0, 96.8)
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*The PPE population consisted of individuals who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 31, 33, 45, 52, and 58) prior to dose 1, and who remained PCR negative to the relevant HPV type(s) through 1 month postdose 3 (Month 7). The data are from Protocol 001.

^t N=Number of individuals randomized to the respective vaccination group who received at least 1 injection

[#]n=Number of individuals contributing to the analysis

^{\$}Number of cases= number of individuals with at least one follow-up visit after Month 7

[†]Subjects were followed for up to 67 months postdose 3 (median 43 months postdose 3)

[#]No cases of cervical cancer, VIN2/3, vulvar and vaginal cancer were diagnosed in the PPE population.

[‡]Includes VIN1/2/3, ValN1/2/3, condyloma

[§]loop electrosurgical excision procedure (LEEP) or conization

[¶]Persistent infection detected in samples from two or more consecutive visits 6 months (\pm 1 month visit windows) apart

^{||}Persistent infection detected in samples from three or more consecutive visits 6 months (\pm 1 month visit windows) apart

[¶]Papanicolaou test

CI=Confidence Interval

ASC-US=Atypical squamous cells of undetermined significance

HR=High Risk

Additional Recommendations

1. The HPV vaccine should be administered in a 3 dose series of intramuscular injections preferably in the deltoid area over a 6-month period. The HPV2 vaccine is given at 0, 1, 6 months. The HPV4 and HPV9 vaccines are given at 0, 2, 6 months. The same vaccine product should be used for the entire 3-dose series.⁴
2. Target Population: For girls, the HPV vaccine is recommended routinely at ages 11-12 years and can be administered beginning at 9 years of age. Girls and women aged 13-26 years who have not started or completed the vaccine series should receive the vaccine. The HPV4 or HPV9 vaccine are recommended routinely for boys aged 11-12 years and can be given beginning at 9 years of age. Boys and men aged 13-21 years who have not started or completed the vaccine series should receive the vaccine as well.⁴
3. Two doses of the HPV vaccine (0, 6-12 month schedule) can be given for persons starting the vaccination series before the 15th birthday.¹¹
 - 3.a. The HPV2 vaccine can be given in 2 doses for those 9-14 years old at 0, 6-12 months.

Supporting Statements:

The antibody titers produced when HPV2 vaccine was given to girls aged 9-14 years in a 2 dose schedule (0, 6 months) were similar to the 3 dose schedule in young women aged 15-25 years old. GMT ratios for these 2 groups of subjects were close to 1 at months 36 and 48, as they were at month 7 when non-inferiority was statistically analyzed. Both schedules had clinically acceptable reactogenicity and safety profiles up to 4 years after the first vaccination. A 2-dose schedule could expedite implementation of HPV vaccination programs and increase vaccine coverage and rates of vaccine completion.¹²

3.b. The HPV4 and the HPV9 vaccine can be given in 2 doses for those 9-14 years old at 0, 6-12 months.

Supporting Statements:

The immune response elicited in the 2-dose schedule (0, 6 months) in adolescents is comparable/non-inferior to the 3 doses in the 16-26 year old young women to the 4 HPV types – 6, 11, 16 and 18. The results are sustained 3 years after vaccination, which indicates that a 2-dose schedule is able to induce high antibody levels for protection against HPV diseases. This is based on the Canadian study performed by Dobson, et al. Antibody GMT against the 9 HPV types assayed 1 month after the last dose were consistently higher in girls (0, 6 months dose), boys (0, 6 months dose), and girls and boys (0, 12 months dose) than for adolescent girls and young women (0, 2, and 6 months dose) in the per protocol population. At 1 month after the last dose, HPV antibody responses in girls and boys given 2 doses were non-inferior to HPV antibody responses in adolescent girls and young women given 3 doses. HPV antibody responses were generally higher in girls and boys who received 2 doses at a 12-month interval than in girls and boys who received 2 doses 6 months apart. These results allow for some flexibility in the spacing of the 2nd dose.¹³

The European Medicines Agency approved the 2-dose regimen of the HPV9 vaccine in April 2016 for young adolescents aged 9 to 14 years old. They are endorsing that the second dose be administered 5-13 months after the initial dose. Likewise, the World Health Organization (WHO) is recommending the 2-dose schedule separated by 6 months or longer, without specifying a maximum interval.

4. For those \geq 15 years old, the HPV2 vaccine is given in 3 doses at 0, 1, 6 months. The HPV4 and HPV9 vaccine are given also in 3 doses at 0, 2, 6 months.

Supporting Statements:

The vaccines are administered in a 3-dose schedule. Each dose is 0.5 mL, administered intramuscularly, preferably in a deltoid muscle or in the upper anterolateral thigh. The 2nd dose is administered 1 to 2 months after the first dose, and the 3rd dose is administered 6 months after the initial dose. The minimum interval between the 1st and 2nd dose of vaccine is 4 weeks and between the 2nd and 3rd dose is 12 weeks. The minimum interval between the 1st and 3rd dose is 24 weeks. Doses that are given earlier than the recommended schedule should be re-administered. Restarting the vaccine series is not necessary if the vaccine schedule is interrupted. Simultaneous administration of a different inactivated or live vaccine with HPV vaccine is allowed.

