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Long-term persistence of anti-HPV-16 and -18 antibodies induced by vaccination with the AS04-adjuvanted cervical cancer vaccine: Modeling of sustained antibody responses ☆

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ABSTRACT

Objectives. Strong and sustained HPV-16 and -18 antibody responses have been observed in previously unexposed women aged 15–25 years vaccinated with the AS04-adjuvanted HPV-16/18 L1 virus-like particle vaccine. While awaiting the extended results of ongoing trials, our objective was to predict the long-term persistence of anti-HPV-16/18 antibodies in vaccinees by applying three statistical models using immunogenicity data from vaccinated women with serum samples collected up to 6.4 years after first vaccination. Two different data lock-points (up to 5.5 years and up to 6.4 years) were used to assess the robustness of the models.

Methods. Three statistical models were applied to estimate the long-term persistence of anti-HPV-16/18 antibodies in 393 women vaccinated with the AS04-adjuvanted HPV-16/18 vaccine. Individual antibody levels for each study participant at each timepoint up to 6.4 years were input to previously published power-law and modified power-law models. The power-law model estimates antibody decay over time. The modified power-law model takes into account both antibody persistence over time and immune memory. A third model, the piece-wise model, fits the data based on three different non-overlapping intervals (between Months 7 and 12, Months 12 and 21, and over 21 months), corresponding to the observed decay of vaccine-induced antibodies.

Results. HPV-16 and -18 antibodies peaked at Month 7 and gradually plateaued at Months 18–24 and remained stable through 6.4 years. Mean antibody levels at the last timepoint were several fold higher than those associated with natural infection. All three models predict that HPV-16 and -18 mean antibody levels will remain well above those associated with natural infection for at least 20 years, when using data from 5.5 as well as 6.4 years' follow-up. Predictions are similar for the modified power-law model and improve with longer follow-up for both the power-law and the piece-wise models.

Conclusions. Vaccination with the AS04-adjuvanted HPV-16/18 vaccine is predicted to provide long-term persistence for both HPV-16 and -18 antibodies, independent of the statistical model applied. Model predictions are based on conservative mathematical assumptions. Since the input of longer term data of up to 6.4 years showed an improved profile compared with that for data up to 5.5 years, the predictions of antibody persistence based on population means are conservative when predicting that antibody levels will remain well above levels induced by natural infection for 20 years.

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Introduction

Approximately 80% of women will acquire a human papillomavirus (HPV) infection in their lifetime [1]. Cervical cancer of both squamous and adenocarcinoma types is considered to be 100% attributable to persistent infection with oncogenic HPV types [2]. HPV-16 and -18 are the predominant oncogenic types worldwide, accounting for a little over 70% of all cases of cervical cancer [3].

Since the risk of HPV infection persists throughout a woman's sexually active life, the duration of protection provided by cervical cancer vaccination will be critical in overall vaccine effectiveness. Strong and sustained HPV-16 and -18 antibody responses have been demonstrated for up to 6.4 years in women 15–25 years of age

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vaccinated with an HPV-16/18 L1 virus-like particle (VLP) AS04-adjuvanted cervical cancer vaccine (*Cervarix*™, GlaxoSmithKline Biologicals, Rixensart, Belgium) [4,5]. The Phase III program with this vaccine is ongoing and will include long-term follow-up to evaluate the duration of protection and the persistence of antibodies.

Until the results of ongoing clinical studies become available, the duration of anti-HPV-16 and -18 antibody responses following vaccination can be explored by statistical modeling. Factors that influence long-term immunity should be considered when developing models, and these include the peak level of antibody response after the primary vaccination schedule, the rates of B-cell decay and proliferation, B-cell immunologic memory, cell-mediated immunity, as well as variability in response between individuals [6]. These factors require further exploration in additional studies as examining each was not an objective of this study.

The contribution of immunologic memory to long-term vaccine-induced protection has been demonstrated in other vaccine studies, such as with hepatitis A and B, by a rapid increase in antibody levels following booster vaccination and by persistence of immunity in individuals with decreasing antibody levels [7–9]. However, whereas classical chronic viral infection, such as that caused by hepatitis B virus, is associated with persistent viremia, HPV infection follows a different course and does not cause systemic infection [10]. Re-infection with HPV is unlike hepatitis viruses due to the fact that infection remains localized at the mucosal level and may remain invisible to the immune system and may, therefore, be unable to trigger the anamnestic response [11,12]. The decision to use a novel Adjuvant System (AS) with the HPV-16/18 vaccine was based on data showing that the AS04-adjuvanted formulation induced more robust and sustained antibody and memory B-cell responses when compared with the same antigens formulated with aluminum hydroxide alone for up to 4 years after the first dose [13].

