

ACIP Meeting Report FEB 2015 (abbreviated meeting due to fear of inclement weather)

Serogroup B meningococcal vaccine

Recommendation to administer to persons ≥ 10 years of age at increased risk due to

- Complement deficiencies
- Asplenia
- Microbiologists routinely exposed to *N. meningitidis*
- Persons at increased risk related to outbreaks of serogroup b disease
-

Vaccine was NOT recommended at this time for use among first year college freshmen living in dorms or travelers, these groups as well as a review of meningococcal outbreak guidance will be considered at upcoming ACIP meetings.

Influenza vaccine

Interim vaccine effectiveness - Update

95% of flu isolates = H3N2, 85% of these = drift variant

H3N2 all ages: 18% (6-29%); NO age-specific estimates statistically significant (small sample sizes).

B, all ages: 45% (14-65%)

VE vaccine-like variant (>6 months): 49% VE (18-69%)

VE drift variant (≥ 6 months): no significant effectiveness

Subgroup analysis of 2-17 year olds; LAIV vs. IIV (Bottom line: no better protection from LAIV against drifted virus)

LAIV: -24% (-74-11%)

IIV: 18% (-7-37%)

Medimmune update on LAIV

Hypothesis for decreased VE against A California H1N1pdm09 strain observed 2010-11 and 2013-14 in US): H1N1 strain has a heat labile HA stalk (previously not seen in LAIV vaccine strains) making the virus unstable when exposed to increased temps, normal US distribution process has multiple exposures to temp $>70^{\circ}\text{F}$; plan to replace with more stable strain. Reduced VE not seen in Canada where temps were cooler during distribution. Analysis (by MedImmune) of temps during distribution in US and Canada (Canada used trivalent formulation, US used quadravalent) consistent with distribution-temperature-related potency loss. Question related to role of quadravalent vs. trivalent not resolved.

ACIP influenza vaccine recommendations 2015-16 season

New No longer recommend preferential use of LAIV among children 2-8 years, either IIV or LAIV acceptable (preferential recommendation first made for 2014-15 season).

HPV vaccine

New formulation: 9-valent vaccine (3 dose schedule) added as option to previous recommendations for females and males. Generally similar AE profile with higher local reactions.

New guidance on timing of administration: Second dose should be administered *at least* 1-2 months after first dose (previously was 1-2 months).

Any HPV product may be used to complete the series for females if transitioning to a new product or past product is uncertain; quadra- or nine-valent vaccine should be used for males.

No guidance at this time on administration of 9-valent vaccine to persons who previously completed a series with bi- or quadravalent HPV vaccine.

Alternative schedules for HPV vaccine administration are being studied; vaccination should not be delayed awaiting guidance on alternate schedules.

Yellow fever vaccine

New: Recommendation for booster dose dropped; new guidance is a single dose recommended for most travelers (92% travelers are seropositive at 10 years post-vaccination). Additional doses recommended for:

- Women pregnant when they received their initial dose should receive one additional dose before next travel that puts them at risk for YF;
- HSCT recipients who were vaccinated prior to HSCT and who are sufficiently immunocompetent should be revaccinated prior to travel that puts them at risk for YF;
- Persons who were HV-infected when last vaccinated with YF vaccine should receive a dose every 10 years if they continue to be at risk for YF;
- High-risk settings: booster can be considered for travelers vaccinated at least 10 years ago and will be in “higher risk settings” (see ACIP guidance for examples);
- Laboratory workers who routinely handle wild-type YF virus should have YF neutralizing antibody levels measured every 10 years to determine if revaccination is needed; if unable to measure neutralizing antibodies, vaccine should be administered every ten years as long as they are at risk.



STATE OF WASHINGTON

DEPARTMENT OF HEALTH

Office of Immunization and Child Profile

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April, 2015**

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National Association of Pediatric Nurses

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STATE OF WASHINGTON
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**Vaccine Advisory Committee
Washington State Department of Health
Membership Policy
April 2015**

Policy:

Members sit on the Vaccine Advisory Committee (VAC) for a two-year term with the option to extend one more term, for a total of four years. The chair reserves the right to reappoint members for service exceeding four years if it is determined that doing so is in the best interest of the committee and is mutually agreed upon by the appointing organization and member.

Whenever possible, terms will be staggered for organizations and entities that have multiple members on the VAC to avoid multiple representatives leaving their positions simultaneously.

Additionally, the Washington State Health Officer, who chairs the committee, appoints consultants representing healthcare providers in pediatrics, family care and obstetrics. Consultants do not have defined terms of membership.

Representation:

The following professional organizations, government agencies, and entities provide representation to the VAC:

- American Indian Health Commission of Washington (1 representative)
- Internal Medicine (1 representative)
- Managed Care Organization (1 representative)
- Naturopathy (1 representative)
- Office of Superintendent of Public Instruction (1 representative)
- Public Health Seattle King County (1 representative)
- State Agency Health Care Purchasers (1 representatives)
- Washington Academy of Family Physicians (2 representatives)
- Washington State Association of Local Public Health Officials (4 representatives)
- Washington State Chapter of the American Academy of Pediatrics (2 representatives)
- Washington State Chapter of the National Association of Pediatric Nurse Practitioners (1 representative)
- Washington State Pharmacy Association (1 representative)



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Vaccine Advisory Committee Washington State Department of Health Purpose Statement October 2010

PURPOSE: To provide recommendations to the Washington State Department of Health on issues related to the use of vaccines and other medications for the public health response to infectious diseases, and for current management of vaccine-preventable diseases across a person's lifespan.

RATIONALE: Current clinical expertise and recommendations provided by healthcare providers experienced in relevant fields (vaccinology, preventive medicine, vaccine preventable disease management, pediatrics, infectious disease, epidemiology, internal medicine and family practice) will provide guidance to the Department of Health and inform the strategic implementation of vaccine usage and vaccine administration at the clinical level.

DESCRIPTION: This committee shall provide guidance and serve as an advisory body to the DOH Health Officer. Clinical issues the committee will address include such topics as vaccine supply shortages and outbreaks of vaccine-preventable disease. The committee will meet quarterly. There shall be minutes taken and provided. An agenda will be prepared prior to the meeting.

MEMBERSHIP: The State Health Officer chairs this meeting. There shall be approximately 20 members total. Of these members, there shall be no more than 15 physician members. To the extent possible, membership shall include representation from the Washington Vaccine Association (WVA) in order to facilitate communication between the VAC and the WVA. They shall represent the following clinical areas:

- Public Health
- Epidemiology
- Pediatrics
- Family Practice
- Internal Medicine
- Pharmacies
- Naturopathic Medicine

LOCATION: Meeting room in the Seattle/Tacoma area, 10:00 a.m. – 12:00 p.m.



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Vaccine Advisory Committee Conflict of Interest Policy January, 2008

In order for the Department of Health (DOH) to pursue its mission and to maintain its reputation with the public and health care providers, it is important that the decisions and actions of the Washington State Vaccine Advisory Committee (VAC) not be unduly influenced by the special interests of individual members. Accordingly, the VAC has adopted the following Conflict of Interest Policy:

Decisions made by committee members should always be based solely on the best interest of DOH and the people of Washington State. Decisions should not be influenced by personal financial interest or by other extraneous considerations. Any affiliation with an organization having fundamental goals that conflict with the DOH and VAC mission should be avoided. Any current, previous (within 2 years), or future potential conflict of interest should be disclosed at the beginning of each VAC meeting.

A potential conflict of interest exists when a committee member has a relationship or engages in any activity, or has any personal financial interest which might impair his/her independence or judgment or inappropriately influence his/her decisions or actions concerning VAC matters.

A potential conflict of interest exists and should be disclosed if the committee member:

- Has a relationship with an entity that benefits financially from the sale of vaccines, such as a consultancy, serving on a speakers bureau, receiving honoraria, research and/or travel support
- Owns a material financial interest in any business that provides or seeks to provide goods or services to the Department of Health.
- Serves as an officer or participates on the board or committees of other related professional societies that receive direct financial benefit from the sale of vaccines.
- Has an affiliation with an organization that has a financial interest in VAC recommendations.
- Has an affiliation with an organization that has a competing activity.

Each committee member has a high duty and obligation to disclose to the entire committee any potential conflict of interest and to abstain from any decision where a significant conflict of interest exists. Ultimately, it is the responsibility of the entire committee to determine what, if any, limitations on activities with regard to the committee member's conflict are required to protect the VAC.

Question 1: What are the CPT and CVX codes for HPV-9?

Answer: The CPT code is 90651 and the CVX code is 165

Question 2: Will the Gardasil Vaccine Information Statement (VIS) be updated?

Answer: We have not heard if the VIS has been updated yet, but expect it will be soon.

Question 3: Should providers use HPV 4 or HPV 9 for male patients 16-18 years of age?

Answer: HPV-9 is not licensed for males beyond age 15. Notes from the ACIP meeting indicate the recommendation will allow providers to use HPV 4 or HPV-9 for males beyond age 15. If a provider has HPV4 in stock, they may use it to vaccinate males ages 16-18.

Question 4: Will the Childhood Vaccine Program continue to supply HPV 4?

Answer: We will continue to supply HPV4 as needed. We are taking it off provider order sets to help providers manage inventory during the transition to HPV 9. We will work closely with Local Health Jurisdictions (LHJs) and providers to make sure providers do not run out of vaccine.

Question 5: How should providers manage inventory if they think a 5-day supply of vaccine is not enough to bridge while they wait for an urgent vaccine order?

Answer: Most providers have at least 45 days of HPV 4 stock on hand. Providers should monitor their inventory and usage closely. If a provider feels their inventory is low enough to warrant an urgent order, and they have more than 5 days' HPV 4 in stock, they should contact their LHJ to place an order. LHJs may also be able to facilitate a vaccine transfer from another provider to meet short-term HPV4 vaccine needs.

Question 6: Is the interval for dosing HPV 9 the same as HPV 4?

Answer: The second dose for HPV 9 is administered *at least* 1 to 2 months after the first dose, and the third dose *at least* 6 months after the first dose. As with most other vaccines, if the schedule is interrupted, the series does not need to be restarted.

Question 7: If I started the HPV vaccine series with HPV 4, do I need to finish it with HPV 4 or can I use HPV 9?

Answer: If vaccination providers do not know or do not have available the HPV vaccine product previously administered, or are in settings transitioning to HPV 9, any available HPV vaccine product may be used to continue or complete the series for females for protection against HPV 16 and 18; either HPV 9 or HPV 4 may be used to continue or complete the series for males.

<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6411a3.htm>

Provider Recommendation Practices and Perceived Barriers to Administering HPV Vaccine: Washington State, 2014

Hanna Oltean, MPH
Office of Communicable Disease Epidemiology

Vaccine Advisory Committee
April 16, 2015

Project Goals (2014-2015)

- Characterize patterns of HPV vaccine coverage and provider attitudes in WA
- Assess predictors for vaccine uptake, missed opportunities, and strong provider recommendations
- Identify areas for improvement in vaccination coverage and promotion
- Make recommendations to DOH for future interventions

HPV Vaccine Coverage in WA

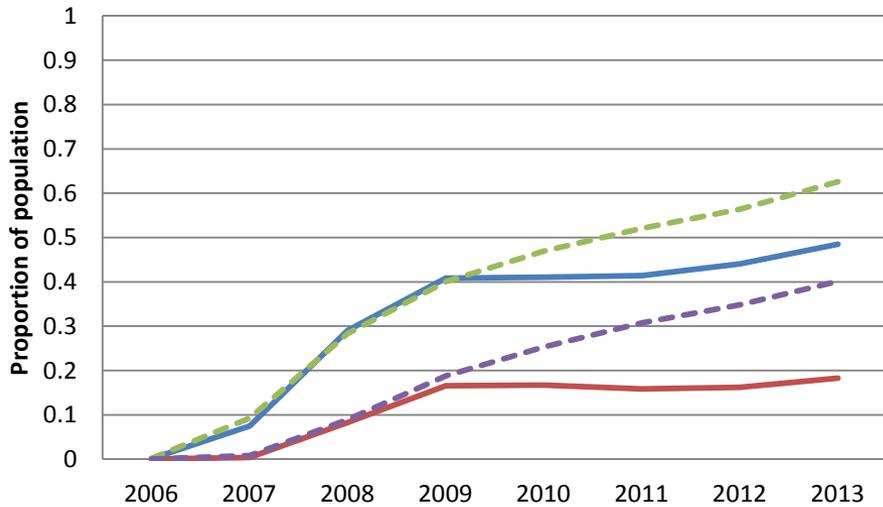
Coverage estimate comparison, NIS-teen data and IIS study data

	NIS-teen National Estimate 2013	NIS-teen WA Estimate 2013	WA IIS/Census Estimate 2013*
Female	(Ages 13-17)	(Ages 13-17)	(Ages 13-17)
≥1 dose	57.3% (±1.9)	60.7% (±9.7)	60.6%
≥2 dose	47.7% (±2.0)	52.3% (±9.9)	48.3%
≥3 dose	37.6% (±1.9)	45.3% (±9.8)	35.0%
Male			
≥1 dose	34.6% (±1.9)	29.8% (±8.0)	34.4%
≥2 dose	23.5% (±1.7)	18.0% (±6.3)	21.4%
≥3 dose	13.9% (±1.4)	12.5% (±5.2)	11.5%

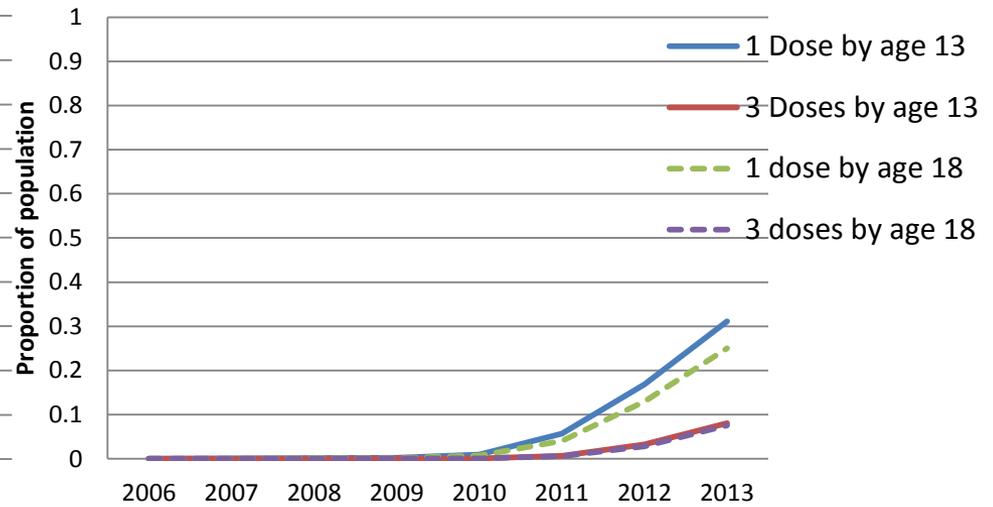
*All 95% confidence intervals for these estimates are $\pm < 0.2\%$

HPV Vaccine Coverage in WA

Females



Males



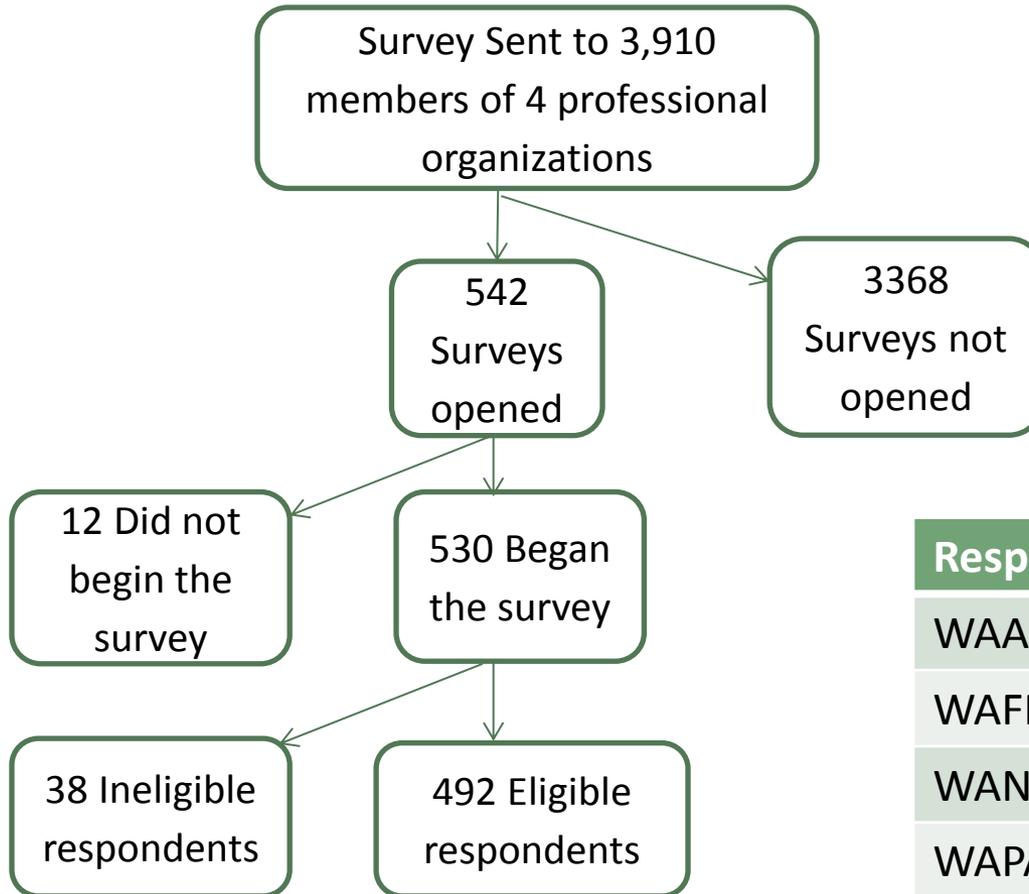
Provider Survey Overview

- Assessed:
 - Provider recommendation practices by patient age group and sex
 - Perceived barriers contributing to missed opportunities
 - Needed educational materials
 - General perception/knowledge about the HPV vaccine
 - Topics used to discuss the HPV vaccine with patients and parents
- Target population: providers in WA who provide healthcare to adolescents

Provider Survey Methods

- Distributed by email through four professional organizations:
 - Washington Chapter of the American Academy of Pediatrics (WAAP)
 - Washington Academy of Family Physicians (WAFP)
 - Washington Association of Naturopathic Physicians (WANP)
 - Washington Academy of Physician Assistants (WAPA)
- Also attempted to survey:
 - ARNPs United
 - Washington Chapter of the National Association of Pediatric Nurses
 - The American Congress of Obstetricians and Gynecologists – Washington State

Provider Survey Results



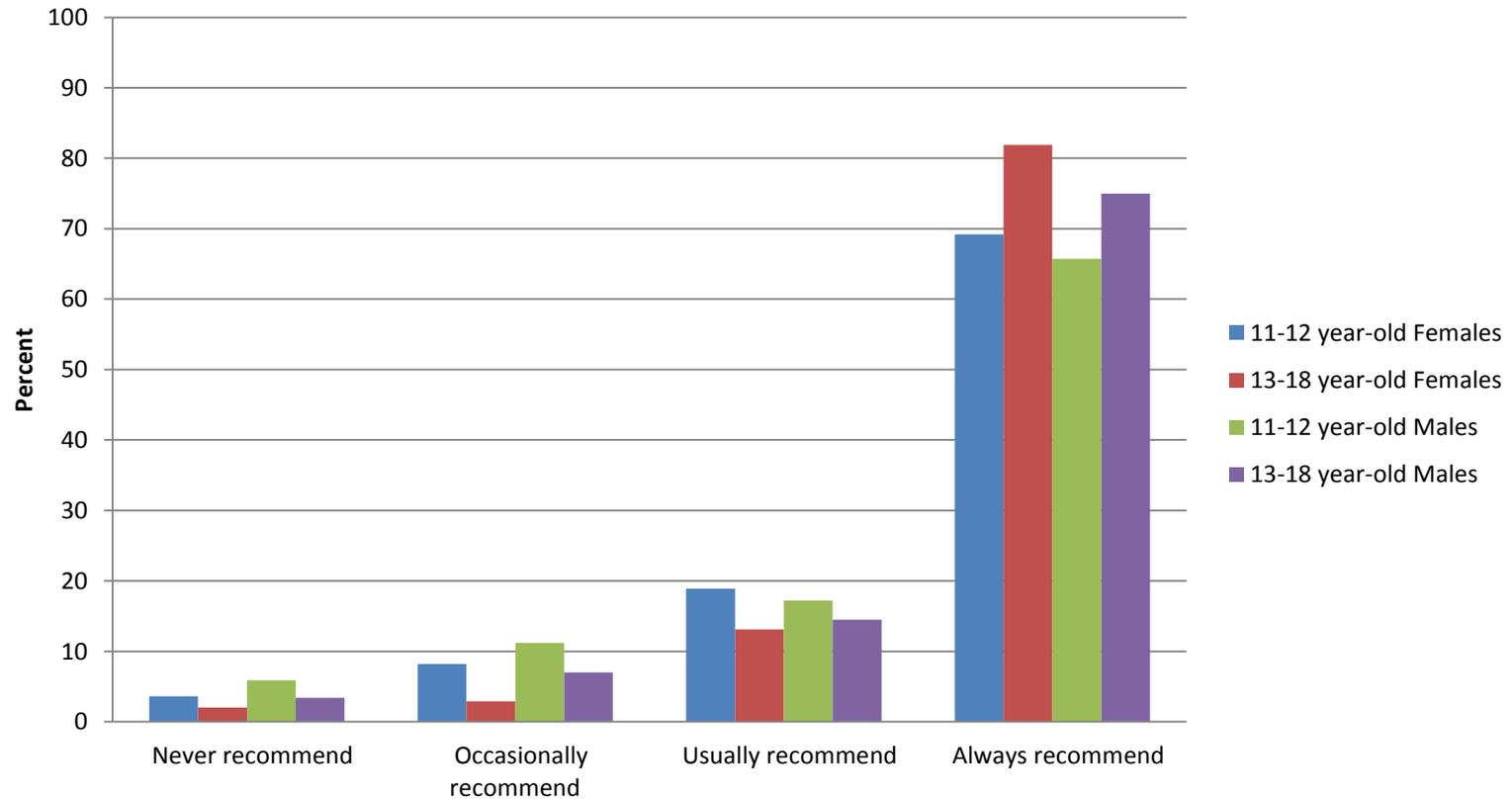
Response Rates	
WAAP	11.1%
WAFP	14.5%
WANP	10.8%
WAPA	16.1%
Overall	13.6%

