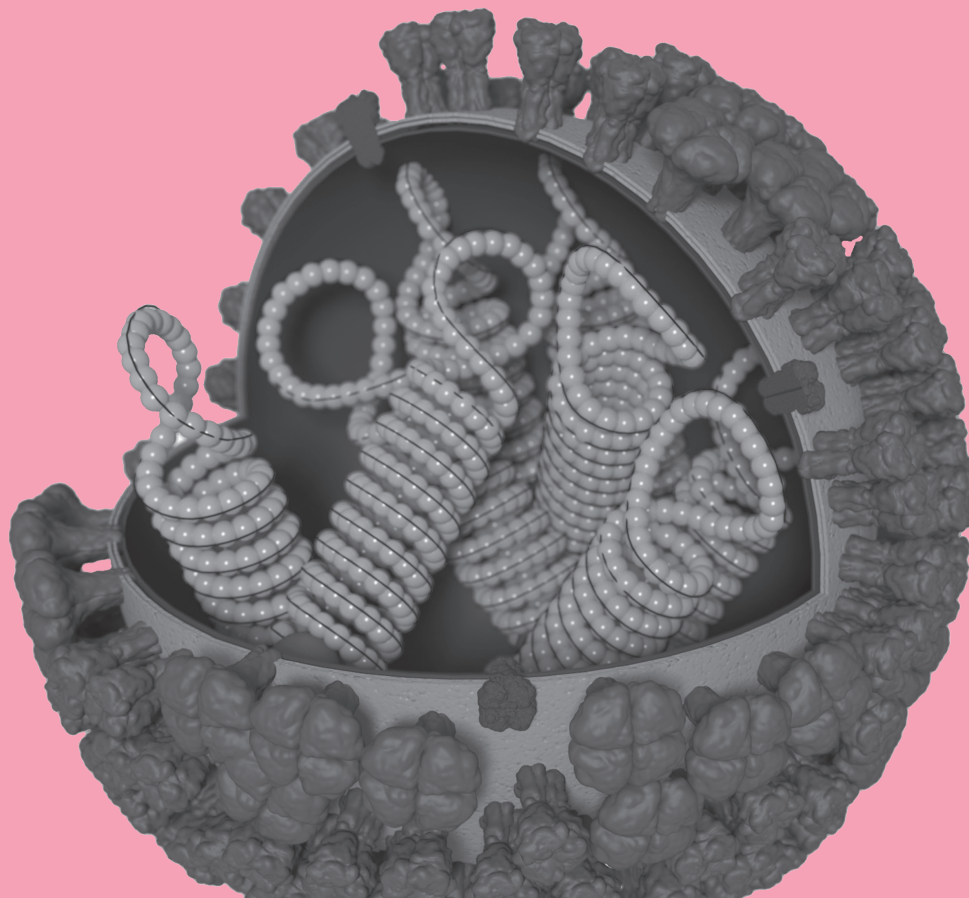


EPIDEMIOLOGY AND PREVENTION OF VACCINE- PREVENTABLE DISEASES

13TH EDITION - Supplement

2017



U.S. Department of
Health and Human Services
Centers for Disease
Control and Prevention

On the cover

This illustration depicts the influenza virus.
Graphic created by Dan J. Higgins, Division of Communication Services, CDC

Suggested Citation:
Centers for Disease Control and Prevention.
Epidemiology and Prevention of Vaccine-Preventable Diseases.
Hamborsky J, Kroger A, Wolfe S, eds. 13th ed., Supplement. Washington D.C.
Public Health Foundation, 2017.

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The editors would like to thank Dr. William L. Atkinson, who summarized, standardized and compiled CDC's vaccine-preventable disease and vaccine teaching materials to create the Pink Book.

