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Original article

Immunization of Early Adolescent Females with Human Papillomavirus Type 16 and 18 L1 Virus-Like Particle Vaccine Containing AS04 Adjuvant

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Abstract

Purpose: In female individuals 15–25-years of age, the AS04-containing human papillomavirus (HPV)–16/18 vaccine is highly immunogenic and provides up to 100% protection against HPV-16/18 persistent infection and associated cervical lesions up to 4.5 years. Optimal cervical cancer prevention will require prophylactic vaccination against oncogenic HPV 16 and 18 before the onset of sexual activity in early adolescent girls. To establish the feasibility of vaccination in girls 10–14 years of age, we compared the immunogenicity and safety in early adolescent female individuals to those 15–25 years in whom vaccine efficacy has been demonstrated.

Methods: We enrolled 773 female participants aged 10–14 years and 15–25 years to receive the HPV-16/18 L1 VLP AS04 vaccine, which was administered at months 0, 1, and 6. Serum samples were collected at months 0 and 7; antibodies to HPV 16 and 18 VLPs were measured by enzyme-linked immunosorbent assay. Vaccine safety was assessed at 7 or 30 days after each dose; serious adverse events were recorded during the entire study period.

Results: Both age groups achieved 100% seroconversion for HPV 16 and 18. Participants in the group aged 10–14 years were not only noninferior to those 15–25 years in terms of HPV 16 and 18 seroconversion rates but also had approximately twice as high geometric mean titers. The vaccine was generally safe and well tolerated.

Conclusions: These findings suggest that HPV vaccination during early adolescence is generally safe, well tolerated, and highly immunogenic. The observed higher antibody titers in the group 10–14 years of age are likely to result in longer antibody persistence. Overall, these data support the implementation of prophylactic HPV vaccination in this age group.

Keywords: Human papillomavirus vaccine; Cervical cancer; Immunogenicity; AS04; Adolescent; Female

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Cervical cancer is the second most common female cancer worldwide, with 493,000 new cases and 274,000 deaths reported in 2002 [1]. Persistent infection with genital human papillomavirus (HPV) types 16 and 18 is associated with highly increased risk for subsequent development of invasive cervical cancer (ICC) [2–4]. More than 99% of ICC cases are positive for at least one of the 15 oncogenic HPV types, which makes HPV infection a logical cause of cervical cancer [5]. In female individuals more than 15 years of age, HPV 16 and 18 are the most common HPV types found in ICC cases and cumulatively contribute to 70% of ICC worldwide [6].

Up to 20% of female adolescents will be infected with an oncogenic HPV type; among these types HPV 16 and 18 are commonly found [7–9]. In fact, 50% of the genital HPV types causing infections over a lifetime in a given woman are acquired during the first 3 years after sexual debut [10,11]. Almost all 40 HPV types that cause genital infections can be found in adolescent populations, and the persistence of genital oncogenic HPVs also among female adolescents is greater than that for nononcogenic HPVs [12].

Vaccination with prophylactic HPV virus–like particle (VLP) vaccines, comprising the L1 protein viral capsid, have demonstrated high levels of protection against HPV 16 and 18 incident infections, persistent infections and associated abnormal cytologic findings, and precancerous lesions [13–17]. Recent evidence of cross-protection against phylogenetically related HPV types using a bivalent HPV-16/18 L1 VLP AS04 vaccine indicates that prevention against incident infection may extend beyond HPV 16 and 18 [15]. The HPV-16/18 L1 VLP AS04 vaccine has also demonstrated a clinically acceptable safety profile up to 4.5 years in young women. These observations are further supported in other clinical trials using a vaccine also adjuvanted with AS04 [14,15,18,19].

