Cervical Cancer Is an Important Cause of Morbidity and Mortality Among Women Throughout the World. Each year, new cases of cervical cancer occur in approximately 529,000 women and 275,000 women die. An estimated 88% of deaths due to cervical cancer occur among women residing in developing countries. In Vietnam, cervical cancer is the fourth leading cause of cancer deaths among women, with significant disparities between regions. Inadequate access to cervical cancer screening and early intervention is the main cause of this health burden in inequity.

Human papillomaviruses (HPVs) are the primary cause of cervical cancer. Of the more than 100 identified HPV types, HPV-16 and HPV-18 account for 70% of cervical cancer cases; however, regional variations do exist. HPV-16 and HPV-18 are included in 2 of the HPV vaccine formulations currently licensed and prequalified by the World Health Organization. These vaccines are highly efficacious in preventing cervical precancers related to HPV-16 and HPV-18 when administered to women naive to these HPV types. Combined with continued strengthening of simple evidence-based screening and treatment approaches, effective HPV vaccine programs could reduce cervical cancer rates in developing countries.1,2

Immunogenicity and Reactogenicity of Alternative Schedules of HPV Vaccine in Vietnam
A Cluster Randomized Noninferiority Trial

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Context Human papillomavirus (HPV) vaccine programs may decrease the morbidity and mortality due to cervical cancer seen among women in low-resource countries. However, the 3-dose schedule over a 6-month period is a potential barrier to vaccine introduction in such settings.

Objective To determine the immunogenicity and reactogenicity of different dosing schedules of quadrivalent HPV vaccine in adolescent girls in Vietnam.

Design, Setting, and Participants Open-label, cluster randomized, noninferiority study (conducted between October 2007 and January 2010) assessing 4 schedules of an HPV vaccine delivered in 21 schools to 903 adolescent girls (aged 11-13 years at enrollment) living in northwestern Vietnam.

Intervention Intramuscular injection of 3 doses of quadrivalent HPV vaccine delivered on a standard dosing schedule (at 0, 2, and 6 months) and 3 alternative dosing schedules (at 0, 3, and 9 months; at 0, 6, and 12 months; or at 0, 12, and 24 months).

Main Outcome Measures Serum anti-HPV geometric mean titers (GMT) measured 1 month after the third dose of the HPV vaccine was administered; GMT was determined by type-specific competitive immunoassay. Noninferiority of each alternative vaccination schedule was achieved if the lower bound of the multiplicity-adjusted confidence interval (CI) of the type-specific GMT ratio for HPV-16 and HPV-18 was greater than 0.5 (primary outcome). Safety outcomes were immediate reactions, local reactions, fever within 7 days after each dose, and serious adverse events up to 30 days following the last dose.

Results In the intention-to-treat analysis, 809 girls who received at least 1 HPV vaccine dose had valid serum measurements 1 month after the third dose. After the third dose, the GMTs for those in the standard schedule group who received doses at 0, 2, and 6 months were 5808.0 (95% CI, 4961.4-6799.0) for HPV-16 and 1729.9 (95% CI, 1504.0-1989.7) for HPV-18; 5368.5 (95% CI, 4632.4-6221.5) and 1502.1 (95% CI, 1302.1-1733.2), respectively, for those who received doses at 0, 3, and 9 months; 5716.4 (95% CI, 4876.7-6700.6) and 1581.5 (95% CI, 1363.4-1834.6), respectively, for those who received doses at 0, 6, and 12 months; and 3692.5 (95% CI, 3145.3-4334.9) and 1335.7 (95% CI, 1191.6-1497.3), respectively, for those who received doses at 0, 12, and 24 months. Prespecified noninferiority criteria were met for the alternative schedule groups that received doses at 0, 3, and 9 months (HPV-16 GMT ratio: 0.92 [95% CI, 0.71-1.20]; HPV-18 GMT ratio: 0.87 [95% CI, 0.68-1.11]) and at 0, 6, and 12 months (HPV-16 GMT ratio: 0.98 [95% CI, 0.75-1.29]; HPV-18 GMT ratio: 0.91 [95% CI, 0.71-1.17]). Prespecified noninferiority criteria were not met for the alternative schedule group that received doses at 0, 12, and 24 months (HPV-16 GMT ratio: 0.64 [95% CI, 0.48-0.84]; HPV-18 GMT ratio: 0.77 [95% CI, 0.62-0.96]). Pain at the injection site was the most common adverse event.

