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Quadrivalent Human Papillomavirus (HPV) Types 6, 11, 16, 18 Vaccine:

For the Prevention of Genital Warts in Males

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Abstract

The quadrivalent HPV types 6, 11, 16, 18 vaccine (Gardasil[®]) is a recombinant vaccine comprising purified virus-like particles derived from the L1 capsid proteins of HPV types 6, 11, 16 and 18.

The vaccine was highly immunogenic. Geometric mean titres (GMTs) and seroconversion rates for all four HPV types at month 7 in males aged 10–15 years were noninferior to those in females aged 16–23 years, and those in males aged 9–15 years were noninferior to those in females aged 9–15 years. In addition, GMTs and seroconversion rates in males aged 16–26 years receiving the vaccine were higher than those receiving amorphous aluminium hydroxyphosphate sulfate adjuvant (AAHS) control.

The quadrivalent HPV vaccine was significantly more effective than AAHS control at decreasing the incidence of HPV 6-, 11-, 16- or 18-related external genital lesions (primary endpoint) in a randomized, double-blind, placebo-controlled, multicentre study in males aged 16–26 years. The most common clinical endpoint was HPV 6- and 11-related condyloma; efficacy was robust against these lesions.

The vaccine is also expected to be protective against genital warts in males aged 9–15 years, as the immune response in males of this age group was noninferior to that in males aged 16–26 years.

The quadrivalent HPV vaccine was generally well tolerated in males aged 9–26 years. The most common adverse events reported were injection-site related, and most of these were of mild to moderate severity.

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Features and properties of the quadrivalent human papillomavirus (HPV) types 6, 11, 16, 18 vaccine (Gardasil®)

Featured indication	
Prevention of genital warts (condyloma acuminata) caused by infection with HPV types 6 and 11 in males aged 9–26 y	
Vaccine composition	
Virus-like particles (VLPs) derived from the L1 capsid proteins of HPV types 6, 11, 16 and 18	
Formulated with a proprietary amorphous aluminium hydroxyphosphate sulfate adjuvant (225 µg per dose)	
Dosage and administration	
Route of administration	Intramuscular injection
Dose	0.5 mL (containing 20, 40, 40 and 20 µg of VLPs for HPV types 6, 11, 16 and 18, respectively)
Administration schedule	Three-dose regimen; injections at months 0, 2 and 6
Most common adverse events (5% of males aged 9–26 years receiving the quadrivalent HPV vaccine)	
Injection-site pain, injection-site erythema, injection-site swelling, headache, pyrexia	

Human papillomavirus (HPV) infection has a well established association with the development of genital warts and many types of cancer, including cervical, anal, oropharyngeal and penile cancer.^[1,2] It is the most common sexually transmitted infection in the US,^[1] with an annual prevalence of 1% of the sexually active population.^[2] It has been estimated that 80% of sexually active women will acquire HPV infection by the time they are aged 50 years.^[1] Rates among men are also high, with estimates of ≈65–70% of males being infected with HPV.^[3] Young people appear to be most at risk, with 74% of annual HPV infections occurring in men and women aged 14–24 years.^[1]

While most HPV infections are transient,^[1,2] ≈10% lead to persistent infection.^[1] Approximately 40 of the >100 known HPV types have been shown to infect the anogenital tract.^[1,2] Fifteen of these have been identified as high-risk (including HPV 16 and 18) and twelve as low-risk (including HPV 6 and 11);^[1] HPV 6 and 11 are strongly associated with genital warts (>90% association^[2]), while HPV 16 and 18 are strongly associated with cervical and anogenital cancers.^[1,2] A total of 99.7% of cervical cancers have detectable levels of HPV DNA,^[1] and almost 90% of vaginal cancers are associated with HPV.^[4] In men, 80–85% of anal cancers^[4] and almost 50% of penile cancers^[4,5] are associated with HPV infection.

The rate of new cases of anogenital warts is increasing; currently, more than 500 000 new cases occur in the US annually, and a 2003 estimate found that ≈1.4 million people in the US had genital warts.^[2] Moreover, results from a recent study have suggested that the incidence and prevalence of genital warts may be becoming higher in men than in women.^[6] The societal burden of genital warts, both in terms of cost and loss of quality of life, is significant.^[7–9]

The quadrivalent HPV types 6, 11, 16, 18 vaccine (Gardasil®; hereafter referred to as the quadrivalent HPV vaccine) is a noninfectious recombinant vaccine, and comprises purified virus-like particles derived from the L1 capsid proteins of HPV types 6, 11, 16 and 18.^[10]