Recently, the impact of vaccination with HPV 16 and 18 VLP vaccines has been estimated to substantially reduce low- and high-grade cervical abnormalities, such as atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial neoplasias (LSIL) abnormalities, high-grade squamous intraepithelial neoplasias (HSIL), and cancer. These estimates suggest that the vaccine may prevent 8–19% of ASCUS, 15–32% of LSIL, 41–57% of HSIL, and 65–77% of cancers. The total percentages of ASCUS, LSIL, HSIL, or cancer prevented by HPV-16/18 vaccination may increase with demonstration of cross-protection against cervical lesions [20].

Mathematical models evaluating the impact of the administration of a HPV-16/18 vaccine in 12-year-old girls, using efficacy estimates against HPV 16 and 18 associated ICC that ranges from 70% to 100%, predict that such a vaccine could contribute to a reduction in the lifetime risk of cancer of approximately 70% [21,22]. To reduce the burden of HPV 16/18 associated cervical disease, one important consideration in preventive strategies is to target early adolescent females before they engage in sexual activity.

The present phase III randomized study was performed to evaluate the immunogenicity and safety of the HPV-16/18 L1 VLP AS04 vaccine in early adolescent females 10–14 years of age as compared with those 15–25 years of age, an age group in which efficacy of the vaccine was previously shown in a clinical trial [14,15].

Methods

Study participants and ethics

The study took place from September 2004 to July 2005 in 17 centers in Denmark, Estonia, Finland, Greece, The Netherlands, and Russia. Study participants were recruited through hospitals, children outpatient clinics, schools, or in the general population. Recruitment tools included school recruitment sessions, recruitment letters, articles in local newspapers, leaflets, or advertisements. All distributed material had received prior approval by the Ethics Review Committees.

Prospective participants were enrolled in the study if they were female, aged 10–25 years, were abstinent from sexual activity, or were using adequate contraceptive precautions for 30 days before vaccination and up to 2 months after completion of the vaccination series if of childbearing potential, had negative pregnancy test results, and had no more than six lifetime sexual partners. 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, were pregnant or planning to become pregnant, breastfeeding, or had previously received HPV vaccine.

Each center's Institutional Review Board approved the study and consent forms. Informed consent was obtained from each participant or participant's parents/legally acceptable representative(s) before the performance of any study specific procedures. Participants below the legal age of consent were required to sign and date an informed assent. This study was registered with the European Clinical Trials Database.

Study design

This study included five parallel treatment groups in two age categories: 15–25 years (n = 458) and 10–14 years (n = 158). Participants aged 15–25 years were randomized to receive HPV-16/18 L1 VLP AS04 vaccine (one of three consistency lots; Groups 1, 2, and 3). Participants aged 10–14 years received HPV-16/18 L1 VLP AS04 vaccine from one of the three consistency lots (Lot 1, Group 4) (Figure 1). In the fifth treatment group, women 15–25 years of age (n = 154) were randomized to receive HPV vaccine