Provider Survey Respondent Demographics

Type of Clinician	PA 12.2%	Family 59.4%	Naturopathic 7.3%	Pediatric 19.3%	Other 1.8%
Gender	Female 61.4%	Male 38.6%			
Age Group	<40 25.3%	40-49 23.4%	50-59 31.1%	≥60 20.1%	
Practice Setting	Rural 19.9%	Suburban 41.9%	Urban 38.2%		
Clinic Type	Private 59.0%	Public 15.7%	University 12.2%	Other 13.1%	
% patients adolescents	0-20% 67.6%	21-40% 25.4%	41-60% 5.6%	61-80% 0.5%	81-100% 0.9%
% patients no insurance	0-20% 43.4%	21-40% 24.6%	41-60% 9.4%	61-80% 12.7%	81-100% 9.9%

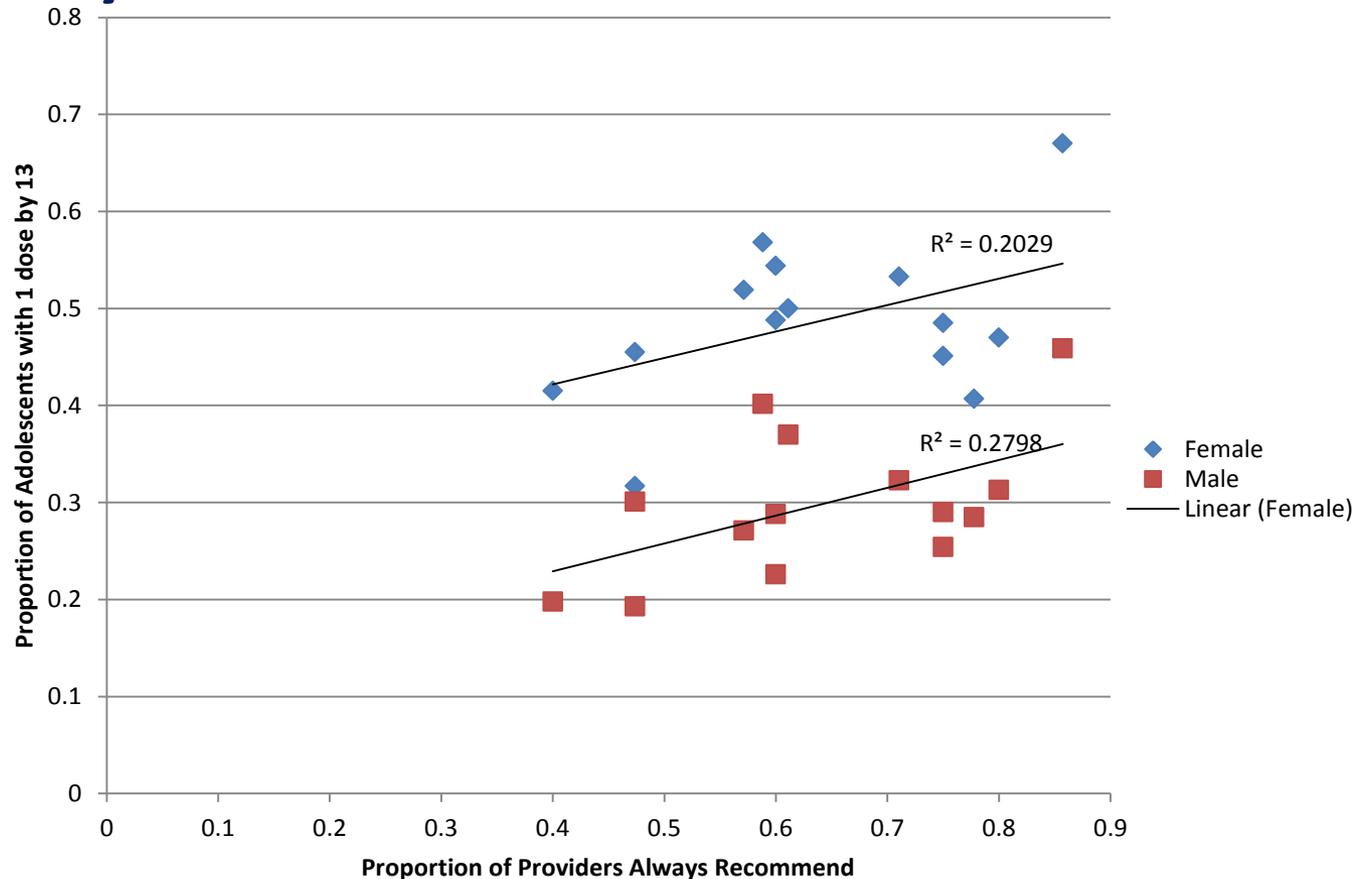
- Avg years of practice = 18 years
- Avg clinic size = 18 providers

Adolescent healthcare provider recommendations for the HPV vaccine in eligible patients



- Providers significantly more likely to recommend vaccine to females than to males and to 13-18 year-olds than 11-12 year olds (all age/gender combinations)

Proportion of county providers who always recommend HPV vaccine by proportion of county 13 year-olds with one dose HPV vaccine



Reported Barriers

- Most frequently reported barriers - perceived parent or patient concerns about the HPV vaccine:
 - Limited parental knowledge or education on HPV or HPV vaccine (75.4%)
 - Parental mistrust of vaccines in general (74.4%)
 - Parental desire to delay vaccination to a later age (67.3%)
 - Parental concerns about HPV vaccine safety or efficacy (66.5%)
 - Parental opposition to HPV vaccination for moral or religious reasons (63.8%)
 - Patient fear of pain or needles (57.5%)
 - Parental concerns that vaccination against a sexually transmitted infection may encourage earlier or riskier sexual behavior (56.3%)
- “Other”: Lack of healthcare visits at this age

Perkins RB, Clark JA. “Providers’ perceptions of parental concerns about HPV vaccination.” *Journal of Health Care for the Poor and Underserved* 2013;24(2):828-39.

- Negative perceptions of parent’s views may lead providers to decrease the strength of their recommendations
- Secondary to feelings that parents are not interested in vaccination and that providers have little ability to influence parental behavior

Educational material needed	N reporting	Easily Accessible from current DOH website?
TV/media/social media campaign	13	No
Videos	2	No
Data on safety and efficacy, including side effects	19	No
Evidence of not encouraging sexual activity	8	No
Information specific to ethnic/cultural groups, addressing their concerns, in multiple languages	7	No
Importance of early vaccination	6	No
Data on benefits	5	No
Information specific to males	3	No
Common myths	3	No
Cancer-specific information	2	No
Information about mechanism of vaccine action	1	No
Information on HPV transmission – types of contact other than intercourse	1	No
Anecdotes from cancer patients	1	No

Perception/Knowledge HPV Vaccine

	Yes, N(%)	No, N(%)	No Response N (%)
Do you believe that administering the HPV vaccine will have a positive impact on adolescents' lives?	405 (82.3)	37 (7.5)	50 (10.2)
Do you believe that HPV vaccine will decrease rates of genital warts and HPV-related cancer?	436 (88.6)	7 (1.4)	49 (10.0)
Have you received information or training within your employment site about HPV or the HPV vaccine?	243 (49.4)	200 (40.7)	49 (10.0)
Do you have either an internal or external forum to talk with other clinicians about the HPV vaccine?	241 (49.0)	202 (41.1)	49 (10.0)
Do you know the ACIP recommendations for HPV vaccine for adolescents?	390 (79.3)	37 (7.5)	65 (13.2)

Provider discussion patterns when discussing HPV vaccination with adolescents and their parents

Emphasize...	Strongly N (%)	Somewhat N (%)	Only if questioned N (%)	Do not discuss N (%)
Prevention of genital warts in the patient	150 (30.5)	193 (39.2)	74 (15.0)	11 (2.2)
Prevention of genital warts in sexual partners	81 (16.5)	197 (40.0)	120 (24.4)	29 (5.9)
Prevention of HPV-related cancer in the patient	394 (80.1)	22 (4.5)	7 (1.4)	5 (1.0)
Prevention of HPV-related cancer in sexual partners	246 (50.0)	120 (24.4)	45 (9.2)	16 (3.3)
Higher vaccine efficacy in younger patients	150 (30.5)	103 (20.9)	78 (15.9)	96 (19.5)
Importance of vaccinating before initiating any sexual activity	302 (61.4)	83 (16.9)	29 (5.9)	14 (2.9)

Univariable Logistic Regression

- Pediatricians significantly more likely to always recommend than other provider types
 - Naturopathic physicians 96% less likely to always recommend than pediatricians
- Providers aged 40 years or older were 40% less likely to always recommend than those under 40
- Providers who see more adolescents or with patient populations on public aid/no insurance more likely to always recommend

Discussion

- Limitations:
 - Poor response rate
 - Missing provider types
 - Response bias
 - Ecological analysis of one-dose coverage and proportion of county providers who report always recommending
- Strengths:
 - Large sample size
 - Varied specialties
 - Results corroborate findings from other studies
 - Assessment of patient-provider discussions

Recap

- >30% of adolescent healthcare providers report not always recommending HPV vaccination to eligible 11-12 year old patients
- Recommendations differ by patient sex and age
- All barriers with $\geq 50\%$ agreement dealt with perceived parent or patient concerns
- >60% of providers discuss HPV vaccine in the context of sexual initiation
- 20% of providers do not strongly emphasize prevention of HPV-related cancer

Conclusions

- Information useful for:
- The design/enhancement of programs aimed at increasing provider recommendations
- Understanding parent-patient-physician dynamics
- Improve educational content available

Acknowledgements

- WA DOH CD-Epi (Kathy Lofy, Chas DeBolt, Marcia Goldoft)
- WA DOH Immunizations Program
- WAAP, WAFP, WANP, WAPA
- Survey based on prior surveys created by: Matthew Daley, Jessica Kahn, Emily McCave, Jennifer Young, and Lainie Friedman Ross

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**WASHINGTON STATE VACCINE ADVISORY COMMITTEE
RECOMMENDATION AND CLINICAL GUIDANCE
FOR USE OF HUMAN PAPILLOMAVIRUS VACCINES**

As unanimously agreed upon and verified at the March 13th, 2012 meeting, the Washington State Vaccine Advisory Committee (VAC) recommends full acceptance of the Advisory Committee for Immunization Practices' (ACIP) recommendations for use of human papillomavirus (HPV) vaccine for males and females as published in MMWR 2007;56(RR02);1-24, MMWR 2010;59(20);626-629, and MMWR 2011;60(50);1705-1708.

The VAC also approves the guidance included in this document in order to assist providers at the clinic level with the specific challenges arising from fully immunizing males and females against HPV.

Summary of ACIP Recommendation

Groups

Gender and Age	Bivalent HPV Vaccine	Quadrivalent HPV vaccine	9- Valent HPV vaccine (HPV9)
Females, 9 through 26 years	Acceptable Eligible	Eligible Acceptable	Eligible
Males, 9 through 26 years	Not Eligible acceptable	Eligible Acceptable	Eligible

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Recommended Schedule

A 3-dose series for HPV vaccine is recommended for females and males at age 11 or 12 years with the following schedule: the quadrivalent HPV vaccine (for use in females and males) or the bivalent HPV vaccine (for use in females) is to be administered in a 3-dose schedule. The second dose should be administered 1 to 2 months after the first dose and the third dose should be administered 6 months after the first dose. The HPV vaccine series should be completed with the same HPV vaccine product whenever possible.

Catch-up vaccination: Vaccination is recommended for females 13 through 26 years of age and males 13 through 21 years of age who have not been previously vaccinated or who have not completed the full series.

Other vaccination: Eligible females and males as young as 9 years old may be vaccinated. Males aged 22 through 26 years may be vaccinated.

Interrupted vaccination schedule: If the vaccine schedule is interrupted for either the quadrivalent or bivalent HPV vaccine, the vaccine series does not need to be restarted.

If the series is interrupted after the first dose, the second dose should be administered as soon as possible, and the second and third doses should be separated by an interval of at least 12 weeks with a minimum interval of 24 weeks between the first and third doses. If only the third dose is delayed, it should be administered as soon as possible.

Dosage Intervals

Between 1 st and 2 nd dose	Between 2 nd and 3 rd dose	Between 1 st and 3 rd dose
4 week minimum	12 week minimum	24 week minimum

For the complete ACIP recommendations for use of bivalent and quadrivalent HPV vaccine in females and quadrivalent HPV vaccine in males, please visit:

- http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5602a1.htm?s_cid=rr5602a1_e
- http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5920a4.htm?s_cid=mm5920a4_e
- <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6050a3.htm>

Washington State Childhood Vaccine Program, Guidelines for the Use of State Supplied HPV Vaccine

Adolescents 9 years of age up to the 19th birthday:

[HPV9 \(Gardasil 9\) is licensed for females age 9 – 26 and males 9 – 15 years of age;](#)
[HPV4 \(Gardasil\) is licensed for females age 9 – 26 and males 9 – 21 years of age;](#)
[HPV2 \(Cervarix\) is licensed for females only.](#)

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HPV vaccine is routinely recommended for:

- [Adolescent females at 11 through 12 years of age \(3 dose series\).](#)
 - [HPV9 \(Gardasil 9\), HPV4 \(Gardasil\) or HPV2 \(Cervarix\) may be used for females.](#)
- [Adolescent males at 11 through 12 years of age \(3 dose series\).](#)
 - [HPV9 \(Gardasil 9\), HPV4 \(Gardasil\) may be used for males.](#)

Series Completion:

[If the type of HPV vaccine previously administered is unknown, not available, or in settings transitioning to HPV 9:](#)

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- [Any available HPV vaccine \(HPV2; HPV4 or HPV9\) may be used to continue or complete the series for females for protection against HPV 16 and 18.](#)
- [Either HPV 9 or HPV 4 may be used to continue or complete the series for males.](#)

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 Catch-up vaccination:

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- Vaccination is recommended for females and males 13 through 18 years of age who have not been previously vaccinated or who have not completed the full series.

Other permitted vaccination:

- Adolescent females and males from 9 years of age up to the 19th birthday

| <http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html>

Clinical-Level Guidance to Providers

HPV vaccination for the first dose administered to females in Washington ranks among the highest in the nation. However, at 69.3% for at least 1 dose and 45.5% for 3 doses¹, there is room for improvement. Those measurements were for female patients 13 through 17 years of age. Providers may face more challenges assuring young men are fully immunized against HPV.

Getting people in their mid-to-late teens into health care visits for a first dose of vaccine is challenging. Getting them to return for a second and third dose of vaccine in the same year will be more challenging. The VAC recommends the following minimum guidelines to support full immunization against HPV infection:

- Continue to follow ACIP guidelines and administer a first dose at 11 to 12 years of age at every opportunity.
- Establish procedures that expand efforts to vaccinate adolescents with a first dose at any age between 9 and 19 years.
- After administration of the first dose, effectively communicate the importance of completing the 3 dose series.
- Establish procedures to avoid missed immunization opportunities for teenagers and adults eligible for any dose of HPV vaccine, regardless of the purpose of their visit (e.g. school physicals, requirements to enter college).
- Implement reminder recall systems for adolescents and adults to help promote completion of the 3 dose series.

¹ 2010 National Immunization Survey, CDC

Legislative Update:

Legislative Session Started January 12.

- **Budget:** The House, Senate and Governor's budget all included Health Care Authority's request for funding to pay for vaccines for kids enrolled in the Children's Health Program, and we anticipate this being included in the final budget.
- **Legislation:**
 - SB5143: This bill, requiring the Department of Health to provide education about immunization to pregnant women, was passed out of the Senate and has been voted out of Health and Wellness Committee. This bill does not require anything new to be done by the department, and we anticipate a floor vote in the house soon.
 - HB2009: A bill to change Washington's exemption law to remove the personal belief exemption. This bill did not pass out of the House, and the department will work with stakeholders over the interim session to determine the best options for increasing immunization rates. We plan on getting input from the VAC at the July meeting.
 - ESSB 5557: This bill requires that pharmacists be reimbursed by health care plans for services rendered that address the ten core functions of health care, which includes vaccinations as a preventative measure. This bill was voted out of the Senate and Health and Wellness Committee after amendments addressing the core functions for which reimbursement is required. We anticipate a floor vote soon.

General Vaccine Supply:

- The delay in availability of DT vaccine has resolved.

Influenza Vaccine:

ACIP voted on its annual influenza vaccine recommendations for the 2015–2016 influenza season. The committee reaffirmed the need for annual vaccination for all people age 6 months and older. Based on new data, ACIP removed the previously-stated preference for the use of live attenuated influenza vaccine (LAIV, Flumist, MedImmune/AstraZeneca) in children age 2 through 8 years, noting that both LAIV and inactivated influenza vaccine (IIV) are acceptable.

HPV 9 (Gardasil 9) Vaccine Transition Planning:

We are on track to start making HPV 9 available in May. To help limit HPV 4 waste and manage the transition to HPV 9 we ask LHJs and providers to take the following steps:

1. Continue to limit HPV 4 vaccine orders to assure providers use up excess inventory of HPV 4 before they transition to HPV 9.
2. When HPV 9 is available in May – providers must order based on their EOQ schedule. LHJ and state staff will not approve off schedule orders for HPV 9.

3. Build HPV 9 safety stock slowly – add only 10% - 15% to the previous month’s usage of HPV 4 to cover the May need for HPV 9 and slowly build a safety stock margin.
4. Follow ACIP guidance for completing the vaccination series using the stock that is available.

Meningococcal B Vaccine Update:

Meningococcal B vaccines – these vaccines are not routinely recommended. The CDC indicates they will contract for only about 30,000 doses nationally. This translates to about 310 doses for Washington each year. Providers will not routinely stock this vaccine. We will implement the vaccines in May, and plan to make them available on a special order basis, similar to the way we manage Menhibrix.

Combination DTaP/IPV Vaccine Update:

The FDA licensed a new DTaP/IPV combination vaccine, Quadracel. Sanofi-pasteur makes the vaccine. We do not know its exact availability date of this vaccine. It is not available on the CDC contract at this time, and we cannot make it available until that time. We will incorporate this vaccine into our Vaccine Choice Process in **October 2015**. The CPT code for this vaccine is 90696 and the CVX code is 130.

Provider Vaccine Selection Coming Soon:

Vaccine selection process will be open from April 15 through the 30. We will send a fax notice to providers on the 15. Only providers who want to change their vaccine products need to participate. All providers wishing to make product changes must do so in the IIS. Providers who do not want to make any product changes do not need to take action. A training video and quick reference guide is available at <http://jitt-wa.stchome.com>.

School Level Data now available on DOH web page:

Each year, the Department of Health receives multiple requests for school-specific immunization data. We have historically posted state level, county level, and school district level data to our web page and have now added school level data: www.doh.wa.gov/DataandStatisticalReports/Immunization/SchoolReports. These tables are under Data Tables of School Immunization and Exemption Rates – School Level Rates heading. Data are available for kindergarten and for all grades (K-12) for school years 2011-12, 2012-13, and 2013-14 by school.

Parent Advocate Selected for 2015 CDC Immunization Champion Award:

The 2015 CDC Immunization Champion for Washington is Kathy Hennessey. Kathy is a parent advocate for childhood immunization. Kathy Hennessey is a second year parent advocate in the Immunity Community (IC) in Bellingham. She worked diligently to appeal to the Bellingham School District to implement the Immunity Community in five of its schools for the 2014-15 school year. She founded the FaceBook group "Informed Parents of Vaccinated Children" in 2011 which has grown to over 1,700 followers.

Pink Book Conference Registration Open:

The training, “Epidemiology and Prevention of Vaccine Preventable Diseases” (the “Pink Book” course) will be held at Hotel Murano in Tacoma, September 16 – 17, 2015. Registration is now open

at www.CDC2day.eventbrite.com Early bird registration is open until July 15. Scholarship information will be available shortly. There will be a pre-conference on September 15, including a provider training on HPV and making a strong recommendation to parents; a DOH presentation; and other events that will be announced.

IIS and Child Profile Transition Update:

The transition of the operations of the IIS and Child Profile from Public Health-Seattle & King County to DOH continues. The IIS help desk has transitioned to STC (the vendor that built and maintains the IIS). This is the major IIS user-facing element of the transition. Providers and other IIS users were notified by fax and by email to LHJs of this transition. We will continue to communicate with users about the features of the new help desk interface and to trouble-shoot any complications that may arise.

Staffing at DOH is continuing for IIS and IT work. The transition of these major areas of work is progressing as staff are brought onboard at DOH.

Staffing at DOH is complete for the Child Profile Health Promotion system. Contracts and major areas of this work continue to pass to DOH according to an agreed schedule.

