Efficacy of fewer than three doses of an HPV-16/18 AS04-adjuvanted vaccine: combined analysis of data from the Costa Rica Vaccine and PATRICIA trials

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Summary

Background There is some evidence to suggest that one or two doses of the HPV vaccine provides similar protection to the three-dose regimen. The main aim of the study was to ascertain HPV-16/18 vaccine efficacy in both full and naive cohorts and to explore protection conferred against non-vaccine HPV types, by number of doses received.

Methods Summary data from the Costa Rica Vaccine Trial (CVT; NCT00128661) and the PATRICIA trial (NCT001226810), two phase 3, double-blind, randomised controlled clinical trials of the HPV-16/18 AS04-adjuvanted vaccine in young women, were combined in a post-hoc analysis (GlaxoSmithKline [GSK] e-track number 202142) to investigate the efficacy of fewer than three doses of the HPV-16/18 vaccine after 4 years of follow-up. Women were randomly assigned to receive three doses of the HPV-16/18 vaccine or to a control vaccine; yet, some received fewer doses. After exclusion of women with less than 12 months of follow-up or those who were HPV-16/18 DNA-positive at enrolment (for the HPV-16/18 endpoint), we calculated vaccine efficacy against one-time detection of incident HPV infections after three, two, and one dose(s). The primary study endpoint was one-time detection of first incident HPV-16/18 infections accumulated during the follow-up phase.

Findings We assessed vaccine efficacy against incident HPV-16/18 infection in the modified total vaccinated cohort (22 327 received three doses, 1185 two doses, 543 one dose). Vaccine efficacy against incident HPV-16/18 infections for three doses was 77·0% (95% CI 74·7–79·1), two doses was 76·0% (62·0–85·3), and one dose was 85·7% (70·7–93·7). Vaccine efficacy against incident HPV-31/33/45 infections for three doses was 59·7% (56·0–63·0), two doses was 37·7% (12·4–55·9), and one dose was 36·6% (–5·4 to 62·2). Vaccine efficacy against incident HPV-16/18 infection for two-dose women who received their second dose at 1 month was 75·3% (54·2–87·5) and 82·6% (42·3–96·1) for those who received the second dose at 6 months (CVT data only). Vaccine efficacy against HPV-31/33/45 for two-dose women who received their second dose at 6 months (68·1%, 27·0–87·0; CVT data only), but not those receiving it at one month (10·1%, –42·0 to 43·3), was similar to the three-dose group.

Interpretation 4 years after vaccination of women aged 15–25 years, one and two doses of the HPV-16/18 vaccine seem to protect against cervical HPV-16/18 infections, similar to the protection provided by the three-dose schedule. Two doses separated by 6 months additionally provided some cross-protection. These data argue for a direct assessment of one-dose efficacy of the HPV-16/18 vaccine.

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Introduction

Cervical cancer is a leading cause of cancer mortality in women worldwide, although the burden disproportionately affects women in low-income countries.[1] Human papillomavirus (HPV) type 16 causes about 50% of cervical cancers, followed by HPV-18 (20%), and the remaining 30% are caused mainly by ten other carcinogenic types.[2] Prevention of HPV infection, especially HPV-16 and HPV-18, could substantially reduce cervical cancer prevalence and subsequent mortality.

Prophylactic HPV vaccination with three doses given by a prime-prime-boost schedule during a 6 month period of either of the two commercially available vaccines (HPV-16/18 AS04-adjuvanted vaccine, Cervarix [GSK group of companies, Rixensart, Belgium] and HPV-6/11/16/18 vaccine, Gardasil [Merck, Whitehouse Station, NJ, USA]) is highly efficacious in prevention of cervical HPV-16/18 infections and related diseases.[3,4] However, costs and infrastructure complexities associated with a three-dose programme are barriers to vaccination provision in many world regions.[5] On the basis of immunological non-inferiority, two-dose schedules of the HPV-16/18 and HPV-6/11/16/18 vaccines are now licensed in adolescents (age 9 years to 13 or 14 years) in several countries.

The only published data for efficacy of fewer than three doses comes from a post-hoc analysis[6] of the Costa Rica Vaccine Trial (CVT) in women who did not complete the three-dose regimen. In women who were HPV-16/18 DNA-negative at the time of first vaccination,

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HPV-16/18 vaccine efficacy was uniformly high against incident HPV-16/18 infections that persisted for at least 6 months for recipients of one (100%, 95% CI 79–100), two (81%, 53–94), or three doses (84%, 77–89) throughout the 4 years after vaccination. Women who received fewer than three doses also had strong and stable antibody responses that persisted during this period, although HPV-16/18 antibody titres in recipients of one dose were almost four times lower than in those of two or three doses.[7] Similar analyses from other studies[8–10] showed stable plateau antibody titres after the immediate decrease in the post-vaccination period after one, two, or three doses.

Since publication of CVT, new data for reduced-dose protection have come from non-inferiority immunogenicity studies,[8–10] in which the minimum titre needed for protection remains unknown as a result of the high vaccine efficacy. In this study, we aimed to confirm the initial CVT dose-stratified vaccine efficacy findings in the PATRICIA trial. Summary-level data from the PATRICIA and CVT trials were combined to evaluate HPV-16/18 vaccine efficacy of fewer doses among HPV-naive women, and establish whether protection against HPV-31, HPV-33, and HPV-45 is present in women who received fewer than three doses.[11]

Methods

Study design and participants

To assess the efficacy of fewer than three doses, we combined data from CVT (NCT00128661)[12,13] and PATRICIA (NCT001226810),[14] the only two large-scale, phase 3, double-blind, randomised controlled clinical trials of the HPV-16/18 AS04-adjuvanted vaccine in young women.[3,12–15] We deemed trials of the quadrivalent and nonavalent HPV vaccines out of the scope of this work because it is currently unknown whether it is the virus-like particle that induces the strong immune response, in which case both vaccines may be efficacious

