# Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16–26 years: a randomised, double-blind trial

*Warner K Huh, Elmar A Joura, Anna R Giuliano, Ole-Erik Iversen, Rosires Pereira de Andrade, Kevin A Ault, Deborah Bartholomew, Ramon M Cestero, Edison N Fedrizzi, Angelica L Hirschberg, Marie-Hélène Mayrand, Angela Maria Ruiz-Sternberg, Jack T Stapleton, Dorothy J Wiley, Alex Ferenczy, Robert Kurman, Brigitte M Ronnett, Mark H Stoler, Jack Cuzick, Suzanne M Garland, Susanne K Kjaer, Oliver M Bautista, Richard Haupt, Erin Moeller, Michael Ritter, Christine C Roberts, Christine Shields, Alain Luxembourg*

## Summary

**Background** **Primary analyses of a study in young women aged 16–26 years showed efficacy of the nine-valent human papillomavirus (9vHPV; HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58) vaccine against infections and disease related to HPV 31, 33, 45, 52, and 58, and non-inferior HPV 6, 11, 16, and 18 antibody responses when compared with quadrivalent HPV (qHPV; HPV 6, 11, 16, and 18) vaccine. We aimed to report efficacy of the 9vHPV vaccine for up to 6 years following first administration and antibody responses over 5 years.**

**Methods** **We undertook this randomised, double-blind, efficacy, immunogenicity, and safety study of the 9vHPV vaccine study at 105 study sites in 18 countries. Women aged 16–26 years old who were healthy, with no history of abnormal cervical cytology, no previous abnormal cervical biopsy results, and no more than four lifetime sexual partners were randomly assigned (1:1) by central randomisation and block sizes of 2 and 2 to receive three intramuscular injections over 6 months of 9vHPV or qHPV (control) vaccine. All participants, study investigators, and study site personnel, laboratory staff, members of the sponsor's study team, and members of the adjudication pathology panel were masked to vaccination groups. The primary outcomes were incidence of high-grade cervical disease (cervical intraepithelial neoplasia grade 2 or 3, adenocarcinoma in situ, invasive cervical carcinoma), vulvar disease (vulvar intraepithelial neoplasia grade 2/3, vulvar cancer), and vaginal disease (vaginal intraepithelial neoplasia grade 2/3, vaginal cancer) related to HPV 31, 33, 45, 52, and 58 and non-inferiority (excluding a decrease of 1·5 times) of anti-HPV 6, 11, 16, and 18 geometric mean titres (GMT). Tissue samples were adjudicated for histopathology diagnosis and tested for HPV DNA. Serum antibody responses were assessed by competitive Luminex immunoassay. The primary evaluation of efficacy was a superiority analysis in the per-protocol efficacy population, supportive efficacy was analysed in the modified intention-to-treat population, and the primary evaluation of immunogenicity was a non-inferiority analysis. The trial is registered with ClinicalTrials.gov, number NCT00543543.**

**Findings** **Between Sept 26, 2007, and Dec 18, 2009, we recruited and randomly assigned 14 215 participants to receive 9vHPV (n=7106) or qHPV (n=7109) vaccine. In the per-protocol population, the incidence of high-grade cervical, vulvar and vaginal disease related to HPV 31, 33, 45, 52, and 58 was 0·5 cases per 10 000 person-years in the 9vHPV and 19·0 cases per 10 000 person-years in the qHPV groups, representing 97·4% efficacy (95% CI 85·0–99·9). HPV 6, 11, 16, and 18 GMTs were non-inferior in the 9vHPV versus qHPV group from month 1 to 3 years after vaccination. No clinically meaningful differences in serious adverse events were noted between the study groups. 11 participants died during the study follow-up period (six in the 9vHPV vaccine group and five in the qHPV vaccine group); none of the deaths were considered vaccine-related.**

**Interpretation** **The 9vHPV vaccine prevents infection, cytological abnormalities, high-grade lesions, and cervical procedures related to HPV 31, 33, 45, 52, and 58. Both the 9vHPV vaccine and qHPV vaccine had a similar immunogenicity profile with respect to HPV 6, 11, 16, and 18. Vaccine efficacy was sustained for up to 6 years. The 9vHPV vaccine could potentially provide broader coverage and prevent 90% of cervical cancer cases worldwide.**

**Funding** **Merck & Co, Inc.**

## Introduction

Human papillomavirus (HPV) infection causes benign, precancerous, and malignant disease, localised primarily in the anogenital area and upper airway, including cancers and precancers of the cervix, vulva, vagina, anus, penis, tonsil, and base of the tongue.[1] HPV infection can also cause anogenital warts and recurrent respiratory papillomatosis.[1] Available HPV vaccines, including the bivalent HPV 16 and 18 L1 virus-like particle vaccine and the quadrivalent HPV 6, 11, 16, and 18 L1 virus-like particle (qHPV) vaccine, prevent infection and disease related to oncogenic HPV 16 and 18.[2] HPV 16 and 18 are

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**Division of Gynecologic Oncology, University of Alabama at Birmingham, Birmingham, AL, USA** (W K Huh MD); **Department of Gynecology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria** (E A Joura MD); **Center for Infection Research in Cancer, Moffitt Cancer Centre, Tampa, FL, USA** (A R Giuliano PhD); **Department of Clinical Science, University of Bergen, Bergen, Norway** (O-E Iversen MD); **Department of Gynecology and Obstetrics, Haukeland University Hospital, Bergen, Norway** (O-E Iversen); **CERHFAC/Universidade Federal do Paraná, Setor de Ciências da Saúde, Departamento de Tocoginecologia, Paraná, Brazil** (R P de Andrade MD); **Department of Obstetrics and Gynecology, University of Kansas Medical Center, Kansas City, KS, USA** (K A Ault MD); **Department of Obstetrics and Gynecology, The Ohio State University Wexner Medical Center, Columbus, OH, USA** (D Bartholomew MD); **Department of Obstetrics and Gynecology, University of California Irvine School of Medicine, UC Irvine Health Orange, CA, USA** (R M Cestero MD); **Department of Obstetrics and Gynecology of The Federal University of Santa Catarina, Santa Catarina, Brazil** (E N Fedrizzi MD); **Department of Obstetrics and Gynecology, Karolinska University Hospital, Stockholm, Sweden** (A L Hirschberg MD);

**Department of Women's and Children's Health, Stockholm, Sweden** (A L Hirschberg); **Department of Obstetrics and Gynecology, University of Montreal, Montreal, QC, Canada** (M-H Mayrand MD); **Centre de Recherche du Centre Hospitalier de l'Université de Montréal [CRCHUM], Montreal, QC, Canada** (M-H Mayrand); **Clinical Research Group, Universidad del Rosario, Bogota-Colombia** (A M Ruiz-Sternberg MD); **Department of Internal Medicine, University of Iowa, Iowa City, IA, USA** (J T Stapleton MD); **Iowa City VA Medical Center, Iowa City, IA, USA** (J T Stapleton); **School of Nursing, University of California, Los Angeles, CA, USA** (D J Wiley PhD); **Department of Pathology, McGill University, Montreal, Quebec, Canada** (A Ferenczy MD); **Department of Gynecology and Obstetrics, Johns Hopkins School of Medicine, Baltimore, MD, USA** (R Kurman MD); **Department of Pathology, Johns Hopkins Medical Institution, Baltimore, MD, USA** (B M Ronnett MD); **Department of Pathology, University of Virginia School of Medicine Charlottesville, VA, USA** (M H Stoler MD); **Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, UK** (J Cuzick PhD); **The University of Melbourne, Department of Obstetrics and Gynaecology, The Royal Women's Hospital, University of Melbourne, Murdoch Childrens Research Institute, Melbourne, VIC, Australia** (S M Garland MD); **Unit of Virus, Lifestyle and Genes, Danish Cancer Society and Department of Gynecology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark** (S K Kjaer MD); **and Merck & Co, Inc, Kenilworth, NJ, USA** (O M Bautista PhD, R Haupt MD, E Moeller MPH, M Ritter BA, C C Roberts PhD, C Shields MSN, A Luxembourg MD)

Correspondence to:
Dr Warner K Huh, Division of Gynecologic Oncology, University of Alabama at Birmingham, Birmingham, AL 35294, USA
**whuh@uabmc.edu**

See Online for appendix

## Research in context

### Evidence before this study

The quadrivalent human papillomavirus (qHPV; 6, 11, 16, and 18) and bivalent HPV (16 and 18) prophylactic vaccines were first licensed in 2006 and 2007, respectively. We searched PubMed with no language restrictions for articles published between Jan 1, 2000, and Sept 1, 2016, with the terms "HPV type detection" AND "cervical cancer" AND "worldwide", and found several epidemiology studies showing that the HPV types most commonly associated with cervical cancer are HPV 16 and HPV 18, and the next five most common types are HPV 31, 33, 45, 52, and 58. Another PubMed search between Jan 1, 2007, and Sept 1, 2016 based on the terms "HPV vaccine" AND "cross-protection" AND ("clinical trial" OR "epidemiology") found that partial cross-protection against oncogenic HPV types other than HPV 16 and HPV 18 has been reported for both licensed vaccines in clinical trials and real-world public health programmes, although its extent, duration, and public health significance remain uncertain. Finally, we searched PubMed with the search terms "HPV vaccine" AND "clinical trial" to identify studies published between Jan 1, 2007, and Sept 1, 2016, that assessed broader spectrum prophylactic HPV vaccines other than the nine-valent (HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58) vaccine (9vHPV). We found one phase 2 study of two tetravalent vaccine candidates targeting HPV 16, 18, 31, and 45 and HPV 16, 18, 33, and 58, respectively; however, vaccine development was unsuccessful because of immune interference.

### Added value of this study

This is the first phase 3 efficacy clinical trial of a 9vHPV vaccine. Primary analyses previously showed efficacy against infection and disease due to HPV 31, 33, 45, 52, and 58 and non-inferior HPV 6, 11, 16, and 18 antibody responses at 1 month after vaccination compared with the qHPV vaccine. Here we document persistence of efficacy against infection and disease for up to 6 years, a similar immunogenicity profile with respect to HPV 6, 11, 16, and 18 over the entire study, and substantial reductions in abnormal cervical cytology and related clinical procedures. Taken together, these results suggest substantial protection against disease caused by HPV 31, 33, 45, 52, and 58 that augments protection against HPV 6, 11, 16, and 18 with the qHPV vaccine.