HPV Grant Update

IACW Subcommittee

- Quarterly meetings January – October
- Chaired by Margaret Madeleine, FHCRC
- Advise on campaign
- Generate synergy and long-term cooperation

HPV Grant Update

Public Education

- Media campaign July – September
- Bid solicitation begins April
- Messages and materials approved by Task Force

HPV Grant Update

Provider Education

- Script reviewed by DOH, WSPA and AIHC
- Piloted in 3 clinics
- Yolanda Evans recruited as the provider presenter
- Online in April
- Approved for CME and CE
- Live training at Pink Book conference

HPV Grant Update

You Are the Key to HPV Cancer Prevention

Understanding the Burden of HPV Disease,
the Importance of the HPV Vaccine Recommendation,
and Communicating about HPV Vaccination

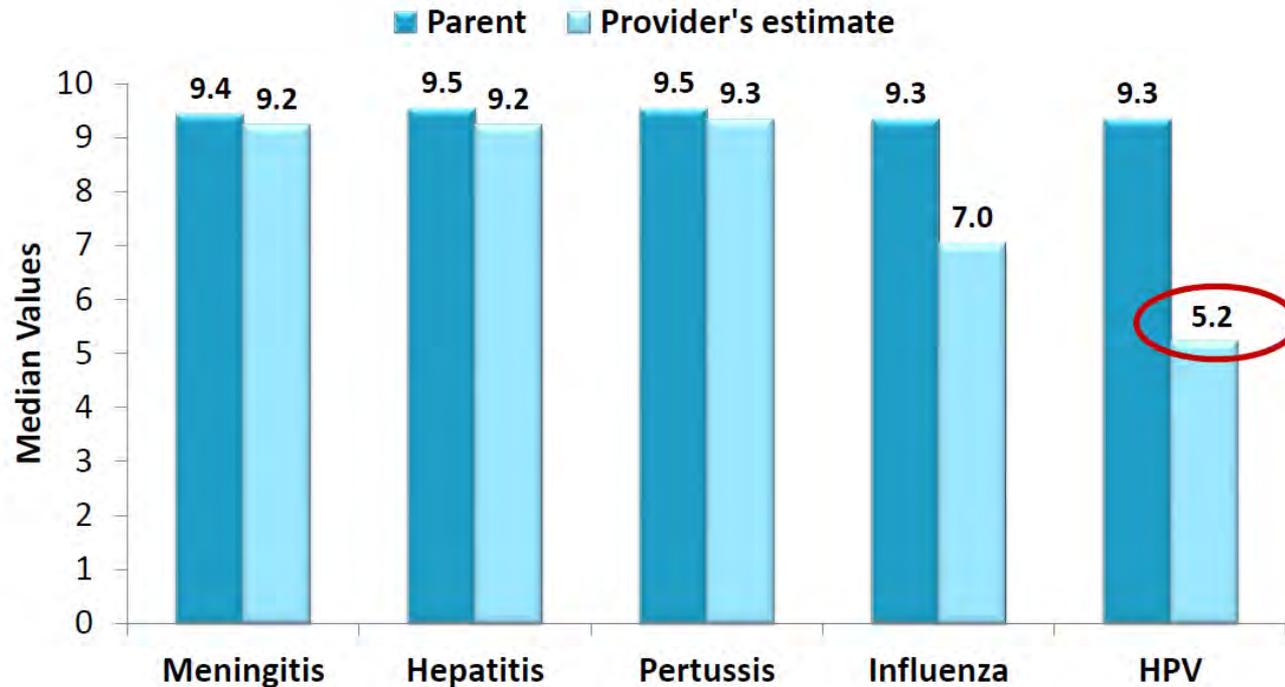
Yolanda N. Evans, MD, MPH

Member, Division of Adolescent Medicine, Seattle Children's Hospital
Assistant Professor of Pediatrics, University of WA, School of Medicine

2015

HPV Grant Update

Clinicians Underestimate the Value
Parents Place on HPV Vaccine



HPV Grant Update

Provider Feedback

- Focused AFIX visits on HPV
- CME approved
- Will compare HPV 1st dose with 1st dose of Tdap and Meningococcal
- Will include goals and strategies
- Providers invited to opt-in for further feedback
- April or May through September

HPV Grant Update

Reminder/Recall

- Rollout April (1000 card trial run)
- Will include all 11 – 18 year olds per VAC recommendation
- Reminders: 11 – 18 year olds
- Quantity still being calculated
- Recalls: 11 – 18 year olds
- 15,000 recall mailings through October

HPV Grant Update

Tweens Need Vaccines



HPV Vaccine is Cancer Prevention

HPV Grant Update

Dear Parent or Guardian,

Your 11- to 12-year-old needs three important vaccines, including one that can prevent cancer:

One dose of Tdap vaccine to protect against tetanus, diphtheria, and pertussis (whooping cough).

Two doses of meningococcal vaccine to protect against four types of meningococcal (meningitis) disease. Kids need one dose at age 11 and a booster dose at age 16 (many universities require it for admission).

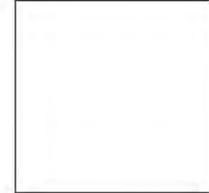
Three doses of human papillomavirus (HPV) vaccine to prevent many types of cancers. HPV vaccine is safe and effective in both boys and girls and is recommended by pediatricians and doctors.

Track your child's HPV vaccines:

Dose 1 ___ / ___	Appointment on ___ / ___
Dose 2 due ___ / ___	Appointment on ___ / ___
Dose 3 due ___ / ___	Appointment on ___ / ___

Learn about other childhood immunizations at:
www.doh.wa.gov/Immunization. Learn more about HPV at
www.doh.wa.gov/HPV#par.

Washington State Department of Health
Office of Immunization and Child Profile
310 Israel Road SE, Olympia, WA 98501



Need a doctor or other resources?

Call the Family Health Hotline at 1-800-322-2588
(711 TTY relay) or visit ParentHelp123.org.

WASHINGTON STATE VACCINE ADVISORY COMMITTEE (VAC) RECOMMENDATION FOR USE OF MENINGOCOCCAL CONJUGATE VACCINES

As unanimously agreed upon and verified at the April 18th, 24th; 2013⁴ meeting, the Washington State Vaccine Advisory Committee (VAC) recommends full acceptance of the Advisory Committee for Immunization Practices' (ACIP) recommendations for use of meningococcal conjugate vaccine as published in MMWR 2005;54(RR-7), MMWR 2011;60(3);72-76, [and MMWR 2011;60\(4\)1391-1392](#), [and MMWR 2013: 62\(3\)52-54](#).

Summary of ACIP Recommendation:

For Routine Vaccination of Persons Aged 11 Through 18 Years

ACIP recommends routine vaccination of persons with quadrivalent meningococcal conjugate vaccine at age 11 or 12 years, with a booster dose at age 16 years. After a booster dose of meningococcal conjugate vaccine, antibody titers are higher than after the first dose and are expected to protect adolescents through the period of increased risk through age 21 years. For adolescents who receive the first dose at age 13 through 15 years, a one-time booster dose should be administered, preferably at age 16 through 18 years, before the peak in increased risk. Persons who receive their first dose of meningococcal conjugate vaccine at or after age 16 years do not need a booster dose. Routine vaccination of healthy persons who are not at increased risk for exposure to *N. meningitidis* is not recommended after age 21 years.

For Persons Aged 2 Through 54 Years with Reduced Immune Response

Data indicate that the immune response to a single dose of meningococcal conjugate vaccine is not sufficient in persons with certain medical conditions. Persons with persistent complement component deficiencies (e.g., C5--C9, properdin, factor H, or factor D) or asplenia should receive a 2-dose primary series administered 2 months apart and then receive a booster dose every 5 years. Adolescents aged 11 through 18 years with HIV infection should be routinely vaccinated with a 2-dose primary series. Other persons with HIV who are vaccinated should receive a 2-dose primary series administered 2 months apart. All other persons at increased risk for meningococcal disease (e.g., microbiologists or travelers to an epidemic or highly endemic country) should receive a single dose.

For Persons under 2 Years of Age

- [Children aged 9 through 23 months with certain risk factors for meningococcal disease receive a 2-dose series of MenACWY-D, 3 months apart. This includes children who have persistent complement component deficiencies \(e.g., C5--C9, properdin, factor H, or factor D\), children who are traveling to or residents of countries where meningococcal disease is hyperendemic or epidemic, and children who are in a defined risk group during a community or institutional meningococcal outbreak.](#)
- [Infants at increased risk for meningococcal disease should be vaccinated with a 4-dose series of Hib-MenCY-TT. These include infants with recognized persistent complement pathway deficiencies and infants who have anatomic or functional asplenia including sickle cell disease. Additionally, Hib-MenCY-TT can be used in infants aged 6 weeks through 18 months who are in communities with serogroups C and Y meningococcal disease outbreaks, but Hib-MenCY-TT is not adequate for infants traveling to the Hajj or the "meningitis belt" of sub-Saharan Africa \(a quadrivalent meningococcal vaccine that contains serogroups A and W135 is required for those infants and may be given starting at age 9 months\).](#)

For the complete ACIP recommendations for meningococcal conjugate vaccine, please visit:

07/2011

<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5407a1.htm>
<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6003a3.htm>
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6040a4.htm?s_cid=mm6040a4_e%0d%0a
<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6203a3.htm>

Washington State Childhood Vaccine Program, Guidelines for the use of State Supplied Meningococcal Conjugate Vaccine

Children 11 up to the 19th birthday and children 6 months – up to the 19th birthday at high risk:*, ** ***

Adolescents age 11 up to the 19th birthday:

A single dose of meningococcal vaccine is recommended at

- 11 through 12 years of age for all adolescents.

A second dose (booster) of meningococcal vaccine is recommended at:

- Age 16 if the first dose was administered at 11-12 years of age.
- Age 16 – 18 if the first dose was administered at 13 – 15 years of age.
- **If** the first dose is administered at or after age 16, no booster dose is required.

*** MCV4 Children age 9 months up to the 19th birthday meeting the following high risk criteria:**

A one dose primary series is recommended for:

- Children 2 years up to the 19th birthday who travel to or reside in countries in which N. meningitidis is hyperendemic or epidemic, particularly if contact with the local population will be prolonged.

A two dose primary series is recommended as follows:

- Children 9 months up to the 2nd birthday who travel to or reside in countries in which N. meningitidis is hyperendemic or epidemic, particularly if contact with the local population will be prolonged
- Children who have terminal complement component deficiencies
- Children who have anatomic or functional asplenia (first dose 2 years of age or older)
- Children previously vaccinated with MPSV4 who remain at increased risk for meningococcal disease
- Children who are infected with human immunodeficiency virus (HIV)

****HibMenCY (Menhibrix) for children age 2 - 8 months of age (may be given as early as 6 weeks of age) meeting the following high risk criteria:**

- a. Persistent complement pathway deficiencies
- b. Asplenia
- c. Sickle cell disease
- d. infants in communities with outbreaks of meningitis from serogroups C and Y.

***in the event of a Hib vaccine shortage, the Washington State Department of Health may authorize the use of HibMenCY for vaccination against Hib disease.

In addition to the primary series, boosters are recommended for children at high risk. The number and spacing of these boosters varies. Please see the ACIP recommendation or ACIP Recommended Schedule.

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6003a3.htm?s_cid=mm6003a3_e%0d%0a

B. Serogroup Meningococcal Vaccines (MenB)

Eligible groups

- Children aged 10 through 18 years at increased risk for meningococcal disease attributable to serogroup B, including:

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- o Children who have persistent complement component deficiencies (including inherited or chronic deficiencies in C3, C5-C9, properdin, factor H, or factor D or taking eculizumab [Soliris®])
- o Children who have anatomic or functional asplenia, including sickle cell disease,
- o Children identified to be at increased risk because of a meningococcal disease outbreak attributable to serogroup B

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Recommended Vaccination Schedule and Intervals

<u>Age Group</u>	<u>Vaccine</u>	<u>Routine Recommendations</u>	<u>Dosing Schedule</u>
<u>10-18 years</u>	<u>MenB (Bexsero®, Novartis)</u>	<u>High-risk only</u>	<u>Two doses, at least one month apart (0 and 1-6 month schedule)</u>
<u>10-18 years</u>	<u>MenB (Trumenba®, Pfizer)</u>	<u>High-risk only</u>	<u>Three doses (0, 2, and 6 month schedule)</u>

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Note: Use of brand names is not meant to preclude the use of other meningococcal vaccines where appropriate.

Recommended dosage

Refer to product package inserts.

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Contraindications and Precautions

Contraindications and Precautions can be found in the package inserts available at <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833>

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Clinical-Level Guidance to Providers:

Persons Aged 11 Through 18 Years: Meningococcal vaccination rates are not as high as hoped for in the United States and Washington State in no exception. Getting persons in their mid-to-late teens to return for a second dose will be just as challenging. The VAC recommends the following minimum guidelines:

- Continue to follow ACIP guidelines and administer a first dose at 11 to 12 years of age when possible but catch up immunization can be done at any time prior to 19 years of age.
- When administering the first dose before 16 years of age, communicate the importance of a second dose for optimal protection.
- Establish procedures to avoid missed immunization opportunities for teenagers eligible for a first or second dose of meningococcal vaccine, regardless of the purpose of their visit (e.g. school physicals, requirements to enter college).

Persons Under 2 Years of Age:

-



PUBLIC HEALTH

**ALWAYS WORKING FOR A SAFER AND
HEALTHIER WASHINGTON**

Childhood Vaccine Supply Update

Vaccine Advisory Committee

April 16, 2015

Meningococcal B Vaccine

- FDA licensure:
 - 10/29/14: Trumenba – Pfizer Pharmaceuticals
 - 1/23/15: Bexsero – Novartis Vaccines
- 2/26/2015: ACIP vote
- 2/26/2015: VFC Resolution
- 3/27/15: MMWR Publication
- 4/1/18: CDC Contract

Defined High Risk Groups

- Persistent complement component deficiencies
- Anatomic or functional asplenia
- Microbiologists routinely exposed to *N. meningitidis*
- Serogroup B outbreak

Meningococcal B Vaccines at a Glance

Characteristic	Bexsero	Trumenba
Manufacturer	Novartis Vaccines	Wyeth Pharmaceuticals
CPT / CVX Codes	90620 / 163	90621 / 162
Age indication	10 through 25 years	10 through 25 years
ACIP – Eligibility	<ul style="list-style-type: none"> High risk only (see definition) 	High risk only (see definition)
Schedule	Two doses, at least one month apart (0 and 1 – 6 month schedule)	Three doses (0,2, and 6 month schedule)
Storage	Store refrigerated, at 36°F to 46°F (2°C to 8°C).	Store refrigerated, at 36°F to 46°F (2°C to 8°C).

Estimated Supply - Children

- CDC will supply vaccine for high risk only
- CDC estimates 30,000 doses nationally (<19, high risk)
- Outbreak response: will be managed outside of these allocations
- Private purchase: some colleges / universities

Ordering Strategy

Meningococcal B vaccines will not be available for routine ordering due to limited supply.

We will work with CDC on outbreak responses as needed

Providers can order directly from the state as needed for high risk patients:

- The provider may order single doses of this vaccine to complete the series for a child.
- The vaccine will be shipped from the distributor in a zip locked baggie with a photocopy of the prescribing information.

Contact information for state staff to assist with order placement:

- Phone: Office of Immunization and Child Profile: 360-236-3595 (ask to speak to a member of the vaccine management team about ordering vaccine).
- E-mail: WAChildhoodVaccine@doh.wa.gov



Meningococcal B Vaccine

- Discussion
- Vote

HPV 9 Valent Vaccine

- Merck Vaccines
- Gardasil 9 (trade name)
- HPV 4 existing strains: 16, 18, 6 and 11
 - 70% of cervical cancers
- New strains (5): 31, 33, 45, 52, and 58.
 - 20% of cervical cancers
 - 97% effective

HPV 9 Valent Vaccine

- 12/14: FDA licensure
 - Females 9 to 26 years
 - Males 9 to 15 years
- CPT Code 90651 / CVX Code 165
- 2/15 ACIP
 - – June 2015
- 3/27/15: MMWR published
- 4/01/15: CDC Contract

HPV 9 Valent Vaccine

- 11 – 12 years of age
- 3 dose series
 - 0
 - at least 1 – 2 months
 - at least 6 months after the first dose.
- Females: HPV 2 (Cervarix) HPV 4 (Gardasil 4) or HPV 9 (Gardasil 9)
- Males: HPV 4 (Gardasil 4) or HPV 9 (Gardasil 9)

HPV 4 & 9 Vaccines at a Glance

Characteristic	Gardasil 9	Gardasil 4
Manufacturer	Merck Vaccines	Merck Vaccines
CPT / CVX Codes	90651 / 165	90649 / 62
Age - licensure	Females: 9 – 26 Males: 9 – 15	Females: 9 – 26 Males: 9 – 23
ACIP – Eligibility	Females: 9 – 26 Males: 9 – 23	Females: 9 – 26 Males: 9 – 23
Schedule	11 – 12 Female / Male 3 doses 0, 2, 6 months	11 – 12 Female / Male 3 doses 0, 2, 6 months
Storage	Store refrigerated, at 36°F to 46°F (2°C to 8°C).	Store refrigerated, at 36°F to 46°F (2°C to 8°C).

HPV Vaccine Interchangeability

- If the type of HPV vaccine previously administered is unknown, not available, or in settings transitioning to HPV 9:
- Any available HPV vaccine (HPV2; HPV4 or HPV9) may be used to continue or complete the series for females for protection against HPV 16 and 18.
- Either HPV 9 or HPV 4 may be used to continue or complete the series for males.
- <http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html>

HPV Vaccine Transition Management

- Continue to limit HPV 4 vaccine orders.
- When HPV 9 is available in May – providers must order based on their EOQ schedule.
- Build HPV 9 safety stock slowly – add only 10% - 15% to the previous month's usage of HPV 4 to cover the May need for HPV 9 and slowly build a safety stock margin.
- Follow ACIP guidance for completing the vaccination series using the stock that is available



HPV 9 Vaccine

- Discussion
- Vote

HPV 9-Valent

ACIP Slides – October 2013:

<http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-oct-2013/03-HPV-Luxembourg.pdf>

Prescribing Information:

<http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf>



PUBLIC HEALTH

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HEALTHIER WASHINGTON**

Remember, cover your cough, wash your hands, and get vaccinated!

Reminder Recall Strategies in the Washington State Immunization Information System (IIS)

The Reminder/Recall feature in the Washington State Immunization Information System (IIS) offers you a remarkable way to monitor your patients' immunization records. If you are new to the Reminder/Recall feature, it is important to know the feature requires a permission on an IIS user account. If you have the permission, you will see the choice, Reminder/Recall, on the IIS navigation menu on the left side of the IIS screen. Two permissions are needed to fully access the feature: **Run Reminder/Recall** and **Manage Reminder/Recall**.

The feature allows you to create Reminder/Recall reports that show you which patients are overdue for immunizations and which patients are coming due. You can set dates into the future to plan for vaccine needed for flu season or back-to-school vaccines and send reminder notices to avoid a rush of patients coming in at one time. You can now define a cohort of patients you may want to review multiple times over a set date range.

The registry's Reminder/Recall feature offers you one or more **outputs** or results. These include:

- Generate a Patient List, can be used as a telephone calling list
- Print **Avery 5160** Mailing Labels
- Print **Avery 8387** Postcards
- Print Custom Postcards
- Print Letters
- Generate Autodialer Content, connects to a subscription service like Televoxx
- Generate Mail-Merge Content
- Create Email Reminder List, requires email address on a patient's demographic screen
- Save Group as a Cohort

The Reminder/Recall feature does not yet offer a text messaging option. The outputs identified are completed by your office, not completed by the IIS.

Reminder/Recall has been updated to offer two different ways to generate a result:

- By Ownership – Recommended, especially if a health care organization is an “owning” organization or medical home
- By Service – Suggested for organizations like community pharmacies or other organizations that have opted to not take ownership of patients

The IIS Help Desk can help explain the difference in those strategies.

Getting Ready to Run Reminder/Recall

Take these steps to prepare to run Reminder/Recall reports. You may be just starting to run Reminder/Recall for the first time or you may have practiced several times. To start from the beginning with clear reports:

1. Find the word, **Settings**, on the navigation menu on the left side of the registry screen. Click on **Personal**. Check your settings for **User Preferences**. Look for the words, **Increment Recall Count**. Make sure the Status displays, **Unchecked**. If it displays **Checked**, click on the word, “Update” at the bottom of the screen. Uncheck the box, and save your changes. Your screen will display the word, **Unchecked**, in the Status column. (Figure 1 below)

Figure 1: Personal Settings – User Preferences

WASHINGTON STATE IMMUNIZATION INFORMATION SYSTEM
Every age. Every vaccination.

Logged in: MARGO HARRIS
Organization (IRMS): 1-WASHINGTON STATE IMMUNIZATION INFORMATION SYSTEM (1033)
Date: November 26, 2014

Personal Settings

Update Contact Information

Street: 401 FIFTH AVENUE STE 900
City: SEATTLE
State: WASHINGTON
Zip Code: 98104
County: KING
Work Phone: (206)263-8326
Email: MARGO.HARRIS@KINGCOUNTY.GOV

Update

+ Patient Defaults

+ Vaccination Defaults

+ Anatomical Injection Site Defaults

+ Lot Defaults

+ VIS Publication Date Defaults

+ Vaccine Default Volume

- User Preferences

Feature	Status
Always use defaults on patient edit	Disabled
Default Patient Search Version	Simple
Default Patient Search Field	First Name
Automatic City / State / Zip Code / County Population	Enabled
Use Arrow Navigation on Vaccination View/Add screen	Enabled
Vaccine List Sort Order	Expiration Date
Default Application	Standard
Default Demographic Screen	IWeb Demographic
Set Low Inventory Quantity For Orders	0
Increment Recall Count	Unchecked
DTT Decrement Vaccine Inventory Default	Unchecked
Default Reminder/Recall screen	Advanced
Maximum Recall Tries	5

Update

2. Find the word, **Reports**, on the navigation menu on the left side of the registry screen. Select the **Report Module** (Figure 2) and locate the report, **Recall for Inactivation**. The result on this report should display “0” patients, unless you have a very formal Reminder/Recall process in place and you are actively monitoring this report. When you are practicing and learning about Reminder/Recall, you want to start with **NO** patients listed on this report.

3. If you do have patient names displayed on the **Recall for Inactivation** report and you want to reset this report (remove those patients from the report), please contact the IIS Help Desk – 800/325-5599 - to clear the results on this report.
4. You may notice a report, **Reminder/Recall Success**, in the Report Module. This may be a useful report for you to use in the future, once you have used the Reminder/Recall feature for some time **AND** you have incremented (counted) the results for your patients. IIS staff can help explain how this report will work for you in the future.

