Immunogenicity and Safety of Human Papillomavirus (HPV)-16/18 AS04-Adjuvanted Vaccine in Healthy Boys Aged 10–18 Years

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Abstract

Purpose: The human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine (Cervarix™) has been shown to be well-tolerated and immunogenic in females aged 10 to 55 years, and up to 100% effective for the prevention of HPV-16/18 infection and associated precancerous cervical lesions in females aged 15 to 25 years. This study is the first to evaluate the immunogenicity and safety of the vaccine in males.

Methods: Healthy males aged 10 to 18 years were randomized (2:1 ratio) to receive HPV-16/18 AS04-adjuvanted vaccine (n = 181) or hepatitis B virus (HBV) control vaccine (n = 89) at 0, 1, and 6 months, and were followed for 7 months.

Results: All initially seronegative subjects in the HPV-16/18 group seroconverted for HPV-16 and 18 (ELISA) at month 2. At month 7, all subjects were seropositive, and the HPV-16 and -18 antibody levels were, respectively, four- and twofold higher than at month 2. The anti-HPV-16 and -18 antibody responses for males aged 10 to 18 years, and 10 to 14 years, respectively, were higher than those reported for females aged 15 to 25 years and 10 to 14 years, respectively, in a previous study. The reactogenicity profiles of the HPV-16/18 AS04 and HBV vaccines were similar, except that pain and swelling at the injection site were more common in the HPV-16/18 group. However, vaccine-related symptoms did not affect compliance with the three-dose course, which was equally high (97%) in both groups.

Conclusions: The HPV-16/18 AS04-adjuvanted vaccine is immunogenic and well tolerated in boys aged 10 to 18 years. However, further data on the potential public health benefits of vaccination of boys are required before any recommendations can be made. © 2009 Society for Adolescent Medicine. All rights reserved.

Keywords: Human papillomavirus; Cervical cancer; Vaccine; Immunogenicity; Male; Adolescent

Infection with human papillomavirus (HPV) types 16 and 18 is associated with highly increased risk for subsequent development of anogenital and oropharyngeal cancers [1–5]. The vast majority of cervical carcinomas are positive for at least one of the oncogenic HPV types [6,7], but the prevalence of HPV in squamous cell carcinomas in other anatomic sites is generally considered to be lower. On the basis of epidemiologic and virologic studies, HPV is estimated to cause approximately 40% of cancers of the external genitalia (including the penis), 30% to 40% of oropharyngeal cancers,
and 90% of anal cancers [8]. HPV infections are rapidly acquired after sexual debut, and up to 20% of adolescent women ≤18 years of age will be infected with an oncogenic HPV type [9–11]. The prevalence of HPV infection in adolescent men is not accurately known, but in a study conducted in men aged 18 to 40 years recruited from the general U.S. population, HPV prevalence in anogenital sites and semen was 51% [12]. If we assume that 50% of the genital HPV types causing infections in the life time of a given woman are acquired during the first 3 years following sexual debut [13], the occurrence of infections in men is probably comparable in the first years of sexually active life. By the ages of 14, 15, and 18 years, respectively, 30%, 50%, and 70% of Finnish adolescent men have had their sexual debut [14], and by analogy up to 35% of them may have acquired HPV infection [15].

Prophylactic HPV L1 protein virus-like particle (VLP) vaccines have demonstrated high levels of protection against HPV-16 and 18 cervical infections and associated precancerous cervical lesions [16,17]. The HPV-16/18 AS04-adjuvanted vaccine (Cervarix™) has been extensively evaluated in women, and is currently licensed for use in females in over 50 countries. (Cervarix™, Engerix-B™ and Boostrix™ are trade marks of the GlaxoSmithKline group of companies.) This vaccine has been administered to approximately 16,000 girls and women aged 10 years and above in Phase II/III clinical trials, and has been shown to be generally well tolerated [18]. The vaccine has also been shown to be immunogenic and efficacious for protection against HPV-16/18 infection and associated cervical lesions in women aged 15 to 25 years for up to 6.4 years after vaccination [17,19,20]. Data from clinical studies show that protection conferred by the HPV-16/18 AS04-adjuvanted vaccine may extend beyond HPV-16 and -18 in females [17,19].