Each dose contains approximately 20, 40, 40 and 20 µg of each virus-like particle type, respectively, and includes 225 µg of amorphous aluminium hydroxyphosphate sulfate adjuvant (AAHS).^[10] It was approved in females in the US in 2006^[11] for the prevention of various diseases caused by HPV types 6, 11, 16 and 18, and has recently been approved in males for the prevention of genital warts caused by HPV types 6 and 11.^[10] Over 61 million doses of the quadrivalent HPV vaccine have been distributed worldwide.^[12]

The quadrivalent vaccine has demonstrated efficacy in the prevention of cervical, vulvar and vaginal cancer, genital warts and precancerous or dysplastic lesions caused by HPV types 6, 11, 16 and 18 in females,^[10] and estimates show that, as well as being potentially cost effective,^[13] national vaccination programmes targeting adolescent females and young women can be expected to result in decreased incidences of HPV infection^[14] and genital warts,^[15] in both females and heterosexual males (HM) as a result of herd immunity.^[15] However, no change was predicted for men who have sex with men (MSM; a group with a high prevalence of HPV infection^[16]) or females outside the age range for vaccination.^[15]

Various arguments exist in favour of nationwide vaccination of males as well as females, including the increased likelihood of herd immunity, increased effect in the MSM population and decreased incidence of HPV-associated disease in males (potentially more so than is associated with decreased transmission of the virus from females).^[11,17] While one analysis indicated that the vaccination of males as well as females may not be cost effective in the US,^[18] this study assumed a higher vaccination rate (75% in both sexes) than is currently observed in women in the US and in most other countries,^[11] mainly focused on the prevention of cervical cancer (only including other factors [e.g. genital warts, lower vaccination rates] in secondary scenarios),^[18] and did not specifically include MSM in any analyses.^[18] Other analyses were more positive, one citing substantial public health benefits and cost effectiveness of vaccinating males aged 9–26 years against HPV 6-, 11-, 16- and 18-related diseases,^[19] another finding that vaccinating MSM was a cost-effective method for prevention of HPV-related anal cancer and genital warts.^[20] It has been suggested that if vaccination of one sex falls below 75%, both sexes will need to be vaccinated to achieve herd immunity.^[17] Nevertheless, debate continues as to the necessity of vaccination in males.

This review focuses on the immunogenicity, prophylactic efficacy and tolerability of the quadrivalent HPV vaccine in males aged 9–26 years. Medical literature on the use of the quadrivalent HPV vaccine in males for the prevention of genital warts caused by HPV types 6 and 11 was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data was also requested from the company developing the drug. Searches were last updated 18 February 2011.

1. Immunogenicity

The minimum geometric mean titre (GMT) of serum anti-HPV antibody that is associated with prophylactic efficacy has not been determined.^[10] The immunogenicity of the

quadrivalent HPV vaccine in males, administered alone, was investigated in three studies (V501-016,^[21] V501-018^[22] and V501-020^[23]); two were randomized, double-blind, placebo-controlled, multicentre studies^[22,23] and one was a substudy of a randomized, double-blind, placebo-controlled, multicentre study investigating expiration data, and was not itself randomized or blinded.^[21] A study in HIV-infected children is briefly mentioned.^[24] Additional studies investigated the coadministration of the quadrivalent HPV vaccine with other vaccines.^[25–28] All studies discussed in this section are fully published.^[21–28] Additional data from study V501-020 were taken from the US FDA review of biologics license application.^[29]

Participants were administered injections on day 1, month 2 (± 3 weeks^[21,23]) and month 6 (± 3 ^[21] or 4^[23] weeks).^[21–23] Serum samples were collected on day 1^[21,22,29] and months 3,^[21] 7,^[21,22,29] 18,^[22] 24^[29] and 36;^[29] neutralizing anti-HPV antibody levels were detected using an HPV type-specific competitive Luminex immunoassay.^[21,22,29]

Noninferiority of the immune response in males aged 10–15 years compared with females aged 16–23 years^[21] and in males aged 9–15 years compared with females aged 9–15 years^[22] was demonstrated if both GMT and seroconversion rates for all four HPV vaccine types met non-inferiority criteria in the per-protocol population (see tables I and II for noninferiority criteria and the definition of seroconversion).