It is anticipated that induction of high levels of neutralizing antibodies in the serum may induce high levels of antibodies at the cervical mucosa through a passive transfer mechanism [10,14–17]. We have attempted to predict the long-term persistence of vaccine-induced anti-HPV-16 and anti-HPV-18 antibodies by retrospectively applying mixed effects statistical models to antibody levels measured in the follow-up phase (NCT00120848) of a primary efficacy study (NCT00689741). Comparison of data up to 5.5 and 6.4 years provides a method for observing how model predictions alter over time.

Materials and methods

Study design: population and sampling timepoints

The HPV-16/18 primary efficacy trial vaccinated 560 healthy young women 15–25 years of age who were HPV-16 and -18 seronegative and DNA negative for 14 oncogenic HPV types. Details of this trial have been described previously [18]. Women ($n = 393$) who participated in the initial efficacy study and received three doses of vaccine were enrolled into an extended follow-up study [19]. The studies and all study materials were approved by ethics committees or institutional review boards.

Blood samples from the 393 women in the HPV group of the extension study were evaluated at Months 0, 7, 12 and 18 (primary study) and annually thereafter up to Month 76 (i.e., up to 6.4 years after first vaccination) for the presence of HPV-16/18 antibodies using a type-specific enzyme-linked immunosorbent assay (ELISA), as described below. For the current evaluation, we included women who had received three doses of AS04-adjuvanted HPV-16/18 vaccine and had at least one timepoint after the third dose with serology results available for at least one vaccine antigen component. The number of samples available at each study visit is shown in Table 1.

Table 1
Number of samples per visit and per test (women who received three vaccine doses, studies NCT00689741 and NCT00120848).

Timing	Antibody	
	HPV-16	HPV-18
M7	364	362
M12	366	366
M18	365	365
M25–M32	89	89
M33–M38	219	219
M39–M44	161	162
M45–M50	234	234
M51–M56	130	130
M57–M62	225	225
M63–M68	130	130
M69–M74	222	222
≥M75	66	66

M7/M12/… = 7/12/… months after Dose 1.
Subjects were enrolled in the follow-up phase (from Month 25 to Month 75) on dates that were independent from the date of first vaccination in the primary efficacy study (until Month 18). As a result, the timepoints for immunogenicity measurement after Month 18 differ between subjects. The timepoints were defined as 6-month intervals indicating the number of months between the first vaccination visit and the blood sampling in the follow-up study.

Laboratory assessments

GSK direct ELISA assays

Samples from all women in the HPV group were tested using a direct ELISA developed in-house by GSK. Quantitation of anti-VLP antibodies was performed using HPV-16 or -18 L1 VLP as coating antigen (2.1 μg/mL and 2.7 μg/mL, respectively). Diluted serum samples were added to VLP-coated plates and incubated for 1 h at room temperature while shaking. Following a washing step, horseradish peroxidase-conjugated anti-human IgG was added to each well as the secondary antibody and reactions were incubated for 1 h at room temperature, followed by incubation with tetramethylbenzidine for a further 20 min. Reactions were terminated with H_2SO_4 (0.36–2 N) and optical density was read at 450/620 nm. ELISA titers were calculated from standard serial dilutions or positive-control pooled reference serum samples using a four parameters equation and expressed as EU/mL. The assay cut-off value was 8 EU/mL for HPV-16 and 7 EU/mL for HPV-18.

Statistical methods

Immunogenicity

Anti-HPV-16 and anti-HPV-18 geometric mean titers (GMT) and the corresponding 95% confidence intervals (CI) were calculated at each timepoint. The GMTs resulting from natural infection were determined by testing pre-vaccination blood samples obtained from women in a large Phase III efficacy study of GSK's cervical cancer vaccine that demonstrated protection against HPV-16/18-related high-grade cervical intraepithelial lesions [20].

Prediction of long-term persistence of HPV-16/18 antibody responses

To assess the persistence of HPV-16 and HPV-18 vaccine-induced antibody responses, the individual antibody levels of each woman at each timepoint, up to 5.5 years and up to 6.4 years, were used to fit three different mixed effects models, separately for both antibodies (against HPV-16 and -18). The power-law model included the rate of B-cell decay to estimate the persistence of antibody levels over time after vaccination [6]. The power-law model used is given below:

$$f(t) = k - a\log(c + t)$$

where $f(t)$ is the log antibody titer at time t post-vaccination, k is the peak log level, a is the decay rate, and c is an arbitrary small

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