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Analysis of cervical HPV infections among unvaccinated young adult women to inform vaccine strategies in this age group: the Costa Rica HPV Vaccine Trial

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ABSTRACT

Introduction Human papillomavirus (HPV) vaccines protect against incident HPV infections, which cause cervical cancer.

Objectives We estimated the prevalence and incidence of HPV infections in young adult women to understand the impact of an HPV vaccination programme in this population.

Methods We collected cervical specimens from 6322 unvaccinated women, aged 18–37 years, who participated in the Costa Rica Vaccine Trial and its long-term follow-up. Women were followed for (median) 4.8 years and had (median) 4.0 study visits. Cervical specimens were tested for the presence/absence of 25 HPV genotypes. For each age band, we estimated the percentage of women with 1+ prevalent or 1+ incident HPV infections using generalised estimating equations. We also estimated the prevalence and incidence of HPV as a function of time since first sexual intercourse (FSI).

Results The model estimated HPV incident infections peaked at 28.0% (95% CI 25.3% to 30.9%) at age 20 years then steadily declined to 11.8% (95% CI 7.6% to 17.8%) at age 37 years. Incident oncogenic HPV infections (HPV16/18/31/33/35/39/45/51/52/56/58/59) peaked and then declined from 20.3% (95% CI 17.9% to 22.9%) to 7.7% (95% CI 4.4% to 13.1%); HPV16/18 declined from 6.4% (95% CI 5.1% to 8.1%) to 1.1% (95% CI 0.33% to 3.6%) and HPV31/33/45/52/58 declined from 11.0% (95% CI 9.3% to 13.1%) to 4.5% (95% CI 2.2% to 8.9%) over the same ages. The percentage of women with 1+ incident HPV of any, oncogenic, non-oncogenic and vaccine-preventable (HPV16/18, HPV31/33/45, HPV31/33/45/52/58, and HPV6/11) types peaked <1 year after FSI and steadily declined with increasing time since FSI (p for trends <0.001). We observed similar patterns for model estimated HPV prevalences.

Conclusion Young adult women may benefit from HPV vaccination if newly acquired vaccine-preventable oncogenic infections lead to cervical precancer and cancer. HPV vaccination targeting this population may provide additional opportunities for primary prevention.

Trial registration number NCT00128661.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Prevalent and incident human papillomavirus (HPV) infections decrease with increasing age.

WHAT THIS STUDY ADDS

⇒ There is a sizeable estimated percentage of vaccine-preventable oncogenic incident infections that occur after age 26 years, the upper age limit for whom vaccination is recommended.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ Women aged 26–35 years may benefit from HPV vaccination if new vaccine-preventable infections at these ages are as likely to progress to precancer/cancer as infections acquired earlier.

INTRODUCTION

Human papillomavirus (HPV) vaccines have demonstrated high efficacy against incident oncogenic HPV infections.[1] WHO recommends prioritising HPV vaccinations in a two-dose schedule for girls aged 9–14 years, and recommends a three-dose schedule for individuals aged 15–26 years as a secondary target, if feasible, affordable and cost-effective.[2]

In recent years, the Food and Drug Administration and the European Medicines Agency extended the approval to use a three-dose schedule of the nonavalent HPV vaccine to individuals aged 27–45 years.[3 4] However, agencies like the US Advisory Committee on Immunization Practices have not expanded catch-up recommendations to cover those 27 years and older.[5 6]

In limited-resource settings, HPV vaccination programmes usually target adolescent girls to obtain the greatest benefit.[7 8] Countries are now trying to understand if it is cost-effective to extend the age range for their programmes. Modelling studies suggest that a small proportion (<10%–20%) of all cervical cancers are caused by vaccine-preventable

HPV infections acquired after the age of 45 years, and therefore may not be cost-effective.[9] However, there is more debate about the utility of vaccination in women in their 20s to mid-30s. Clearly, the two determinants are the incidence of HPV infection in young women and the proportion of those infections that progress to cervical cancer. Here, we aim to provide insight about the first determinant.