5. The HPV2 and HPV4 vaccines are not interchangeable to complete the 3 doses.

Supporting Statements:

Whenever feasible, the same HPV vaccine should be used for the entire vaccination series. No studies address interchangeability of HPV vaccines. However, if the vaccine provider does not know or have available the HPV vaccine product previously administered, either HPV vaccine can be used to complete the series to provide protection against HPV 16 and 18. For protection against HPV 6 or 11-related genital warts, a vaccination series with less than 3 doses of HPV4 vaccine might provide less protection against genital warts than a complete 3-dose series.¹⁴

6. Women who previously received the HPV4 vaccine may be given the HPV9 vaccine.

Supporting Statements:

Studies using a mixed regimen (interchangeability) of HPV vaccines were not performed for the HPV9 vaccine. The safety and immunogenicity of a 3-dose regimen of the HPV9 vaccine was analyzed in girls and women 12–26 years of age who had previously received a 3-dose regimen of the HPV4 vaccine. The HPV9 vaccine was generally well tolerated.

Discontinuations and vaccine-related serious adverse reactions were not common. Seroconversion for all 9 vaccine HPV types was achieved in > 98% of study participants who received a 3-dose regimen of the HPV9 vaccine. Anti-HPV 6/11/16/18 GMT rose substantially following the initial dose of HPV9 vaccine, but did not change much following further vaccine administrations, which is consistent with a memory response to these 4 HPV types. Anti-HPV 31/33/45/52/58 GMT increased after the HPV9 vaccine administrations which is consistent with a primary response.

A cross-study comparison of HPV9 vaccine immunogenicity in prior HPV4 vaccine recipients vs. subjects with no prior HPV vaccination in the pivotal efficacy study of HPV9 vaccine (protocol V503-001) revealed that the anti-HPV 6/11/16/18 GMT at month 7 were higher in prior HPV4 vaccine recipients while anti-HPV 31/33/45/52/58 GMT at month 7 were lower in prior HPV4 vaccine recipients. These indicate that the immunogenicity profile of the HPV9 vaccine may be different in prior HPV4 vaccine recipients. However, these results should be interpreted with caution, since they are based on nonrandomized, cross-study analyses. Stronger responses to HPV 6/11/16/18 in prior HPV4 vaccine recipients are consistent with a memory response.¹⁵

If the decision is made to administer the HPV9 vaccine after receiving 3 doses of HPV4, there should be an interval of at least 12 months between completion of vaccination with HPV4 vaccine and the start of vaccination with the HPV9 vaccine. There is no Advisory Committee on Immunization Practices (ACIP) recommendation for additional HPV9 doses for persons who previously completed a series of HPV2 or HPV4. If a person who completed the HPV4 series desires the 5 additional types prevented by HPV9, the benefit of protection against the 5 additional subtypes would mostly be limited to females for prevention of cervical cancer and precancer.¹⁶ Revaccination with the HPV9 vaccine in individuals who previously received the 3-dose series with the HPV2 or HPV4 vaccine currently is not a routine recommendation.¹⁷

Precautions and Contraindications

7. HPV vaccines can be given to women with minor acute illnesses. (GPP)

Supporting Statements:

HPV vaccines can be administered to persons with minor acute illnesses. Vaccination of persons with moderate or severe acute illnesses should be deferred until after the patient improves.¹⁴

8. Women who receive HPV vaccination should be observed for syncope in the clinic for 15 minutes. (GPP)

Supporting Statements:

Syncope can occur after vaccination. This has been noted among adolescents and young adults. To avoid serious injury related to a syncopal episode, vaccine providers should consider observing patients for 15 minutes after they are vaccinated.¹⁴

9. HPV vaccination should not be given to patients with a history of adverse reactions to any vaccine component. (GPP)

Supporting Statements:

HPV vaccines are contraindicated for persons with a history of immediate hypersensitivity to any vaccine component. The HPV4 vaccine is produced in *Saccharomyces cerevisiae* (baker's yeast) and is contraindicated for persons with a history of immediate hypersensitivity to yeast. Prefilled syringes of HPV2 have latex in the rubber stopper and should not be used in persons with anaphylactic latex allergy. HPV2 single dose vials contain no latex.¹⁴

10. HPV2 and HPV4 are not live vaccines, and can be administered to females who are immunosuppressed (from disease or medications). However, the immune response and vaccine efficacy might be less than that in immunocompetent persons.¹⁴

11. HPV vaccines are not recommended for use in pregnant women.¹⁸

Supporting Statements:

If a woman is found to be pregnant after starting the vaccination series, the remainder of the 3-dose series should be delayed until completion of pregnancy. Pregnancy testing is not needed before vaccination. If a vaccine dose has been administered during pregnancy, no intervention is needed.