- The quadrivalent HPV vaccine showed high immunogenicity in males aged 9–15 years in studies V501-016^[21] and -018.^[22] Seroconversion rates for anti-HPV 6, 11, 16 and 18 were all 99% in these younger male participants (table II).^[21,22] Noninferiority to the immunogenicity observed in females aged 9–15^[22] and 16–23^[21] years was demonstrated with regard to GMTs (table I) and seroconversion rates (table II) at month 7 ($p < 0.001$; co-primary endpoints in V501-016^[21]).
- High immunogenicity was also evident in males aged 16–26 years receiving the quadrivalent HPV vaccine compared with those receiving placebo (AAHS control) in study V501-020.^[23,29] GMTs (table I) and seroconversion rates (table II) were higher at month 7 in vaccine recipients than in AAHS control recipients for all four anti-HPV types.^[29]
- In *post hoc* analyses, immunogenicity in younger males was shown to be noninferior to that in older males.^[29] Anti-HPV responses (GMTs and seroconversion rates at month 7) were compared between males aged 9–15 years (from studies V501-016 and -018) and males aged 16–26 years (from study V501-020).^[29] The noninferiority criteria (lower bound of the 95% confidence interval [CI] of >0.5 for the fold difference between the two groups in GMTs and greater than or equal to -5% for the difference between the two groups in seroconversion rates, for all HPV types) for younger versus older males were met (all $p < 0.001$).^[29]
- Further *post hoc* analyses found that month 7 anti-HPV GMTs in males aged 16–26 years appeared to be lower than those in females aged 16–23 years for HPV types 6, 11 and 18 (GMTs of 447 vs 545 milli-Merck Units (mMU)/mL, 624 vs 749 mMU/mL and 402 vs 476 mMU/mL, respectively) but not for HPV type 16 (GMTs

of 2403 vs 2411 mMU/mL); these differences appeared to persist at month 24.^[29] However, these differences did not appear to correlate with any difference in prophylactic efficacy with regard to the incidence of genital warts.^[29] Moreover, males and females aged 9–15 years appeared to have similar GMTs (table I^[22]).

- In a mixed-sex, *post hoc* analysis of several studies (including studies V501-016 and -018), results indicated that the participant's age at the time of first vaccination dose was inversely proportional to the anti-HPV response associated with the quadrivalent HPV vaccine.^[30] Additionally, participants who were seropositive on day 1 to a particular HPV type appeared to respond more robustly to that type, compared with those who were seronegative at day 1. No other baseline demographic factors appeared to impact on immunogenicity.^[30]
- A phase II, randomized, double-blind, placebo-controlled immunogenicity study in 126 HIV-infected children (both male and female) aged >7 to <12 years demonstrated that the quadrivalent HPV vaccine was immunogenic and had no significant effect on the CD4 percentage or plasma HIV RNA.^[24] Seroconversion to the four HPV antigens occurred in >96% of vaccine recipients and no placebo recipients, and GMTs were many times greater than the seropositivity cutoff value.

Longer-Term Immunogenicity

- Immunogenicity was generally maintained in the longer term, although antibody levels substantially decreased compared with the levels at month 7.^[10,22,29]
- At month 18 in study V501-018, 92.5% of males aged 9–15 years remained seropositive (97.8%, 99.3%, 99.3% and 92.5% for anti-HPV 6, 11, 16 and 18, respectively), and GMTs were ≈4- to 7-fold lower than those at month 7 (227, 292, 1402 and 233 mMU/mL, respectively).^[22] Similar results were observed in females aged 9–15 years with regard to seroconversion rates (97.9%, 99.2%, 99.8% and 91.5%, respectively) and GMTs (213, 300, 1250 and 181 mMU/mL, respectively).^[22] GMTs fell lower still by month 37 (126.6, 148.8, 708.8 and 113.0 mMU/mL, respectively).^[10]
- In study V501-020, immunogenicity appeared to persist into month 24.^[29] GMTs for anti-HPV 6, 11, 16 and 18 at month 24 were 80.3, 94.5, 347.8 and 38.7 mMU/mL in vaccine recipients versus <7, <8, <11 and <10 mMU/mL in AAHS control recipients.^[29] Corresponding seroconversion rates at month 24 were 90.8%, 95.6%, 99.3% and 62.3% versus 2.1%, 1.2%, 0.8% and 1.1%.^[29]
- Month 36 GMTs in 16- to 26-year-old male vaccine recipients decreased further, with anti-HPV 6, 11, 16 and 18 GMTs of 72.4, 80.3, 306.7 and 33.4 mMU/mL.^[10]

Concomitant Administration with Other Vaccines

The effect of coadministering quadrivalent HPV vaccine with other vaccines on the immunogenicity of the vaccines administered has been investigated in three studies in a mixed-sex population^[25–27] and one in a solely female population.^[28] Data in males alone

are not available; however, the immunogenicity of the quadrivalent HPV vaccine in males has been shown to be noninferior to that in females.^[21,22]

