Immunogenicity of Quadrivalent HPV Vaccine Among Girls 11 to 13 Years of Age Vaccinated Using Alternative Dosing Schedules: Results 29 to 32 Months After Third Dose

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Background. Immune response to quadrivalent human papillomavirus (HPV) vaccine delivered at 0, 2, and 6 months in young adolescent females plateaus around 24 months after immunization. Antibody levels >24 months postvaccination using extended dosing schedules is unknown.

Methods. We conducted a follow-up immunogenicity study of adolescent girls in Vietnam who participated in a noninferiority trial to investigate whether immune responses using 3 alternative dosing schedules (0, 3, 9 months; 0, 6, 12 months; or 0, 12, 24 months) are noninferior to the standard schedule at >2 years after immunization.

Results. Quadrivalent HPV vaccine immunogenicity delivered on 3 alternative dosing schedules was noninferior for types 6, 11, 16, and 18 at 32 months post-dose 3 compared to the standard schedule. Pre-dose 3 antibody levels for the 0, 12, 24 month schedule were similar to those measured 32-months post-dose 3.

Conclusions. We found similar antibody concentrations ≥29 months after 3 doses of HPV vaccine regardless of dose-timing, and extended schedules do not produce inferior immune responses. Our findings also suggested that 2 doses of HPV vaccine delivered at 0 and 12 months might afford similar protection. Evidence supporting dosing flexibility could be important for national HPV vaccination policies.

Keywords. human papillomavirus; HPV vaccine; immunogenicity; adolescents; vaccination schedule; Vietnam.

BACKGROUND

Human papillomavirus (HPV) vaccines have elicited strong and sustained immune responses in both adult women followed for vaccine efficacy [1–7] and adolescent populations included in immune-bridging studies [8–10]. The 3-dose schedule (0, 2, and 6 months) induced high strain-specific antibody concentrations 1 month post-dose 3, and this response plateaued 24 months (after the first dose), with levels higher in younger populations [3, 5, 8, 9, 11–14]. Vaccine efficacy at least 8 years postimmunization is being maintained in adult women [3, 7], and recent studies have suggested that 2 doses are also efficacious [15].

A study among adolescents in Vietnam demonstrated that the immune response to HPV vaccines delivered on alternative schedules at 0, 3, 9 months and 0, 6, 12 months was noninferior to that produced when 3 doses were delivered according to the 0, 2, 6 month standard schedule [16]. This study was the first to our knowledge to measure immunogenicity of 3 doses delivered over a 2-year period. The results for the 0, 12, 24 month schedule were mixed: geometric mean titers (GMTs) for types 11 and 18 were similar to those found in the girls on the 0, 2, 6 month schedule, and GMTs for types 6 and 16 were lower than the standard schedule [16]. It was unclear whether the lower antibody responses seen with the yearly schedule were due to an age-dependent immune response (because the girls were older when they received the third dose).
or were an artifact of the time of the measurement—
1 month after the third dose of vaccine. When delivered on the
standard schedule, the immune response to HPV vaccine in
young adolescent females plateaus at 18 or 24 months after first
dose [9, 17, 18]. Whether a similar immune response plateau is
generated using alternative or extended schedules is still unknown.
Data from long-term immunogenicity studies in adolescents
could provide early indications on the persistence of antibody
titers, which is critical for understanding long-term duration of
protection and the effects of alternative schedules [19].

To understand the duration of the antibody response of
quadrivalent HPV vaccine generated with alternative vaccina-
tion schedules, we extended our previous study of girls 11–13
years of age in Vietnam[16] to investigate whether anti-HPV
16 and anti-HPV 18 immune responses >24 months post-dose
3 are noninferior using 3 different alternative dosing schedules
(0, 3, 9 months; 0, 6, 12 months; or 0, 12, 24 months) to those
obtained when the vaccine is administered on the standard
3-dose schedule of 0, 2, 6 months.