### Implications of all the available evidence

The 9vHPV vaccine is licensed in more than 60 countries for the prevention of HPV-related anogenital cancers and pre-cancers, and genital warts. The results of this study support comprehensive vaccination programmes and inform public health decisions related to implementation. Additionally, these findings inform further refinement of cervical cancer screening algorithms for vaccinated populations. Previously developed HPV vaccines cover oncogenic HPV 16 and 18, which cause approximately 70% of cervical cancer cases worldwide; the 9vHPV vaccine could potentially provide broader coverage and prevent 90% of cervical cancer cases worldwide. It could also prevent nearly 90% of HPV-related vulvar and vaginal cancers, 70–85% of high-grade cervical disease in females, as well as 90% of anal cancers and of genital warts in both males and females.

responsible for approximately 70% of cervical cancer cases worldwide.[3] The qHPV vaccine was also shown to prevent anogenital warts related to HPV 6 and 11.[2,4] Although partial cross-protection has been observed against HPV 31 for the qHPV vaccine and HPV 31 and 45 for the bivalent HPV vaccine in clinical studies and in real-world public health programmes where high coverage has occurred, its extent, duration, and public health significance remain uncertain.[2,5,6]

A nine-valent HPV (9vHPV; HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58) vaccine (Gardasil 9; Merck & Co, Inc, Kenilworth, NJ, USA) was developed to provide direct protection against the HPV types already covered by the qHPV vaccine and the next five HPV types most commonly associated with cervical cancer worldwide: HPV 31, 33, 45, 52, and 58.[3] On the basis of epidemiological studies, the 9vHPV vaccine could prevent around 90% of cervical cancers, 90% of HPV-related vulvar and vaginal cancers, and 70–85% of high-grade cervical disease in women[7,8] and around 90% of HPV-related anal cancers and genital warts in both men and women worldwide.[1,9,10]

A phase 3 efficacy, immunogenicity, and safety study of the 9vHPV vaccine was undertaken in women aged 16–26 years.[11] The results of this study were published after sufficient numbers of prespecified endpoints were met for the endpoint-driven efficacy assessment.[12] This primary analysis established nearly 97% efficacy of the 9vHPV vaccine against high-grade cervical, vulvar, and vaginal disease associated with HPV 31, 33, 45, 52, and 58 while showing non-inferior HPV 6, 11, 16, and 18 antibody responses 1 month after vaccination compared with the qHPV vaccine. The protocol (appendix) prespecified that the study would continue after the primary analyses were done for additional efficacy and safety follow-up, and that the study could be terminated after participants completed visits at least until month 42. With continued follow-up of the study participants, we extended the efficacy analyses to a follow-up period of up to 6 years following initial vaccination and evaluated antibody response kinetics over the entire study period. We aimed to report the effect of vaccination on cervical cytological abnormalities; cervical, vulvar, and vaginal high-grade disease (histology); and the number of related clinical procedures (cervical biopsy and cervical definitive therapy) avoided due to protection against disease caused by HPV 31, 33, 45, 52, and 58.

## Methods

### Study design and participants

This randomised, double-blind, controlled, dose-ranging, efficacy, immunogenicity, and safety study of the 9vHPV vaccine (protocol V503-001) was carried out at 105 study sites located in 18 countries (Austria, Brazil, Canada, Chile, Colombia, Denmark, Germany, Hong Kong, Japan, South Korea, Mexico, New Zealand, Norway, Peru, Sweden, Taiwan, Thailand, and the USA [including Puerto Rico]). Women aged 16–26 years old who were generally healthy, had no history of abnormal cervical cytology, no more than four lifetime sexual partners, and no previous abnormal cervical biopsy results were included in the study (the appendix shows the complete list of the eligibility criteria). The study was based on a phase 2/3 adaptive design that has been described extensively elsewhere.[11,13,14] Participants were enrolled in two parts: in part A participants were assessed for dose selection and in part B participants were assessed for efficacy together with part A participants who received the selected dose of 9vHPV vaccine or control (qHPV vaccine).[11,13,14] The last participant visit occurred on March 10, 2014. A small subset of participants randomly selected from seven sites in Europe and Latin America (n=150) continued in a study extension after that date to further assess antibody persistence; the last participant visit in the study extension occurred on Jan 14, 2015.

The study was done in accordance with principles of Good Clinical Practice, and the study was approved by the appropriate institutional review boards and regulatory agencies. All participants provided written, informed consent before study participation in accordance with local laws and regulations. A scientific advisory committee comprising sponsor and non-sponsor scientists contributed to the development of the protocol, formulation of the statistical analysis plan, analysed and interpreted the data, and authored this manuscript. An external data monitoring committee, who were not masked to the study, assessed safety findings throughout.

### Randomisation and masking

We used central randomisation in the study. An Interactive Voice Response System was used to allocate study participants and balance randomisation between sites. Participants were randomly assigned (1:1) using block sizes of 2 and 2 to either the 9vHPV vaccine or the qHPV vaccine for efficacy evaluation. The use of a placebo comparator was deemed unacceptable for ethical reasons;[11] thus, the qHPV vaccine was used as the control. All participants, study investigators, and study site personnel, laboratory staff, members of the sponsor's study team, and members of the adjudication pathology panel were masked to vaccination groups. The 9vHPV and qHPV vaccines were packaged identically using the same vials and labels. Each vial contained the same amount of vaccine (0·75 mL). Both vaccines had a similar appearance (a white, semi-translucent suspension when thoroughly mixed).

### Procedures

Participants received three intramuscular injections of the 9vHPV vaccine or control (qHPV vaccine) at day 1, month 2, and month 6. A dose of 9vHPV vaccine contained 30 µg of HPV 6, 40 µg of HPV 11, 60 µg of HPV 16, 40 µg of HPV 18, 20 µg of HPV 31, 20 µg of HPV 33, 20 µg of HPV 45, 20 µg of HPV 52, and 20 µg of HPV 58 virus-like particles, and 500 µg of amorphous aluminum hydroxyphosphate sulphate (AAHS). A dose of qHPV vaccine contained 20 µg of HPV 6, 40 µg of HPV 11, 40 µg of HPV 16, and 20 µg of HPV 18 virus-like particles, and 225 µg of AAHS.[12] Vaccine was not administered to participants with fever (oral temperature ≥37·8°C) or found to be pregnant (β-human chorionic gonadotropin testing). Gynaecological samples, including cervical cytology and labial, vulvar, perineal, perianal, endocervical, and ectocervical swabs, were collected at day 1, month 7, month 12, and every 6 months thereafter for laboratory analysis up to month 54.[11] Cervical cytological samples (ThinPrep Pap test; Hologic Inc, Marlborough, MA, USA) were evaluated by a designated central laboratory (from initiation of the study until April 22, 2013: Diagnostic Cytology Laboratories, Indianapolis, IN, USA; and from April 23, 2013, to end of study: Dianon Pathology, Shelton, CT, USA, a subsidiary of the Laboratory Corporation of America, Burlington, NC, USA) with the Bethesda System-2001. For a diagnosis of atypical squamous cells of undetermined significance (ASC-US), the central laboratory did reflex testing for high-risk and low-risk probes (Digene Hybrid Capture II Assay; Qiagen, Hilden, Germany) on residual ThinPrep material. Cytology results were reported to the investigator for participant clinical management. For samples that tested positive to one of the probes, site personnel, participants, and the sponsor remained masked to which probe was positive. Participants with abnormal cervical cytology results had to come for additional visits and undergo specialised examination of the cervix (colposcopy) in accordance with a protocol-mandated triage algorithm and collection of tissue samples (biopsy and definitive therapy) for pathological examination to detect potential HPV-related disease (ie, study endpoints).[11,12] External genital examinations were done on day 1, month 7, month 12, and every 6 months thereafter up to month 54. Identified lesions suspected to be HPV-related were biopsied. Participants with histologically confirmed HPV-related external genital or vaginal lesions were referred for colposcopy if the external genital or vaginal biopsy was not obtained during colposcopy. Histological sections were first read for clinical management by pathologists at the central laboratory who were masked to treatment-group assignment and HPV status, and then read for endpoint determination by a masked adjudication panel comprising four pathologists. Genital swabs and tissue samples were tested for detection of HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 by PCR assay, as previously described.[15,16]

Serum samples were collected at day 1 and months 3, 7, 12, 24, 36, 42, and 60 to assess serological responses. A 10-mL blood specimen was collected in a non-heparinised tube. Serum was separated, aliquoted, and stored frozen at –20°C until testing by immunoassay.

### Outcomes

The primary outcomes were efficacy of 9vHPV vaccine versus qHPV vaccine to prevent the combined endpoint of high-grade cervical disease (cervical intraepithelial neoplasia grade 2 or 3, adenocarcinoma in situ, invasive cervical carcinoma), vulvar disease (vulvar intraepithelial neoplasia grade 2/3, vulvar cancer), and vaginal disease (vaginal intraepithelial neoplasia grade 2/3, vaginal cancer) related to HPV 31, 33, 45, 52, and 58 and non-inferiority (excluding a decrease of 1·5 times) of HPV 6, 11, 16, and 18 antibody geometric mean titres (GMTs) compared with qHPV vaccine. Secondary and key exploratory outcomes included incidence of persistent infection, cervical, vulvar, and vaginal disease of any grade, and cervical cytological abnormalities related to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58, as well as GMTs and seroconversion for HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at month 7 as well as each subsequent serum collection timepoint (outcomes are listed in the appendix). All outcomes were centrally assessed. The use of invasive cancer (cervical, vulvar, or vaginal) as an efficacy endpoint is not acceptable for ethical reasons; also, the time from infection with HPV to development of cancer usually exceeds 10 years.[2] Thus, HPV vaccine efficacy trials evaluate the effect on HPV-related high-grade (precancerous) lesions (cervical intraepithelial neoplasia grade 2 or 3, adenocarcinoma in situ, vulvar intraepithelial neoplasia grade 2/3, and vulvar vaginal intraepithelial neoplasia grade 2/3) used as surrogate efficacy endpoints for cancer, as previously described.[2,11] One endpoint of cervical, vulvar, or vaginal high-grade lesion as a result of the given HPV type occurred if a participant developed a lesion with a consensus diagnosis by the pathology panel of cervical intraepithelial neoplasia grade 2, cervical intraepithelial neoplasia grade 3, adenocarcinoma in situ, invasive cervical cancer, vulvar intraepithelial neoplasia grade 2/3, vaginal intraepithelial neoplasia grade 2/3, vulvar cancer or vaginal cancer; and PCR testing detected the relevant HPV type in an adjacent section from the same tissue block, as described previously.[4] If multiple HPV types were detected, the lesion was classified as related to each of the HPV types detected. For all efficacy endpoints, HPV DNA detection by PCR was considered as a surrogate marker of HPV infection. Endpoints of persistent infection were defined as a participant who was positive by PCR for the same HPV type in genital swabs or tissue specimens collected at consecutive visits at least 6 months (plus or minus 1-month visit windows) apart. At least two positive specimens were required to define a persistent 6-month infection and at least three positive specimens were required to define a persistent 12-month infection. Abnormal cervical cytology endpoints considered for evaluation of vaccine efficacy included atypical squamous cells of undetermined significance positive for high-risk HPV or worse. This comprises the cytology diagnoses of atypical squamous cells of undetermined significance positive for high-risk HPV (as determined by Digene Capture II Assay, Qiagen), low-grade squamous intraepithelial lesion; high-grade squamous intraepithelial lesion; atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; atypical glandular cells; adenocarcinoma; and squamous cell carcinoma. Abnormal cervical cytology was considered related to the HPV type or types detected in a genital swab collected at the same visit as the cytology sample. A cervical biopsy, cervical definitive therapy, or external genital procedure was considered HPV-related if on the excised tissue assessed for pathology, the relevant HPV type was detected by PCR testing in an adjacent section from the same tissue block.