- Immunogenicity of the quadrivalent HPV vaccine was not affected by coadministration with a diphtheria, tetanus, pertussis and poliomyelitis vaccine (Repevax[®]),^[25] a meningococcal polysaccharide conjugate vaccine (Menactra[®]) plus a tetanus, diphtheria and pertussis vaccine (AdacelTM)^[26] or a tetanus, diphtheria and pertussis vaccine (BoostrixTM) plus an investigational quadrivalent meningococcal glycoconjugate vaccine^[27] in three randomized, open-label trials in mixed-sex populations aged 11–17,^[25] 10–17^[26] and 11–18^[27] years (n = 843–1620). The noninferiority of the immune response associated with the quadrivalent HPV vaccine with concomitant versus nonconcomitant administration was established for all three vaccination combinations.^[25–27] Moreover, the immune responses related to the other vaccines being investigated were also noninferior with concomitant versus sequential administration.^[25–27]
- Neither of the immune responses associated with the quadrivalent HPV vaccine or a hepatitis B vaccine (Recombivax HB[®]) were affected when coadministered in a population of women aged 16–23 years (n = 1877).^[28] The quadrivalent HPV vaccine seroconversion rates and GMTs observed when the vaccine was coadministered with the hepatitis B vaccine were noninferior (p < 0.001) to those observed when the vaccines were administered alone.

2. Prophylactic Efficacy

The prophylactic efficacy of the quadrivalent HPV vaccine in males has been investigated in the randomized, double-blind, placebo-controlled, multicentre study V501-020; this study also included a substudy in MSM. Data from V501-020 are fully published^[23] and were supplemented by data from the FDA clinical review of biologics license application^[29] and the US manufacturer's prescribing information.^[10]

Participants were randomized to receive a 0.5 mL intramuscular injection of the vaccine (n = 2032) or placebo (consisting of normal saline with 225 µg of AAHS; n = 2033) on day 1, month 2 (±3 weeks) and month 6 (±4 weeks).^[23]

Included participants were males aged 16–26 years (HM aged 16–23 years, MSM aged 16–26 years), who were required to have no history of relevant disease (such as anogenital warts or gross genital lesions indicative of sexually transmitted infections) and to have had 5 lifetime sexual partners (MSM participants must have engaged in insertive or receptive anal intercourse or oral sex with another male in the past year; HM participants were required to be nonvirgins).^[23]

Exclusion criteria included prior HPV vaccination, the administration of any blood product or component in the past 6 months, known immune or coagulation disorders, HIV infection or immunocompromised, or vaccination with inactivated vaccines within the past 14 days or live vaccines within the past 21 days.^[29]

The primary endpoint was the incidence of HPV 6-, 11-, 16- or 18-related external genital lesions (EGL; defined as external genital warts, penile/perianal/perineal intraepithelial neoplasia [PIN], or penile, perianal or perineal cancer) in the per-protocol population.^[23]

Secondary endpoints included the incidence of persistent HPV 6, 11, 16 or 18 infection (DNA of the same HPV type detected by polymerase chain reaction [PCR] assay in two consecutive samples at least 6 months apart) and the incidence of HPV 6, 11, 16 or 18 detection (incident infection; DNA detected at one or more visits).^[23]

The per-protocol population (1397 vaccine and 1408 AAHS control recipients) included participants who had received all three doses and had serology results at month 7.^[23] In addition, to be included in the per-protocol population for each HPV type, participants were required to be seronegative and PCR negative for that type at day 1 (for HPV 6 and HPV 11, participants were required to be seronegative for both anti-HPV 6 and anti-HPV 11^[29]).^[23] Cases of EGL were counted from month 7.

Additional analyses were conducted in the naive-to-relevant-HPV-type population (participants who had received 1 dose of vaccine or AAHS control and were naive [seronegative and PCR negative] to the HPV type being analysed), the modified intent-to-treat (mITT) population (participants who had received 1 dose of vaccine or AAHS control, regardless of HPV status at enrolment) and the generally HPV-naive population (participants who had received 1 dose of vaccine or AAHS control and were generally HPV-naive [seronegative and PCR negative to all vaccine HPV types and PCR negative to multiple other HPV types]).^[23,29]

Baseline characteristics were generally similar between vaccine and AAHS control groups.^[23,29] The mean age was 20.5 years, 38% of participants were circumcised and 99.4% were nonvirgins.^[29] Of the nonvirgins, participants had a median of three lifetime sexual partners, the mean age at first sexual intercourse was 16.8 years, 4% had a sexually transmitted infection, 19% had never used a condom, and 33% had used a condom less than half the time.^[29] A total of 83% of participants were naive to all four vaccine HPV types at baseline.^[10]

- A correlation between neutralizing antibody titres and protection from disease has not yet been demonstrated in males receiving the quadrivalent HPV vaccine.^[29]

External Genital Lesions

- After a median follow-up of 2.9 years, the quadrivalent HPV vaccine was significantly ($p < 0.001$) more effective than AAHS control with regard to decreasing the incidence of HPV 6-, 11-, 16- or 18-related EGL (primary endpoint) in the per-protocol population of males aged 16–26 years (figure 1).^[23] The vaccine was 90.4% effective (95% CI 69.2, 98.1) for this combined efficacy endpoint.
- The vaccine efficacy was 89.4% (95% CI 65.5, 97.9) against genital warts (comprising most cases of EGL) [figure 1].^[23] Efficacy of the vaccine against grade 1 PIN (efficacy 100% [95% CI –431.1, 100]) or grade 2 or 3 PIN (considered

an important measure of efficacy against cancer precursors; efficacy 100% [95% CI –3788.2, 100]) was not demonstrated;^[29] a low number of cases (figure 1) resulted in a wide confidence interval.