For preventive strategies it is important to consider at what age to target adolescents, and whether vaccination of both adolescent women and men is beneficial. The HPV-16/18 AS04-adjuvanted vaccine is currently only licensed for use in women, although another HPV vaccine has been licensed for use in boys aged 9 to 15 years in some countries. A mathematical model evaluating the impact of HPV vaccination in 12-year-old women in Finland, assuming that the vaccine has 100% efficacy against HPV-16-associated invasive cervical cancer and 70% coverage, predicts that vaccination could contribute to a reduction in the lifetime risk of HPV-16-associated cervical cancer of up to 70% [21]. Using the same model, it is reported that the concomitant vaccination of male adolescents would result in the prevention of up to an additional 20% of cases of cervical cancer [21]. However, a cost-effectiveness analysis found no real added benefit for male vaccination if very high vaccine coverage is achieved in women [22].

The present study was performed to evaluate the immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine in boys aged 10 to 18 years. An additional objective of the study was to compare the immune response of boys to that of adolescent and young adult women in a separate trial [23], in whom protective efficacy of this vaccine has previously been demonstrated [17,19].

Methods

Study participants and ethics

The study (580299/011/NCT00309166) took place from April 2006 to January 2007 at seven study sites in Finland. Study participants were recruited by population-based recruitment letters sent to the entire target male birth cohort (parents or legal guardian in the case of minors) in the study site communities by the population census register and by school recruitment sessions. All distributed material had received prior approval by the Ethical Review Committee of the Pirkanmaa Hospital District (PSHP).

Boys aged 10 to 18 years were eligible to participate in this study. Individuals were excluded from enrollment if they had used an investigational drug or vaccine within 30 days, chronic immune-modifying drugs within 6 months, immunoglobulins or blood products within 3 months, or planned to use any of these during the study period, had previously received an HPV vaccine, or had previously been vaccinated against hepatitis B virus (HBV), had a known clinical history of HBV infection, or known exposure to HBV within the previous 6 weeks, or had any confirmed or suspected immunosuppressive or immunodeficient condition including HIV infection.

Informed consent was obtained from each participant or their parents/legal guardian prior to the performance of any study procedures. Participants below the legal age of consent (15 years) were also required to sign and date an informed assent. These participants were informed about the trial to an extent compatible with their understanding. The PSHP Ethical Review Committee approved the study and consent forms, and this study is registered with the European Clinical Trials Database.

Study design

This was a phase I/II, observer-blind, parallel-group, randomized study. The 270 participants were age-stratified according to three age groups: 10 to 12 years (n = 70), 13 to 15 years (n = 104), and 16 to 18 years (n = 96). Participants were randomized (2:1 ratio) to receive either the HPV-16/18 AS04-adjuvanted vaccine or a HBV control vaccine. A randomization blocking scheme was used to ensure that balance between treatments (2:1) and approximately equal distribution across the three age strata was maintained. The study vaccines were assigned treatment numbers from a randomization list generated at GlaxoSmithKline Biologics (Rixensart, Belgium) using a standard SAS program (SAS Institute, Cary, NC). Participants were assigned a vaccine treatment number; blinding was maintained to the individual treatment allocated. All study personnel were blinded to the
than 50 mm, fever higher than 39.0°C that prevented normal activity, redness or swelling larger than 50 mm, fever higher than 39.0°C that prevented normal activity, redness or swelling larger than 50 mm, fever higher than 39.0°C that prevented normal activity, redness or swelling larger than 50 mm, fever higher than 39.0°C that prevented normal activity, redness or swelling larger than 50 mm, fever higher than 39.0°C that prevented normal activity, redness or swelling larger than 50 mm, fever higher than 39.0°C that prevented normal activity, redness or swelling larger than 50 mm, fever higher than 39.0°C that prevented normal activity, redness or swelling larger than 50 mm, fever higher than 39.0°C that prevented normal activity, redness or swelling larger than 50 mm, fever higher than 39.0°C that prevented normal activity, redness or swelling larger than 50 mm, fever higher than 39.0°C that prevented normal activity, redness or swelling larger than 50 mm, fever higher than 39.0°C that prevented normal activity, redness or swelling larger than