Conclusions Among adolescent girls in Vietnam, administration of the HPV vaccine on standard and alternative schedules was immunogenic and well tolerated. The use of 2 alternative dosing schedules (at 0, 3, and 9 months and at 0, 6, and 12 months) compared with a standard schedule (at 0, 2, and 6 months) did not result in inferior antibody concentrations.

Trial Registration clinicaltrials.gov Identifier: NCT00524745

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tries to the low levels currently observed in many developed countries.\textsuperscript{12-14}

One challenge to broadly implementing HPV vaccination programs in developing countries will be delivering the currently recommended 3 doses of vaccine to adolescents within 6 months (dosing schedules at 0, 2, and 6 months or at 0, 1, and 6 months). Even in settings in which such vaccination schedules are feasible, schedule variations may occur. We conducted a school-based, cluster-randomized noninferiority trial in northwestern Vietnam to determine the immunogenicity and reactogenicity of alternative schedules of quadrivalent HPV vaccine.

**METHODS**

This open-label, cluster randomized, noninferiority study compared the immunogenicity and safety of 3 alternative dosing schedules of quadrivalent (HPV-6, HPV-11, HPV-16, and HPV-18) HPV vaccine (Gardasil, Merck & Co Inc, Whitehouse Station, New Jersey) with the standard dosing schedule in 11- to 13-year-old girls in Hoa Binh province, a mountainous primarily rural region in northwestern Vietnam. Hoa Binh has a population of approximately 785,000, of which an estimated 33\% are adolescents.\textsuperscript{15} The study was conducted between October 2007 and January 2010. Twenty-one schools in the province were pre-stratified to achieve 4 school groups similar in size, urban or rural location, and ethnic mix of the student population. Written informed consent was obtained from all parents and written assent was obtained from all participants.

Each school group was randomly assigned by PATH staff by pulling folded pieces of paper with each group number from an opaque container to a 3-dose HPV vaccine schedule at 0, 2, and 6 months (standard schedule) or 1 of 3 alternative dosing schedules at 0, 3, and 9 months, 0, 6, and 12 months, or 0, 12, and 24 months. The alternative dosing schedule at 0, 3, and 9 months would be less restrictive than the currently licensed schedule at 0, 2, and 6 months, but would still be completed within a single school year. This schedule also could be useful in quarterly outreach services that are conducted in isolated parts of Vietnam. The semiannual schedule (with doses administered at 0, 6, and 12 months) could be planned to coincide with semiannual health days held in certain low-resource countries.\textsuperscript{16} The annual vaccination schedule (at 0, 12, and 24 months) could be part of annual health programs at schools and may ultimately be compatible with efforts to reach school-aged girls with tetanus toxoid vaccine as part of the initiative to eliminate neonatal tetanus.\textsuperscript{17}

Our study was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice (as defined by the International Conference on Harmonisation), and Vietnamese regulatory requirements and was approved by the institutional review board of the National Institute of Hygiene and Epidemiology in Vietnam, the institutional review board of the Vietnam Ministry of Health, and the Western institutional review board in the United States.

Healthy adolescent girls aged 11 through 13 years in grades 6 or 7 were enrolled in the study. The vaccine schedules were not known to the schools or students at the time of enrollment. Exclusion criteria included prior HPV vaccination; pregnant or lactating or intending to become pregnant during the study period; moderate or severe acute illness at the time of vaccination; clinical history of a bleeding disorder; clinical history of impaired immune responsiveness; hypersensitivity to the active substances or any excipient of the HPV vaccine or reactions to other vaccines in the past; and receipt of an investigational drug or vaccine from 30 days prior to 30 days after any dose of the study vaccine.

Ethnicity was classified by the participants according to options defined by the investigators. Ethnicity was assessed to enable adjustment for potential differences among study groups in the analysis.

Participants who met the eligibility criteria for enrollment received three 0.5-mL doses of quadrivalent HPV vaccine administered intramuscularly in the deltoid region according to the schedule assigned to their school. Once the vaccinations began, participants, schools, and study staff were no longer masked to the assigned vaccine schedule.