- When examined by HPV type, prophylactic efficacy was most robust with regard to HPV 6- and 11-related EGL (figure 2; efficacy 84.3% [95% CI 46.5, 97.0] and 90.9% [95% CI 37.7, 99.8]).^[23] Few cases of HPV 16- or 18-related EGL were reported in either group, again resulting in a wide confidence interval (figure 2; efficacy 100% [–420.8, 100] and 100% [–3804.6, 100]).
- No cases of penile/perianal/perineal cancer were reported in either group.^[29]
- The prophylactic efficacy of the quadrivalent HPV vaccine (with regard to the primary endpoint) when investigated in other participant populations (naïve-to-relevant-HPV-type and mITT) generally supported that observed in the per-protocol population, with a significantly lower overall incidence of HPV 6-, 11-, 16- or 18-related EGL in vaccine than AAHS control recipients in both populations (p-value not reported); genital warts were the most common EGL observed in all populations.^[23]
- In general, participant characteristics in the mITT population did not significantly affect the prophylactic efficacy of the quadrivalent HPV vaccine against any HPV type investigated.^[29] However, evidence of prior exposure to or current infection with HPV 6 and/or 11 appeared to be associated with lower efficacy against any HPV type-related genital warts (20.9% efficacy [95% CI –53.2, 59.5]), with 19 cases in vaccine recipients (n = 186) versus 22 cases in AAHS control recipients (n = 178).
- The overall efficacy of the quadrivalent HPV vaccine against genital warts in a naïve, preadolescent population was inferred by investigating the generally HPV-naïve population in this study, which yielded an efficacy of 85.3% (95% CI 62.1, 95.5).^[29]
- As the immune response associated with the quadrivalent HPV vaccine that was observed in males aged 9–15 years was demonstrated to be noninferior to that observed in males aged 16–26 years (section 1), protection from genital warts in this younger age group can be inferred.^[29]

Persistent Human Papillomavirus (HPV) Infection

- The quadrivalent HPV vaccine was effective in the prevention of persistent HPV infection.^[23] The efficacy of the vaccine at preventing HPV 6-, 11-, 16- or 18-related persistent infection was 85.6% (95% CI 73.4, 92.9; $p < 0.001$) in the per-protocol population. When examined by HPV types, the efficacy was 88.0% (95% CI 66.3, 96.9), 93.4% (95% CI 56.8, 99.8), 78.7% (95% CI 55.5, 90.9) and 96.0% (95% CI 75.6, 99.9) for HPV types 6, 11, 16 and 18, respectively.^[23]

Incident HPV Infection

- The efficacy of the quadrivalent HPV vaccine was also demonstrated with regard to incident HPV infection, with an overall efficacy of 44.7% (95% CI 31.5, 55.6; $p < 0.001$) in the per-protocol population.^[23] When examined by HPV types, the efficacy was 49% (95% CI 27.9, 64.4), 57.0% (95% CI 20.7, 77.6), 41.1% (95% CI 18.5, 57.7) and 62.1% (95% CI 39.2, 77.1) for HPV types 6, 11, 16 and 18, respectively.

In Subpopulations By Sexual Orientation

- In HM participants in the per-protocol population ($n = 3463$), efficacy of the quadrivalent HPV vaccine against HPV 6-, 11-, 16- or 18-related EGL was 92.4% (95% CI 69.6, 99.1), and against HPV 6, 11, 16 or 18 persistent infection and incident infection was 83.7% (95% CI 71.1, 91.5) and 43.6% (28.7, 55.6).^[23] Corresponding efficacies in MSM participants ($n = 602$) were 79.0% (95% CI -87.9, 99.6), 94.4% (95% CI 64.4, 99.9) and 48.8 (11.6, 71.2).^[23]

3. Tolerability

Tolerability data for the quadrivalent HPV vaccine in males were taken from the trials discussed in sections 1 and 2 (studies V501-016,^[21] -018^[22] and -020^[23] and the concomitant administration studies^[25-28]), the US manufacturer's prescribing information^[10] and several post-licensure safety profile reports.^[31-34]