Antibodies to the nine vaccine-relevant HPV types were assessed in serum samples using a 9v-competitive Luminex immunoassay (HPV-9 cLIA).[17] Antibody titres for each individual HPV type were determined through competition with type-specific monoclonal antibodies; thus, it was not possible to directly compare assay results across HPV types. A subset of randomly selected participants was also assessed for HPV 16 and HPV 18 antibodies with a pseudovirion-based neutralisation assay, as previously described.[18]

Serious adverse events were predefined as any adverse events that resulted in death, were deemed by the investigator to be life-threatening, resulted in a persistent or significant disability or incapacity, resulted in or prolonged an existing inpatient hospital stay, or were congenital anomalies, cancers, or other so-called important medical events. Deaths and serious vaccine-related adverse events were reported throughout the study. Other serious adverse events were reported from day 1 to 6 months following the last vaccination; events of fetal loss were reported as serious adverse events for any pregnancy with a last menstrual period before 6 months following the last vaccination. Analyses of non-serious adverse events (reported within 15 days of each vaccination visit), new medical conditions reported after 15 days following vaccination that were not evaluated as serious adverse events, and pregnancy outcomes across the study period were published separately.[19]

### Statistical analysis

Under specific assumptions on incidence, attrition, and exclusions from per-protocol analyses provided in detail in the statistical analysis plan, around 14000 participants needed to be enrolled to accumulate at least 30 cases of the primary efficacy endpoint on the basis of a median follow-up of 30 months after randomisation. We undertook the primary efficacy analyses in the per-protocol efficacy (PPE) population, which consisted of participants who were seronegative at day 1 and PCR-negative from day 1 to

month 7 for the HPV type being analysed, received all three doses of the correct clinical material within 1 year, and had no protocol deviations that could affect the evaluation of vaccine prophylactic efficacy.[11] Participants showing anti-HPV serum cLIA concentrations of less than 30 milli-Merck units per millilitre (mMU/mL) for HPV 6, 16 mMU/mL for HPV 11, 20 mMU/mL for HPV 16, 24 mMU/mL for HPV 18, 10 mMU/mL for HPV 31, 8 mMU/mL for HPV 33, 8 mMU/mL for HPV 45, 8 mMU/mL for HPV 52, and 8 mMU/mL for HPV 58 were classified as seronegative. We calculated vaccine efficacy, which was the percentage risk reduction.

$$\text{Vaccine efficacy} = 100 \times \left(1 - \frac{\text{9vHPV incidence rate}}{\text{qHPV indicence rate}}\right)$$

We calculated the 95% CI for vaccine efficacy with the use of a binomial distribution-based exact method.[20] We analysed supportive efficacy in the modified intention-to-treat (mITT) population. The mITT population included participants who received one or more doses of vaccine and had efficacy follow-up for the relevant endpoint, including participants who tested positive or negative for HPV DNA at the time of vaccination. We calculated the estimate of average risk reduction in the mITT population as the sample-size-weighted average of the percentage risk reduction in the two subgroups of participants representing those who were and were not infected with HPV at baseline. Participants who were not HPV-infected at baseline were participants who were negative at day 1 for squamous intraepithelial lesions, seronegative and PCR-negative for the nine HPV types covered by the 9vHPV vaccine, and PCR-negative for non-vaccine HPV 35, 39, 51, 56, and 59. All other participants comprised the baseline HPV-infected subgroup. The sample-size-weighted average reduction in risk approximated the efficacy expected from a population with characteristics similar to those of the study population, as previously described.[12] The Kaplan-Meier method was used to generate cumulative incidence plots in exploratory analyses. Because the 9vHPV vaccine is prophylactic and not therapeutic, HPV infection status at the time of vaccination is a baseline covariate that has a known interaction with treatment effect (or vaccine efficacy). A per-protocol analysis was used as a means of adjusting for the expected treatment-effect-by-baseline covariate interaction that would be present in an ITT analysis. By using a per-protocol analysis, the subgroup in which the expected vaccine efficacy is zero was eliminated, thereby coming close to an unbiased estimate of prophylactic vaccine efficacy (appendix).

We analysed primary immunogenicity in the per-protocol immunogenicity population, consisting of participants in the PPE population who received doses two and three of the correct clinical material within 36–84 days and 148–218 days after dose one, respectively; and had an evaluable serology result within 21–49 days after dose three.[11] GMTs and seropositivity rates with associated 95% CIs were computed. GMTs and seropositivity rates with associated 95% CIs were computed. We did formal non-inferiority hypothesis testing, which compared the 9vHPV and qHPV vaccine groups with respect to immune response to HPV 6, 11, 16, and 18, for the month 7 timepoint on the ratio of GMTs (9vHPV/qHPV) and difference of seropositivity rates (9vHPV–qHPV). Successful demonstration of non-inferiority on the ratio of GMTs required the lower limit of the 95% CI of the ratio of GMT to be more than 0·67 for each of the HPV types, thereby excluding a decrease of 1·5 times. The 95% CI of the ratio of the GMT (9vHPV/qHPV) was derived from an analysis of variance model with log anti-HPV as the response and the vaccination group as the fixed effect. Successful demonstration of non-inferiority on the difference of seropositivity rates required the lower limit of the 95% CI of the difference of seropositivity rates to be more than –5%, thereby excluding a decrease of more than 5 percentage points.[12] All other evaluations after month 7 were exploratory in nature without hypotheses testing.

We implemented strict control of type I error against potential sources of inflation of type I error, as previously described[11,13] (appendix).

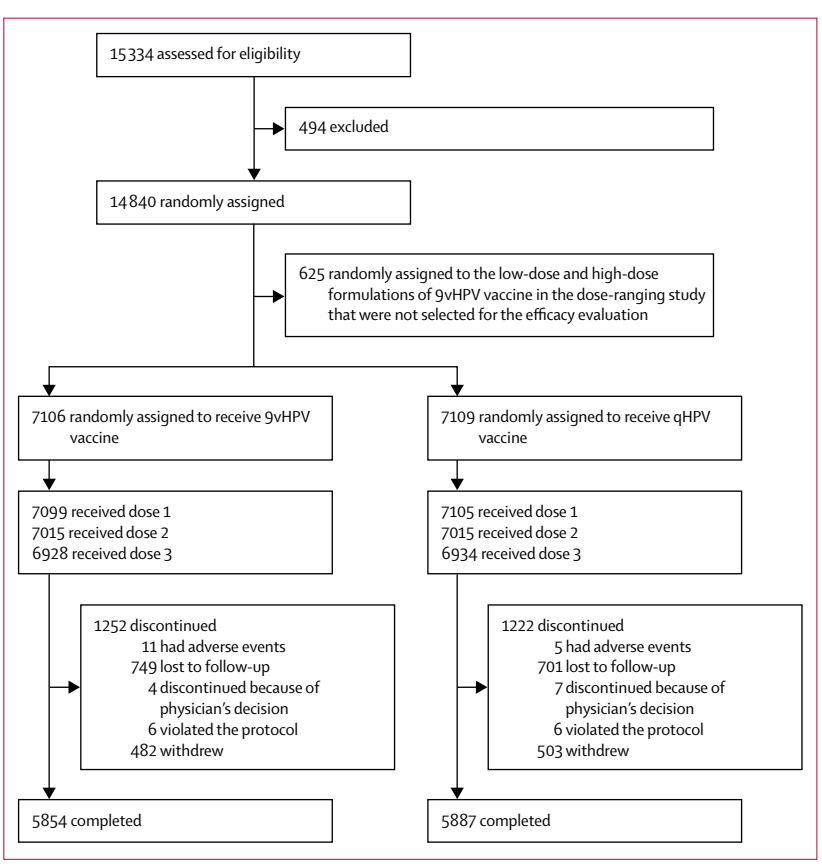



***Figure* 1: Trial profile**
9vHPV=nine-valent human papillomavirus. qHPV=quadrivalent human papillomavirus.

The analysis of safety data consisted of a summary of serious adverse events occurring throughout the study. We summarised these events as frequencies and percentages across study group and type of event. Formal testing of statistical significance was not done for these data. This study is registered with ClinicalTrials.gov, number NCT00543543.

### Role of the funding source

Employees of Merck & Co, Inc (Kenilworth, NJ, USA), the sponsor and funder of the study, designed, managed, and analysed the study in conjunction with external investigators. The sponsor was directly involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and the preparation and review of the manuscript. Each author had access to all study data upon request. The corresponding author had full access to all the data in the study and a final version of the paper was approved by each co-author. The presentation also underwent formal review by the sponsor. The decision to submit the manuscript for publication was made by the corresponding author in conjunction with the sponsor and co-authors. The sponsor did not have the potential to prevent submission of the manuscript. The opinions expressed in the manuscript represent the collective views of the authors and do not necessarily reflect the official position of the sponsor.

## Results

We enrolled participants for part A from Sept 26, 2007, to Dec 13, 2007, and for part B from Sept 15, 2008, for sites that also participated in part A, and from Feb 23, 2009, at sites that only participated in part B; enrolment for part B ended on Dec 18, 2009. We randomly assigned 14 215 participants to participate in the efficacy portion of the study and to receive either the 9vHPV vaccine or the qHPV vaccine (figure 1). At the time the study was terminated, more than 82% of participants were still in the

| | 9vHPV vaccine (N=7099)* | | qHPV vaccine (N=7105)* | | Risk reduction (%; 95% CI) |
|---|---|---|---|---|---|
| | n/total n† | Cases per 10 000 person-years | n/total n† | Cases per 10 000 person-years | |
| **6 months' persistent infection** | | | | | |
| Related to HPV 6, 11, 16, or 18 | 68/5812 | 36·6 | 95/5830 | 51·1 | 28·5 (1·8 to 48·4) |
| Related to HPV 31, 33, 45, 52, or 58 | 41/5941 | 21·5 | 946/5955 | 538·8 | 96·0 (94·6 to 97·1) |
| **12 months' persistent infection** | | | | | |
| Related to HPV 6, 11, 16, or 18 | 25/5812 | 13·4 | 35/5830 | 18·7 | 28·5 (–22·9 to 57·7) |
| Related to HPV 31, 33, 45, 52, or 58 | 23/5941 | 12·1 | 657/5955 | 366·2 | 96·7 (95·1 to 97·9) |
| **Cervical, vulvar, and vaginal disease (any grade)** | | | | | |
| Related to HPV 6, 11, 16, or 18 | 6/5883 | 3·1 | 9/5898 | 4·6 | 33·1 (–101·6 to 76·3) |
| Related to HPV 31, 33, 45, 52, or 58 | 3/6016 | 1·5 | 127/6017 | 63·8 | 97·7 (93·3 to 99·4) |
| Low grade‡ | | | | | |
| Related to HPV 6, 11, 16, or 18 | 5/5883 | 2·6 | 7/5898 | 3·6 | 28·3 (–141·0 to 77·8) |
| Related to HPV 31, 33, 45, 52, or 58 | 2/6016 | 1·0 | 102/6017 | 51·1 | 98·0 (93·2 to 99·7) |
| High grade | | | | | |
| Related to HPV 6, 11, 16, or 18 | 1/5883 | 0·5 | 3/5898 | 1·5 | 66·6 (–203·2 to 98·7) |
| Related to HPV 31, 33, 45, 52, or 58 | 1/6016 | 0·5 | 38/6017 | 19·0 | 97·4 (85·0 to 99·9) |
| **Cervical disease (any grade)** | | | | | |
| Related to HPV 6, 11, 16, or 18 | 1/5824 | 0·5 | 3/5832 | 1·6 | 66·6 (–203·0 to 98·7) |
| Related to HPV 31, 33, 45, 52, or 58 | 2/5949 | 1·0 | 110/5943 | 57·2 | 98·2 (93·7 to 99·7) |
| Cervical intraepithelial neoplasia 1 | | | | | |
| Related to HPV 6, 11, 16, or 18 | 0/5824 | 0 | 2/5832 | 1·1 | 100 (–248·1 to 100) |
| Related to HPV 31, 33, 45, 52, or 58 | 1/5949 | 0·5 | 87/5943 | 45·2 | 98·9 (94·1 to 99·9) |
| High grade (cervical intraepithelial neoplasia 2, cervical intraepithelial neoplasia 3, adenocarcinoma in situ, and cervical cancer) | | | | | |
| Related to HPV 6, 11, 16, or 18 | 1/5824 | 0·5 | 1/5832 | 0·5 | –0·3 (–∞ to 97·4) |
| Related to HPV 31, 33, 45, 52, or 58 | 1/5949 | 0·5 | 35/5943 | 18·1 | 97·1 (83·5 to 99·9) |
| Cervical intraepithelial neoplasia 2 | | | | | |
| Related to HPV 6, 11, 16, or 18 | 1/5824 | 0·5 | 0/5832 | 0 | NA |
| Related to HPV 31, 33, 45, 52, or 58 | 1/5949 | 0·5 | 32/5943 | 16·6 | 96·9 (81·5 to 99·8) |
| Cervical intraepithelial neoplasia 3, adenocarcinoma in situ, and cervical cancer | | | | | |
| Related to HPV 6, 11, 16, or 18 | 0/5824 | 0 | 1/5832 | 0·5 | 100 (–∞ to 100) |
| Related to HPV 31, 33, 45, 52, or 58 | 0/5949 | 0 | 7/5943 | 3·6 | 100 (39·4 to 100) |