Participants were monitored by study staff for immediate adverse events, which were defined as those occurring within 30 minutes following a vaccine injection. Solicited adverse events (local reactions and fever) and unsolicited adverse events were recorded for 7 days by the participants on a daily diary card beginning on the day of the vaccination. Axillary temperature was measured using a digital thermometer and recorded by the participant on the diary card. All serious adverse events occurring up to 30 days following the last dose of vaccine were documented by study staff. Serious adverse events were classified using the US regulatory definition, in line with guidance by the International Conference on Harmonisation, and identified by query at each participant visit or by parental or participant report at any time.

For assessment of immune responses to the HPV vaccine, blood samples were taken by local study staff before each participant received the first vaccine dose, and immediately before and 30 days following the third dose. Levels of neutralizing antibodies were quantified using a type-specific competitive Luminex immunoassay performed by Merck & Co Inc.\textsuperscript{18} Merck & Co Inc were masked to participant identification and group vaccination schedule assignment.

The primary study outcome was immunogenicity to HPV-16 and HPV-18 determined by anti-HPV geometric mean titer (GMT) 1 month after receipt of the third dose of the HPV vaccine. A secondary outcome was immunogenicity to HPV-6 and HPV-11 determined by anti-HPV GMT 1 month after receipt of the third dose of vaccine. The GMTs for the different HPV
For the primary immunogenicity analysis, anti–HPV-16 and anti–HPV-18 GMTs were summarized for each vaccination schedule study group. Each of the 3 alternative schedules was evaluated separately against the standard group. Multiplicity-adjusted \( 98.3\% \) confidence intervals (CIs) were calculated for the ratio of HPV type-specific GMTs measured postvaccination dose 3 for each of the 3 alternative schedules compared with the standard schedule using a \( t \) test. The primary objective of 1-sided noninferiority testing for each alternative vaccination schedule compared with the standard schedule for HPV-16 and HPV-18 was achieved at a significance level of .008 if the lower bound of the multiplicity-adjusted CI of the type-specific GMT ratio for HPV-16 and HPV-18 was greater than 0.5. The noninferiority margin was based on preestablished standards from the US Food and Drug Administration that are used by Merck & Co Inc for other bridging studies.\(^{19-21}\)

**Figure.** Trial of Alternative Schedules of Human Papillomavirus Vaccine (HPV) in Adolescent Girls in Northwestern Vietnam

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1. **Dose 1**
   - 21 Schools in Vietnam prestratified to 4 groups based on location, size, and ethnic distribution (N = 1857 girls enrolled in grades 6 and 7)
   - 5 Schools randomized to standard HPV vaccination schedule at 0, 2, and 6 mo (227 girls; mean: 45 girls/school; range: 26-62)
   - 6 Schools randomized to alternative HPV vaccination schedule at 0, 3, and 9 mo (229 girls; mean: 38 girls/school; range: 28-51)
   - 4 Schools randomized to alternative HPV vaccination schedule at 0, 6, and 12 mo (206 girls; mean: 34 girls/school; range: 2-62)

2. **Dose 2**
   - 21 Schools in Vietnam prestratified to 4 groups based on location, size, and ethnic distribution (N = 1857 girls enrolled in grades 6 and 7)
   - 5 Schools randomized to standard HPV vaccination schedule at 0, 2, and 6 mo (227 girls; mean: 45 girls/school; range: 26-62)
   - 6 Schools randomized to alternative HPV vaccination schedule at 0, 3, and 9 mo (229 girls; mean: 38 girls/school; range: 28-51)
   - 4 Schools randomized to alternative HPV vaccination schedule at 0, 6, and 12 mo (206 girls; mean: 34 girls/school; range: 2-62)

3. **Dose 3**
   - 21 Schools in Vietnam prestratified to 4 groups based on location, size, and ethnic distribution (N = 1857 girls enrolled in grades 6 and 7)
   - 5 Schools randomized to standard HPV vaccination schedule at 0, 2, and 6 mo (227 girls; mean: 45 girls/school; range: 26-62)
   - 6 Schools randomized to alternative HPV vaccination schedule at 0, 3, and 9 mo (229 girls; mean: 38 girls/school; range: 28-51)
   - 4 Schools randomized to alternative HPV vaccination schedule at 0, 6, and 12 mo (206 girls; mean: 34 girls/school; range: 2-62)
Assuming standard deviations of the natural log titers used by Merck & Co Inc for other bridging studies and allowing for a dropout rate of 15%, a sample size of 200 participants per group provided at least 90% power for the primary immunogenicity hypothesis. A secondary immunogenicity analysis was conducted on anti-HPV-6 and anti-HPV-11 responses using the same methods.