- The quadrivalent HPV vaccine was generally well tolerated in males aged 9–26 years; the most common adverse events (evaluated using vaccination report card-aided surveillance) were injection-site related.^[21-23] The most frequent (5% of vaccine recipients and more frequent than in placebo [either AAHS control or saline] recipients) injection-site reactions across all age groups (pooled data) on days 1–5 postinjection were pain (61.5% of vaccine recipients vs 50.8% of AAHS control and 41.6% of saline recipients), erythema (16.7% vs 14.1% and 14.5%) and swelling (13.9% vs 9.6% and 8.2%).^[10] Of the participants reporting an injection-site adverse event, 96.4% rated it as being of mild or moderate severity.^[10]
- The most common (5% of vaccine recipients [$n = 3092$] and more frequent than in placebo recipients [$n = 2303$]) systemic adverse events on days 1–15 postinjection across all age groups were headache (12.3% of vaccine recipients vs 11.2% of placebo recipients) and pyrexia (8.2% vs 6.5%).^[10] In this instance, placebo refers to both the AAHS control and saline placebo.^[10]
- The incidence of conditions potentially indicative of a systemic autoimmune disorder in males of all ages was reported in 1.4% of quadrivalent HPV vaccine recipients and 1.4% of AAHS control or saline placebo recipients.^[10] The most common of these was arthralgia/arthritis/reactive arthritis (1% vs 0.7%).
- In all age groups and both male and female participants, serious adverse events occurred in 0.8% of 15 706 quadrivalent HPV vaccine recipients and 1.0% of 13 617 AAHS control or saline placebo recipients.^[10] A total of 0.04% of these serious adverse events were judged to be vaccine related, including headache,

gastroenteritis, appendicitis, pelvic inflammatory disease, urinary tract infection, pneumonia, pyelonephritis, pulmonary embolism, bronchospasm, asthma, injection-site pain and injection-site joint movement impairment (all with an incidence of <0.05% in either group).^[10]

- A total of 18 deaths occurred in 15 706 quadrivalent HPV vaccine recipients and 19 deaths occurred in 13 617 AAHS control or saline placebo recipients, none of which were considered vaccine related.^[10]
- In males aged 16–26 years (study V501-020), the tolerability profile of the quadrivalent HPV vaccine was generally similar to that in the any-age and either-sex population.^[23] A total of 63.9% of vaccine recipients and 58.2% of AAHS control recipients reported at least one vaccine-related adverse event (60.1% vs 53.6% were vaccine-related injection-site adverse events, 14.1% vs 14.6% were vaccine-related systemic adverse events).^[23] The most common adverse events (5% of vaccine recipients) in study V501-020 are shown in figure 3.^[29]
- No vaccine-related serious adverse events occurred in either group in males aged 16–26 years; in general, 0.4% of quadrivalent HPV vaccine recipients versus 0.6% of AAHS control recipients reported serious adverse events.^[23] A total of 0.2% versus 0.5% died (none vaccine related);^[23] 0.3% versus 0.7% discontinued because of adverse events, and 0.2% versus 0.5% discontinued because of serious adverse events.^[29]
- The tolerability profile of the quadrivalent HPV vaccine in the substudy of study V501-020 involving MSM participants was similar to that observed in all men in the study, with 70% of vaccine versus 71% of AAHS control recipients reporting at least one adverse event (58% vs 59% were injection-site adverse events); no serious adverse events were reported in this subgroup.^[35]
- Among younger males, the tolerability profile of the quadrivalent HPV vaccine was also generally similar to that in the pooled analyses.^[21,22] Injection-site reactions that were significantly less common in males aged 10–15 years than in females aged 16–23 years were pain (71.4% vs 86.3%; $p < 0.01$) and erythema (18.6% vs 26.2%; $p = 0.04$).^[21] Additionally, in both males and females aged 9–15 years, adverse events reported significantly ($p < 0.01$) more often by vaccine recipients than by saline recipients were injection site pain (73.2% vs 45.4%), erythema (20.3% vs 13.2%) and swelling (20.7% vs 7.7%).^[22]
- Post-licensure safety studies have demonstrated that quadrivalent HPV vaccine after approval has a generally similar tolerability profile to that observed in clinical trials,^[31,32] with the possible exception of syncope and venous thromboembolic events, which were reported disproportionately higher than in clinical trials.^[31] The vaccine is associated with a greater incidence of injection-site pain than placebo, but does not appear to differ from placebo in the incidence of systemic and serious adverse events, as well as the incidence of medical conditions that are consistent with auto-immune disease.^[32]