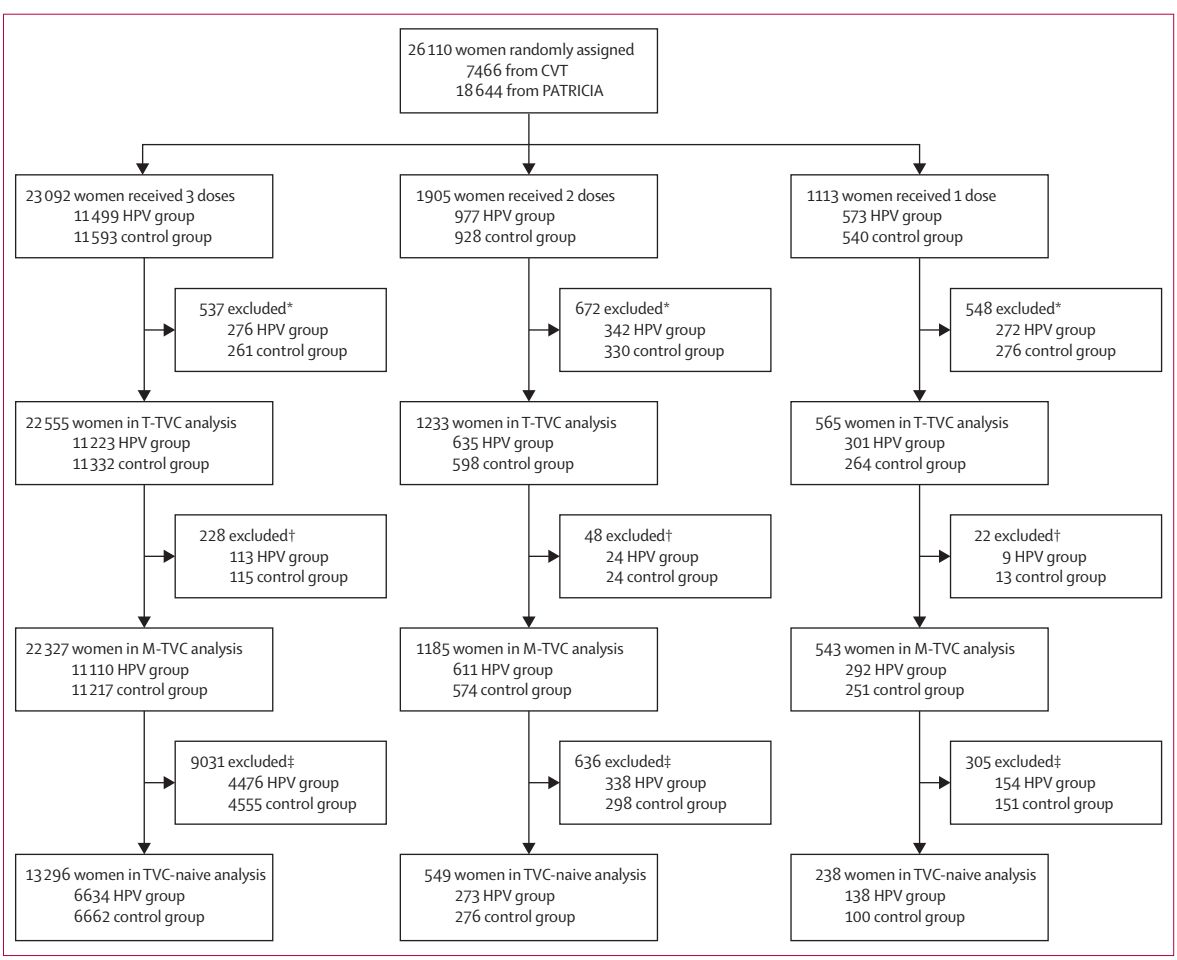


Figure 1: **Trial profile for the Costa Rica Vaccine Trial (CVT) and PATRICIA trial combined**
Women who were randomly assigned into both trials were stratified by vaccine group and number of doses received. *Women were excluded if they had less than 12 months' follow-up (time total vaccinated cohort, T-TVC). †Women were additionally excluded if their enrolment cervical status was HPV-16 and HPV-18 DNA-positive (or missing) or if they had fewer than 300 days between first and last PCR result; modified total vaccinated cohort (M-TVC) for assessment of HPV-16/18-related endpoints. ‡Women were further excluded from the total vaccinated naive cohort (TVC-naive) if their cervical status at enrolment was HPV DNA-positive for any oncogenic type (or missing), or HPV-16 or HPV-18 seropositive (or missing), or had enrolment cytology abnormal (or missing).

with a single dose, or whether the special adjuvant of the HPV-16/18 vaccine is the cause of one-dose efficacy. Moreover, differences existed in the trial designs between the HPV-16/18 vaccine programmes and the quadrivalent or nonavalent programme—eg, in inclusion criteria, assays for HPV DNA and serology, and colposcopy algorithms. Consequently, we focused on only the HPV-16/18 vaccine.

In CVT,[12,13] 7466 young women were enrolled between June 28, 2004, and Dec 21, 2005; the main eligibility requirements were being aged 18–25 years, of good general health, and neither being pregnant nor breastfeeding. Women were excluded if they had pre-existing medical conditions that precluded vaccination, had a history of hepatitis A or previous vaccination against it, or were unwilling to use contraception during the vaccination period. In PATRICIA,[14] women were enrolled between May 6, 2004, and June 27, 2005; 18 644 women aged 15–25 years were enrolled and vaccinated. Women who reported no more than six lifetime sexual partners before study enrolment (in some countries this criteria was not considered for women younger than 18 years), agreed to adequate contraception (barrier methods in combination with a spermicide or hormonal contraception) during the vaccination period, and had an intact cervix were eligible for inclusion. Main exclusion criteria included a history of hepatitis A or previous vaccination against it, history of colposcopy, pregnancy or breastfeeding, chronic or autoimmune disease, or immunodeficiency.

Investigators from both trials generated study-specific analyses independently according to a prespecified analytical plan; the summary data were merged to generate the combined analytical estimates. These studies[11–14] were generally harmonised at the design phase, thus increasing the validity of the combined analysis (GSK e-track number 202142). Importantly, the same vaccines were given on the same schedules, the baseline characteristics were similar (ie, age), HPV DNA testing and serological analyses were done with the same assays at the same laboratories, thus eliminating potential differences in outcome misclassification for virological endpoints, the main outcome measures for this analysis; referral algorithms for women who needed additional work up (repeat cytological testing or referral to colposcopy) were also similar. The main difference between the two trials as they relate to this study is that PATRICIA collected cervical samples for HPV DNA testing in women twice a year, whereas the CVT collected cervical samples for HPV DNA testing annually, although more frequent visits occurred when clinically indicated. The clinical protocols and other materials were approved by independent ethics committees or institutional review boards. Participants in both trials provided written informed consent.

Procedures

At enrolment for both trials, each participant underwent a risk factor interview, blood collection, and, if sexually active, a pelvic examination in which cervical cells were collected for cytology and HPV DNA detection or genotyping. Women were then randomly assigned (1:1) to receive either the HPV-16/18 AS04-adjuvanted vaccine or hepatitis A vaccine (HAV) as a control given

	Costa Rica Vaccine Trial						PATRICIA					
	1 dose		2 doses		3 doses		1 dose		2 doses		3 doses	
	HPV (n=192)	Control (n=185)	HPV (n=419)	Control (n=379)	HPV (n=2927)	Control (n=2992)	HPV (n=109)	Control (n=79)	HPV (n=216)	Control (n=219)	HPV (n=8296)	Control (n=8340)
Age at enrolment (years)	21·3 (2·3)	21·4 (2·4)	20·9 (2·3)	20·9 (2·4)	21·1 (2·3)	21·1 (2·3)	21·3 (2·7)	21·0 (3·0)	21·1 (2·9)	21·3 (2·8)	19·9 (3·1)	19·9 (3·1)
Follow-up (months)	54·2 (8·8)	54·5 (9·1)	54·2 (10·0)	54·1 (10·3)	54·1 (8·3)	54·3 (8·3)	43·8 (9·3)	43·1 (9·4)	43·0 (9·2)	43·1 (8·6)	44·9 (7·2)	44·9 (7·4)
Number of non-vaccine study visits	4·7 (1·5)	4·5 (1·5)	4·3 (1·3)	4·4 (1·5)	4·4 (1·2)	4·5 (1·3)	4·8 (1·7)	4·5 (1·7)	4·4 (1·6)	4·4 (1·7)	5·5 (1·2)	5·5 (1·2)
HPV-16 status at enrolment												
Negative	122 (64%)	116 (63%)	278 (66%)	265 (70%)	2098 (72%)	2091 (70%)	92 (84%)	60 (76%)	165 (76%)	176 (80%)	6669 (80%)	6682 (80%)
Positive*	66 (34%)	63 (34%)	131 (31%)	106 (28%)	791 (27%)	849 (28%)	17 (16%)	18 (23%)	46 (21%)	39 (18%)	1553 (19%)	1565 (19%)
HPV-18 status at enrolment												
Negative	129 (67%)	122 (66%)	290 (69%)	273 (72%)	2152 (74%)	2196 (73%)	100 (92%)	66 (84%)	180 (83%)	191 (87%)	7177 (87%)	7218 (87%)
Positive*	57 (30%)	56 (30%)	118 (28%)	95 (25%)	710 (24%)	729 (24%)	9 (8%)	13 (16%)	33 (15%)	27 (12%)	1054 (13%)	1051 (13%)

Data are mean (SD) or n (%). Patients stratified by study, number of vaccine doses received, and vaccine group using available data in the total vaccinated cohort in women with 12 or more months of follow-up time (T-TVC). *Positive indicates positivity for HPV serology or DNA for the HPV type in question or both.

