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Enclosed please find a copy of the article, "Recommendations on the Use of Quadrivalent Human Papillomavirus Vaccine in Males— Advisory Committee on Immunization Practices (ACIP), 2011" published in *Morbidity and Mortality Weekly Report*, Volume 60, No. 50, December 23, 2011.

This information is provided as a service to the health care community by Merck. It does not include all of the information regarding GARDASIL® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant], that is set forth in the Prescribing Information and may contain statements that differ from the Prescribing Information. Merck does not recommend the use of its products other than as described in the Prescribing Information.

Indication

GARDASIL is a vaccine indicated in females 9 through 26 years of age for the prevention of cervical, vulvar, and vaginal cancers and for males and females 9 through 26 years of age for the prevention of anal cancer, precancerous or dysplastic lesions, and genital warts caused by human papillomavirus (HPV) Types 6, 11, 16, and 18.

GARDASIL does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening. Recipients of GARDASIL should not discontinue anal cancer screening if it has been recommended by a health care professional.

GARDASIL has not been demonstrated to provide protection against diseases from vaccine and non-vaccine HPV types to which a person has previously been exposed through sexual activity.

GARDASIL is not intended to be used for treatment of active external genital lesions; cervical, vulvar, vaginal, and anal cancers; or cervical intraepithelial neoplasia (CIN), vulvar intraepithelial neoplasia (VIN), vaginal intraepithelial neoplasia (VaIN), or anal intraepithelial neoplasia (AIN).

GARDASIL has not been demonstrated to protect against diseases due to HPV types not contained in the vaccine.

Not all vulvar, vaginal, and anal cancers are caused by HPV, and GARDASIL protects only against those vulvar, vaginal, and anal cancers caused by HPV Types 16 and 18.

Recommendations on the Use of Quadrivalent Human Papillomavirus Vaccine in Males — Advisory Committee on Immunization Practices (ACIP), 2011

On October 25, 2011, the Advisory Committee on Immunization Practices (ACIP) recommended routine use of quadrivalent human papillomavirus (HPV) vaccine (HPV4; Gardasil, Merck & Co. Inc.) in males aged 11 or 12 years. ACIP also recommended vaccination with HPV4 for males aged 13 through 21 years who have not been vaccinated previously or who have not completed the 3-dose series; males aged 22 through 26 years may be vaccinated. These recommendations replace the October 2009 ACIP guidance that HPV4 may be given to males aged 9 through 26 years (1). For these recommendations, ACIP considered information on vaccine efficacy (including data available since October 2009, on prevention of grade 2 or 3 anal intraepithelial neoplasia [AIN2/3], a precursor of anal cancer), vaccine safety, estimates of disease and cancer resulting from HPV, cost-effectiveness, and programmatic considerations. The evidence for HPV4 vaccination of males was evaluated using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methods (2).

Background of HPV Vaccination Program in the United States

HPV4 is directed against HPV types 6, 11, 16, and 18, and was licensed by the Food and Drug Administration (FDA) for use in females in June 2006. Bivalent HPV vaccine (HPV2; Cervarix, GlaxoSmithKline) is directed against HPV 16 and 18, and was licensed for use in females in October 2009. ACIP recommends either vaccine for routine use in females aged 11 or 12 years (3). In 2009, HPV4 was licensed for use in males for prevention of genital warts; in December 2010, FDA added prevention of anal cancer in males and females as an indication for use (4). Since 2006, HPV vaccine coverage in females has increased but remains low. In 2010, coverage with at least 1 dose among females aged 13 through 17 years was 48.7%, and 3-dose coverage was 32.0% (5). Coverage with at least 1 dose among males aged 13 through 17 years was <2%.

Burden of Disease and Cancer in Males

HPV-associated cancers in males include some anal, penile, and oropharyngeal cancers caused primarily by HPV 16 (6–9). An estimated 22,000 HPV 16- and 18-associated cancers occur annually in the United States, including an estimated 7,000 HPV 16- and 18-associated cancers in males (9). Data from U.S. cancer registries have shown increases in the incidence of oropharyngeal and anal cancers in men (8,9); an evaluation of data from 1973–2007 found increases of 1% per year for oropharyngeal cancers and 3% per year for anal cancers (9).

Nononcogenic HPV types, primarily 6 and 11, cause >90% of genital warts (condylomata) and most cases of recurrent respiratory papillomatosis. Approximately 250,000 cases of genital warts occur each year in the United States among sexually active males (10,11).

