

EFFICACY OF THE QUADRIVALENT HPV VACCINE AGAINST HPV 6/11/16/18-RELATED GENITAL INFECTION IN YOUNG MEN

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OBJECTIVE

In males, anogenital infection with human papillomavirus (HPV) can lead to genital warts, penile, perianal, anal and perineal cancer. In addition, male HPV infection contributes significantly to infection and subsequent cervical disease in women. This study examined the efficacy of the quadrivalent HPV (type 6/11/16/18) L1 virus-like particle vaccine against HPV 6/11/16/18-related infection as well as the incidence of HPV 6/11/16/18-related external genital lesions (external genital warts, penile/perianal/perineal intraepithelial neoplasia [PPPIN], penile, perianal, or perineal cancer) in young men (men having sex with men and heterosexual men).

METHODS

In this randomized, double-blind, placebo-controlled trial, 4,065 young men aged 16-26 were administered quadrivalent HPV vaccine or placebo at enrollment, month 2, and month 6. Subjects underwent detailed anogenital exams as well as sampling from the penis, scrotum, anal (MSM cohort only) and perianal region at enrollment, month 7, and every 6 months thereafter. Total follow-up period will be 36 months for each subject. Endpoints in this analysis included HPV 6/11/16/18 infection at one or more visits, as well as persistent infection with HPV types 6/11/16/18 (defined as detection of HPV 6/11/16/18 DNA at two or more visits ≥ 6 months apart [± 1 month visit windows]). The primary efficacy analysis was performed in a per-protocol population seronegative at day 1 and PCR negative at day 1 and month 7 to the relevant vaccine HPV type.

CONCLUSIONS

Among 1,390 vaccine subjects and 1,400 placebo subjects, efficacy against persistent infection with HPV 6/11/16/18 was 85.6% (95% CI: 75.1, 92.2). Efficacy against persistent infection with individual HPV types 6, 11, 16, and 18 was 88.0% (95% CI: 66.3, 96.9), 93.4% (95% CI: 56.8, 99.8), 78.7% (95% CI: 55.5, 90.9), and 96.0% (95% CI: 75.6, 99.9), respectively. Vaccine efficacy against HPV 6/11/16/18-related infection at one or more visits was 44.7% (95% CI: 31.5, 55.6). In summary, quadrivalent HPV vaccine is effective in decreasing the incidence and persistence of infection with HPV 6/11/16/18 in a population of young men aged 16-26.

UPDATE ON LONG TERM IMMUNITY WITH THE HPV 6/11/16/18 VACCINE**Stanley M, UK**

The key to long-term immunity following vaccination is the stimulation of a robust neutralizing antibody response and the induction of immune memory. Vaccination with human papillomavirus (HPV) 6/11/16/18 virus-like particles (VLPs) has been shown to elicit a strong neutralizing antibody response, immune memory and to provide long-term disease protection through at least 5 years. A competitive Luminex immunoassay has been effectively used to monitor vaccine-induced antibodies to a single, type-specific, neutralizing epitope. To more fully understand the complete neutralizing antibody response to HPV virions following natural infection or vaccination with an HPV 6/11/16/18 VLP vaccine, a multiplexed assay to measure total human IgG antibodies in serum to VLPs was developed. The VLP antigens are coupled to Luminex microspheres and antibody titers are determined in a direct binding format, where the IgG₁₋₄ specific, phycoerythrin (PE)-labeled monoclonal antibody (HP6043), detects human serum IgG antibodies bound to the VLPs. VLP adsorption experiments showed that the assay is >99% specific for IgG that bind VLPs. For HPV, no minimum serological correlate of protection has been established and there is no standardized assay or methods for setting serostatus cutoffs. Three different methods were used to evaluate serostatus cutoffs: 1) a clinical sensitivity/specificity analysis based on samples from non-vaccinees, 2) evaluating upper tolerance limits on samples from "likely negatives" and 3) evaluating upper tolerance limits from the same "likely negative" sample set after VLP-adsorption. Depending on the method to set the serostatus cutoff, the percentage of seropositive type 18 samples at the month 48 time point post-vaccination ranged from 70% to 100%. Demonstration of seroconversion and the level of seropositivity are measurable parameters, however the level of seropositivity depends on the method used to set the serostatus cutoff. Disease prevention remains the most important measure of the long-term duration of vaccine efficacy.

