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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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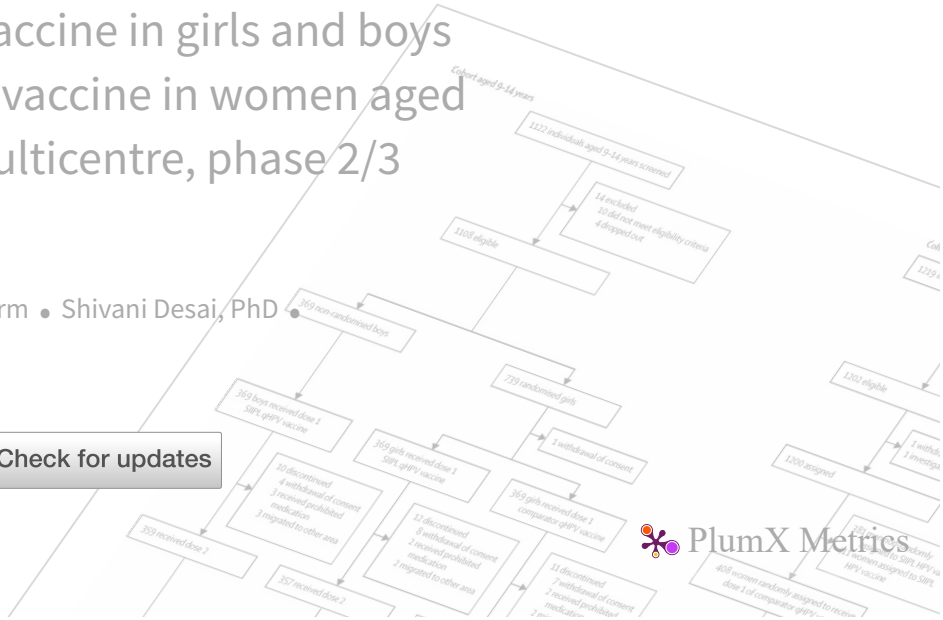

Summary

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. 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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