Figure 2: Report Module



Review the Reminder/Recall Screen (Figure 3)

Select the **Reminder Recall** link on the navigation menu on the left side of the registry screen. Reminder/Recall is a permission in the IIS. If you do not have Reminder/Recall listed on your navigation menu, contact the IIS Help Desk. The first time you look at the Reminder/Recall screen in the IIS, it may seem overwhelming. The IIS offers you an **Advanced** screen option (Figure 3 below) or a **Simple** version. Click back and forth on the options to review the differences. The IIS recommends a default setting for the **Advanced** option, but the **Simple** version may be just right for a smaller provider. Contact the Help Desk if you would like to know more about the two options.

In the current version, you can make a number of choices for the “Due Date Timeframe.” (Figure 4 below) In the past, this was called, “Reminder Recall Date Range.” Choosing “Custom” from the dropdown list sets the previous conditions, a default range of

1/1/1990 – the current date. Keep in mind that whatever choice you make, the choice links to the forecast displaying on the patients owned at your medical organization or patients to whom you provided service, if you are using the By Service option. For example, if you choose “Due Now,” the records on your Reminder/Recall result will display patients who have one or more vaccines that are indicating the vaccines are now due on their forecast in IIS during the Due Date timeframe.

Figure 3: Reminder/Recall Screen

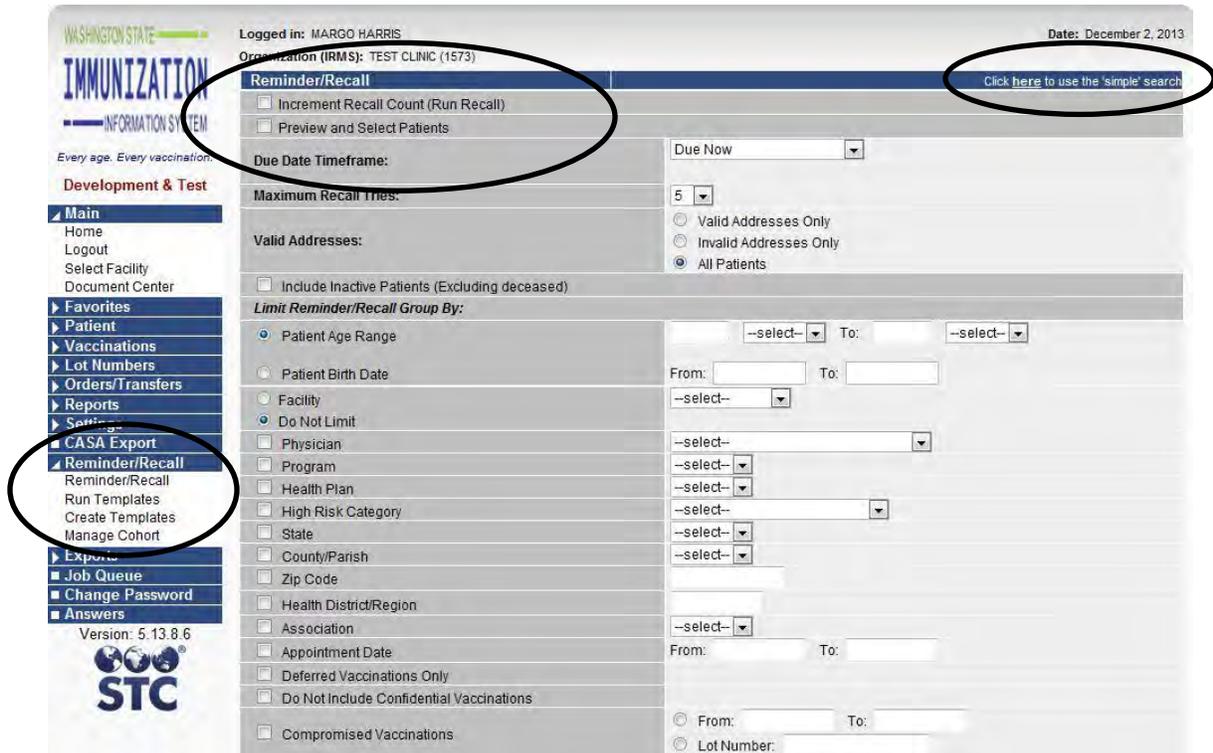
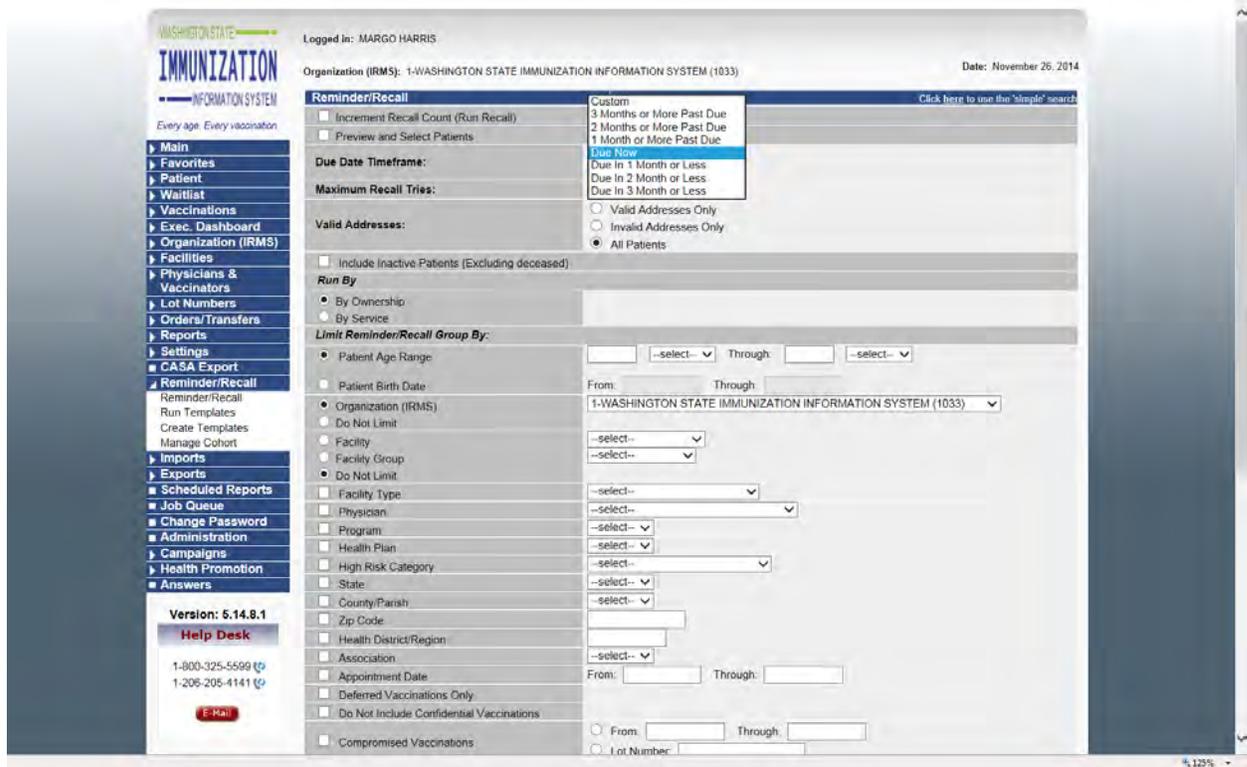


Figure 4: Reminder/Recall Due Date Timeframe



Define Your Reminder/Recall Criteria

You may want to print out the Reminder/Recall screen from your computer and take some notes as you think through what criteria will make your Reminder/Recall results or output a success for your clinic. Ask yourself some of these questions.

1. What age range is a good starting point for your report? If the Local Health Department is coming to visit soon, and they plan to assess the immunization records of your patients who are 24 – 35 months of age, that would be a good age range to begin with. An adolescent age range may also be a good starting point, considering the school requirement for Tdap and CDC’s increasing emphasis on adolescent immunization rates.
2. Does your clinic have a policy or priority for recall that you want to implement? You may want to generate a Coverage Rate Report in the IIS to inform the prioritization of recall groups.
3. What is a manageable number of records for you to work on at the start? You may want to use a recall timeframe of “three months or more past due” to get a start on the process. You don’t want to “drown” in the results you get as you learn to use Reminder/Recall. Select “Custom” and limit the Due Date Timeframe to limit the number of records in your results.

4. What are the important vaccines to choose for assessment? If you want to match the Local Health Department assessment for 24 – 35 month old patients, you want to find:

4 DTaP	3 Hib
3 Hep B	1 Varicella
1 MMR	4 PCV
3 IPV	

You may want to look at only one vaccine, e.g. DTaP, and only one dose such as the 4th dose of DTaP. The 4th DTaP is one of the most frequently missing vaccines in registry records. The Vaccine Family section offers many vaccines and doses to choose from. The Coverage Rate Report may give you additional information to help make this decision.

Note: It is possible to use Reminder/Recall for any age patient group and any single vaccine or series of vaccines.

Take a Look at an Example and Run Your Report

Click on the **Reminder/Recall** link on the navigation menu on the left side of the registry screen to find the Reminder/Recall screen. We will separate the Reminder/Recall screen into two parts:

Part 1 – includes the Due Date Timeframe, the Patient Age Range **OR** the Patient Birth Date Range, and your selection of a Facility if needed. This version of Reminder/Recall defaults to the Patient Age Range choice. You can change the radio button to Patient Birth Date Range if you prefer that version.

Part 2 – includes the Vaccine Families and Optional Needed Dose Number.

Part 1 – In the screenshot below (Figure 5), I have:

- Verified that the top box is **unchecked**, “Increment Recall Count (Run Recall)”
- Set a Due Date Timeframe
- Set a Patient Age Range **OR** Patient Birth Date range that covers patients who are two years old at the time I am running this report (Note: CDC defines a 2 year old patient as a patient who is 24 – 35 months of age “as of” a date in time.)
- Verified that my clinic location or Facility is displayed

There are other features I can use on this part of the Reminder/Recall screen, but those are the key data fields to complete when you are just starting to use the Reminder/Recall feature.

Figure 5: Reminder/Recall Detail

Washington State IMMUNIZATION INFORMATION SYSTEM
 Logged in: MARGO HARRIS Organization (IRMS): TEST CLINIC (1573) Date: December 2, 2013

Reminder/Recall [Click here to use the 'simple' search](#)

Increment Recall Count (Run Recall)
 Preview and Select Patients

Due Date Timeframe: 3 Months or More Past Due

Maximum Recall Tries: 5

Valid Addresses:
 Valid Addresses Only
 Invalid Addresses Only
 All Patients

Include Inactive Patients (Excluding deceased)

Limit Reminder/Recall Group By:
 Patient Age Range 24 Months To: 35 Months
 Patient Birth Date From: To:
 Facility TEST CLINIC
 Do Not Limit

Part 2 – In the screen shot below (Figure 6), I have:

- Selected or checked the vaccines of most interest to me and/or my Local Health Department. (You can leave all vaccines selected, and the IIS will report only the ages appropriate for the patients selected.)
- Unchecked the vaccines I do not wish to include in the Reminder/Recall Report
- Not indicated any specific dose numbers. I can go back and do that later if I want more specific information.

Figure 6: Reminder/Recall Vaccine Selection

Vaccine Families:	and Optional Needed Dose Number:
<input checked="" type="checkbox"/> DTaP/DT/Td	<input type="text"/>
<input checked="" type="checkbox"/> HIB	<input type="text"/>
<input checked="" type="checkbox"/> POLIO	<input type="text"/>
<input checked="" type="checkbox"/> HEP-B 3 DOSE	<input type="text"/>
<input checked="" type="checkbox"/> MMR	<input type="text"/>
<input checked="" type="checkbox"/> VARICELLA	<input type="text"/>
<input type="checkbox"/> MENINGOCOCCAL	<input type="text"/>
<input type="checkbox"/> HEP-A	<input type="text"/>
<input type="checkbox"/> FLU	<input type="text"/>
<input checked="" type="checkbox"/> PNEUMO (PCV)	<input type="text"/>
<input type="checkbox"/> PNEUMO (PPSV)	<input type="text"/>
<input type="checkbox"/> ROTAVIRUS	<input type="text"/>
<input type="checkbox"/> HPV	<input type="text"/>
<input type="checkbox"/> HERPES ZOSTER	<input type="text"/>
<input type="checkbox"/> Tdap	<input type="text"/>

* DTaP or DT should be given to patients under 7 years of age. One dose of Tdap should be administered to underimmunized children 7 years of age and older or as a booster dose. Td should be administered when appropriate.
 ** If an adolescent has already begun the routine 3 dose Hep-B schedule, they should not be changed to the 2 dose schedule.

Notice the bottom of the screen where you see three buttons:

- Clear
- Run Reminder/Recall
- Schedule

If you do not see the Schedule button on your screen, contact the IIS Help Desk and ask for the UFM permission to be added to your account. The UFM or User Feedback Module allows you to schedule reports like Reminder/Recall after hours, when IIS usage is lower.

I am now ready to click the **Run Reminder Recall** button to create my report. This report may take a minute or two to run depending on the number of patients you have, the recall date range, and/or the birth date range you select. When the report is completed, you arrive at the screen below:



These are the output types mentioned at the beginning of this document. You learn the number of patients in your recall group, and the number of patients with valid addresses. If you select an output option that utilizes addresses, no patients with invalid addresses will be included. For instance, your results may indicate, “There are 15 patients in your recall group. There are 12 patients with valid addresses in your recall group.” If you select Print Avery 5160 labels, you will see only 12 labels generated.

You may want to use one or more of the available output types. The IIS is set to display the address that your office entered into the IIS, whether you manually entered data or sent data via an EHR or data file.

Additional Reminder/Recall Features

This document covers the basic Reminder/Recall Report process. The Reminder/Recall feature offers you and your clinic much more.

- Cohorts – You will find advanced features in Reminder/Recall to Create Templates, Manage Templates, and Create Cohorts. Check the “Answers” feature on the Navigation menu to learn more about this advanced Reminder/Recall feature. This feature is particularly helpful if you define a cohort of patients you plan to review on a regular or continuing basis.
- If you use the Deferral feature for a vaccine that may be in short supply or out of stock, you can run Reminder/Recall specific to that vaccine once the vaccine supply is restored. The Deferral feature is a good tool to use whenever you have a vaccine shortage.
- If you have a number of families or patients who have refused all or some vaccines, and you do not want those patients included in your Reminder/Recall results, it is possible to block patients from inclusion in those results. This is a manual process, which involves setting the “Block Recall” feature on the patient’s Demographic screen in the registry.
- If you set the “High Risk Categories” on your patient demographic records, you can run Reminder/Recall specific to High Risk patients. There are seven high risk categories you can set: asthma, cochlear implant, diabetes, immunosuppression, perinatal hepatitis B risk, RSV, and sickle cell disease.

Experiment with the advanced Reminder/Recall features to develop a strategy that works best for your practice.

Note: Recall reports are designed to identify patients past due or coming due. **Reminder** reports are designed to identify patients who will come due at some future time. You can actually combine those two features by setting a Reminder/Recall Due Date Timeframe that goes back several months/years in the “From” box, and setting a future date in the “To” box.

Plan for a Formal Reminder/Recall Process

If you are just starting to use Reminder/Recall or if you have used the feature for some time, it may be time to consider a formal Reminder/Recall process for your medical organization. The IIS is built to customize that process. You can:

1. Establish a timed basis to conduct reminder recall, such as monthly, quarterly, once or twice/year. Once your process is in place, you will check the box to “Increment Recall Count.”
2. Determine the number of recall attempts you want to make before you decide a patient is no longer coming to your practice or clinic for care.
3. Create a policy for inactivation of patients. If you have recalled a patient five times, and the patient does not come in for care that may be the determinant for inactivation. If your Reminder/Recall address labels show that your patient has

- moved out of the area or out of state that may be the determinant for inactivation. Your goal should be to remind or recall patients who truly are your patients, not those patients who no longer come to you for care.
4. Review the various Reminder/Recall outputs, and determine which one or more outputs work for your practice. Is email the best choice? Do telephone calls work well? Patients or their parents may have a reminder preference that motivates them to act by making an appointment and getting patient immunizations up-to-date. You may increase the success of your Reminder/Recall process if you use more than one output and focus on a patient or parent's preferred contact method.

Reminder/Recall Support

The IIS Help Desk is always ready to help you create a successful Reminder/Recall Output. Contact the Help Desk - 800/325-5599 – IIS staff can walk you through the Reminder/Recall process and answer any of your questions.



DOH 348-266 December 2014

Should a Local Health Jurisdiction (LHJ) enter an online order on behalf of a provider?

The LHJ should not enter vaccine orders in the IIS for providers except in rare cases when a provider has no internet access to place their own orders. The LHJ is responsible for the accuracy of the information entered into the system.

How does the provider's delivery information get verified?

We now have the ability to update VTrckS (the CDC's ordering system) through a download from the Immunization Information System (IIS). If a provider changes their delivery information on the order form in the WA IIS it will be automatically updated in VTrckS when the order is submitted.

How will the State make sure the right amount of vaccine is ordered in the system?

The provider is responsible for correctly entering the order. We have some additional quality assurance checks in the IIS that will help you know if you make a mistake. LHJs are responsible for reviewing and approving the accuracy and appropriateness of each order in the system. We've developed a decision tree for handling mistakes. If you make repeated ordering mistakes, additional training and a corrective action plan may be required before you can submit future vaccine orders. You may also be required to pay for vaccines that expire or spoil due to ordering mistakes.

How can I minimize ordering mistakes?

1. Always verify that the correct shipping information is included on every order. Shipping information includes:
 - Shipping Address – Contact your LHJ immediately if your delivery address changes or is incorrect. DO NOT order vaccine until the address is corrected.

- Contact Name – This is your primary vaccine coordinator, not necessarily the person submitting the order.
 - Shipping Days and Times – These should be your core business hours and should not change often. These should be the days of the week and times during each day that the office will be open and able to receive vaccine deliveries.
 - If your office will be closed, be sure to uncheck the boxes for the days the office is scheduled to be closed.
 - Shipping Instructions – Include any special instructions for the delivery driver. (For example: “Closed 12-1 for lunch”, “Deliver to receptionist”, etc.)
2. Double check your vaccine order entries before you click the Submit button:
- Are doses used last month and physical inventory entered for every vaccine on the order form?
 - Are you ordering the correct vaccines?
 - Is the order quantity for each vaccine within recommended order quantity guidelines?

What should I do if I realize there is a mistake on my online order?

Contact your LHJ immediately if you discover an entry error has occurred.

What happens if the delivery information is incorrect on my online order?

Shipping information errors could lead to missed deliveries. Missed deliveries are returned to the distributor.

- If the delivery is for vaccines shipped by McKesson (most vaccines), McKesson contacts the State for corrected shipping information and reships the vaccines.
- If the delivery is for vaccines shipped by Merck (frozen vaccines), Merck does not contact the State and vaccines are not automatically reshipped. You may not be aware of the missed delivery until the shipment doesn’t arrive within the expected 15 days. Contact your LHJ if a delivery is late.

What happens if I order too much vaccine?

If you order too much vaccine you should keep the amount that can be stored and used by the expiration date. Contact your LHJ for approval to transfer the excess vaccine to another provider. If the vaccine cannot be transferred locally, the LHJ should contact the State to see if it can be transferred to another provider within the state. If you make repeated ordering mistakes, additional training and a corrective action plan may be required before you can submit future vaccine orders. You may also be required to pay for vaccines that expire or spoil due to ordering mistakes.

What happens if I order the wrong vaccine?

If you order a vaccine that is not used by your practice, contact your LHJ for approval to transfer the vaccine to another provider. If the vaccine cannot be transferred locally, the LHJ should contact the State to see if it can be transferred to another provider within the state. If you make repeated ordering mistakes, additional training and a corrective action plan may be required before you can submit future vaccine orders. You may also be required to pay for vaccines that expire or spoil due to ordering mistakes.

What happens if I order too little vaccine?

If you order too little vaccine and do not have enough vaccine to meet demand before your next order, contact your LHJ for approval to place a supplemental off-schedule order. If you make repeated ordering mistakes, additional training and a corrective action plan may be required before you can submit future vaccine orders.

I want to submit my vaccine orders online. How do I get started?

Contact your LHJ to receive training and to be sure your user account is set up for online ordering in the system. To learn more about online ordering check out the training videos and guides at: <http://jitt-wa.stchome.com>

Where can I get help with online vaccine ordering?

Contact your LHJ with online ordering questions. Contact the WA IIS Help Desk at 1-800-325-5599 for help with technical problems. For a refresher on how to order online, access the training videos and guides at: <http://iitt-wa.stchome.com/>

Do I still need to enter my doses used and physical inventory if I enter my order online?

Doses used last month and physical inventory counts are required for all vaccines listed on the order form with every vaccine order.

How can I be sure I'm ordering the right amount of vaccine?

Calculating an appropriate order quantity is very important. It helps to ensure that you don't run out of vaccine and helps to keep the amount of expired vaccine low. Use the Recommended Order Quantity Calculator to assist you in determining how much vaccine to order. The State does not require you to use the calculator. Your LHJ may request that you use the calculator as a guideline before entering your order in the system. Access the calculator at: [Economic Order Quantity :: Washington State Dept. of Health](#)

We are working on a recommended order quantity calculator within the IIS. When it is turned on, you will see a recommended order quantity for each vaccine on your order form after you enter the doses used and physical inventory counts.

How does my local health jurisdiction know that I've submitted an online vaccine order?

We recommend that LHJs establish a set schedule during their assigned ordering period to check the system for orders. LHJs may request that providers contact them by phone or email if they submit an off-schedule or urgent order.

Assessment, Feedback, Incentives & Exchange (AFIX)

What is AFIX?

AFIX is a quality improvement process for clinics who want to learn about and improve their immunization practices and rates.