Cost information

Brand	DESCRIPTION	COST
Cervarix	HPV2 (16,18), 0.5 mL in a pre-filled syringe	P1,500/ prefilled syringe
Gardasil	HPV4 (6,11,16,18), 0.5 mL in a prefilled syringe	P2,300/ prefilled syringe
Gardasil 9	HPV9 (6,11,16,18,31,33,45,52,58), 0.5 mL in a prefilled syringe	P6,000/ prefilled syringe

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DENGUE VACCINE

Analyn T. Fuentes-Fallarme, MD, MPH, FPOGS, FPIDSOG

Dengue is a significant public health concern worldwide, with approximately half of the world's population at risk.¹ It is a mosquito-borne flaviviral disease that has spread to most tropical and many subtropical countries, causing significant burden of disease and economic costs. It is the most rapidly spreading mosquito-borne viral disease, with a 30-fold increase in global incidence over the past 50 years. Close to 75% of the global population exposed to dengue are in the Asia-Pacific region. Global prediction shows approximately 390 million dengue infections each year will occur, of which 96 million are clinically apparent, and up to 2 million considered severe cases with 20,000 deaths.^{2,3} In the Philippines, the Department of Health (DOH) National Epidemiology Center reported more 200,000 dengue fever cases in 2015-2016, with more than 1,000 dengue related fatalities in 2016. As of April 1, 2017, there were 26,433 suspected cases of dengue reported from January 1, 2017. This is 35.8% lower compared with 41,170 cases for the same period in 2016.⁴

In December 2015, the first ever vaccine against dengue infection was licensed in Mexico. This vaccine was developed by Sanofi Pasteur under the brand name Dengvaxia, a 3-dose live recombinant tetravalent vaccine based on the YF17D backbone (CYD-TDV). It was licensed in individuals 9-45 years living in endemic areas. In early 2016, Dengvaxia was licensed by the governments of Philippines, Brazil, Costa Rica, El Salvador, Mexico, and Paraguay.

This vaccine is hoped to accomplish the objectives of the World Health Organization (WHO) Global Strategy for dengue prevention and control (2012-2020) in reducing dengue morbidity by at least 25% and mortality by at least 50%.

Question:

Is dengue vaccine effective in preventing dengue infection?

Inclusion criteria for the systematic literature review:

Population	2-16 years old
Intervention	Immunization with tetravalent, live, attenuated dengue vaccine CYD-TDV (Dengvaxia) at 0-6-12 months
Control/comparator intervention	Intramuscular injection of normal saline vaccine diluent
Outcomes/endpoints	Symptomatic, confirmed dengue fever
Study design	Prospective cohort study RCT

Recommendation

- Consider giving dengue vaccine only in geographic settings (national or subnational) with high endemicity, as indicated by seroprevalence of approximately 70% or greater in the age group targeted for vaccination or other suitable epidemiologic markers. The vaccine is not recommended where seroprevalence is below 50.

Recommended Schedule

Dengue vaccine is indicated for 9-45 years old living in endemic areas given at 0-6-12 months.

Supporting Statements

Sanofi Dengue Vaccine Efficacy Trials (CYD)

Site(s)	Design	N	Ages (yrs)	Pre-existing DENV Ab (%)
Ratchaburi, Thailand	Phase 2B	4002	4-11	69.5
Asia Indonesia Malaysia Philippines Thailand Vietnam	Phase 3	10,275	2-14	67.5
Latin America Colombia Brazil Mexico Puerto Rico Honduras	Phase 3	20,869	9-16	79.4

Results of Efficacy Trials Sanofi Vaccine (per protocol results)

DENV specific	Phase IIB-Thailand N=4,002		Phase III-Asia N=10,275		Phase III-Latin America N=20,869	
	Efficacy	95% CI	Efficacy	95% CI	Efficacy	95% CI
All DENV	30.2	-13-57	56.5	44-66	60.8	52-68
DENV 1	55.6	22-84	50.0	25-67	50.3	29-65
DENV 2	9.2	-75-51	35.0	-9-61	42.3	14-61
DENV 3	75.3	-38-100	78.4	53-91	74.0	62-82
DENV 4	100	25-100	75.3	55-87	77.7	60-88

Only prospective cohort study and randomized controlled trials (RCTs) written in English were included in the literature search. The topic of interest is the efficacy and safety of tetravalent, live, attenuated dengue vaccine (Dengvaxia).

The vaccine demonstrated efficacy in the first year of observation period (from 28 days after the third dose) of 56.7% in Asia⁵ and 60.8% in Latin America.⁶ Pooled vaccine efficacy against symptomatic virologically-confirmed dengue (VCD) of any serotype in the year starting 1 month after the 3rd dose was 59.2% (95% confidence interval [CI] 52.3, 65.0)⁷

Vaccine efficacy was substantially higher among participants who had already been exposed to dengue (pooled VE from immunological subset: 78.2%, 95% CI 65.4-86.3) compared with participants who were naive at baseline (pooled VE: 38.1%, 95% CI -3.4, 62.9).⁷

During the first 2 years after immunization, compared with placebo controls, Dengvaxia reduced the prevalence of dengue, mild and severe, by 57%, with a lower efficacy against illnesses caused by DENV-1 and DENV-2, compared with DENV-3 and DENV-4. However, during the third year after vaccination, the protective efficacy dropped to 16.7% (65 cases among 22, 177 vaccine recipients vs. 39 cases among 11,089 placebo recipients). Furthermore, there was also note of higher protection in older children than the younger ones; and higher protection against hospitalized and severe dengue compared to mild diseases. Some level of protection was also seen even after the 1st dose.^{5,7,8}

Question:

Is dengue vaccine safe?