METHODS

Costa Rica Vaccine Trial study design

Costa Rica Vaccine Trial (CVT) evaluated the efficacy of the bivalent HPV16/18 vaccine (Cervarix, GlaxoSmithKline Biologicals, Rixensart, Belgium). CVT enrolled 7466 women aged 18–25 years during 2004–2005. Participants were randomised to three doses of Cervarix or the control hepatitis A virus vaccine (Havrix, GlaxoSmithKline Biologicals, Rixensart, Belgium). Participants were followed-up annually for 4 years (more frequently, if clinically indicated). Cervical samples from sexually experienced women were collected for cytology and HPV-DNA testing at study visits.[10] At year 4 (2009–2010), the control group received HPV vaccination and was exited from the study.[11]

CVT transitioned into a long-term follow-up (LTFU). The HPV vaccine arm returned for additional study visits and a new unvaccinated control group (UCG) was recruited for comparison.[11] The UCG consisted of 2836 women from the same birth cohort and geographical region as the original controls. UCG was recruited concurrent with CVT participants year 4 visits. UCG women underwent intensive screening to identify/treat prevalent disease at enrolment. During the LTFU, the HPV and UCG groups returned for visits at years 7, 9 and 11, with additional visits if clinically indicated. Cervical samples from sexually experienced women were collected for cytology and HPV DNA testing at study visits.[11]

Laboratory methods

HPV determination was made using two validated methods with similar sensitivity and specificity.[12] In the first method (DDL Diagnostic Laboratory, The Netherlands), the L1 region of HPV was amplified using the SPF10 PCR primer system, followed by detection using DNA enzyme immunoassay.[13 14] The DNA enzyme immunoassay-positive SPF10 amplimers were used to identify 25 HPV genotypes by reverse hybridisation with the HPV line probe assay (LiPA25).[15] SPF10-LiPA25 was used in years 0–4 and year 7.

The second method (NCI Cancer Genomics Research Laboratory), a next-generation sequencing based-assay (TypeSeq), generates a positive/negative result for 51 HPV genotypes.[16] SPF10-LiPA25 and TypeSeq results had a 93.1% positive agreement for detection of any oncogenic HPV type, 93.2% for HPV16/18 and ranged from 71.4% (HPV59) to 100% (HPV58) for individual oncogenic types. No difference in vaccine efficacy was observed when using either test to define outcomes.[12] TypeSeq was used in years 9 and 11 and in the clinical management visits after year 4.

Analytic population

Our analysis was restricted to 6322 unvaccinated women (online supplemental figure 1). Women's age and number of women attending each visit are shown in online supplemental table 1. Women treated with loop electrosurgical excision procedure (LEEP) were censored, as excision of the cervical transformation zone changes the natural history of HPV-associated lesions. Women who were biopsied but not LEEP-treated were not excluded, as biopsy can treat small lesions but likely does not change the biology of the cervix with regards to HPV infection.

Outcomes

We focused analyses on the main study visits at years 0, 1, 2, 3, 4, 7, 9 and 11. We modelled the percentage of women with 1+ prevalent or 1+ incident infections at a study visit. An incident infection is an infection detectable at the study visit that was absent at a visit 1 year earlier. If the HPV results from one of the main study visits was missing, we used the HPV results from the immediately preceding additional visit (either 6 months or colposcopy visits), if available.

Statistical analysis

We estimated the prevalence and incidence of HPV infections by age for: any HPV type (HPV6/11/16/18/31/33/34/35/39/40/42/43/44/45/51/52/53/54/56/58/59/66/70/74/68/73), all oncogenic HPV types (HPV16/18/31/33/35/39/45/51/52/56/58/59), all non-oncogenic types (HPV6/11/34/40/42/43/44/53/54/66/70/74/68/73) and all vaccine-preventable types (HPV16/18, HPV31/33/45, HPV31/33/45/52/58, HPV6/11). For calculations of prevalence and incidence, see online supplemental tables 2 and 3.