Assessment

AFIX assessments look at whether your patients, 24-35 months old and/or 13-18 years old are up-to-date with recommended vaccines. We pull your clinic's data from the Washington State Immunization Information System (IIS) and analyze it with software called CoCASA. This allows us to show you the immunization rates for your clinic.

Feedback

During your feedback visit you get reports showing your immunization rates, we discuss your clinic's immunization practices, and identify your strengths and opportunities for improvement. Site visit staff can work with you to set and create a plan to meet your clinic's immunization goals.

How will participating in AFIX benefit my clinic?

AFIX can help improve your:

- Immunization coverage rates.
- Immunization workflow and services.
- Immunization knowledge.

How can you start improving your immunization rates?

Completing the following steps can improve your immunization rates and the quality and completeness of your clinic's data in the IIS.

Complete immunization records

CoCASA looks at the immunizations recorded for your patients. If immunizations are missing from a patient's record in the IIS, CoCASA shows that the patient is not up-to-date.

Example of how to add missing or historical immunizations in the IIS:

Run the IIS Reminder/Recall Report for your 24 month – 35 month old patients. Look at the report and identify any immunizations that are past due. If any of the past due immunizations are recorded in your clinic's electronic medical record or chart, add the missing immunizations in the IIS. For more information on how to enter historical vaccinations, see the [Vaccinations Quick Reference Guide](#).

Set contraindications

If a child had chickenpox, you can set a **permanent** contraindication in the IIS for this vaccine. Setting this contraindication helps improve your varicella immunization rates because CoCASA recognizes these patients as up-to-date for varicella.

You can also set contraindications for parent refusals, adverse reactions, and other reasons. For more information on how to set contraindications, see the [Vaccinations Quick Reference Guide](#).

Inactivate patients

When you get record transfer requests or learn that a patient is no longer coming to your clinic for care, inactivate the patient's record in the IIS. When you inactivate patients they are no longer tied to your clinic and will not be included in your AFIX assessment. You can inactivate patients through the **Patient Demographics Edit** screen. For instructions on how to inactivate patients, see the [Patient Search/Add Quick Reference Guide](#).

Use Reminder/Recall

The IIS Reminder/Recall Report shows patients coming due or overdue for vaccines. When developing your reminder/recall process, think about:

- How often you plan to recall patients – monthly, quarterly, etc.
- How you plan to contact patients about due or overdue vaccines.
- Who will be responsible for reminder/recall activities.
- For more information about Reminder/Recall, see [Reminder Recall Strategies in the IIS](#) or contact the IIS Help Desk.

For More Information about the Washington State Immunization Information System Contact the Help Desk:

(800) 325-5599

WAIIHelpDesk@doh.wa.gov

For More Information about AFIX Contact:

Nicole Pender

AFIX Coordinator

Washington State Department of Health

nicole.pender@doh.wa.gov



STATE OF WASHINGTON

DEPARTMENT OF HEALTH

Office of Immunization and Child Profile

PO Box 47843 • Olympia, Washington 98504-7843

(360) 236-3595 • FAX (360) 236-3590 • TDD Relay Service: 1-800-833-6388

Vaccine Advisory Committee
Agenda

SeaTac Conference Center, Seattle, WA
Beijing Room
April 16th, 2015
11:00 a.m. – 2:00 p.m.

Table with 3 columns: Time, Agenda Item, and Facilitator. It lists the schedule for the Vaccine Advisory Committee meeting, including items like Welcome, Conflict of Interest Declaration, Updates, Communicable Disease Update, Lunch, and Meningococcal B Vaccine Recommendations.

	<ul style="list-style-type: none"> ○ written? ○ What else should be considered? • Vote 	
1:20-1:50	<p>VII. Provider response to HPV</p> <ul style="list-style-type: none"> • Assessment of Data • Grant Updates 	Hanna Oltean Paul Throne
1:50-1:55	<p>VIII. Input for July Meeting</p> <ul style="list-style-type: none"> • School requirements, 2014-15 school year data, future policy work, NIS data • 2015-16 Influenza season and vaccination recommendations 	Kathy Lofy
1:55-2:00	IX. Public Comment / Adjourn	
<p>2015 VAC Meetings: SeaTac Conference Center July 16, 2015: SeaTac Conference Center October 15, 2015 SeaTac Conference Center Time: 11:00-2:00</p>		

If you have a disability and need this document in a different format, please call 1-800-525-0127 (TDD/TTY 1-800-833-6388).

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GARDASIL 9 safely and effectively. See full prescribing information for GARDASIL 9.

GARDASIL[®]9

(Human Papillomavirus 9-valent Vaccine, Recombinant)
Suspension for intramuscular injection

Initial U.S. Approval: 2014

INDICATIONS AND USAGE

GARDASIL 9 is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of the following diseases:

- Cervical, vulvar, vaginal, and anal cancer caused by Human Papillomavirus (HPV) types 16, 18, 31, 33, 45, 52, and 58. (1.1)
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11. (1.1)

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma *in situ* (AIS). (1.1)
- Cervical intraepithelial neoplasia (CIN) grade 1. (1.1)
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3. (1.1)
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3. (1.1)
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3. (1.1)

GARDASIL 9 is indicated in boys 9 through 15 years of age for the prevention of the following diseases:

- Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58. (1.2)
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11. (1.2)

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3. (1.2)

Limitations of Use and Effectiveness:

- GARDASIL 9 does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening. (1.3, 17)
- Recipients of GARDASIL 9 should not discontinue anal cancer screening if it has been recommended by a health care provider. (1.3, 17)
- GARDASIL 9 has not been demonstrated to provide protection against disease from vaccine HPV types to which a person has previously been exposed through sexual activity. (1.3)
- GARDASIL 9 has not been demonstrated to protect against diseases due to HPV types other than 6, 11, 16, 18, 31, 33, 45, 52, and 58. (1.3)
- GARDASIL 9 is not a treatment for external genital lesions; cervical, vulvar, vaginal, and anal cancers; CIN; VIN; VaIN; or AIN. (1.3)
- Not all vulvar, vaginal, and anal cancers are caused by HPV, and GARDASIL 9 protects only against those vulvar, vaginal, and anal cancers caused by HPV 16, 18, 31, 33, 45, 52, and 58. (1.3)
- GARDASIL 9 does not protect against genital diseases not caused by HPV. (1.3)

- Vaccination with GARDASIL 9 may not result in protection in all vaccine recipients. (1.3)
- Safety and effectiveness of GARDASIL 9 have not been assessed in individuals older than 26 years of age. (1.3)

DOSAGE AND ADMINISTRATION

0.5-mL suspension for intramuscular injection at the following schedule: 0, 2 months, 6 months. (2.1)

DOSAGE FORMS AND STRENGTHS

0.5-mL suspension for injection as a single-dose vial and prefilled syringe. (3, 11)

CONTRAINDICATIONS

Hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after a previous dose of GARDASIL 9 or GARDASIL[®]. (4, 11)

WARNINGS AND PRECAUTIONS

Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following HPV vaccination. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position. (5.1)

ADVERSE REACTIONS

- The most common ($\geq 10\%$) local and systemic adverse reactions in females 16 through 26 years of age were injection-site pain (89.9%), injection-site swelling (40.0%), injection-site erythema (34.0%) and headache (14.6%). (6.1)
- The most common ($\geq 10\%$) local and systemic reactions in girls 9 through 15 years of age were injection-site pain (89.3%), injection-site swelling (47.8%), injection-site erythema (34.1%) and headache (11.4%). (6.1)
- The most common ($\geq 10\%$) local and systemic reactions in boys 9 through 15 years of age were injection-site pain (71.5%), injection-site swelling (26.9%), and injection-site erythema (24.9%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

USE IN SPECIFIC POPULATIONS

Safety and effectiveness of GARDASIL 9 have not been established in the following populations:

- Pregnant women. A pregnancy registry is available. Patients and health care providers are encouraged to register women exposed to GARDASIL 9 around the time of conception or during pregnancy by calling 1-800-986-8999. (8.1)
- Children below the age of 9 years. (8.4)
- Immunocompromised individuals. Response to GARDASIL 9 may be diminished. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2014

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- 1.2 Boys
- 1.3 Limitations of Use and Effectiveness

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Girls and Women

GARDASIL[®]9 is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of the following diseases:

- Cervical, vulvar, vaginal, and anal cancer caused by Human Papillomavirus (HPV) types 16, 18, 31, 33, 45, 52, and 58
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 1
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

1.2 Boys

GARDASIL 9 is indicated in boys 9 through 15 years of age for the prevention of the following diseases:

- Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

1.3 Limitations of Use and Effectiveness

The health care provider should inform the patient, parent, or guardian that vaccination does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening. Women who receive GARDASIL 9 should continue to undergo cervical cancer screening per standard of care. [See *Patient Counseling Information (17)*].

Recipients of GARDASIL 9 should not discontinue anal cancer screening if it has been recommended by a health care provider [see *Patient Counseling Information (17)*].

GARDASIL 9 has not been demonstrated to provide protection against disease from vaccine HPV types to which a person has previously been exposed through sexual activity.

GARDASIL 9 has not been demonstrated to protect against diseases due to HPV types other than 6, 11, 16, 18, 31, 33, 45, 52, and 58.

GARDASIL 9 is not a treatment for external genital lesions; cervical, vulvar, vaginal, and anal cancers; CIN; VIN; VaIN; or AIN.

Not all vulvar, vaginal, and anal cancers are caused by HPV, and GARDASIL 9 protects only against those vulvar, vaginal, and anal cancers caused by HPV 16, 18, 31, 33, 45, 52, and 58.

GARDASIL 9 does not protect against genital diseases not caused by HPV.

Vaccination with GARDASIL 9 may not result in protection in all vaccine recipients.

Safety and effectiveness of GARDASIL 9 have not been assessed in individuals older than 26 years of age.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

Administer GARDASIL 9 intramuscularly as a 0.5-mL dose at the following schedule: 0, 2 months, 6 months.

2.2 Method of Administration

For intramuscular use only.

Shake well before use. Thorough agitation immediately before administration is necessary to maintain suspension of the vaccine. GARDASIL 9 should not be diluted or mixed with other vaccines. After thorough agitation, GARDASIL 9 is a white, cloudy liquid. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use the product if particulates are present or if it appears discolored.

Administer GARDASIL 9 intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.

Observe patients for 15 minutes after administration [see *Warnings and Precautions (5)*].

Single-Dose Vial Use

Withdraw the 0.5-mL dose of vaccine from the single-dose vial using a sterile needle and syringe and use promptly.

Prefilled Syringe Use

This package does not contain a needle. Shake well before use. Attach a needle by twisting in a clockwise direction until the needle fits securely on the syringe. Administer the entire dose as per standard protocol.

2.3 Administration of GARDASIL 9 in Individuals Who Have Been Previously Vaccinated with GARDASIL[®]

Safety and immunogenicity of GARDASIL 9 were assessed in individuals who previously completed a three-dose vaccination series with GARDASIL [see *Adverse Reactions (6.1)* and *Clinical Studies (14.4)*]. Studies using a mixed regimen of HPV vaccines to assess interchangeability were not performed for GARDASIL 9.

3 DOSAGE FORMS AND STRENGTHS

GARDASIL 9 is a suspension for intramuscular administration available in 0.5-mL single-dose vials and prefilled syringes. See *Description (11)* for the complete listing of ingredients.

4 CONTRAINDICATIONS

Hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after a previous dose of GARDASIL 9 or GARDASIL [see *Description (11)*].

5 WARNINGS AND PRECAUTIONS

5.1 Syncope

Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following HPV vaccination. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position.

5.2 Managing Allergic Reactions

Appropriate medical treatment and supervision must be readily available in case of anaphylactic reactions following the administration of GARDASIL 9.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

The safety of GARDASIL 9 was evaluated in six clinical studies that included 13,234 individuals who received at least one dose of GARDASIL 9 and had safety follow-up. Study 1 and Study 3 also included 7,378 individuals who received at least one dose of GARDASIL as a control and had safety follow-up. The vaccines were administered on the day of enrollment and the subsequent doses administered approximately two and six months thereafter. Safety was evaluated using vaccination report card (VRC)-aided surveillance for 14 days after each injection of GARDASIL 9 or GARDASIL.

The individuals who were monitored using VRC-aided surveillance included 8,022 women 16 through 26 years of age and 5,212 girls and boys 9 through 15 years of age (3,436 girls and 1,776 boys) at enrollment who received GARDASIL 9 and 7,078 women 16 through 26 years of age and 300 girls 9 through 15 years of age at enrollment who received GARDASIL. The race distribution of the integrated safety population for GARDASIL 9 was similar between women (56.3% White; 25.4% Other Races or Multiracial; 14.7% Asian; 3.7% Black) and girls and boys (62.0% White; 19.2% Other Races or Multiracial; 13.5% Asian; 5.4% Black). The race distribution of the safety population for GARDASIL was determined in two studies (Study 1 and Study 3) that had different profiles. In Study 1, the race distribution was similar to the integrated database for GARDASIL 9: 55.3% White; 26.9% Multiracial; 14.2% Asian; 3.3% Black; 0.2% Unknown; 0.1% American Indian or Alaskan Native; and 0.1% Native Hawaiian or other Pacific Islander. Study 3 race distribution was 98.0% White; 1.3% Multiracial; 0.3% Asian; and 0.3% Black.

Solicited Injection-Site and Systemic Adverse Reactions

Injection-site reactions (pain, swelling, and erythema) and oral temperature were solicited using VRC-aided surveillance for five days after each injection of GARDASIL 9 during the clinical studies. The rates and severity of these solicited adverse reactions that occurred within five days following each dose of GARDASIL 9 compared with GARDASIL in Study 1 (girls and women 16 through 26 years of age) and Study 3 (girls 9 through 15 years of age) are presented in Table 1. Among subjects who received GARDASIL 9, the rates of injection-site pain were approximately equal across the three reporting time periods. Rates of injection-site swelling and injection-site erythema increased following each successive dose of GARDASIL 9. Recipients of GARDASIL 9 had numerically higher rates of injection-site reactions compared with recipients of GARDASIL.

Table 1: Rates (%) and Severity of Solicited Injection-Site and Systemic Adverse Reactions Occurring within Five Days of Each Vaccination with GARDASIL 9 Compared with GARDASIL (Studies 1 and 3)

	GARDASIL 9				GARDASIL			
	Post-dose 1	Post-dose 2	Post-dose 3	Post any dose	Post-dose 1	Post-dose 2	Post-dose 3	Post any dose
Girls and Women 16 through 26 Years of Age								
Injection-Site Adverse Reactions	N=7069	N=6997	N=6909	N=7071	N=7076	N=6992	N=6909	N=7078
Pain, Any	70.7	73.5	71.6	89.9	58.2	62.2	62.6	83.5
Pain, Severe	0.7	1.7	2.6	4.3	0.4	1.0	1.7	2.6
Swelling, Any	12.5	23.3	28.3	40.0	9.3	14.6	18.7	28.8
Swelling, Severe	0.6	1.5	2.5	3.8	0.3	0.5	1.0	1.5
Erythema, Any	10.6	18.0	22.6	34.0	8.1	12.9	15.6	25.6
Erythema, Severe	0.2	0.5	1.1	1.6	0.2	0.2	0.4	0.8
Systemic Adverse Reactions	n=6995	n=6913	n=6743	n=7022	n=7003	n=6914	n=6725	n=7024
Temperature ≥100°F	1.7	2.6	2.7	6.0	1.7	2.4	2.5	5.9
Temperature ≥102°F	0.3	0.3	0.4	1.0	0.2	0.3	0.3	0.8
Girls 9 through 15 Years of Age								
Injection-Site Adverse Reactions	N=300	N=297	N=296	N=299	N=299	N=299	N=294	N=300
Pain, Any	71.7	71.0	74.3	89.3	66.2	66.2	69.4	88.3
Pain, Severe	0.7	2.0	3.0	5.7	0.7	1.3	1.7	3.3
Swelling, Any	14.0	23.9	36.1	47.8	10.4	17.7	25.2	36.0
Swelling, Severe	0.3	2.4	3.7	6.0	0.7	2.7	4.1	6.3
Erythema, Any	7.0	15.5	21.3	34.1	9.7	14.4	18.4	29.3
Erythema, Severe	0	0.3	1.4	1.7	0	0.3	1.7	2.0
Systemic Adverse Reactions	n=300	n=294	n=295	n=299	n=299	n=297	n=291	n=300
Temperature ≥100°F	2.3	1.7	3.0	6.7	1.7	1.7	0	3.3
Temperature ≥102°F	0	0.3	1.0	1.3	0.3	0.3	0	0.7

The data for girls and women 16 through 26 years of age are from Study 1 (NCT00543543), and the data for girls 9 through 15 years of age are from Study 3 (NCT01304498).

N=number of subjects vaccinated with safety follow-up

n=number of subjects with temperature data

Pain, Any=mild, moderate, severe or unknown intensity

Pain, Severe=incapacitating with inability to work or do usual activity

Swelling, Any=any size or size unknown

Swelling, Severe=maximum size greater than 2 inches

Erythema, Any=any size or size unknown

Erythema, Severe=maximum size greater than 2 inches

Unsolicited Adverse Reactions

Unsolicited injection-site and systemic adverse reactions (assessed as vaccine-related by the investigator) observed among recipients of either GARDASIL 9 or GARDASIL in Studies 1 and 3 at a frequency of at least 1% are shown in Table 2. Few individuals discontinued study participation due to adverse experiences after receiving either vaccine (GARDASIL 9 = 0.1% vs. GARDASIL <0.1%).

Table 2: Rates (%) of Unsolicited Injection-Site and Systemic Adverse Reactions Occurring among $\geq 1.0\%$ of Individuals after Any Vaccination with GARDASIL 9 Compared with GARDASIL (Studies 1 and 3)

	Girls and Women 16 through 26 Years of Age		Girls 9 through 15 Years of Age	
	GARDASIL 9 N=7071	GARDASIL N=7078	GARDASIL 9 N=299	GARDASIL N=300
Injection-Site Adverse Reactions (1 to 5 Days Post-Vaccination, Any Dose)				
Pruritus	5.5	4.0	4.0	2.7
Bruising	1.9	1.9	0	0
Hematoma	0.9	0.6	3.7	4.7
Mass	1.3	0.6	0	0
Hemorrhage	1.0	0.7	1.0	2.0
Induration	0.8	0.2	2.0	1.0
Warmth	0.8	0.5	0.7	1.7
Reaction	0.6	0.6	0.3	1.0
Systemic Adverse Reactions (1 to 15 Days Post-Vaccination, Any Dose)				
Headache	14.6	13.7	11.4	11.3
Pyrexia	5.0	4.3	5.0	2.7
Nausea	4.4	3.7	3.0	3.7
Dizziness	3.0	2.8	0.7	0.7
Fatigue	2.3	2.1	0	2.7
Diarrhea	1.2	1.0	0.3	0
Oropharyngeal pain	1.0	0.6	2.7	0.7
Myalgia	1.0	0.7	0.7	0.7
Abdominal pain, upper	0.7	0.8	1.7	1.3
Upper respiratory tract infection	0.1	0.1	0.3	1.0

The data for girls and women 16 through 26 years of age are from Study 1 (NCT00543543), and the data for girls 9 through 15 years of age are from Study 3 (NCT01304498).

N=number of subjects vaccinated with safety follow-up

In an uncontrolled clinical trial with 639 boys and 1,878 girls 9 through 15 years of age (Study 2), the rates and severity of solicited adverse reactions following each dose of GARDASIL 9 were similar between boys and girls. Rates of unsolicited injection-site and systemic adverse reactions in boys 9 through 15 years of age were similar to those among girls 9 through 15 years of age. Solicited and unsolicited adverse reactions reported by boys in this study are shown in Table 3.

Table 3: Rates (%) of Solicited and Unsolicited* Injection-Site and Systemic Adverse Reactions among Boys 9 through 15 Years of Age who Received Gardasil 9

	GARDASIL 9 N=639
Solicited Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)	
Injection-Site Pain	71.5
Injection-Site Erythema	24.9
Injection-Site Swelling	26.9
Oral Temperature $\geq 100.0^{\circ}\text{F}^{\dagger}$	10.4
Unsolicited Injection-Site Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)	
Injection-Site Hematoma	1.3
Injection-Site Induration	1.1
Unsolicited Systemic Adverse Reactions (1-15 Days Post-Vaccination, Any Dose)	
Headache	9.4
Pyrexia	8.9
Nausea	1.3

The data for GARDASIL 9 are from Study 2 (NCT00943722).

*Unsolicited adverse reactions reported by $\geq 1\%$ of individuals

N=number of subjects vaccinated with safety follow-up

[†]For oral temperature: number of subjects with temperature data N=637

Serious Adverse Events in Clinical Studies

Serious adverse events were collected throughout the entire study period (range one month to 48 months post-last dose) for the six integrated clinical studies for GARDASIL 9. Out of the 13,236 individuals who were administered GARDASIL 9 and had safety follow-up, 305 reported a serious adverse event; representing 2.3% of the population. As a comparison, of the 7,378 individuals who were administered GARDASIL and had safety follow-up, 185 reported a serious adverse event; representing

2.5% of the population. Five GARDASIL 9 recipients each reported at least one serious adverse event that was determined to be vaccine-related. The vaccine-related serious adverse reactions were pyrexia, allergy to vaccine, asthmatic crisis, headache, and tonsillitis.

Deaths in the Entire Study Population

Across the clinical studies, ten deaths occurred (five each in the GARDASIL 9 and GARDASIL groups); none were assessed as vaccine-related. Causes of death in the GARDASIL 9 group included one automobile accident, one suicide, one case of acute lymphocytic leukemia, one case of hypovolemic septic shock, and one unexplained sudden death 678 days following the last dose of GARDASIL 9. Causes of death in the GARDASIL control group included one automobile accident, one airplane crash, one cerebral hemorrhage, one gunshot wound, and one stomach adenocarcinoma.