Table 1: **Baseline characteristics of study population for both trials**

at 0, 1, and 6 months. Women who were not vaccinated within the prespecified dosing windows did not receive the scheduled dose. In both studies, pregnancy was a contraindication for vaccination. Women who were pregnant at vaccination visits did not receive that dose if the vaccination window was closed. In the CVT only, women referred to colposcopy missed the dose if the vaccination window was closed when they returned to regular study visits.

The protocols required all women to be observed every 6 months (PATRICIA) or annually (CVT) during the 4 year follow-up. At each visit, clinicians collected exfoliated cervical cells from sexually active women for cytological assessment and HPV DNA testing. Women identified to have low-grade squamous intraepithelial neoplasia or carcinogenic HPV-positive atypical squamous cells of undetermined significance underwent intensified follow-up (ie, repeat testing or referral to colposcopy or both, and, if indicated, biopsy and cervical excision treatment); missing or inadequate cytology was similarly sent to intensified follow-up in CVT. Women with high-grade disease or persistent low-grade abnormalities were referred to colposcopy for assessment and directed biopsy, with treatment if needed. HPV DNA testing was done as previously described.[16–18]

See Online for appendix

	Number of women	Number of events	Person-years	Rate per 100 person-years (95% CI)	Vaccine efficacy (95% CI)
Incident one-time detection of HPV-16/18					
3 doses (standard regimen)					
HPV	11 110	529	43 140	1·23 (1·12–1·34)	77·0% (74·7–79·1)
Control	11 217	2172	40 682	5·34 (5·12–5·57)	
2 doses					
HPV	611	22	2538	0·87 (0·56–1·29)	76·0% (62·0–85·3)
Control	574	82	2271	3·61 (2·89–4·46)	
1 dose					
HPV	292	8	1220	0·66 (0·30–1·25)	85·7% (70·7–93·7)
Control	251	45	982	4·58 (3·38–6·08)	
Incident detection of HPV-16/18 that persisted for at least 6 months					
3 doses					
HPV	11 104	114	43 706	0·26 (0·22–0·31)	89·1% (86·8–91·0)
Control	11 209	1000	41 913	2·39 (2·24–2·54)	
2 doses					
HPV	611	4	2573	0·16 (0·05–0·38)	89·7% (73·3–96·9)
Control	574	35	2308	1·52 (1·07–2·09)	
1 dose					
HPV	292	1	1234	0·08 (0·00–0·40)	96·6% (81·7–99·8)
Control	250	24	1017	2·36 (1·55–3·46)	
Incident detection of HPV-16/18 that persisted for at least 12 months					
3 doses					
HPV	11 104	84	43 775	0·19 (0·15–0·24)	87·0% (83·7–89·7)
Control	11 203	627	42 589	1·47 (1·36–1·59)	
2 doses					
HPV	611	3	2576	0·12 (0·03–0·32)	89·6% (68·9–97·5)
Control	574	26	2324	1·12 (0·75–1·62)	
1 dose					
HPV	292	1	1234	0·08 (0·00–0·40)	95·1% (73·2–99·8)
Control	249	17	1021	1·67 (1·00–2·61)	

Table 2: **Dose-stratified vaccine efficacy against incident HPV-16/18 infection for women in the modified total vaccinated cohort (Costa Rica Vaccine Trial and PATRICIA combined)**

Statistical analysis

This post-hoc analysis followed a statistical analysis plan prepared before the study. The primary study endpoint was one-time detection of first incident HPV-16/18 infections accumulated during the follow-up phase. Women with several events were counted only once at the time of the first event, at which time her person-time ended. Secondary endpoints were incident HPV infections that persisted for at least 6 months (defined as two or more type-specific positive tests at least 150 days apart, with no intervening HPV-negative results) and at least 12 months (as for 6 months, but for >300 days). The distinction between the endpoints of one-time detection of incident HPV infection and persistent infection is that a case of persistent infection was defined as a second detection of the HPV type in question occurring within the interval specified, without an HPV-negative result (for the HPV type in question) occurring between the two positive tests. However, this did not mean that a one-time detection of HPV did not also persist, but only that the criteria for an incident event was met when an infection was detected once. All endpoints were assessed for both HPV-16/18 and HPV-31/33/45 and by individual HPV type within these groups. Data safety monitoring groups reviewed safety data during the vaccination phase and as needed during follow-up.

Balance by arm and dose was assessed in the time total vaccinated cohort (T-TVC), which included all women with at least 12 months of follow-up. Endpoints were assessed in two analytical cohorts: the modified total vaccinated cohort (M-TVC), which excluded women who were HPV DNA-positive for the type in question at the enrolment visit (subsequently each M-TVC can have different sample sizes because of the differing number of excluded women) and total vaccinated cohort-naive (TVC-naive), which excluded women who were HPV DNA-positive for any of 14 high-risk types, HPV-16/18 seropositive (even in analyses of protection by non-HPV-16/18 types), and who had positive cytology at the enrolment visit (women who were negative for carcinogenic HPV types by Hybrid Capture II [Digene, Gaithersburgh, MD, USA] but ASCUS [atypical squamous cells of undetermined significance]-positive were considered negative and included in the TVC-naive cohort).

For both analytical cohorts, person-time was counted from 1 day after enrolment. The number of vaccine study visits (ie, visits at enrolment, 1 month, and 6 months) were directly linked to the number of doses a woman received (ie, women who received only one or two vaccine doses in most instances did not attend the 1 month or

6 month vaccine study visits [or both of these visits] and as a result did not receive the full vaccine series). Outcome assessment therefore began at the 12 month study visit (≥301 days after enrolment) because this visit was the first study visit potentially attended by women in all dose groups. We used enrolment HPV results to exclude events if the HPV type detected at follow-up was also present at enrolment. Women with unknown HPV DNA status at baseline were excluded. We did not include HPV results between 1 and 300 days after enrolment because of the bias by number of doses in sample availability (and thus HPV ascertainment) in this timeframe. Participants were required to have a cervical sample available (so HPV DNA status could be established) at least 301 days after the start of outcome assessment. Follow-up ended at the time of an event (eg, the date of the first HPV-positive test in the sequence of HPV-positive tests that defined the event). For women who did not have an event, follow-up ended on the date of the final negative test (including untested visits for virgins) to ensure parallelism in outcome assessment between women who did and did not have events.

