Long-term Immunogenicity and Safety of the AS04-adjuvanted Human Papillomavirus–16/18 Vaccine in Four- to Six-year-old Girls

Three-year Follow-up of a Randomized Phase III Trial

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Background: The burden of human papillomavirus (HPV) diseases is high in Latin America. HPV vaccines offer protection against most HPV-related cancers, especially when introduced into national immunization programs. Barriers to optimal vaccine uptake are, however, lowering the impact of adolescent HPV vaccination programs. Immunization of children might overcome these barriers and be a strategy of choice for some countries.

Methods: This multicenter phase III randomized, controlled, single-blind study (NCT01627561) was conducted in Colombia, Mexico and Panama to assess safety and immunogenicity of 2-dose vaccination with AS04-adjuvanted HPV-16/18 vaccine in girls 4–6 years of age. We report safety outcomes and anti–HPV-16/18 antibody titers measured by enzyme-linked immunosorbent assay in HPV-vaccinated girls that were followed over a 36-month period.

Results: Over 36 months (ie, 30 months after the second vaccine dose), among 74 girls included in the HPV group, 1 serious adverse event unrelated to vaccination has been reported. No withdrawal because of (serious) adverse events has been reported. At month 36, all girls in the per-protocol–cohort were still seropositive for anti–HPV-16 and anti–HPV-18 with geometric mean concentrations of 1680.6 and 536.4 enzyme-linked immunosorbent assay units/mL, respectively.

Conclusions: The AS04-adjuvanted HPV-16/18 vaccine administered according to a 2-dose schedule to girls 4–6 years of age induced a high and sustained immunologic response with an acceptable safety profile during the 30 months following vaccination.

Key Words: human papillomavirus, AS04-adjuvanted HPV-16/18 vaccine, safety, immunogenicity, young girls

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Human papillomavirus (HPV) is known as one of the most common sexually transmitted agents worldwide, with an estimated prevalence of 11.7% in women above 14 years old.1 HPV infections are associated with a heavy disease burden as they are estimated to be responsible for 8.6% of all cases of cancers in women across the world in 2012.2,3 HPV types have been classified as of high (oncogenic) and low (nononcogenic) risk for carcinogenesis.4 To date, HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 are considered as oncogenic. Infection by one of these oncogenic HPV types is a necessary cause of cervical cancer, the fourth most common cancer in women worldwide.5 In addition to cervical cancer, a substantial proportion of other genital cancers (vulva, vagina, penis) as well as anal and oropharyngeal cancers in men and women are caused by an oncogenic HPV type infection. Other low-risk types, such as HPV-6 and HPV-11, are associated with genital warts.6

Among all oncogenic HPV types, HPV-16 and HPV-18 are responsible for approximately 70% of cervical cancers.7 HPV-16 alone is involved in 60% of all cervical cancer cases as well as other HPV-related cancers, such as anal, penile, vaginal and vulvar cancers. HPV 18, 31, 33 and 45 also contribute to these cancers but to a lower degree. Three vaccines are currently available for preventing HPV-related lesions: the AS04-adjuvanted HPV-16/18 vaccine (AS04-HPV-16/18), the 4-valent HPV-6/11/16/18 vaccine, and the 9-valent HPV-6/11/16/18/31/33/45/52/58 vaccine. All vaccines contain virus-like particles from HPV-16 and HPV-18, and demonstrated high efficacy against HPV-16/18 lesions.8–10

The 4-valent HPV-6/11/16/18 vaccine and 9-valent HPV-6/11/16/18/31/33/45/52/58 vaccine also include virus-like particles of additional HPV types 6/11 and 6/11/31/33/45/51/52/58, respectively, inducing protection against HPV-related diseases associated with these types. The AS04-HPV-16/18 vaccine showed protection against some HPV types not included in the vaccine.11–14 Some level of cross-protection was also seen with the 4-valent HPV-6/11/16/18 vaccine.15 Such a protection of the licensed vaccines
is likely conferred by the cross-reactivity of antigens (ie, phylogenetically related nonvaccine oncogenic types presumably share epitopes with vaccine types); cross-protection indeed largely mirrors antibody-mediated cross-neutralization.16

Latin America and the Caribbean region experience one of the heaviest HPV-related burdens. In 2018, cervical cancer was estimated to be the second most common cancer in women 15 to 74 years of age from Latin America and the Caribbean region,2 and in some countries of South and Central America, it is the leading cause of cancer incidence and mortality among women.17 These variations across the South and Central American region are attributed to the disparity in Human Development Index, which is known to correlate the standard of detection practices and disparities in healthcare access.18 Countries of medium Human Development Index, such as Bolivia, El Salvador, Guatemala, Nicaragua and Suriname, endure the highest burden of cervical cancer when compared with high Human Development Index countries.