Systemic Autoimmune Disorders

In all of the clinical trials with GARDASIL 9 subjects were evaluated for new medical conditions potentially indicative of a systemic autoimmune disorder. In total, 2.4% (321/13,234) of GARDASIL 9 recipients and 3.3% (240/7,378) of GARDASIL recipients reported new medical conditions potentially indicative of systemic autoimmune disorders, which were similar to rates reported following GARDASIL, AAHS control, or saline placebo in historical clinical trials.

Clinical Trials Experience for GARDASIL 9 in Individuals Who Have Been Previously Vaccinated with GARDASIL

A clinical study (Study 4) evaluated the safety of GARDASIL 9 in 12- through 26-year-old girls and women who had previously been vaccinated with three doses of GARDASIL. The time interval between the last injection of GARDASIL and the first injection of GARDASIL 9 ranged from approximately 12 to 36 months. Individuals were administered GARDASIL 9 or saline placebo and safety was evaluated using vaccination report card (VRC)-aided surveillance for 14 days after each injection of GARDASIL 9 or saline placebo in these individuals. The individuals who were monitored included 608 individuals who received GARDASIL 9 and 305 individuals who received saline placebo. Few (0.5%) individuals who received GARDASIL 9 discontinued due to adverse reactions. The vaccine-related adverse experiences that were observed among recipients of GARDASIL 9 at a frequency of at least 1.0% and also at a greater frequency than that observed among saline placebo recipients are shown in Table 4. Overall the safety profile was similar between individuals vaccinated with GARDASIL 9 who were previously vaccinated with GARDASIL and those who were naïve to HPV vaccination with the exception of numerically higher rates of injection-site swelling and erythema among individuals who were previously vaccinated with GARDASIL (Tables 1 and 4).

Table 4: Rates (%) of Solicited and Unsolicited* Injection-Site and Systemic Adverse Reactions among Individuals Previously Vaccinated with GARDASIL Who Received GARDASIL 9 or Saline Placebo (Girls and Women 12 through 26 Years of Age)

	GARDASIL 9 N=608	Saline Placebo N=305
Solicited Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)		
Injection-Site Pain	90.3	38.0
Injection-Site Erythema	42.3	8.5
Injection-Site Swelling	49.0	5.9
Oral Temperature $\geq 100.0^{\circ}\text{F}^{\dagger}$	6.5	3.0
Unsolicited Injection-Site Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)		
Injection-Site Pruritus	7.7	1.3
Injection-Site Hematoma	4.8	2.3
Injection-Site Reaction	1.3	0.3
Injection-Site Mass	1.2	0.7
Unsolicited Systemic Adverse Reactions (1-15 Days Post-Vaccination, Any Dose)		
Headache	19.6	18.0
Pyrexia	5.1	1.6
Nausea	3.9	2.0
Dizziness	3.0	1.6
Abdominal pain, upper	1.5	0.7
Influenza	1.2	1.0

The data for GARDASIL 9 and saline placebo are from Study 4 (NCT01047345).

*Unsolicited adverse reactions reported by $\geq 1\%$ of individuals

N=number of subjects vaccinated with safety follow-up

[†]For oral temperature: number of subjects with temperature data GARDASIL 9 N=604; Saline Placebo N=304

Safety in Concomitant Use with Menactra and Adacel

In Study 5, the safety of GARDASIL 9 when administered concomitantly with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] was evaluated in a randomized study of 1,241 boys (n = 620) and girls (n = 621) with a mean age of 12.2 years [see *Clinical Studies (14.5)*].

Of the 1,237 boys and girls vaccinated, 1,220 had safety follow-up for injection-site adverse reactions. The rates of injection-site adverse reactions were similar between the concomitant group and non-concomitant group (vaccination with GARDASIL 9 separated from vaccination with Menactra and Adacel by 1 month) with the exception of an increased rate of swelling reported at the injection site for GARDASIL 9 in the concomitant group (14.4%) compared to the non-concomitant group (9.4%). The majority of injection-site swelling adverse reactions were reported as being mild to moderate in intensity.

6.2 Postmarketing Experience

There is no post-marketing experience following administration of GARDASIL 9. However, the post-marketing safety experience with GARDASIL is relevant to GARDASIL 9 since the vaccines are manufactured similarly and contain the same antigens from HPV types 6, 11, 16, and 18. Because these events were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or to establish a causal relationship to vaccine exposure. The following adverse experiences have been spontaneously reported during post-approval use of GARDASIL and may also be seen in post-marketing experience with GARDASIL 9:

Blood and lymphatic system disorders: Autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, lymphadenopathy.

Respiratory, thoracic and mediastinal disorders: Pulmonary embolus.

Gastrointestinal disorders: Nausea, pancreatitis, vomiting.

General disorders and administration site conditions: Asthenia, chills, death, fatigue, malaise.

Immune system disorders: Autoimmune diseases, hypersensitivity reactions including anaphylactic/anaphylactoid reactions, bronchospasm, and urticaria.

Musculoskeletal and connective tissue disorders: Arthralgia, myalgia.

Nervous system disorders: Acute disseminated encephalomyelitis, dizziness, Guillain-Barré syndrome, headache, motor neuron disease, paralysis, seizures, syncope (including syncope associated with tonic-

clonic movements and other seizure-like activity) sometimes resulting in falling with injury, transverse myelitis.

Infections and infestations: Cellulitis.

Vascular disorders: Deep venous thrombosis.

7 DRUG INTERACTIONS

7.1 Use with Systemic Immunosuppressive Medications

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune responses to vaccines [see *Use in Specific Populations (8.6)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B:

Reproduction studies have been performed in female rats at a dose approximately 240 times the human dose (mg/kg basis) and have revealed no evidence of impaired female fertility or harm to the fetus due to GARDASIL 9. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, GARDASIL 9 should be used during pregnancy only if clearly needed.

Clinical Studies in Humans

In clinical studies, women underwent serum or urine pregnancy testing prior to administration of each dose of GARDASIL 9. Women who were found to be pregnant before completion of a three-dose regimen of GARDASIL 9 were instructed to defer completion of their vaccination regimen until resolution of the pregnancy.

The overall proportion of pregnancies occurring at any time during the studies that resulted in an adverse outcome defined as the combined numbers of spontaneous abortion, late fetal death and congenital anomaly cases out of the total number of pregnancy outcomes for which an outcome was known (and excluding elective terminations), was 14.1% (145/1,028) in women who received GARDASIL 9 and 17.0% (168/991) in women who received GARDASIL. The proportions of adverse outcomes observed were consistent with pregnancy outcomes observed in the general population.

Further sub-analyses were conducted to evaluate pregnancies with estimated onset within 30 days or more than 30 days from administration of a dose of GARDASIL 9 or GARDASIL. For pregnancies with estimated onset within 30 days of vaccination, no cases of congenital anomaly were observed in women who have received GARDASIL 9 or GARDASIL. In pregnancies with onset more than 30 days following vaccination, 20 and 21 cases of congenital anomaly were observed in women who have received GARDASIL 9 and GARDASIL, respectively. There was no clear pattern of anomaly types that differed from those occurring in pregnancies in the general population of the same age.

For pregnancies with estimated onset within 30 days of vaccination, the proportion of pregnancies that resulted in a spontaneous abortion out of the total number of pregnancies with a known outcome (excluding elective terminations) was 27.4% (17/62) and 12.7% (7/55) in women who received GARDASIL 9 or GARDASIL, respectively. For pregnancies with estimated onset more than 30 days following vaccination, that proportion was 10.9% (105/960) and 14.6% (136/933) in women who received GARDASIL 9 or GARDASIL, respectively.

Pregnancy Registry for GARDASIL 9

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., maintains a Pregnancy Registry to monitor fetal outcomes of pregnant women exposed to GARDASIL 9. Patients and health care providers are encouraged to register women exposed to GARDASIL 9 around the time of conception or during pregnancy by calling 1-800-986-8999.

8.3 Nursing Mothers

It is not known whether GARDASIL 9 is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when GARDASIL 9 is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness have not been established in pediatric patients below 9 years of age.

8.5 Geriatric Use

The safety and effectiveness of GARDASIL 9 have not been evaluated in a geriatric population, defined as individuals aged 65 years and over.

8.6 Immunocompromised Individuals

The immunologic response to GARDASIL 9 may be diminished in immunocompromised individuals [see *Drug Interactions (7.1)*].

11 DESCRIPTION

GARDASIL 9, Human Papillomavirus 9-valent Vaccine, Recombinant, is a non-infectious recombinant 9-valent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The L1 proteins are produced by separate fermentations using recombinant *Saccharomyces cerevisiae* and self-assembled into VLPs. The fermentation process involves growth of *S. cerevisiae* on chemically-defined fermentation media which include vitamins, amino acids, mineral salts, and carbohydrates. The VLPs are released from the yeast cells by cell disruption and purified by a series of chemical and physical methods. The purified VLPs are adsorbed on preformed aluminum-containing adjuvant (Amorphous Aluminum Hydroxyphosphate Sulfate or AAHS). The 9-valent HPV VLP vaccine is a sterile liquid suspension that is prepared by combining the adsorbed VLPs of each HPV type and additional amounts of the aluminum-containing adjuvant and the final purification buffer.

GARDASIL 9 is a sterile suspension for intramuscular administration. Each 0.5-mL dose contains approximately 30 mcg of HPV Type 6 L1 protein, 40 mcg of HPV Type 11 L1 protein, 60 mcg of HPV Type 16 L1 protein, 40 mcg of HPV Type 18 L1 protein, 20 mcg of HPV Type 31 L1 protein, 20 mcg of HPV Type 33 L1 protein, 20 mcg of HPV Type 45 L1 protein, 20 mcg of HPV Type 52 L1 protein, and 20 mcg of HPV Type 58 L1 protein.

Each 0.5-mL dose of the vaccine also contains approximately 500 mcg of aluminum (provided as AAHS), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate, <7 mcg yeast protein, and water for injection. The product does not contain a preservative or antibiotics.

After thorough agitation, GARDASIL 9 is a white, cloudy liquid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

HPV only infects human beings. Animal studies with analogous animal papillomaviruses suggest that the efficacy of L1 VLP vaccines may involve the development of humoral immune responses. Efficacy of GARDASIL 9 against anogenital diseases related to the vaccine HPV types in human beings is thought to be mediated by humoral immune responses induced by the vaccine, although the exact mechanism of protection is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

GARDASIL 9 has not been evaluated for the potential to cause carcinogenicity or genotoxicity.

Reproduction

GARDASIL 9 administered to female rats at a dose approximately 240 times the human dose (mg/kg basis) had no effects on mating performance, fertility, or embryonic/fetal survival.

Development

GARDASIL 9 administered to female rats at a dose approximately 160 times the human dose (mg/kg basis) had no effects on development, behavior, reproductive performance or fertility of the offspring. Antibodies against all 9 HPV types were transferred to the offspring during gestation and lactation.

14 CLINICAL STUDIES

In these studies, seropositive is defined as anti-HPV titer greater than or equal to the pre-specified serostatus cutoff for a given HPV type. Seronegative is defined as anti-HPV titer less than the pre-specified serostatus cutoff for a given HPV type. The serostatus cutoff is the antibody titer level above the assay's lower limit of quantification that reliably distinguishes sera samples classified by clinical likelihood of HPV infection and positive or negative status by previous versions of Competitive Luminex Immunoassay (cLIA). The lower limits of quantification and serostatus cutoffs for each of the 9 vaccine HPV types are shown in Table 5 below. PCR positive is defined as DNA detected for a given HPV type. PCR negative is defined as DNA not detected for a given HPV type. The lower limit of detection for the multiplexed HPV PCR assays ranged from 5 to 34 copies per test across the 9 vaccine HPV types.

Table 5: Competitive Luminex Immunoassay (cLIA) Limits of Quantification and Serostatus Cutoffs for GARDASIL 9 HPV Types

HPV Type	cLIA Lower Limit of Quantification (mMU*/mL)	cLIA Serostatus Cutoff (mMU*/mL)
HPV 6	16	30
HPV 11	6	16
HPV 16	12	20
HPV 18	8	24
HPV 31	4	10
HPV 33	4	8
HPV 45	3	8
HPV 52	3	8
HPV 58	4	8

*mMU=milli-Merck Units

14.1 Efficacy Data for GARDASIL

Efficacy of GARDASIL is relevant to GARDASIL 9 since the vaccines are manufactured similarly and contain four of the same HPV L1 VLPs.

Females and males 16 through 26 years of age: Efficacy of GARDASIL was assessed in six AAHS-controlled, double-blind, randomized clinical trials evaluating 24,596 individuals (20,541 girls and women 16 through 26 years of age, 4,055 boys and men 16 through 26 years of age).

The results of these trials are shown in Table 6 below.

Table 6: Analysis of Efficacy of GARDASIL in the PPE* Population for Vaccine HPV Types

Disease Endpoints	GARDASIL		AAHS Control		% Efficacy (95% CI)
	N	Number of cases	N	Number of cases	
16- through 26-Year-Old Girls and Women†					
HPV 16- or 18-related CIN 2/3 or AIS	8493	2	8464	112	98.2 (93.5, 99.8)
HPV 16- or 18-related VIN 2/3	7772	0	7744	10	100.0 (55.5, 100.0)
HPV 16- or 18-related VaIN 2/3	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	7864	9	7865	225	96.0 (92.3, 98.2)
HPV 6-, 11-, 16-, or 18-related Genital Warts	7900	2	7902	193	99.0 (96.2, 99.9)
HPV 6- and 11-related Genital Warts	6932	2	6856	189	99.0 (96.2, 99.9)
16- through 26-Year-Old Boys and Men					
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)
HPV 6-, 11-, 16-, or 18-related Endpoint					
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)

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

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

N=Number of individuals with at least one 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: Table 6 does not include cases due to HPV types not covered by the vaccine.

AAHS = Amorphous Aluminum Hydroxyphosphate Sulfate, CIN = Cervical Intraepithelial Neoplasia, VIN = Vulvar Intraepithelial Neoplasia, VaIN=Vaginal Intraepithelial Neoplasia, PIN=Penile Intraepithelial Neoplasia, AIN=Anal Intraepithelial Neoplasia, AIS=Adenocarcinoma In Situ

In an extension study in females 16 through 26 years of age, prophylactic efficacy of GARDASIL through Month 60 against overall cervical and genital disease related to HPV 6, 11, 16, and 18 was 100% (95% CI: 12.3%, 100%).

Females 27 through 45 years of age: A clinical trial evaluated efficacy in 3,253 women 27 through 45 years of age, based on a combined endpoint of HPV 6-, 11-, 16- or 18-related persistent infection, genital warts, vulvar and vaginal dysplastic lesions of any grade, CIN of any grade, AIS, and cervical cancer. These women were randomized 1:1 to receive either GARDASIL or AAHS control. The efficacy estimate for the combined endpoint was driven primarily by prevention of persistent infection. No statistically significant efficacy was demonstrated for GARDASIL in prevention of cervical intraepithelial neoplasia grades 2 and 3 (CIN2/3), adenocarcinoma in situ (AIS) or cervical cancer related to HPV types 16 and 18.

14.2 Clinical Trials for GARDASIL 9

Efficacy and/or immunogenicity of GARDASIL 9 were assessed in five clinical trials. Study 1 evaluated the efficacy of GARDASIL 9 to prevent HPV-related cervical, vulvar, and vaginal disease using GARDASIL as a comparator.

The analysis of efficacy for GARDASIL 9 was evaluated in the per-protocol efficacy (PPE) population of 16- through 26-year-old girls and women, who were naïve to the relevant HPV type(s) by serology and PCR of cervicovaginal specimens prior to dose one and who remained PCR negative for the relevant HPV type(s) through one month Post-dose 3 (Month 7). Overall, approximately 52% of subjects were negative to all vaccine HPV types by both PCR and serology at Day 1.

The primary analysis of efficacy against HPV Types 31, 33, 45, 52, and 58 is based on a combined endpoint of Cervical Intraepithelial Neoplasia (CIN) 2, CIN 3, Adenocarcinoma *in situ* (AIS), invasive cervical carcinoma, Vulvar Intraepithelial Neoplasia (VIN) 2/3, Vaginal Intraepithelial Neoplasia (VaIN) 2/3, vulvar cancer, or vaginal cancer. Other endpoints evaluated include cervical, vulvar and vaginal disease of any grade, persistent infection, cytological abnormalities and invasive procedures. For all endpoints, the efficacy against the HPV Types 31, 33, 45, 52 and 58 in GARDASIL 9 was evaluated compared with GARDASIL. Efficacy of GARDASIL 9 against anal lesions caused by HPV Types 31, 33, 45, 52, and 58 was not assessed due to low incidence. Effectiveness of GARDASIL 9 against anal lesions was inferred from the efficacy of GARDASIL against anal lesions caused by HPV types 6, 11, 16 and 18 in men and antibody responses elicited by GARDASIL 9 against the HPV types covered by the vaccine.

Effectiveness against disease caused by HPV Types 6, 11, 16, and 18 was assessed by comparison of geometric mean titers (GMTs) of type-specific antibodies following vaccination with GARDASIL 9 with those following vaccination with GARDASIL (Study 1 and Study 3). The effectiveness of GARDASIL 9 in girls and boys 9 through 15 years old was inferred for all clinical endpoints studied in 16- to 26-year-old girls and women by comparison between these two age groups of type-specific antibody GMTs following vaccination with GARDASIL 9. Immunogenicity analyses were performed in the per-protocol immunogenicity (PPI) population consisting of individuals who received all 3 vaccinations within one 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) prior to dose 1 and through Month 7.

Study 1 evaluated immunogenicity of GARDASIL 9 and efficacy to prevent infection and disease caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in 16- through 26-year-old girls and women. Study 2 evaluated immunogenicity of GARDASIL 9 in girls and boys 9 through 15 years of age and women 16 through 26 years of age. Study 3 evaluated immunogenicity of GARDASIL 9 compared with GARDASIL in girls 9 through 15 years of age. Study 4 evaluated administration of GARDASIL 9 to girls and women 12 through 26 years of age previously vaccinated with GARDASIL. Study 5 evaluated GARDASIL 9 concomitantly administered with Menactra and Adacel in girls and boys 11 through 15 years of age. Together, these five clinical trials evaluated 12,233 individuals who received GARDASIL 9 (8,048 girls and women 16 through 26 years of age at enrollment with a mean age of 21.8 years; 2,927 girls 9 through 15 years of age at enrollment with a mean age of 11.9 years; and 1,258 boys 9 through 15 years of age at enrollment with a mean age of 11.9 years. The race distribution of the 16- through 26-year-old girls and women in the clinical trials was as follows: 56.3% White; 25.4% Other; 14.7% Asian; and 3.7% Black. The race distribution of the 9- through 15-year-old girls in the clinical trials was as follows: 60.3% White; 19.3% Other; 13.5% Asian; and 7.0% Black. The race distribution of the 9- through 15-year-old boys in the clinical trials was as follows: 46.6% White; 34.3% Other; 13.3% Asian; and 5.9% Black.

14.3 Efficacy – HPV Types 31, 33, 45, 52 and 58 in Girls and Women 16 through 26 Years of Age

Studies Supporting the Efficacy of GARDASIL 9 against HPV Types 31, 33, 45, 52, and 58

The efficacy of GARDASIL 9 in 16- through 26-year-old girls and women was assessed in an active comparator-controlled, double-blind, randomized clinical trial (Study 1) that included a total of 14,204 women (GARDASIL 9 = 7,099; GARDASIL = 7,105) who were enrolled and vaccinated without pre-screening for the presence of HPV infection. Subjects were followed up with a median duration of 40 months (range 0 to 64 months) after the last vaccination.

The primary efficacy evaluation was based on a composite clinical endpoint of HPV 31-, 33-, 45-, 52-, and 58-related cervical cancer, vulvar cancer, vaginal cancer, CIN 2/3 or AIS, VIN 2/3, and VaIN 2/3. Efficacy was evaluated in the PPE population of 16- through 26-year-old girls and women, who were naïve to the relevant HPV type(s) by serology and PCR of cervicovaginal specimens prior to dose one and who remained PCR negative to the relevant HPV type(s) through Month 7. Efficacy was further evaluated with the clinical endpoints of HPV 31-, 33-, 45-, 52-, and 58-related CIN 1, vulvar and vaginal disease of any grade, and persistent infection. In addition, the study also evaluated the impact of GARDASIL 9 on the rates of HPV 31-, 33-, 45-, 52-, and 58-related abnormal Papanicolaou (Pap) tests, cervical and external genital biopsy, and definitive therapy [including loop electrosurgical excision procedure (LEEP) and conization]. Efficacy for all endpoints was measured starting after the Month 7 visit.

GARDASIL 9 prevented HPV 31-, 33-, 45-, 52-, and 58-related persistent infection and disease and also reduced the incidence of HPV 31-, 33-, 45-, 52-, and 58-related Pap test abnormalities, cervical and external genital biopsy, and definitive therapy (Table 7).

Table 7: Analysis of Efficacy of GARDASIL 9 against HPV Types 31, 33, 45, 52, and 58 in the PPE* Population of 16- through 26-Year-old Girls and Women

Disease Endpoint	GARDASIL 9 N [†] =7099		GARDASIL N [†] =7105		GARDASIL 9 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	30	96.7 (80.9, 99.8)
HPV 31-, 33-, 45-, 52-, 58-related CIN 1	5948	1	5943	69	98.6 (92.4, 99.9)
HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3 or AIS	5948	1	5943	27	96.3 (79.5, 99.8)
HPV 31-, 33-, 45-, 52-, 58-related Vulvar or Vaginal Disease	6009	1	6012	16	93.8 (61.5, 99.7)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥6 Months [§]	5939	26	5953	642	96.2 (94.4, 97.5)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥12 Months [¶]	5939	15	5953	375	96.1 (93.7, 97.9)
HPV 31-, 33-, 45-, 52-, 58-related ASC-US HR-HPV Positive or Worse Pap [#] Abnormality	5881	35	5882	462	92.6 (89.7, 94.8)
HPV 31-, 33-, 45-, 52-, 58-related Biopsy	6016	7	6017	222	96.9 (93.6, 98.6)
HPV 31-, 33-, 45-, 52-, 58-related Definitive Therapy [‡]	6012	4	6014	32	87.5 (65.7, 96.0)

*The PPE population consisted of individuals who received all 3 vaccinations within one year of enrollment, did not have major deviations from the study protocol, 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 one month post-dose 3 (Month 7); data from Study 1 (NCT00543543).