"He just thought it up and did it." – Apocalypse Now

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Chapter 11: Human Papillomavirus 9-Valent Human Papillomavirus Vaccine

The 9-valent human papillomavirus vaccine (Gardasil 9) (9vHPV) is FDA-approved for males and females 9 through 26 years of age. In addition to the two high-risk (types 16 and 18) (oncogenic) and two low-risk (types 6 and 11) HPV types targeted by the quadrivalent vaccine (Gardasil) (4vHPV), Gardasil 9 vaccine targets an additional five high-risk types--31, 33, 45, 52, and 58. All three HPV vaccines (Gardasil 9, Gardasil, and Cervarix [2vHPV]) protect against the high-risk HPV types 16 and 18, which are responsible for 66% of cervical cancers and 64% of all invasive HPV-associated cancers in the United States. The five additional high-risk HPV types covered by Gardasil 9 account for another 15% of cervical cancers and 11% of all HPV-associated cancers (14% in females and 4% in males). The seven high-risk types (types 16, 18, 31, 33, 45, 52, and 58) targeted by Gardasil 9 vaccine cause 75% of all cervical intraepithelial neoplasias grade 2 or worse.

Gardasil 9 has been shown to have similar immunogenicity to Gardasil for the four shared types, and is approximately 95% effective against the five additional HPV types in the vaccine.

ACIP recommends routine vaccination at age 11 or 12 years. For those not vaccinated at the routine age, females age 13 through 26 years and males age 13 through 21 years should be vaccinated. Vaccination is also recommended through age 26 years for men who have sex with men and immunocompromised men (including those with HIV infection). Females can be vaccinated with Cervarix, Gardasil, or Gardasil 9. Males can be vaccinated with Gardasil or Gardasil 9. Regardless of the HPV product used, the schedule is the same. The second dose should be administered 1 to 2 months after the first dose, and the third dose 6 months after the first dose. A schedule begun with Gardasil or Cervarix can be completed with Gardasil 9. If vaccination providers do not know or do not have available the HPV vaccine product previously administered, or are in settings transitioning to Gardasil 9, any available HPV vaccine product may be used to continue or complete the series for females for protection against HPV 16 and 18; Gardasil 9 or Gardasil may be used to continue or complete the series for males.

There is no ACIP recommendation for routine additional vaccination with Gardasil 9 for persons who have completed a 3-dose vaccination series with one of the other HPV vaccines. As of April 2016, there are no data on efficacy or immunogenicity of 1, 2, or 3 doses of Gardasil 9 among persons who have received 1 or 2 doses of Gardasil. In an immunogenicity and safety clinical trial, 3 doses of Gardasil 9 (on a 0, 2, 6 month schedule) were given to females who had completed a 3-dose Gardasil vaccine series. The first dose of Gardasil 9 vaccine was administered 12 to 36 months after completing a Gardasil series. After 3 doses, more than 98% of vaccinees developed antibodies to all 5 additional types. Antibody was also measured after the first dose of Gardasil 9. Most, but not

all, of the vaccinees in this trial developed antibody against all 5 additional types; only 67% of recipients developed antibody to HPV 45. Antibody titers were higher after the third dose than after the first dose. Antibody titers were not measured after the second dose.

In a cross-study comparison, geometric antibody titers for the 5 additional types among persons who received 3 doses of Gardasil 9 after 3 doses of Gardasil were lower than those of persons who received 3 doses of Gardasil 9 vaccine without prior HPV vaccination. The significance of the lower antibody titers is not known because there is no level of antibody identified that correlates with protection.

