Immunogenicity and safety of a new quadrivalent HPV vaccine in girls and boys aged 9–14 years versus an established quadrivalent HPV vaccine in women aged 15–26 years in India: a randomised, active-controlled, multicentre, phase 2/3 trial

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Summary

Background To meet global cervical cancer elimination efforts, a wider range of affordable and accessible vaccines against human papillomavirus (HPV) are needed. We aimed to evaluate the immunogenicity and safety of a quadrivalent HPV vaccine (targeting HPV types 6, 11, 16, and 18), developed and manufactured by the Serum Institute of India (SIIPL). Here we report outcomes in the 9–14 years cohort.

Methods This randomised, active-controlled, phase 2/3 trial was conducted at 12 tertiary care hospitals across India. Healthy participants aged 9–14 years or 15–26 years with no history of HPV vaccination were eligible for enrolment. Female participants were randomly assigned (1:1) with an interactive web response system, by use of a central computer-generated schedule and block randomisation (block sizes of 2, 4, 6, and 8), to receive the SIIPL quadrivalent HPV vaccine (Cervavac; SIIPL, Pune, India) or the comparator quadrivalent HPV vaccine (Gardasil; Merck Sharp & Dohme, Harleem, the Netherlands). Participants, investigators, laboratory technicians, and sponsors were masked to treatment allocation of female participants. Male participants were given the SIIPL quadrivalent HPV vaccine in an open-label manner. Study vaccines were administered intramuscularly with a two-dose schedule (at day 0 and 6 months) in the cohort aged 9–14 years, and with a three-dose schedule (at day 0, month 2, and month 6) in the cohort aged 15–26-years. Immunogenicity was assessed 30 days after the last dose by use of multiplexed ELISA. The primary outcome was the non-inferiority of immune response in terms of the geometric mean titre (GMT) of antibodies against HPV types 6, 11, 16, and 18 generated by the SIIPL quadrivalent HPV vaccine in girls and boys (aged 9–14 years) compared with the GMT generated by the comparator quadrivalent HPV vaccine in women aged 15–26 years at month 7 in the modified per-protocol population (ie, all participants who received all doses of study vaccines per assigned treatment group and had both day 0 and 1-month immunogenicity measurements after the last dose following protocol-defined window periods with no major protocol deviations). Non-inferiority was established if the lower bound of the 98·75% CI of the GMT ratio was 0·67 or higher. The co-primary outcome of occurrence of solicited adverse events (within 7 days of each dose) and unsolicited adverse events (up to 30 days after the last dose) was assessed in all participants who were enrolled and received at least one dose of study vaccine. The trial is registered with the Clinical Trials Registry – India (CTRI/2018/06/014601), and long-term follow-up is ongoing.

Findings Between Sept 20, 2018, and Feb 9, 2021, 2341 individuals were screened, of whom 2307 eligible individuals were enrolled and vaccinated: 1107 (738 girls and 369 boys) in the cohort aged 9–14 years and 1200 (819 women and 381 men) in the cohort aged 15–26 years. No race or ethnicity data were collected. 350 girls and 349 boys in the SIIPL quadrivalent HPV vaccine group and 338 women in the comparator vaccine group were included in the modified per-protocol population for the primary endpoint analysis. The median follow-up for the analyses was 221 days (IQR 215–231) for girls and 222 days (217–230) for boys in the SIIPL quadrivalent HPV vaccine group, 223 days (216–232) for girls in the comparator vaccine group, and 222 days (216–230) for women in the comparator vaccine group. GMT ratios were non-inferior in girls and boys receiving the SIIPL quadrivalent HPV vaccine compared with women receiving the comparator vaccine: GMT ratios for girls were 1·97 (98·75% CI 1·67–2·32) for HPV type 6, 1·63 (1·38–1·91) for HPV type 11, 1·90 (1·60–2·25) for HPV type 16, and 2·16 (1·79–2·61) for HPV type 18. For boys the GMT ratios were 1·86 (1·57–2·21) for HPV type 6, 1·46 (1·23–1·73) for HPV type 11, 1·62 (1·36–1·94) for HPV type 16, and 1·80 (1·48–2·18) for HPV type 18. The safety population comprised all 1107 participants (369 girls and 369 boys in the SIIPL quadrivalent HPV vaccine group, and 369 girls in the comparator group). Solicited adverse events occurred in 176 (48%) of 369 girls and 124 (34%) of 369 boys in the SIIPL vaccine group and 179 (49%) of 369 girls in the comparator vaccine group. No grade 3–4 solicited adverse events occurred within 7 days of each dose.

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Unsolicited adverse events occurred in 143 (39%) girls and 147 (40%) boys in the SIIPL vaccine group, and 143 (39%) girls in the comparator vaccine group. The most common grade 3 unsolicited adverse event was dengue fever, in one (<1%) girl in the SIIPL vaccine group and three (1%) girls in the comparator group. There were no grade 4 or 5 adverse events. Serious adverse events occurred in three (1%) girls and three (1%) boys in the SIIPL vaccine group, and five (1%) girls in the comparator vaccine group. No vaccine-related serious adverse events were reported. There were no treatment-related deaths.

Interpretation **We observed a non-inferior immune response with the SIIPL quadrivalent HPV vaccine in girls and boys aged 9–14 years and an acceptable safety profile compared with the comparator vaccine. These findings support extrapolation of efficacy from the comparator vaccine to the SIIPL quadrivalent HPV vaccine in the younger population. The availability of the SIIPL quadrivalent HPV vaccine could help meet the global demand for HPV vaccines, and boost coverage for both girls and boys globally.**

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Introduction

Cervical cancer is the fourth leading cause of death due to cancer in women globally, accounting for 342 000 deaths and 604 000 new cases worldwide in 2020, and predominantly affecting women in low-income and middle-income countries (LMICs).[1] The disease burden associated with human papillomavirus (HPV) is also increasing in male populations, especially in high-income countries.[2] HPV is a major cause of cervical cancer, with 12 HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) identified as oncogenic. Among these, HPV types 16 and 18 are responsible for approximately 70% of all cervical cancer cases globally and are considered to be the most oncogenic.[3,4] Moreover, these types are associated with nearly all squamous cell carcinomas of the anus, and as well as cancers of the vagina (78%), vulva (15–48%, depending on age), oropharynx (13–60%, depending on region), and penis (53%).[3,5] HPV types 6 and 11 are responsible for about 90% of anogenital warts and recurrent respiratory papillomatosis.[5]

HPV virus-like particle (VLP) vaccines confer protection arbitrated by polyclonal neutralising antibodies generated against L1, the major viral coat protein of the above-mentioned four HPV types. Vaccination provides a much stronger serological response than that generated following natural infection. This might be due to a channelised targeting of lymph node cells caused by vaccines, adjuvants included in the vaccines to enhance immunological responses, and the high antigen dose used in vaccines. Long-lived plasma cells incessantly produce IgG antibodies, which are

Research in context

Evidence before this study

We searched PubMed on July, 2017, for published research materials and articles, with no language or date restrictions, using the search terms "human papilloma virus", "vaccine", and "clinical trial". At the time of the search, there were no peer-reviewed randomised controlled trials available on the quadrivalent human papillomavirus (HPV) vaccine produced by the Serum Institute of India (SIIPL). Two vaccines licensed globally were available in India at that time; a quadrivalent vaccine (Gardasil) against HPV types 6, 11, 16, and 18, and a bivalent vaccine (Cervarix) against HPV types 16 and 18.

Added value of this study

This is the first report of the SIIPL quadrivalent HPV vaccine, evaluated as a two-dose schedule in girls and boys aged 9–14 years in India. In this phase 2/3 trial, the SIIPL quadrivalent HPV vaccine was found to be safe and immunogenic, and was non-inferior to an established quadrivalent HPV vaccine (Gardasil). Inclusion of boys is one of the major strength of this study, as they are at risk of many HPV-associated cancers including anal cancer, penile cancer, and HPV-related head and neck cancer, as well as genital warts. Furthermore, HPV vaccination in boys could facilitate the rapid reduction in the prevalence of diseases caused by HPV.