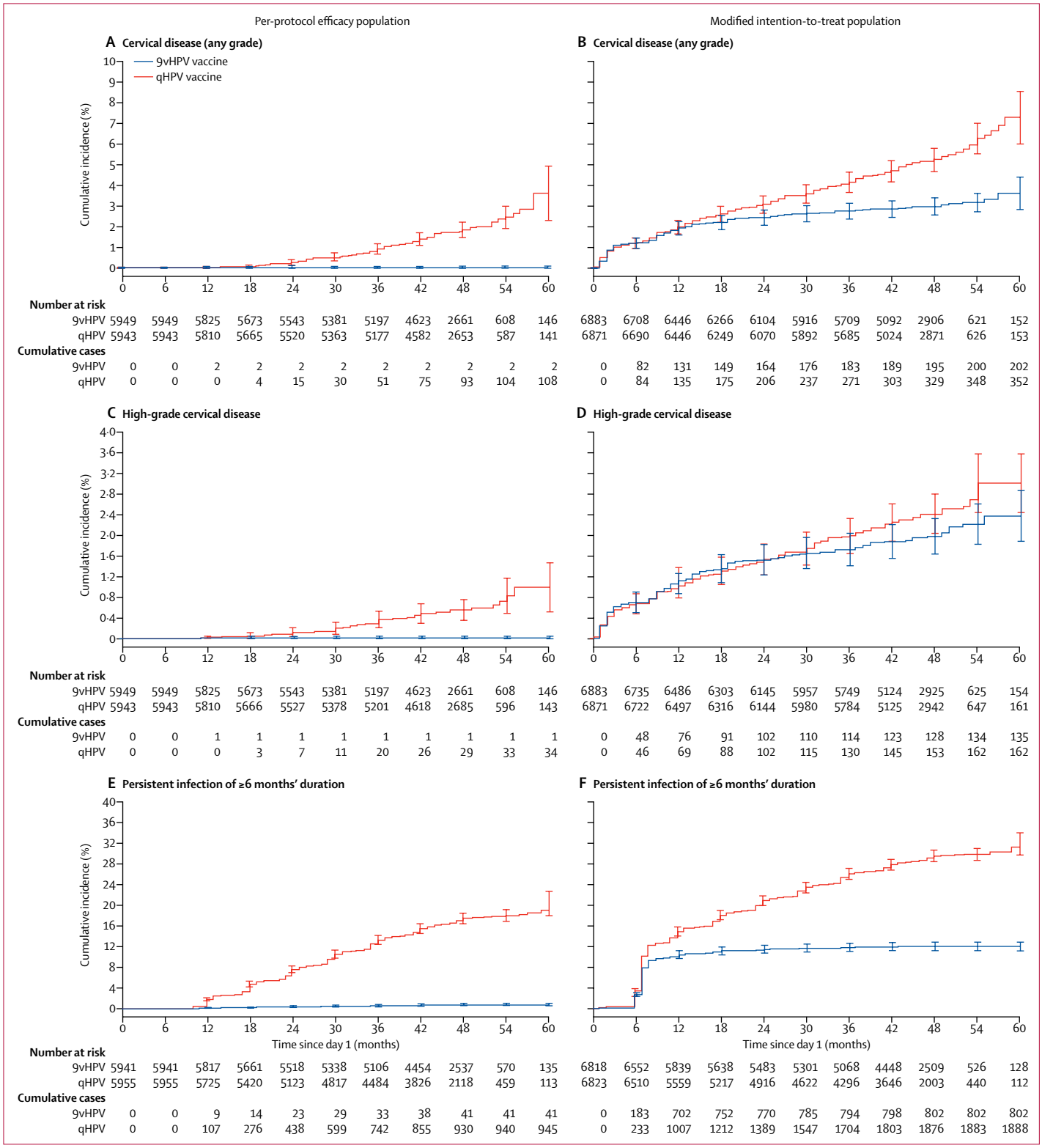
(Table 1 continues on next page)

| | 9vHPV vaccine (N=7099)* | | qHPV vaccine (N=7105)* | | Risk reduction (%; 95% CI) |
|---|---|---|---|---|---|
| | n/total n† | Cases per 10 000 person-years | n/total n† | Cases per 10 000 person-years | |
| (Continued from previous page) | | | | | |
| **Vulvar and vaginal disease (any grade)** | | | | | |
| Related to HPV 6, 11, 16, or 18 | 5/5876 | 2·6 | 6/5893 | 3·1 | 16·4 (–201·8 to 75·0) |
| Related to HPV 31, 33, 45, 52, or 58 | 1/6009 | 0·5 | 18/6012 | 9·0 | 94·4 (67·7 to 99·7) |
| Low grade | | | | | |
| Related to HPV 6, 11, 16, or 18 | 5/5876 | 2·6 | 5/5893 | 2·6 | –0·4 (–250·8 to 71·3) |
| Related to HPV 31, 33, 45, 52, or 58 | 1/6009 | 0·5 | 16/6012 | 8·0 | 93·8 (61·5 to 99·7) |
| Condyloma | | | | | |
| Related to HPV 6, 11, 16, or 18 | 5/5876 | 2·6 | 2/5893 | 1·0 | –150·9 (–∞ to 48·0) |
| Related to HPV 31, 33, 45, 52, or 58 | 0/6009 | 0 | 4/6012 | 2·0 | 100 (–11·5 to 100) |
| Vulvar intraepithelial neoplasia 1 or vaginal intraepithelial neoplasia 1 | | | | | |
| Related to HPV 6, 11, 16, or 18 | 0/5876 | 0 | 3/5893 | 1·5 | 100 (–72·0 to 100) |
| Related to HPV 31, 33, 45, 52, or 58 | 1/6009 | 0·5 | 13/6012 | 6·5 | 92·3 (54·6 to 99·6) |
| High grade | | | | | |
| Related to HPV 6, 11, 16, or 18 | 0/5876 | 0 | 2/5893 | 1·0 | 100 (–248·3 to 100) |
| Related to HPV 31, 33, 45, 52, or 58 | 0/6009 | 0 | 3/6012 | 1·5 | 100 (–71·5 to 100) |
| Vulvar intraepithelial neoplasia 2/3 and vulvar cancer | | | | | |
| Related to HPV 6, 11, 16, or 18 | 0/5876 | 0 | 0/5893 | 0 | NA |
| Related to HPV 31, 33, 45, 52, or 58 | 0/6009 | 0 | 0/6012 | 0 | NA |
| Vaginal intraepithelial neoplasia 2/3 and vaginal cancer | | | | | |
| Related to HPV 6, 11, 16, or 18 | 0/5876 | 0 | 2/5893 | 1·0 | 100 (–248·3 to 100) |
| Related to HPV 31, 33, 45, 52, or 58 | 0/6009 | 0 | 3/6012 | 1·5 | 100 (–71·5 to 100) |
| **Cervical cytological abnormalities (ASC-US positive for high-risk HPV types or worse)** | | | | | |
| Related to HPV 6, 11, 16, or 18 | 69/5761 | 37·4 | 93/5773 | 50·4 | 25·7 (–1·5 to 46·3) |
| Related to HPV 31, 33, 45, 52, or 58 | 37/5883 | 19·6 | 506/5882 | 277·2 | 92·9 (90·2 to 95·1) |
| ASC-US positive for high-risk HPV | | | | | |
| Related to HPV 6, 11, 16, or 18 | 18/5761 | 9·7 | 37/5773 | 20·0 | 51·3 (15·0 to 72·4) |
| Related to HPV 31, 33, 45, 52, or 58 | 16/5883 | 8·5 | 283/5882 | 152·1 | 94·4 (91·0 to 96·7) |
| Low-grade squamous intraepithelial lesion | | | | | |
| Related to HPV 6, 11, 16, or 18 | 55/5761 | 29·8 | 59/5773 | 31·9 | 6·6 (–37·3 to 36·5) |
| Related to HPV 31, 33, 45, 52, or 58 | 23/5883 | 12·2 | 331/5882 | 179·2 | 93·2 (89·8 to 95·6) |
| High-grade squamous intraepithelial lesion or worse§ | | | | | |
| Related to HPV 6, 11, 16, or 18 | 1/5761 | 0·5 | 2/5773 | 1·1 | 49·9 (–540·3 to 98·3) |
| Related to HPV 31, 33, 45, 52, or 58 | 1/5883 | 0·5 | 21/5882 | 11·1 | 95·2 (73·9 to 99·8) |
| **Cervical biopsy** | | | | | |
| Related to HPV 6, 11, 16, or 18 | 5/5880 | 2·6 | 12/5895 | 6·1 | 58·2 (–19·8 to 85·8) |
| Related to HPV 31, 33, 45, 52, or 58 | 6/6013 | 3·0 | 253/6014 | 128·7 | 97·7 (95·1 to 99·0) |
| **Cervical definitive therapy** | | | | | |
| Related to HPV 6, 11, 16, or 18 | 0/5880 | 0 | 2/5895 | 1·0 | 100 (–248·4 to 100) |
| Related to HPV 31, 33, 45, 52, or 58 | 4/6013 | 2·0 | 41/6014 | 20·6 | 90·2 (75·0 to 96·8) |
| **External genital procedures** | | | | | |
| Related to HPV 6, 11, 16, or 18 | 5/5876 | 2·6 | 9/5893 | 4·6 | 44·3 (–70·0 to 81·9) |
| Related to HPV 31, 33, 45, 52, or 58 | 2/6009 | 1·0 | 26/6012 | 13·0 | 92·3 (72·4 to 98·7) |

The per-protocol efficacy population consisted of participants who received all three doses of vaccine within 1 year, were seronegative at day 1 and PCR-negative from day 1 to month 7 for the vaccine HPV type being analysed, and had no protocol violations that could affect the evaluation of vaccine prophylactic efficacy. 9vHPV=nine-valent human papillomavirus. HPV=human papillomavirus. qHPV=quadrivalent human papillomavirus. NA=not available (ie, not calculable). ASC-US=atypical squamous cells of undetermined significance. *Includes participants who received at least one dose of a study vaccine. †Number of participants with an endpoint among the participants who were eligible for the per-protocol efficacy analysis population and had at least one follow-up visit with evaluable data relating to the indicated endpoint. ‡Includes low-grade cervical intraepithelial neoplasia, condyloma, low-grade vulvar intraepithelial neoplasia, and low-grade vaginal intraepithelial neoplasia. §Includes high-grade squamous intraepithelial lesion; atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; atypical glandular cells, adenocarcinoma, and squamous cell carcinoma.

***Table 1:*** **Effect of the 9vHPV vaccine on the incidence of persistent infection, cervical, vulvar, and vaginal disease, cervical cytological abnormalities, and medical procedures related to HPV 6, 11, 16, or 18 and HPV 31, 33, 45, 52, or 58 in the per-protocol efficacy population**

study (figure 1). Participants were enrolled in the study over a period of more than 1 year and, therefore, had various durations of follow-up at the end of the study. Overall, 11459 (81%) completed their month 42 visit, 8865 (62%) completed their month 48 visit, and 3686 (26%) of participants completed their month 54 visit (appendix).