For each group, event rates expressed per 100 person-years were calculated as the ratio of number of events to the total follow-up time. Analyses were done separately on women who received only one dose, two doses irrespective of the schedule, and the full three-dose regimen (which served as a benchmark to interpret the fewer-dose vaccine efficacy estimates). Additionally, in our exploratory analysis, further stratification of the two-dose vaccine efficacy by time of the second dose (at 1 month or at 6 months) was assessed in CVT; PATRICIA was excluded because only 26 women received two doses on the 0–6 month schedule.

The main analysis estimated differences in HPV infection rates accumulated over the 4 year follow-up period between the HPV-vaccinated and HAV-vaccinated women by number of doses received. Numbers in the numerators were combined across the two studies, as were the denominators, and these summary counts were used to generate a combined vaccine efficacy by dose for each endpoint. Study-specific vaccine efficacies are shown in the appendix, as are individual HPV-type vaccine efficacies combined across the two trials. Vaccine efficacy was defined as the percentage reduction in endpoint related to vaccine administration, estimated as the complement of the ratio of the attack rates in the HPV and control groups. The analysis was conditioned on the total number of events, and the 95% CI around the vaccine efficacy was derived from the ratio of the events in the vaccine group to the total events; exact confidence limits were calculated using the mid-p exact approach. Significant vaccine efficacy was defined as

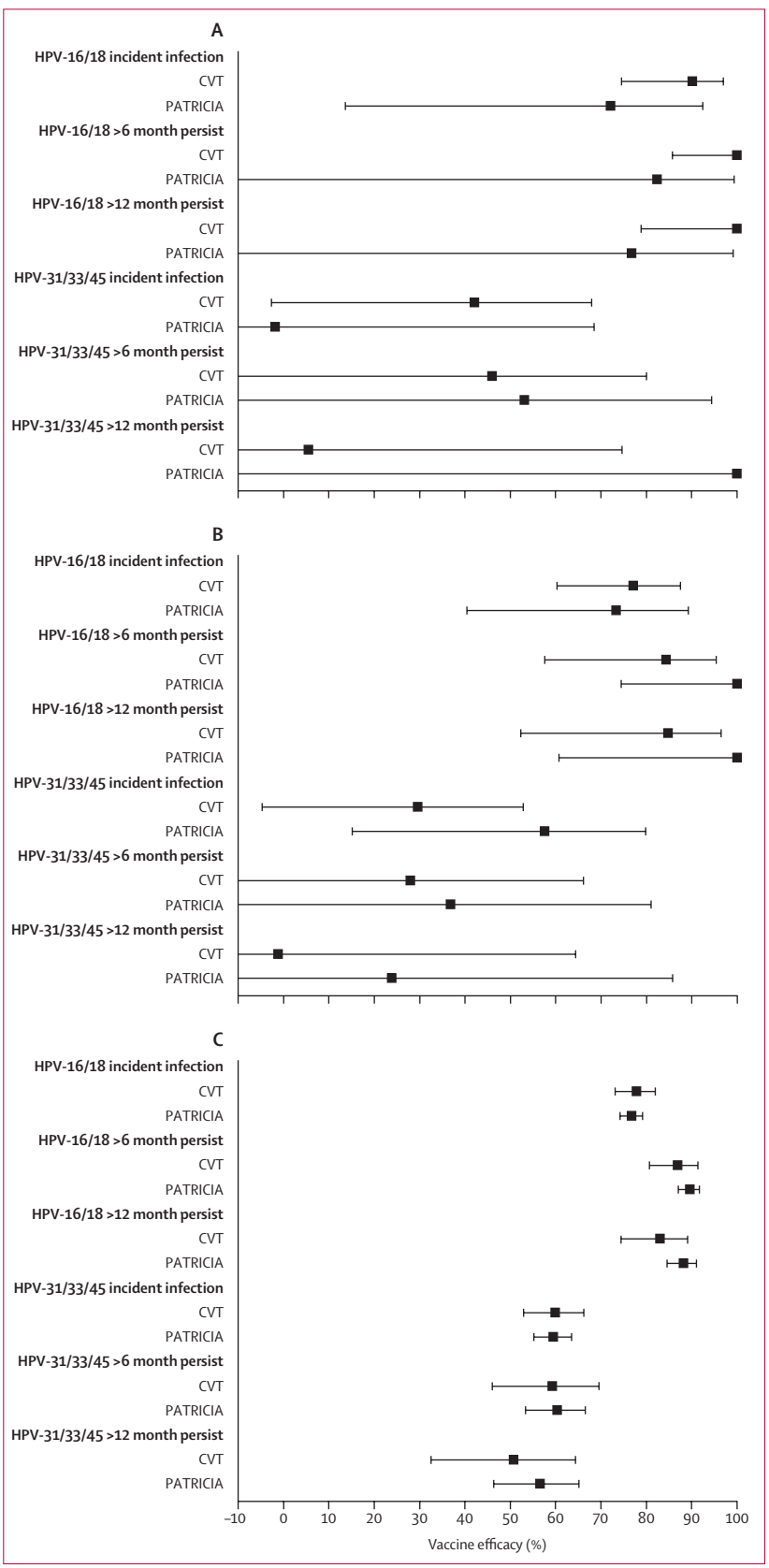
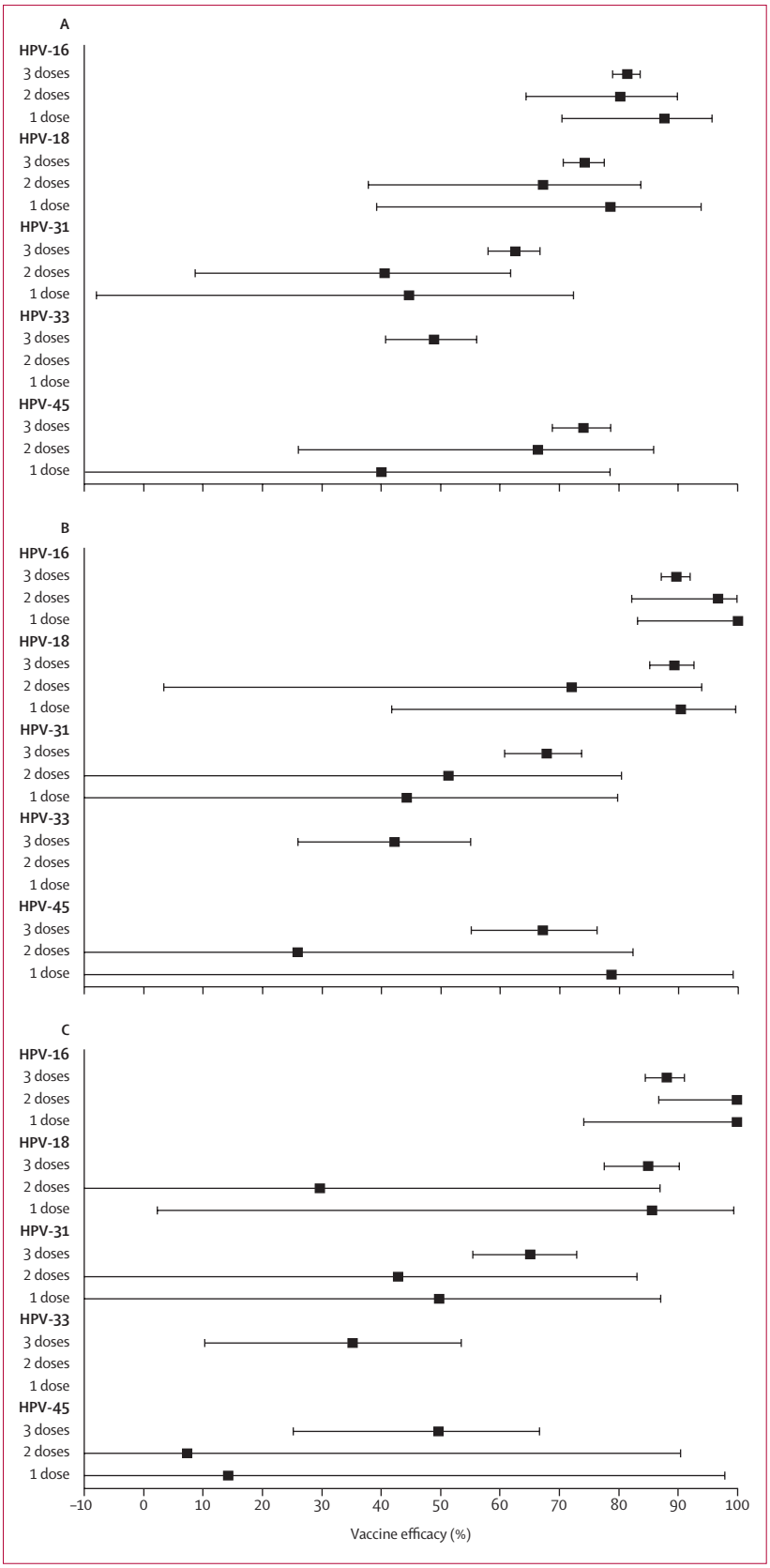