Study vaccines

Each dose of HPV-16/18 L1 VLP AS04-adjuvanted candidate vaccine (Cervarix™) contained 20 µg each of HPV-16 and -18 L1 proteins self-assembled as VLP and adjuvanted with AS04 (50 µg 3-O-desacyl-4′-monophosphoryl lipid A [MPL] and 500 µg aluminum hydroxide). The vaccine was produced using a Baculovirus Expression Vector System in which each type of VLP antigen was produced on a Hi-5 cell line derived from Trichoplusia ni. Each dose of the hepatitis B virus control vaccine (Engerix-B™) contained 10 µg hepatitis B surface (HBs) antigen and 250 µg aluminum hydroxide. The vaccines were supplied in identifiable 0.5-mL prefilled syringes and administered into the deltoid muscle on a 0-, 1-, and 6-month schedule.

Serologic evaluation

Blood samples were collected from each participant before the first vaccination and 1 month after the second and third doses (months 2 and 7, respectively) to evaluate immunogenicity. All blood samples were evaluated for HPV-16 and HPV-18 antibodies using a type-specific enzyme-linked immunosorbent assay (ELISA) as reported elsewhere [19]. Seropositivity was defined as a titer greater than or equal to the assay threshold established at eight ELISA Units/mL (EU/mL) for HPV-16 and 7 EU/mL for HPV-18 [19].

The HBV vaccine used in this study is marketed in Finland with an upper age limit of 15 years. Hence, as this formulation was considered investigational for subjects aged 16 to 18 years, levels of anti-HBs antibodies at month 7 were evaluated by ELISA in boys aged 16 to 18 years who received the HBV vaccine, to ensure that sufficient protection against HBV was provided. If a boy was not seroprotected (anti-HBs antibody concentration of at least 10 mIU/mL) he was offered an additional dose of HBV vaccine using the formulation licensed for use in Finland according to the age of the boy. Individual data were provided to the investigator and are not reported here.

Vaccine safety

Participants used diary cards to report solicited local and general symptoms during a 7-day follow-up period after each vaccine dose (days 0–6). Solicited local adverse events included pain, redness, and swelling at the injection site. Solicited general adverse events included fever, headache, fatigue, gastrointestinal symptoms (i.e., nausea, vomiting, diarrhea, abdominal pain), arthralgia, myalgia, rash, and urticaria. Grade 3 solicited adverse events were defined as pain that prevented normal activity, redness or swelling larger than 50 mm, fever higher than 39.0°C (axillary temperature), urticaria distributed on at least four body areas, or events that prevented normal, everyday activities. Urticaria or rash that appeared within 30 minutes of each vaccine dose was also documented by the investigator.

Unsolicited signs and symptoms were reported within 30 days after each dose. Serious adverse events (SAEs), new onset chronic diseases (NOCs) (e.g., diabetes mellitus, autoimmune diseases, asthma, allergies, etc.), and other medically significant conditions (MSCs) were reported throughout the study period. An SAE was defined as any untoward medical occurrence that resulted in death, was life-threatening, required hospitalization, resulted in disability or incapacity, was an important medical event or was a congenital anomaly/birth defect in the offspring of a study subject. MSCs were defined as nonserious adverse events prompting either emergency room or physician visits not related to either common diseases or routine visits for physical examination or vaccination, or SAEs not related to common diseases. Common diseases included upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, and injury.

Statistical analysis

We estimated that 144 evaluable boys in the HPV-16/18 AS04-adjuvanted vaccine group were needed to demonstrate with at least 98% power, that the seroconversion rates at month 7 were not less than 90% for a given HPV antigen. All sample size calculations were done with Pass 2005, using a one proportion power analysis, one-sided test, type I error of 2.5% with the Bonferroni adjustment of beta.