Safety has been evaluated in approximately 15,000 subjects in the Gardasil 9 clinical development program; approximately 13,000 subjects in six studies were included in the initial application submitted to FDA. The vaccine was well-tolerated, and most adverse events were injection site-related pain, swelling, and erythema that were mild to moderate in intensity. The safety profiles were similar in Gardasil and Gardasil 9 vaccinees. Among females aged 9 through 26 years, Gardasil 9 recipients had more injection-site adverse events, including swelling (40.3% in the Gardasil 9 group compared with 29.1% in the Gardasil group), and erythema (34.0% in the Gardasil 9 group compared with 25.8% in the Gardasil group). Males had fewer injection site adverse events. In males aged 9 through 15 years, injection site swelling and erythema in Gardasil 9 recipients occurred in 26.9% and 24.9%, respectively. Rates of injection-site swelling and erythema both increased following each successive dose of Gardasil 9. Compared with persons in other studies who were vaccinated with Gardasil 9 vaccine and had never received any HPV vaccination, those who received Gardasil 9 after a 3-dose Gardasil series had higher rates of injection site swelling and redness.

Two-Dose HPV Schedule

In October 2016, a two-dose series of 9-valent HPV vaccine was approved by FDA for adolescents who initiate the vaccination series at ages 9 years through 14 years. ACIP recommends a 2-dose schedule of HPV vaccine for persons who receive the first valid dose before the 15th birthday (except for persons with certain immunocompromising conditions; see below). The second and final dose should be administered 6–12 calendar months after the first dose. If the second dose has already been administered at least 5 months after the first dose, it can be counted. The 4-day grace period can be applied to this 5-month minimum interval. (If the second dose is administered at a shorter interval, an additional dose should be administered at least 12 weeks after the second dose, and at least 6-12 months after the first dose.)

For persons who have already received one dose of HPV before the 15th birthday, and now are 15 years old or older, providers should offer the two-dose series.

Persons who initiate the series on or after the 15th birthday, and persons with certain immunocompromising conditions

should be vaccinated with the 3-dose series. Persons who should receive 3 doses are those with primary or secondary immunocompromising conditions that might reduce cell-mediated or humoral immunity, such as B lymphocyte antibody deficiencies, T lymphocyte complete or partial defects, HIV infection, malignant neoplasm, transplantation, autoimmune disease, or immunosuppressive therapy, since immune response to vaccination may be attenuated. In a 3-dose schedule, the second dose should be administered 1–2 months after the first dose, and the third dose should be administered 6 months after the first dose (0, 1–2, 6 month schedule).

Chapter 14: Meningococcal Disease

Serogroup B Meningococcal Vaccine

[P237 after 1st complete paragraph]

Two recombinant serogroup B meningococcal (MenB) vaccines are licensed in the United States. MenB-FHbp (Trumenba), manufactured by Pfizer, was licensed by the FDA in October 2014. MenB-4C (Bexsero), manufactured by GlaxoSmithKline, was licensed by the FDA in January 2015. Trumenba consists of two factor H binding protein fusion protein (FHbp) antigens from *Neisseria meningitidis* serogroup B, one from each FHbp subfamily (A and B). Bexsero consists of three recombinant proteins (Neisserial adhesin A [NadA]; FHbp subfamily B; Neisserial Heparin Binding Antigen [NHBA]); and outer membrane vesicles containing the outer membrane protein PorA from serosubtype P1.4.

Immunogenicity

[P239 Top]

For both Trumenba and Bexsero antibody responses were measured by serum bactericidal activity using human complement against select meningococcal serogroup B strains. Immunogenicity was assessed as the proportion of subjects who achieved a fourfold or greater increase in serum bactericidal activity using human complement (hSBA) titer for each of the serogroup B strains tested, and the proportion of subjects who achieved a titer greater than or equal to the lower limit of quantification of the assay for all strains (composite response). The lower limit of quantification was defined as the lowest amount of the antibody in a sample that can be reliably quantified. In a multicenter study conducted among adolescents 11–17 years of age in the United States, 81% of subjects who received Trumenba and concomitant 4vHPV had a composite response, and 83.9% of subjects who received Trumenba with saline had a composite response. In another study where Trumenba was administered with 4vHPV, MenACWY, Tdap or a combination Tdap-IPV vaccine, the immune response to MenB did not interfere with the other antigens, with one exception. The non-inferiority criteria for the geometric mean titer ratio after three doses of 4vHPV was not met for HPV18 strain in 4vHPV. However, greater than or equal to 99% of subjects achieved seroconversion to all four HPV strains.