***Figure 2*: Vaccine efficacy by study (CVT and PATRICIA) for multiple endpoints in the modified total vaccinated cohort, by dose in the modified total vaccinated cohort for one dose (A), two doses (B), or three doses (C)**
CVT=Costa Rica Vaccine Trial.



the lower bound of the 95% CI greater than 0. Statistical adjustment of vaccine efficacy estimates was not used to account for underlying risk differences by dose and group because strong differences were not reported in baseline characteristics. A Poisson regression model with an interaction term for vaccination group and number of doses was used to test for heterogeneity in the trend variables between the two groups. Exact methods were used in all instances except when they did not work because the sample size was too large; in those instances, standard asymptotic methods were used to calculate p values.

We tested heterogeneity in vaccine efficacy between the two studies using a Poisson regression model with an interaction term for vaccination group by trial. All calculations were done with SAS version 9.2.

Role of the funding source

The PATRICIA trial was funded by GlaxoSmithKline Biologicals SA, who designed the study in collaboration with investigators, and coordinated collection, analysis, and interpretation of data, and preparation of the manuscript. Investigators from the PATRICIA study group collected data for the trial and cared for the subjects. The Costa Rica HPV Vaccine Trial was sponsored and funded by the National Cancer Institute (NCI), with funding support from the National Institutes of Health Office of Research on Women's Health. GlaxoSmithKline Biologicals SA provided vaccine and support for aspects of the trial associated with regulatory submission needs of the company. The NCI and Costa Rica investigators are responsible for the design and conduct of the study and collection, management, analysis, and interpretation of samples and data. All authors of this report had full access to all the trial data for the trial they participated in and access to summary-level trial data for both trials. All authors gave final approval to this manuscript.

Results

Individual CONSORT diagrams for CVT and PATRICIA are shown in the appendix. General characteristics and reasons for not receiving all three vaccine doses are described within dose, group, and study, as are follow-up times from enrolment within each study (restricted to women with ≥12 months of follow-up; T-TVC; figure 1).

In the T-TVC group, the most common reason for missed doses was pregnancy in PATRICIA for all groups and dose categories (range 53 [49%] of 109 to 143 [66%] of 216 women) and in CVT for women who received two doses of vaccine (150 [36%] of 419 women assigned to HPV vaccine; 142 [37%] of 379 assigned to control). For women who received one dose of vaccine in CVT, doses

Figure 3: **Vaccine efficacy for individual HPV types by dose, for incident HPV infections that were detected one time (A), that persisted for more than 6 months (B), and that persisted for more than 12 months (C) in the modified total vaccinated cohort**

were missed mainly because of colposcopy referral (range 40 [22%] of 185 to 55 [29%] of 192 women) and the second most common reason for missed doses was pregnancy (appendix). Mean follow-up was similar between groups and dose categories in CVT and PATRICIA (table 1); overall mean follow-up was 47·6 months (SD 8·8). In both studies and for all dose groups, women who received the HPV or control vaccines were of similar mean age at entry (table 1). The number of non-vaccine study visits was balanced for all dose groups in CVT and for women who received one or two doses in PATRICIA; women who received three doses in PATRICIA had on average one additional study visit, although mean visits for women who received three doses of vaccine in the HPV and control groups were balanced (table 1). For each study, HPV-16/18 status at enrolment seemed balanced between groups within dose categories, although fluctuations were present because of the small number of women in some categories. Differences were reported in enrolment HPV-16/18 status across studies. To further show balance in underlying HPV risk by dose group within the HPV and control groups during the 4 year follow-up, we assessed cumulative incident HPV infections for types that the vaccine does not protect against[11] as composites of oncogenic and non-oncogenic HPV types. Similar HPV attack rates were reported in this assessment in both PATRICIA and CVT studies across and within all treatment groups (one, two, or three vaccine doses; appendix).

In the PATRICIA trial, vaccine efficacy against one-time detection of incident HPV-16/18 infection for three doses was 76·8% (95% CI 74·2–79·2), two doses was 73·3% (40·4–89·2), and one dose was 72·2% (13·6–92·4), thereby confirming the original report from CVT of high vaccine efficacy against HPV-16/18 irrespective of dose group. In this analysis, we identified no evidence for heterogeneity between studies in dose-stratified vaccine efficacies against HPV-16/18 (appendix).

In both trials combined, the analysis in the M-TVC cohort assessing HPV-16/18-related endpoints included (for one-time detection) 22 327 women who received three doses (11 110 HPV *vs* 11 217 control), 1185 women who received two doses (611 HPV *vs* 574 control), and 543 women who received one dose (292 HPV *vs* 251 control). This cohort excluded women with inadequate follow-up (either the women had no visit at 12 months or later or women for whom there were fewer than 300 days between their 12 month or later visit and the last visit; figure 1). Women were also excluded for having positive or missing PCR results for both HPV-16 and HPV-18 at enrolment (figure 1). In the M-TVC, vaccine efficacy against one-time detection of incident HPV-16/18 infections for three doses was 77·0% (95% CI 74·7–79·1), two doses was 76·0% (62·0–85·3), and one dose was 85·7% (70·7–93·7; table 2); no significant difference was present in vaccine efficacy by dose (p_{trend}=0·36). Study-specific dose-stratified vaccine efficacies were also similar (minimum p value=0·15), indicating consistency of the findings (figure 2; appendix). Combined vaccine efficacies were similar by dose for the 6 month and 12 month persistent HPV-16/18 infection endpoints (table 2). Vaccine efficacies for incident HPV-16 alone and HPV-18 alone were high irrespective of dose and endpoint (figure 3; appendix).