METHODS

We designed a cross-sectional immunogenicity study of adoles-
cents who received 3 doses of HPV vaccine and collected a
single 7-mL blood sample from girls who completed a previous
open-label, cluster-randomized trial of alternative dosing
schedules (NCT00524745) [16]. Girls on the standard 0, 2, 6
month schedule were followed up for 29 months, and those on
the alternative schedules were followed up for 32 months. An
interim immunogenicity measure at 20 months post-dose 3
was performed for girls on the 0, 12, 24 month alternative
schedule (Figure 1).

Consenting Procedures and Ethics Review

Parents of all girls eligible for this study were contacted by local
study personnel in collaboration with school leaders and teach-
ers at both primary and secondary schools in the study area
of Hoa Binh province, Vietnam. Parents were given written
information on this study—including the purpose, risks, and
benefits—and they were invited to attend a study information
meeting. Local study staff was available to answer parental
questions. Parents could consent at the time of approach, or
they could return the signed consent form with their daughter
up to the date of the scheduled blood draw. Written assent was
also obtained from the girl, either at the time of parental
consent or at the scheduled date of the blood draw. All consents
were additionally verified by study staff, and assent by the girl
was reaffirmed at the time of the blood draw.

This follow-up study and its procedures were approved by
institutional review boards in Vietnam (Ministry of Health and
National Institute of Hygiene and Epidemiology) and the
United States (Western Institutional Review Board).

Specimen Collection, Handling, and Analysis

All procedures for the collection, handling, storage, and trans-
port of blood/serum samples were completed in accordance
with the same procedures of the original trial [16]. Blood speci-
mens were collected and centrifuged in the field and stored on

![Figure 1](https://academic.oup.com/jid/article-abstract/208/8/1325/2193296)

**Figure 1.** Study schedule, cluster-randomized trial and follow-up study of alternative dosing schedules, quadrivalent human papillomavirus (HPV) vaccine, adolescent girls aged 11–13 years, Vietnam.
dry ice for transport to the central laboratory at the National Institute of Hygiene and Epidemiology in Hanoi, Vietnam. Two air shipments of samples were sent to Merck Research Laboratories (United States) in August 2011 and August 2012. The same type-specific competitive Luminex immunoassay was used by Merck (United States) to quantify levels of neutralizing antibodies for all 4 HPV types included in the vaccine.

Data Analysis
The primary outcome of noninferiority was defined as in the original trial: the lower bound of the multiplicity-adjusted 98.3% confidence interval for both the anti-HPV 16 and anti-HPV 18 GMT ratios between each alternative schedule and standard schedule was >0.50 [16]. The GMT ratios were compared using a t-test. A secondary outcome of noninferiority to non-cancer-causing HPV types 6 and 11 was also measured using the same GMT ratio thresholds. These noninferiority margins were based on those used in other quadrivalent vaccine immune-bridging studies [8, 9]. Geometric mean antibody titer levels for the 4 genotypes contained in the vaccine were also measured in samples collected at 20 months post-dose 3 from girls vaccinated on the 0, 12, 24 month alternative schedule, although noninferiority comparisons with the standard schedule were not performed, as a blood sample at a similar time point was not available from the standard schedule group. Mean age differences between girls participating in the follow-up study—and those who did not participate (but who were in the original trial)—were compared using ANOVA, and ethnic and urban/rural distributions were compared using the Cochran-Mantel-Haenszel test, adjusting for study groups. All statistical analyses were performed using SAS software version 9.3 (SAS Institute, Cary, North Carolina). No data were imputed; all missing data were treated as missing at random.

RESULTS
Of the 809 girls 11–13 years of age who completed the original study per protocol, 743 were eligible for this follow-up study (Figure 2). Due to the staggered start of the original trial, 66 girls from 2 schools vaccinated on the standard schedule were ineligible for the follow-up study, as the receipt of the third dose of HPV vaccine was more than 32 months from the start of the follow-up study. A total of 590 girls and their parents provided written consent to participate in the follow-up study.