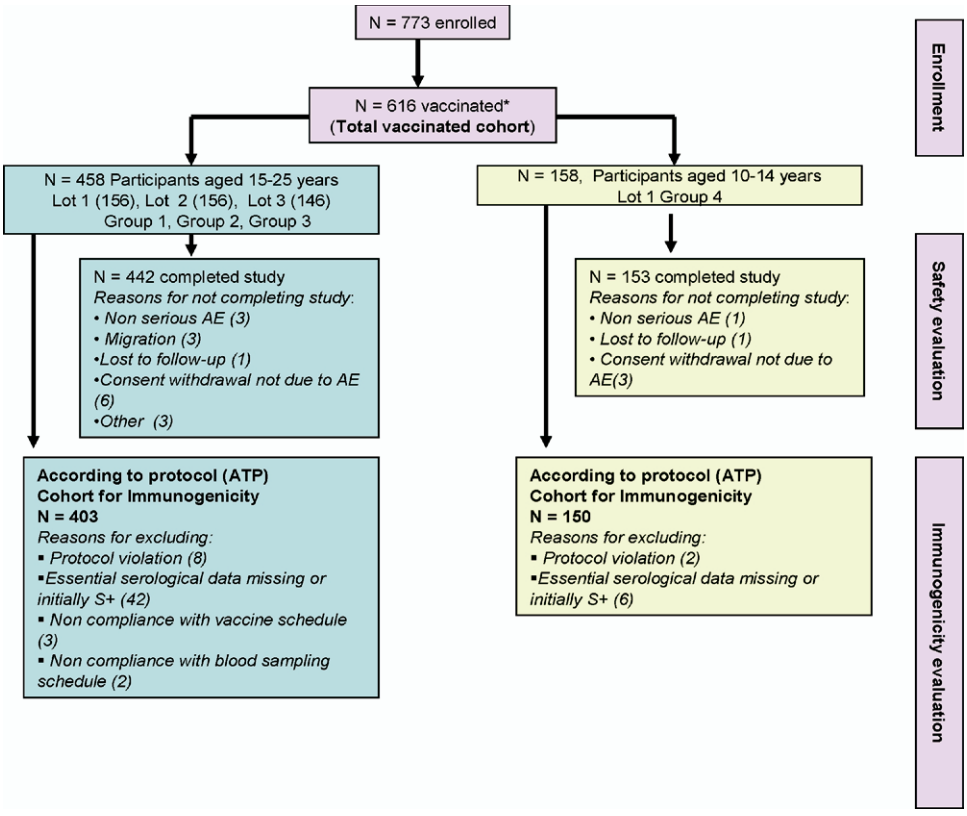

Figure 1. Description of study cohorts for analysis of endpoints. N = number of individuals. *Three participants were enrolled in the study but did not receive any vaccine dose. A total of 154 participants were randomized to receive the human papillomavirus (HPV) vaccine prepared using a modified manufacturing process (results not included). AE = adverse event; ATP = according to protocol; S+ = seropositive.

prepared using a modified manufacturing process. These results are not included here.

A randomization blocking scheme (1:1:1:1:1) was used to ensure that treatments were assigned equally and randomly among the groups. The study vaccines were assigned treatment numbers from a randomization list generated at GlaxoSmithKline Biologicals (Rixensart, Belgium) using a standard SAS program (SAS Institute, Cary, NC). Participants were assigned a vaccine treatment number, and blinding was maintained to the individual treatment allocated. For all study participants, study personnel were blinded to the vaccine lot number.

Study objectives

One of the primary objectives of this study was to demonstrate lot-to-lot consistency of the vaccine in participants 15–25 years old (Groups 1, 2, and 3) in terms of immunogenicity. The secondary objectives were: (1) to demonstrate the noninferiority of the group aged 10–14 years compared with that in the group aged 15–25 years in terms of immunogenicity with the same vaccine lot; and (2) to compare immunogenicity results for all three lots combined: all groups aged 15–25 years together with immunogenicity results in those aged 15–25 years, in whom efficacy has been demonstrated [14]. In addition, vaccine safety was evaluated after each dose in all study participants. As a second primary endpoint, noninferiority in terms of immunogenicity between manufacturing processes, was also assessed. These results are not included here.

Study vaccines

Each dose of HPV-16/18 L1 VLP AS04 candidate vaccine (GlaxoSmithKline Biologicals, Rixensart, Belgium) contained 20 μg each of HPV 16 and 18 L1 proteins self-assembled as virus-like particles (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 (BEVS) in which each type of VLP antigen was produced on a Hi-5 cell line derived from Trichoplusia ni. The vaccine was supplied in individual 0.5-ml prefilled syringes and administered into the deltoid muscle on a 0-, 1-, and 6-month schedule.

In the group 15–25 years of age, each participant received one of three manufacturing lots produced in a consecutive manner (consistency lots: Lots 1, 2, 3). Individuals in the group 10–14 years received the same vaccine lot (Lot 1) as one of the groups 15–25 years of age.

