FDA Licensure of Quadrivalent Human Papillomavirus Vaccine (HPV4, Gardasil) for Use in Males and Guidance From the Advisory Committee on Immunization Practices (ACIP)

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Continued advances in the ability to detect and identify STEC O157 outbreaks and their sources of contamination have provided opportunities to improve food safety. However, despite beef testing and monitoring and interventions at beef slaughtering and processing facilities aimed at preventing STEC O157 contamination, contaminated beef continues to cause outbreaks. In the two outbreaks described in this report, 99 cases were identified. Because an estimated 20 STEC illnesses occur for every one reported, the number of cases reported in the outbreaks likely represent a small proportion of the actual number of persons who became ill.

The outbreaks were notable because of two findings. First was the discovery in outbreak 2 of STEC O157 bacterial contamination of an intact cut of beef intended for grinding at a retail chain. Ground beef (and mechanically tenderized steaks) can be contaminated during processing throughout the product, resulting in a risk to consumers if ground beef is only cooked at the surface. STEC O157 is considered an adulterant in intact products such as ground beef, and FSIS considers its presence unacceptable in intact products intended for use as ground beef. Contamination of intact cuts of beef generally occurs as a consequence of handling during hide removal and dressing of carcasses. Meat contamination at slaughter facilities can indicate that the facility is not adequately addressing contamination from hides.

The second notable finding was that the two outbreaks caused widespread illness and were linked to multiple contaminated meat products, but were traced to a single beef slaughter facility. The detection of two STEC O157 outbreaks linked to the same beef slaughter facility suggests that improved processing controls were needed within the plant. FSIS recommended changes designed to improve the ability to detect contamination events, both within that facility and industrywide, including the initiation of a testing program at establishments processing trim derived from intact cuts, because trim is often converted into ground beef, and institution of new verification procedures by inspectors aimed at further minimizing contamination during slaughter.

Public health agencies should continue to educate consumers regarding the dangers associated with handling raw ground beef and consuming undercooked ground beef or other undercooked nonintact beef products. Consumers should know that preventive measures include thorough hand washing after handling raw beef; washing any surfaces that have come into contact with raw beef with hot, soapy water; keeping raw beef separate from other food products; and cooking ground beef to 160°F (71.1°C), as measured by a food thermometer.

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References

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1 table omitted

On October 16, 2009, the Food and Drug Administration licensed quadrivalent human papillomavirus vaccine (HPV4; Gardasil, Merck & Co. Inc.) for use in males aged 9 through 26 years for prevention of genital warts caused by human papillomavirus (HPV) types 6 and 11. HPV4 had been licensed previously for use in females aged 9 through 26 years for prevention of HPV 6, 11, 16, and 18-related outcomes (i.e., vaginal, vulvar, and cervical precancers and cancers and genital warts). The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of females at age 11 or 12 years and catch-up vaccination for females aged 13 through 26 years. On October 21, 2009, ACIP provided guidance that HPV4 may be given to males aged 9 through 26 years to reduce their likelihood of acquiring genital warts; ACIP does not recommend HPV4 for routine use among males. This report presents the ACIP policy statement and summarizes back-
ground data. Issues reviewed by ACIP included efficacy, immunogenicity, and safety of the HPV4 vaccine in males, epidemiology of HPV and burden of HPV-associated diseases and cancers in males, cost-effectiveness of male vaccination, and programmatic considerations.

HPV types 6 and 11 cause approximately 90% of genital warts and most cases of recurrent respiratory papillomatosis. Approximately 500,000 cases of genital warts are estimated to occur each year in the United States among sexually active men and women.2-3 Direct medical costs related to genital warts are estimated at $200 million per year2,3 in addition, genital warts can have an adverse impact on quality of life.4 HPV-associated cancers in males include certain anal, penile, and oropharyngeal and oral cavity cancers caused primarily by HPV 16.