![Figure 2](https://academic.oup.com/jid/article-abstract/208/8/1325/2193296)

<table>
<thead>
<tr>
<th>Schedule</th>
<th>N</th>
<th>Completed original trial*</th>
<th>Eligible for follow-up study</th>
<th>Consented</th>
<th>Withdraw</th>
<th>Complete study procedures</th>
<th>Loss to follow-up</th>
<th>Completed study procedures</th>
<th>Analysis population of follow-up study</th>
</tr>
</thead>
<tbody>
<tr>
<td>0, 2, 6 months</td>
<td>206</td>
<td>n=140†</td>
<td>n=197</td>
<td></td>
<td>n=8</td>
<td>n=101</td>
<td>n=20</td>
<td>n=135 (69%)</td>
<td></td>
</tr>
<tr>
<td>0, 3, 9 months</td>
<td>197</td>
<td>n=109</td>
<td></td>
<td>n=155</td>
<td></td>
<td>n=8</td>
<td></td>
<td></td>
<td>n=135 (69%)</td>
</tr>
<tr>
<td>0, 6, 12 months</td>
<td>193</td>
<td>n=193</td>
<td></td>
<td>n=167</td>
<td></td>
<td>n=7</td>
<td></td>
<td></td>
<td>n=160 (83%)</td>
</tr>
<tr>
<td>0, 12, 24 months</td>
<td>213</td>
<td>n=213</td>
<td></td>
<td>n=159</td>
<td></td>
<td>n=1</td>
<td></td>
<td></td>
<td>n=124 (58%)</td>
</tr>
</tbody>
</table>

*Completed all original trial study procedures and adapted from Neuzil KM, et al JAMA 2011 (see reference [16]). †Girls recruited from 2 schools in the original trial were ineligible for the follow-up study as the receipt of the third dose of HPV vaccine was >32 months from the start of the follow-up study.
of which 36 withdrew after consenting; 34 of those vaccinated on the 0, 12, 24 month schedule were lost to follow-up before the 32-month follow-up visit; and the remaining 520 provided a blood sample at 29–32 months post-dose 3. Samples from 2 subjects from the 0, 2, 6 month schedule were inadequate for testing, resulting in 518 girls (ie, 64% of those who completed the original trial) in this follow-up study (Figure 2).

The demographic information of girls participating in this follow-up study is summarized in Table 1. The mean age and urban/rural status of girls participating in the follow-up study were different compared to those who did not participate, adjusting for vaccination schedule (both P values < .01); however, ethnic distributions did not differ. Girls originally vaccinated on the 0, 12, 24 month schedule were consequently older at the 32-month follow-up visit, compared to girls who received 3 doses of HPV vaccine within a 1-year schedule (0, 2, 6 months; 0, 3, 9 months; or 0, 6, 12 months).

We found the immunogenicity of quadrivalent HPV vaccine—when delivered on any of the 3 alternative dosing schedules—was noninferior for types 6, 11, 16, and 18 at 32 months post-dose 3, compared to girls at 29 months post-dose 3 who were vaccinated on the 0, 2, 6 month standard schedule (Table 2). Anti-HPV 6, 11, 16, and 18 geometric mean titers produced were robust even at 29 to 32 months post-dose 3 for all vaccine administration schedules, with girls vaccinated on a 0, 12, 24 month schedule having consistently higher titers, regardless of HPV type, than all other schedules (Figures 3 and 4). The original trial noted that the antibody levels for all 4 HPV types prior to the administration of dose 3 (or “pre-dose 3”) were higher among girls vaccinated on the 0, 12, 24 month schedule in comparison to those vaccinated on other schedules [16]. The antibody levels 29 to 32 months post-dose 3 were similar to those previously reported prior to the third dose (Figures 3 and 4). The interim antibody titer measure at 20 months post-dose 3, among girls vaccinated on the 0, 12, 24 month schedule, showed lower titers than those measured 1 month after dose 3, but this was still elevated from the titers measured at 32 months post-dose 3, regardless of HPV type (Figures 3 and 4).