Participants were followed for a maximum of 6·0 years after dose one (median 4·0 years, range 0–6·0) or 5·6 years after dose three (median 3·5 years, range 0–5·6). Baseline characteristics have been reported previously[12] and were similar for both study groups, and sample sizes for participants eligible for the efficacy and immunogenicity analyses were also similar (appendix). In the PPE population (table 1), the efficacy of the 9vHPV vaccine compared with the qHPV vaccine with respect to endpoints related to HPV 31, 33, 45, 52, and 58 was 97·4% (95% CI 85·0–99·9; 0·5 cases per 10 000 person-years in the 9vHPV group and 19·0 cases per 10 000 person-years in the qHPV group) for the primary outcome of high-grade cervical, vulvar, and vaginal disease (p<0·0001); 97·1% (83·5–99·9; 0·5 cases and 18·1 cases per 10 000 person-years, respectively) for high-grade cervical disease; and 96·0% (94·6–97·1; 21·5 cases and 538·8 cases per 10 000 person-years, respectively) for 6-month persistent infection; and 96·7% (95·1–97·9; 12·1 cases and 366·2 cases per 10 000 person-years, respectively) for 12-month persistent infection. Efficacy for these endpoints remained within the ranges previously reported at the time of the primary analyses.[12] Efficacy was 100% (95% CI 39·4, 100; 0·0 and 3·6 cases per 10 000 person-years) for cervical intraepithelial neoplasia grade 3, adenocarcinoma in situ, or cervical cancer related to vaccine types, and more than 90% for any grade of cervical and external genital disease related to HPV 31, 33, 45, 52, and 58 (table 1). Substantial reductions in cervical cytological abnormalities and clinical procedures related to HPV 31, 33, 45, 52, and 58 were observed in the 9vHPV vaccine group relative to qHPV recipients (table 1). Efficacy of the 9vHPV vaccine was 90% or higher for cervical cytological abnormalities, cervical biopsy, and cervical definitive therapy, including loop electrosurgical excision procedure and conisation, related to HPV 31, 33, 45, 52, and 58. Analyses in the mITT population (appendix) showed that the 9vHPV vaccine reduced the incidence of persistent infection related to HPV 31, 33, 45, 52, and 58 and disease in participants who were not HPV infected at day 1. In participants who were infected with HPV at baseline, incidence of disease related to HPV 31, 33, 45, 52, and 58 was similar between the two vaccine groups. In the qHPV vaccine group, the incidence of persistent infection and cervical disease related to HPV 31, 33, 45, 52, or 58 continued to increase over time in the PPE and mITT populations. In the 9vHPV vaccine group, the incidence of these endpoints in the mITT population began to plateau (figure 2). Vaccine efficacy in the PPE population was robust (>90%) for infection and disease endpoints related to each of the five HPV types (31, 33, 45, 52, and 58; table 2 and appendix). Measured efficacy was 83·4% for HPV 58-related cervical intraepithelial neoplasia grade 2. The participant in the 9vHPV group with a case of HPV 58-related cervical intraepithelial neoplasia grade 2 was infected with HPV 56 at baseline and at all study visits until the diagnosis; she was positive for HPV 58 only at the time of diagnosis. Therefore, HPV 58 is unlikely to have caused the lesion. In the qHPV vaccine group, the incidence of 6 months' persistent infection related to HPV for each of the five HPV types continued to increase over time in the PPE population (appendix). Vaccine efficacy against persistent infection related to HPV 31, 33, 45, 52, or 58 was high (>90%) across subgroups, defined by baseline characteristics such as age, race, smoking status, and hormonal contraceptive use (table 3).

Robust antibody responses to all nine HPV types were observed at month 3 (1 month after dose two) and month 7 (1 month after dose three); cLIA GMTs decreased over time from month 7 to month 36 to reach a plateau after that (table 4). For the 9vHPV vaccine, nearly all participants (99·6–100%) in the per-protocol immunogenicity population seroconverted at month 7, and most participants (77·5–100%) remained seropositive at month 60 (appendix). Anti-HPV 6, 11, 16, and 18 cLIA GMTs at month 7 were non-inferior in the 9vHPV group compared with the qHPV group (ie, the lower bound of the 95% CI of the GMT ratio [9vHPV:qHPV] was greater than 0·67), as previously reported.[12] GMT ratios (9vHPV:qHPV) and associated 95% CIs varied only minimally over time; from month 7 to month 42, GMT ratios ranged from 1·02–1·03 for HPV 6, 0·80–0·83 for HPV 11, 0·96–1·02 for HPV 16, and 1·17–1·26 for HPV 18 (table 4). HPV antibody persistence was assessed in a subset of participants from the 9vHPV vaccine group who were followed up until month 60 in a study extension; however, no immunogenicity analysis was done in the qHPV vaccine group beyond month 42 because participants in that group were offered vaccination with the 9vHPV vaccine after the base study was terminated. An analysis of 600 randomly selected participants to assess anti-HPV 16 and anti-HPV 18 GMTs at month 7 with two different immunoassays (cLIA and pseudovirion-based neutralisation assay) showed that GMT ratios (9vHPV:qHPV) were similar with the two immunoassays for both HPV 16 (GMT ratio of 0·92 with both immunoassays) and HPV 18 (GMT ratio of 1·16 with cLIA and and 1·19 with pseudovirion-based neutralisation assay; table 4). Incidences of cervical, vulvar, and vaginal

***Figure* 2: Time to the development of cervical disease and of persistent infection related to HPV 31, 33, 45, 52, or 58**

Data shown are 95% CI. Cervical disease of any grade was defined as grade 1, 2, or 3 cervical intraepithelial neoplasia or adenocarcinoma in situ. High-grade cervical disease was defined as grade 2 or 3 cervical intraepithelial neoplasia or adenocarcinoma in situ. (A, C, E) Analyses of the per-protocol efficacy population, which included participants who received all three doses of vaccine within 1 year, were seronegative at day 1, and PCR-negative from day 1 to month 7 for the HPV type being analysed, and had no protocol deviations that could affect the evaluation of vaccine prophylactic efficacy. (B, D, F) Analyses of the modified intention-to-treat population including participants who received one or more doses of vaccine and had efficacy follow-up for the relevant endpoint, including participants who tested positive or negative for HPV DNA at the time of vaccination. The graphs terminate at 60 months because only a small number of participants were evaluated after 60 months. HPV=human papillomavirus. 9vHPV=nine-valent human papillomavirus. qHPV=quadrivalent human papillomavirus.

| | 9vHPV vaccine (N=7099)* | | qHPV vaccine (N=7105)* | | Risk reduction (%; 95% CI) |
|---|---|---|---|---|---|
| | n/total n† | Cases per 10 000 person-years | n/total n† | Cases per 10 000 person-years | |
| **6 months' persistent infection** | | | | | |
| Related to HPV 6, 11, 16, or 18 | | | | | |
| Total | 68/5812 | 36·6 | 95/5830 | 51·1 | 28·5 (1·8 to 48·4) |
| HPV 6 | 14/4697 | 9·3 | 8/4757 | 5·2 | −76·9 (−339·6 to 27·5) |
| HPV 11 | 0/4697 | 0 | 1/4755 | 0·7 | 100 (−∞ to 100) |
| HPV 16 | 44/4772 | 28·6 | 75/4841 | 48·3 | 40·9 (14·0 to 60·2) |
| HPV 18 | 10/5374 | 5·8 | 11/5416 | 6·3 | 8·4 (−137·7 to 61·6) |
| Related to HPV 31, 33, 45, 52, or 58 | | | | | |
| Total | 41/5941 | 21·5 | 946/5955 | 538·8 | 96·0 (94·6 to 97·1) |
| HPV 31 | 9/5252 | 5·3 | 177/5198 | 107·7 | 95·1 (90·5 to 97·6) |
| HPV 33 | 1/5553 | 0·6 | 128/5560 | 72·3 | 99·2 (96·0 to 100) |
| HPV 45 | 5/5649 | 2·8 | 156/5660 | 86·9 | 96·8 (92·8 to 98·8) |
| HPV 52 | 13/5264 | 7·7 | 453/5161 | 285·5 | 97·3 (95·5 to 98·6) |
| HPV 58 | 13/5297 | 7·6 | 262/5284 | 158·0 | 95·2 (91·8 to 97·5) |
| **12 months' persistent infection** | | | | | |
| Related to HPV 6, 11, 16, or 18 | | | | | |
| Total | 25/5812 | 13·4 | 35/5830 | 18·7 | 28·5 (−22·9 to 57·7) |
| HPV 6 | 7/4697 | 4·6 | 1/4757 | 0·7 | −607·7 (−∞ to −1·1) |
| HPV 11 | 0/4697 | 0 | 0/4755 | 0 | NA |
| HPV 16 | 12/4772 | 7·8 | 26/4841 | 16·7 | 53·4 (4·4 to 78·6) |
| HPV 18 | 6/5374 | 3·5 | 8/5416 | 4·6 | 24·4 (−122·0 to 73·8) |
| Related to HPV 31, 33, 45, 52, or 58 | | | | | |
| Total | 23/5941 | 12·1 | 657/5955 | 366·2 | 96·7 (95·1 to 97·9) |
| HPV 31 | 4/5252 | 2·4 | 122/5198 | 73·9 | 96·8 (92·1 to 98·9) |
| HPV 33 | 1/5553 | 0·6 | 91/5560 | 51·2 | 98·9 (94·4 to 99·9) |
| HPV 45 | 2/5649 | 1·1 | 90/5660 | 49·9 | 97·8 (92·4 to 99·6) |
| HPV 52 | 7/5264 | 4·1 | 297/5161 | 184·6 | 97·8 (95·4 to 99·0) |
| HPV 58 | 9/5297 | 5·3 | 177/5284 | 106·0 | 95·0 (90·5 to 97·6) |
| **Cervical disease (any grade)** | | | | | |
| Related to HPV 6, 11, 16, or 18 | | | | | |
| Total | 1/5824 | 0·5 | 3/5832 | 1·6 | 66·6 (−203·0 to 98·7) |
| HPV 6 | 0/4708 | 0 | 1/4759 | 0·6 | 100 (−∞ to 100) |
| HPV 11 | 0/4708 | 0 | 0/4759 | 0 | NA |
| HPV 16 | 0/4783 | 0 | 2/4844 | 1·3 | 100 (−251·2 to 100) |
| HPV 18 | 1/5387 | 0·6 | 0/5420 | 0 | NA |
| Related to HPV 31, 33, 45, 52, or 58 | | | | | |
| Total | 2/5949 | 1·0 | 110/5943 | 57·2 | 98·2 (93·7 to 99·7) |
| HPV 31 | 1/5260 | 0·6 | 22/5200 | 13·0 | 95·5 (75·6 to 99·8) |
| HPV 33 | 0/5566 | 0 | 18/5563 | 9·9 | 100 (79·1 to 100) |
| HPV 45 | 0/5659 | 0 | 8/5659 | 4·4 | 100 (46·4 to 100) |
| HPV 52 | 0/5275 | 0 | 46/5159 | 27·4 | 100 (92·8 to 100) |
| HPV 58 | 1/5308 | 0·6 | 29/5284 | 16·9 | 96·6 (80·7 to 99·8) |
| **High-grade cervical disease** | | | | | |
| Related to HPV 6, 11, 16, or 18 | | | | | |
| Total | 1/5824 | 0·5 | 1/5832 | 0·5 | −0·3 (−∞ to 97·4) |
| HPV 6 | 0/4708 | 0 | 1/4759 | 0·6 | 100 (−∞ to 100) |
| HPV 11 | 0/4708 | 0 | 0/4759 | 0 | NA |
| HPV 16 | 0/4783 | 0 | 0/4844 | 0 | NA |
| HPV 18 | 1/5387 | 0·6 | 0/5420 | 0 | NA |