Recommendation

- Dengue vaccine can be safely given to children living in dengue endemic area and high background of previous DENV infection.

Supporting Statements

Interim results from long-term safety follow up (48 months) demonstrated an elevated risk of hospitalization and severe dengue among 2-5 year old participants (at vaccination) in the 3rd year after receipt of the 1st dose (relative risk [RR] 7.45, 95% CI 1.15-313.80), though this dissipated in years 4 and 5. The biologic mechanism behind this increased risk is currently not understood but may be related to naïve vaccine serostatus and/or age. A significant increase in hospitalizations was not seen in those older than 5 years. Because of the safety signal of increased risk of hospitalized and severe dengue identified in the 2–5 year age group, CYD-TDV is not recommended for use in children under 9 years of age, consistent with current labelling. No safety signals were identified in older age groups.^{5,7}

There are insufficient data on the use of CYD-TDV in pregnant and lactating women. However, the limited data on inadvertent pregnancies collected during the clinical trials have yielded no evidence of harm to the fetus or pregnant woman. Women of childbearing age who are targeted for vaccination do not need to be tested for pregnancy.

Until data become available from forthcoming studies, CYD-TDV is not recommended in immunocompromised individuals, travelers or health-care workers.⁹

Cost Information

Brand	COST
Dengvaxia	P3,000/vial

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ZOSTER VACCINE

Ricardo M. Manalastas, Jr., MD, MSc, FPOGS, FPIDSOG

Recommendations

- The Zoster vaccine is indicated for vaccination of adults aged 50 years and older for the prevention of herpes zoster, prevention of post-herpetic neuralgia, and reduction of acute and chronic herpes-associated pain. The vaccine prevents herpes zoster by 51.3%, post-herpetic neuralgia by 66.5%, and it reduces acute and chronic herpes zoster-associated pain by 61.1% (strong recommendation with high quality of evidence).
- Contraindications include anaphylactic/anaphylactoid reaction to gelatin, neomycin, or to any vaccine component. It is also contraindicated to persons with immunosuppression or severe state of immunodeficiency. It is not given to people with active untreated tuberculosis, and among pregnant women (strong recommendation with high quality of evidence).
- The Varicella-Zoster virus vaccine is administered as a single dose, preferably subcutaneously (inadvertent intramuscular dose is also valid) without the need for prior antibody testing (strong recommendation with high quality of evidence).
- For storage and handling, the preparation being a live attenuated vaccine, should be refrigerated (not frozen) at 2-8 degrees Centigrade. Upon reconstitution (mixing the diluent with the freeze-dried powder), the vaccine should be administered within 30 minutes (strong recommendation with high quality of evidence).

Cost Information

TYPE	COST
Varicella Zoster vaccine	P5,000/vial

References

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YELLOW FEVER VACCINE

Judith Perez Peralta, MD, FPOGS, FPIDSOG

Yellow fever (YF) is a mosquito-borne viral infection that is endemic to sub-Saharan Africa and tropical South America. World Health Organization (WHO) global statistics estimate 200,000 clinical cases and 30,000 deaths annually. Clinical manifestations range from mild, nonspecific febrile disease to a severe form with jaundice and hemorrhage. The case fatality ratio for YF is 20-50% (Monath, 2013). Prevention through immunization with the YF 17D substrain virus vaccine is key to decreasing morbidity and mortality from YF since there is no specific cure for this viral infection.

The risk of YF infection depends on the season, activities, duration and area of travel. For a 2-week stay in South America, the unvaccinated traveler's risk of YF infection is 5 cases per 100, 000 population. However, the risk of YF infection is 10 times higher in West Africa, at 50 cases per 100,000 populations.

Current recommendations are:

1. Yellow fever vaccine is recommended for persons \geq 9 months who travel to and reside in endemic areas. (ACIP, WHO, CDC 2010)
2. To prevent importation and spread of YF to non-endemic countries, International Health Regulations allow countries to require proof of YF vaccination prior to entrance to their country. (WHO 2005)

Previously, YF vaccination was required every 10 years based on the International Health Regulations' specification that the International Certificate of Vaccination or Prophylaxis (i.e. yellow card) valid for 10 years.