Immunogenicity analyses were based on the according-to-protocol (ATP) cohort and were performed on participants initially seronegative for the considered antigen (i.e., participants seropositive for HPV-16 antigen at baseline were eliminated from the HPV-16 analysis, but were still evaluable for HPV-18 analysis provided they were HPV-18 seronegative, and vice versa). Seropositivity rates and geometric mean titers (GMT) with 95% confidence intervals (95% CI) were calculated for antibodies to each HPV antigen. Asymptotic two-sided confidence intervals for the ratio of GMTs were computed using an analysis of variance model on log_{10} transformed titers. Antibody titers below the cutoff of the assay were given an arbitrary value of half the cutoff value for the purpose of GMT calculations.

The immune responses induced by the HPV-16/18 AS04-adjuvanted vaccine in boys in this study were compared to those induced in adolescent and young adult women in a separate study [23]. The separate historic comparator study was a randomized, parallel-group trial conducted at six study sites in Denmark, Estonia, and Finland, and included women aged 10 to 25 years stratified into two age groups (10–14 years and 15–25 years). The HPV-16/18 AS04-adjuvanted vaccine schedule was the same as that used in this study (0, 1, and 6 months), and anti-HPV-16/18 antibody levels were measured at months 0, 7, 18, and 24. Noninferiority of the immune responses induced by the HPV-16/18 AS04-adjuvanted vaccine in boys in this study compared to those
induced in women aged 15 to 25 years in the historic comparator study was demonstrated if the upper limit of the 95% confidence interval (CI) for the difference between the percentage of participants who seroconverted in each group 1 month after the third dose (month 7) was below 10% and if the upper limit of the 95% CI for the GMT ratio between each group 1 month after the third dose (month 7) was below 2 (tests performed sequentially).

Safety analyses were based on the total vaccinated cohort. Incidence rates of solicited symptoms during the 7-day follow-up period and unsolicited symptoms during the 30-day follow-up period were tabulated with exact 95% CI over all vaccine doses and for each treatment group. For the analysis of solicited symptoms, missing or nonevaluable measurements were not replaced, and included only boys with documented safety data (i.e., symptom sheet completed) per dose. All vaccinated boys were included in the analysis of unsolicited adverse events, SAEs, NOCDs, and MSCs. Participants who did not report an event were considered to have not experienced an event.

Statistical analyses were performed with SAS version 8.2 (SAS Institute) and ProcStatXact 5 (Cytel Inc., Cambridge, MA).

Results

A total of 270 participants (HPV-16/18 group, n = 181; HBV group, n = 89) were enrolled and vaccinated over a period of approximately 2 months (April 5 to June 10, 2006). Study compliance was excellent (Figure 1), and 97% of boys in both groups (HPV-16/18 and HBV) received all three vaccine doses. The demographic profile of the two groups was similar. In the total vaccinated cohort the mean age of boys was 14.4 years. As this was a study in one country only, the distribution of ethnicity was homogeneous in both groups (Table 1).

The trial profile for ATP analyses and total vaccinated cohort analyses were almost identical (Figure 1).

Immunogenicity

At study entry, 11.2% of the participants were seropositive for HPV-16 and/or -18 antibodies (3.5% seropositive for HPV-16 alone [n = 9], 7% for HPV-18 alone [n = 18] and 0.8% for both HPV-16 and HPV-18 [n = 2]). In the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic characteristics of participants receiving the HPV-16/18 AS04 or HBV vaccines (total vaccinated cohort)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HPV-16/18 N = 181</td>
</tr>
<tr>
<td>Mean (SD) age (years)</td>
<td>14.4 (2.14)</td>
</tr>
<tr>
<td>Ethnic origin n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>177 (97.8)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Arabic/North African</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Central/South Asian</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

N = number of study participants.
 n (%) = number and percentage of participants.

boys in both groups (HPV-16/18 and HBV) received all three vaccine doses. The demographic profile of the two groups was similar. In the total vaccinated cohort the mean age of boys was 14.4 years. As this was a study in one country only, the distribution of ethnicity was homogeneous in both groups (Table 1).