The intention-to-treat (ITT) analysis was defined as all participants who received at least 1 dose of vaccine regardless of baseline serostatus. The per-protocol analysis was based on all participants who received 3 doses of vaccine according to 1 of the study’s vaccine dosing schedules, were seronegative to the relevant HPV type at baseline, and had a valid serology result after the third dose of the HPV vaccine.

PATH staff performed and were responsible for the statistical analysis. All statistical analyses were performed using SAS software version 9.1.3 (SAS Institute Inc, Cary, North Carolina). No data were imputed; all missing data were treated as missing at random.

The reactogenicity analysis was conducted for the ITT population. Adverse events were summarized descriptively as frequencies and percentages by group, type of event, and severity. The safety profile was parameterized as the proportion of participants experiencing specific symptoms in the following categories: immediate reactogenicity (≤30 minutes postvaccination); solicited (local reactogenicity and fever) and unsolicited events occurring during the first 7 days following each vaccination; and all serious adverse events occurring up to 1 month following the last dose of the vaccine. Proportions of these safety end points were calculated along with their exact 95% CIs for each study group.

**RESULTS**

Between September and December 2007, 903 girls from 21 schools were enrolled. Of these, 809 girls (89.6%) received all 3 doses of vaccine and had a serum sample available for testing after the final dose of the HPV vaccine. Detailed participant loss to follow-up and discontinuations are shown in the FIGURE. Among all blood draws during the study, serum measurements were missing for only 2 participants. There were no significant differences in the ages of the adolescent girls at the time of enrollment in the 4 vaccination schedule groups. There were statistically significant differences in the distribution of ethnicity and urban or rural residence of the girls among the 4 vaccination schedule groups (Table 1).

A school-based measles vaccine campaign occurred in the fall of 2007 in Vietnam and coincided with the timing of this study. Girls attending the schools randomized to the standard dosing schedule at 0, 2, and 6 months and the alternative dosing schedule group at 0, 3, and 9 months received the measles vaccine more than 30 days before receipt of the HPV vaccine. However, nearly all of the girls in the alternative dosing schedule groups at 0, 6, and 12 months (204/206 girls) and at 0, 12, and 24 months (236/241 girls) received the measles vaccine 12 to 27 days prior to their first HPV dose.

For all 4 vaccination schedule groups and vaccine types, the HPV GMTs were low at baseline and increased significantly after receipt of 3 doses of the vaccine. For the ITT population and compared with the standard schedule group at 0, 2, and 6 months, the alternative schedule groups at 0, 3, and 9 months and 0, 6, and 12 months met noninferiority criteria for the anti–HPV-16 and anti–HPV-18 responses at 1 month after receipt of the third dose (Table 2). Compared with the standard schedule group, the alternative schedule group at 0, 12, and 24 months met noninferiority criteria for HPV-18 but not for HPV-16. Results were similar among the groups after adjustment for the baseline characteristics of age, ethnicity, and urban or rural residence (eTable 1 at http://www.jama.com). Because only 3 girls were seropositive for HPV-16 at baseline and no girls were seropositive to HPV-18, the results of the per-protocol analysis for the primary outcome were similar to the ITT analysis (Table 2).

Compared with the standard dosing schedule group at 0, 2, and 6 months, the alternative schedule groups at 0, 3, and 9 months and 0, 6, and 12 months met noninferiority criteria for the anti–HPV-6 and HPV-11 responses at 1 month after receipt of

**Table 1. Participant Demographics**

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Standard Schedule at 0, 2, 6 mo (n = 227)</th>
<th>Alternative Schedule at 0, 3, 9 mo (n = 229)</th>
<th>At 0, 6, 12 mo (n = 206)</th>
<th>At 0, 12, 24 mo (n = 241)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muong</td>
<td>192 (84.6)</td>
<td>155 (67.7)</td>
<td>150 (72.8)</td>
<td>179 (74.3)</td>
</tr>
<tr>
<td>Khinh</td>
<td>34 (15.0)</td>
<td>70 (30.6)</td>
<td>52 (25.2)</td>
<td>61 (25.3)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.4)</td>
<td>4 (1.7)</td>
<td>4 (1.9)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>School location</td>
<td>Rural 183 (80.6)</td>
<td>150 (65.5)</td>
<td>149 (72.3)</td>
<td>189 (78.4)</td>
</tr>
<tr>
<td>Urban</td>
<td>44 (19.4)</td>
<td>79 (34.5)</td>
<td>57 (27.7)</td>
<td>52 (21.6)</td>
</tr>
</tbody>
</table>