HPV prevalence: we modelled the prevalence of an infection using the 24 318 study visits and generalised estimating equations (GEEs). The dependent variable (Y) is the presence/absence of a HPV infection at a visit and the independent variables are indicator variables for each age ($X_{17},\ldots,X_{37}$). We included a binary variable (P) to adjust for the two phases of the trial (CVT/LTFU) and a binary variable (G) to adjust for the two HPV genotyping assays (LiPA/TypeSeq). We used a logistic-link, clustered by individual, and assumed an independent correlation matrix. The model can be described by $\text{logit}(Y)= \sum_{A=18}^{37} \beta_A X_A + \beta_P P + \beta_G G$. The coefficient for each given age, β_A and its 95% CI was converted to a prevalence by $\exp(\beta_A)/(1+\exp(\beta_A))$. Implicitly, this model estimated prevalence for a woman participating in CVT using the LiPA assay. We estimate a p value for trend by including age as a continuous covariate and omitting the categorical age. The dependent variable is the presence of 1+ HPV types in the evaluated group.

HPV incidence: we modelled the incidence of an infection using GEE. Since an incident infection is dependent on two testing results, we adjusted for assay type for the study visit of interest and for the preceding visit with a 3-category variable (both by LiPA, LiPA followed by TypeSeq, both by TypeSeq). The few occasions where samples were tested by TypeSeq followed by LiPA were excluded from the incidence analysis. To account for the time since last HPV test, we included an adjustment using a 4 df spline for log(time between visits) parameterised so the reference would be 1 year between visits.

We estimated the expected number, μ_A, of incident infections at a study visit for a participant who is A years old, $A \in \{18,\ldots,37\}$. We estimate these means using GEEs with number of infections as the dependent variable, a log-link and the same covariates as above (ie, $\hat{\mu}_A = exp\left(\hat{\beta}\right)$. We then approximated the expected total number of incident infections observed in a woman who is annually screened between 18 years old and 37 years old, $\hat{\mu}_T = \sum_{A=18}^{37} \hat{\mu}_A$. We similarly estimated the proportion, θ_{A^*}, of those incident infections expected to occur at or after a given age A* by $\hat{\theta}_{A^*} = \sum_{A=A^*}^{37} \hat{\mu}_A/\hat{\mu}_T$ / $\hat{\mu}_T$. We calculated the corresponding 95% CIs using the bootstrap procedure and assuming estimates follow a normal distribution.

We also estimated the HPV incidence and prevalence as function of time since first sexual intercourse (FSI) by replacing age with years-since-FSI in the GEEs. All statistical analyses were conducted using PROC GENMOD in SAS V.9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Participant characteristics

At entry, women were aged 18–32 years (median 23, IQR: 20–25) and were followed for a median of 4.8 years (IQR: 4.3–6.1 years); 86.2% of the women were sexually active, the median age of sexual debut was 17 years (IQR: 15–19); 53.9% of the women were or lived as married, 79.7% used oral contraceptives, 60.3% used condoms, 85.8% never smoked and 50.9% had body mass index between 18.5 and <25 kg/m^2 (table 1).

Prevalence of HPV infection

We estimated the percentage of women with 1+ prevalent HPV infections at ages 18–37 years (figure 1A). Prevalent infections increased from 18 to 21/24 years and then decreased with increasing age. At their peak, the percentage of women with prevalent HPV infections of any, oncogenic and non-oncogenic types were 38.7% (95% CI 36.6% to 40.9%), 28.9% (95% CI 26.8% to 31.1%) and 19.0% (95% CI 17.4% to 20.8%). Among 37 year olds, these percentages were 21.2% (95% CI 14.8% to 29.3%), 13.0% (95% CI 8.1% to 20.3%) and 10.2% (95% CI 6.3% to 16.3%) (online supplemental table 3). We observed similar patterns for prevalent vaccine-preventable infections (figure 1B).