The trial profile for ATP analyses and total vaccinated cohort analyses were almost identical (Figure 1).

Figure 1. Description of study cohorts for analysis of endpoints.
10- to 12-year age group, no individual was seropositive for either HPV-16 or HPV-18.

At month 2, 100% of initially seronegative boys who received the HPV-16/18 AS04-adjuvanted vaccine had seroconverted for HPV-16 and HPV-18 (ELISA) and all boys were seropositive 1 month after completion of the full vaccination course at month 7. At month 7, antibody levels for HPV-16 and HPV-18 were, respectively, fourfold and two-fold higher, compared to month 2 (Figure 2).

The immune response in boys aged 10 to 18 years in this study was shown to be noninferior for both seroconversion rates and GMTs to that seen in women aged 15 to 25 years in the historic comparator study [23], an age range in which a high degree of protection against HPV-16/18 infection and associated cervical lesions has been shown [17, 24]. With regard to seroconversion rates, 100% of boys and women seroconverted for anti-HPV-16 and anti-HPV-18 antibodies at month 7. With regard to antibody levels, the HPV-16/18 AS04-adjuvanted vaccine elicited substantially higher GMTs at month 7 for both antigens in boys aged 10 to 18 years (HPV-16: 22639.7 [19825.5–25853.4] and HPV-18: 8416.1 [7215.0–9817.1]) compared with women aged 15 to 25 years (HPV-16: 7292.9 [6623.7–8029.7] and HPV-18: 3318.8 [3023.1–3643.5]) [23] (Figure 3). The antibody levels at month 7 in the subset of boys aged 10 to 14 years in this study (HPV-16: 27891.6 [23975.6–32447.2] and HPV-18: 10593.7 [8875.8–12644.0]) were also higher than those reported in girls of the same age in the historic comparator study (HPV-16: 17272.5 [15117.9–19734.1] and HPV-18: 6863.8 [5976.3–7883.0]) [23] (Figure 3). Antibody levels at month 7 in the subset of boys aged 10 to 14 years in this study were also higher than those reported in the subset of boys aged 15 to 18 years (HPV-16: 18606.3 [15095.7–22933.5] and HPV-18: 6805.5 [5346.8–8662.0]).

**Safety**

Pain and swelling at the injection site were more frequent in the HPV-16/18 vaccine group than in the control HBV vaccine group (Table 2). However, higher levels of solicited local symptoms did not affect compliance with vaccination, as evidenced by 97% of boys in both vaccine groups completing the three-dose vaccination course.
The most frequently reported solicited general symptoms were headache, fatigue, and myalgia; myalgia was more frequent in the HPV-16/18 vaccine group than in the control vaccine group (Table 3). Most solicited adverse events were transient (lasting not longer than 2–3 days) and the incidence of adverse events did not increase with subsequent doses. Grade 3 adverse events were reported infrequently. Very low to low frequencies of urticaria (0.8% in both the HPV-16/18 and control HBV vaccine groups) or rash (3.6% and 1.9% in the two groups, respectively) were reported by the investigator within 30 minutes of vaccine administration for any study participant.

In general, the frequency of unsolicited symptoms reported during the 30-day postvaccination period following each dose was similar between groups: 15.7% and 15.6% in the HPV-16/18 and control HBV vaccine groups, respectively.

Two SAEs occurred in 2 participants receiving the HPV-16/18 AS04-adjuvanted vaccine (Crohn’s disease and epilepsy). The boy diagnosed with Crohn’s disease had symptoms that may have been related to the disease prior to the first dose of vaccine, and the boy with epilepsy had a family history of this condition. Neither of the SAEs were fatal, and both events were considered by the investigator to be unrelated to study vaccination. No participants withdrew from the study because of a SAE. One participant in the HPV-16/18 vaccine group withdrew from the study because of a nonserious adverse event (panic reaction after the first vaccine dose), which was not considered related to the study vaccine. Three NOCDs were reported: two in the HPV-16/18 group (Crohn’s disease and atopic dermatitis) and one in the control HBV vaccine group (asthma). The percentage of MSCs reported did not differ between groups (12.2% in the HPV-16/18 group and 11.2% in the control vaccine group).