The TVC-naive cohort included 13 296 women who received three doses (6634 HPV *vs* 6662 control), 549 women who received two doses (273 HPV *vs* 276 control), and 238 women who received a single dose (138 HPV *vs* 100 control). In this cohort, vaccine efficacy for three doses against one-time detection of incident HPV-16/18 infections was 81·4% (95% CI 78·7–83·8), for two doses was 81·2% (59·5–92·3), and for one dose was 87·5% (60·9–97·1; table 3). In this analytical cohort,

	Number of women	Number of events	Person-years	Rate per 100 person-years (95% CI)	Vaccine efficacy (95% CI)
Incident one-time detection of HPV-16/18					
3 doses (standard regimen)					
HPV	6634	241	25 750	0·94 (0·82–1·06)	81·4% (78·7–83·8)
Control	6662	1220	24 275	5·03 (4·75–5·32)	
2 doses					
HPV	273	7	1114	0·63 (0·27–1·24)	81·2% (59·5–92·3)
Control	276	36	1074	3·35 (2·38–4·59)	
1 dose					
HPV	138	3	556	0·54 (0·14–1·47)	87·5% (60·9–97·1)
Control	100	17	394	4·32 (2·60–6·77)	
Incident detection of HPV-16/18 that persisted for at least 6 months					
3 doses					
HPV	6634	38	26 046	0·15 (0·10–0·20)	93·6% (91·2–95·5)
Control	6660	567	24 818	2·28 (2·10–2·48)	
2 doses					
HPV	273	2	1121	0·18 (0·03–0·59)	87·9% (54·0–98·1)
Control	276	16	1089	1·47 (0·87–2·33)	
1 dose					
HPV	138	0	562	0·00 (0·00–0·53)	100% (67·4–100)
Control	100	8	403	1·99 (0·92–3·77)	
Incident detection of HPV-16/18 that persisted for at least 12 months					
3 doses					
HPV	6634	27	26 073	0·10 (0·07–0·15)	92·6% (89·2–95·1)
Control	6656	351	25 186	1·39 (1·25–1·55)	
2 doses					
HPV	273	2	1121	0·18 (0·03–0·59)	83·7% (35·7–97·5)
Control	276	12	1093	1·10 (0·59–1·87)	
1 dose					
HPV	138	0	562	0·00 (0·00–0·53)	100% (41·1–100)
Control	99	5	403	1·24 (0·45–2·75)	

*Excluded women who were HPV DNA-positive for any of 14 high-risk types, HPV-16/18 seropositive, or who had greater than negative cytology at the enrollment visit for Costa Rica Vaccine Trial and PATRICIA combined.

Table 3: **Dose-stratified vaccine efficacy against incident HPV-16/18 infection for women in the total vaccinated cohort-naive***

which was subset to women who were HPV-negative at enrolment, vaccine efficacies were similar and high (all >80%) by dose for the 6 month and 12 month persistent HPV-16/18 infection endpoints (table 3), and were consistent across studies (appendix). Cross-protective efficacy was assessed in the M-TVC excluding women who were HPV DNA-positive for HPV-31/33/45 infections at the enrolment visit. Vaccine efficacy against one-time detection of incident HPV-31/33/45 infections was 59·7% (95% CI 56·0–63·0) for three doses, 37·7% (12·4–55·9) for two doses, and 36·6% (–5·4 to 62·2) for one dose (table 4). For the 6 month and 12 month persistent HPV-31/33/45 infection endpoints, only the three-dose vaccine efficacy was statistically significant. Consistency was reported across studies (appendix).

In a post-hoc additional analysis, vaccine efficacy for two doses was further classified by timing of the second vaccine dose in the M-TVC of CVT (table 5): no vaccine efficacy was noted against incident HPV-31/33/45 for women who received their second dose 1 month after dose one, whereas women who received their second dose 6 months after dose one had a higher efficacy estimate (p value=0·029 for comparing the vaccine efficacies between women who received two doses by the timing of the second dose). In the same cohort, for the endpoint of incident HPV-16/18, vaccine efficacy was high irrespective of timing of the second dose. For individual HPV types for which cross-protection has been reported,[10] vaccine efficacy was significant for three doses against HPV-31, HPV-33, and HPV-45, and for two doses for HPV-31 and HPV-45 (appendix).

There was an absence of heterogeneity in vaccine efficacy by study for all cohorts and endpoints (minimum p=0·15) in all analyses except one (women who received two doses, TVC-naive analysis of HPV-31/33/45 infections [data not shown]; p=0·035).

	Number of women	Number of events	Person-years	Rate per 100 person-years (95% CI)	Vaccine efficacy (95% CI)
Incident one-time detection of HPV-31/33/45					
3 doses (standard regimen)					
HPV	11156	710	42990	1·65 (1·53 to 1·78)	59·7% (56·0 to 63·0)
Control	11272	1713	41837	4·09 (3·90 to 4·29)	
2 doses					
HPV	615	55	2490	2·21 (1·68 to 2·85)	37·7% (12·4 to 55·9)
Control	577	81	2285	3·54 (2·83 to 4·38)	
1 dose					
HPV	293	26	1185	2·19 (1·46 to 3·17)	36·6% (–5·4 to 62·2)
Control	253	35	1012	3·46 (2·45 to 4·75)	
Incident detection of HPV-31/33/45 that persisted at least 6 months					
3 doses					
HPV	11150	266	43507	0·61 (0·54 to 0·69)	60·1% (54·0 to 65·4)
Control	11269	659	42997	1·53 (1·42 to 1·65)	
2 doses					
HPV	615	18	2549	0·71 (0·43 to 1·09)	30·7% (–27·9 to 63·0)
Control	577	24	2355	1·02 (0·67 to 1·49)	
1 dose					
HPV	293	9	1222	0·74 (0·36 to 1·35)	48·8% (–16·9 to 78·5)
Control	253	15	1043	1·44 (0·84 to 2·32)	
Incident detection of HPV-31/33/45 that persisted at least 12 months					
3 doses					
HPV	11150	175	43682	0·40 (0·34 to 0·46)	54·9% (46·2 to 62·3)
Control	11266	386	43447	0·89 (0·80 to 0·98)	
2 doses					
HPV	615	11	2569	0·43 (0·23 to 0·74)	7·6% (–117·8 to 60·8)
Control	577	11	2373	0·46 (0·24 to 0·81)	
1 dose					
HPV	293	5	1230	0·41 (0·15 to 0·90)	46·1% (–66·8 to 84·0)
Control	253	8	1061	0·75 (0·35 to 1·43)	

Table 4: **Dose-stratified vaccine efficacy against incident HPV-31/33/45 infection for women in the modified total vaccinated cohort in Costa Rica Vaccine Trial and PATRICIA combined**

Discussion

Findings in the PATRICIA trial confirm, in an independent randomised controlled trial, the original report from CVT that one and two doses of the HPV-16/18 vaccine provide protection against cervical HPV-16/18 infections similar to the protection provided by the three-dose schedule during 4 years of post-vaccination follow-up,[6] and extend the findings to efficacy against HPV types not included in the vaccine (panel). Further, in analyses combining data from the two trials, the result of high HPV-16/18 vaccine efficacy irrespective of dose was replicated in a cohort of women naive to HPV-16/18 infection at the time of vaccination, which alleviates concerns that the initial findings might have been due to vaccination boosting of natural immunity in our cohort of older-aged women in CVT (the original analysis did not have sufficient power to create an HPV-naive cohort).[6] Thus, these results are probably relevant to girls in the preferred age range for HPV vaccination (ie, 11–12 years).