**DISCUSSION**

Antibody concentrations of quadrivalent HPV vaccine among adolescent girls produced following alternative dosing schedules, including a 0, 12, 24 month vaccination schedule, were noninferior to the concentrations generated from a standard 0, 2, 6 month vaccination schedule at 29 to 32 months post-vaccination. These results are in contrast to the original trial finding, in which the 0, 12, 24 month schedule was inferior to the standard schedule for 2 of 4 genotypes at 1 month post-dose 3 [16]. At the time, this finding was difficult to explain, because the pre-dose 3 antibody measurements were highest for the annual schedule. Our leading hypothesis at present is that the timing of the peak antibody response may differ depending on the schedule. Thus, a 1-month post-dose 3 measurement may not correlate well in assessing durability of titer levels over time when alternative schedules are employed.

This follow-up study also showed that the genotype-specific GMTs generated in adolescent girls in Vietnam at 29 to 32 months following the third dose were similar to those obtained from other follow-up immunogenicity studies among adolescent and young adult female populations (Table 3) [5, 8, 9, 16, 17, 20, 21, 22–24]. Table 3 summarizes the long-term immunogenicity studies of quadrivalent HPV vaccine in both adolescent and adult female populations using the same competitive Luminex immunoassay as our study measuring antibody levels in milli-Merck units with standardized cutoffs. These studies illustrate consistent antibody concentrations despite the differences in timing of the follow-up measurement. These studies illustrate consistent antibody concentrations despite the differences in timing of the follow-up measurement. These studies illustrate consistent antibody concentrations despite the differences in timing of the follow-up measurement. These studies illustrate consistent antibody concentrations despite the differences in timing of the follow-up measurement. These studies illustrate consistent antibody concentrations despite the differences in timing of the follow-up measurement. These studies illustrate consistent antibody concentrations despite the differences in timing of the follow-up measurement.
also found HPV vaccine-type antibodies depreciate over time with plateaus observed 18–24 months post-dose 3 [8, 9, 20, 21]. Dobson et al measured adolescent antibody responses to quadrivalent HPV vaccine at months 18, 24, and 36 and found similar plateaus [17, 23]. The antibody concentrations measured in our study were within similar ranges and may reflect plateauing as well, even though the length of time between vaccine initiation and the immunogenicity measurement ranged between 35 and 56 months. However, the difference in the timing of the measurements across studies must be considered when comparing results.

In a study by Block and colleagues, children 9–11 years of age produced higher concentrations of antibodies to quadrivalent HPV vaccine than children 13–15 years of age; children 12 years of age fell between these 2 groups [8]. Krajden and colleagues have noted a similar difference between children 9–3 years of age, and individuals 15–25 years of age, even when the younger age group was given only 2 doses of vaccine [25]. B-cell memory and T-cell immune responses have also been demonstrated to be stronger in younger adolescents [26]. We did not find a difference in antibody responses by age in this follow-up study, possibly because girls enrolled in the original trial were, on average, 12 years of age at the time of the first dose, for all 4 vaccination schedules. Girls vaccinated on the 0, 12, 24 schedule received their last dose at 14 or 15 years of age —ages where 1-month post-dose 3 antibody concentrations from immune-bridging studies have been demonstrated to be lower compared to younger girls [8, 9].

To achieve maximum public health benefits, HPV vaccination programs should reach as many girls as possible before onset of sexual activity and elicit protective immune responses throughout the period of sexual activity. In this regard, antibody concentrations measured 1 month after the third dose among pre-sexually active adolescents aged 11–13 years may be less clinically relevant than the long-term robustness of that response, maintained at a level at least as high as what has been demonstrated as efficacious in long-term follow-up studies [3, 5]. This emphasizes the importance of the finding that our 3-dose schedule delivered annually, while inferior at 1 month, was noninferior at >2 years after the third dose.