Implications of all the available evidence

The efficacy of HPV vaccines is mediated by vaccine-induced antibodies and HPV immunisation in younger age groups has been recommended on the basis of immunological bridging (ie, the demonstration of similar or higher antibody titres in girls and boys *vs* women, in whom clinical efficacy against HPV-related genital cancers and warts has been established). The present safety and immunogenicity data successfully bridge the SIIPL quadrivalent HPV vaccine to the comparator vaccine, Gardasil, in girls and boys. Although data for the cohort of men and women aged 15–26 years will be published at a later date, the positive results presented here support widespread regulatory approvals and use of the SIIPL quadrivalent HPV vaccine across India and other low-income and middle-income countries.

responsible for the persistence of long-term HPV-specific antibodies. Existing vaccines pre-qualified by WHO to prevent HPV infection include bivalent vaccines (Cervarix[6] and Cecolin[7]) targeting HPV types 16 and 18; a quadrivalent HPV vaccine (Gardasil[8]) vaccine targeting HPV types 6, 11, 16, and 18; and a nonavalent vaccine (Gardasil-9[9]) targeting HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The high cost and restricted availability of these vaccines calls for the development of a new, affordable, and accessible vaccine to meet this demand, especially in LMICs. An adequate and affordable vaccine supply will accelerate cervical cancer elimination efforts globally by facilitating vaccination of both girls and boys at different ages, making vaccination programmes more equitable and resilient.[10]

To respond to this demand, the Serum Institute of India (SIIPL; Pune, India) developed a quadrivalent HPV vaccine (Cervavac) against HPV types 6, 11, 16, and 18, primarily targeting females and males aged 9–26 years. SIIPL conducted a pivotal, partially double-blinded, active-controlled, multicentre, randomised, phase 2/3 trial for licensure of this vaccine. The trial aimed to assess the immunogenicity and safety of SIIPL's quadrivalent HPV vaccine versus an established quadrivalent HPV vaccine (Gardasil). As SIIPL's vaccine and the comparator vaccine contain the same HPV types in similar concentration, the efficacy of the comparator vaccine might be bridged to SIIPL's vaccine by use of an immunobridging approach in accordance with WHO recommendations to assure the quality, safety, and efficacy of recombinant HPV VLP vaccines.[3] Additionally, as per the WHO IARC technical expert group recommendations on primary endpoints for prophylactic HPV vaccine trials, demonstration of equivalent immunogenicity outcomes (seroconversion rates and antibody titres) between a new vaccine formulation and an approved standard-of-care vaccine is a sound basis to claim equivalence of protection against types that are common between the two vaccines.[11] This strategy for licensure was approved by national regulatory authority. We hypothesised that the antibody response to HPV types 6, 11, 16, and 18 at 7 months (1 month after the last dose) among girls and boys aged 9–14 years receiving two doses of the SIIPL quadrivalent HPV vaccine would be non-inferior to the response in women aged 15–26 years receiving three doses of the comparator; and the antibody response to HPV types 6, 11, 16, and 18 at 7 months (1 month after the last dose) among women and men aged 15–26 years receiving three doses of the SIIPL quadrivalent HPV vaccine would be non-inferior to women aged 15–26 years receiving three doses of the comparator vaccine. Here, we report the immunogenicity and safety data of SIIPL quadrivalent HPV vaccine for the cohort of girls and boys aged 9–14 years compared with the women who received the comparator vaccine from the cohort aged 15–26 years.

Methods

Study design and participants

This randomised, active-controlled, multicentre, phase 2/3, trial was conducted in two age-based cohorts, girls and boys aged 9–14 years and women and men aged 15–26 years; each cohort had three treatment groups. The three treatment groups comprised the SIIPL quadrivalent HPV vaccine for females; the SIIPL quadrivalent HPV vaccine for males, and the comparator quadrivalent HPV vaccine for females. Women aged 15–26 years were chosen as the comparator group because the efficacy of the comparator quadrivalent HPV vaccine in this age group has already been established.[12] Participants were recruited from 12 tertiary care hospitals across major cities in India (appendix p 2). Phase 2 of the study included both age-based cohorts in a smaller sample size with ten sites taking part in phase 2, and was followed by further recruitment of larger number of participants to assess the immunogenicity, safety, and tolerability of the vaccine as a part of phase 3, with recruitment occurring at an additional two sites.

See Online for appendix

A data safety monitoring board (DSMB) was convened to review the safety data of phase 2 participants reported up to day 210. Phase 3 was initiated only after obtaining approval from the DSMB. Participants recruited in phase 2 were included in phase 3.

Eligible participants were healthy individuals aged 9–26 years, non-pregnant females with an intact uterus, and agreed to use effective contraception throughout the 7-month study period, if sexually active. Individuals were excluded if they were already vaccinated against HPV; involved in other clinical studies of investigational agents or studies involving collection of cervical or genital specimens; diagnosed with or being treated for genital warts, cervical pre-cancer or cancer, penile cancer, or anal cancer; if they were trying to become pregnant; and if they were immunocompromised. Participant sex was self-reported. The options provided were male or female. Full eligibility criteria are in the protocol (appendix p 9). All individuals aged 18 years and older signed the informed consent form, and those younger than 18 years signed an assent, with the informed consent form signed by a parent. Audio-visual recording of the consent process was done as per Drugs Controller General of India (DCGI) guidelines. A participant could be removed from the study if eligibility criteria were not met or in the event of incorrect enrolment or randomisation; following a withdrawal request from the participant or their parent, or both; if a female participant reported a pregnancy after the first vaccination and before the last vaccination; at the discretion of the investigator (based on safety or the participant's compliance with the protocol); or if the sponsor decided to suspend or discontinue development of the investigational vaccine or to terminate agreement with the study site. In the event of a participant's withdrawal or early termination, all efforts were made to complete and report observations as thoroughly as possible up to the last available date while

on study. Follow-up on all previously documented adverse events and serious adverse events was done to report the outcome. In case of pregnancy, participants were followed up until the outcome of the pregnancy. A blood sample was collected for immunogenicity assessment before participant withdrawal, if such consent could be obtained from the participant or their parent, or both.

The study was conducted in accordance with approved clinical trial protocols, study-specific manuals, and the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines; and commenced after having attained approvals from the Institutional Ethics Committee (IEC) and the DCGI.

Randomisation and masking

Female participants were randomly assigned (1:1) to either the SIIPL quadrivalent HPV vaccine or the comparator vaccine group, and male participants were enrolled in a non-randomised open-label manner receive the SIIPL quadrivalent HPV vaccine. Boys or men could not receive the comparator since it is not yet licensed for males in India. A central computer-generated randomisation schedule was generated for female participants by use of block randomisation of variable size (block sizes of 2, 4, 6, and 8) by a biostatistician not involved in the analysis of the study data. The contract research organisation integrated the randomisation schedule into the interactive web response system (IWRS). Blinded study assignment was implemented with the IWRS to eliminate any selection bias with respect to any vaccine group. The responsible site investigator or coordinator checked all the eligibility criteria and used the IWRS to receive a randomisation allocation and number. Once allocated, the group a participant was assigned to could not be changed. Participants, investigators, staff performing clinical evaluations, laboratory technicians, other study team members, and the sponsor were masked to participants' treatment assignments. Site personnel who were responsible for preparing and administering study vaccines were unmasked. The unmasked site personnel were not involved in the safety assessment of participants, nor in any other aspect of the study. For male participants, the enrolment list was generated and male participants were enrolled consecutively to the SIIPL quadrivalent HPV vaccine group after meeting eligibility criteria. The safety data (up to day 210 after the first dose) of participants enrolled in phase 2 were analysed with group-level unmasking (ie, data were grouped as group A, B, and C without disclosing the actual vaccine received by each participant) and were presented to the DSMB. This safety report was prepared by an unmasked statistician while the rest of the study team and DSMB members and participants were masked to treatment allocation.