By the end of 2018, HPV vaccines had been included in the national immunization programs of approximately 80 countries around the world.19 The remaining countries where no HPV vaccination program is implemented are mainly located in Africa and Asia. This heterogeneity also correlates with the socio-economic level of these countries.20 HPV vaccination programs are mainly targeting young adolescent girls before initiation of their sexual activity. Currently, all available HPV vaccines are indicated from the age of 9 or above. The World Health Organization recommends vaccination of girls 9 to 14 years of age according to a 2-dose schedule.21 Programs and coverage, however, vary across countries.22 In Latin America, 20 countries had implemented HPV vaccination programs as of 2017. The estimated full-course (3 doses) mean coverage reported in 2014 for the 18 countries having implemented HPV vaccination was 71.0% in Latin America and the Caribbean region, which is substantially higher than the worldwide average of 39.7%.20 Recently, concerns have, however, been raised as HPV vaccine uptakes in many Latin American and Caribbean countries are reported to decrease.23 Among other reasons, the high cost of HPV vaccines, as well as the requirement for multiple doses, are thought to limit acceptance and uptake in the population, especially in low- and middle-income countries. The target population may play a role in vaccine uptake. Many countries have implemented the pediatric Expanded Program on Immunization schedule and accompanying strategies that have been successful for increasing childhood vaccination coverage rates.24-25 Vaccination of preschool children who have regular medical appointments indeed favors its uptake and adherence when compared with adolescent vaccination. Thus, extending the HPV vaccine indication to younger age groups would facilitate programmatic aspects of immunization programs and would benefit from the same infrastructure and strategies. This idea is supported by the observed higher immune responses induced by the AS04-HPV-16/18 vaccine in the younger age groups that is, 9–14 years old.26,27

While data from clinical trials and safety surveillance indicate that the AS04-HPV-16/18 vaccine is well tolerated in adolescent girls and women,26,29 safety and immunogenicity of the vaccine in children below 9 years of age are yet to be demonstrated. Therefore, we conducted this first phase III clinical trial investigating the administration of 2 doses of the AS04-HPV-16/18 vaccine in 4–6-year-old girls from Colombia, Panama and Mexico. The recently-published primary results showed that 6 months after the second dose, the vaccine was well tolerated and immunogenic.30 All initially seronegative girls had seroconverted for both anti–HPV-16 and anti–HPV-18. Antibody geometric mean concentrations (GMCs) peaked at month 7 (ie, 1 month after the second vaccine dose) and thereafter decreased. This article presents the long-term immunogenicity and safety assessment of the same population up to month 36 (ie, 30 months after vaccination).

MATERIALS AND METHODS

Study Design and Subjects

This multicenter phase III, randomized, controlled, single-blind study (NCT01627561) was conducted in Colombia, Panama and Mexico from October 2012 to October 2016. Healthy girls between, and including, 4 and 6 years of age at the time of first vaccination, were eligible if they had previously received 4 doses of a diphtheria-tetanus-pertussis–containing vaccine (3 doses in their first year of life and the fourth dose in their second year of life) and only one dose of the measles-mumps-rubella vaccine in their second year of life. Detailed enrollment criteria can be found in the primary publication.30 Eligible girls were randomized (1:1) to either the HPV or control group. Girls from the HPV group received 2 doses of AS04-HPV-16/18 vaccine (Cervarix, GSK, Belgium) at months 0 and 6 while girls from the control group were given 1 dose of the measles-mumps-rubella (Priorix, GSK, Belgium) vaccine at month 0 and 1 dose of the diphtheria-tetanus-acellular pertussis (Infanrix, GSK, Belgium) vaccine at month 6 (Fig. 1). AS04 is a GlaxoSmithKline (GSK) proprietary Adjuvant System containing 3-O-desacyl-4′-monophosphoryl lipid A (50 µg) adsorbed on aluminum salt (500 µg Al3+). Randomization of supplies within groups was performed centrally before distribution to study centers. Treatment allocation at the investigator site was performed using a central randomization system on internet. The study was single-blinded up to 6 months after administration of the second dose (month 12). Then, the treatment allocation was unblinded for the subjects and their parents, and the study was concluded for the control group. Girls in the HPV group were invited to participate in an additional 24-month follow-up (Fig. 1).