[†]N=Number of individuals randomized to the respective vaccination group who received at least one injection

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

[§]Persistent infection detected in samples from two or more consecutive visits at least six months apart

[¶]Persistent infection detected in samples from two or more consecutive visits over 12 months or longer

[#]Papanicolaou test

[‡]Including loop electrosurgical excision procedure (LEEP) and conization

CI=Confidence Interval

CIN=Cervical Intraepithelial Neoplasia, VIN=Vulvar Intraepithelial Neoplasia, VaIN=Vaginal Intraepithelial Neoplasia,

AIS=Adenocarcinoma In Situ, ASC-US=Atypical squamous cells of undetermined significance

HR=High Risk

14.4 Immunogenicity

The minimum anti-HPV titer that confers protective efficacy has not been determined.

Type-specific immunoassays (i.e., cLIA) with type-specific standards were used to assess immunogenicity to each vaccine HPV type. These assays measured antibodies against neutralizing epitopes for each HPV type. The scales for these assays are unique to each HPV type; thus, comparisons across types and to other assays are not appropriate. Immunogenicity was measured by (1) the percentage of individuals who were seropositive for antibodies against the relevant vaccine HPV type, and (2) the Geometric Mean Titer (GMT).

Studies Supporting the Effectiveness of GARDASIL 9 against HPV Types 6, 11, 16, and 18

Effectiveness of GARDASIL 9 against persistent infection and disease related to HPV Types 6, 11, 16, or 18 was inferred from non-inferiority comparisons in Study 1 (16- through 26-year-old girls and women) and Study 3 (9- through 15-year-old girls) of GMTs following vaccination with GARDASIL 9 with those following vaccination with GARDASIL. A low number of efficacy endpoint cases related to HPV types 6, 11, 16 and 18 in both vaccination groups precluded a meaningful assessment of efficacy using disease endpoints associated with these HPV types. The primary analyses were conducted in the per-protocol population, which included subjects who received all three vaccinations within 1 year of enrollment, did

not have major deviations from the study protocol, and were HPV-naïve. HPV-naïve individuals were defined as seronegative to the relevant HPV type(s) prior to dose 1 and among female subjects 16 through 26 years of age in Study 1 PCR negative to the relevant HPV type(s) in cervicovaginal specimens prior to dose 1 through Month 7.

Anti-HPV 6, 11, 16 and 18 GMTs at Month 7 for GARDASIL 9 among girls 9 through 15 years of age and young women 16 to 26 years of age were non-inferior to those among the corresponding populations for GARDASIL (Table 8). At least 99.7% of individuals included in the analyses for each HPV type became seropositive by Month 7.

Table 8: Comparison of Immune Responses (Based on cLIA) Between GARDASIL 9 and GARDASIL for HPV Types 6, 11, 16, and 18 in the PPI* Population of 9- through 26-Year-Old Girls and Women

POPULATION	GARDASIL 9		GARDASIL		GARDASIL 9/ GARDASIL	
	N [†] (n [‡])	GMT mMU [§] /mL	N [†] (n [‡])	GMT mMU [§] /mL	GMT Ratio	(95% CI) [¶]
Anti-HPV 6						
9- through 15-year-old girls	300 (273)	1679.4	300 (261)	1565.9	1.07	(0.93, 1.23)
16- through 26-year-old girls and women	6792 (3993)	893.1	6795 (3975)	875.2	1.02	(0.99, 1.06)
Anti-HPV 11						
9- through 15-year-old girls	300 (273)	1315.6	300 (261)	1417.3	0.93	(0.80, 1.08)
16- through 26-year-old girls and women	6792 (3995)	666.3	6795 (3982)	830.0	0.80	(0.77, 0.83)
Anti-HPV 16						
9- through 15-year-old girls	300 (276)	6739.5	300 (270)	6887.4	0.97	(0.85, 1.11)
16- through 26-year-old girls and women	6792 (4032)	3131.1	6795 (4062)	3156.6	0.99	(0.96, 1.03)
Anti-HPV 18						
9- through 15-year-old girls	300 (276)	1956.6	300 (269)	1795.6	1.08	(0.91, 1.29)
16- through 26-year-old girls and women	6792 (4539)	804.6	6795 (4541)	678.7	1.19	(1.14, 1.23)

*The PPI population consisted of individuals who received all three vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, were naïve (PCR negative and seronegative) to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1, and among 16- through 26-year-old girls and women PCR negative to the relevant HPV type(s) through one month Post-dose 3 (Month 7). The data for 16- through 26-year-old girls and women are from Study 1 (NCT00543543), and the data for 9- through 15-year-old girls are from Study 3 (NCT01304498).

[†]N=Number of individuals randomized to the respective vaccination group who received at least one injection

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

[§]mMU=milli-Merck Units

[¶]Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67

CI=Confidence Interval

GMT=Geometric Mean Titers

cLIA=Competitive Luminex Immunoassay

Study Supporting the Effectiveness of GARDASIL 9 against Vaccine HPV Types in 9- through 15-Year-Old Girls and Boys

Effectiveness of GARDASIL 9 against persistent infection and disease related to vaccine HPV types in 9- through 15-year-old girls and boys was inferred from non-inferiority comparison in Study 2 of GMTs following vaccination with GARDASIL 9 among 9- to 15-year-old girls and boys with those among 16- through 26-year-old girls and women. The primary analyses were conducted in the per-protocol population, which included subjects who received all three vaccinations within one year of enrollment, did not have major deviations from the study protocol, and were HPV-naïve. HPV-naïve individuals were defined as seronegative to the relevant HPV type(s) prior to dose 1 and among female subjects 16 through 26 years of age PCR negative to the relevant HPV type(s) in cervicovaginal specimens prior to dose 1 through Month 7. Anti-HPV GMTs at Month 7 among 9- through 15-year-old girls and boys were non-inferior to anti-HPV GMTs among 16- through 26-year-old girls and women (Table 9).

Table 9: Comparison of Immune Responses (Based on cLIA) Between the PPI* Populations of 16- through 26-Year-Old Girls and Women, 9- through 15-Year-Old Girls, and 9- through 15-Year-Old Boys for All GARDASIL 9 Vaccine HPV Types

Population	N [†]	n [‡]	GMT (95% CI) mMU [§] /mL	GMT Ratio relative to 16- through 26-year-old women (95% CI) [¶]
Anti-HPV 6				
9- through 15-year-old girls	630	503	1703.1	1.89 (1.68, 2.12)
9- through 15-year-old boys	641	537	2083.4	2.31 (2.06, 2.60)
16- through 26-year-old girls and women	463	328	900.8	1
Anti-HPV 11				
9- through 15-year-old girls	630	503	1291.5	1.83 (1.63, 2.05)
9- through 15-year-old boys	641	537	1486.3	2.10 (1.88, 2.36)
16- through 26-year-old girls and women	463	332	706.6	1
Anti-HPV 16				
9- through 15-year-old girls	630	513	6933.9	1.97 (1.75, 2.21)
9- through 15-year-old boys	641	546	8683.0	2.46 (2.20, 2.76)
16- through 26-year-old girls and women	463	329	3522.6	1
Anti-HPV 18				
9- through 15-year-old girls	630	516	2148.3	2.43 (2.12, 2.79)
9- through 15-year-old boys	641	544	2855.4	3.23 (2.83, 3.70)
16- through 26-year-old girls and women	463	345	882.7	1
Anti-HPV 31				
9- through 15-year-old girls	630	506	1894.7	2.51 (2.21, 2.86)
9- through 15-year-old boys	641	543	2255.3	2.99 (2.63, 3.40)
16- through 26-year-old girls and women	463	340	753.9	1
Anti-HPV 33				
9- through 15-year-old girls	630	518	985.8	2.11 (1.88, 2.37)
9- through 15-year-old boys	641	544	1207.4	2.59 (2.31, 2.90)
16- through 26-year-old girls and women	463	354	466.8	1
Anti-HPV 45				
9- through 15-year-old girls	630	518	707.7	2.60 (2.25, 3.00)
9- through 15-year-old boys	641	547	912.1	3.35 (2.90, 3.87)
16- through 26-year-old girls and women	463	368	272.2	1
Anti-HPV 52				
9- through 15-year-old girls	630	517	962.2	2.21 (1.96, 2.49)
9- through 15-year-old boys	641	545	1055.5	2.52 (2.22, 2.84)
16- through 26-year-old girls and women	463	337	419.6	1
Anti-HPV 58				
9- through 15-year-old girls	630	516	1288.0	2.18 (1.94, 2.46)
9- through 15-year-old boys	641	544	1593.3	2.70 (2.40, 3.03)
16- through 26-year-old girls and women	463	332	590.5	1

*The PPI population consisted of individuals who received all three vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, were naïve seronegative to the relevant HPV type(s) prior to dose 1 and among 16- to 26-year-old girls and women PCR negative to the relevant HPV types prior to dose 1 through one month Post-dose 3 (Month 7). The data are from Study 2 (NCT00943722).

[†]N=Number of individuals randomized to the respective vaccination group who received at least one injection

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

[§]mMU=milli-Merck Units

[¶]Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67

cLIA=Competitive Luminex Immunoassay

CI=Confidence Interval

GMT=Geometric Mean Titers

Immune Response to GARDASIL 9 Across All Clinical Trials

Across all clinical trials, at least 99.5% of individuals included in the analyses for each of the nine vaccine HPV types became seropositive by Month 7. Anti-HPV GMTs at Month 7 among 9- through 15-year-old girls and boys were comparable to anti-HPV responses among 16- through 26-year-old girls and women in the combined database of immunogenicity studies for GARDASIL 9.

Persistence of Immune Response to GARDASIL 9

The duration of immunity following a complete schedule of vaccination with GARDASIL 9 has not been established. The peak anti-HPV GMTs for each vaccine HPV type occurred at Month 7. Proportions of individuals who remained seropositive to each vaccine HPV type at Month 24 were similar to the corresponding seropositive proportions at Month 7.

Administration of GARDASIL 9 to Individuals Previously Vaccinated with GARDASIL

Study 4 evaluated the immunogenicity of GARDASIL 9 in 921 girls and women (12 through 26 years of age) who had previously been vaccinated with GARDASIL. Prior to enrollment in the study, over 99% of subjects had received three injections of GARDASIL within a one year period. The time interval between the last injection of GARDASIL and the first injection of GARDASIL 9 ranged from approximately 12 to 36 months.

Seropositivity to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in the per protocol population ranged from 98.3 to 100% by Month 7 in individuals who received GARDASIL 9. The anti-HPV 31, 33, 45, 52 and 58 GMTs for the population previously vaccinated with GARDASIL were 25-63% of the GMTs in the combined populations from Studies 1, 2, 3, and 5, who had not previously received GARDASIL, although the clinical relevance of these differences is unknown. Efficacy of GARDASIL 9 in preventing infection and disease related to HPV Types 31, 33, 45, 52, and 58 in individuals previously vaccinated with GARDASIL has not been assessed.

Concomitant Use of Hormonal Contraceptives

Among 7,269 female recipients of GARDASIL 9 (16 through 26 years of age), 60.2% used hormonal contraceptives during the vaccination period of clinical studies 1 and 2. Use of hormonal contraceptives did not appear to affect the type specific immune responses to GARDASIL 9.

14.5 Studies with Menactra and Adacel

In Study 5, the safety and immunogenicity of co-administration of GARDASIL 9 with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] (same visit, injections at separate sites) were evaluated in 1,237 boys and girls 11 through 15 years of age at enrollment.

One group received GARDASIL 9 in one limb and both Menactra and Adacel, as separate injections, in the opposite limb concomitantly on Day 1 (n = 619). The second group received the first dose of GARDASIL 9 on Day 1 in one limb then Menactra and Adacel, as separate injections, at Month 1 in the opposite limb (n = 618). Subjects in both vaccination groups received the second dose of GARDASIL 9 at Month 2 and the third dose at Month 6. Immunogenicity was assessed for all vaccines one month post vaccination (one dose for Menactra and Adacel and three doses for GARDASIL 9).

Assessments of post-vaccination immune responses included type-specific antibody GMTs for each of the vaccine HPV types at four weeks following the last dose of GARDASIL 9; GMTs for anti-filamentous hemagglutinin, anti-pertactin, and anti-fimbrial antibodies at four weeks following Adacel; percentage of subjects with anti-tetanus toxin and anti-diphtheria toxin antibody concentrations ≥ 0.1 IU/mL at four weeks following Adacel; and percentage of subjects with ≥ 4 -fold rise from pre-vaccination baseline in antibody titers against *N. meningitidis* serogroups A, C, Y, and W-135 at four weeks following Menactra. Based on these measures, concomitant administration of GARDASIL 9 with Menactra and Adacel did not interfere with the antibody responses to any of the vaccines when compared with non-concomitant administration of GARDASIL 9 with Menactra and Adacel.

16 HOW SUPPLIED/STORAGE AND HANDLING

GARDASIL 9 is supplied in vials and syringes.

Carton of one 0.5-mL single-dose vial. NDC 0006-4119-02

Carton of ten 0.5-mL single-dose vials. NDC 0006-4119-03

Carton of ten 0.5-mL single-dose prefilled Luer Lock syringes with tip caps. NDC 0006-4121-02

Store refrigerated at 2 to 8°C (36 to 46°F). Do not freeze. Protect from light.

GARDASIL 9 should be administered as soon as possible after being removed from refrigeration. GARDASIL 9 can be administered provided total (cumulative multiple excursion) time out of refrigeration (at temperatures between 8°C and 25°C) does not exceed 72 hours. Cumulative multiple excursions between 0°C and 2°C are also permitted as long as the total time between 0°C and 2°C does not exceed 72 hours. These are not, however, recommendations for storage.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Inform the patient, parent, or guardian:

- Vaccination does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening. Women who receive GARDASIL 9 should continue to undergo cervical cancer screening per standard of care.
 - Recipients of GARDASIL 9 should not discontinue anal cancer screening if it has been recommended by a health care provider.
 - GARDASIL 9 has not been demonstrated to provide protection against disease from vaccine and non-vaccine HPV types to which a person has previously been exposed through sexual activity.
 - Since syncope has been reported following HPV vaccination sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended.
 - Vaccine information is required to be given with each vaccination to the patient, parent, or guardian.
 - Provide information regarding benefits and risks associated with vaccination.
 - Safety and effectiveness of GARDASIL 9 have not been established in pregnant women. A pregnancy registry is available. Women exposed to GARDASIL 9 around the time of conception or during pregnancy are encouraged to register by calling 1-800-986-8999.
 - It is important to complete the full vaccination series unless contraindicated.
 - Report any adverse reactions to their health care provider.
-

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Pertussis – Department of Health Website Information and Resources

Main Page: <http://www.doh.wa.gov/YouandYourFamily/IllnessandDisease/WhoopingCough>

The screenshot shows the Washington State Department of Health website. At the top, there is a navigation bar with links for Home, Newsroom, Publications, and About Us. Below this is a search bar with a 'Go' button. A secondary navigation bar contains links for You and Your Family, Community and Environment, Licenses, Permits and Certificates, Data and Statistical Reports, Emergencies, and For Public Health and Healthcare Providers. The main content area is titled 'Pertussis in Washington' and includes a breadcrumb trail: Home > You and Your Family > Illness and Disease > Whooping Cough. A left sidebar lists various health topics, with 'Illness and Disease' selected. The main text area features a section for 'Pertussis in Washington' with links to 'La tos ferina (en Español)', a description of the illness, and links to 'Resources and materials', 'About the vaccine', and 'Whooping cough activity and surveillance'. A 'More Resources' box on the right contains a link to 'Pertussis (whooping cough) (CDC)' and a graphic that says 'Whooping Cough. Get Your Tdap Shot.' with the website URL www.doh.wa.gov. Below the main text is a 'Resources and Materials' section with a list of links to various documents and materials. This is followed by an 'About the Vaccine' section with a list of links to information about DTaP and Tdap vaccines. The final section is 'Whooping Cough Activity and Surveillance', which includes links to 'Cases in Washington State in 2015 (PDF)' and 'Pertussis 2014 annual summary (PDF)'. A list of links for public health partners is also present at the bottom.

Washington State Department of Health

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Tools A-Z

You and Your Family | Community and Environment | Licenses, Permits and Certificates | Data and Statistical Reports | Emergencies | For Public Health and Healthcare Providers

Home > You and Your Family > Illness and Disease > Whooping Cough Print

Pertussis in Washington

[La tos ferina \(en Español\)](#)

[Pertussis or Whooping cough](#) is an illness that causes a severe cough and may last for months. Vaccination is the best protection.

[Resources and materials](#)

[About the vaccine](#)

[Whooping cough activity and surveillance](#)

More Resources

[Pertussis \(whooping cough\) \(CDC\)](#)

Whooping Cough. Get Your Tdap Shot.

www.doh.wa.gov

Resources and Materials

- [Whooping Cough Fact Sheet \(PDF\)](#)
- [Frequently Asked Questions](#)
- [For pregnant women](#)
- [Public service announcements](#)
- [For healthcare providers](#)
 - [Training and materials for providers](#)
 - [Pertussis materials for public health partners](#)
- [For parents](#) (multiple languages)
- [For grandparents \(PDF\)](#)
- [For childcare providers \(PDF\)](#)
- [For healthcare providers \(PDF\)](#)

About the Vaccine

- [DTaP](#) vaccine
 - Kids aged 7 to 10 years
- [Tdap](#) vaccine
 - Everyone 11 years and older.
 - All pregnant women during each pregnancy, even if they have gotten it before. This helps protect their baby until they are old enough to get vaccinated. [More Pertussis information for pregnant women.](#)
- [Where to get a whooping cough vaccine](#)

Whooping Cough Activity and Surveillance

[Cases in Washington State in 2015 \(PDF\)](#)
This weekly report includes the current number of whooping cough cases for the state and each county.

[Pertussis 2014 annual summary \(PDF\)](#)
This report reflects pertussis activity in Washington in 2013.

- [For public health partners](#)

School Level Data now available on DOH web page

Each year, the Department of Health receives multiple requests for school-specific immunization data. We have historically posted state level, county level, and school district level data to our web page and have now added school level data:

www.doh.wa.gov/DataandStatisticalReports/Immunization/SchoolReports. These tables are under Data Tables of School Immunization and Exemption Rates – School Level Rates heading. Data are available for kindergarten and for all grades (K-12) for school years 2011-12, 2012-13, and 2013-14 by school.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TRUMENBA safely and effectively. See full prescribing information for TRUMENBA.

TRUMENBA™ (Meningococcal Group B Vaccine)

Suspension for intramuscular injection

Initial U.S. Approval: 2014

INDICATIONS AND USAGE

- Trumenba is indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B. Trumenba is approved for use in individuals 10 through 25 years of age. (1)
- Approval of Trumenba is based on demonstration of immune response, as measured by serum bactericidal activity against four serogroup B strains representative of prevalent strains in the United States. The effectiveness of Trumenba against diverse serogroup B strains has not been confirmed. (1)

DOSAGE AND ADMINISTRATION

- For intramuscular use only. (2)
- Three doses (0.5 mL each) by intramuscular injection according to a 0-, 2-, and 6-month schedule. (2.1)

DOSAGE FORMS AND STRENGTHS

- Suspension for intramuscular injection in 0.5 mL single-dose prefilled syringe. (3)

CONTRAINDICATIONS

- Severe allergic reaction after a previous dose of Trumenba. (4)

ADVERSE REACTIONS

The most common solicited adverse reactions were pain at the injection site ($\geq 85\%$), fatigue ($\geq 40\%$), headache ($\geq 35\%$), muscle pain ($\geq 30\%$), and chills ($\geq 15\%$). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer, Inc. at 1-800-438-1985 or VAERS at 1-800-822-7967 or <http://vaers.hhs.gov>.

USE IN SPECIFIC POPULATIONS

- Pregnancy:** Trumenba should be used during pregnancy only if clearly needed. (8.1)
- Pediatric Use:** Safety and effectiveness have not been established in children <10 years of age. In a clinical study, 90% of infants <12 months of age who were vaccinated with a reduced dosage formulation had fever. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2014

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Trumenba is indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B. Trumenba is approved for use in individuals 10 through 25 years of age.

Approval of Trumenba is based on demonstration of immune response, as measured by serum bactericidal activity against four serogroup B strains representative of prevalent strains in the United States. The effectiveness of Trumenba against diverse serogroup B strains has not been confirmed.

2 DOSAGE AND ADMINISTRATION

For intramuscular use only.

2.1 Dose and Schedule

Administer Trumenba as a three dose series (0.5 mL each) according to a 0-, 2-, and 6-month schedule.

2.2 Administration

Shake syringe vigorously to ensure that a homogenous white suspension of Trumenba is obtained. Do not use the vaccine if it cannot be re-suspended. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if particulate matter or discoloration is found.

Inject each 0.5 mL dose intramuscularly, using a sterile needle attached to the supplied prefilled syringe. The preferred site for injection is the deltoid muscle of the upper arm. Do not mix Trumenba with any other vaccine in the same syringe.

2.3 Use of Trumenba with other Meningococcal Group B Vaccines

Sufficient data are not available on the safety and effectiveness of using Trumenba and other meningococcal group B vaccines interchangeably to complete the vaccination series.

3 DOSAGE FORMS AND STRENGTHS

Trumenba is a suspension for intramuscular injection in 0.5 mL single-dose prefilled syringe.

4 CONTRAINDICATIONS

Severe allergic reaction after a previous dose of Trumenba.

5 WARNINGS AND PRECAUTIONS

5.1 Management of Allergic Reactions

Epinephrine and other appropriate agents used to manage immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur following administration of Trumenba.

5.2 Altered Immunocompetence

Individuals with altered immunocompetence may have reduced immune responses to Trumenba.