Concomitant Administration with Other Vaccines

- Overall, coadministration of the quadrivalent HPV vaccine with other vaccines was generally well tolerated.^[25–28]
- Concomitant administration of the quadrivalent HPV vaccine with meningococcal (groups A, C, Y and W-135) polysaccharide diphtheria toxoid conjugate vaccine and tetanus, reduced diphtheria and acellular pertussis vaccine adsorbed was generally well tolerated in a mixed-sex study in participants aged 10–17 years.^[26] An increase in injection-site swelling was observed at the HPV vaccine site (10.9% of recipients of concomitant administration vs 6.9% of recipients of non-concomitant administration; $p = 0.037$) and increased injection-site bruising (5.8% vs 2.2%; $p < 0.05$) and pain (81.9% vs 75.6%; $p < 0.05$) at the other vaccination site.^[26] Most injection-site swelling was reported as mild to moderate in intensity.^[10]
- Coadministration of the quadrivalent HPV vaccine with diphtheria, tetanus, pertussis and poliomyelitis vaccine in boys and girls aged 11–17 years was generally well tolerated; however, there was a small increase in the incidence of headache (26.9% vs 19.4%; risk difference 3.8% [95% CI 0.5, 7.4]) and HPV vaccine injection-site swelling (8.6% vs 4.8%; risk difference 7.5% [95% CI 1.8, 13.2]) in the concomitant group compared with the non-concomitant group.^[25]
- The coadministration of the quadrivalent HPV vaccine and a tetanus, diphtheria and pertussis vaccine plus an investigational quadrivalent meningococcal glycoconjugate vaccine was also generally well tolerated in male and female participants aged 11–18 years.^[27]
- In females aged 16–23 years, coadministration of the quadrivalent HPV vaccine and a hepatitis B vaccine was generally well tolerated, with similar rates of systemic and injection-site adverse events among recipients of concomitant administration compared with recipients of one of the vaccines alone.^[28]

4. Dosage and Administration

The quadrivalent HPV vaccine is indicated in males aged 9–26 years for the prevention of genital warts caused by HPV types 6 and 11, and should be administered as a 0.5 mL intramuscular injection in a three-dose regimen, with the initial dose followed by doses at months 2 and 6.^[10] The injection should be in the deltoid region of the upper arm or in the higher anterolateral area of the thigh. The recipient should be observed for 15 minutes after administration for signs of syncope.^[10]

The safety and efficacy of the quadrivalent HPV vaccine have not been established in males aged <9 years or ≥ 27 years.^[10]

Local prescribing information should be consulted for contraindications, precautions and warnings, drug interactions, dosage modifications, and participant monitoring requirements.

5. Quadrivalent HPV Types 6, 11, 16, 18 Vaccine: Current Status in Males

The quadrivalent HPV vaccine is approved in the US for the prevention of genital warts caused by HPV types 6 and 11 in males aged 9–26 years.^[10] It has shown high immunogenicity in younger (aged 9–15 years) and older (aged 16–26 years) males, as well as prophylactic efficacy in older males in this indication, and immunobridging has allowed the inferred extended efficacy into younger males. The quadrivalent HPV vaccine was generally well tolerated. In addition, several trials are ongoing, including extension studies investigating long-term protection.^[29]

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Fig. 1.

Prophylactic efficacy of the quadrivalent human papillomavirus (HPV) vaccine (qHPV) in males aged 16–26 years. Incidence of HPV 6-, 11-, 16- or 18-related external genital lesions (EGL; primary endpoint), and the subcomponents of genital warts and penile/perianal/perineal intraepithelial neoplasia (PIN) grade 1 (PIN1) and grade 2 or 3 (PIN2/3) in a randomized, double-blind, placebo (amorphous aluminium hydroxyphosphate sulfate adjuvant control) [PL]-controlled, multicentre study, after a median follow-up of 2.9 years.^[23] qHPV or PL was administered as three 0.5 mL doses on day 1 and months 2 and 6. Analyses were conducted in the per-protocol population. θ indicates zero cases were reported. * $p < 0.001$ vs PL.

Fig. 2.

Prophylactic efficacy of the quadrivalent human papilloma-virus (HPV) vaccine (qHPV) in males aged 16–26 years. Incidence of HPV 6-, 11-, 16- or 18-related external genital lesions (EGL), by HPV type, in a randomized, double-blind, placebo (amorphous aluminium hydroxyphosphate sulfate adjuvant control) [PL]-controlled, multi-centre study, after a median follow-up of 2.9 years.^[23] qHPV or PL was administered as three 0.5 mL doses on day 1 and months 2 and 6. Analyses were conducted in the per-protocol population. θ indicates zero cases were reported.

Fig. 3.

Tolerability of the quadrivalent human papillomavirus (HPV) vaccine (qHPV). Adverse events with an incidence of $\geq 5\%$ on days 1–15 (systemic) or days 1–5 (injection-site) following any vaccination visit in a randomized, double-blind, placebo (amorphous aluminium hydroxy-phosphate sulfate adjuvant control) [PL]-controlled, multicentre study.^[29] qHPV or PL was administered as three 0.5 mL doses on day 1 and months 2 and 6. * $p < 0.001$ vs PL.