Two doses of the HPV-16/18 AS04-adjuvanted vaccine protected against a composite endpoint of HPV-31/33/45 infection when the second dose was given 6 months after the initial vaccine. Yet, on the basis of these new data, one dose or two priming doses separated by a short interval (ie, 1 month) might not be adequate to induce measurable cross protection. This finding is supported by results from CVT that antibody concentrations for two doses, when given at least 6 months apart, are very close to those for three doses.[19,20] A study[21] with an investigational HPV-16/18 vaccine showed that a 0, 2 month schedule in girls aged 9–14 years did not achieve immunological non-inferiority compared with the licensed three-dose schedule in women aged 15–25 years, indicating that the interval between the prime and boost doses is an important factor for the induction of the immune response necessary to afford cross-protection with a two-dose formulation.

One-time detection of incident infection was our primary endpoint, rather than persistent infection or disease. Results using this endpoint suggest that, within the limits of the PCR assay, the vaccine conferred sterilising immunity (defined as protection not only against clinical disease, but also infection) for most HPV-16/18 exposures, even for women who received one vaccine dose. Immunogenicity data from CVT suggest that one-dose vaccination recipients had antibody titres between months 6–48 that were lower than those elicited with two or three doses, but the titres were stable and several times higher than those identified for natural immunity.[20] We can now infer that these lower, vaccine-induced antibody titres provide as strong HPV prevention as the titres from two or three doses, at least in the short term. Compared with persistent infection, one-time detection has the limitation of including both short-term infection that regresses spontaneously in addition to persistent infections, which have a higher risk of progression to cervical lesions. Furthermore, some outcomes might have resulted from undetected infections present before vaccination, which explains why efficacy estimates for this endpoint are generally lower than those for persistent infection. Yet, results using persistence as an endpoint reinforced the one-time detection findings. Additional analysis of efficacy and immunogenicity data from one-dose recipients might also aid in the identification of an immune correlate of protection, in view of the absence of efficacy reported against related HPV types; analyses are being considered and will be the subject of a future report.

The structure of the HPV virus-like particles, the key component of HPV prophylactic vaccines, present closely spaced, repetitive epitopes to the immune system that induce highly potent, protective antibody responses, which might reduce or even eliminate the need for doses beyond the priming dose.[20,22–24] Furthermore, the immune-stimulatory effects of a Toll-like receptor agonist adjuvant in the HPV-16/18 vaccine might also contribute to the magnitude and durability of the immune response to this vaccine. If the protective effect afforded by one dose is mainly due to the repetitive display of the virus-like particles, this result might be attained for the quadrivalent (and nonavalent; both Merck) HPV vaccines as well.[25] Alternatively, if the protective effect is mainly due to the adjuvant used (or differences in manufacturing of the virus-like particles), strong vaccine efficacies in fewer doses could be unique to the HPV-16/18 AS04-adjuvanted vaccine.

Our data for estimation of the efficacy of fewer than three doses, summarised here, have important limitations. The biggest concerns for this post-hoc, non-randomised study are that women who received one dose of vaccine have the possibility of increasingly greater immune response, and lower risk of infection, which could introduce biases. In previously published work from CVT, we assessed these possibilities directly and showed that antibody concentrations after the first dose in women who received one dose, two doses, or three doses are equivalent and HPV infection rates are also equivalent in the control group by dose group.[6,7] In this analysis, we are further reassured that biases do not explain these findings because the most common reason for missing doses seemed unrelated to vaccination group (ie, pregnancy) rather than immune-related events (eg, syncope or erythema), which could have suggested differential immune response by number of doses eventually received. Follow-up time was equivalent in all groups in both CVT and PATRICIA, and risk of HPV acquisition in the control group was generally similar in the groups who had a similar number of study visits (ie, all women who received one or two doses of control vaccine, and women in CVT who received three doses of control vaccine). Finally, despite combining of data from two large trials, the number of women who received one dose was small, allowing for assessment of virological endpoints but not histological endpoints. Most women received their second of only two doses 1 month after the first, a schedule now recognised as inferior to two doses given 6 months apart.[26] Continued active surveillance of women who received fewer than three doses after the 4 year study period is essential to ensure long-term duration of protection.

Post-hoc analyses in two randomised controlled trials independently identified similar results for efficacy against cervical HPV-16/18 infections, irrespective of the number of doses, during the 4 year study period. By combining summary-level data, we provide further support for the possibility that the benefit of vaccine efficacy against

	Number of women	Number of events	Person-years	Rate per 100 person-years (95% CI)	Vaccine efficacy (95% CI)
Incident one-time detection of HPV-16/18					
1 month					
HPV	300	12	1334	0·90 (0·49 to 1·53)	75·3% (54·2 to 87·5)
Control	283	44	1208	3·64 (2·68 to 4·85)	..
6 months					
HPV	97	3	441	0·68 (0·17 to 1·85)	82·6% (42·3 to 96·1)
Control	72	12	307	3·91 (2·12 to 6·65)	..
Incident one-time detection of HPV-31/33/45					
1 month					
HPV	303	36	1304	2·76 (1·96 to 3·78)	10·2% (–42·0 to 43·3)
Control	286	38	1236	3·07 (2·21 to 4·18)	..
6 months					
HPV	98	8	431	1·86 (0·86 to 3·53)	68·1% (27·0 to 87·0)*
Control	72	17	292	5·82 (3·50 to 9·13)	..

*The observed difference in the cross-protective vaccine efficacies was significantly greater in women who received their second dose at 6 months compared with 1 month (p=0·029).

Table 5: **Two-dose vaccine efficacy stratified by timing of the second dose for the modified total vaccinated cohort in the Costa Rica Vaccine Trial only**

Panel: Research in context

Systematic review

We searched the scientific literature before this study and found that convincing immunogenicity data now exist that suggest that two doses of the HPV vaccine given to adolescents 6 months apart evokes an immune response similar to that of three doses, for at least 4 years. Only one study published so far has assessed the efficacy of fewer than three doses of HPV vaccine—the Costa Rica Vaccine Trial—in a post-hoc analysis nested in this randomised controlled trial. Its findings suggested that strong efficacy was provided by the HPV-16/18 vaccine irrespective of the number of doses received.

Interpretation

These new data show similar findings of protection for 4 years irrespective of the number of doses received in the PATRICIA trial. Further, by combining the Costa Rica Vaccine Trial and PATRICIA trial data, we provide new evidence suggesting that two and one doses of the HPV-16/18 vaccine provide protection against cervical HPV-16/18 infections, similar to the protection provided by the full three-dose schedule for 4 years after vaccination. Two doses given 6 months apart also seemed to provide partial protection against HPV-31/33/45, similar to that reported for three doses. These data strongly argue for a direct assessment of one-dose efficacy of the HPV-16/18 vaccine.

heterologous HPV types is retained with two doses given 6 months apart, but perhaps not with administration of one dose or two closely spaced, priming doses. Because of the non-randomised nature of these analyses, the small sample size in the one-dose group, and the use of incident infection as the primary endpoint of this analysis, an endpoint not accepted by regulators as a surrogate for cervical cancer, policy is unlikely to change to recommend one dose of vaccine in response to this work. Yet, these new data argue strongly for additional assessments of this question.[27] Long-term population-effectiveness studies of girls vaccinated at young ages will be informative, but trials to directly investigate the vaccine efficacy of one dose will be necessary to motivate policy change. We recognise that decisions about implementation of HPV vaccination and cervical cancer screening are region specific, and typically need some microcosting or cost-effectiveness modelling. If one-dose HPV vaccine administration provides strong protection against HPV-16/18 for the long term, this approach might be what is necessary to overcome the barriers prohibiting vaccine uptake in many world regions.

