Supplemental information and guidance for vaccination providers regarding use of 9-valent HPV vaccine

A 9-valent human papillomavirus (HPV) vaccine (Gardasil 9, Merck & Co., Inc) was licensed for use in females and males in the United States in December 2014.[1,2,3,4] 9-valent HPV vaccine is the third HPV vaccine licensed by the Food and Drug Administration (FDA); the other vaccines are bivalent HPV vaccine, licensed for use in females, and quadrivalent HPV vaccine, licensed for use in females and males.[5] In February 2015, the Advisory Committee on Immunization Practices (ACIP) recommended 9-valent HPV vaccine as one of 3 HPV vaccines that can be used for routine vaccination of females and one of 2 HPV vaccines for routine vaccination of males. A Policy Note was published in the MMWR in March 2015.[6] The information below summarizes some of the recommendations included in the Policy Note and provides additional guidance for issues that were not addressed in the Policy Note but are likely to arise during the transition from quadrivalent HPV vaccine to 9-valent HPV vaccine.

Information about the vaccines

What are some of the similarities and differences in the characteristics of the three licensed HPV vaccines?

- Each of the three currently licensed HPV vaccines is a noninfectious, virus-like particle (VLP) vaccine.
- Bivalent, quadrivalent and 9-valent HPV vaccines each target HPV 16 and 18, types that cause about 66% of cervical cancers and the majority of other HPV-associated cancers in both women and men in the United States. 9-valent HPV vaccine also targets five additional cancer causing types (HPV 31, 33, 45, 52, 58) which account for about 15% of cervical cancers. Quadrivalent and 9-valent HPV vaccines also protect against HPV 6 and 11, types that cause anogenital warts.
- Quadrivalent and 9-valent HPV vaccines are licensed for use in females and males; bivalent HPV vaccine is licensed for use in females.

What percent of HPV-associated cancers in females and males are caused by the 5 additional types in the 9-valent HPV vaccine?

- About 14% of HPV-associated cancers in females (approximately 2800 cases annually) and 4% of HPV-associated cancers in males (approximately 550 cases annually) are caused by the 5 additional types in the 9-valent HPV vaccine.

Information for persons who started an HPV vaccination series with quadrivalent or bivalent HPV vaccine

If a series was started with quadrivalent HPV vaccine or bivalent HPV vaccine, can it be completed with 9-valent HPV vaccine?

- Yes, ACIP recommendations state that 9-valent HPV vaccine may be used to continue or complete a series started with a different HPV vaccine product.

Are additional 9-valent HPV vaccine doses recommended for a person who started a series with quadrivalent or bivalent HPV vaccine and completed the series with one or two doses of 9-valent HPV vaccine?

- There is no ACIP recommendation for additional 9-valent HPV vaccine doses for persons who started the series with quadrivalent or bivalent HPV vaccine and completed the series with 9-valent HPV vaccine.

National Center for Immunization and Respiratory Diseases
Office of the Director

CS258131

If a series was started with quadrivalent HPV vaccine or bivalent HPV vaccine and will be completed with 9-valent HPV vaccine, what are the intervals for the remaining doses in the 3-dose series?

- The current recommended HPV vaccination schedule is for the second dose to be given 1-2 months after the first dose and the third dose 4 months after the second dose (6 months after the first dose). ACIP does not state maximum intervals between HPV doses.
- Antibody titers have not been found to be diminished after longer than standard intervals between doses. Data from a few studies of bivalent and quadrivalent HPV vaccines showed similar or higher antibody titers when 2 doses were administered at an interval of 6 months compared with 2 months. An ongoing immunogenicity study is evaluating 2 doses of 9-valent HPV vaccine in 9-14 year olds separated by an interval of 6 or 12 months.

If a person desires protection against the 5 additional types prevented by the 9-valent HPV vaccine and has started a series with another HPV vaccine product, what issues should be considered?