Our results suggest that the degradation curve of antibody titers after vaccination with quadrivalent HPV vaccine has a reduced slope when dosing intervals are 6 to 12 months apart, compared to the standard schedule of 0, 2, 6 months. This may suggest that delivering a single priming dose of HPV, followed by a booster dose or doses, may elicit the desired antibody response. Post hoc analysis comparing pre-dose 3 antibody GMTs measured in our original trial with those assessed 32 months after dose 3 for the 3 alternative schedules revealed that as the dosing schedule extended, type-specific pre-dose 3 antibody concentrations were either the same or higher than those measured 32 months post-dose 3 (Figures 3 and 4). Thus, for the 0, 3, 9 month schedule, antibody levels of HPV 6 and 18 were lower pre-dose 3 (P < .05) when compared to 32 months after dose 3; however, for the 0, 6, 12 month schedule, there were no differences in the antibody concentrations for any vaccine type between pre-dose 3 and 32 months post-dose 3 (P > .05) and for the 0, 12, 24 month schedule pre-dose 3 antibody concentrations were similar for HPV 6, 16, and 18 (P > .05) and higher for HPV 11 (P < .05) to those found 32 months post-dose 3. All pre-dose 3 vaccine-type antibody concentrations for the standard 0, 2, 6 month schedule were lower

<table>
<thead>
<tr>
<th>Abbreviations: CI, confidence interval; HPV, human papillomavirus.</th>
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<tbody>
<tr>
<td>a Noninferiority defined as lower-bound of the 98.3% CI for the GMT ratio is &gt;0.50 for both HPV 16 and HPV 18, and both HPV 6 and HPV 11.</td>
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<tr>
<td>b Adapted from Neuzil KM, et al JAMA 2011 (see reference [16]).</td>
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<tr>
<td>c Did not meet definition of noninferiority in the original trial.</td>
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</tbody>
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<table>
<thead>
<tr>
<th></th>
<th>Original Study, Intent-to-Treat Populationb</th>
<th>Follow-up Study Population</th>
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<tbody>
<tr>
<td></td>
<td>GMT ratio</td>
<td>GMT ratio</td>
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<tr>
<td></td>
<td>Compared to 0, 2, 6</td>
<td>Compared to 0, 2, 6</td>
</tr>
<tr>
<td>1 mo. post-dose 3 all schedules (98.3% CI)</td>
<td></td>
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<tr>
<td>HPV-16</td>
<td>0.92 (.71–1.20)</td>
<td>0.90 (.68–1.20)</td>
</tr>
<tr>
<td></td>
<td>0.98 (.75–1.29)</td>
<td>0.95 (.74–1.21)</td>
</tr>
<tr>
<td></td>
<td>0.64 (.48–.84)c</td>
<td>1.22 (.93–1.61)</td>
</tr>
<tr>
<td>HPV-18</td>
<td>0.87 (.68–1.11)</td>
<td>1.00 (.69–1.45)</td>
</tr>
<tr>
<td></td>
<td>0.91 (.71–1.17)</td>
<td>1.02 (.74–1.40)</td>
</tr>
<tr>
<td></td>
<td>0.77 (.62–.96)</td>
<td>1.16 (.81–1.66)</td>
</tr>
<tr>
<td>HPV-6</td>
<td>1.10 (.82–1.47)</td>
<td>0.94 (.71–1.26)</td>
</tr>
<tr>
<td></td>
<td>1.13 (.84–1.52)</td>
<td>1.04 (.82–1.33)</td>
</tr>
<tr>
<td></td>
<td>0.65 (.47–.92)c</td>
<td>1.37 (1.04–1.80)</td>
</tr>
<tr>
<td>HPV-11</td>
<td>0.86 (.70–1.06)</td>
<td>1.04 (.79–1.38)</td>
</tr>
<tr>
<td></td>
<td>0.86 (.69–1.06)</td>
<td>1.07 (.83–1.37)</td>
</tr>
<tr>
<td></td>
<td>0.96 (.80–1.16)</td>
<td>1.34 (.99–1.82)</td>
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than those measured 29 months post-dose 3. It may be that a longer delay for the administration of dose 2 (as long as 12 months after dose 1) allows the second dose to be the “boosting” dose, potentially negating the need for a third dose to perform this role. Other immunologic studies of HPV vaccines have suggested that the mechanism of action of HPV vaccines, due to its unique virus-like particle (VLP) structure, and the adjuvants incorporated in them, combine to generate an immune response that results in sufficient neutralizing antibody and B-cell immune memory to sustain high levels of protection [27–29].

