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Can a single dose of human papillomavirus (HPV) vaccine prevent cervical cancer? Early findings from an indian study

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ABSTRACT

Background: Human papillomavirus (HPV) vaccination is a major strategy for preventing cervical and other ano-genital cancers. Worldwide HPV vaccination introduction and coverage will be facilitated if a single dose of vaccine is as effective as two or three doses or demonstrates significant protective effect compared to 'no vaccination'.

Methods: In a multi-centre cluster randomized trial of two vs three doses of quadrivalent HPV vaccination (GARDASIL©) in India, suspension of the vaccination due to events unrelated to the study led to per protocol and partial vaccination of unmarried 10–18 year old girls leading to four study groups, two by design and two by default. They were followed up for the primary outcomes of immunogenicity in terms of L1 genotype-specific binding antibody titres, neutralising antibody titres, and antibody avidity for the vaccine-targeted HPV types and HPV infections. Analysis was per actual number of vaccine doses received. This study is registered with ISRCTN, number ISRCTN98283094; and with ClinicalTrials.gov, number NCT00923702.

Findings: Of the 17,729 vaccinated girls, 4348 (25%) received three doses on days 1, 60, 180 or later, 4979 (28%) received two doses on days 1 and 180 or later, 3452 (19%) received two doses on days 1 and 60, and 4950 (28%) received one dose. One dose recipients demonstrated a robust and sustained immune response against HPV 16 and 18, albeit inferior to that of 3- or 2-doses and the antibody levels were stable over a 4 year period. The frequencies of cumulative incident and persistent HPV 16 and 18 infections up to 7 years of follow-up were similar and uniformly low in all the vaccinated study groups; the frequency of HPV 16 and 18 infections were significantly higher in unvaccinated age-matched control women than among vaccine recipients. The frequency of vaccine non-targeted HPV types was similar in the vaccinated groups but higher in the unvaccinated control women.

Conclusion: Our results indicate that a single dose of quadrivalent HPV vaccine is immunogenic and provides lasting protection against HPV 16 and 18 infections similar to the three- and two-dose

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vaccine schedules, although the study suffer from some limitations. Data on long term protection beyond 7 years against HPV infection and cervical precancerous lesions are needed before policy guidelines regarding a single dose can be formulated and implemented. Significant and long-lasting protective effect of a single dose can be a strong argument to introduce one dose of the HPV vaccine in many low income countries where the current standard of care for cervical cancer prevention is 'no intervention'.

1. Introduction

Human papillomavirus (HPV) vaccination is a major public health strategy for preventing cervical cancer by reducing the frequency of HPV infection in the general population. Along with screening, it offers a powerful tool for substantially reducing cervical cancer burden globally. Judicious combination of vaccination and screening might potentially eliminate cervical cancer in vaccinated populations. The vaccine is highly efficacious against the high grade precursors of vulvar, vagina and anal cancers in females, suggesting a comprehensive protection against the female anogenital tract malignancies [1].