Procedures

Both vaccines were given as 0·5 mL intramuscular injections. The SIIPL quadrivalent HPV vaccine is prepared from the highly purified VLPs of the recombinant major capsid (L1) proteins of HPV types 6, 11, 16, and 18. The L1 proteins are produced by separate fermentations in recombinant *Hansenula polymorpha* (yeast) and self-assembled into VLPs. Each 0·5 mL dose of SIIPL's quadrivalent HPV vaccine contains at least 20 µg of HPV 6 L1 protein, 40 µg of HPV 11 L1 protein, 40 µg of HPV 16 L1 protein, 20 µg of HPV 18 L1 protein, and aluminium hydroxide as an adjuvant (≤1·25 mg).

Each 0·5 mL dose of the comparator quadrivalent HPV vaccine, Gardasil; Merck Sharp & Dohme, Harleem, the Netherlands) contains approximately 20 µg of HPV 6 L1 protein, 40 µg of HPV 11 L1 protein, 40 µg of HPV 16 L1 protein, 20 µg of HPV 18 L1 protein, and approximately 225 µg of aluminium (as amorphous aluminium hydroxyphosphate sulfate adjuvant). The L1 proteins are produced by separate fermentations in recombinant *Saccharomyces cerevisiae* (yeast).

Participants in the cohort aged 9–14 years were vaccinated in a two-dose schedule and those in the cohort aged 15–26 years were vaccinated in a three-dose schedule. After receiving the first dose on day 0, participants in the age 9–14 years cohort received the second dose at 6 months and those in the age 15–26 years cohort received their second and third doses at months 2 and 6. After each dose, all participants were observed for a minimum of 30 min at the study clinic to record any immediate adverse events. Participants were followed up for safety 7 days after vaccination and again at 2 and 4 months for the age 9–14 years cohort and at 4 months for the age 15–26 years cohort. All participants in both cohorts attended a follow-up visit at day 210 (1 month after the last vaccination). Blood samples to test HPV type-specific antibody titres were collected at baseline and at day 210. Due to the COVID-19 pandemic and lockdowns in different parts of the country, some participants could not reach sites for vaccination, as per schedule. In view of this limitation, the study protocol was revised (version 3, dated June 27, 2020; appendix p 9) during phase 3 of the study to extend the window period for second and third dose visits from an additional 14 days to an additional 30 days. Before amendment, for day 210 follow-up the window period was an additional 14 days in phase 2 and an additional 30 days in phase 3. In the amended protocol, this window period for day 210 was extended by 30 days for phase 2 and phase 3 and participants were considered for analysis if they visited within these windows of additional days.

Solicited localised adverse events (pain, erythema, swelling, and pruritis at the injection site), and systemic adverse events (fever, headache, nausea, dizziness, and pain in extremity) were reported for each treatment group for 7 days after each vaccination, as were unsolicited adverse events up to 30 days after the last dose of vaccine (ie, day 210). Participants were given a digital thermometer and a diary with detailed instructions on how to record their daily temperature and the

occurrence of any solicited local adverse events during the 7-day follow-up period after vaccination. Adverse events were captured from the diary during the follow-up visits and severity was assigned with grading scale, predefined in the protocol. Grade 1–4 solicited local and systemic adverse events (except for fever) were derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (version 2.1). All deaths related to an adverse event were classified as grade 5. The grading for fever was derived from the Common Terminology Criteria for Adverse Events (version 4.03). Other adverse events were graded with the functional table provided in DAIDS guidance (version 2.1). Adverse events were classified by the Medical Dictionary for Regulatory Activities (MedDRA; version 22.1) and the concomitant medication and vaccinations were coded as per the WHO Drug Dictionary (September, 2019). All serious adverse events, regardless of relationship, were captured from the time of obtaining informed consent up to the day 210 visit.

Participants recruited in phases 2 and 3 will be followed up for 3 years from the first dose of the vaccine to assess long-term immunogenicity and safety.

Immunogenicity analysis of phase 2 serum samples was done with three different assays: a pseudovirion-based neutralisation assay (PBNA) at the Deutsches Krebsforschungszentrum laboratory (Heidelberg, Germany); and ELISA and a multiplexed ELISA on a Meso Scale Discovery (MSD) platform at the Syngene Bioanalytical Laboratory (Bangalore, India), which is National Accreditation Board for Testing and Calibration Laboratories accredited and Good Laboratory Practice certified. The PBNA assay used in this study has been previously used in another study conducted in India, which showed efficacy of the comparator quadrivalent HPV vaccine against persistent infections with HPV types 16 and 18 when compared with an unvaccinated cohort with a different dose schedule at different timepoints.[13,14] The multiplexed ELISA on MSD platform was used for immunogenicity testing of phase 3 samples because it correlated well with the PBNA (appendix p 6), is a more sensitive and robust assay with high-throughput capacity, and can test more samples in parallel for different HPV types.[15]

Outcomes

The primary outcome was the non-inferiority of immune response in terms of geometric mean titres (GMTs) of IgG antibodies against HPV types 6, 11, 16, and 18 generated by the SIIPL quadrivalent HPV vaccine in girls and boys (aged 9–14 years) compared with those generated by the comparator quadrivalent HPV vaccine in women (aged 15–26 years) at 7 months. The co-primary outcome was the occurrence and intensity of solicited and unsolicited adverse events following two doses of the SIIPL quadrivalent HPV vaccine and the comparator quadrivalent HPV vaccine in the cohort aged 9–14 years. The secondary outcome was non-inferiority of GMTs of antibodies to all four HPV types generated by the SIIPL quadrivalent HPV vaccine in girls and boys aged 9–14 years versus those generated by the comparator vaccine in girls aged 9–14 years at 7 months. The seroconversion rate at 7 months was also evaluated as a secondary outcome. Seroconversion was defined as participants who were seronegative at baseline and seropositive after baseline, at any scheduled visit. Seropositivity was based on cutoff values (HPV 6 0·197 AU/mL; HPV 11 0·152 AU/mL; HPV 16 0·333 IU/mL; HPV 18 0·695 IU/mL) derived with the method developed by the US Centers for Disease Control and Prevention (CDC) for multiplexed MSD assays.[16] The secondary outcome of GMT assessment in girls and boys aged 9–14 years versus women aged 15–26 years at 24 and 36 months will be reported elsewhere once follow-up at 24 and 36 months is completed and immunogenicity and safety results have been analysed, as will outcomes for the cohort aged 15–26 years.

Statistical analysis

Immunogenicity was analysed in the modified per-protocol population as per the amended protocol (version 3, dated June 27, 2020). The modified per-protocol population comprised all participants who received all doses per their assigned vaccination group and had immunogenicity measurements at baseline and 1 month after the last dose, with no major protocol deviations and those who completed dosing and day 210 visits within the allowed window period. Specific criteria for exclusion of participants from the modified per-protocol population are included in statistical analysis plan (SAP; appendix). The modified per-protocol analysis comprised participants who provided blood samples within 210 (and an additional 60) days of the last dose of vaccine. The original per-protocol analysis specified that the blood sample would be collected within 210 (and an additional 30) days. The window period was extended by additional 30 days to accommodate the delay due to restrictions induced by the COVID-19 pandemic. Safety was analysed in all participants who were enrolled and received at least one dose of the study vaccine.