However in 2013, this regulation was revised on the basis of: (Gotuzzo, 2013)

- a. Systematic review of published articles on the duration of immunity after a single dose of YF vaccine.
 - b. Data showing that vaccine failures are extremely rare and the frequency of vaccine failure does not increase with time from vaccination.
-
3. "The WHO Strategic Advisory Group of Experts (SAGE) on Immunization concluded that a single primary dose of YF vaccine is sufficient to confer sustained immunity and lifelong protection against yellow fever disease, and that a booster dose is not needed." (WHO June 2013, MMWR June 2015)

In May 2014, the World Health Assembly adopted this recommendation: "Remove the 10-year booster dose requirement from the International Health Regulations by June 2016." The Philippine Department of Health (DOH), Bureau of Quarantine currently follows this recommendation.

Question:

Should a booster dose of YF vaccine every 10 years be given to healthy travelers?

Inclusion criteria for the systematic literature review:

Population	Adult healthy travellers
Intervention	Follow current recommendation to remove booster doses of YF vaccine. One lifetime dose is adequate.
Control/comparator intervention	
Outcomes/endpoints	Benefits: Vaccine efficacy, seropositivity Harms: Serious adverse events, viscerotropic disease, neurologic disease
Study design	

The benefits and harms of YF vaccine booster doses were identified as critical outcomes and ranked according to relative importance as shown in Table 1.

Table 1. Ranked Outcome Measures of YF Vaccine Booster Doses

OUTCOME	IMPORTANCE	INCLUDE IN EVIDENCE	AVAILABLE DATA
BENEFITS			
1. Vaccine Efficacy	Critical	Yes	No
2. Vaccine Effectiveness	Critical	Yes	Yes
3. Seroprotection	Critical	Yes	No
4. Seropositivity	Critical	Yes	Yes
HARMS			
1. Serious adverse events	Critical	Yes	Yes
2. Viscerotropic disease	Critical	Yes	Yes
3. Neurologic disease	Critical	Yes	Yes
4. Anaphylaxis	Important	No	--
5. Systemic adverse events	Important	No	--

Critically important benefits included vaccine efficacy, effectiveness, seroprotection and seropositivity. However, there is no available data for YF vaccine efficacy so vaccine effectiveness was evaluated as a lack of vaccine failure. The accepted basis for an established seroprotective YF titer is data from a long-term immunogenicity study using log 10 neutralization index (LNI),

which is not available. Instead, seropositivity, defined as the presence of YF virus-specific antibodies, was used as a surrogate outcome for seroprotection. Critically important harms included any serious adverse events, viscerotropic disease, neurologic disease that are vaccine-related. The evidence type for each critical outcome was determined based on study design, risk of bias, inconsistency, indirectness, imprecision, and other factors. (Ahmed 2011).

Recommendation

- A single dose of YF vaccine is sufficient to confer sustained immunity and lifelong protection against YF disease; therefore a booster dose is not needed.

Supporting Statements

The search strategy used by a GRADE evaluation published in Center for Disease Control and Prevention (CDC) Morbidity and Mortality Weekly Report (MMWR) June 2015 was repeated with additional search terms. Published literature were identified by conducting a search in Cochrane Library, Pub Med, Embase, including Ovid, Web of Science, Medline, Global Health, Popline and Uptodate, in English as of June 15, 2017 to identify new articles. Keywords used were “yellow fever vaccine”, “immunogenicity”, “immunity”, “long-term”, “efficacy”, “effectivity”, “adverse events”, “safety”, or “side effects”, “randomized controlled trials”. The abstracts/full papers, as well as reference lists of relevant articles were reviewed. Articles that contained data on YF vaccine were included if they involved human subjects, reported primary data and presented data relevant to the assessed outcome measures. Case reports of adverse events were excluded. Unpublished data from the Brazilian Health Ministry on duration of immunity and vaccine safety, CDC data on antibody titers in vaccine recipients, and VAERS data on vaccine safety were also considered.

Summary of Critical Outcomes

Benefits

1. Vaccine Effectiveness

The evidence from 9 studies (8 published and 1 unpublished) was used to evaluate vaccine effectiveness (Table 2). These studies documented YF in individuals even after YF immunization.

Four out of 8 published studies were conducted in Brazil and likely included the same individuals in more than one of the studies. This

unpublished study is based on the Brazilian Ministry of Health national data, used in lieu of the four studied to prevent possible overlap.

Table 2. Vaccine Effectiveness Measured by Reported Vaccine Failures After YF Immunization

STUDY	POPULATION	TYPE	AGE GROUP	NO. OF CASES	LAB CONFI RMED	TIMING POST VACCINE	OUTCOME
Elliot 1944	Non-endemic	Obs	Adult	3	0	15 months 16 months 16 months	Died (2) Survived (2)
Ross 1953	Non-endemic	Obs	Adult	1	0	4 years	Died
Nolla Salas 1988	Non-endemic	Obs	Adult	1	0	5 years	Survived
Akoua-Koffi 2001	Endemic	Obs	Unknown	6	0	Unknown but within 10 years	Survived (6)
Brazil 2014 (unpublished) in lieu of (Tuboi 2007, de Filippis 2004, Saraiva 2013, Cmara 2013)	Endemic	Obs	Unknown	7	7	10 days-10 years (5) 20 years (1) 27 years (1)	Unknown
All	Non-endemic/ Endemic	Obs (5)	Adult or Unknown	18	7	10 days – 27 yrs	Died (3) Unknown (7) Survived (8)

*CDC MMWR June 17, 2015

There were a total of 23 vaccine failures after the administration of more than 540 million doses of YF vaccine (WHO 2013). Five out of the 23 cases were excluded because vaccine failure occurred less than 10 days after vaccination, when protective antibodies are not known to have yet developed (Monath 2013). Vaccine failures occurred within 10 years of the YF vaccine dose, in 16 out of the remaining 18 cases (89%). Vaccine failures occurred 10 or more years after the last YF vaccine dose in 2 cases, 20 and 27 years after vaccination.