The study was conducted in accordance with the guidelines from the International Conference on Harmonization-Good Clinical Practices, the Declaration of Helsinki and all applicable

![FIGURE 1. Study design. D indicates day; HPV, human papillomavirus; M, month.](image-url)
regulatory requirements. Safety data and ethical aspects of the study were overseen by an Independent Data Monitoring Committee. Written informed consent was obtained from the parent, or the legally-acceptable representative, of each girl before study enrollment, in compliance with specific local regulations. Anonymous individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

**Study Objectives**

The primary study objectives were the evaluation of the reactogenicity, safety and immunogenicity of the AS04-HPV-16/18 vaccine up to 1 month after 2-dose vaccination. These results have already been presented in the previous publication along with the secondary objectives’ assessment of compliance with full vaccination course and 6-month safety and immunogenicity follow-up. The present article discloses the secondary objectives long-term safety and immunogenicity persistence up to month 36 (ie, 30 months after the 2-dose vaccination). The present article does not disclose the secondary objectives evaluation of the immunogenicity of the measles, mumps and rubella vaccine and of the diphtheria-tetanus-acellular pertussis vaccine.

**Safety Assessment**

Adverse events (AEs) and serious AEs (SAEs) leading to withdrawal, as well as SAEs related to the study vaccines, were recorded during the entire follow-up period (ie, until month 36).

**Immunogenicity Assessment**

Blood samples in the HPV group were collected at baseline and at months 7, 12, 18, 24 and 36. Antibody titers against HPV-16 and HPV-18 in serum were measured by an enzyme-linked immunosorbent assay with type-specific L1 virus-like particles as coating antigens, as described in the pivotal vaccine efficacy study in women 15–25 years of age and in the pivotal immunobridging study in adolescent girls 9–14 years of age; the cutoff values were, however, revised as 19 enzyme-linked immunosorbent assay units (EU)/mL for anti–HPV-16 and 18 EU/mL for anti–HPV-18 antibodies, as described in long-term follow-up efficacy studies with the 2-dose vaccination schedule in adolescent girls and women 15–25 years of age.

**Statistical Analysis**

The statistical analyses were performed using SAS version 9.3 on SAS Drug Development. Safety analyses were conducted on the total vaccinated cohort, which included all subjects who received at least one dose of vaccine in this study. Immunogenicity analyses were conducted on the according-to-protocol cohort for immunogenicity adapted for each time point. These adapted cohorts include subjects meeting all eligibility criteria, receiving 2 doses of HPV vaccines and having blood samples taken according to the procedures defined in the protocol, with no elimination criteria and for whom immunogenicity data were available.

Seropositivity rates and GMCS for HPV-16 and HPV-18 antibodies were calculated with 95% confidence intervals (CIs). Seropositivity corresponded to an antibody titer greater than or equal to the enzyme-linked immunosorbent assay cutoff value. Antibody titers below the cutoff of the assay were given an arbitrary value of half of the cutoff for GMC calculation.

**RESULTS**

**Study Participants**

A total of 148 girls participated in the study, of which 74 were included in the HPV group (total vaccinated cohort). Among
them, 73 subjects completed the 36 months follow-up and 1 subject was withdrawn from the study because of loss of follow-up from month 24 onwards (Fig. 2). The number of subjects included in the according-to-protocol cohorts for immunogenicity analysis at months 7, 12, 18, 24 and 36 were 65, 66, 67, 68 and 68, respectively (Fig. 2).