(Table 2 continues on next page)

| | 9vHPV vaccine (N=7099)* | | qHPV vaccine (N=7105)* | | Risk reduction (%; 95% CI) |
|---|---|---|---|---|---|
| | n/total n† | Cases per 10 000 person-years | n/total n† | Cases per 10 000 person-years | |
| (Continued from previous page) | | | | | |
| Related to HPV 31, 33, 45, 52, or 58 | | | | | |
| Total | 1/5949 | 0·5 | 35/5943 | 18·1 | 97·1 (83·5 to 99·9) |
| HPV 31 | 0/5260 | 0 | 7/5200 | 4·1 | 100 (40·1 to 100) |
| HPV 33 | 0/5566 | 0 | 9/5563 | 5·0 | 100 (57·2 to 100) |
| HPV 45 | 0/5659 | 0 | 3/5659 | 1·6 | 100 (–71·4 to 100) |
| HPV 52 | 0/5275 | 0 | 16/5159 | 9·5 | 100 (75·9 to 100) |
| HPV 58 | 1/5308 | 0·6 | 6/5284 | 3·5 | 83·4 (–23·7 to 99·3) |
| **Cervical cytological abnormalities (ASC-US positive for high-risk HPV types or worse)** | | | | | |
| Related to HPV 6, 11, 16, or 18 | | | | | |
| Total | 69/5761 | 37·4 | 93/5773 | 50·4 | 25·7 (–1·5 to 46·3) |
| HPV 6 | 10/4670 | 6·7 | 8/4714 | 5·3 | –26·2 (–226·1 to 51·4) |
| HPV 11 | 6/4670 | 4·0 | 0/4714 | 0 | NA |
| HPV 16 | 48/4746 | 31·4 | 77/4813 | 49·9 | 37·1 (10·4 to 57·1) |
| HPV 18 | 7/5333 | 4·1 | 10/5378 | 5·8 | 29·4 (–98·0 to 77·2) |
| Related to HPV 31, 33, 45, 52, or 58 | | | | | |
| Total | 37/5883 | 19·6 | 506/5882 | 277·2 | 92·9 (90·2 to 95·1) |
| HPV 31 | 8/5217 | 4·8 | 92/5154 | 55·8 | 91·5 (82·9 to 96·4) |
| HPV 33 | 8/5509 | 4·5 | 86/5512 | 48·7 | 90·7 (81·7 to 96·1) |
| HPV 45 | 6/5599 | 3·3 | 91/5602 | 50·9 | 93·5 (85·8 to 97·2) |
| HPV 52 | 12/5228 | 7·1 | 225/5116 | 139·2 | 94·9 (91·1 to 97·2) |
| HPV 58 | 7/5262 | 4·1 | 158/5239 | 94·8 | 95·6 (91·0 to 98·0) |
| **Cervical definitive therapy** | | | | | |
| Related to HPV 6, 11, 16, or 18 | | | | | |
| Total | 0/5880 | 0 | 2/5895 | 1·0 | 100 (–248·4 to 100) |
| HPV 6 | 0/4745 | 0 | 1/4806 | 0·6 | 100 (–∞ to 100) |
| HPV 11 | 0/4745 | 0 | 0/4806 | 0 | NA |
| HPV 16 | 0/4804 | 0 | 1/4868 | 0·6 | 100 (–∞ to 100) |
| HPV 18 | 0/5431 | 0 | 0/5475 | 0 | NA |
| Related to HPV 31, 33, 45, 52, or 58 | | | | | |
| Total | 4/6013 | 2·0 | 41/6014 | 20·6 | 90·2 (75·0 to 96·8) |
| HPV 31 | 1/5305 | 0·6 | 7/5249 | 4·0 | 85·9 (1·0 to 99·4) |
| HPV 33 | 1/5621 | 0·5 | 8/5625 | 4·3 | 87·5 (20·1 to 99·4) |
| HPV 45 | 0/5721 | 0 | 3/5722 | 1·6 | 100 (–71·3 to 100) |
| HPV 52 | 0/5317 | 0 | 13/5213 | 7·5 | 100 (71·5 to 100) |
| HPV 58 | 2/5358 | 1·1 | 15/5337 | 8·5 | 86·7 (49·3 to 97·8) |

The per-protocol efficacy population consisted of participants who received all three doses of vaccine within 1 year, were seronegative at day 1 and PCR-negative from day 1 to month 7 for the vaccine HPV type being analysed, and had no protocol violations that could affect the evaluation of vaccine prophylactic efficacy. 9vHPV=nine-valent human papillomavirus. HPV=human papillomavirus. qHPV=quadrivalent human papillomavirus. NA=not available (ie, not calculable). ASC-US=atypical squamous cells of undetermined significance. *Includes participants who received at least one dose of a study vaccine. †Number of participants with an endpoint among the participants who were eligible for the per-protocol efficacy analysis population and had at least one follow-up visit with evaluable data relating to the indicated endpoint.

***Table* 2: Effect of the 9vHPV vaccine on the incidence of persistent infection, cervical disease, cervical cytological abnormalities, and cervical definitive therapy related to each HPV type in the per-protocol efficacy population**

disease; persistent infection; cervical cytological abnormalities; and cervical and genital procedures related to HPV 6, 11, 16, and 18 were similar between the two vaccine groups (table 1). A higher reduction of HPV 16-related persistent infection and cytological abnormalities was observed in the 9vHPV group compared with the qHPV group (table 2).

In the combined 9vHPV and qHPV groups, 417 (3%) of 14 149 reported serious adverse events irrespective of causality (appendix). Seven participants experienced serious adverse events that were considered vaccine-related by the reporting investigator (four in the 9vHPV group and three among qHPV participants; appendix). 11 participants died during the study follow-up period (six

| | 9vHPV vaccine (N=7099)† | | qHPV vaccine (N=7105)† | | Risk reduction (%; 95% CI) |
|---|---|---|---|---|---|
| | n/total n‡ | Cases per 10 000 person-years | n/total n‡ | Cases per 10 000 person-years | |
| All participants | 41/5941 | 21·5 | 946/5955 | 538·8 | 96·0 (94·6–97·1) |
| Age (years) | | | | | |
| ≤20 | 17/1770 | 29·6 | 398/1870 | 747·2 | 96·0 (93·7–97·7) |
| ≥21 | 24/4171 | 18·0 | 548/4085 | 448·0 | 96·0 (94·0–97·4) |
| Ethnic origin | | | | | |
| Asian | 3/868 | 11·2 | 74/859 | 294·3 | 96·2 (89·2–99·0) |
| Black | 1/198 | 15·0 | 37/185 | 679·8 | 97·8 (87·3–99·9) |
| White | 16/3277 | 15·4 | 506/3273 | 525·7 | 97·1 (95·3–98·2) |
| Other | 21/1598 | 39·9 | 329/1638 | 675·0 | 94·1 (91·0–96·3) |
| Ethnic origin | | | | | |
| Hispanic | 22/2123 | 31·0 | 430/2130 | 669·7 | 95·4 (93·0–97·1) |
| Not Hispanic | 19/3818 | 15·9 | 516/3825 | 463·3 | 96·6 (94·7–97·9) |
| Geographic region | | | | | |
| Asia-Pacific | 4/776 | 16·6 | 74/782 | 321·9 | 94·8 (86·7–98·3) |
| Europe | 11/2032 | 16·8 | 313/2003 | 526·5 | 96·8 (94·4–98·4) |
| Latin America | 22/2010 | 32·5 | 414/2029 | 673·0 | 95·2 (92·7–97·0) |
| North America | 4/1123 | 12·0 | 145/1141 | 458·6 | 97·4 (93·5–99·1) |
| Smoking status on day 1 | | | | | |
| Currently a smoker | 10/869 | 36·5 | 157/791 | 686·6 | 94·7 (90·3–97·4) |
| Not currently a smoker | 31/5072 | 19·0 | 789/5164 | 516·7 | 96·3 (94·7–97·4) |
| Hormonal contraception use on day 1 | | | | | |
| Hormonal contraception | 22/3611 | 18·9 | 576/3632 | 533·6 | 96·5 (94·7–97·8) |
| No hormonal contraception | 19/2330 | 25·7 | 370/2323 | 547·1 | 95·3 (92·6–97·2) |
| Lifetime number of sex partners by day 1 | | | | | |
| None | 0/133 | 0 | 12/163 | 242·2 | 100 (64·1–100) |
| 1–2 | 15/3201 | 14·4 | 451/3139 | 475·9 | 97·0 (95·1–98·3) |
| ≥3 | 26/2607 | 31·8 | 483/2653 | 636·7 | 95·0 (92·6–96·7) |
| Cervical cytological abnormality status on day 1 | | | | | |
| Negative for squamous intraepithelial lesion | 32/5246 | 18·9 | 800/5258 | 512·1 | 96·3 (94·8–97·5) |
| ASC-US or worse | 8/639 | 42·0 | 138/647 | 770·5 | 94·6 (89·3–97·7) |
| Borderline abnormal Pap test§ | 0/223 | 0 | 53/256 | 733·6 | 100 (93·2–100) |
| Abnormal Pap test¶ | 8/416 | 66·1 | 85/391 | 795·5 | 91·7 (83·6–96·5) |
| Status unknown‖ | 1/56 | 53·5 | 8/50 | 555·7 | 90·4 (38·6–99·6) |

The per-protocol efficacy population consisted of participants who received all three doses of vaccine within 1 year, were seronegative at day 1 and PCR-negative from day 1 to month 7 for the vaccine HPV type being analysed, and had no protocol violations that could affect the evaluation of vaccine prophylactic efficacy. 9vHPV=nine-valent human papillomavirus. HPV=human papillomavirus. qHPV=quadrivalent human papillomavirus. ASC-US=atypical squamous cells of undetermined significance. Pap=Papanicolaou. *Persistent infection was defined as detection of the same HPV type in genital swab or tissue specimen collected on two or more consecutive visits, with an interval of at least 6 months (plus or minus 1-month visit windows) between visits. †Includes participants who received at least one dose of a study vaccine. ‡Number of participants with an endpoint among the participants with the indicated baseline characteristics who were eligible for the per-protocol efficacy analysis population and had at least one follow-up visit with evaluable data relating to persistent infection related to HPV 31, 33, 45, 52, and 58. §Included ASC-US not positive for high-risk HPV types. ¶Included ASC-US positive for high-risk HPV types, low-grade squamous intraepithelial lesion; atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; high-grade squamous intraepithelial lesion, or worse. ‖Includes Pap test results such as unsatisfactory, specimen rejected beyond stability, improper specimen, or missing.

***Table 3*: Effect of the 9vHPV vaccine on the incidence of 6 months' persistent infection* related to HPV 31, 33, 45, 52, or 58 in subgroups of the per-protocol efficacy population**

in the 9vHPV vaccine group and five in the qHPV vaccine group); none of the deaths were considered vaccine-related (additional information on serious vaccine-related adverse events and deaths is shown in the appendix). In both vaccine groups, the most common serious adverse events were spontaneous abortions, elective abortions, and appendicitis; other serious adverse events were of low frequency and affected various system organ classes. Only one adverse event of anaphylaxis was reported and was caused by a non-study medication (parenteral iron given for anaemia at 5 days after dose three).