New data from a vaccine trial suggest that efficacy against 12-month persistent HPV infection (a necessary precursor to cervical neoplasia) can be achieved with 2 doses of bivalent HPV vaccine, [15] with immune responses in adult women 18–25 years of age being lower than adolescents vaccinated with the same vaccine and followed up for the same amount of time [7, 11, 30]. Romanowski, et al found that 2 doses of bivalent HPV vaccine administered at 0, 6 months among adolescents resulted in higher level of antibodies 24 months after the last dose, compared to women 15–25 years of age who received 3 doses at 0, 1, and 6 months [18]. Even though these 2-dose, long-term immunogenicity data are for bivalent HPV vaccine, similar findings are emerging for quadrivalent HPV vaccine (Table 3) [17, 23]. Dobson et al recently reported that adolescent girls 9–13 years of age vaccinated with 2 doses of
quadrivalent HPV vaccine (0, 6 months) had immune responses 18, 24, and 36 months after dose 1 that were noninferior to those measured among adult women aged 16–26 years who were vaccinated at 0, 2, and 6 months [23].

Dosing flexibility without reduction in immunogenicity could facilitate more feasible vaccine delivery strategies. Even though immunogenicity does not infer efficacy, and there has yet to be determined a correlate of protection for HPV vaccines, [5] governments are taking action with the available evidence base, and adjusting the recommended dosing schedule in their national HPV vaccination programs. The provincial government of Quebec, Canada, and the national governments of Mexico and Colombia, have adopted a 0, 6, 60 month schedule [31]—presupposing that if current trends in immunogenicity hold true, the third dose may not be necessary. The provincial government of British Columbia, Canada, started their program with a 0, 6, 60 month schedule, and recently switched to a 2-dose 0, 6 month schedule [32]. The Chilean government’s national advisory committee for immunizations has recommended a 0, 12 month 2-dose schedule, based in part on the pre-dose 3 GMT immunogenicity reported in our original trial of alternative dosing schedules [16, 33].

Two dose schedules could be compelling for low-resource settings, as it would reduce the financial burden of purchasing and delivering 3 doses to adolescent girls, who may be difficult to follow up over time [34, 35]. Costing studies have found that the incremental financial costs of delivering HPV vaccine in low-resource settings ranges from US$0.50 to US$3.00 per

Figure 4. Anti-HPV 6 and anti-HPV 11 GMT antibody response (mMU/mL) pre-dose 3, and 1 month, 20 months*, and 29–32 months post-dose 3 by schedule†, adolescent females, Vietnam, 2007–2012. *20 month post-dose 3 measurement only assessed in Group 4 (0, 12, 24 month schedule). †All data points restricted subjects that completed all study procedures for both the original trial and follow-up study. Abbreviations: GMT, gross mean titer; HPV, human papillomavirus.
Table 3. Comparison of HPV16 and HPV18 GMT Antibody Responses, Competitive Luminex Immunoassay (cLIA), Studies of Quadrivalent HPV Vaccine, Female Adolescents and Young Adults

<table>
<thead>
<tr>
<th>Author</th>
<th>Reference</th>
<th>Ages/sex</th>
<th>Doses</th>
<th>Sched.</th>
<th>Just prior to dose 3</th>
<th>At mo. 7</th>
<th>At mo. 10–13</th>
<th>At mo. 18</th>
<th>At mo. 24–25</th>
<th>At mo. 35–36</th>
<th>At mo. 41–44</th>
<th>At mo. 56–60</th>
<th>At mo. 72</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reisinger K. S., et al; Ferris D., et al</td>
<td>[9, 22]  9–15 yo F</td>
<td>3</td>
<td>0, 2, 6</td>
<td>4490</td>
<td>1250</td>
<td>520.5c</td>
<td></td>
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<tr>
<td>Block S. L., et al</td>
<td>[8]</td>
<td>10–15 yo F</td>
<td>3</td>
<td>0, 2, 6</td>
<td>4697</td>
<td></td>
<td></td>
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<tr>
<td>Reisinger K. S., et al; Ferris D., et al</td>
<td>[9, 22]  9–15 yo F</td>
<td>3</td>
<td>0, 2, 6</td>
<td>1071</td>
<td>181</td>
<td>71c</td>
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<tr>
<td>Block S. L., et al</td>
<td>[8]</td>
<td>10–15 yo F</td>
<td>3</td>
<td>0, 2, 6</td>
<td>916</td>
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<td>3</td>
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<td>181</td>
<td>71c</td>
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<td></td>
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</table>

Abbreviations: CI, confidence interval; GMT, gross mean titer; HPV, human papillomavirus.