Abbreviation: HPV, human papillomavirus.

aValues are expressed as numbers (percentage) unless otherwise indicated.

bEthnic minority (dominant ethnic group in this province).

cLargest ethnic group in Vietnam.

For the standard schedule group, there was 1 person who was Nung. For the alternative schedule group at 0, 3, and 9 months, there were 2 persons who were Dao and 2 who were Tay. For the alternative schedule group at 0, 6, and 12 months, there were 2 persons who were Tay, and 1 person each who were Thai and Nung. For the alternative schedule group at 0, 12, and 24 months, there was 1 person who was Dao.
the third dose (Table 2). Noninferiority was demonstrated for the alternative dosing group at 0, 12, and 24 months compared with the standard schedule group for HPV-11 but not for HPV-6. Because only 19 girls were seropositive to HPV-6 and 2 girls were seropositive to HPV-11 at baseline, the results of the ITT and per-protocol analyses for the secondary immunogenicity outcome were similar (Table 2).

For the prespecified exploratory analysis, robust anti–HPV GMTs prior to dose 3 were observed in all groups for all HPV types (Table 3). In contrast to the results after the third dose, the GMTs prior to the third dose were lowest in the standard schedule group and highest in the alternative schedule group at 0, 12, and 24 months for all 4 HPV types.

Safety was evaluated in all 903 girls who received at least 1 dose of

<table>
<thead>
<tr>
<th>Table 2. Noninferiority of Geometric Mean Titer (GMT) Ratios After the Third Dose in Girls Receiving Human Papillomavirus (HPV) Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GMT Ratio (98.3% CI)</strong> for Alternative Schedule Dosing Group/Standard Schedule Dosing Group</td>
</tr>
<tr>
<td><strong>ITT Analysis</strong>a</td>
</tr>
<tr>
<td><strong>Dose at 0, 3, 9 mo</strong> (n = 197)/ at 0, 2, 6 mo</td>
</tr>
<tr>
<td>HPV-16 0.92 (0.71-1.20)</td>
</tr>
<tr>
<td>HPV-18 0.87 (0.68-1.11)</td>
</tr>
<tr>
<td>HPV-6 1.10 (0.82-1.47)</td>
</tr>
<tr>
<td>HPV-11 0.86 (0.70-1.05)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ITT, intention to treat.

†In the standard schedule dosing group at 0, 2, and 6 months, there were 206 girls. The number of participants in the column headings reflects the number of girls in each alternative schedule dosing group.

‡Includes only girls who were seronegative at baseline, received the 3 doses of vaccine on schedule, and had a valid serology result after the third dose.

§In the standard schedule dosing group at 0, 2, and 6 months, there were 205 girls for HPV-16, HPV-18, and HPV-11 and there were 203 girls for HPV-6. The number of participants in each row and column reflects the number of girls in each alternative schedule dosing group.

<table>
<thead>
<tr>
<th>Table 3. Geometric Mean Titer (GMT) Antibody Response Before and After the Third Vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GMT (95% CI)</strong></td>
</tr>
<tr>
<td><strong>Intention-to-Treat Population</strong></td>
</tr>
<tr>
<td><strong>At 0, 2, 6 mo</strong></td>
</tr>
<tr>
<td>HPV-16 Predose 3 667.8 (584.6-762.9)</td>
</tr>
<tr>
<td>Postdose 3 5808.0 (4961.4-6799.0)</td>
</tr>
<tr>
<td>HPV-18 Predose 3 77.5 (67.5-89.1)</td>
</tr>
<tr>
<td>Postdose 3 1729.9 (1504.0-1989.7)</td>
</tr>
<tr>
<td>HPV-6 Predose 3 119.8 (105.6-135.9)</td>
</tr>
<tr>
<td>Postdose 3 1008.7 (851.0-1195.7)</td>
</tr>
<tr>
<td>HPV-11 Predose 3 181.3 (161.0-204.0)</td>
</tr>
<tr>
<td>Postdose 3 1612.1 (1434.7-1811.4)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HPV, human papillomavirus.