Incidence of HPV infection

We estimated the percentage of women with 1+ incident infection at ages 18–37 years (figure 1C). Incident infections peaked around age 20 years and steadily declined after that (p for trend <0.001) (figure 1C). At their peak, the percentage of women with incident HPV infections of any, oncogenic and non-oncogenic types were 28.0% (95% CI 25.3% to 30.9%), 20.3% (95% CI 17.9% to 22.9%) and 15.5% (95% CI 13.7% to 17.5%).

The percentage of vaccine-preventable incident HPV infections peaked at age 20 years and steadily declined with increasing age (p for trend <0.05) (figure 1D). The frequency of infections at age 30+ years was non-negligible (online supplemental table 4). Among women aged 37 years, the percentage of women with incident HPV infections of any, oncogenic and non-oncogenic types were 11.8% (95% CI 7.6% to 17.8%), 7.7% (95% CI 4.4% to 13.1%) and 5.7% (95% CI 3.2% to 10.0%).

Analyses restricted to sexually active women yield similar results (data not shown).

Number of incident infections

We estimated that a woman who reported for annual visits between ages 18 and 37 years would have a total of 6.0 (5.6–6.4) incident infections. Of those infections, we would expect 28.1% (95% CI 25.2% to 30.9%) to occur at age 30+ years (online supplemental table 5). Similarly, a woman who reported for annual visits between ages 18 and 37 years would have a total of 3.5 (3.2–3.8) incident oncogenic infections and 2.1 (1.9–2.3) vaccine-preventable oncogenic infections, of which 27.4% (95% CI 24.1% to 30.9%) and 27.0% (95% CI 23.2% to 31.1%), respectively, are expected to occur at age 30+ years.

We estimated that a woman who reported having 1, 2–3 or 4+ lifetime number of sexual partners between ages 18 and 37

Table 1 Baseline characteristics at enrolment of the 6322 unvaccinated young adult women (18–32 years) included in the analysis

Characteristics	N (%)
Sexual behaviour	
Sexual debut	
Yes	5447 (86.2)
No	875 (13.8)
Age at first sexual intercourse (years) (among sexually active)	
Mean	17.3
SD	2.9
Range	4–33
Median	17
IQR	15–19
Lifetime number of sexual partners	
0	875 (13.9)
1	2012 (32.0)
2–3	2218 (35.3)
4+	1186 (18.9)
Monthly frequency of sexual intercourse since the last visit (among sexually active)	
1 or less	774 (14.4)
2–4	1360 (25.4)
5–9	1229 (22.9)
10–13	1261 (23.5)
14+	738 (13.8)
Married/Living as married	
Yes	3399 (53.9)
No	2910 (46.1)
Contraceptive use (among sexually active)	
Use of oral contraceptives	
Never	1093 (20.3)
Ever	4289 (79.7)
Use of injectable contraceptives	
Never	2706 (50.4)
Ever	2665 (49.6)
Use of condom	
Never	2153 (39.7)
Ever	3269 (60.3)
Use of other contraceptive method*	
Never	4668 (85.9)
Ever	767 (14.1)
Number of full-term pregnancies	
0	2490 (39.4)
1	1977 (31.3)
2	1217 (19.3)
>2	638 (10.1)
Smoking behaviour	
Smoking status	
Never smoked	5415 (85.8)
Past	426 (6.8)
Current smoker	469 (7.4)
Among smokers, smoking intensity (# cigarettes/week)	
1–5	343 (38.6)
6–10	142 (16.0)
11–20	202 (22.7)
>20	201 (22.6)
Among smokers, age at smoking initiation (years)	
≤14	151 (16.9)
15–18	486 (54.4)
≥19	257 (28.7)