YF virus infection was confirmed by laboratory detection of anti-YF virus IgM antibodies in 7 out of the 18 cases (Brazil 2014). The remaining 11 out of 18 cases (61%) were not confirmed by any laboratory tests.

2. Seropositivity

The evidence from 13 observational studies (12 published and 1 unpublished) where used to evaluate seropositivity, ten or more years after the initial dose of YF vaccine. Included studies were published from 1952-2014 (60 years) also gathered data on several other vaccines, and tests that have been discontinued or obsolete.

Table 3. Seropositivity ≥ 10 Years After YF Immunization

STUDY	POPULATION	TYPE	SEROPOSITIVITY CRITERIA	YEARS POST VACCINATION	SEROPOSITIVE NO (%)
Dick 1952	Endemic	Obs	Mouse protection	10	156/202 (77)
de Melo 2011	Endemic	Obs	PRNT 50 \geq 20	10	20/20 (100)
Reinhardt 1998	Non- endemic	Obs	PRNT 90 \geq 10	≥ 10	5/5 (100)
Machado 2013	Endemic	Obs	PRNT 80 \geq 10	≥ 10	19/19 (100)
CG YF vaccines 2014	Endemic	Obs	PRNT 50 \geq 10	10-18	307/329 (93)
Rosenzweig 1963	Non- endemic	Obs	Mouse protection	10-15	24/24 (100)
Courtois 1954		Obs	Mouse protection	12	76/79 (96)
Groot 1962	Non- endemic	Obs	Mouse protection	17	105/108 (97)
Gomez 2008		Obs	PRNT 75 \geq 20	10-24	13/19 (68)
Niedrig 1999	Non- endemic	Obs	PRNT 90 \geq 20	11-38	38/51 (75)
Coulange Boudilis 2011	Non- endemic	Obs	PRNT 80 \geq 20	10-60	80/84 (95)
CDC 2014	Non- endemic	Obs	PRNT 90 \geq 20	10-69	68/81 (84)
Poland 1981	Non- endemic	Obs	PRNT 90 \geq 20	30-35	91/116 (78)
ALL	NON- ENDEMIC/ ENDEMIC	OBS (13)	MULTIPLE	10-60	1,002(88) 1,137
				≥ 10 years	92% (95% CI 85% - 96%)
				≥ 20 years	80% (95% CI 74% - 86%)

*CDC MMWR June 17, 2015

Out of the 13 studies, 1,137 subjects with available immunogenicity data at ≥ 10 years post-vaccination. YF virus antibodies were detected in 1,002 out of these 1,137 individuals. Thus, 88% were still seropositive ≥ 10 years after vaccination. YF virus antibodies were detected in 132 subjects out of 164 subjects who were given YF vaccine ≥ 20 years prior. Therefore, 80% were still seropositive ≥ 20 years after vaccination. The seropositivity values ranged from 68% to as high as 100%. After using a random effects model, and correcting for dissimilarities in study size and variability, the

estimated seropositivity was 92% after \geq 10 years from vaccination with a 95% confidence interval (CI) of 85-96%. The seropositivity was 80% at \geq 20 years after vaccination with a 95% CI of 74-86%.

Harms

1. Serious Adverse Events (SAE)

The evidence came from 8 published and unpublished observational studies, including surveillance data from national authorities and vaccine manufacturers for an estimated 333 million doses of vaccine. A total of 1,255 subjects reported SAE after YF vaccination, although the dose type (primary or booster) was unknown in 83% of the subjects. Data show that 7% of subjects (14 out of 201 known dose type) developed SAE after a booster dose.