Mean age at baseline for these 74 subjects was 4.3 years (standard deviation: ± 0.5), and all were of American Hispanic or Latino ethnicity. At baseline, serum HPV antibody results were available for 73 subjects in HPV groups. All 73 subjects were seronegative for anti–HPV-16 antibodies. Among them 2 subjects were seropositive for anti–HPV-18 antibodies, with very low antibody titers being 19.0 EU/mL and 23.0 EU/mL, respectively (ie, assay cutoff value is 18 EU/mL), as compared with the vaccine-induced antibody response. These results might be explained by a natural immune response induced by previous exposure to HPV.35–39

Safety
During the entire 36-month period, 1 girl from the HPV group reported an SAE (acute gastroenteritis) 176 days after the second vaccine dose. The subject recovered after 4 days, and the SAE was assessed to be unrelated to the vaccine. There were no withdrawals due to AEs or SAEs during the study period.

Immunogenicity
At month 36 (ie, 30 months postvaccination), in the according-to-protocol cohort for immunogenicity, all subjects who had seroconverted at month 7 remained seropositive for anti–HPV-16 and anti–HPV-18 antibodies. GMCs at month 36 were 1680.6 EU/mL (95% CI: 1384.2–2040.4) and 536.4 EU/mL (95% CI: 420.6–684.0).

### TABLE 1. Anti–HPV-16 and anti–HPV-18 Antibody Geometric Mean Concentrations (GMCs) in Initially Seronegative Subjects (According-to-Protocol Cohort for Immunogenicity)

| Month | Subjects With Available Results, n | Seropositive Subjects, n (%) | GMC, EU/mL | 95% CI, LL UL |
|-------|-----------------------------------|-----------------------------|------------|--------------|
| 7     | 64                                | 64 (100)                    | 20,080.0   | 16,831.8 23,954.9 |
| 12    | 65                                | 65 (100)                    | 3,246.5    | 2617.4 4026.8 |
| 18    | 66                                | 66 (100)                    | 2,800.5    | 2325.8 3372.0 |
| 24    | 67                                | 67 (100)                    | 1,951.9    | 1553.7 2452.2 |
| 36    | 67                                | 67 (100)                    | 1,680.6    | 1384.2 2040.4 |
| 7     | 62                                | 62 (100)                    | 10,621.8   | 8865.3 12,726.3 |
| 12    | 63                                | 63 (100)                    | 1,216.6    | 953.1 1553.0 |
| 18    | 64                                | 64 (100)                    | 802.9      | 632.4 1,019.5 |
| 24    | 65                                | 65 (100)                    | 766.6      | 603.3 974.2 |
| 36    | 65                                | 65 (100)                    | 536.4      | 420.6 684.0 |

CI indicates confidence interval; EU, enzyme-linked immunosorbent assay units; LL, lower limit; n, number of subjects; UL, upper limit.

FIGURE 3. Geometric mean concentrations for anti–HPV-16 and anti–HPV-18 antibodies in initially seronegative subjects (according-to-protocol immunogenicity cohort, adapted for each time point). Dashed lines are natural infection levels reported in Paavonen et al,41 for HPV-16 (29.8 EU/mL) and HPV-18 (22.7 EU/mL). Dotted lines are cutoff values for HPV-16 (19.0 EU/mL) and HPV-18 (18.0 EU/mL). CI indicates confidence interval; EU, enzyme-linked immunosorbent assay units; GMC, geometric mean concentration; HPV, human papillomavirus.
420.6–684.0) for anti–HPV-16 and anti–HPV-18, respectively (Table 1). Kinetics for anti–HPV-16 and anti–HPV-18 antibody concentrations are presented in Figure 3. The antibody response peak was observed at month 7, which is 1 month after the second vaccine dose. A decrease was then observed at month 12 and followed thereafter by a plateau till month 36. Figure 4 elaborates on the findings in a form that could be shared with patients by health care professionals.

**DISCUSSION**

HPV vaccination has most impact when targeting HPV-naive females and is currently recommended and approved for young adolescents from the age of 9 years. In Latin America, where the burden of HPV-related cancers is high, vaccination through pediatric immunization programs could increase vaccine uptake. This is the first time that safety and immunogenicity of the AS04-HPV-16/18 vaccine were assessed in girls 4–6 years of age and followed up during a 36-month period (ie, 30 months after completion of the 2-dose vaccination schedule).

In this young population, the safety profile of the AS04-HPV-16/18 vaccine observed over 30 months following the last dose was acceptable as no SAE related to the vaccine was reported. All girls seroconverted for anti–HPV-16 and anti–HPV-18 at month 7, that is, 1 month after the second dose. The seroconversion rate remained at 100% at month 36. The kinetic of anti–HPV-16 and anti–HPV-18 antibody GMCs in serum over 3 years postvaccination followed the known trends, reaching plateau between month 18 and month 36.