Continued

Table 1 Continued

Characteristics	N (%)
BMI at enrolment	
Underweight (<18.5 kg/m^2)	384 (6.1)
Normal (18.5 to <25 kg/m^2)	3215 (50.9)
Overweight (25 to <30 kg/m^2)	1604 (25.4)
Obese (≥30 kg/m^2)	1118 (17.7)

*Use of other contraceptive methods (diaphragm, sponge, spermicide, intrauterine device and others).
BMI, body mass index.

years would have a total of 4.1 (2.5–4.3), 6.9 (5.0–6.3) and 9.8 (8.8–10.3) incident infections, respectively. Similar results were obtained for oncogenic and vaccine-preventable types (data not shown).

Time since first sexual intercourse

We estimated the percentage of women with 1+ prevalent or 1+ incident infections by years since FSI (figure 2, online supplemental tables 6 and 7). The percentage of women with 1+ incident HPV infections of any, oncogenic and non-oncogenic types peaked immediately after FSI (41.7% (95% CI 36.7% to 46.9%), 32.1% (95% CI 27.6% to 37.1%), 23.5% (95% CI 19.3% to 28.2%), respectively) and steadily declined with increasing time since FSI (p for trends<0.001) (figure 2C). Incidence of HPV16/18, HPV31/33/45, HPV31/33/45/52/58 and HPV6/11 peaked at <1 year since FSI (8.7% (95% CI 6.2% to 12.1%), 10.7% (95% CI 7.9% to 14.2%), 16.5% (95% CI 13.0% to 20.6%), 3.0% (95% CI 1.7% to 5.4%), respectively) and declined as time since FSI increased (p value for trends <0.001) (figure 2D). Similar results were obtained for prevalent infections (figures 2A and 2B).

DISCUSSION

We described the prevalence and incidence of cervical HPV infections by age and time since FSI in a cohort of unvaccinated women aged 18–32 years in Costa Rica followed for a median of 4.8 years to quantify the burden of vaccine-preventable HPV infections and inform the potential impact of older age HPV vaccination programmes.

We observed that the percentage of prevalent HPV infections peaked between ages 21 and 24 years and declined thereafter, consistent with previous publications.[17] We also observed that the percentage of incident HPV infections peaked at age 20 years and decreased thereafter with the maximum incidence being shortly after initiation of sexual activity, consistent with previously reported age-specific patterns.[17]

We did not evaluate duration of the infection, but we evaluated HPV prevalence, which is a function of incidence and persistence/duration of infection. We observed declines in the percentage of prevalent oncogenic HPV, HPV16/18 and HPV6/11 with increasing age. While non-statistically significant, we observed declines in the percentage of prevalent HPV31/33/45/52/58 and non-oncogenic types with increasing age. The declines in prevalence in women in their late 20s and early 30s may reflect a decline in the number of new partners and acquired natural immunity.[18] While we cannot directly interpret time since FSI in terms of duration of an underlying HPV infection, first HPV acquisition often occurs soon after sexual debut.[19] The vast majority of these infections clear rapidly.[20] We observed that the percentage of incident HPV infections peaked within the first year since sexual initiation and declined thereafter.

Notably, there was a sizeable percentage of incident infections in participants aged 30–37 years. We predicted that approximately 27.4% of all oncogenic and 27.0% of all vaccine-preventable infections that occur between ages 18 and 37 will occur at 30+ years. However, it is unknown whether infections