Serologic evaluation

At the initial and month 7 study visits, blood samples were collected from each participant 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 [15]. Seropositivity was defined as a titer greater than or equal to the assay threshold established at 8 ELISA U/ml (EU/ml) for HPV 16 and 7 EU/ml for HPV 18 [15].

Vaccine safety

On the day of vaccination, diary cards were given to participants to report solicited local and general symptoms during a 7-day follow-up period (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, areas of redness or swelling greater 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 were reported throughout the study period. Serious adverse events were defined as any untoward medical occurrence that was life-threatening, required hospitalization, resulted in disability or incapacity, was an important medical event, resulted in death, or was a congenital anomaly/birth defect in the offspring of a study participant.

Statistical analysis

It was estimated that 360 evaluable participants aged 15–25 years (120 per group) were needed to achieve more than 92% power for consistency for the primary objective. This approach was used to rule out the null hypothesis that at least two of the three vaccine lots differed by more than twofold with respect to their geometric mean titers (GMTs).

Lot-to-lot consistency was demonstrated for all pairs of lots if, 1 month after the third dose, the two-sided 90% confidence intervals (CI) of the GMT ratio (i.e., ratio between GMTs) were within the clinical limit interval (0.5, 2).

To achieve the secondary objectives, 120 evaluable participants aged 10–14 years were needed. This approach provided 90% power to rule out that for a given HPV antigen, the difference between the percentage of individuals who seroconverted in the older age group when compared with the younger age group, was greater than 10%. Furthermore, it also provided 97% power to rule out that for a given HPV antigen, the GMT in the older group was more than twofold greater than in the younger group.

Noninferiority was demonstrated if, 1 month after the third dose, the upper limit of the 95% CI for the difference between the percentage of participants who seroconverted in each group was less than 10%, and if the upper limit of the 95% CI for the GMT ratio between each group was less than 2 (tests performed sequentially).

All sample size calculations were done using Pass 2000, assuming a standard deviation of 0.6 for the $\log_{10}$ transformed titers (based on another previously published study [14]) and assuming a baseline seroconversion rate of 95%.

The 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 cut-off of the assay were given an arbitrary value of half the cut-off value for the purpose of GMT calculation.

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% CIs 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 subjects with documented safety data (i.e., symptom sheet completed) per dose. The analysis of unsolicited adverse events and serious adverse events included all vaccinated participants. Participants who did not report an event were considered not to have experienced an event.

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

Results

A total of 773 participants were enrolled within 3 months (September 5 to December 4, 2004). Study compliance was high (Figure 1), with almost all study participants (>95% in each group) receiving all three vaccine doses. The mean age was 20.2 years for the group 15– 25 years and was 12.4 years for the group 10–14 years. Distribution of ethnicity was comparable among all groups (Table 1). In all, 21 participants withdrew from the study, including four for nonserious adverse events.

A computer programming error in the randomization web-based application used for treatment allocation to study participants was discovered during the trial. The extent of this web-based application error on the results was evaluated, and statistical analyses demonstrated that there was no statistically relevant effect on the validity of the immunogenicity results.

The trial profile for according-to-protocol (ATP) analyses and total vaccinated cohort analyses is described in Figure 1. Immunogenicity analyses were based on the ATP cohort and were performed on initially seronegative participants only. Participants seropositive for one HPV antigen at baseline were eliminated from the analysis for that anti-

Table 1
Demographic characteristics of participants receiving the human papillomavirus (HPV)–16/18 L1 VLP AS04 vaccine (total vaccinated cohort)

	Subjects 15–25-years N = 458 (Lots 1–3)	Subjects 10–14-years N = 158 (Lot 1)
Mean age (years)	20.2	12.4
Country	n (%)	n (%)
The Netherlands	90 (19.7)	30 (19.0)
Russia	72 (15.7)	24 (15.2)
Greece	63 (13.8)	16 (10.1)
Estonia	59 (12.9)	21 (13.3)
Denmark	116 (25.3)	43 (27.2)
Finland	58 (12.7)	24 (15.2)
Ethnic origin	n (%)	n (%)
White/Caucasian	441 (96.3)	150 (94.9)
Black	5 (1.1)	2 (1.3)
Arabic/North African	1 (0.2)	5 (3.2)
East/South East Asia	1 (0.2)	0 (0.0)
Other	10 (2.2)	1 (0.6)

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

gen but were still evaluable for the analysis for the other HPV antigen.