Contributors

ARK, FS, MRDR-R, AH, SRS, SW, SMG, RH, M-PD, and CMW formed the manuscript core writing team. All authors, including group coauthors listed in the group below, have qualified for authorship in adherence with the ICMJE guidelines and have reviewed and commented upon a draft, gave final approval, and had final responsibility for the decision to submit for publication. All authors contributed towards study design, acquisition of data or statistical analyses, and interpretation of data.

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Declaration of interests
DD, FS, GD, and M-PD are employees of the GSK group of companies. M-PD, DD, GD, and FS own stock shares and stock options in the GSK group of companies and GD holds a relevant patent. CMW received funding to conduct the clinical trial and reimbursement for travel from the GSK group of companies via University of New Mexico, and reagents and equipment for HPV genotyping studies were provided to the University of New Mexico by Roche Molecular Systems. SMG reports she was a member of the Merck Cervical Cancer Global Advisory Board, Merck Scientific advisory board, and received fare and accommodation related to her participation, grants from the GSK group of companies paid via her institution to perform phase 3 trials of HPV vaccines, a researcher initiated grant from Merck Sharp & Dohme to perform surveillance RRP in Australia post-HPV vaccine, and a grant to her institution from CSL Bio for research on HPV and cancers. SRS has received, via her institution, grants for clinical trials, travel reimbursements, and honoraria to attend advisory board meetings and to present at educational meetings from the GSK group of companies. FXB has received grants for clinical trials and speaker fees from Merck Sharp & Dohme, Sanofi Pasteur MSD, and the GSK group of companies, and grants from Merck Sharp & Dohme and the GSK group of companies for educational presentations. XC has received grants from Merck Sharp & Dohme, Sanofi Pasteur MSD, and the GSK group of companies, and he has received non-financial support from Sanofi Pasteur MSD. AC has received honoraria for speaking engagements from Merck Sharp & Dohme and the GSK group of companies. DJML has received grants from the GSK group of companies via St George's University of London and University of Surrey for vaccine trials in Innovative Medicines Initiative project BIOVACSAFE. DRL reports that as a part of his US Government supported research at the National Cancer Institute/ National Institute of Health, he is the inventor of technology that underlies the L1-based prophylactic virus-like particle (VLP) HPV vaccine and technology that underlies an L2-based candidate prophylactic HPV vaccine. The NIH has licensed the technology for the L1 VLP vaccine to Merck, the manufacturer of Gardasil, to the GSK group of companies, the manufacturer of Cervarix, and Indian Immunologicals Ltd. The L2-based vaccine technology is the subject of a cooperative research and development agreement between the NCI, John Hopkins University, and Shantha Biotech, and has been licensed to Shantha, PanVax, Acambis Inc, and the GSK group of companies. US Federal Law entitles DRL to a limited share of royalties the NIH receives for their technologies. KP has received grants from the GSK group of companies for conducting the study. MRDR-R has received honorarium, travel support, and payment for lectures including speakers bureaus from the GSK group of companies. BRo has received grants for clinical trials from Merck Sharp & Dohme and the GSK group of companies and support for travel to meetings for the study or other purposes and consulting fees/honoraria paid via the B Romanowski corporation. JSa has received grants from Merck Sharp & Dohme, the GSK group of companies, and Qiagen. TFS has received honoraria from the GSK group of companies for being a member of advisory boards, lecturing, and conducting clinical trials. JTS is the inventor on US government owned patents and has several patents related to HPV VLP technology with royalties paid by the GSK group of companies and Merck Sharp & Dohme. JCT reports grants, personal fees and non-financial support from the GSK group of companies. AH, ARK, SW, RH, S-NC, FD-M, MJG, PG, DMH, SJ, GL, PN, LAP, CP, WAJP, BRa, ACR, MSa, MES, MSc, JSc, and WAAT have nothing to disclose.

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Could one dose of bivalent HPV vaccine prevent cervical cancer?

If human papillomavirus vaccines (HPV) could be delivered as one dose, while retaining their efficacy against the most oncogenic HPV types 16 and 18, we could substantially decrease the global burden of cervical cancer. Recent experience has shown how effective single vaccine dose pulse campaigns can be in even the most resource poor settings (eg meningitis A vaccines in sub-Saharan Africa[1]) and one could imagine mass campaigns every 5 to 10 years aiming to give a dose of HPV vaccine to, for example, all 9–14 year old girls. This campaign would not need ongoing resources to sustain annual vaccination programmes against HPV in settings with many pressing health priorities and small numbers of health-care workers. In *The Lancet Oncology*, Kreimer and colleagues[2] expand on the findings of the earlier analysis of the Costa Rica Vaccine Trial, which strongly suggests high efficacy of one or two doses of vaccine but without the power to definitively conclude this.[3] This analysis, which incorporates both the Costa Rican data and data from the large PATRICIA trial of the HPV-16/18 vaccine, confirms these findings of high efficacy against HPV-16/18 infection in women free from infection at baseline, irrespective of number of doses received.

The greatest challenge for the authors in interpretation of their findings is overcoming the fact that women were not randomly assigned to the dosage groups. Women who received only one or two doses did so mainly because they became pregnant, implying that these women might be at a lower risk of HPV infection than other women. However, because vaccine efficacy is a relative measure, comparison of event rates in the vaccine versus control group in each dose group requires women in each dose group to have the same HPV risk whether they received HPV vaccine or control vaccine. The data presented are very reassuring in this regard, with both age and rates of actual HPV infection with other non-vaccine-targeted HPV types being similar. Thus confounding or bias does not seem to explain the findings of high efficacy in each dose group. The plausibility of the finding is also high, in view of the corresponding immunogenicity data available from the Costa Rica trial, showing high concentrations of sustained HPV antibodies even after one dose.[4] This finding might relate to the adjuvant used by the bivalent vaccine or the antigen display by the virus-like particles in the vaccine mimicking the real virus.[5] Even though the endpoint chosen for the analysis of one-time HPV detection is a mechanistically distant surrogate for cancer, it is in fact a high bar for vaccine efficacy estimates because one-time detection might represent deposition from a partner rather than true infection, with such misclassification causing a relative dilution of our ability to measure the real effect of vaccination. Importantly, strong vaccine protection irrespective of dose was also shown for persistent infection, a recommended outcome measure for assessment of protection in prophylactic HPV vaccine trials.[6]

A new finding of this analysis is that fewer than three doses of bivalent HPV vaccine do not seem to have the same benefit against closely related HPV types (cross-protection) as three doses of the bivalent HPV vaccine. Hopefully further analysis investigating the magnitude and characteristics of the antibody concentrations against these non-targeted HPV types will provide some clues about what the immune-correlate of protection against HPV infection might be. A subanalysis within the study suggests that cross-protection might still occur if two doses are given separated by at least 6 months, corresponding to immunogenicity data supporting improved equivalence of such a prime-boost schedule to the three dose schedule. WHO endorsed two dose HPV schedules with a 6-month interval in young adolescents in 2014.[7]

These data suggest that one dose of bivalent HPV vaccine might be adequate to protect against HPV-16 and HPV-18 persistent infections and, therefore, probably disease. HPV-16 and HPV-18 cause more than 70% of cervical cancers and the vast majority of HPV-related cancers at other anatomic sites.[8] If this finding is confirmed, it opens up a great opportunity to extend the reach of protection using HPV vaccines to more people than we would have previously thought possible.

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