No formal sample size calculation was done for phase 2. A sample size of 600 participants was planned to evaluate safety and immunogenicity: 300 girls and boys aged 9–14 years in the first cohort (100 girls in the SIIPL quadrivalent HPV vaccine group, 100 girls in the comparator vaccine group, and 100 boys in SIIPL quadrivalent HPV vaccine group) and 300 women and men aged 15–26 years in the second cohort (100 women in the SIIPL quadrivalent HPV vaccine group, 100 women in the comparator vaccine group, and 100 men in the SIIPL quadrivalent HPV vaccine group). From the phase 2 immunogenicity analysis, the $\log_{10}$SD observed for the ELISA-MSD assay was 0·48. However, for the calculation of the total sample size for phase 2/3,

the log_{10}SD was assumed to be 0·5. With the assumed GMT ratio of 1 and a non-inferiority margin of 0·67, the final sample size for the phase 2/3 study was estimated to be 323 evaluable participants per treatment group. The one-sided significance level (one-sided α) was adjusted for four comparisons as one-sided α/4=0·625%. The estimated sample size had 90% overall power for all four HPV types of each treatment group comparison. Assuming an approximate 10% dropout rate, 366 individuals were required to be randomly assigned to each group. Thus, the total sample size required was 2196 for six study groups, which included the 600 participants enrolled in phase 2.

Immunogenicity data obtained at 1 month after last dose of all 600 participants enrolled in phase 2 were analysed in a blinded manner to compare ELISA and ELISA-MSD with PBNA. To assess the association of ELISA and ELISA-MSD with PBNA, correlation coefficients of immunogenicity data were evaluated by calculating Pearson's correlation coefficient. Log10-transformed IgG antibody titres of each assay were used to determine the correlation coefficient.

All girls and boys enrolled in both phase 2 and 3 were included in the primary immunogenicity and safety analysis. In view of the then-prevailing situation due to the COVID-19 pandemic and nationwide lockdown from March 25, 2020, to May 31, 2020, some participants were unable to receive all doses within the allowable time window period and were therefore unlikely to be included in the per-protocol population. To bridge this gap and maintain the power of study, the protocol was amended and approval from the DCGI was obtained, according to which it was decided to enrol additional participants during phase 3. The additional number was not prespecified; however, we enrolled 114 additional participants to maintain a power of 90% for the analysis.

For primary immunogenicity endpoints, GMT was calculated along with corresponding two-sided 98·75% CIs. For secondary immunogenicity endpoints, GMT was calculated along with the corresponding two-sided 95% CIs for each treatment group, by taking the anti-log of the corresponding log10-transformed means. Non-inferiority was shown if primary comparisons for each HPV type established the lower bound of the two-sided 98·75% CI of the GMT ratio for the comparison to be 0·67 or higher. The non-inferiority criteria for secondary immunogenicity endpoints was 0·67 or higher. However, in a prespecified analysis the results were also interpreted with a non-inferiority margin of 0·5, considering the latest evidence showing that even a single dose of a HPV vaccine appears to be as efficacious as two or three doses, despite inducing lower antibody titres,[17] and in accordance with WHO recommendations for clinical evaluation of HPV vaccines, which state that under specific circumstances national regulatory authorities can consider allowing a lower bound of 0·5 for comparison of non-inferiority.[3] One-sided 99·375% CIs or 97·5% CIs (two-sided 98·75% or 95% CIs) for the ratios of GMT were constructed by assuming normal distribution for log10 (titres). The log10 values were used to calculate confidence intervals from mixed-model analysis of covariance (ANCOVA) with maximum likelihood estimation (MLE) through the MIXED procedure. The baseline data were considered as covariates in the mixed model analysis to find adjusted confidence intervals during statistical analysis and not considered during sample size calculation to keep the analysis simple but powered. The modified per-protocol population served as the primary analysis population. Participants who were seropositive for any particular HPV type at baseline were not excluded from the modified per-protocol population. For the seroconversion rate analysis, the modified per-protocol population was used excluding participants who were seropositive at baseline for each HPV type. For seroconversion rates, 95% CIs were calculated with the Clopper-Pearson method. The adverse event data for boys and girls receiving the SIIPL quadrivalent HPV vaccine and for girls receiving the comparator vaccine are presented here; data for men and women will be presented elsewhere. For solicited adverse events, two-sided 95% exact CIs for each adverse event were calculated with the Clopper-Pearson Exact method; for the difference between proportions of the SIIPL quadrivalent HPV vaccine and the comparator vaccine, two-sided 95% exact CIs were calculated with the Newcombe method. For comparison, p values were estimated with Fisher's exact test; p values less than 0·05 were considered significant. For unsolicited adverse events, data are presented with descriptive statistics only. All statistical analyses were done in SAS (version 9.4).

The study is registered with the Clinical Trial Registry India (CTRI/2018/06/014601).

Role of the funding source

The Biotechnology Industry Research Assistance Council (BIRAC), Government of India, had no role in study design, data collection, data analysis, data interpretation, or writing of the report. SIIPL was involved in study design, data interpretation, and writing of the report, but was not involved in data collection and data analysis.

Results

Between Sept 20, 2018, and Feb 9, 2021, 1122 girls and boys aged 9–14 years were screened, of whom 1108 eligible individuals were enrolled (figure). One individual withdrew consent before vaccination. During the same period, 1219 women and men aged 15–26 years were screened, of whom 1202 were eligible and enrolled. In phase 2, 300 girls and boys aged 9–14 years were enrolled between Sept 20, 2018, and Feb 16, 2019, and vaccinated (100 girls and 100 boys received the SIIPL quadrivalent HPV vaccine and 100 girls received the comparator vaccine). After analysis of group-level unblinded safety