Immunogenicity

Serostatus at study entry showed that 25% of the participants 15–25 years old were seropositive for HPV 16 and/or 18 antibodies 10% seropositive HPV 16 alone (n = 45), 9% HPV 18 alone (n = 40), and 6% for both HPV 16 and 18 (n = 27) Among participants 10–14 years old, 3% were positive for HPV 16 (n = 5), 4% for HPV 18 (n = 6), and none was infected with both HPV 16 and 18 types.

Using the pre-defined statistical criteria, consistency was demonstrated among the three vaccine lots of vaccine. The GMTs (EU/ml) (95% CI) for HPV 16 were 7438.9 (6324.6–8749.6), 7150.3 (6038.1–8467.3), and 7297.2 (6136.8–8677.0) for Groups 1, 2, and 3, respectively; and for HPV 18 were 3070.1 (2600.0–3625.4), 3173.4 (2714.3–3710.2), and 3743.3 (3173.3–4415.7) for Groups 1, 2, and 3, respectively (Figure 2). One month after completion of the full vaccination course, seroconversion rates were 100% for both antigens, in all groups.

Immunogenicity in the group aged 10–14 years was shown to be noninferior to that in the group 15–25 years in terms of seroconversion rates (both 100%). With regard to the antibody levels, the HPV-16/18 L1 VLP AS04 vaccine elicited substantially higher GMTs for both antigens in the group aged 10–14 years (HPV 16 GMT: 17272.5 [15117.9–19734.1] and HPV 18: 6863.8 [5976.3–7883.0]) compared with the group aged 15–25 years (GMT ratio <0.5) (Figure 2).

In the group aged 15–25 years, immunogenicity results of the present study were compared with results obtained in a subset of female individuals aged 15–25 years in whom the efficacy of the vaccine had been demonstrated [14]. GMTs from the samples collected in the primary vaccine efficacy study for HPV 16 were 4415.9 (3976.7–4903.6) (n = 339) and in the current study were 7292.9 (6623.7–8029.7) (n = 359); for HPV 18, GMT values were 3471.8 (3161.9–3811.9) (n = 325) and 3318.8 (3023.1–3643.5) (n = 364), respectively. The upper limits of the 95% CIs for both seroconversion rates and GMT ratios were below the predefined limits for demonstrating noninferiority (Figure 2).

Safety

Compliance in returning symptom sheets was high (greater than 98% for all groups). Safety profiles were indistinguishable between the study groups; in addition, there was a similar frequency of reporting solicited local and general symptoms among groups. The most commonly reported solicited local symptom was pain at the injection site (Table 2). No urticaria or rash was reported by the investigator within 30 minutes of vaccine administration for any study participant.

The most frequently reported solicited general symptoms were fatigue, headache, and myalgia (Table 3). Most solicited adverse events were transient, lasting no longer than 2–3 days; more importantly, the incidence of adverse events did not increase with increasing number of doses. Grade 3 adverse events were reported infrequently.

In general, the frequency of unsolicited symptoms reported during the 30-day postvaccination period after each dose was similar between groups. Fewer symptoms were reported in the group aged 10–14 years (incidence of any grade unsolicited symptom: 16.5%; Grade 3: 2.1%) than in the group 15–25 years (pooled lots, incidence of any grade unsolicited symptom: 23.0%; Grade 3: 2.5%). The most frequently reported unsolicited adverse events were injection site reactions, headache, and influenza (reported respectively after 4.4%, 2.7%, and 1.4% of vaccine doses in the pooled group aged 15–25 years and after 1.5%, 1.3%, and 0.4% of vaccine doses in the group 10–14 years).

