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Evidence for single-dose protection by the bivalent HPV vaccine—Review of the Costa Rica HPV vaccine trial and future research studies

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ABSTRACT

The Costa Rica Vaccine Trial (CVT), a phase III randomized clinical trial, provided the initial data that one dose of the HPV vaccine could provide durable protection against HPV infection. Although the study design was to administer all participants three doses of HPV or control vaccine, 20% of women did not receive the three-dose regimens, mostly due to involuntary reasons unrelated to vaccination. In 2011, we reported that a single dose of the bivalent HPV vaccine could be as efficacious as three doses of the vaccine using the endpoint of persistent HPV infection accumulated over the first four years of the trial; findings independently confirmed in the GSK-sponsored PATRICIA trial. Antibody levels after one dose, although lower than levels elicited by three doses, were 9-times higher than levels elicited by natural infection. Importantly, levels remained essentially constant over at least seven years, suggesting that the observed protection provided by a single dose might be durable. Much work has been done to assure these non-randomized findings are valid. Yet, the group of recipients who received one dose of the bivalent HPV vaccine in the CVT and PATRICIA trials was small and not randomly selected nor blinded to the number of doses received. The next phase of research is to conduct a formal randomized, controlled trial to evaluate the protection afforded by a single dose of HPV vaccine. Complementary studies are in progress to bridge our findings to other populations, and to further document the long-term durability of antibody response following a single dose.

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1. Introduction

Cervical cancer affects more than half a million women annually, with 88% of mortality occurring in low-income nations, where cervical cancer is the third leading cause of cancer mortality in women [1]. If current trends go unabated, the absolute number of cases is expected to increase due to population growth and aging [2], yet, tools to interrupt this trajectory are available. The 70th World Health Assembly endorsed an updated list of evidence-based interventions to be used in the prevention and control of some of the world's deadliest diseases, including cancer [3]. Vaccinating girls aged 9–13 years against human papillomavirus (HPV) and screening women aged 30–49 years for cervical cancer were named as some of the most cost-effective and feasible for implementation [3].

HPV vaccines were licensed and recommended a decade ago [4], in order to reduce individual- and population-prevalence of HPV, a necessary cause of cervical carcinogenesis [5]. These vaccines were initially tested and approved in three-dose regimens [4]. Vaccine uptake has been poor in many world regions [6], likely

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the consequence of high costs and the intensive infrastructure required for administering three doses over a six-month period. In time, serological data provided consistent evidence that two doses administered among adolescents (9–14 year olds) at least six-months apart evoked immunological responses that were non-inferior compared to three doses among the 16-to 26-year-old women who experienced protection in the trials [7,8]. Consequently, the European recommending bodies reduced the dosing recommendation for adolescents to two doses in 2014 [9]; the US made a parallel recommendation in 2016 [10].

The Costa Rica Vaccine Trial (CVT) [11] and the PATRICIA Trial [12], both of which tested the bivalent HPV vaccine, showed similar vaccine efficacy for four years in *post hoc* analyses, even among women who received a single dose of the HPV vaccine. Further, in the CVT stable antibody responses were documented at levels between five- and ninefold higher for HPV 16 and 18 than those induced by natural immunity; yet, they were fourfold lower compared with levels elicited by three doses [13]. We have now extended our evaluation of reduced-dose HPV vaccine protection and immunogenicity to seven years in order to document durability of protection [14], an important determinant of the long-term impact of a vaccination program.

At present, HPV vaccine uptake and cervical cancer screening implementation has been insufficient in most world regions and the expected number of cervical cancers is projected to increase over the coming decades [6]. We hypothesize that one-dose HPV vaccination, if sufficiently efficacious, would make broader vaccination of the neediest populations a reality.

The objective of this manuscript is to summarize the evidence to date for single-dose efficacy of the bivalent HPV vaccine from *post hoc* analysis of the CVT, review the validity of these findings by discussing potential biases, and present our future efforts to additionally address critical questions around single-dose protection afforded by the HPV vaccines.