HPV4 has high efficacy for prevention of genital warts. The phase III efficacy study enrolled 4,065 males aged 16 through 26 years. Participants were enrolled from North America, South America, Europe, Australia, and Asia. The efficacy for prevention of genital warts related to HPV types 6, 11, 16, or 18 among males who received all 3 vaccine doses were seronegative at day 1, and DNA negative day 1 through month 7 to the respective HPV type (per protocol population) was 89.4%; the efficacy for HPV 6 or 11-related genital warts alone was approximately the same.5 The efficacy for prevention of HPV6, 11, 16, or 18-related genital warts among males who received at least 1 vaccine dose and were seronegative at day 1, and DNA negative day 1 through month 7 to the respective HPV type (per protocol population) was 89.4%; the efficacy for HPV 6 or 11-related genital warts alone was approximately the same.5 The efficacy for prevention of HPV6, 11, 16, or 18-related genital warts among males who received at least 1 vaccine dose and were seronegative at day 1, and DNA negative day 1 through month 7 to the respective HPV type (per protocol population) was 89.4%; the efficacy for HPV 6 or 11-related genital warts alone was approximately the same.5 The efficacy for prevention of HPV6, 11, 16, or 18-related genital warts among males who received at least 1 vaccine dose and were seronegative at day 1, and DNA negative day 1 through month 7 to the respective HPV type (per protocol population) was 89.4%; the efficacy for HPV 6 or 11-related genital warts alone was approximately the same.5 The efficacy for prevention of HPV6, 11, 16, or 18-related genital warts among males who received at least 1 vaccine dose and were seronegative at day 1, and DNA negative day 1 through month 7 to the respective HPV type (per protocol population) was 89.4%; the efficacy for HPV 6 or 11-related genital warts alone was approximately the same.5 The efficacy for prevention of HPV6, 11, 16, or 18-related genital warts among males who received at least 1 vaccine dose and were seronegative at day 1, and DNA negative day 1 through month 7 to the respective HPV type (per protocol population) was 89.4%; the efficacy for HPV 6 or 11-related genital warts alone was approximately the same.5 The efficacy for prevention of HPV6, 11, 16, or 18-related genital warts among males who received at least 1 vaccine dose and were seronegative at day 1, and DNA negative day 1 through month 7 to the respective HPV type (per protocol population) was 89.4%; the efficacy for HPV 6 or 11-related genital warts alone was approximately the same.5 The efficacy for prevention of HPV6, 11, 16, or 18-related genital warts among males who received at least 1 vaccine dose and were seronegative at day 1, and DNA negative day 1 through month 7 to the respective HPV type (per protocol population) was 89.4%; the efficacy for HPV 6 or 11-related genital warts alone was approximately the same.5 The efficacy for prevention of HPV6, 11, 16, or 18-related genital warts among males who received at least 1 vaccine dose and were seronegative at day 1, and DNA negative day 1 through month 7 to the respective HPV type (per protocol population) was 89.4%; the efficacy for HPV 6 or 11-related genital warts alone was approximately the same.5 The efficacy for prevention of HPV6, 11, 16, or 18-related genital warts among males who received at least 1 vaccine dose and were seronegative at day 1, and DNA negative day 1 through month 7 to the respective HPV type (per protocol population) was 89.4%; the ef

As observed previously with females, the clinical trials for males, the most common adverse events were injection-site reactions, most of which were mild or moderate in intensity.3 Headache and fever were the most commonly reported systemic adverse reactions in both treatment groups.3 Postlicensure data in females indicate that HPV4 adverse events are similar to adverse events reported following administration of other vaccines to adolescents.6 Mathematical modeling suggests that adding male HPV vaccination to a female-only HPV vaccination program is not the most cost-effective vaccination strategy for reducing the overall burden of HPV-associated conditions in males and females when vaccination coverage of females is high (>80%).7 When coverage of females is less than 80%, male vaccination might be cost-effective, although results vary substantially across models.7 Because the health burden is greater in females than males, and numerous models have shown vaccination of adolescent girls to be a cost-effective use of public health resources, improving coverage in females aged 11 and 12 years could potentially be a more effective and cost-effective strategy than adding male vaccination.

Men who have sex with men (MSM) are at particular risk for conditions associated with HPV types 6, 11, 16, and 18; diseases and cancers that have a higher incidence among MSM include anal intraepithelial neoplasias, anal cancers, and genital warts.8,9 HPV4 has high efficacy for prevention of anal intraepithelial neoplasia in MSM10; however, this information was not available before the October 2009 ACIP meeting and has not yet been reviewed by FDA.

**Vaccine Guidance**

The 3-dose series of HPV4 may be given to males aged 9 through 26 years to reduce their likelihood of acquiring genital warts. HPV4 would be most effective when given before exposure to HPV through sexual contact.

**Administration, Special Situations, Precautions, and Contraindications**

HPV4 is administered in a 3-dose schedule. The second dose is administered 1 to 2 months after the first dose, and the third dose is administered 6 months after the first dose. The minimum interval between the first and second dose of vaccine is 4 weeks, and the minimum interval between the second and third dose is 12 weeks. The minimum interval between the first and third dose is 24 weeks. Doses received after a dosing interval that is shorter than recommended should be readministered.

If the HPV vaccine schedule is interrupted, the vaccine series does not need to be restarted. Co-administration of a different inactivated or live vaccine, either simultaneously or at any time before or after HPV4 is permitted because HPV4 is not a live vaccine.

HPV4 can be administered to persons who are immunosuppressed (from disease or medications). However, the immune response and vaccine efficacy might be less than that in immunocompetent persons.

HPV4 can be administered to persons with minor acute illnesses. Vaccination of persons with moderate or severe acute illnesses should be deferred until after the patient improves.

Syncope can occur after vaccination and has been observed among adolescents and young adults. To avoid serious injury related to a syncopal episode, vaccine providers should consider observing patients for 15 minutes after the patient improves.

HPV4 is contraindicated for persons with a history of immediate hypersensitivity to any vaccine component. HPV4 is a recombinant vaccine produced in *Saccharomyces cerevisiae* (baker’s yeast) and is contraindicated for persons with a history of immediate hypersensitivity to yeast.

**REFERENCES**

10 Available.