No participants withdrew from the study because of a serious adverse event. Four participants withdrew from the study because of nonserious adverse events. Three participants in the group 15–25 years of age reported three of the four nonserious adverse events that were considered by the investigator not to be related to study vaccination (fatigue, abortion threatened, and perioral rash). One participant in the group 10–14 years of age reported nausea, which was considered by the investigator to be causally related to vaccination.

Eight serious adverse events occurred in eight participants: seven in the group 15–25 years old (myocarditis, pericarditis, gastric ulcer, acute sinusitis, heat stroke, insulin-dependent diabetes mellitus, and threatened abortion) and one in the group 10–14 years old (depression). None were fatal, and none were considered by the investigator to be related to study vaccination.

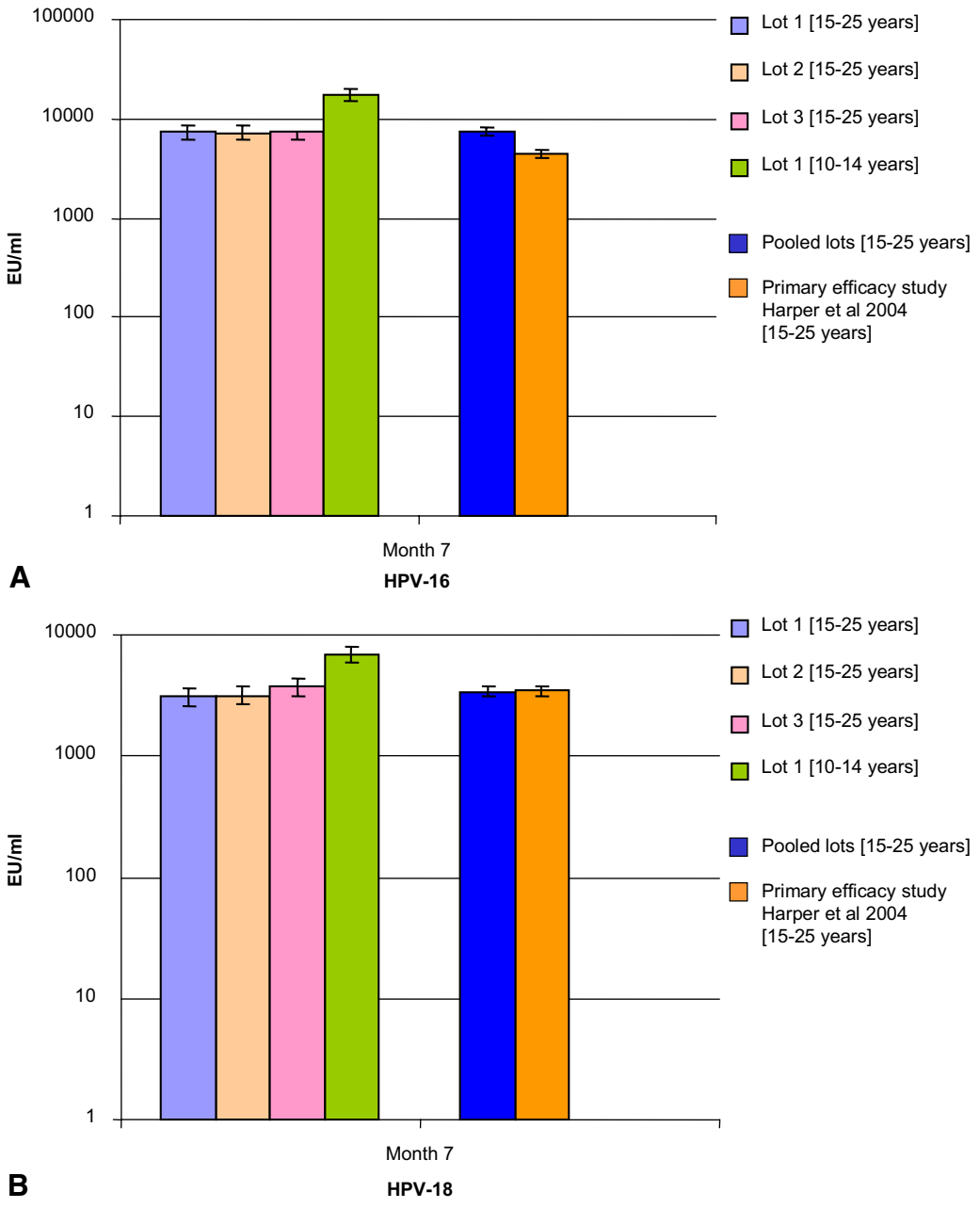

Figure 2. Geometric mean titers according to human papillomavirus (HPV) vaccine type and by age in the according-to-protocol cohort. Serum samples were collected at months 0 and 7. Seropositivity was defined as a titer greater than or equal to the assay threshold established at 8 enzyme-linked immunosorbent assay (ELISA) units/ml (EU/ml) for HPV 16 and 7 EU/ml for HPV 18. EU/ml = ELISA unit per milliliter.

Discussion

Besides demonstration of consistency between different lots of the HPV-16/18 L1 VLP AS04 vaccine, this study showed that 100% seroconversion for both HPV 16 and 18 was achieved in all age groups. The immunogenicity of the vaccine was significantly higher when administered to early adolescents, with post-vaccination GMTs that were at least twofold higher than in the group aged 15–25 years for both HPV 16 and 18.