- The majority of all HPV-associated cancers that can be prevented by vaccination are due to HPV 16 and 18. These are the HPV types prevented by all three vaccines: bivalent vaccine, quadrivalent vaccine and 9-valent vaccine.
- The benefit of protection against the 5 additional types targeted by 9-valent HPV vaccination is mostly limited to females for prevention of cervical cancers and precancers. This is because only a small percentage of HPV-associated cancers in males is due to the 5 additional types in 9-valent HPV vaccine.
- Available data show no serious safety concerns in persons who were vaccinated with 9-valent HPV vaccine after having received a 3-dose series of quadrivalent HPV vaccine at least 12 months earlier.
- Cervical cancer screening is recommended beginning at age 21 years and continuing through age 65 years for both vaccinated and unvaccinated women.

What data are available on the number of doses of 9-valent vaccine needed for protection against the 5 additional types for a series started with quadrivalent HPV vaccine and completed with 9-valent HPV vaccine?

- There are no data on efficacy or immunogenicity of 1, 2 or 3 doses of 9-valent HPV vaccine among persons who have received 1 or 2 doses of quadrivalent HPV vaccine.
- In an immunogenicity and safety clinical trial, 3 doses of 9-valent HPV vaccine (on a 0,2,6 month schedule) were given to females who had completed a 3-dose quadrivalent HPV vaccine series; the first dose of 9-valent HPV vaccine was administered 12 to 36 months after completing a quadrivalent vaccine series.
  - After 3 doses, over 98% of vaccinees developed antibodies to all 5 additional types. Antibody was also measured after the first dose of 9-valent HPV vaccine; most but not all of the vaccinees in this trial developed antibody against all 5 additional types. Antibody titers were higher after the third dose than after the first dose. Antibody was 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 9-valent HPV vaccine after 3 doses of quadrivalent HPV vaccine were lower than those of persons who received 3 doses of 9-valent HPV vaccine without prior HPV vaccination. The significance of the lower antibody titers is not known because there is no immune correlate of protection.
- An immunogenicity trial of 2 doses of 9-valent HPV vaccine in HPV vaccine naïve adolescents 9-14 years is ongoing; results are expected to be available within a year. In this trial, the 2 doses are separated by an interval of 6 or 12 months.
  - Results from this trial will not directly address additional 9-valent vaccination in persons who already received quadrivalent HPV vaccine.

What data are available on the safety of 9-valent HPV vaccination after a series started with another HPV vaccine product?

- In a randomized trial, 9-valent HPV vaccine was compared with placebo in females aged 12-26 years who had previously received 3 doses of quadrivalent HPV vaccine. Among the 608 females who received 9-valent HPV vaccine, there was an acceptable safety profile.
- Compared to persons in other studies who were vaccinated with 9-valent HPV vaccine and had never received any HPV vaccination, those who received 9-valent HPV vaccine after a 3-dose quadrivalent vaccine series had higher rates of injection site swelling and redness.

- Otherwise, the safety profiles of 9-valent vaccine given to HPV vaccine naïve persons and 9-valent vaccine given to persons who had previously completed a 3-dose series were generally similar.

Information for persons who previously completed a 3-dose HPV vaccination series

Is additional vaccination with 9-valent HPV vaccine recommended for persons who have completed a 3-dose series of either quadrivalent or bivalent HPV vaccine?

- There is no ACIP recommendation for routine additional 9-valent HPV vaccination of persons who previously completed a quadrivalent or bivalent vaccination series.

If a person desires protection against the 5 additional types prevented by the 9-valent HPV vaccine and has completed a 3-dose series of quadrivalent HPV vaccine, what issues should be considered?

- The majority of all HPV-associated cancers that can be prevented by vaccination are due to HPV 16 and 18. These are the HPV types prevented by all three vaccines: bivalent vaccine, quadrivalent vaccine and 9-valent vaccine.
- The benefit of protection against the 5 additional types targeted by 9-valent HPV vaccination would be mostly limited to females for prevention of cervical cancers and precancers. This is because only a small percentage of HPV-associated cancers in males is due to the 5 additional types in 9-valent HPV vaccine.
- Available data show no serious safety concerns in persons who were vaccinated with 9-valent HPV vaccine after having completed a 3-dose quadrivalent HPV vaccination series.
- Cervical cancer screening is recommended beginning at age 21 years and continuing through age 65 years for both vaccinated and unvaccinated women.