2. Methods

2.1. Study population

CVT was a publicly funded, four-year, community-based, randomized phase III clinical trial (registered with Clinicaltrials.gov NCT00128661) [15]. From 2004 to 2005, 7466 women were consented and randomized to receive either the AS04-HPV-16/18 vaccine (Cervarix®, GlaxoSmithKline Biologicals, Rixensart, Belgium) or a control hepatitis A vaccine (Havrix®,GlaxoSmithKline Biologicals) in a 1:1 ratio at 0, 1, and 6 months. Participants were followed annually for 4 years, with more frequent follow-up when clinically indicated. Protocols were approved by the Institutional Review Boards (IRB) of the U.S. National Cancer Institute, the Costa Rican INCIENSA (for the CVT) and the National University Review Board (for the Long-term follow-up [LTFU] component), and all participants signed informed consent.

2.2. Study design

At enrollment and follow-up visits, participants provided a serum sample, and for sexually-experienced women, a pelvic exam was performed at which time cervical cells were collected for cytology and HPV DNA testing. At the end of the four-year trial, participants were offered the vaccine they had not received at enrollment (cross-over vaccination) and were invited to stay in a long-term follow-up observational study [16]. During this observational study, HPV-vaccinated participants were followed biennially for six additional years, where each clinic visit consisted of a pelvic exam with collection of a cervical sample, and a serum sample. To replace the original control group, this observational study recruited 2836 unvaccinated women from the same birth cohorts and geographic regions as the original trial participants into an Unvaccinated Control Group (UCG) who were also followed biennially. We extensively documented that this new control group had similar characteristics to the trial participants, particularly with regard to risk of HPV acquisition [9].

As part of the study design, time windows for each vaccine dose were pre-defined based on the first vaccination date. Women who became pregnant during the vaccination phase or who were referred to colposcopy were deferred, and missed that dose if the vaccination window was closed; this occurred in roughly 20% of women in the CVT [11]. Reasons for missing vaccine doses are discussed in the results section of this manuscript.

In this report, we summarize the published data to date. We compared multiple vaccine groups with their corresponding control groups, as follows: (i) women who received one HPV16/18 vaccine dose; (ii) women who received two HPV16/18 vaccine doses at enrollment and 1 month later; (iii) women who received two HPV16/18 vaccine doses at enrollment and 6 months later; (iv) women who received all three HPV16/18 vaccine doses; (v) women randomized to the original control arm; and (vi) women from the new unvaccinated control group. We evaluated these groups for virologic and serologic endpoints.

2.3. Laboratory methods

HPV DNA detection and genotyping from cervical specimens were performed at DDL Diagnostic Laboratory [17–19]. Extracted DNA was used for PCR amplification with the SPF10 primer sets. The same SPF10 amplimers were used on SPF10-DEIA–positive samples to identify HPV genotype by reverse hybridization on a line probe assay (LiPA; SPF10-DEIA/HPVLiPA25, version 1; Labo Bio-Medical Products, Rijswijk, the Netherlands), which detects 25 HPV genotypes.

HPV16 and HPV18 serum antibody levels were measured by ELISA using HPV16 and HPV18 virus like particle (VLP) at the NCI HPV Immunology Laboratory, as previously described [13]. The laboratory-determined seropositivity cut-offs for HPV16 and HPV18 were 8 EU/mL and 7 EU/mL, respectively. Laboratory-blinded replicates were included in each batch and the inter-plate coefficient of variation (CV) was $\leq$10%.

HPV16 avidity was measured in serum by coating plates with HPV16 L1 VLP. Each serum sample was tested at a dilution that yielded an absorbance reading of 1.0 ± 0.5 as previously determined in an HPV16 VLP ELISA. Guanidine-HCl (GuHCl) was added to the samples at various concentrations (0.5–3.5 M); the concentration of GuHCl that reduced the optical density by 50%, compared with sample wells without GuHCl treatment, defined the Avidity Index.

HPV16 and HPV31 neutralization titers were determined using a previously described pseudovirion-based secreted alkaline phosphatase neutralization (SEAP) assay [13], using specimens collected at the last (48 month) clinic visit.

2.4. Statistical analysis

For analyses of the efficacy of <3 doses during the randomized, blinded phase (first four years of study), the primary endpoint was newly detected HPV 16 or 18 infection that persisted for at least 6 months. Endpoint definition required detections of the same genotype consecutively at least four months apart with no intervening negatives. We required detection of the first infection to start at the 12-month study visit or later to avoid prevalent infections at enrollment and differential assessment by missed visits during the vaccination phase (i.e.: possible bias from assessing outcomes differentially

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