Efficacy

In a phase III efficacy trial, HPV4 had high efficacy for prevention of genital warts among 4,055 males aged 16 through 26 years. Exclusion criteria included history of genital warts, history of genital lesions possibly HPV-related, and less than one or more than five lifetime sex partners. Among those who received all 3 vaccine doses and were seronegative at day 1 and DNA-negative day 1 through month 7 to the respective HPV type (per protocol population), efficacy for prevention of HPV 6-, 11-, 16-, and 18-related genital warts was 89.3% (95% confidence interval [CI] = 65.3%–97.9%); efficacy for HPV 6- and 11-related genital warts was similar. Efficacy for prevention of HPV 6-, 11-, 16- and 18-related genital warts among males who received at least 1 vaccine dose, regardless of baseline infection or serology (intent to treat population), was 68.1% (CI = 48.8%–80.7%) (4). No efficacy was observed among males who were infected with the respective HPV type at baseline. Although grade 1, 2, and 3 penile/perineal/perianal intraepithelial neoplasias were evaluated, too few were observed, and efficacy was not demonstrated (4).

A substudy of the phase III efficacy trial included 598 men who have sex with men (MSM), aged 16 through 26 years; outcomes were genital warts; AIN grades 1, 2, or 3 (AIN1/2/3); and AIN2/3. Per protocol efficacy for prevention of HPV 6-, 11-, 16-, and 18-related genital warts was 88.1% (CI = 13.9%–99.7%) (Carlos Sattler, MD, Merck, personal communication, August 2011). Per protocol efficacy for prevention of HPV 6-, 11-, 16-, 18- related AIN1/2/3 was 77.5% (CI = 39.6%–93.3%), and against AIN2/3 was 74.9% (CI = 8.8%–95.4%) (Table) (4). In the intent to treat population, efficacy for prevention of HPV 6-, 11-, 16-, and 18-related AIN1/2/3 was 50.3% (CI = 25.7%–67.2%), and prevention of HPV 6-, 11-, 16-, and 18-related AIN2/3 was 54.2% (CI = 18.0%–75.3%) (4). In the intent to treat population, efficacy for prevention of any HPV type-related AIN2/3 was 24.3% (CI = -13.8%–50.0%) (4). No studies have evaluated the efficacy of HPV4 for prevention of recurrent respiratory papillomatosis or oropharyngeal cancer.

The efficacy of HPV4 for prevention of HPV-related precancerous lesions and disease is supported further by studies

TABLE. Efficacy of quadrivalent HPV vaccine for prevention of HPV 6-, 11-, 16-, and 18-related genital warts, AIN1/2/3, or AIN 2/3, per protocol,* in males aged 16 through 26 years[†]

| Condition | Control | | Vaccine | | Vaccine efficacy | |
|-----------------------|---------|-------|---------|-------|------------------|-------------|
| | No. | Cases | No. | Cases | % | (95% CI) |
| Genital warts | 1,404 | 28 | 1,394 | 3 | 89.3 | (65.3–97.9) |
| AIN1/2/3 [§] | 208 | 24 | 194 | 5 | 77.5 | (39.6–93.3) |
| AIN2/3 [§] | 208 | 13 | 194 | 3 | 74.9 | (8.8–95.4) |

Abbreviations: HPV = human papillomavirus; AIN = anal intraepithelial neoplasia; CI = confidence interval.

Source: Food and Drug Administration. Highlights of prescribing information. Gardasil (human papillomavirus quadrivalent [types 6, 11, 16 and 18]). Available at <http://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm111263.pdf>.

* Per protocol population included males who received all 3 vaccine doses, were seronegative at day 1 and DNA negative at day 1 through month 7 to the respective HPV type, with case counting beginning after month 7.

[†] Participants were enrolled from North America, South America, Europe, Australia, and Asia; median duration of follow-up was 2.3 years for the study in all males and 2.6 years for the study in men who have sex with men (MSM).

[§] Efficacy for AIN studied in MSM.

among females. In three trials, HPV4 had high efficacy (>98%) for prevention of HPV 6-, 11-, 16-, and 18-related grade 2 or 3 cervical intraepithelial neoplasia (CIN2/3) or adenocarcinoma in situ (AIS), grade 2 or 3 vulvar intraepithelial neoplasia (VIN2/3), and grade 2 or 3 vaginal intraepithelial neoplasia (VaIN2/3) (12).