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the HPV vaccine. The vaccine was generally well tolerated in each dosing schedule group. Eight girls experienced a reaction, including weakness, nausea, sweating, pale skin, and vomiting, within 30 minutes of injection. No episodes of fainting, allergic, or anaphylactic reactions occurred during the 30-minute observation period. The proportion of participants who reported solicited adverse events following any vaccination was comparable across groups (TABLE 4). Unsolicited events also were similar (eTable 2 at http://www.jama.com).

Pain at the injection site was the most common adverse event in all groups. Pain was most commonly reported on the day of vaccination, and most episodes were classified as mild. No serious adverse events occurred within 30 days of each vaccination. No deaths, vaccine-related serious adverse events, or pregnancies were reported throughout the study.

**COMMENT**

In this cluster-randomized, open-label noninferiority trial, the quadrivalent HPV vaccine administered on standard and alternative schedules was highly immunogenic in adolescent girls in Vietnam. The majority of girls were seronegative to all HPV vaccine types at baseline as expected given that the mean age at enrollment was 12 years and the average age for onset of sexual activity in Vietnam is 19.6 years. For the alternative dosing schedule groups at 0, 3, and 9 months and at 0, 6, and 12 months, the antibody response after the third dose was noninferior to the standard dosing schedule at 0, 2, and 6 months based on our prespecified definition. These data are consistent with the results of a study in college-aged women in the United States, in which quadrivalent HPV vaccine given on a schedule at 0, 2, and 12 months was noninferior to the standard schedule. The quadrivalent HPV vaccine administered on all 3 alternative dosing schedules was well tolerated and the safety profiles were comparable with the standard dosing schedule.

The efficacy of the quadrivalent HPV vaccine in preventing precancerous lesions and genital warts related to HPV-6, HPV-11, HPV-16, and HPV-18 has been established in women aged 16 to 26 years. A minimum HPV antibody concentration that confers protective efficacy has not been determined. However, the US Food and Drug Administration and other regulatory agencies have allowed licensure of the vaccine in other age groups based on immunogenicity bridging studies. In such studies, the HPV antibody concentrations elicited after receipt of 3 doses of the quadrivalent vaccine have been consistently higher among adolescent cohorts compared with cohorts of women aged 16 to 26 years. Similarly, the anti–HPV GMTs in the standard and alternative dosing groups (including the yearly schedule) in this group of Vietnamese adolescents were higher than what has been reported in women aged 16 years or older for all 4 HPV types. Likewise, the antibody responses for the standard dosing schedule and the alternative schedules at 0, 3, and 9 months and 0, 6, and 12 months were comparable with those reported among adolescents in other regions.

For the yearly vaccination schedule, the results relative to the standard dosing schedule differed by HPV vaccine type. Our primary hypothesis required that both HPV-16 and HPV-18 serotypes meet noninferiority criteria. The lower bound of the CI for the HPV-16 serotype fell just below 0.5; thus, the prespecified noninferiority criterion was not reached. However, while antibody concentrations were lower than those achieved with other dosing schedules in this study, they were above what has been reported in women aged 16 to 26 years. Thus, without a correlate of protection, it is difficult to know if these lower anti–HPV GMTs will translate to significantly different efficacies against important clinical outcomes, such as high-grade precancerous lesions.

**Table 4. Participants With Solicited Adverse Events Reported During Days 1 Through 7 Postvaccination**

<table>
<thead>
<tr>
<th>HPV Vaccination Schedule</th>
<th>Fever</th>
<th>Pain at injection site</th>
<th>Itching</th>
<th>Redness</th>
<th>Swelling</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 0, 2, 6 mo</td>
<td>(n = 227)</td>
<td>5 (2.2)</td>
<td>120 (52.9)</td>
<td>5 (2.2)</td>
<td>28 (13.3)</td>
</tr>
<tr>
<td>At 0, 3, 9 mo</td>
<td>(n = 229)</td>
<td>6 (2.6)</td>
<td>133 (68.1)</td>
<td>8 (3.5)</td>
<td>42 (19.4)</td>
</tr>
<tr>
<td>At 0, 6, 12 mo</td>
<td>(n = 206)</td>
<td>4 (1.9)</td>
<td>96 (46.6)</td>
<td>7 (3.4)</td>
<td>13 (6.7)</td>
</tr>
<tr>
<td>At 0, 12, 24 mo</td>
<td>(n = 240)</td>
<td>7 (2.9)</td>
<td>114 (47.5)</td>
<td>6 (2.5)</td>
<td>28 (13.1)</td>
</tr>
</tbody>
</table>