6 ADVERSE REACTIONS

In clinical studies, the most common solicited adverse reactions were pain at the injection site ($\geq 85\%$), fatigue ($\geq 40\%$), headache ($\geq 35\%$), muscle pain ($\geq 30\%$), and chills ($\geq 15\%$).

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in clinical practice.

The safety of Trumenba was evaluated in 4,282 subjects 11 through 25 years of age in 7 clinical studies (4 randomized controlled and 3 supportive non-controlled studies) conducted in the US, Europe, and Australia. A total of 4,250 adolescents (11 through 18 years of age) and 32 adults (19 through 25 years of age) received at least one dose of Trumenba. A total of 1,004 subjects 11 through 25 years of age in the control groups received saline placebo and/or one of the following vaccines: Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant [HPV4]; a non-US licensed tetanus toxoid, reduced diphtheria toxoid, acellular pertussis and inactivated polio virus vaccine; or Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Sanofi Pasteur Ltd.).

The safety evaluation in the 7 studies included an assessment of: (1) solicited local and systemic reactions, and use of antipyretic medication after each vaccination in an electronic diary maintained by the subject or the subject's parent/legal guardian; and (2) spontaneous reports of adverse events (AEs), including serious adverse events (SAEs), throughout the study (day of vaccination through one month or 6 months after the last vaccination, depending on the study and safety parameter).

In controlled studies, demographic characteristics were generally similar with regard to gender, race, and ethnicity among subjects who received Trumenba and those who received control. Overall, across the 7 studies, among the subjects who received Trumenba, 56.1% were male and 44.0% were female, and the majority were White (90.8%) and non-Hispanic/non-Latino (91.4%).

Solicited Local and Systemic Adverse Reactions

In a randomized, active-controlled, observer-blinded, multicenter trial in the US, 1,982 adolescents 11 to <18 years of age received Trumenba at 0-, 2-, and 6-months. Subjects were randomized to 1 of 3 groups: Trumenba + HPV4 (Group 1), Trumenba + Saline (Group 2), Saline + HPV4 (Group 3). 81.6% of subjects were White, 13% were Black or African-American, 1.2% were Asian and 17.4% were Hispanic or Latino. Overall, 66.5% of subjects were male, 65.9% of participants were 11 to ≤ 14 years age and 34.1% were 15 to <18 years of age.

Local adverse reactions at the Trumenba injection site (Groups 1 and 2), and saline injection site (Group 3) were assessed in this study. Table 1 presents the percentage and severity of reported local adverse reactions within 7 days following each dose of Trumenba (Groups 1 and 2 combined) or saline control (Group 3).

Local adverse reactions were reported more frequently following Trumenba compared to saline (see Table 1).

Table 1: Percentage of Subjects 11 to <18 Years of Age Reporting Local Adverse Reactions Within 7 Days After Each Vaccination^a

Local Reaction	Trumenba			Saline		
	Dose 1 N=1970	Dose 2 N=1826	Dose 3 N=1688	Dose 1 N=496	Dose 2 N=468	Dose 3 N=438
Pain ^b						
Any ^c	92.8	86.1	84.5	36.9	29.1	23.3
Mild	42.5	49.9	44.1	33.1	24.6	20.8
Moderate	42.1	31.6	34.7	3.6	4.5	2.3
Severe	8.2	4.6	5.7	0.2	0.0	0.2
Redness ^d						
Any ^c	20.4	14.9	15.8	1.2	1.7	1.1
Mild	9.0	6.6	7.3	1.0	1.7	0.9
Moderate	9.1	7.0	7.0	0.2	0.0	0.2
Severe	2.2	1.3	1.4	0.0	0.0	0.0
Swelling ^d						
Any ^c	21.6	18.2	20.1	2.8	2.8	1.8
Mild	12.5	10.8	11.7	1.8	2.1	1.4
Moderate	8.5	7.1	8.2	1.0	0.6	0.5
Severe	0.5	0.3	0.2	0.0	0.0	0.0

^a National Clinical Trial (NCT) number NCT01461993
^b Mild (does not interfere with activity); Moderate (interferes with activity); Severe (prevents daily activity).
^c “Any” is defined as the cumulative frequency of subjects who reported a reaction as “mild”, “moderate” or “severe” within 7 days of vaccination.
^d Mild (2.5-5.0 cm); Moderate (5.5-10.0 cm); Severe (>10.0 cm).

Table 2 presents the percentage of subjects who had at least one injection and who also reported a solicited systemic adverse reaction within 7 days of vaccination, by study group. These reactions resolved within 8 days in 90% of subjects. Fever (temperature $\geq 38.0^{\circ}\text{C}$) resolved within 3 days in 84% of subjects.

Table 2: Percentage of Subjects 11 to <18 Years of Age Reporting Systemic Adverse Reactions and Use of Antipyretic Medications Within 7 Days After Each Vaccination^a

	Group 1			Group 2			Group 3		
	Trumenba + HPV4			Trumenba + Saline			Saline + HPV4		
	Dose 1 N=985	Dose 2 N=919	Dose 3 N=842	Dose 1 N=985	Dose 2 N=907	Dose 3 N=846	Dose 1 N=496	Dose 2 N=468	Dose 3 N=438
Systemic Reactions									
Fever ($\geq 38.0^{\circ}\text{C}$)									
$\geq 38.0^{\circ}\text{C}^{\text{b}}$	8.3	2.1	2.1	6.4	1.3	1.1	0.8	0.9	0.7
38.0° to $<38.5^{\circ}\text{C}$	4.9	1.2	1.1	3.7	1.1	0.8	0.4	0.4	0.2
38.5° to $<39.0^{\circ}\text{C}$	2.5	0.4	0.6	1.5	0.1	0.1	0.0	0.2	0.0
39.0° to $\leq 40.0^{\circ}\text{C}$	0.6	0.3	0.4	1.0	0.1	0.1	0.2	0.2	0.2
Vomiting ^c									
Any ^{d,e}	7.8	2.8	2.4	7.4	2.4	2.5	3.4	3.0	1.6
Mild	5.8	2.1	2.1	5.3	1.4	1.8	3.2	2.4	0.9
Moderate	1.9	0.7	0.2	1.7	0.9	0.5	0.2	0.6	0.7
Severe	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Diarrhea ^f									
Any ^d	14.5	10.9	9.3	15.2	9.3	8.9	15.5	11.1	9.4
Mild	12.6	9.1	7.7	13.3	7.5	7.3	12.5	9.8	7.8
Moderate	1.7	1.6	1.1	1.7	1.8	1.2	2.6	1.3	1.6
Severe	0.2	0.1	0.5	0.2	0.0	0.4	0.4	0.0	0.0

Table 2: Percentage of Subjects 11 to <18 Years of Age Reporting Systemic Adverse Reactions and Use of Antipyretic Medications Within 7 Days After Each Vaccination^a

	Group 1			Group 2			Group 3		
	Trumenba + HPV4			Trumenba + Saline			Saline + HPV4		
	Dose 1 N=985	Dose 2 N=919	Dose 3 N=842	Dose 1 N=985	Dose 2 N=907	Dose 3 N=846	Dose 1 N=496	Dose 2 N=468	Dose 3 N=438
Headache ^e									
Any ^d	56.9	44.8	41.0	54.8	40.8	34.8	43.1	36.5	27.4
Mild	37.7	32.9	30.0	36.1	28.3	24.0	33.3	25.4	21.0
Moderate	17.8	11.1	10.5	16.5	10.7	10.2	9.3	10.5	6.2
Severe	1.4	0.9	0.5	2.1	1.8	0.6	0.6	0.6	0.2
Fatigue ^e									
Any ^d	64.4	48.9	44.1	62.4	44.8	42.9	50.6	34.4	31.5
Mild	39.5	33.4	28.4	39.1	30.8	30.9	37.1	25.6	24.2
Moderate	20.6	12.8	14.3	19.7	12.3	10.9	13.1	7.9	7.1
Severe	4.3	2.6	1.4	3.7	1.7	1.2	0.4	0.9	0.2
Chills ^g									
Any ^d	30.3	19.2	17.5	29.0	17.4	15.6	16.7	12.0	8.2
Mild	21.5	13.8	13.1	22.0	13.6	12.5	13.9	9.6	7.1
Moderate	7.4	4.1	3.7	5.6	2.9	3.0	2.6	2.1	1.1
Severe	1.3	1.2	0.7	1.4	1.0	0.1	0.2	0.2	0.0
Muscle pain (other than muscle pain at the injection site) ^e									
Any ^d	41.1	36.6	35.3	42.4	30.5	30.9	28.6	24.6	20.8
Mild	24.7	25.0	22.2	25.7	19.8	21.3	23.4	19.4	16.2
Moderate	13.3	10.2	11.2	13.9	9.3	8.5	4.6	4.9	3.9
Severe	3.1	1.3	1.9	2.8	1.4	1.1	0.6	0.2	0.7
Joint pain ^e									
Any ^d	21.6	15.5	19.2	21.6	15.4	17.0	13.7	12.2	11.0
Mild	15.7	11.1	13.4	14.7	11.8	13.7	10.9	9.8	8.7
Moderate	5.0	3.8	4.9	5.9	3.0	3.1	2.8	2.4	1.6
Severe	0.9	0.5	1.0	1.0	0.7	0.2	0.0	0.0	0.7
Use of Antipyretic medication	26.3	16.1	16.5	27.0	17.5	17.0	13.3	13.9	6.6

^a NCT01461993

^b Eight subjects reported 9 episodes of fever which could not be further classified as 38.0° to <38.5°C, 38.5° to <39.0°C, 39.0° to ≤40.0°C or >40.0°C. 3 of these episodes occurred in Group 1, dose 1; 2 occurred in Group 2, dose 1; 1 occurred in Group 3, dose 1; 1 occurred in Group 1, dose 2; 1 occurred in Group 1, dose 3; and 1 occurred in Group 3, dose 3.

^c Mild (1-2 times in 24 hours); Moderate (>2 times in 24 hours); Severe (requires IV hydration).

^d “Any” is defined as the cumulative frequency of subjects who reported a reaction as “mild”, “moderate” or “severe” within 7 days of vaccination.

^e Nine subjects reported vomiting which could not be further classified. 1 of these reports occurred in Group 1, dose 1; 4 occurred in Group 2, dose 1; 1 occurred in Group 1, dose 2; 1 occurred in Group 2, dose 2; and 2 occurred in Group 2, dose 3.

^f Mild (2-3 loose stools in 24 hours); Moderate (4-5 loose stools in 24 hours); Severe (6 or more loose stools in 24 hours).

^g Mild (does not interfere with activity); Moderate (interferes with activity); Severe (prevents daily activity).

Serious Adverse Events

Overall in clinical studies in which 4282 subjects 11 through 25 years of age received at least one dose of Trumenba, serious adverse events were reported in 88 (2.0%) subjects. Among the 4 controlled studies (Trumenba N=2557, control N=1004), serious adverse events were reported in 44 (1.7%) subjects who received Trumenba and 16 (1.6%) control subjects, for individuals who received at least one dose.

Non-serious Adverse Events

Overall in clinical studies in which 4282 subjects 11 through 25 years of age received Trumenba, non-serious AEs within 30 days after any dose were reported in 1049 (24.5%) subjects. Among the 4 controlled studies (Trumenba N=2557, control N=1004), AEs that occurred within 30 days of vaccination were reported in 739 (28.9%) subjects who received Trumenba and 313 (31.2%) subjects in the control group, for individuals who received at least one dose. AEs that occurred at a frequency of at least 2% and were more frequently observed in subjects who received Trumenba than subjects in the control group were injection site pain and headache.

7 DRUG INTERACTIONS

In a clinical trial, Trumenba was administered concomitantly with HPV4 in adolescents 11 to <18 years of age [see *Clinical Studies (14.2) and Adverse Reactions (6.1)*].

Data are insufficient to assess the safety and immunogenicity of concomitant administration of Trumenba with meningococcal serogroups A, C, Y, W conjugate vaccine or Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Reproduction studies have been performed in female rabbits at a dose approximately 17 times the human dose (on a mg/kg basis) and revealed no evidence of impaired female fertility or harm to the fetus due to Trumenba. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of the human response, this vaccine should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether Trumenba is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Trumenba is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness have not been established in children <10 years of age. In a clinical study, 90% of infants <12 months of age who were vaccinated with a reduced dosage formulation had fever.

8.5 Geriatric Use

Safety and effectiveness of Trumenba in adults older than 65 years of age have not been established.

11 DESCRIPTION

Trumenba is a sterile suspension composed of two recombinant lipidated factor H binding protein (fHBP) variants from *N. meningitidis* serogroup B, one from fHBP subfamily A and one from subfamily B (A05 and B01, respectively).¹ The proteins are individually produced in *E. coli*. Production strains are grown in defined fermentation growth media to a specific density. The recombinant proteins are extracted from the production strains and purified through a series of column chromatography steps. Polysorbate 80 (PS80) is added to the drug substances and is present in the final drug product.

Each 0.5 mL dose contains 60 micrograms of each fHBP variant (total of 120 micrograms of protein), 0.018 mg of PS80 and 0.25 mg of Al³⁺ as AlPO₄ in 10 mM histidine buffered saline at pH 6.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Protection against invasive meningococcal disease is conferred mainly by complement-mediated antibody-dependent killing of *N. meningitidis*. The effectiveness of Trumenba was assessed by measuring serum bactericidal activity using human complement (hSBA).

fHBP is one of many proteins found on the surface of meningococci and contributes to the ability of the bacterium to avoid host defenses. fHBPs can be categorized into two immunologically distinct subfamilies, A and B.¹ The susceptibility of serogroup B meningococci to complement-mediated antibody-dependent killing following vaccination with Trumenba is dependent on both the antigenic similarity of the bacterial and vaccine fHBPs, as well as the amount of fHBP expressed on the surface of the invading meningococci.

13 NONCLINICAL TOXICOLOGY

Trumenba has not been evaluated for carcinogenic or mutagenic potential or impairment of fertility in males.

14 CLINICAL STUDIES

In a randomized study conducted in the US, the immunogenicity of Trumenba following a 3-dose series was evaluated in adolescents (11 to <18 years of age). Serum bactericidal antibodies were measured with hSBA assays that used each of four meningococcal group B strains. The four test strains express fHBP variants representing the two subfamilies (A and B) and, when taken together, are representative of prevalent strains in the US. The studies assessed the proportions of subjects with a 4-fold or greater increase in hSBA titer for each of the four strains, and the proportion of subjects who achieved a titer greater than or equal to the lower limit of quantitation (LLOQ) of the assay for all four strains (composite response). The LLOQ was defined as the lowest amount of the antibody in a sample that can be reliably quantified.

14.1 Immunogenicity

In an active-controlled, observer-blinded, multicenter trial conducted in the US, adolescents 11 to <18 years of age, were assigned randomly into 3 groups: Group 1 received Trumenba + HPV4, Group 2 received Trumenba + Saline, and Group 3 received Saline + HPV4 [see *Clinical Trial Experience (6.1)*]. The hSBA responses observed after the second dose and completion of a 3-dose series are presented in Table 3.

Table 3: Percentage of Adolescents With a ≥ 4 -Fold Rise in hSBA Titer and Composite Response^{a,b}

	Group 1^c	Group 2^c
	Trumenba + HPV4	Trumenba + Saline
fHBP Variant^d	% (95% CI)^e	% (95% CI)^e
4-fold Response^f		
A22		
Dose 2	73.1 (69.9, 76.2)	74.2 (71.0, 77.3)
Dose 3	85.3 (82.6, 87.7)	86.4 (83.8, 88.7)
A56		
Dose 2	92.5 (90.4, 94.3)	92.6 (90.4, 94.4)
Dose 3	95.0 (93.2, 96.5)	95.3 (93.6, 96.8)
B24		
Dose 2	61.3 (57.7, 64.8)	63.4 (59.9, 66.9)
Dose 3	83.4 (80.5, 85.9)	84.8 (82.0, 87.2)
B44		
Dose 2	45.7 (42.1, 49.3)	47.4 (43.8, 51.0)
Dose 3	77.0 (73.9, 79.9)	80.7 (77.8, 83.4)
Composite Response^{f,g}		
Before Dose 1	0.3 (0.0, 1.0)	0.7 (0.2, 1.6)
Dose 2	49.9 (46.1, 53.6)	51.9 (48.2, 55.6)
Dose 3	81.0 (78.0, 83.7)	83.9 (81.1, 86.4)

Abbreviations: CI = Confidence interval; hSBA = Serum bactericidal activity measured using human complement; LLOQ = Lower limit of quantitation.

Note: LLOQ = 1:16 for PMB80 (A22); 1:8 for PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44).

Note: The 4-fold increase is defined as follows: (1) For subjects with a baseline hSBA titer $< 1:4$, a response was defined as an hSBA titer $\geq 1:16$. (2) For subjects with a baseline hSBA titer $\geq 1:4$, a 4-fold response was defined as an hSBA titer ≥ 4 times the LLOQ or ≥ 4 times the baseline titer, whichever was higher.

^a Evaluable Immunogenicity Population.

^b NCT01461993

^c The denominator ranged from 710-792 for Group 1; 723-788 for Group 2.

^d The strains expressing variant A22, A56, B24, and B44 correspond to strains PMB80, PMB2001, PMB2948, and PMB2707, respectively.

^e Exact 2-sided confidence interval (Clopper and Pearson) based upon the observed proportion of subjects.

^f Serum was obtained approximately one month after the second and one month after the third doses.

^g Composite Response = hSBA \geq LLOQ for all 4 primary Meningococcal B strains.

In a study conducted in Europe in which subjects 11 through 18 years of age were administered Trumenba on a 0-, 2-, 6-month schedule, the hSBA responses following completion of the 3-dose series were similar to those shown in Table 3.

14.2 Concomitant Vaccine Administration

In a study conducted in the US, the immunogenicity of concomitantly administered Trumenba and HPV4 was evaluated in adolescents 11 to <18 years of age [see *Clinical Studies (14.1) and Adverse Reactions (6.1)*]. Immune responses were evaluated by comparisons of geometric mean titer [GMT] for each HPV type at 1 month after the third HPV4 vaccination (Group 1 vs. Group 3), and hSBA GMTs using two meningococcal serogroup B strains [variants A22 and B24] 1 month after the third Trumenba vaccination (Group 1 vs. Group 2).

The noninferiority criteria for comparisons of the GMT ratio (lower limit of the 2-sided 95% confidence interval of the GMT ratio >0.67) were met for three HPV types (6, 11 and 16) and for the meningococcal serogroup B strains. For HPV-18, the lower bound of the 95% confidence interval (CI) for the GMT ratio was 0.62 at one month after the third HPV4 vaccination.

15 REFERENCES

1. Wang X, et al. Prevalence and genetic diversity of candidate vaccine antigens among invasive *Neisseria meningitidis* isolates in the United States. *Vaccine* 2011; 29:4739-4744.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Trumenba is supplied in the following strengths and package configurations:

Prefilled Syringe, 1 Dose (10 per package) – NDC 0005-0100-10.

Prefilled Syringe, 1 Dose (5 per package) – NDC 0005-0100-05.

After shipping, Trumenba may arrive at temperatures between 2°C to 25°C (36°F to 77°F).

The tip cap and rubber plunger of the prefilled syringe are not made with natural rubber latex.

16.2 Storage and Handling

Upon receipt, store refrigerated at 2°C to 8°C (36°F to 46°F).

Store syringes in the refrigerator horizontally (laying flat on the shelf) to minimize the re-dispersion time.

Do not freeze. Discard if the vaccine has been frozen.

17 PATIENT COUNSELING INFORMATION

Prior to administration of this vaccine, the healthcare professional should inform the individual, parent, guardian, or other responsible adult of the following:

- The importance of completing the 3-dose immunization series.
- Report any suspected adverse reactions to a healthcare professional.

Provide the Vaccine Information Statements, which are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).



US Govt. License No. 3

LAB-0722-2.0

VAC Biographies

New Members

Tara Tumulty, MSN, CPNP, ARNP –Tara Tumulty comes to the VAC with a wealth of experience as a nurse practitioner, most recently with Healthy Future Pediatrics in Olympia. Representing the National Association Pediatric Nurse Practitioners, Tara is excited to share her experience and perspective as a pediatric nurse with the VAC. Tara holds a Master of Science and Nursing degree from Northeastern University in Boston, Massachusetts and has worked in the medical field since 2004.

Dr. Susan Westerlund – Susan Westerlund represents the Washington Academy of Family Physicians. Since receiving her Medical Doctorate from the University of Washington, Susan has been practicing medicine for over 30 years. Susan has served on several state boards and committees during her career, including the Washington State Vaccine Committee, which predated VAC by over five years. Susan’s continued commitment to and historical knowledge of public health practices will provide important insight to the issues and questions VAC discusses.

New Staff

Mary Huynh – CDC Senior Health Advisor - Mary holds an MPH/MPP dual degree from the University of Michigan School of Public Health and Gerald R. Ford School of Public Policy. In 2005, Mary joined the CDC Public Health Prevention Service as a Fellow and was assigned to the Virginia Department of Health serving under the State Epidemiologist. In 2008, she continued work at CDC for the Vaccines for Children Program and AFIX immunization quality improvement process. Mary spent the last few years as a Public Health Advisor assigned to the Immunization Programs in the U.S. Affiliated Pacific Islands of Guam, Republic of Marshall Islands, and Commonwealth of Northern Mariana Islands.

Joanna Eavey –Assessment Coordinator - Joanna “Joey” Eavey, our new Assessment Coordinator, comes to us from New York with over 10 years’ experience in public health data management and analysis. After receiving her BS from Western Washington University, she spent three years as a US Peace Corps volunteer in rural Niger, West Africa. She graduated from Tulane University with an MSPH and worked with the Louisiana Office of Public Health for three years. From there, she moved to New York and worked at the NYC DOHMH for six years, first with the HIV/AIDS program and then with the Bureau of Immunization. Recently, Joey moved back to Washington and is excited to be part of the OICP team. Her focus is on data standardization and routinizing data analysis and timely, useful release of immunization data to stakeholders in order to support increasing immunization coverage in Washington