Nearly 70–80% of cervical cancers are attributed to HPV 16 and 18 in different regions of the world [2,3]. Currently, three HPV vaccines targeted to prevent persistent genital tract infections with HPV 16 and HPV 18 are commercially available. These are a bivalent vaccine (Cervarix™) targeting HPV types 16 and 18, a quadrivalent vaccine (Gardasil™) targeting HPV 16 and 18 and HPV 6 and 11 (which cause genital warts) and a 9-valent HPV vaccine (Gardasil 9™) targeting HPV types 31, 33, 45, 52 and 58 in addition to HPV types 6, 11, 16 and 18. These vaccines were initially evaluated in large randomized clinical trials and licensed in three-dose regimens given over a 6 month period. The currently recommended HPV vaccine dose schedules include two doses over 6–12 months for persons <15 years old and three doses over 6 months for those aged 15 years or more or those immunocompromised [4,5]. The World Health Organization (WHO) recommends a two-dose schedule for <15 year old girls based on the fact that the antibody responses (geometric mean titres, GMTs) following two doses of HPV vaccines administered at least 6 months apart to adolescents aged 9–14 years were non-inferior to three doses among 16–26 year old women in whom the efficacy of the vaccine was established [5]. Currently HPV vaccination has been introduced as part of national immunization program in ≥70 countries and several countries have now reduced the dosage recommendations to two-doses over a 6–12 month period for 9–14 year old girls. A post hoc analysis in the context of the Costa Rica Vaccine Trial (CVT) [6–8] and PATRICIA Trial [8] reported robust and sustainable antibody responses for 4 years following one dose of bivalent HPV vaccine, although antibody levels were lower than that following two or three doses over a 6 month period and similar HPV 16 and 18 infection frequency irrespective of the number of doses received. Recently we reported consistent results of immune response over a 36 month period and similar frequency of incident and persistent infection with vaccine targeted HPV types following the administration of one, two or three doses of quadrivalent HPV vaccine in our multi-centre observational study in India [9]. At the time of writing, published data in terms of immunogenicity and frequency of incident and persistent vaccine targeted HPV types extends up to four years only. In this report we present further results from our evaluation of the antibody response over a 48 month period and frequency of HPV infection in the period up to 7 years following one-dose of quadrivalent vaccine.

2. Materials and methods

The study design and methods have been described previously [9]. Ten national institutions in India in collaboration with the International Agency for Research on Cancer (IARC), Lyon, France, initiated a multi-centre cluster randomised study in India in September 2009 to evaluate the comparative efficacy of two- versus three-doses of quadrivalent HPV vaccine (Gardasil™) in preventing persistent HPV infection and cervical neoplasia [9]. The ethical review committees of the participating national institutions in India and IARC as well as the Health Ministry Screening Committee (HMSC) of Government of India approved the study. Written informed consent was obtained from one of the parents, or legal guardian, along with the assent of the participating girl. At follow-up, a fresh consent was obtained from the girls when they completed 18 years of age. A data safety monitoring board (DSMB) was constituted to regularly monitor the safety and outcomes of the study. The study is registered with ISRCTN (registration number ISRCTN98283094) and with ClinicalTrials.gov (registration number NCT00923702).

The study planned to recruit 20,000 unmarried girls aged 10–18 years and randomly allocate them to receive either two doses on days 1 and 180 (n = 10,000) or three doses (n = 10,000) on days 1, 60 and 180 of quadrivalent HPV vaccine [9]. Recruitment and vaccination of the eligible girls was initiated in September 2009 and progressed satisfactorily until April 2010, with more than 95% participation of the invited girls, when the Indian authorities suspended further vaccination of subjects in all HPV vaccination trials in India, due to events unrelated to our study. As a consequence of suspension of vaccination in our study, randomization was lost and several girls could not complete their allocated vaccine schedules and received incomplete doses leading to four groups of vaccinated girls. Thus what was planned as a randomised trial of two vs three doses of HPV vaccination ended up as an observational cohort study of four different dose groups, two groups by default and two by design: those vaccinated on days 1, 60 and 180 or more (three-dose group); on days 1 and 180 or more (two-dose group); on days 1 and 60 by default (two-dose/D group); and those who received one dose only by default (one-dose/D group).

As foreseen in the study protocol, the study participants were followed up at regular intervals to monitor and evaluate outcomes such as safety, immunogenicity by measuring antibody levels (both total and neutralizing) and their avidity at different time points over a 48 month period from the beginning of vaccination, frequency of incident infection and persistence of both the vaccine-included HPV types (HPV 16 and 18) and other HPV types.

During the follow up of the participants, details regarding marriage, pregnancy, antenatal events, delivery, perinatal events, any other medically significant event in the intervening period as well as the biological samples such as blood and cervical cells were collected according to protocol.

To assess sero-conversion, immunogenicity, antibody levels and durability of the immune response, blood samples were obtained by nurses during the vaccination session at a clinic or during

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