## Discussion

The 9vHPV vaccine shows high and sustained efficacy for prevention of persistent infection and disease related to HPV 31, 33, 45, 52, and 58 up to 6 years following the

| | 9vHPV vaccine (N=6792)* | | qHPV vaccine (N=6795)* | | GMT ratio (9vHPV/qHPV; 95% CI) |
|---|---|---|---|---|---|
| | n† | GMT (95% CI) | n† | GMT (95% CI) | |
| **Persistence of antibody response (HPV-9 cLIA assay)‡** | | | | | |
| Anti-HPV 6 | | | | | |
| Day 1 | 3993 | <16 (<16 to <16) | 3975 | <16 (<16 to <16) | .. |
| Month 3 | 788 | 734·0 (692·8 to 777·7) | 761 | 719·6 (678·5 to 763·2) | .. |
| Month 7 | 3993 | 893·1 (871·7 to 915·1) | 3975 | 875·2 (854·2 to 896·8) | 1·02 (0·99 to 1·06) |
| Month 12 | 800 | 330·6 (312·2 to 350·1) | 781 | 319·4 (301·4 to 338·6) | 1·03 (0·95 to 1·12) |
| Month 24 | 715 | 208·6 (195·5 to 222·7) | 690 | 205·1 (191·9 to 219·1) | 1·02 (0·93 to 1·12) |
| Month 36 | 685 | 163·9 (153·0 to 175·6) | 666 | 158·9 (148·2 to 170·4) | 1·03 (0·94 to 1·14) |
| Month 42 | 692 | 147·2 (137·3 to 157·8) | 675 | 144·3 (134·5 to 154·8) | 1·02 (0·92 to 1·13) |
| Month 60 | 101 | 143·1 (117·9 to 173·7) | .. | .. | .. |
| Anti-HPV 11 | | | | | |
| Day 1 | 3995 | <6 (<6 to <6) | 3982 | <6 (<6 to <6) | .. |
| Month 3 | 790 | 529·1 (499·7 to 560·1) | 762 | 678·3 (640·1 to 718·9) | .. |
| Month 7 | 3995 | 666·3 (649·6 to 683·4) | 3982 | 830·0 (809·2 to 851·4) | 0·80 (0·77 to 0·83) |
| Month 12 | 810 | 212·4 (200·1 to 225·6) | 788 | 264·5 (248·9 to 281·1) | 0·80 (0·74 to 0·87) |
| Month 24 | 763 | 123·3 (115·8 to 131·2) | 735 | 148·1 (138·9 to 157·8) | 0·83 (0·76 to 0·91) |
| Month 36 | 690 | 89·6 (83·3 to 96·3) | 671 | 110·9 (103·1 to 119·4) | 0·81 (0·73 to 0·90) |
| Month 42 | 696 | 84·9 (79·0 to 91·3) | 677 | 104·0 (96·7 to 111·9) | 0·82 (0·74 to 0·90) |
| Month 60 | 112 | 82·9 (68.1 to 100.9) | .. | .. | .. |
| Anti-HPV 16 | | | | | |
| Day 1 | 4032 | <12 (<12 to <12) | 4062 | <12 (<12 to <12) | .. |
| Month 3 | 794 | 2435·8 (2303·5 to 2575·6) | 785 | 2475·1 (2340·0 to 2618·0) | .. |
| Month 7 | 4032 | 3131·1 (3057·1 to 3206·9) | 4062 | 3156·6 (3082·3 to 3232·7) | 0·99 (0·96 to 1·03) |
| Month 12 | 819 | 1041·7 (979·9 to 1107·4) | 805 | 1031·6 (969·9 to 1097·3) | 1·01 (0·93 to 1·10) |
| Month 24 | 778 | 520·7 (484·7 to 559·4) | 759 | 508·0 (472·5 to 546·3) | 1·02 (0·93 to 1·13) |
| Month 36 | 695 | 386·5 (356·3 to 419·4) | 689 | 387·1 (356·7 to 420·1) | 1·00 (0·89 to 1·12) |
| Month 42 | 709 | 346·8 (319·3 to 376·7) | 690 | 362·9 (333·8 to 394·6) | 0·96 (0·85 to 1·07) |
| Month 60 | 128 | 324·4 (266.7 to 394.7) | .. | .. | .. |
| Anti-HPV 18 | | | | | |
| Day 1 | 4539 | <8 (<8 to <8) | 4541 | <8 (<8 to <8) | .. |
| Month 3 | 908 | 470·8 (442·8 to 500·7) | 877 | 371·0 (348·5 to 395·0) | .. |
| Month 7 | 4539 | 804·6 (782·7 to 827·1) | 4541 | 678·7 (660·2 to 697·7) | 1·19 (1·14 to 1·23) |
| Month 12 | 929 | 198·6 (184·9 to 213·4) | 901 | 160·2 (148·9 to 172·2) | 1·24 (1·12 to 1·37) |
| Month 24 | 886 | 86·0 (79·0 to 93·6) | 847 | 68·1 (62·4 to 74·3) | 1·26 (1·12 to 1·43) |
| Month 36 | 789 | 78·5 (71·9 to 85·6) | 768 | 62·4 (57·1 to 68·1) | 1·26 (1·11 to 1·42) |
| Month 42 | 806 | 70·8 (64·8 to 77·3) | 770 | 60·4 (55·2 to 66·1) | 1·17 (1·03 to 1·33) |
| Month 60 | 142 | 62·5 (49.5 to 78.9) | .. | .. | .. |
| Anti-HPV 31 | | | | | |
| Day 1 | 4466 | <4 (<4 to <4) | 4377 | <4 (<4 to <4) | .. |
| Month 3 | 881 | 437·6 (406·7 to 470·8) | 838 | 6·3 (5·8 to 6·7) | .. |
| Month 7 | 4466 | 658·4 (636·7 to 680·9) | 4377 | 9·7 (9·4 to 10·1) | .. |
| Month 12 | 909 | 196·5 (183·5 to 210·4) | 858 | 4·1 (<4 to 4·4) | .. |
| Month 24 | 863 | 101·9 (94·9 to 109·5) | 805 | <4 (<4 to <4) | .. |
| Month 36 | 772 | 72·7 (67·5 to 78·4) | 724 | <4 (<4 to <4) | .. |
| Month 42 | 783 | 70·4 (65·3 to 75·9) | 730 | <4 (<4 to <4) | .. |
| Month 60 | 135 | 69·2 (56.6 to 84.4) | .. | .. | .. |
| Anti-HPV 33 | | | | | |
| Day 1 | 4702 | <4 (<4 to <4) | 4691 | <4 (<4 to <4) | .. |
| Month 3 | 937 | 287·8 (272·9 to 303·5) | 893 | <4 (<4 to <4) | .. |

(Table 4 continues on next page)

| | 9vHPV vaccine (N=6792)* | | qHPV vaccine (N=6795)* | | GMT ratio [9vHPV/qHPV] (95% CI) |
|---|---|---|---|---|---|
| | n† | GMT (95% CI) | n† | GMT (95% CI) | |
| (Continued from previous page) | | | | | |
| Month 7 | 4702 | 415·9 (405·6 to 426·4) | 4691 | <4 (<4 to <4) | .. |
| Month 12 | 958 | 126·2 (119·9 to 132·9) | 921 | <4 (<4 to <4) | .. |
| Month 24 | 909 | 65·3 (61·7 to 69·0) | 868 | <4 (<4 to <4) | .. |
| Month 36 | 813 | 46·8 (44·0 to 49·8) | 785 | <4 (<4 to <4) | .. |
| Month 42 | 835 | 44·3 (41·6 to 47·1) | 789 | <4 (<4 to <4) | .. |
| Month 60 | 141 | 44·7 (37·0 to 54·1) | .. | .. | .. |
| Anti-HPV 45 | | | | | |
| Day 1 | 4792 | <3 (<3 to <3) | 4750 | <3 (<3 to <3) | .. |
| Month 3 | 956 | 160·4 (151·7 to 169·7) | 910 | <3 (<3 to <3) | .. |
| Month 7 | 4792 | 252·8 (246·2 to 259·6) | 4750 | <3 (<3 to <3) | .. |
| Month 12 | 976 | 69·2 (65·4 to 73·3) | 937 | <3 (<3 to <3) | .. |
| Month 24 | 928 | 33·0 (31·0 to 35·0) | 882 | <3 (<3 to <3) | .. |
| Month 36 | 835 | 22·9 (21·4 to 24·4) | 800 | <3 (<3 to <3) | .. |
| Month 42 | 846 | 21·1 (19·8 to 22·5) | 802 | <3 (<3 to <3) | .. |
| Month 60 | 148 | 20·8 (17·0 to 25·5) | .. | .. | .. |
| Anti-HPV 52 | | | | | |
| Day 1 | 4455 | <3 (<3 to <3) | 4335 | <3 (<3 to <3) | .. |
| Month 3 | 895 | 241·3 (229·7 to 253·4) | 835 | <3 (<3 to <3) | .. |
| Month 7 | 4455 | 379·7 (371·6 to 388·0) | 4335 | <3 (<3 to <3) | .. |
| Month 12 | 916 | 118·9 (113·0 to 125·0) | 857 | <3 (<3 to <3) | .. |
| Month 24 | 867 | 57·9 (54·7 to 61·2) | 809 | <3 (<3 to <3) | .. |
| Month 36 | 777 | 47·9 (45·0 to 50·9) | 732 | <3 (<3 to <3) | .. |
| Month 42 | 791 | 43·2 (40·6 to 46·0) | 735 | <3 (<3 to <3) | .. |
| Month 60 | 134 | 33·7 (27·6 to 41·1) | .. | .. | .. |
| Anti-HPV 58 | | | | | |
| Day 1 | 4486 | <4 (<4 to <4) | 4446 | <4 (<4 to <4) | .. |
| Month 3 | 884 | 281·1 (265·3 to 297·7) | 863 | <4 (<4 to <4) | .. |
| Month 7 | 4486 | 482·5 (469·9 to 495·3) | 4446 | <4 (<4 to <4) | .. |
| Month 12 | 905 | 153·3 (145·5 to 161·6) | 883 | <4 (<4 to <4) | .. |
| Month 24 | 852 | 80·3 (75·7 to 85·3) | 835 | <4 (<4 to <4) | .. |
| Month 36 | 765 | 55·0 (51·4 to 58·8) | 747 | <4 (<4 to <4) | .. |
| Month 42 | 784 | 52·0 (48·7 to 55·6) | 756 | <4 (<4 to <4) | .. |
| Month 60 | 132 | 50·9 (40.9 to 63.3) | .. | .. | .. |
| **PBNA substudy of month 7 antibody response§** | | | | | |
| Anti-HPV 16 | | | | | |
| cLIA | 176¶ | 2902·3 | 192¶ | 3168·1 | 0·92 (0·79 to 1·06) |
| PBNA | 176 | 40 327·0 | 192 | 43 848·4 | 0·92 (0·77 to 1·10) |
| Anti-HPV 18 | | | | | |
| cLIA | 211¶ | 771·2 | 208¶ | 665·4 | 1·16 (0·97 to 1·38) |
| PBNA | 211 | 15 197·0 | 208 | 12 795·5 | 1·19 (0·98 to 1·44) |

The per-protocol immunogenicity population includes all participants who received all three vaccinations within acceptable day ranges, were seronegative at day 1 and PCR-negative from day 1 to month 7 for the relevant HPV type or types, had a month-7 serum sample collected within an acceptable day range, and had no protocol violations that could interfere with the immunogenicity evaluation. Assessment of antibody response by cLIA at months 3, 12, 24, 36, and 48 included a subset of 20% of participants randomly selected before the database was unmasked. The GMT values at day 1 (<16, <6, <12, <8, <4, <4, <3, <3, and <4 for HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58, respectively) denote that the cLIA results are below the lower limit of quantitation of the assay. The PBNA substudy included a subset of 600 participants randomly selected before the database was unmasked. HPV-9 cLIA=nine valent-competitive Luminex immunoassay. PBNA=pseudovirion-based neutralisation assay. 9vHPV=nine-valent human papillomavirus. qHPV=quadrivalent human papillomavirus. GMT=geometric mean titre. HPV=human papillomavirus. *Includes participants who received at least one dose of a study vaccine in the immunogenicity substudy cohort. †Number of participants who were eligible for the per-protocol immunogenicity analysis population with evaluable immunogenicity data at the indicated timepoint. ‡cLIA GMT is expressed in milliMerck units/mL (mMU/mL). §PBNA GMT is expressed as $EC_{50}$ (reciprocal of the serum dilution that caused 50% reduction in luciferase reporter activity compared with controls). ¶Number of participants who were eligible for the per-protocol immunogenicity analysis population, with evaluable cLIA immunogenicity data and included in the PBNA substudy with evaluable PBNA immunogenicity data for the indicated HPV type.