Immunogenicity

Data on immunogenicity in males are available from the phase III trial conducted among males aged 16 through 26 years and from bridging immunogenicity studies conducted among males aged 9 through 15 years (4). Seroconversion was high for all four HPV vaccine types and postvaccination antibody titers were significantly higher in males aged 9 through 15 years compared with males aged 16 through 26 years (4). Data from a follow-up study of 500 boys who were in an immunogenicity study showed no cases of persistent infection or disease related to any of the four HPV vaccine types during 6 years of follow-up (13). The high efficacy found in the clinical trials in females and males to date has not allowed identification of a minimum protective antibody titer.

Safety

Clinical trial data in approximately 5,300 males found that the most common adverse events were mild or moderate, and were most commonly injection-site reactions (4). Headache and fever were the most commonly reported systemic adverse events in vaccine recipients and controls (4). Since licensure, at least 40 million doses of HPV4 have been distributed in the United States through September 2011. National postlicensure safety data indicate that HPV4 adverse events were similar to those from prelicensure trials (14). Postlicensure safety data from the Vaccine Safety Datalink study, including data from >600,000 HPV4 doses administered, showed no statistically significant increased risk for the outcomes studied, including Guillain-Barré syndrome, stroke, venous thromboembolism,

appendicitis, seizures, syncope, allergic reactions, and anaphylaxis (15). Postlicensure safety data from a manufacturer-sponsored study found no increased risk for outcomes such as anaphylaxis and venous thromboembolism; however, persons who were vaccinated with HPV4 were more likely to faint on the day they were vaccinated than another period in which vaccine was not administered (16). ACIP recommends that vaccination providers should consider observing patients for 15 minutes after all vaccinations, including HPV vaccination.

Cost-Effectiveness

The cost-effectiveness* of male vaccination is sensitive to a range of assumptions, such as vaccine efficacy, vaccine coverage of females, the range of health outcomes included, and the effect of HPV-associated diseases on quality of life (17–20). Adding male vaccination to female-only vaccination becomes more cost-effective when all HPV-associated health outcomes are included in the model and vaccine coverage of females is low (e.g., 3-dose vaccine coverage <50% by age 12 years). Adding male vaccination to female-only vaccination becomes less cost-effective when considering scenarios such as only the health outcomes for which evidence of vaccine efficacy is available, when vaccine coverage of females is high (such as 3-dose vaccine coverage >70% by age 12 years), if vaccinated males have mostly vaccinated sex partners, and when male vaccination is compared with a strategy of increased vaccine coverage of females (20). At the current vaccine price, adding male vaccination at age 12 years to a female-only vaccination

* By charter, when considering recommendations for use of a vaccine, ACIP members' deliberations should include consideration of vaccine efficacy, as well as cost-benefit and risk-benefit analyses. No predefined threshold for cost-effectiveness is considered. To ensure that economic data presented to ACIP and its working groups are uniform in presentation, understandable, and of the highest quality, lead economists and the Health Economics Research Group at CDC developed *Guidance for Health Economics Studies Presented to the ACIP*, available at <http://www.cdc.gov/vaccines/recs/acip/economic-studies.htm>. The guidance specifically mandates technical review of any economic study that is presented to ACIP.

strategy would cost approximately \$20,000–\$40,000 per quality-adjusted life year (QALY) in the more favorable scenarios and approximately \$75,000 to >\$250,000 per QALY in less favorable scenarios (18–20). Vaccination of adult males becomes less cost-effective as age at vaccination increases, and models suggest the cost per QALY gained by vaccinating males >21 years would be approximately 2–4 times that of vaccinating males aged <18 years (21).

Special Populations

MSM are at higher risk for conditions associated with HPV types 6, 11, 16, and 18 than are heterosexual men; diseases and cancers that have a higher incidence among MSM include AIN, anal cancers, and genital warts (22,23). HPV4 clinical trial data demonstrated high efficacy for prevention of genital warts, AIN1/2/3, and AIN2/3 (4). HPV4 is not licensed for males aged >26 years, and no information is available on the efficacy for prevention of outcomes in MSM aged >26 years. A cost-effectiveness analysis estimated <\$50,000 per QALY for vaccination of MSM through age 26 years, using various assumptions (24).

Persons infected with the human immunodeficiency virus (HIV) also have a high burden of HPV-associated outcomes. Genital warts are more common and more difficult to treat in HIV-infected persons (25). AIN and anal cancer are common in HIV-infected MSM, and data suggest that effective antiretroviral therapy has not reduced the burden of anal cancer (26). One small trial in HIV-infected boys and girls found HPV4 to be safe and immunogenic (27), as did a study in HIV-infected men (28). Antibody titers to vaccine types 6 and 18 were lower in HIV-infected children than those observed in age-matched HIV-uninfected children; the clinical significance of this is not known (27). Ongoing studies will evaluate the efficacy and duration of immune response in HIV-infected persons.