### Discussion

This is the first study in which *Cervarix*™ has been administered to boys. This HPV-16/18 AS04-adjuvanted vaccine was highly immunogenic, inducing seroconversion for both antigens in all boys and very high antibody titers for both HPV-16 and HPV-18. The immune response was shown to be noninferior in terms of seroconversion rates between boys aged 10 to 18 years in this study compared with women aged 15 to 25 years from a separate study [23], an age range for which efficacy for the prevention of HPV-16/18 infection and associated precancerous cervical lesions has been demonstrated [17,19]. The HPV-16/18 AS04-adjuvanted vaccine elicited substantially higher antibody levels for

### Table 2
Incidence of solicited local symptoms reported during the 7-day follow-up period following administration of HPV-16/18 AS04 or HBV vaccines, overall per dose (total vaccinated cohort)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Type</th>
<th>HPV-16/18 N = 523</th>
<th>HBV control N = 259</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>(95% CI)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Pain</td>
<td>378 (72.3)</td>
<td>(68.2, 76.1)</td>
<td>57 (22.0)</td>
</tr>
<tr>
<td>Grade 3a</td>
<td>10 (1.9)</td>
<td>(0.9, 3.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Redness</td>
<td>87 (16.6)</td>
<td>(13.5, 20.1)</td>
<td>29 (11.2)</td>
</tr>
<tr>
<td>&gt;50 mm</td>
<td>0 (0.0)</td>
<td>(0.0, 0.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Swelling</td>
<td>56 (10.7)</td>
<td>(8.2, 13.7)</td>
<td>8 (3.1)</td>
</tr>
<tr>
<td>&gt;50 mm</td>
<td>2 (0.4)</td>
<td>(0.0, 1.4)</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

N = number of documented doses (with safety diary cards returned); CI = exact confidence interval; n (%) = number/percentage of doses that were followed by at least one symptom.

### Table 3
Incidence of solicited general symptoms reported during the 7-day follow-up period following administration of HPV-16/18 AS04 or HBV vaccines, overall per dose (total vaccinated cohort)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Type</th>
<th>HPV-16/18 N = 523</th>
<th>HBV control N = 259</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>(95% CI)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>All</td>
<td>35 (6.7)</td>
<td>(4.7, 9.2)</td>
</tr>
<tr>
<td>Grade 3a</td>
<td>0 (0.0)</td>
<td>(0.0, 0.7)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>All</td>
<td>130 (24.9)</td>
<td>(21.2, 28.8)</td>
</tr>
<tr>
<td>Grade 3a</td>
<td>4 (0.8)</td>
<td>(0.2, 1.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Fever</td>
<td>All</td>
<td>52 (9.9)</td>
<td>(7.5, 12.8)</td>
</tr>
<tr>
<td>&gt;39.0°C</td>
<td>0 (0.0)</td>
<td>(0.0, 0.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>All</td>
<td>61 (11.7)</td>
<td>(9.0, 14.7)</td>
</tr>
<tr>
<td>Grade 3a</td>
<td>4 (0.8)</td>
<td>(0.2, 1.9)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>All</td>
<td>111 (21.2)</td>
<td>(17.8, 25.0)</td>
</tr>
<tr>
<td>Grade 3a</td>
<td>5 (1.0)</td>
<td>(0.3, 2.2)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>All</td>
<td>141 (27.0)</td>
<td>(23.2, 31.0)</td>
</tr>
<tr>
<td>Grade 3a</td>
<td>3 (0.6)</td>
<td>(0.1, 1.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Rash</td>
<td>All</td>
<td>19 (3.6)</td>
<td>(2.2, 5.6)</td>
</tr>
<tr>
<td>Grade 3a</td>
<td>0 (0.0)</td>
<td>(0.0, 0.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>All</td>
<td>4 (0.8)</td>
<td>(0.2, 1.9)</td>
</tr>
<tr>
<td>Grade 3b</td>
<td>0 (0.0)</td>
<td>(0.0, 0.7)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