LATEST CLINICAL UPDATES AND LONG-TERM ASPECTS OF CERVICAL CANCER VACCINATION WITH AN HPV-16/18 AS04-ADJUVANTED VACCINE

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Objectives: Virtually all cervical cancers are caused by persistent infection with oncogenic human papillomavirus (HPV) types. HPV-16 is consistently the most common type in invasive cervical cancers, followed by HPV-18, together accounting for 70%. Other prevalent oncogenic types are HPV-45 and -31, and globally these four types account for approximately 80% of the cervical cancer burden. HPV-16, -18 and -45 account for the vast majority of adenocarcinomas. Presented here are data on the long-term immunogenicity and efficacy shown against HPV-16/18-related cervical intraepithelial neoplasia in women vaccinated with an HPV-16/18 AS04-adjuvanted vaccine (*Cervarix*[™], GSK Biologicals), and the cross-protection shown against non-vaccine oncogenic types (45 and 31) that are phylogenetically related to HPV-16 and -18

Methods: Long-term immunogenicity and vaccine efficacy up to 6.4 years, induced by the AS04-adjuvanted HPV-16/18 vaccine, were assessed in 776 women 15-25 years old who had participated in the extended follow-up (NCT00120848)¹ of an initial Phase IIb efficacy study (NCT00689741). Cross-protection against incident infection caused by HPV-45 and -31 was evaluated over the same period in the same study. Additional data have been reported against persistent infection and CIN2+ in the total vaccinated cohort for efficacy (TVC-E; N=18,525) of unscreened women 15-25 years old in the interim analysis of the Phase III PATRICIA study (NCT00122681) and in a subset of previously unexposed women from this study (HPV-16 and -18 seronegative and DNA negative for 14 oncogenic types)². The TVC-E and the subset were followed up for 14.8 months.²

Conclusions: Up to 6.4 years, ≥98% of women remained seropositive for both HPV-16 and -18 in the Phase IIb study; total IgG and neutralizing antibody levels were several fold higher than natural infection levels for both types. In addition, vaccine efficacy (VE) was 100% (95% CI: 51-100%) against CIN2+ caused by HPV-16/18 and substantial cross-protection against incident infection with HPV-45 and -31 was maintained. Interim results of the PATRICIA study have shown VE against HPV-16/18-associated CIN2+ up to 100% (97.9% CI: 74.2-100%) based on a post-hoc analysis that took into account multiple infections when assigning probable causality to lesions, and cross-protection against 6-month persistent infections with HPV-45 (VE=59.9% [97.9% CI 2.6-85.2%]) and HPV-31 (VE=36.1% [0.5-59.5%]). In the unexposed subset of PATRICIA, cross-protection against HPV-45 was confirmed (VE=83.4% [97.9% CI: 32.9-97.8]), and VE against HPV-31 was 41.7% [97.9% CI: <0.0-75.5]. Statistically significant cross-protection was observed with HPV-31 combined with HPV-45 (VE=59.6% [20.5-80.7]), and against the five most prevalent types after 16/18 (31, 33, 45, 52, 58) [VE=40.6% (16.4-58.1)]. These results are consistent with the AS04-adjuvanted HPV-16/18 vaccine inducing high and sustained efficacy up to 6.4 years and broad protection against persistent infection by non-vaccine types, notably HPV-45, the third most frequent type both in adenocarcinoma and squamous cell carcinoma.

1. Harper D et al. Lancet 2006; 367:1247-55.
2. Paavonen J et al. Lancet 2007; 369:2161-70.

THE EFFICACY OF QUADRIVALENT HPV (TYPES 6/11/16/18) VACCINE IN REDUCING THE INCIDENCE OF HPV-RELATED GENITAL DISEASE IN YOUNG MEN

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OBJECTIVE

In males, anogenital infection with human papillomavirus (HPV) can lead to genital warts, penile, perianal, anal and perineal cancer. In addition, male HPV infection contributes significantly to infection and subsequent cervical disease in women. This study examined the efficacy of the quadrivalent HPV (type 6/11/16/18) L1 virus-like particle vaccine against HPV 6/11/16/18-related infection as well as the incidence of HPV 6/11/16/18-related external genital lesions (external genital warts, penile/perianal/perineal intraepithelial neoplasia [PPPIN], penile, perianal, or perineal cancer) in young men (men having sex with men and heterosexual men).

METHODS

In this randomized, double-blind, placebo-controlled trial, 4,065 young men aged 16-26 were administered quadrivalent HPV vaccine or placebo at enrollment, month 2, and month 6. Subjects underwent detailed anogenital exams as well as sampling from the penis, scrotum, anal (MSM cohort only) and perianal region at enrollment, month 7 and at 6 month intervals afterwards. After enrollment, all new lesions were biopsied for pathological diagnosis. All biopsies collected were processed and reviewed by a central pathology laboratory, the diagnosis of which was used for clinical management. In addition, all biopsy slides were reviewed by a blinded panel of experts for the purpose of determining study endpoints. The primary efficacy analysis was performed in a per-protocol population seronegative at day 1 and PCR negative at day 1 and month 7 to the relevant vaccine HPV type. Adverse experience assessment was performed via vaccine report card.