Table 1

Geometric mean titre (GMT) of the antibodies against human papillomavirus (HPV) types 6, 11, 16 and 18 associated with the quadrivalent human papillomavirus vaccine (qHPV) at month 7.^[21,22,29] Participants received a 0.5 mL intramuscular injection of the vaccine^[21,22,29] or placebo (saline placebo)^[22] or amorphous aluminium hydroxyphosphate sulfate adjuvant control^[29] on day 1 and months 2 and 6. Analyses were performed in the per-protocol population^[21,22,29]

Study	Participants	Vaccine	n ^a	GMT (mMU/mL)			
				anti-HPV 6	anti-HPV 11	anti-HPV 16	anti-HPV 18
V501-016 ^[21]	Males aged 10–15 y	qHPV	427–429	1042	1318	5638	1212
	Females aged 16–23 y	qHPV	306–340	575	706	2548	453
	Fold difference (95% CI)			1.81 (1.58, 2.08) ^b	1.87 (1.60, 2.17) ^b	2.21 (1.84, 2.66) ^b	2.68 (2.24, 3.19) ^b
V501-018 ^[22]	Males aged 9–15 y	qHPV	455–458	1007	1334	6316	1581
	Females aged 9–15 y	qHPV	489–494	808	1187	4490	1071
	Fold difference (95% CI)			1.3 (1.0, 1.5) ^b	1.1 (0.9, 1.4) ^b	1.4 (1.1, 1.8) ^b	1.5 (1.2, 1.9) ^b
V501-020 ^[29]	Males aged 16–26 y	qHPV	1093–1175	447	624	2403	402
	Males aged 16–26 y	PL	1109–1205	<7	<8	<11	<10

^a Participants who had received all three doses^[21,22,29] and had serology results at month 7.^[21,29] In addition, to be included in the per-protocol population for each HPV type, participants were required to be seronegative for that type at day 1 (for HPV 6 and HPV 11, participants were required to be seronegative for both anti-HPV 6 and anti-HPV 11 antibodies^[21,29]). The number of participants evaluated varied between viral particle types.

^b Noninferiority demonstrated ($p < 0.001$). The lower bound of the 95% CI for the fold difference between the two groups was >0.5 for all HPV types.^[21,22]

mMU/mL = milli-Merck Units per millilitre; n = number of participants evaluated; PL = placebo.

Table II

Seroconversion rates associated with the quadrivalent human papillomavirus (HPV) vaccine (qHPV) at month 7.^[21,22,29] Participants received a 0.5 mL intramuscular injection of the vaccine^[21,22,29] or placebo (saline placebo^[22] or amorphous aluminium hydroxyphosphate sulfate adjuvant control^[29]) on day 1 and months 2 and 6. Analyses were performed in the per-protocol population^[21,22,29]

Study	Participants	Vaccine	n ^a	Seroconversion ^b rate (%)			
				anti-HPV 6	anti-HPV 11	anti-HPV 16	anti-HPV 18
V501-016 ^[21]	Males aged 10–15 y	qHPV	427–429	100	100	100	99.7
	Females aged 16–23 y	qHPV	306–340	100	100	100	99.1
	Difference (95% CI)			0.0 (–1.0, 1.3) ^c	0.0 (–1.0, 1.3) ^c	0.0 (–1.0, 1.4) ^c	0.6 (–0.6, 2.4) ^c
V501-018 ^[22]	Males aged 9–15 y	qHPV	455–458	99.8	99.8	99.5	99.8
	Females aged 9–15 y	qHPV	489–494	99.8	99.8	99.8	99.6
	Difference (95% CI)			0.0 (–1.0, 1.0) ^c	0.0 (–1.0, 1.0) ^c	–0.2 (–1.4, 0.8) ^c	0.2 (–0.8, 1.3) ^c
V501-020 ^[29]	Males aged 16–26 y	qHPV	1093–1175	98.9	99.2	98.8	97.4
	Males aged 16–26 y	PL	1109–1205	1.6	2.1	1.8	1.7

^aParticipants who had received all three doses^[21,22,29] and had serology results at month 7.^[21,29] In addition, to be included in the per-protocol population for each HPV type, participants were required to be seronegative for that type at day 1 (for HPV 6 and HPV 11, participants were required to be seronegative for both anti-HPV 6 and anti-HPV 11^[21,29]). The number of participants evaluated varied between viral particle types.

^bSeroconversion was defined as anti-HPV 6, 11, 16 and 18 titres during follow-up greater than or equal to 20, 16, 20 and 24 milli-Merck Units (mMU)/mL, respectively, in individuals who were seronegative at baseline.^[21,22,29]

^cNoninferiority demonstrated ($p < 0.001$). The lower bound of the 95% CI for the difference between the two groups was greater than or equal to –5% for all HPV types.^[21,22]

n = number of participants evaluated; **PL** = placebo.