One of the limitations of this study is the lack of an immunogenicity control group. Nevertheless, we compared the HPV antibody response data in the preschool girl population (4–6 years old) from the present study with the response detected in the young adolescent girl population (9–14 years old) from a pivotal immunobridging phase III study. At month 36, the anti–HPV-16 level among preschool girls of the present study was higher than the level detected in the young adolescent girl population with the same (M0, 6) vaccine schedule (1210.2 EU/mL; 95% CI: 1124.8–1302.1), with nonoverlapping 95% CI. It was, however, similar to the concentration also measured at month 36 in the young adolescent girl population vaccinated with 2 doses at months 0 and 12 (M0, 12) (1559.3 EU/mL; 95% CI: 1431.2–1699.0). The anti–HPV-18 level detected at month 36 among girls 4–6 years of age in the present study was similar to the concentration detected in the young adolescent girl population with the same (M0, 6) 2-dose schedule (562.8 EU/mL; 95% CI: 516.4–613.4). It was, however, lower than the concentration detected at month 36 in the young adolescent girl population vaccinated according to the (M0, 12) 2-dose schedule (804.0 EU/mL; 95% CI: 731.8–883.4), with nonoverlapping 95% CI. The flaw of this comparison lies in the difference of ethnicity background of the 2 populations in these studies: predominantly American Hispanic or Latino for the preschool population in the present study while predominantly White Caucasian European, North American and Asian for the young adolescent population in the pivotal immunobridging study.

We also compared the HPV antibody response data in the preschool girl population (4–6 years old) of the present study with those from adolescent/young adult population (15–25 years old) from a previous large phase IIb vaccine efficacy trial. In a subset of adolescent/young adult women of Hispanic origin recruited in Brazil, anti–HPV-16 and anti–HPV-18 levels 30 months after the (M0, 1, 6) 3-dose schedule were 447.2 EU/mL (95% CI: 365.1–547.8) and 336.7 EU/mL (95% CI: 278.6–406.9), respectively, which were lower than those observed in preschool girls in the present study. It was observed that the plateau levels for anti–HPV-16 and anti–HPV-18 GMCs reached at month 36 were sustained for at least 9 years, remaining 10-fold higher than antibody levels elicited...
by natural infection (29.8 EU/mL for HPV-16 and 22.6 EU/mL for HPV-18). Further clinical research is needed to confirm the non-inferiority or superiority of the vaccine-induced immune response in this preschool age population as compared with the current standard vaccine regimen (2-dose regimen at month 0 and 6 or 12) in young adolescent women (9 to 14 years old) but also to investigate the vaccine safety profile in this preschool-age population.

Data from long-term follow-up were used for modeling the persistence of immunogenicity over several decades. Combined with the high antibody levels observed at month 36 for the young subjects of our study, these predictions of immunogenicity persistence induced by the AS04-HPV-16/18 vaccine are crucial for assessing the benefit of vaccination at a younger age, although no correlate of protection was established so far. Although a booster dose is not recommended in the current vaccination schedules, reactivation of the immune response has been demonstrated after the administration of a challenge dose. This immune memory provides the basis for protection of women against HPV-16/18 infections that can be sustained throughout their period of sexual activity.

Another limitation from the study is that data were collected from Latin American children only. Caution should, therefore, be taken for generalizing our observations. It is also important to note that study participants were 4–6 years old at the time of vaccination, and even at the end of the 3-year follow-up period, very unlikely to be sexually active. This is also a reason why no assessment of vaccine efficacy was performed in this population. Despite the high retention rate (ie, 73 of 74 subjects completed 36 months follow-up), it is recognized that the sample size is too small to detect the common and uncommon or even rare serious or clinically relevant AEs and thus cannot address the long-term risk.

CONCLUSIONS

In this study, vaccination of girls 4–6 years of age with 2 doses of AS04-HPV-16/18 vaccine induced high immune response that translated to antibody plateau sustained for 30 months after doses of AS04-HPV-16/18 vaccine induced high immune response in this young population. These results suggest that pediatric HPV vaccination might be a valuable strategy to overcome limitations of some adolescent immunization programs.

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