Previously published results in female individuals aged 15–25 years who were seronegative for HPV 16 and 18, and DNA negative for high-risk HPV types at study entry, show high vaccine efficacy for up to 4.5 years in the prevention of HPV 16/18 incident and persistent infections and associated cytohistological abnormalities [14,15]. When comparing the antibody responses reported in this published study to our current results, we observed that the GMTs in the group 10–14 years of age were substantially higher than the antibody levels obtained at 50–53 months postvaccination,

Table 2
Incidence of solicited local symptoms reported during the 7-day follow-up period, overall per dose (total vaccinated cohort)

Symptom	Type	Subjects 15–25 years (N = 1341)		Subjects 10–14 years (N = 463)	
		n (%)	(95% CI)	n (%)	(95% CI)
Pain	All	1147 (85.5)	(83.5–87.4)	387 (83.6)	(79.9–86.8)
	Grade 3[a]	69 (5.1)	(4.0–6.5)	17 (3.7)	(2.2–5.8)
Redness	All	530 (39.5)	(36.9–42.2)	165 (35.6)	(31.3–40.2)
	>50 mm	17 (1.3)	(0.7–2.0)	4 (0.9)	(0.2–2.2)
Swelling	All	448 (33.4)	(30.9–36.0)	155 (33.5)	(29.2–38.0)
	>50 mm	22 (1.6)	(1.0–2.5)	6 (1.3)	(0.5–2.8)

N = number of documented doses (with safety diary cards returned); CI = exact confidence interval; n (%) = number/percentages of doses that were followed by at least one symptom.
[a] Pain that prevented normal activity.

and where sustained vaccine efficacy has been observed [15]. In the group 15–25 years of age, GMT values are comparable between studies. These observations suggest that similar vaccine efficacy against HPV 16/18 related virological and clinical outcomes could be expected in the present study population.

In both age groups, the high level of antibody titers induced by the HPV-16/18 L1 VLP AS04 vaccine may in part be explained by the presence of the AS04 adjuvant in the vaccine formulation. Recently published clinical data show that the vaccine formulated with AS04 induced higher and sustained antibody levels against HPV 16 and HPV 18 and more robust memory B-cell responses when compared with the same HPV VLP vaccine formulated with conventional aluminum salt only [23].