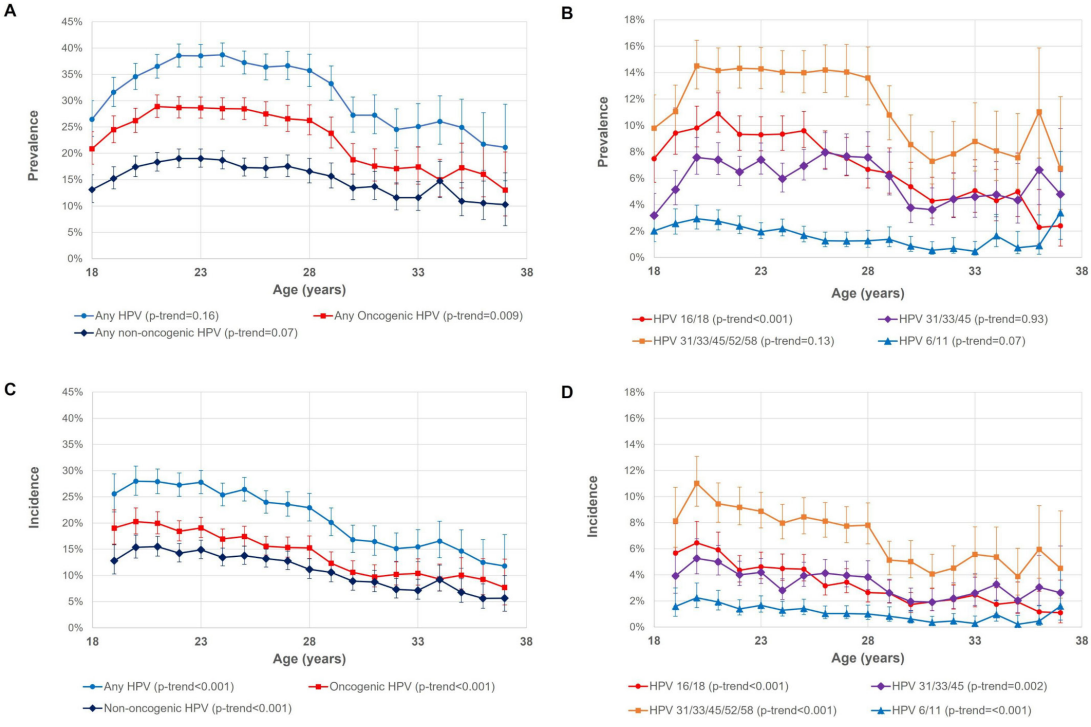

Figure 1 Model estimated prevalence and incidence of cervical human papillomavirus (HPV) infections among unvaccinated young adult women in the Costa Rica Vaccine Trial followed for a median of 4.8 years, by age, using generalised estimating equations (GEE). Prevalence by HPV group (A) and by vaccine-preventable HPV types (B). Incidence by HPV group (C) and by vaccine-preventable HPV types (D).