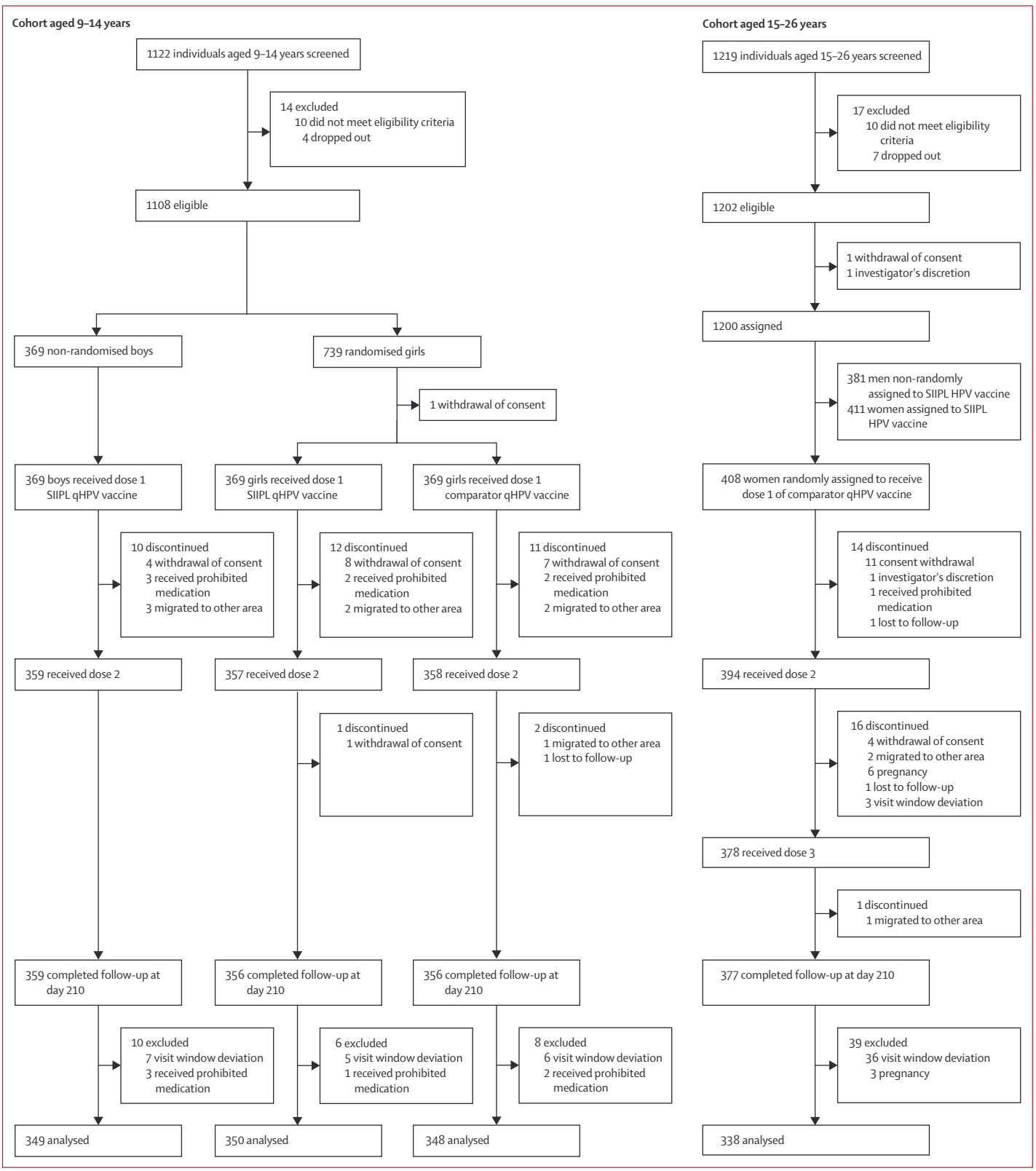

Figure: **Trial profile**
SIIPL=Serum Institute of India. HPV=human papillomavirus.

data from phase 2 participants (appendix p 5), the DSMB did not observe any safety concerns and approved recruitment of the participants in phase 3. In phase 3, 538 girls were randomly assigned; 269 to the SIIPL quadrivalent HPV vaccine and 269 to the comparator vaccine. Additionally, 269 boys were assigned to receive the SIIPL quadrivalent HPV vaccine. 308 women (aged 15–26 years) received three doses of the comparator vaccine in phase 3.

Thus, in phase 2 and 3, of the 1108 enrolled and randomly assigned participants, 369 boys and 369 girls received the first dose of the SIIPL quadrivalent HPV vaccine and 369 received the first dose of the comparator vaccine. The second dose was received by 1074 participants and the day 210 visit was completed by 1071. The median follow-up for the analyses was 221 days (IQR 215–231) in girls assigned to receive the SIIPL quadrivalent HPV vaccine, 222 days (217–230) in boys assigned to receive the SIIPL quadrivalent HPV vaccine, 223 days (216–232) in girls assigned to receive the comparator vaccine, and 222 days (216–230) in women assigned to receive the comparator vaccine. The data cutoff date was Nov 25, 2021.

Of 1071 participants, 1047 (350 girls and 349 boys in the SIIPL vaccine group, and 348 girls who received the comparator vaccine) constituted the modified per-protocol population. 24 participants were excluded from the analysis, with reasons for exclusion including visit window deviations (n=18) and receipt of prohibited medications (n=6). Additionally, 338 women aged 15–26 years in the comparator vaccine group were included in the modified per-protocol population and the main reason for exclusion was visit window deviation (figure).

The median age of participants in the aged 9–14 years cohort was 12·0 years (IQR 10·6–13·3). Baseline demographic data are summarised in table 1 and the appendix (p 4). No data on race or ethnicity, socioeconomic status, or education were collected. 36 (3%) of 1107 participants reported a medical history finding at screening in the aged 9–14 years cohort (nine [2%] of 369 girls assigned to the SIIPL vaccine group; 13 [4%] of 369 boys assigned to the SIIPL vaccine group; and 14 [4%] of 369 girls assigned to the comparator vaccine group). No noteworthy differences in demographic characteristics and medical history were observed between treatment groups (appendix p 3).

Per protocol, immunogenicity analysis of phase 2 (600 enrolled participants) was done with three different assay methods: PBNA, ELISA, and multiplex ELISA on MSD platform. Of 581 participants whose immunogenicity data were available at the visit on day 210, 381 female participants (girls and women aged 9–26 years) were included in the analysis and the data were presented to the DSMB in a blinded manner. High

	SIIPL quadrivalent HPV vaccine, girls (n=369)	SIIPL quadrivalent HPV vaccine, boys (n=369)	Comparator quadrivalent HPV vaccine, girls (n=369)
Sex			
Male	NA	369 (100%)	NA
Female	369 (100%)	NA	369 (100%)
Age, years	12·1 (10·5–13·4)	12·0 (10·6–13·4)	12·1 (10·7–13·2)
Bodyweight, kg	37·1 (29·2–43·8)	35·0 (30·0–43·3)	37·5 (30·2–45·0)
Height, cm	146 (137–153)	144 (137–155)	146 (139–153)

Data are n, n (%) or median (IQR). SIIPL=Serum Institute of India. HPV=human papillomavirus. NA=not applicable.

Table 1: **Demographics and baseline characteristics of the cohort aged 9–14 years**

	Cohort aged 9–14 years receiving two doses of SIIPL quadrivalent HPV vaccine			Women aged 15–26 years receiving three doses of comparator quadrivalent HPV vaccine			GMT ratio for comparison between SIIPL quadrivalent HPV and comparator quadrivalent HPV vaccines
	n	Pre-vaccination GMT of IgG	LSE for GMT of IgG at 7 months	n	Pre-vaccination GMT of IgG	LSE for GMT of IgG at 7 months	
Girls aged 9–14 years in SIIPL quadrivalent HPV vaccine group							
HPV type 6	350	0·06 (0·05–0·08)	304·17 (270·85–341·58)	338	0·06 (0·05–0·08)	154·59 (137·38–173·97)	1·97 (1·67–2·32)
HPV type 11	350	0·04 (0·03–0·05)	339·13 (302·91–379·69)	338	0·04 (0·03–0·05)	208·66 (186·00–234·08)	1·63 (1·38–1·91)
HPV type 16	350	0·08 (0·06–0·10)	1340·17 (1189·37–1510·09)	338	0·09 (0·07–0·12)	706·17 (625·40–797·38)	1·90 (1·60–2·25)
HPV type 18	350	0·20 (0·16–0·25)	528·08 (462·23–603·30)	338	0·22 (0·18–0·26)	244·50 (213·51–279·99)	2·16 (1·79–2·61)
Boys aged 9–14 years in SIIPL quadrivalent HPV vaccine group							
HPV type 6	349	0·07 (0·06–0·08)	288·13 (255·51–324·91)	338	0·06 (0·05–0·08)	154·80 (137·00–174·90)	1·86 (1·57–2·21)
HPV type 11	349	0·04 (0·03–0·05)	305·01 (270·65–343·72)	338	0·04 (0·03–0·05)	208·85 (184·97–235·81)	1·46 (1·23–1·73)
HPV type 16	349	0·10 (0·08–0·13)	1155·94 (1019·34–1310·86)	338	0·09 (0·07–0·12)	711·93 (626·52–808·98)	1·62 (1·36–1·94)
HPV type 18	349	0·22 (0·18–0·27)	440·71 (385·13–504·31)	338	0·22 (0·18–0·26)	245·40 (213·99–281·43)	1·80 (1·48–2·18)

Data in parentheses are 98·75% CIs. GMT values for HPV types 6 and 11 are expressed in AU/mL and for HPV types 16 and 18 are expressed in IU/mL. SIIPL=Serum Institute of India. HPV=human papillomavirus. n=number of participants contributing to the analysis. GMT=geometric mean titre. LSE=least squares estimation.