CONCLUSIONS

Among 1,397 vaccine subjects and 1,408 placebo subjects, efficacy against any HPV 6/11/16/18-related external genital lesion in the per-protocol population was 90.4% (95% CI: 69.2, 98.1). Vaccine efficacy against condyloma and PPPIN was 89.4% (95% CI: 65.5, 97.9) and 100% (95% CI: <0, 100). Efficacy against HPV 6-, 11-, 16-, and 18-related external genital lesions was 84.3% (95% CI: 46.5, 97.0), 90.9% (95% CI: 37.7, 99.8), 100% (95% CI: <0, 100), and 100% (95% CI: <0, 100), respectively. Slightly more injection-site adverse experiences were seen among vaccine recipients. No vaccine-related serious adverse experiences were seen. In summary, the quadrivalent HPV vaccine is effective in decreasing the incidence of HPV-related external genital lesions in young men aged 16-26 naïve to the relevant vaccine HPV type at baseline.

EXPRESSION OF HPV L1 CAPSID PROTEIN IN PAP TEST: A POTENTIAL BIOMARKER IN RISK ASSESSMENT FOR HIGH GRADE CERVICAL SQUAMOUS LESIONS

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Objectives: HPV testing has dramatically increased the sensitivity of detection of cervical dysplasia. However, as only <10% of HPV-infected women will eventually develop a high grade dysplastic lesion, searching for molecular biomarker in identifying women with high risk in developing significant cervical lesion is necessary. Expression of L1 is linked to HPV episomal stage, but is gradually lost during the viral integration into the host genome. The goal of this study is to assess the expression pattern of HPV L1 protein in different squamous lesions in Pap tests and its usefulness in risk assessment.

Methods: Immunocytochemical analysis of HPV L1 capsid protein (Cytoimmun, Germany) was carried out on 120 cases of ThinPrep Pap tests obtained from women who were positive for HR-HPV detected by Digene HC-II and had cytologic diagnoses of ASC (35), LSIL (35), ASC-H (25), and HSIL (25). Histologic follow-up was available for all patients 2-14 months following initial cytologic diagnosis.

Results: Histologic examination revealed that 120 HPV-positive cases consisted of 42 benign, 41 CIN 1 and 37 CIN 2-3. Nuclear expression of L1 was seen in 27% (32/120) of cases, which included 21 (65%) of CIN 1, 11 (35%) of benign cervix and 0% of CIN 2-3. Among 88 L1-negative cases, 40 (46%) were CIN 2-3, 31 (35%) were benign and 17 (19%) were CIN 1. None of L1-positive cases had histologic CIN 2-3 regardless of cytologic diagnosis. In contrast, among L1-negative cases, approximately 35% of ASC-H, 30% of LSIL, and 15% of ASC had CIN 2-3 lesions on histologic follow up. Among 35 cytologic LSIL cases, 63% were L1-positive and none of L1-positive LSIL had CIN 2-3 on follow up. But 31% of L1-negative LSIL harbored CIN 2-3 lesions. All 37 women with CIN 2-3 lesions were L1-negative in their PAP tests.

Conclusions: Expression of HPV L1 capsid protein is associated with benign or transient HPV infection since none of the HPV-pos/L1-pos cases developed significant high grade SIL lesions regardless of cytologic diagnoses. In contrast, 46% of HPV-pos/L1-neg and cytologically abnormal cases had CIN 2-3 lesions. Our study suggests that detection of L1 capsid protein in PAP tests among HPV-positive women can be a helpful molecular biomarker in risk assessment and prognostic prediction.

COMPLIANCE WITH HPV VACCINATION IN GIRLS AND YOUNG WOMEN IN GERMANY: FIRST RESULTS

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Objectives

We undertook a quantitative ad-hoc study on compliance with vaccination with Gardasil®[®], a quadrivalent human papillomavirus (HPV) vaccine, in Germany. The aims of the study were to assess understanding of the vaccination schedule, to identify the key actors in the vaccination process, and to measure compliance with vaccination in mothers of girls and in young women who had already received at least one of the three recommended doses of vaccine.

Methods

The study was carried out between 22 February and 3 March 2008 among mothers of girls aged 9–17 years and young women aged 18–26 years in Germany. A total of 255 women (50 young women and 205 mothers) responded to a questionnaire proposed by Internet.

Conclusions

At the time of the study, nearly one third of the girls and young women had received all three doses of HPV vaccine. While 85% of respondents knew that three doses were necessary, the vaccination schedule (0, 2 and 6 months) was less well-understood; only 30% of respondents knew that the recommended interval between doses one and two was two months, and 15% of respondents knew that the recommended interval between doses two and three was four months. The initial dose of HPV vaccine was most frequently prescribed by gynaecologists (60% of cases). For 96% of vaccinees, the same doctor had prescribed all three doses of vaccine. Of the girls and young women who were eligible to receive the third dose, 88% had actually completed the full course of vaccination. Of these, 90% had respected the maximum recommended interval of one year.