***Table 4:*** **HPV-9 cLIA and PBNA geometric mean titres in the per-protocol immunogenicity population**

first vaccination visit. Results of the data analysis indicated that vaccine efficacy through study completion remained unchanged compared with earlier analyses,[12] thereby showing that vaccine efficacy persisted through the end of the study. Furthermore, robust efficacy to prevent cervical intraepithelial neoplasia grade 3 or worse, abnormal cervical cytology, and cervical procedures related to HPV 31, 33, 45, 52, and 58 was shown. Overall, the efficacy was remarkably consistent across all the endpoints assessed in these analyses. In the mITT analyses, nearly all cases of high-grade disease occurred among participants who were infected with HPV before vaccination, which highlights the value of implementing vaccination before exposure to HPV. The immunogenicity profile of the 9vHPV vaccine with respect to HPV 6, 11, 16, and 18 was similar to that of the qHPV vaccine; moreover, incidence of persistent infections, abnormal cervical cytology, high-grade disease, and medical procedures related to HPV 6, 11, 16, and 18 were comparable between the two vaccine groups, suggesting that the 9vHPV vaccine prevented these outcomes as efficaciously as the qHPV vaccine. The observed higher efficacy of the 9vHPV vaccine versus qHPV vaccine to prevent persistent infection and cytological abnormalities related to HPV 16 is unlikely to have a clinical significance since the qHPV vaccine is highly efficacious to prevent these endpoints. Finally, the 9vHPV vaccine showed a similar safety profile to the qHPV vaccine, except with more injection-site reactions, as shown here and in a previous report.[19] Overall, 16–17% participants discontinued from the study, representing a discontinuation rate of approximately 4% per year, which was within the range of assumptions used for the study design. Given the age of the participants (16–26 years) and the long duration of the study, it was anticipated that some participants might move away to pursue college, careers, or family endeavours, and therefore, potentially discontinue from the study. Consistent with that assumption, the preponderance of reasons for discontinuations were loss-to-follow-up and withdrawal by participant. Since discontinuations between the two vaccination groups were balanced, they do not bias the results of comparisons of the two vaccination groups overall.

The study achieved its key objectives, which were to show efficacy against the primary and secondary endpoints of high-grade cervical, vulvar, and vaginal disease related to HPV 31, 33, 45, 52, and 58, and 6 months' persistent infection related to HPV 31, 33, 45, 52, and 58. Additionally, the vaccine was found to be highly efficacious in preventing these efficacy endpoints for each of the types separately. Because of the small number of cases, statistical significance was not reached for the endpoint of high-grade cervical, vulvar, and vaginal disease related to HPV 45. The relatively low incidence of high-grade disease related to HPV 18 and HPV 45 (relative to the incidence of cervical cancer related to HPV 18 and HPV 45) has been recognised in the scientific literature;[3,21–23] however, the reason for this relatively low incidence is not completely understood. A possible explanation for our results is that HPV 45 might generate occult pathology that is difficult to detect by routine screening methods (eg, HPV 45 has a propensity for endocervical glandular lesions that are less efficiently detected by cytological screening).[24] It is also possible that HPV 45-related infection might result in a short time of progression to cancer, possibly without clinical detection in a preinvasive setting. Importantly, in a large epidemiologic study,[3] HPV 45-specific cervical cancers were typically seen in much younger women. The secondary endpoint of HPV 45-related persistent infection was useful to ensure a sufficient number of cases and demonstrate consistency of vaccine efficacy across the five new HPV types (31, 33, 45, 52, and 58), including HPV 45.

This study shows that many important individual clinical and global public health outcomes are prevented by 9vHPV vaccination: HPV infection, abnormal cytology, histological disease, and treatment procedures. The robust methods we used strengthened the clinical evidence to support vaccination for the prevention of HPV-related cancers. For example, participants were frequently screened to assure clinical-endpoint detection and used methods similar to those used to study the qHPV vaccine (which allowed comparison between the two vaccine programmes; the similarity between the two vaccines helped reinforce the efficacy and safety of the 9vHPV vaccine). Because HPV disease is a global health issue, the study was done in multiple countries; the results showed that the vaccine was similarly efficacious in various populations and regions, thereby supporting the generalisability of the results. This outcome was similar to previous results showing the qHPV vaccine to be efficacious in subgroups of young women aged 16–26 years differing by age and region of residence.[25–29] The results of this study might support public health decisions on the implementation of the 9vHPV vaccination programme in many countries and could stimulate future research on possible synergies between HPV vaccination and screening for cervical disease.

Although some might posit these findings are limited by the use of an active control group, it would be ethically irresponsible to treat some participants with placebo when the existing HPV vaccines are highly efficacious in prevention of disease and infection caused by oncogenic HPV 16 and 18.[11] Thus, showing non-inferiority of the 9vHPV vaccine over the qHPV vaccine for immunogenicity at month 7 and comparable incidence of infection and disease outcome is an important accomplishment.[11,12] These initial immunogenicity results were further strengthened by the consistent results over time for the immunogenicity comparisons, in addition to the use of two different immunoassays, including a primary assay that is highly type-specific to test antibodies to each of the nine HPV types and a secondary in-vitro neutralising assay for additional testing of antibody response to HPV 16

and HPV 18, and the persistence of antibody responses 5 years after vaccination. Moreover, supportive analyses showed comparable incidence of infection, disease, cytological abnormalities, and procedures related to HPV 6, 11, 16, and 18 between the two vaccine groups. Taken together, these results strongly support the assertion that the additional HPV types (31, 33, 45, 52, and 58) do not negatively affect 9vHPV vaccine immunogenicity and efficacy for the original HPV types (6, 11, 16, and 18). This study used immunogenicity outcomes to infer efficacy of a new HPV vaccine, an unprecedented approach in HPV vaccine development that might open new options for future HPV vaccine development. The study was limited in duration. Long-term follow-up studies[30] of the qHPV vaccine have shown persistence of protection for at least 10 years' post-vaccination, suggesting that the 9vHPV vaccine could also offer long-term protection. A 10-year long-term follow-up study extension (protocol V503-021; NCT02653118) is underway to assess duration of protection.

These data show that prophylactic administration of the 9vHPV vaccine is highly efficacious in preventing infection, cervical cytological abnormalities, histologically detected high-grade disease, and medical procedures associated with vaccine HPV types. Broad immunisation of adolescent populations might result in such a substantial decrease in high-grade cervical disease that the evaluation of optimal screening algorithms in women vaccinated with the 9vHPV vaccine will be necessary.

#### Contributors

WKH analysed data, interpreted the results, and wrote the draft manuscript. EAJ collected data. ARG collected data, interpreted it, and extensively reviewed manuscript drafts. O-EI acquired data and interpreted it. RPdA was involved in the study conception, design, and planning, analysed data, and provided study materials and recruited participants. KAA was involved in the study design, recruited participants, provided care for the patients during the protocol, acquired data, and interpreted the results. RMC acquired data, analysed it, and interpreted the results. ENF acquired data, analysed it, and recruited participants and study materials. DB and ALH acquired data. M-HM acquired data and interpreted it. AMR-S enrolled patients and contributed to data collection. JTS was the principal investigator at a study site, collected data, and interpreted the results. DJW was a principal investigator at a study site, acquired data, interpreted the results, and was involved in site data-quality management. AF was one of the pathology panel members for assessment of histological materials and interpreted the results. RK was involved in the study conception, design, and planning, acquired data, and interpreted it. BMR acquired data (generated data by reading slides as a member of the pathology panel). MHS acquired data and interpreted the results. JC designed the study and analysed and interpreted data. SMG was involved in the study conception, design, and planning, analysed data, and interpreted the results. SKK acquired data and interpreted the results. OMB analysed data and interpreted the results. RH was involved in the study conception, design, and planning, and interpreted the results. EM was involved in the study conception, design, and planning. MR designed the study and actively supported the study from the sponsor's perspective. CCR generated and analysed HPV PCR and immunogenicity data. CS was involved in the study conception, design, and planning. AL was involved in the study conception, design, and planning, analysed data, interpreted the results, and drafted the manuscript. EAJ and JTS critically reviewed data and drafts, and all other authors critically reviewed and revised the manuscript for important intellectual content. All authors approved the final version.

#### Declaration of interests

WKH has received fees as a consultant for Merck & Co, Inc (Kenilworth, NJ, USA). EAJ has received grants and personal fees from Merck & Co, Inc, and Sanofi Pasteur MSD. ARG's institution has received grants from Merck & Co, Inc, on her behalf for her research; she is a member of the scientific advisory board for Merck & Co, Inc. O-EI has received personal fees from Merck & Co, Inc, for clinical HPV vaccine trials and for scientific advisory committee meetings and has received lecture fees from Sanofi Pasteur MSD. RPdA has received grants from Merck & Co, Inc, as a trial principal investigator. KAA is a former employee of Emory University (Atlanta, GA, USA) and received payments from Emory University for clinical trial conduct. RMC has received grants from Merck & Co, Inc, as a principal investigator for this and other studies. ENF has received grants and personal fees from Merck & Co, Inc. M-HM has received grants from Merck & Co, Inc. AMR-S received funding from Merck & Co, Inc, through Rosario University for clinical trials of HPV vaccines. JTS's institution has received grants from Merck & Co, Inc. DJW has received personal fees for speakers bureaus and support as a site principal investigator from Merck & Co, Inc. AF has acted as pathologist consultant for Merck & Co, Inc, in HPV vaccine clinical trials. RK has acted as a consultant as part of the central pathology panel for Merck & Co, Inc. BMR has a consulting agreement with Merck & Co, Inc, paid to Johns Hopkins University (Baltimore, MD, USA). MHS is part of the central pathology panel and a consultant on this clinical trial and the University of Virginia (Charlottesville, VA, USA) received support from Merck & Co, Inc, for this activity. JC has received personal fees from GlaxoSmithKline and Merck & Co, Inc, and grant support from Abbott, Becton Dickinson, Gen-Probe, Hologic, Qiagen, and Roche. SMG has received institutional grants for HPV studies from Merck & Co, Inc, GlaxoSmithKline, CSL, and Commonwealth Department of Health in Australia; received scientific advisory board support from Merck & Co, Inc; and received speaking fees from Merck & Co, Inc, and Sanofi Pasteur MSD. SKK has received scientific advisory board fees from Merck & Co, Inc, Sanofi Pasteur MSD, and BD. Unrestricted research grants have been obtained through her affiliating institute from Merck & Co, Inc. OMB is an employee of, owns stock, and has received stock options from Merck & Co, Inc. RH is a former employee and stock owner of Merck & Co, Inc. EM is an employee of Merck & Co, Inc, and has received stock options from Merck & Co, Inc. MR is an employee of, owns stock, and has received stock options from Merck & Co, Inc. CCR is a former employee and stock owner of Merck & Co, Inc. CS is an employee of Merck & Co, Inc, and might own stock or stock options. AL is an employee of, owns stock, and has received stock options from Merck & Co, Inc. DB and ALH have no competing interests.

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