Table 4. SAE Reported Following YF Vaccination by Dose Type

Study	Location	Reporting Period	Type	Doses	Number of cases by dose type		
					Primary	Booster	Unknown
CDC 2015	Non-endemic	2007-2013	Obs	3,631,535	96	11 ¹	0
Cottin 2013	Non-endemic/Endemic	1993-2010	Obs	276,000,000 ²	-- ³	--	805
Schumacher 2010	Non-endemic	1991-2001	Obs	272,727	--	--	7
Lindsey 2008	Non-endemic	2003-2006 ⁴	Obs	902,500	54	1 ⁵	0
Khromava 2005	Non-endemic	1990-2002	Obs	9,600,000	13	2 ⁶	32
Biscayart 2014	Endemic	2008-2009	Obs	1,940,000	24	--	9
Breugelmans 2013	Endemic	2007-2010	Obs	38,009,411	--	--	164
Fernandes 2007	Endemic	1999-2005	Obs	499,714	--	--	24
Fitzner 2004	Endemic	2001	Obs	2,600,000	--	--	13 ⁷
All	Non-endemic/Endemic	1990-2013	Obs (9)	333,455,887	187	14	1054

Obs = observational study

¹All 11 serious adverse event cases were reported in adults who were hospitalized following their second (n=10) or third (n=1) dose of YF vaccine. The cases included: 1) Guillain-Barré syndrome (GBS) 16 days post vaccination; 2) GBS 7 days post vaccination; 3) encephalitis 4 days post vaccination; 4) bilateral optic neuritis 2 days post vaccination; 5) anaphylaxis with angioedema on the day of vaccination; 6) lower extremity cellulitis 7 days post vaccination; 7) acute appendicitis requiring surgery 2 days post vaccination; 8) fever and right lower quadrant pain 5 days post vaccination; 9) fever and syncope 1 day post vaccination; 10) myalgia and upper extremity weakness 3 days post vaccination; and 11) lymphadenitis 26 days post vaccination, subsequently diagnosed as Hodgkin's lymphoma.

²Of the 276 million doses, 16.2 million (5.8%) doses were given to non-endemic populations (e.g., travelers).

³Indicates that cases are not reported for the specific dose type.

⁴The published study includes data from 2000-2006 but 2000-2002 removed to prevent overlap with data from Khromova 2005.

⁵One case of appendicitis requiring surgery at 1 day post vaccination.

⁶One case reporting numbness and weakness at 12 days post vaccination and one case with abdominal pain and yellow stools requiring hospitalization at 7 days post vaccination.

⁷Cases not explicitly defined as having serious adverse events but 13 out of 87 adverse events required hospitalization and were considered to be serious.

*CDC MMWR June 2015

2. Viscerotropic Disease

Evidence from 8 observational studies, including surveillance data from national authorities and vaccine manufacturers were used to evaluate YF vaccine-associated viscerotropic disease (YEL-AVD). There were 72 cases or YEL-AVD out of 437 million doses, although the dose type was unknown 57% (1 out of 72) of these cases. YEL-AVD occurred after a booster dose in 3% (1 out of 31) of those with a known dose type.

Table 5. YEL-AVD by Dose Type

Study	Location	Reporting Period	Type	Doses	Number of cases by dose type		
					Primary	Booster	Unknown
Cottin 2013	Non-endemic/Endemic	1993-2010	Obs	276,000,000 ¹	4	1 ²	7
Lindsey 2008	Non-endemic	2003-2006 ³	Obs	902,500	6	-- ⁴	--
Khromava 2005	Non-endemic	1990-2002	Obs	9,600,000	8	--	--
Kitchner 2004	Non-endemic	1991-2003	Obs	3,046,007	--	--	4
Biscayart 2014	Endemic	2008-2009	Obs	1,940,000	12	--	--
Breugelmans 2013	Endemic	2007-2010	Obs	38,009,411	--	--	5
Martins 2010	Endemic	1999-2009	Obs	107,649,393	--	--	20
Whittembury 2009	Endemic	2007	Obs	42,742	--	--	5
All	Non-endemic/Endemic	1990-2010	Obs (8)	437,190,053	30	1	41

Obs = observational study

¹Of the 276 million doses, 16.2 million (5.8%) doses were given to non-endemic populations (e.g., travelers).

²One suspect case in a 55-year-old male who had illness onset 2 days following a booster dose of yellow fever (YF) vaccine. He presented with polyarthralgia, and liver cytolysis; no YF specific-testing was performed. He was reported as recovering from his illness.

³The published study includes data from 2000–2006 but 2000–2002 removed to prevent overlap with data from Khromova 2005.

⁴Indicates that cases are not reported for the specific dose type.

*CDC MMWR June 2015

3. Neurologic Disease

Evidence from 8 observational studies, including surveillance data from national authorities and vaccine manufacturers were used to evaluate YF vaccine-associated neurologic disease YEL-AND. Out of about 462 million doses of vaccine, 218 subjects reported YEL-AND, although the dose type was unknown in 50% (108 out of 218) of the subjects. YEL-AND occurred after a booster dose in 3% (3 out of 110) of those with a known dose type.