This is the first study of compliance to be carried out since Gardasil®[®] was introduced in Germany in October 2006, and the results show that compliance had already reached a satisfactory and encouraging level in a population of vaccinated girls and young women. Results also suggest that health professionals have an important role to play in determining the success of the vaccination policy, not only in providing information about the vaccine to the patient, but also in ensuring that the patient has understood the vaccination calendar and reminding the patient when injections are due to be performed.

COMPLIANCE WITH HPV VACCINATION IN GIRLS AND YOUNG WOMEN IN FRANCE: FIRST RESULTS

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Objectives

We undertook a quantitative ad-hoc study on compliance with vaccination with Gardasil®[®], a quadrivalent human papillomavirus (HPV) vaccine, in France. The aims of the study were to assess understanding of the vaccination schedule, to identify the key actors in the vaccination process, and to measure compliance with vaccination in mothers of girls and in young women who had already received at least one of the three recommended doses of vaccine.

Methods

The study was carried out between 18 and 25 April 2008 among mothers of girls aged 9–17 years and young women aged 18–26 years in France. A total of 248 women (47 young women and 201 mothers) responded to a questionnaire proposed by Internet.

Conclusions

At the time of the study, 18% of the girls and young women had received all three doses of HPV vaccine. While 84% of respondents knew that three doses were necessary, the vaccination schedule (0, 2 and 6 months) was less well-understood; 48% of respondents knew that the recommended interval between doses one and two should be two months, and only 29% of respondents knew that the recommended interval between doses two and three should be four months. The initial dose of HPV vaccine was most frequently prescribed by general practitioners (66% of cases). For 95% of vaccinees, the same doctor had prescribed all three doses of vaccine. Of the girls and young women who were eligible to receive the third dose, 82% had actually completed the full course of vaccination. Of these, all had received the three doses of vaccine within nine months (the maximum recommended interval being one year).

This is the first study of compliance to be carried out since Gardasil®[®] was introduced in France in November 2006, and the results show that compliance had already reached a satisfactory and encouraging level in a population of vaccinated girls and young women. Results also suggest that health professionals have an important role to play in determining the success of the vaccination policy, not only in providing information about the vaccine to the patient, but also in ensuring that the patient has understood the vaccination calendar and reminding the patient when injections are due to be performed.

ABBOTT REALTIME HIGH RISK HPV ASSAY FOR DETECTING AND PARTIALLY GENOTYPING HIGH RISK HPV DNA IN CERVICAL SPECIMENS

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Objectives

The Abbott RealTime High Risk (HR) HPV is a fully automated assay that detects high risk HPV DNA in cervical cells collected in liquid media. This assay detects all fourteen HR types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) and differentiates signals between HPV 16, HPV 18 and Other HR HPV (non-HPV 16 and non-HPV 18) in a single well, therefore allowing for detection and partial genotyping within one test. This study evaluates the analytical and clinical performance of the assay using the automated Abbott *m2000* system.

Methods

Total nucleic acids are isolated by the *m2000sp* using magnetic microparticle technology. Sample eluates and reagents are then assembled in a PCR plate. Homogenous amplification and detection takes place in the *m2000rt* instrument. HPV targets are amplified with modified consensus GP5+/6+ primers targeting the conserved L1 region and detected with fluorescently labeled probes. Internal control (IC) is amplified by a primer set targeting a human beta globin sequence and is detected with an IC probe. Probes for HPV 16, HPV 18, Other HR HPV and IC are labeled with four different fluorophores allowing their signals to be distinguishable in a single well. 441 specimens collected in PreservCyt medium were tested by the RealTime HR HPV and Hybrid Capture 2 (HC2) and the discordant specimens were resolved with Linear Array HPV Genotyping Test. The analytical sensitivity and specificity (i.e. detection of HR HPV) of both RealTime HR HPV and HC2 were determined after resolution of the discordant specimens. Clinical sensitivity and specificity of RealTime HR HPV were determined by testing 380 CIN2+ specimens and 675 specimens from general screening population of women over 30 years of age, respectively.

Conclusions

Abbott RealTime HR HPV can detect all fourteen HR HPV types and differentiate between HPV 16, HPV 18 and Other HR HPV in mixed infections. With 441 specimens tested, the resolved analytical sensitivities were 97% with Abbott RealTime HR HPV and 98% with HC2, and the resolved analytical specificities were 100% with RealTime HR HPV and 88% with HC2. The clinical sensitivity of the Abbott RealTime HR HPV (% of CIN2+ positives) was 98%. The clinical specificity of the Abbott RealTime HR HPV was 94% with 675 blindly collected specimens from the general screening population of women over 30 years of age.