* Reference [22].

b Reference [1].

c Reference [3].

d Placebo arm of coadministration with Hepatitis B vaccine study; reference [24].

e Antibody response measured just prior to administration of 4th dose of HPV vaccine; reference [21].
dose, based on annual cohorts of girls 10 years of age receiving 3 doses [36, 37]. For many governments, the administrative cost of implementation is still too high. However, modeling studies could estimate implementation costs of annual campaigns of HPV vaccine for 2 doses to all girls 10 and 11 years of age (10 years of age for dose 1, and 11 years of age for dose 2), which could inform whether this delivery strategy and schedule could be more cost-effective than 3 doses. The financial cost may be reduced by at least one-third, with further reduction possible due to the need to mobilize health workers only once a year. For countries in Latin America, which already dedicate financial and human resources to implement Vaccination of the Americas week, [38] attaching HPV vaccine campaigns during this annual event may provide more savings over other delivery strategies for HPV vaccinations.

Limitations

Although we have been rigorous, we note limitations of our study. First, not all girls who participated in the original trial were available, or they were unable to participate in this follow-up study; also, they were not randomly selected for participation. Those who did participate may not represent the original trial population. In post hoc analysis, we restricted the original trial analysis to only those girls who participated in the follow-up study, and we found no difference in HPV 16, 18, 6, or 11 antibodies measured pre-dose 3 or 1-month post-dose 3, compared to those girls who were not in the follow-up study, for all 4 vaccine-dosing schedules. Therefore, we are confident that in terms of immune response, girls in the follow-up study are similar to those from the original trial. Second, we did not measure GMTs at 20 months among girls on all vaccine-dosing schedules; therefore, the 20-month post-dose 3 measurement provided for girls vaccinated at 0, 12, 24 months is exploratory, and caution should be used in interpretation. Third, we did not randomize girls to a 2-dose schedule; thus, all comparisons to pre-dose 3 GMTs with those measured after 3 doses should be tempered. Our post hoc analysis comparing these GMTs was also exploratory and the variation in duration between pre-dose 3 and 32-month post-dose 3 immune measures for each of the vaccination schedules may make interpretation difficult. However, the finding that pre-dose 3 GMTs were similar or higher to GMTs at 29–32 months as dosing intervals were extended is thought-provoking and warrants further research. Finally, an immune correlate of protection for HPV vaccine is unknown; the levels of HPV-type specific antibodies reported in this follow-up study are not necessarily the same as what may be necessary to be protected against disease endpoints. Further long-term studies of persistent infection and cervical neoplasia should be performed to understand HPV vaccine efficacy when administered on alternative dosing schedules.

Our follow-up study of the immune response of quadrivalent HPV vaccine administered on alternative dosing schedules has generated new evidence for dosing flexibility, suggesting that antibody titers plateau at similar levels 29–32 months after the third dose of vaccine, regardless of the timing of doses, and extended schedules do not produce inferior immune responses. Our finding that antibody concentrations after 2 doses of HPV vaccine on a 0, 12, 24 month schedule were similar to those measured at 29 months after the third dose of a 0, 2, 6 month schedule suggests that 2 doses of HPV vaccine delivered on an annual 0, 12 month schedule might afford similar protection. This hypothesis warrants exploration in a properly designed trial. The new data generated from this study combined with results from other follow-up studies of immunogenicity provide an expanded understanding of immune duration that countries can use, and have used, [31–33] when deliberating an appropriate vaccination schedule for their national HPV vaccination policy.

Notes

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