In a randomized, controlled trial in the United Kingdom among college students 18–24 years of age, 88% of recipients of both doses of Bexsero had a composite response at 1 month following the second dose. At 11 months after the second dose, 66% of recipients had a response. In a randomized control trial in Australia and Canada among adolescents 11–17 years of age, 63% of recipients had a response 1 month after the second dose.

Vaccine Recommendations

[P241, after 2nd paragraph]

Bexsero or Trumenba should be administered to certain persons 10 years of age or older who are at increased risk of meningococcal disease. These include persons with persistent complement component deficiencies (including persons taking the drug eculizumab [Soliris®], which impairs complement function); persons who have anatomic or functional asplenia, including sickle cell disease; microbiologists who are routinely exposed to isolates of *Neisseria meningitidis*; or anyone identified to be at increased risk because of a serogroup B meningococcal disease outbreak.

Providers may also consider serogroup B meningococcal vaccination for adolescents and young adults 16 through 23 years of age. The preferred age for serogroup B meningococcal vaccination is 16 through 18 years of age. This is an ACIP category B recommendation, meaning the recommendation is for individual clinical decision making.

There is no preference for one brand of serogroup B meningococcal vaccine. Bexsero is licensed as a 2-dose series at 0 and 1-6 months. Trumenba is licensed as a 3-dose series at 0, 1-2 months, and 6 months. Providers should not shorten the 4-week interval between dose 1 and dose 2 of Bexsero, and they should not shorten the 4-week interval between dose 1 and dose 2 of Trumenba or the 4-month interval between dose 2 and dose 3 of Trumenba. However, if these intervals are violated, the doses do not have to be repeated, no matter how short the intervals.

Serogroup B meningococcal vaccine may be administered simultaneously or at any interval with other live or inactivated vaccines, including meningococcal conjugate vaccines.

Trumenba and Bexsero are not interchangeable. The same serogroup B meningococcal vaccine brand must be used for all doses of the series. If doses of both brands have been administered to the same patient, the provider should ensure that the patient receives a complete series of either brand, and ignore any doses of the other brand. The next dose of the selected brand should be given no sooner than the recommended interval after the previous dose of the same brand AND at least 4 weeks after the last (or only) dose of the other brand.

Serogroup B meningococcal vaccine should be administered intramuscularly in a separate syringe and at a separate site than other vaccines. As of April 2016 no booster doses of either serogroup B meningococcal vaccine are recommended following the primary series for any group including those at increased risk.

Contraindications and Precautions

[P241 after 3rd complete paragraph]

Vaccination with Bexsero or Trumenba is contraindicated for persons who have had a severe allergic (anaphylactic) reaction to a vaccine component or following a prior dose. Severe or moderate acute illness is a precaution for Bexsero

or Trumenba. No randomized controlled clinical trials have been conducted to evaluate use of MenB vaccines in pregnant or lactating women. Vaccination of pregnant and lactating women should be deferred unless the woman is at increased risk and, after consultation with her health care provider, the benefits of vaccination are considered to outweigh the potential risks.

Adverse Events

[P242, after 3rd complete paragraph]

A total of 59,091 participants in vaccination campaigns following outbreaks received at least 1 dose of Bexsero, and three serious adverse events (rhabdomyolysis, anaphylaxis, and fever) were reported. All resolved without negative after effects. The adverse event profile was consistent with findings from clinical trials.