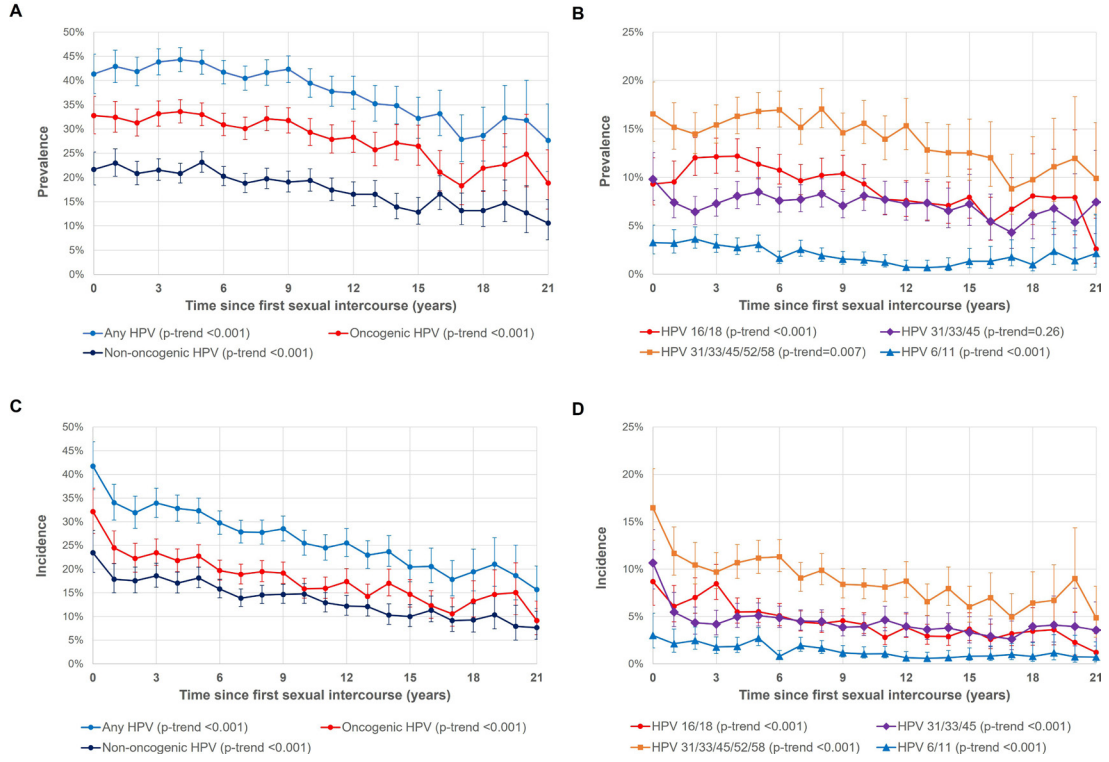

Figure 2 Model estimated prevalence and incidence of cervical human papillomavirus (HPV) infections among unvaccinated young adult women in the Costa Rica Vaccine Trial followed for a median of 4.8 years, by time since first sexual intercourse, using generalised estimating equations (GEE). Prevalence by HPV group (A) and by vaccine-preventable HPV types (B). Incidence by HPV group (C) and by vaccine-preventable HPV types (D).

that occur later in life are as likely to progress to cancer as those occurring earlier in life. We cannot account for infections that happened early on in women who entered the study when they were older.

Modelling work suggests that among all cervical cancers, 50% and 75% of women acquired their causal HPV infection by ages 20.6 and 30.6 years, respectively.[9] In those models, available prophylactic HPV vaccines have reduced population-level impact if women are vaccinated after the peak age of causal infections. Under the assumption that HPV16/18 vaccination is 95% efficacious in preventing HPV16/18 infections, the reduction in lifetime risk of developing cervical cancer is 38%, 21% and 15% among women vaccinated at ages 18, 25 and 30 years, respectively, compared with unvaccinated women. Likewise, assuming HPV16/18/31/33/45/52/58 vaccination is 95% efficacious in preventing these vaccine-targeted infections, the reduction in lifetime risk of developing cervical cancer is 54%, 29% and 22% among those vaccinated by the ages of 18, 25 and 30 years, respectively.[9] Our study has limitations. Because women were recruited as a part of a clinical trial, the cohort may not be representative of the underlying population with regard to their risk for HPV. While we included >90% of the women enrolled in the control group and UCG in the analysis, only ~30% (7466/24 467) of women invited to participate in CVT were enrolled in the study which could affect generalisability of the results.[10] It is possible that the use of a more sensitive assay (TypeSeq) in the later study years could have led to an overestimation of the proportion of infections that occurred at age 30+ years. To minimise this bias, we adjusted for the two HPV genotyping assays in the analyses and restricted the analyses to the same 25 types detected with SPF10-LiPA25. We might have underestimated the prevalence and incidence of HPV infection by age and time since FSI due to the long intervals between visits as most of these infections clear spontaneously within 12 months.[20] We may have introduced bias when using the HPV results from the additional study visits to complete missing data in the main study visits because women underwent an accelerated visit schedule if clinically indicated, and consequently would have more HPV-DNA results available than the rest of the participants. To minimise this bias, we only used the result of the earliest and closest additional visit to the corresponding missing main study visit, and the visit was selected based only on visit type and timing not the HPV result. Additional biases could be introduced because women who had additional visits were more likely to have visits available to complete the missing data; however, these women were also more likely to have missed a main study visit. Overall, the main study visits account for 92% of the visits used in this analysis (range from 84% to 100%), suggesting that the biases introduced by using the additional visits is minimal. We were unable to calculate the prevalence or incidence of HPV infections that occurred before age 18 or after age 37 years because CVT excluded women <18 years and only 1% (21/2313) of the unvaccinated women had aged to 38 years by the 11-year visit. We expect the proportion of infections at later ages (eg, 35–44 years) to be ~10%, as previously reported.[21] We note that both assays will report a small number of false positives for each HPV type. These false positives will result in biases that overestimate the rates of HPV prevalence/incidence, and underestimate the relative change in these rates across age groups. In general, the number of women falsely recorded as having 1+ HPV infections and these resulting biases will increase with the number of HPV types evaluated. Therefore, these biases, although minimal, may be more noticeable when considering analyses evaluating any HPV type, as compared with those evaluating a small number of HPV types. The strengths of the present study include the large sample size and the use of well-validated HPV detection/