Antibody responses in the group aged 10–14 years did not compromise the safety profile of the vaccine; on the contrary, there were actually fewer adverse reactions reported among individuals 10–14 years of age than in those 15–25 years. Assessments of safety show that the HPV-16/18 L1 VLP AS04 vaccine was well tolerated and similar safety profiles were observed in both age groups.

High prevalence of HPV 16/18 has been shown in adolescents, although a majority of HPV infections are frequently transient; there are a high number of infections that develop into abnormal cervical cytologic findings or precancerous cervical lesions [2,10]. Furthermore, adolescent girls may also have greater susceptibility to HPV infection and malignancy based on the anatomical features of the cervix, where there is an enlarged cervical transformation zone, the area in which almost all cancerous cervical lesions arise [24–26]. Thus, the administration of a prophylactic HPV vaccine before sexual debut should be considered when determining vaccine implementation

Table 3
Incidence of solicited general symptoms reported during the 7-day follow-up period after administration of human papillomavirus (HPV)– 16/18 L1 VLP AS04 vaccine, overall per dose (total vaccinated cohort)

Symptom	Type	Subjects 15–25-years (N = 1342)		Subjects 10–14 years (N = 463)	
		n (%)	(95% CI)	n (%)	(95% CI)
Arthralgia	All	125 (9.3)	(7.8–11.0)	45 (9.7)	(7.2–12.8)
	Grade 3[a]	4 (0.3)	(0.1–0.8)	1 (0.2)	(0.0–1.2)
Fatigue	All	399 (29.7)	(27.3–32.3)	137 (29.6)	(25.5–34.0)
	Grade 3[a]	11 (0.8)	(0.4–1.5)	7 (1.5)	(0.6–3.1)
Fever	All	46 (3.4)	(2.5–4.5)	18 (3.9)	(2.3–6.1)
	>39.0°C	0 (0.0)	(0.0–0.3)	2 (0.4)	(0.1–1.6)
Gastrointestinal	All	187 (13.9)	(12.1–15.9)	55 (11.9)	(9.1–15.2)
	Grade 3[a]	5 (0.4)	(0.1–0.9)	7 (1.5)	(0.6–3.1)
Headache	All	402 (30.0)	(27.5–32.5)	126 (27.2)	(23.2–31.5)
	Grade 3[a]	12 (0.9)	(0.5–1.6)	5 (1.1)	(0.4–2.5)
Myalgia	All	403 (30.0)	(27.6–32.6)	140 (30.2)	(26.1–34.6)
	Grade 3[a]	16 (1.2)	(0.7–1.9)	5 (1.1)	(0.4–2.5)
Rash	All	50 (3.7)	(2.8–4.9)	24 (5.2)	(3.3–7.6)
	Grade 3[a]	1 (0.1)	(0.0–0.4)	2 (0.4)	(0.1–1.6)
Urticaria	All	22 (1.6)	(1.0–2.5)	5 (1.1)	(0.4–2.5)
	Grade 3[b]	0 (0.0)	(0.0–0.3)	0 (0.0)	(0.0–0.8)

N = number of documented doses (with safety diary cards returned); CI = exact confidence interval; n (%) = number/percentages of doses that were followed by at least one symptom.
[a] Symptom that prevented normal activity.
[b] Urticaria present over at least four body areas.

strategies that may provide potentially substantial public health benefits.

The present study demonstrates that the HPV-16/18 L1 VLP AS04 vaccine is generally safe and well tolerated and induces excellent immunogenicity in female individuals 10–25 years of age. The findings provide evidence that HPV vaccination during early adolescence is feasible and induces even higher HPV 16/18 antibody levels than in young adult women. Additional data and analyses are needed to determine long-term immunogenicity and safety of the HPV-16/18 L1 VLP AS04 vaccine when administered to an early adolescent population. However, all the presently available evidence is in support of administering the vaccine to early adolescent females.

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