Both Bexsero and Trumenba contain factor H binding protein. In animal models, antibodies generated after vaccination with Bexsero were cross-reactive with human factor H, but it is not known whether anti-factor H antibodies develop in human recipients of the vaccine, or whether this poses a risk for autoimmunity as an adverse reaction. Autoantibodies to human factor H have previously been described in persons with atypical hemolytic uremic syndrome and alternative pathway-mediated glomerulopathies. FDA reviewed safety data from six trials of Bexsero and seven trials of Trumenba involving 3,100 and 4,500 vaccine recipients and, in most cases where an autoimmune condition was reported, symptoms had started before receipt of vaccine. Post-licensure safety surveillance will be important to identify any clinical implications of this hypothetical biologic mechanism for particular types of autoimmune disease. Onset of autoimmune disease related symptoms could be delayed well beyond vaccination and ongoing safety surveillance will be important.

Adverse Reactions

[P242, after 4th complete paragraph]

The safety of Trumenba was evaluated in seven clinical trials, in which a total of 9,808 subjects received at least 1 dose of Trumenba. Four subjects reported seven serious adverse events (pyrexia, vomiting, vertigo, chills, headache, anaphylaxis and neutropenia). All resolved without sequelae. Subjects were asked about particular outcomes in the first seven days after administration; the most common adverse reactions were pain at the injection site, fatigue, headache, myalgia, and chills.

The safety of Bexsero was assessed in three clinical trials. Among 2,716 recipients, five serious adverse events (tremor, dyspnea, acute thyroiditis, and two cases of juvenile arthritis) were reported. All resolved without sequelae. The most common adverse reactions within 7 days after receipt of Bexsero in the clinical trials included injection site reactions, myalgia, erythema, fatigue, headache, induration, nausea and arthralgia.

Chapter 17: Pneumococcal Disease **Pneumococcal Vaccine Recommendations (PCV13 and PPSV23)**

[P291, before the first complete paragraph]

When elective splenectomy, immunocompromising therapy, or cochlear implant placement is being planned, providers should choose the vaccines appropriate to the level of risk for invasive pneumococcal disease which would exist AFTER the surgery or treatment. For example, a person who will undergo elective splenectomy should be considered asplenic when applying these vaccine recommendations. The choice of vaccine also depends on past history of pneumococcal vaccination. After assessing the past history, if PCV13 (Prevnar 13) and PPSV23 (Pneumovax 23) are both recommended, they both need to be administered, preferably before treatment or surgery, but they cannot be administered at the same time. Prevnar 13 should be administered first. The interval to the dose of Pneumovax 23 should be at least 8 weeks, determined by the risk of invasive pneumococcal disease which would exist AFTER the treatment or surgery, as well as the past history of pneumococcal vaccination. If treatment or surgery (elective splenectomy, immunocompromising therapy, or cochlear implant placement) cannot be delayed for more than 8 weeks or longer, providers can consider administering Pneumovax 23 after the treatment or surgery.

Prevnar 13 and Pneumovax 23 should not be administered simultaneously or at an interval less than 8 weeks. However, in adults, if Prevnar 13 and Pneumovax 23 are administered simultaneously or at an interval less than 8 weeks, neither dose needs to be repeated. In children, if Prevnar 13 and Pneumovax 23 are administered simultaneously, the Prevnar 13 dose should be repeated, and should be administered no earlier than 8 weeks after the pair of vaccines that was administered simultaneously.

High-risk patients (patients with functional or anatomic asplenia, altered immunocompetence, or renal disease) are recommended to receive 2 doses of Pneumovax 23, separated by a 5-year interval, unless the first dose was administered after the 65th birthday (in which case, no additional doses are recommended). The interval between these 2 doses is 5 years. If this 5 year interval is violated, both doses should be considered valid and neither dose needs to be repeated.

Selected References

Petrosky E, Bocchini Jr. JA., Hariri S. Use of 9-Valent Human Papillomavirus (HPV) Vaccine: Updated HPV Vaccination Recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep* 2015;64: 300-304.

Minor Errata

Updates, errata, and clarifications can also be found at:
<http://www.cdc.gov/vaccines/pubs/pinkbook/pink-errata.html>