GRADE

Data on HPV4 for males were reviewed according to GRADE methods (2). Factors considered in determining the recommendation included benefits and harms, evidence type, values and preferences, and health economic analysis.[†]

Rationale

Although the largest number of HPV-associated cancers occur in women (approximately 15,000 HPV 16- and 18-associated cancers each year), an estimated 7,000 HPV 16- and 18-associated cancers occur each year in men in the United States. These include anal, oropharyngeal, and penile

cancers. HPV4 has high efficacy for prevention of genital warts, AIN1/2/3, and AIN2/3 in males. HPV4 also has high efficacy for prevention of genital warts, CIN1/2/3 or AIS, CIN2/3, VIN2/3, and VaIN2/3 in females. Although data show HPV4 prevents various outcomes, no data are available on the efficacy for prevention of oropharyngeal or penile cancers. Vaccination of males would provide direct benefits and likely would reduce HPV 6, 11, 16, and 18 transmission, and resulting infection, disease, and cancers in females (through herd immunity). However, no clinical efficacy data demonstrating that HPV4 prevents HPV transmission are available.

Because HPV4 is prophylactic, it would be most effective when given before exposure to HPV through sexual contact. The recommendation for vaccination at ages 11 or 12 years is supported by data from the efficacy trial, demonstrating highest efficacy in males who had no evidence of previous or current HPV vaccine type infection, data on sexual behavior in the United States, and immunogenicity studies showing higher antibody titers after vaccination of males at ages 9 through 15 years compared with those aged 16 through 26 years. Other vaccines are recommended at age 11 or 12 years, including HPV vaccine for females. The population level benefits decrease with increasing age at vaccination, especially after age 21 years.

Recommendations

ACIP recommends routine vaccination of males aged 11 or 12 years with HPV4 administered as a 3-dose series (recommendation category: A, evidence type: 2[§]). The vaccination series can be started beginning at age 9 years. Vaccination with HPV4 is recommended for males aged 13 through 21 years who have not been vaccinated previously or who have not completed the 3-dose series. Males aged 22 through 26 years may be vaccinated. Recommendations for administration and precautions are unchanged from previous recommendations (1).

Recommendations for Special Populations

HPV4 is not a live vaccine and can be administered to persons who are immunocompromised as a result of infection (including HIV), disease, or medications. The immune response and vaccine efficacy might be less than that in immunocompetent persons. For immunocompromised males, ACIP recommends routine vaccination with HPV4 as for all males, and vaccination through age 26 years for those who have not been vaccinated previously or who have not completed the 3-dose series.

[†] Additional information is available at <http://www.cdc.gov/vaccines/recs/acip/grade/table-refs.htm>.

[§] Recommendation category A: recommendation that applies to all persons in an age or risk-based group. Evidence type 2: randomized controlled trials with important limitations or exceptionally strong evidence from observational studies.

MSM are at higher risk for infection with HPV types 6, 11, 16, and 18 and associated conditions, including genital warts and anal cancer. For MSM, ACIP recommends routine vaccination with HPV4 as for all males, and vaccination through age 26 years for those who have not been vaccinated previously or who have not completed the 3-dose series.

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Select Safety Information

GARDASIL® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant] is contraindicated in individuals with hypersensitivity, including severe allergic reactions to yeast, or after a previous dose of GARDASIL.

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 vaccination with GARDASIL. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion.

GARDASIL is not recommended for use in pregnant women.

The most common adverse reaction was headache. Common adverse reactions that were observed among recipients of GARDASIL at a frequency of at least 1.0% and greater than placebo were fever, nausea, dizziness; and injection-site pain, swelling, erythema, pruritus, and bruising.

Dosage and Administration

GARDASIL should be administered in 3 separate intramuscular injections in the deltoid region of the upper arm or in the higher anterolateral area of the thigh over a 6-month period with the first dose at an elected date, the second dose 2 months after the first dose, and the third dose 6 months after the first dose.

Before administering GARDASIL, please read the accompanying Prescribing Information. For additional copies of the Prescribing Information, call 1-800-672-6372, visit MerckVaccines.com®, or contact your Merck representative.

Sincerely,

A handwritten signature in black ink, appearing to read 'Carlos Sattler', with a stylized flourish at the end.

Carlos Sattler, MD
Senior Director, Adolescent Vaccines
Medical Affairs and Policy
Merck Vaccines

Enclosures: Prescribing Information and Patient Product Information for GARDASIL.