What data are available on efficacy and immunogenicity of 9-valent HPV vaccination when administered after a complete 3-dose series of another HPV vaccine product?

- In an immunogenicity and safety clinical trial, 3 doses of 9-valent HPV vaccine (on a 0,2,6 month schedule) were given to females who had completed a 3-dose quadrivalent HPV vaccine series; the first dose of 9-valent HPV vaccine was administered 12 to 36 months after completing a quadrivalent vaccine series.
  - After 3 doses, over 98% of vaccinees developed antibodies to all 5 additional types. Antibody was also measured after the first dose of 9-valent HPV vaccine; most but not all of the vaccinees in this trial developed antibody against all 5 additional types. Antibody titers were higher after the third dose than after the first dose. Antibody was 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 9-valent HPV vaccine after 3 doses of quadrivalent HPV vaccine were lower than those of persons who received 3 doses of 9-valent HPV vaccine without prior HPV vaccination. The significance of the lower antibody titers is not known because there is no immune correlate of protection.
- An immunogenicity trial of 2 doses of 9-valent HPV vaccine in HPV vaccine naïve persons is ongoing; results will be available within a year. In this trial, the 2 doses are separated by an interval of 6 or 12 months.
  - Results from this trial will not directly address additional 9-valent vaccination in persons who already received quadrivalent HPV vaccine.

What data are available on the safety of 9-valent HPV vaccination when administered after a complete 3-dose series of another HPV vaccine product?

- In a randomized trial, 9-valent HPV vaccine was compared with placebo in females aged 12-26 years who had previously received 3 doses of quadrivalent HPV vaccine. Among the 608 who received 9-valent HPV vaccine, there was an acceptable safety profile.
- Compared to persons in other studies who were vaccinated with 9-valent HPV vaccine and had never received any HPV vaccination, those who received 9-valent HPV vaccine after a 3-dose quadrivalent vaccine series had higher rates of injection site swelling and redness.
- Otherwise, the safety profiles of 9-valent vaccine given to HPV vaccine naïve persons and 9-valent vaccine given to persons who had previously completed a 3-dose series were generally similar.

What is the cost effectiveness of 3 additional doses of 9-valent HPV vaccine for persons who already have received a complete 3-dose HPV vaccination series?

- The estimated cost per quality-adjusted life year (QALY) gained for giving 3 doses of 9-valent HPV vaccine to females aged 13-18 years who have received 3 doses of quadrivalent vaccine is over $100,000.
- The potential benefit would be lower and the cost per QALY gained higher in females older than 18 years and in males of any age.
- In contrast, models have estimated that routine 9-valent HPV vaccination in the United States would be cost-saving, compared with routine quadrivalent HPV vaccination.

References

1. Food and Drug Administration. Highlights of prescribing information. Gardasil 9 (human papillomavirus 9-valent vaccine, recombinant). Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2014. Available at http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf
2. Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. NEJM 2015;372:711–23.
3. Van Damme P, Olsson S, Block S, et al. Immunogenicity and safety of a 9-valent HPV vaccine. Pediatrics 2015;136:e28-39.
4. Vesikari T, Brodszki N, van Damme P, et al. A randomized, double-blind, Phase III Study of the immunogenicity and safety of a 9-valent human papillomavirus L1 virus-like particle vaccine (V503) versus Gardasil®in 9-15-year-old girls. Pediatr Infect Dis J 2015 (Epub ahead of print).
5. Markowitz LE, Dunne EF, Saraiya M, et al. Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2014;63:1–30.
6. Petrosky E, Bocchini J, Hariri S, et al. Use of 9-Valent Human Papillomavirus (HPV) Vaccine: Updated HPV Vaccination Recommendations of the Advisory Committee on Immunization Practices. MMWR 2015:64;300-4.