Table 2: **Summary of GMT of antibodies to HPV types 6, 11, 16, and 18 at 7 months (1 month after the last dose) in girls and boys aged 9–14 years receiving two doses of SIIPL quadrivalent HPV vaccine and women aged 15–26 years receiving three doses of comparator quadrivalent HPV vaccine, in the modified per-protocol population**

	Girls aged 9–14 years in SIIPL quadrivalent HPV vaccine group			Boys aged 9–14 years in SIIPL quadrivalent HPV vaccine group			Women aged 15–26 years in comparator quadrivalent HPV vaccine group		
	N	n	Seroconversion rate (95% CI)	N	n	Seroconversion rate (95% CI)	N	n	Seroconversion rate (95% CI)
HPV type 6	276	276	100% (98·7–100)	278	278	100% (98·7–100)	270	270	100% (98·6–100)
HPV type 11	275	275	100% (98·7–100)	268	268	100% (98·6–100)	258	258	100% (98·6–100)
HPV type 16	279	279	100% (98·7–100·0)	264	264	100% (98·6–100)	261	261	100% (98·6–100)
HPV type 18	273	273	100% (98·7–100)	274	274	100% (98·7–100)	272	272	100% (98·7–100)

Seroconversion was defined as individuals who were seronegative at baseline and were seropositive post-baseline at any scheduled visit. Seroconversion cutoff for HPV type 6 was 0·197 AU/mL; HPV type 11 was 0·152 AU/mL; HPV type 16 was 0·333 IU/mL; and HPV type 18 was 0·695 IU/mL. SIIPL=Serum Institute of India. HPV=human papillomavirus. N=number of evaluable participants for each HPV type. n=number of participants who achieve seroconversion.

Table 3: **Summary of seroconversion rate for girls and boys aged 9–14 years in the SIIPL quadrivalent HPV vaccine group and women aged 15–26 years in the comparator quadrivalent HPV vaccine group, modified per-protocol population**

GMTs of antibodies were observed at day 210 by PBNA and multiplex ELISA on MSD (appendix pp 6–7). The data were assessed to establish a correlation between the ELISA and multiplex ELISA on MSD platform with PBNA. Both assays—ELISA and ELISA-MSD—showed high correlation (correlation coefficient >0·9) with the PBNA (appendix p 6). The neutralisation titres at day 210 (assessed in phase 2 only) in girls and boys aged 9–14 years receiving two doses of the SIIPL quadrivalent HPV vaccine were high compared with those in women aged 15–26 years receiving three doses of comparator vaccine (appendix pp 7–8).

The primary immunogenicity assessment showed non-inferiority of the SIIPL quadrivalent HPV vaccine in girls (aged 9–14 years) who received two doses compared with women (aged 15–26 years) who received three doses of the comparator vaccine; GMT ratios were 1·97 (98·75% CI 1·67–2·32) for HPV type 6, 1·63 (1·38–1·91) for HPV type 11, 1·90 (1·60–2·25) for HPV type 16, and 2·16 (1·79–2·61) for HPV type 18. GMT ratios with two doses of the SIIPL quadrivalent HPV vaccine were non-inferior to three doses of the comparator vaccine even in boys; GMT ratios were 1·86 (98·75% CI 1·57–2·21) for HPV type 6, 1·46 (1·23–1·73) for HPV type 11, 1·62 (1·36–1·94) for HPV type 16, and 1·80 (1·48–2·18) for HPV type 18 (table 2). The geometric mean fold rise (GMFR) for all four HPV types was more than 1000-fold, indicating a robust immune response. At 7 months (1 month after dose two) 100% seroconversion rates were observed in girls and boys aged 9–14 years receiving the SIIPL quadrivalent HPV vaccine, for all four HPV types (table 3). The secondary immunogenicity assessment also showed non-inferior GMT ratios for IgG antibodies against HPV types 6 and 18 in both girls and boys aged 9–14 years receiving two doses of the SIIPL quadrivalent HPV vaccine, compared with girls aged 9–14 years receiving two doses of comparator quadrivalent HPV vaccine, because the lower bounds of the 95% CIs for the GMT ratios were all higher than 0·67 (table 4). For HPV type 16, the lower bound of the 95% CI for the GMT ratio was higher than 0·67 in girls, but lower than 0·67 in boys. However, a prespecified analysis with a lower non-inferiority margin of 0·5 (as defined prospectively in the SAP) showed that the response was non-inferior to that observed in girls who received the comparator vaccine. For HPV type 11, non-inferiority was not achieved in girls and boys against girls receiving the comparator vaccine with a stringent non-inferiority margin of 0·67, but it was shown when a non-inferiority margin of 0·5 was applied (table 4).

	Cohort aged 9–14 years receiving two doses of SIIPL quadrivalent HPV vaccine		Girls aged 9–14 years receiving two doses of comparator quadrivalent HPV vaccine		GMT ratio for comparison between SIIPL quadrivalent HPV and comparator quadrivalent HPV vaccine
	n	LSE for GMT of IgG	n	LSE for GMT of IgG	
Girls aged 9–14 years in SIIPL quadrivalent HPV vaccine group					
HPV Type 6	350	304·21 (277·39–333·63)	348	321·08 (292·69–352·23)	0·95 (0·83–1·08)
HPV Type 11	350	339·15 (310·66–370·25)	348	490·96 (449·61–536·11)	0·69 (0·61–0·78)
HPV Type 16	350	1334·66 (1208·48–1474·03)	348	1519·74 (1375·66–1678·91)	0·88 (0·76–1·01)
HPV Type 18	350	525·98 (475·00–582·43)	348	417·04 (376·51–461·93)	1·26 (1·09–1·46)
Boys aged 9–14 years in SIIPL quadrivalent HPV vaccine group					
HPV Type 6	349	288·24 (262·00–317·11)	348	321·41 (292·10–353·65)	0·90 (0·78–1·03)
HPV Type 11	349	305·11 (278·06–334·78)	348	491·25 (447·64–539·10)	0·62 (0·54–0·71)
HPV Type 16	349	1154·57 (1040·14–1281·59)	348	1527·27 (1375·69–1695·54)	0·76 (0·65–0·88)
HPV Type 18	349	439·56 (396·36–487·47)	348	417·95 (376·82–463·57)	1·05 (0·91–1·22)

Data in parentheses are 95% CIs. GMT values for HPV types 6 and 11 are expressed in AU/mL and those for HPV types 16 and 18 are expressed in IU/mL. SIIPL=Serum Institute of India. HPV=human papillomavirus. GMT=geometric mean titre. n=Number of participants contributing to the analysis. LSE=least squares estimation.

Table 4: **Summary of GMT of antibodies to HPV types 6, 11, 16 and 18 at 7 months (1 month after the last dose) between cohort aged 9–14 years receiving two doses of SIIPL quadrivalent HPV vaccine and girls aged 9–14 years receiving two doses of comparator quadrivalent HPV vaccine**

At least one solicited adverse event was reported in 176 (49%) of 369 girls in the SIIPL quadrivalent HPV vaccine group and in 179 (48%) of 369 girls in the comparator vaccine group (p=0·88). The frequency of solicited adverse events was significantly lower in boys receiving the SIIPL quadrivalent HPV vaccine (124 [34%] of 369) than in girls receiving comparator quadrivalent HPV vaccine (p<0·0001). Pain at the injection site was