N = number of documented doses (with safety diary cards returned); CI = exact confidence interval; n (%) = number/percentage of doses that were followed by at least one symptom.

a Symptom that prevented normal activity.

b Urticaria distributed on at least four body areas.
both antigens in boys aged 10 to 18 years or 10 to 14 years, respectively, when compared with women aged 15 to 25 years or girls aged 10 to 14 years, respectively, from a previous study [23]; postvaccination antibody levels for both HPV-16 and -18 antibodies were observed to be up to threefold higher in boys than in women. This observation has also been described for another HPV vaccine [25]. As already described in women [23], the HPV-16/18 AS04-adjuvanted vaccine elicited higher antibody levels for both antigens in the group of young boys aged 10 to 14 years compared with the group of boys aged 15 to 18 years.

The HPV-16/18 AS04-adjuvanted vaccine was generally well tolerated, with a similar safety profile to the HBV vaccine used as a control, with the exception of increased reporting of some solicited symptoms (pain/swelling and myalgia). These differences in reactogenicity did not, however, impact on acceptance of the vaccine, with almost all boys completing the full three-dose vaccination course. The reactogenicity profile of the HPV-16/18 AS04-adjuvanted vaccine in boys in this study was similar to that reported previously in women [18,23,24]. Furthermore, the reactogenicity profile was also similar to that reported for a combined diphtheria, tetanus, and acellular pertussis vaccine (Boostrix™) in adolescents aged 10 to 18 years [26], in whom localized pain was reported for 75% to 90% of subjects, and localized swelling was reported for 21% to 35% of subjects (compared to 72.3% and 10.7%, respectively, for the HPV-16/18 AS04-adjuvanted vaccine in this study). In a previous direct comparison of the HPV-16/18 AS04-adjuvanted vaccine and placebo containing aluminum hydroxide in women aged 15 to 25 years of age [24], greater local reaction rates were observed in the vaccine group, but general symptom rates were equivalent to placebo, and neither local nor general vaccine related symptoms affected overall subject compliance.

Because HPV infections can be rapidly acquired after sexual debut, an important target population for the HPV-16/18 AS04-adjuvanted vaccine is preteens and young adolescents to provide protection prior to onset of sexual activity and exposure to oncogenic HPVs. The vaccine formulated with AS04 has been shown to induce higher and more sustained antibody levels against both HPV-16 and HPV-18 and more robust memory B-cell responses when compared to the same HPV-16/18 antigens formulated with conventional aluminum salts only [27]. Results of this study indicate that the HPV-16/18 AS04-adjuvanted vaccine is generally safe and well tolerated, and induces excellent immunogenicity in boys aged 10 to 18 years. However, the public health value of vaccination of boys against oncogenic HPV types has yet to be determined. The burden of HPV-associated diseases such as anal, penile, and oropharyngeal cancers in men is much less than that of cervical cancer in women [8], and potential public health benefits of male vaccination on this basis alone would be expected to be limited. However, HPV infection is common in men [12] and is readily transmitted [28], influencing disease rates in both men and women.

The impact of vaccination of both male and female adolescents on the reduction of female disease (cases of cervical cancer) has been explored in a number of mathematical modeling studies. Results of these studies vary, with some suggesting that vaccination of adolescent men may confer additional benefit over vaccination of women alone [19,21,29,30], whereas others show no real added benefit for male vaccination when very high vaccine coverage is achieved in women [22]. As such models are dependent on underlying assumptions such as the epidemiology of HPV infection in the region or country of interest, and vaccine coverage, it is not surprising that estimates of the benefits of male vaccination vary. Further data are clearly required before recommendations can be made regarding the use of HPV vaccines in males.

References

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