Table 6. YEL-AND By Dose Type

Study	Location	Reporting Period	Type	Doses	Number of cases by dose type		
					Primary	Booster	Unknown
Cottin 2013	Non-endemic/Endemic	1993-2010	Obs	276,000,000 ¹	10	1 ²	13
Lindsey 2008	Non-endemic	2003-2006 ³	Obs	902,500	6	-- ⁴	--
Khromava 2005	Non-endemic	1990-2002	Obs	9,600,000	10	--	--
Kitchner 2004	Non-endemic	1991-2003	Obs	3,046,007	--	--	4
Martins 2014	Endemic	2009-2012 ⁵	Obs	30,745,743 ⁶	59	2 ⁷	--
Biscayart 2014	Endemic	2008-2009	Obs	1,940,000	12	--	--
Breugelmans 2013	Endemic	2007-2010	Obs	38,009,411	--	--	6
Martins 2010	Endemic	2000-2008	Obs	101,564,083	--	--	85
All	Non-endemic/Endemic	1990-2010	Obs (8)	461,807,744	107	3	108

Obs = observational study

¹Of the 276 million doses, 16.2 million (5.8%) doses were given to non-endemic populations (e.g., travelers).

²One suspected case in a 45-year-old female who had illness onset 13 days following a booster dose of the vaccine. Her clinical features were listed as a suspected “multiple sclerosis syndrome”; no yellow fever (YF) specific-testing performed. She had “favorable outcome with corticosteroids”.

³The published study includes data from 2000–2006 but 2000–2002 removed to prevent overlap with data from Khromova 2005.

⁴Indicates that cases are not reported for the specific dose type.

⁵The study includes data from 2007–2012 but 2007–2008 removed to prevent overlap with Martins 2010.

⁶Approximately 13 million doses were administered as booster doses. Total number of booster doses was derived by dividing the total number of booster doses administered by the number of years and assumed roughly the same number of doses delivered each year.

⁷One probable case in a 62-year-old female who was diagnosed with Guillain Barre syndrome at an unknown time post vaccination; one probable case in a 20-year-old male who became symptomatic 14 days post vaccination and was diagnosed with acute disseminating encephalomyelitis.

*CDC MMWR June 2015

Table 8. Summary of Evidence Quality Across Outcomes for Benefits and Harms for YF Vaccine Booster Doses in Adult Healthy Travelers

Outcome	No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Evidence Type	Quality
BENEFITS								
Vaccine Effectiveness	5	Obs	Yes Risk of bias due to incomplete case capture and no comparison group	No serious	Yes Different populations; unknown number of persons at risk did not receive a booster	No serious	4	O
Sero-positivity	13	Obs	Yes Risk of bias in tested	No serious	Yes Different populations. No available data on efficacy; uncorrelated assay levels to assess long-term immunity; used different assay types	No serious	4	OO
HARMS								
Serious side effects	9	Obs	No serious	No serious	Yes Mostly unknown if primary or booster dose so rates for AE for dose type can't be calculated	No serious	4	OO
Viscero tropic disease	88	Obs	No serious	No serious	Yes Mostly unknown if primary or booster dose so rates for AE for dose type can't be calculated	No serious	4	OO
Neurologic disease			No serious	No serious	Yes Mostly unknown if primary or booster dose so rates for AE for dose type can't be calculated	No serious	4	OO

Evidence type:

- 1- RCT or overwhelming evidence from observational studies
- 2- RCT with important limitations
- 3- Observational Studies or RCT with notable limitations
- 4- Clinical experience and observations, observational studies with important limitations or RCTs with several major limitations

Considerations for Formulating Recommendations:

1. Type of evidence for benefits and harms

Type 4 evidence for vaccine effectiveness, seroprotection, and serious adverse events

Low grade of evidence because of risk of bias and indirectness

2. Risk: Benefit ratio

Low risk based on very few vaccine failures identified following YF vaccine
Serious adverse events after booster doses are uncommon.

Majority (92%) of vaccine recipients are seropositive at ≥ 10 years post vaccination with YF vaccine.

3. Value

Prevents a serious illness that has no available treatment and poor outcomes.

Provides traveler information to make decisions about YF vaccine

Cost Information

Vaccine cost in Bureau of Quarantine is P1,500 (multi-dose vial) to P2,000 (single-dose injection), which is paid for by travelers.

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APPENDIX

Recommended Vaccines for Adult Women by Age and Pregnancy Status

Age (years)	Influenza	Td/TDaP	Zoster	Pneumococcal ^a	MMR	HPV ^b	Hep A	Hep B	Dengue	Yellow Fever
19-49	✓	✓	*	*	✓	✓	*	*	*	*
> 50	✓	✓	✓	✓	✓	✓	*	*	*	*
Pregnancy	✓	✓	✗	✗	✗	✗	*	*	✗	✗

Legend:

- ✓ Recommended
- * May be recommended if with additional risk factors
- ✗ Contraindicated

^aA single dose of PCV13 is administered first prior to PPV23. It is recommended that the dosing interval between the vaccines in healthy adults be 1 year and in high-risk individuals, 8 weeks apart. Revaccination with PPV23 is recommended for adults < 65 years after 5 years.

^bHPV2 vaccination is recommended for use in females > 9 years old. HPV4 vaccination is recommended for use in females 9-45 years old and in males 9-26 years old. HPV9 vaccination is recommended for use in females and males > 9 years old. The HPV2 vaccine can be given in 2 doses for those 9-14 years old at 0, 6-12 months. The HPV4 and HPV9 vaccine can be given in 2 doses for those 9-14 years old at 0, 6-12 months.

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