	Girls aged 9–14 years in the SIIPL quadrivalent HPV vaccine group (n=369)	Boys aged 9–14 years in the SIIPL quadrivalent HPV vaccine group (n=369)	Girls aged 9–14 years in the comparator quadrivalent HPV vaccine group (n=369)	Girls in the SIIPL quadrivalent HPV vaccine group *vs* girls in the comparator quadrivalent HPV vaccine group (95% CI; p value*)	Boys in the SIIPL quadrivalent HPV vaccine group *vs* girls in the comparator quadrivalent HPV vaccine group (95% CI; p value*)
Local events					
Pain or tenderness	146 (39·6%; 34·5 to 44·8), 192 events	106 (28·7%; 24·2 to 33·6), 128 events	147 (39·8%; 34·8 to 45·0), 194 events	−0·3 (−7·2 to 6·7; >0·99)	−11·1 (−17·8 to −4·4; 0·0019)
Erythema or redness	7 (1·9%; 0·8 to 3·9), 7 events	7 (1·9%; 0·8 to 3·9), 7 events	5 (1·4%; 0·4 to 3·1), 6 events	0·5 (−3·7 to 4·8; 0·77)	0·5 (−3·7 to 4·8; 0·77)
Induration or swelling	8 (2·2%; 0·9 to 4·2), 9 events	8 (2·2%; 0·9 to 4·2), 9 events	17 (4·6%; 2·7 to 7·3), 18 events	−2·4 (−6·7 to 1·9; 0·10)	−2·4 (−6·7 to 1·9; 0·10)
Pruritus	16 (4·3%; 2·5 to 6·9), 1 event	6 (1·6%; 0·6 to 3·5), 6 events	6 (1·6%; 0·6 to 3·5), 6 events	2·7 (−1·8 to 7·2; 0·049)	0·0 (−4·2 to 4·2; >0·99)
Systemic events					
Nausea	17 (4·6%; 2·7 to 7·3), 1 event	10 (2·7%; 1·3 to 4·9), 11 events	14 (3·8%; 2·1 to 6·3), 15 events	0·8 (−3·7 to 5·3; 0·71)	−1·1 (−5·4 to 3·3; 0·53)
Headache	41 (11·1%; 8·1 to 14·8), 48 events	23 (6·2%; 4·0 to 9·2), 28 events	51 (13·8%; 10·5 to 17·8), 61 events	−2·7 (−7·9 to 2·5; 0·36)	−7·6 (−12·4 to −2·8; 0·0008)
Fever	3 (0·8%; 0·2 to 2·4), 3 events	4 (1·1%; 0·3 to 2·8), 4 events	11 (3·0%; 1·5 to 5·3), 11 events	−2·2 (−6·3 to 2·0; 0·055)	−1·9 (−6·1 to 2·3; 0·11)
Dizziness	15 (4·1%; 2·3 to 6·6), 16 events	3 (0·8%; 0·2 to 2·4), 3 events	15 (4·1%; 2·3 to 6·6), 16 events	0·0 (−4·5 to 4·5; >0·99)	−3·3 (−7·4 to 0·9; 0·0069)
Pain in extremities	44 (11·9%; 8·8 to 15·7), 56 events	21 (5·7%; 3·6 to 8·6), 23 events	34 (9·2%; 6·5 to 12·6), 39 events	2·7 (−2·4 to 7·9; 0·28)	−3·5 (−8·2 to 1·1; 0·092)

Data are n (%; 95% CI), number of events, unless otherwise indicated. No grade 3, 4, or 5 events occurred, so data are only shown for grade 1–2 events. Two-sided 95% exact CIs for each solicited adverse event are also provided with Clopper-Pearson exact method. Two-sided 95% CIs for the difference between two study vaccine groups provided with Newcombe Method. SIIPL=Serum Institute of India. HPV=human papillomavirus. n=number of participants with at least one event (ie, counted only once if the individual reported one or more events). *p values provided with Fisher's exact test.

Table 5: **Summary of grade 1–2 solicited adverse events, safety population**

	Girls aged 9–14 years in the SIIPL quadrivalent HPV vaccine group (n=369)	Boys aged 9–14 years in the SIIPL quadrivalent HPV vaccine group (n=369)	Girls aged 9–14 years in the comparator quadrivalent HPV vaccine group (n=369)
Grade 1–2 events (mild to moderate)			
Infections and infestations			
Upper respiratory tract infection	52 (14%), 63 events	49 (13%), 53 events	51 (14%), 64 events
Grade 3 events (severe)			
General disorders and administration site conditions			
Pyrexia	1 (<1%), 1 event	0	0
Infections and infestations			
Dengue fever	1 (<1%), 1 event	0	3 (1%), 3 events
Typhoid fever	1 (<1%), 1 event	0	1 (<1%), 1 event
Injury, poisoning and procedural complications			
Humerus fracture	0	1 (<1%), 1 event	0
Radius fracture	0	1 (<1%), 1 event	0
Renal and urinary disorders			
Ureterolithiasis	0	1 (<1%), 1 event	0

Data are n (%), number of events. Adverse events reported by 10% or more of individuals at grade 1–2 and all grade 3 events are listed. There were no grade 4 or 5 events. SIIPL=Serum Institute of India. HPV=human papillomavirus. n=number of participants with at least one event (ie, counted only once if the individual reported one or more events).

Table 6: **Summary of unsolicited adverse events, safety population**

the most frequently reported local solicited adverse event following vaccination (table 5). The next most frequently reported local solicited adverse events were swelling at the injection site and pruritus. The most frequently reported solicited systemic adverse events were pain in an extremity and headaches. Pyrexia was the least commonly reported event in both vaccination groups. No grade 3 or 4 solicited adverse events were reported within 7 days of each dose (table 5). All local solicited events and most systemic solicited events were considered to be related to the study vaccine.

Unsolicited adverse events were reported in 143 (39%) of 369 girls and 147 (40%) of 369 boys in the SIIPL quadrivalent HPV vaccine group and 143 (39%) of 369 girls in the comparator vaccine group. Most events were either grade 1 or grade 2, and upper respiratory tract infection was the most frequently reported unsolicited adverse event (table 6). Ten grade 3 unsolicited adverse events were reported, which included an event each of pyrexia, ureterolithiasis, humerus fracture, radius fracture, and events of typhoid fever (reported in two participants), and four events of dengue fever (table 6). No grade 4 or 5 adverse events were reported. Of 713 unsolicited events reported in this cohort, 710 events recovered or resolved without sequelae. 11 serious adverse events were reported up to day 210, in three (1%) girls in the SIIPL quadrivalent HPV vaccine group (one dengue fever, one typhoid fever, one pyrexia), three (1%) boys in the SIIPL quadrivalent HPV vaccine group (one humerus fracture, one radius fracture, one ureterolithiasis), and five [1%] girls in the comparator vaccine group (one COVID-19, three dengue

fever, one typhoid fever). All serious adverse events resulted in hospital admission, and all participants recovered completely. No deaths were reported during the 7-month follow-up period. None of the serious adverse events led to discontinuation from the trial, and no serious adverse event was considered to be related to the vaccine by the investigators and sponsor.

Discussion

A two-dose regimen of the SIIPL quadrivalent HPV vaccine was shown to be safe and highly immunogenic in girls and boys aged 9–14 years, with immunogenic non-inferiority shown in comparison with women aged 15–26 years receiving the comparator vaccine. There is no established correlate of protection for HPV vaccines, hence the immunobridging approach was followed in our study, which is in alignment with WHO recommendations for HPV VLP vaccines and guidance published by the WHO IARC expert group.[3,11] A similar pathway was followed for licensure of the comparator quadrivalent HPV vaccine in pre-adolescent and adolescent girls[3] and for the nonavalent HPV vaccine in girls and boys aged 9–15 years.[3,18,19]

The antibody response to all four HPV types was measured with a multiplex VLP-based immunoassay on MSD platform. Although PBNA is considered the gold standard because of its ability to detect neutralising potential, and has been used in studies assessing virological endpoints,[13,14] the assay is labour-intensive and time-consuming. Hence, a VLP-based assay, such as the MSD assay, that is technically simple and has high throughput, can be acceptable, provided that strong correlation is established with the gold standard.[20] Consistent with WHO guidance, we showed a strong correlation of the MSD assay with PBNA in phase 2 and then further used the MSD assay for the immunogenicity assessment in phase 3. In another study evaluating multiple serological assays, a high correlation of the MSD assay was observed with the simplex SEAP-NA assay that measures direct neutralisation potential.[15] Thus, with a well validated assay we showed immunogenic non-inferiority of the SIIPL quadrivalent HPV two-dose schedule in girls and boys aged 9–14 years for HPV types 6, 11, 16, and 18, versus women receiving three doses of the comparator vaccine, which has established efficacy.[12] Age is an important determinant of antibody responses following HPV vaccination, with young boys and girls having significantly higher antibody GMTs than young women.[3] However, for sample size estimation we assumed the GMT ratio between SIIPL quadrivalent HPV vaccine and the comparator quadrivalent HPV vaccine to be 1, since no previous data were available on the immunity induced by the SIIPL quadrivalent HPV vaccine.