genotyping methods.[12] HPV vaccination has shown to reduce the HPV prevalence and HPV-related diseases, in countries with high vaccine coverage.[22–24] Evidence suggests that the bivalent and quadrivalent vaccines induce cross-protection against the not targeted types HPV31/33/45.[23 24] In Costa Rica, quadrivalent HPV vaccination was introduced in 2019 targeting girls aged 10 years, thus our estimates of prevalence/incidence of HPV infection did not benefit from the indirect protection by the vaccine-eligible cohorts of the vaccination programme. These data provide a baseline for future HPV studies in Costa Rica, to inform the HPV vaccine effectiveness of the current programme by evaluating changes in prevalence of targeted and non-vaccine targeted HPV genotypes.

Our findings suggest that young adult women acquire vaccine-preventable infections and thus may benefit from HPV vaccination, if these incident infections have the potential to persist and progress to cervical precancer and cancer. Therefore, vaccination targeting this population could be an important element in accelerating cervical cancer elimination.

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Contributors All authors, qualify for authorship in adherence to the ICMJE guidelines. The NCI and Costa Rica investigators are responsible for the design and conduct of CVT. MSS, SHT and AH wrote the manuscript and JNS and JS conducted the statistical analysis. All authors contributed and were involved in the interpretation of results, commented on a draft and approved the final, submitted version of the manuscript. MSS, SHT and AH are listed as guarantors of the paper. MSS and SHT contributed equally to this work.

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Disclaimer Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer / World Health Organization.

Competing interests SHT is now an employee of Merck Sharp & Dohme (MSD), a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey, USA, but completed all work associated with this manuscript while employed at the National Cancer Institute. MSD was not involved in this work.

Patient consent for publication Not applicable.

Ethics approval Study protocols were approved by the US National Cancer Institute (NCI) and the Costa Rican Institutional Review Boards (04-C-N191/IC-200403). Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available upon reasonable request Participant data can be shared with outside collaborators for research to understand more about the performance of the HPV vaccine, immune response to the vaccine, and broader study factors associated with the natural history of HPV infection and risk factors for infection and disease. Outside collaborators can apply to access our protocols and data from the blinded phase of the Costa Rica Vaccine Trial (NCT00128661). Outside collaborators can apply for access to the data online. Data for the long-term follow-up phase are not yet available. For the trial summary, current publications, and contact information for data access see: Human Papillomavirus (HPV) Vaccine Trial in Costa Rica (CVT) - National Cancer Institute (https://dceg.cancer.gov/research/who-we-study/cohorts/costa-rica-vaccine-trial). The data that support the findings of this study are available from the corresponding author upon reasonable request.

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