The results of our study are consistent with other studies immunobridging pre-adolescent and adolescent girls and boys to young adult women with a vaccine that has established efficacy against cervical cancer and other HPV-associated diseases.[18,19,21,22]

Dobson and colleagues[18] conducted a phase 3, randomised, multicentre, post-licensure, age-stratified, non-inferiority immunogenicity trial and found that the immune response of two doses of a comparator quadrivalent HPV vaccine in girls aged 9–13 years was non-inferior to that observed with three doses in women aged 16–26 years. In an immunobridging study by Iversen and colleagues,[19] the immune responses in girls and boys aged 9–15 years who received two doses of a nonavalent HPV vaccine were non-inferior to those observed in women aged 16–26 years who received three doses. Another study conducted to bridge efficacy findings from women aged 16–23 years to girls and boys aged 10–15 years found that the immune response in younger age groups was non-inferior to that in older age groups in which efficacy was shown.[21]

A similar immunobridging study was the basis for licensure of the bivalent HPV vaccine Cecolin (Xiamen Innovax Biotech, Xiamen, China), administered with two doses in young adolescent girls aged 9–14 years.[22] We showed immunogenic non-inferiority for primary endpoints with a 0·67 non-inferiority margin but we also assessed results with a 0·5 non-inferiority margin since this criterion is accepted by regulatory authorities worldwide for HPV vaccines.[18,19,21,22] Consistent with the outcomes of the above-mentioned studies, two doses of the SIIPL quadrivalent HPV vaccine generated nearly double the antibody response against HPV types 16 and 18 in adolescent girls and boys compared with the response generated with three doses of the comparator quadrivalent HPV vaccine in young adult women, and non-inferiority against HPV types 6 and 11 was also shown.

Administration of the SIIPL quadrivalent HPV vaccine was well tolerated in girls and boys aged 9–14 years. The adverse events observed in our study were well within the acceptable limits, as reported in the published literature,[21] with no anaphylactic reactions reported.[5] The most frequently reported local solicited adverse event was injection-site pain and the most frequently reported systemic solicited adverse events were headache and pain in an extremity. Most local and systemic solicited events were grade 1 or grade 2 in severity and resolved without any sequelae. Overall, no substantial difference was observed in the solicited adverse events profile between the SIIPL quadrivalent HPV vaccine group and comparator quadrivalent HPV vaccine group. No safety concerns were observed during the 7-month follow-up period. These safety findings are consistent with the previous studies of the comparator quadrivalent HPV vaccine and nonavalent HPV vaccines in Indian girls and boys.[23]

Strengths of our study were the inclusion of different age cohorts in equal proportions and the use of a validated multiplex immunogenicity assay. Enrolment of boys is another key strength because boys and men

remain at risk of anal cancer, penile cancer, HPV-related head or neck cancer, and genital warts. A gender-neutral approach to HPV vaccination is important to maximise effectiveness in the susceptible population and prevent transmission through herd immunity.

Limitations of the study design include the fact that we could not compare boys receiving the SIIPL quadrivalent HPV vaccine with the male population receiving the comparator quadrivalent HPV vaccine because the comparator quadrivalent HPV vaccine is not licenced in India for boys and men. This is a limitation with respect to interpretation of the final safety results; however, the safety results reported here are in line with the published literature.[23] Moreover, the non-inferiority margin of 0·67 was not achieved for the secondary immunogenicity endpoint for HPV type 11 for girls and boys and for HPV type 16 for boys. However, for these types, for secondary comparisons, an acceptable pre-specified non-inferiority margin of 0·5 was shown.

On the basis of the results of this study, the National Regulatory Authority of India has approved the vaccine in girls and boys aged 9–14 years.[24] Additionally, the National Technical Advisory Group on Immunization in India has recommended the SIIPL quadrivalent HPV vaccine in its National Immunization Programme for girls aged 9–14 years. This recommendation will have far-reaching consequences on the cervical cancer elimination drive in India and globally.

Despite bearing a fifth of the global burden of cervical cancer, India has yet to introduce an HPV vaccine into its national immunisation programme, and one of the main reasons cited for this is the high procurement cost of vaccines.[25] In India, 14 in 1000 girls is likely to develop cervical cancer at some point in their lifetime without HPV vaccination. Modelling studies have shown that vaccinating girls in India at age 10 years could reduce the lifetime risk of cervical cancer in future vaccinated birth cohorts by up to 79%, thus preventing nearly 1 million future cervical cancer cases in girls who are currently aged 10 years or younger.[26] With an affordable vaccine and assured supply, India should target girls aged 9–14 years, as recommended by WHO, to have the greatest impact in saving lives from cervical cancer. Accordingly, India's Ministry of Health has initiated preparations for introducing the vaccine in seven states in the first phase, ultimately aiming to vaccinate 68 million girls over the next 2 years.[27] Initiation of such a long-awaited nationwide HPV vaccination campaign in India will substantially boost global cervical cancer elimination efforts. Considering the proposed likely cost of the vaccine, and the net health and financial impact of achieving 90% coverage in all Gavi-eligible countries at current Gavi-negotiated prices, SIIPL's quadrivalent HPV vaccine is likely to be beneficial for many other LMICs.[28,29] With an affordable vaccine that can mitigate the current supply crisis globally, nearly half of LMICs that are yet to introduce an HPV vaccine into their nationwide campaigns will be able to do so, and the rest could increase the catch-up age for vaccination or expand their vaccination programmes to include boys, or carry out a combination of both approaches, thus aiding global efforts targeted towards elimination of cervical cancer and other diseases preventable by this vaccine.

Contributors

HS, SPa, PP, and SS were responsible for the conception, design, conduct, and monitoring of the study, as well as analysis and interpretation of the data. NB, SJ, SPi, AK, LB, AT, VS, SL, RU, VK, RM, AR, AP, URP, and DB were responsible for the on-site conduct of the study at their respective sites; participated in monitoring, supervision, acquisition, and interpretation of the data; and contributed to the provision of clinical services at the study sites. SG and VD were responsible for the overall supervision of immunogenicity analyses. RS, PB, and RM were involved in analysis and interpretation of the data. HR and US produced the vaccine candidate and were involved in project administration. The original manuscript draft was written by SD, HS, SPa, PP, and SS, and all authors contributed to editing of the manuscript and approving the final draft. SPa, PP, SS, and NB directly accessed and verified the underlying study data. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

HS, SPa, PP, SS, SD, HR, VD, SG, and US are employees of SIIPL. SJ received funding support from SIIPL for research projects including the current study and cervical cancer prevention programme. All other authors declare no competing interests.

Data sharing

Data collected for the study, including de-identified individual participant data and a data dictionary defining each field in the set, will be made available to other researchers on request. Data may be requested by contacting the corresponding author of the study. These data will be shared upon approval of analysis proposals and if signed data-access agreements are in place. The anonymised study protocol and statistical analysis plan are provided in the appendix.

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