Abbreviation: HPV, human papillomavirus. Values are expressed as number (percentage) of participants. Indicates temperature of 37.8°C or higher.
uous lesions. Similarly, for the secondary immunogenicity outcome, noninferiority criteria were met for HPV-11 but not for HPV-6; thus, the overall predefined noninferiority criteria were not achieved.

There was a consistent trend when we performed a predefined exploratory analysis comparing antibody levels prior to the third dose between the study groups for all HPV types of increased antibody levels with increasing dosing intervals between the first and second doses. The highest antibody levels prior to the third dose appeared in the alternative schedule group at 0, 12, and 24 months (Table 3). This is surprising given that antibody levels wane over time and the schedule group at 0, 12, and 24 months had the longest interval between receipt of the second dose and timing of the blood draw prior to the third dose. Thus, one might speculate that antibody levels were higher in the dosing schedule group at 0, 12, and 24 months than in the other dosing schedule groups following the second dose of vaccine. The robust GMTs prior to the third dose in relation to the GMTs after the third dose in the yearly dosing group is puzzling. Because age is an important determinant of antibody response, it is possible that the older age of the girls at the time of receipt of the third dose of vaccine (on average 12.5 and 14 years for the standard and yearly schedules, respectively) led to the lower postdose antibody response. An alternative hypothesis is that the high antibody concentrations prior to the third dose inhibited or altered the kinetics of the response to the third dose of vaccine. With the standard dosing schedule, antibody levels of women aged 16 to 26 years reach a steady state approximately 2 years after receipt of the third dose of vaccine. Extended follow-up of participants in our study is under way and will be informative in determining whether longer-term antibody responses are affected by dosing schedule. Furthermore, particularly in low-resource settings, understanding the performance of a 2-dose relative to a 3-dose schedule is important to inform options for use of the vaccine. Such a study is ongoing in adolescent girls in Canada, and antibody concentrations after the second dose have been robust in interim analyses.

This study was limited by its cluster-randomized design. For logistic reasons, we randomized the groups by school and not by individual. To account for any potential effects of differences among groups, we adjusted for baseline differences in ethnicity and urban or rural distribution in our analysis. However, because a school measles vaccine campaign was conducted during the time of the third study, receipt of the measles vaccine occurred within 30 days of the first dose of the HPV vaccine in the majority of girls in the alternative dosing groups at 0, 6, and 12 months and at 0, 12, and 24 months while the girls in the standard dosing schedule group at 0, 2, and 6 months and in the alternative dosing group at 0, 3, and 9 months received the measles vaccine outside of the 30-day window.

While the measles vaccine has been shown to affect certain T-cell–mediated immune responses, it has not been shown to have an effect on the antibody response to inactivated vaccines; however, a specific effect on the HPV vaccine has not been studied. In a post hoc analysis, we found no significant association between timing of administration of the measles vaccine and antibody response at the time points prior to the third dose and after the third dose for the dosing schedule groups at 0, 6, and 12 months and at 0, 12, and 24 months. It is unlikely that receipt of measles vaccine in proximity to dose 1 accounted for the lower antibody levels after the third dose in the schedule group at 0, 12, and 24 months, given the high concentrations prior to dose 3.

The similarity of the immunogenicity and reactogenicity profiles of the HPV vaccine reported from this predominantly ethnic minority population in a low-resource area of Vietnam and other populations throughout the world is reassuring and supports more widespread introduction of the vaccine. The World Health Organization acknowledges that programmatic constraints must be considered in the decision to commence national HPV immunization programs. The option of delivering HPV vaccine on flexible schedules will allow countries to minimize costs and maximize feasibility according to local vaccination practices.

Although the price of HPV vaccines in certain low-resource markets has declined since 2006, price remains a significant barrier to widespread introduction of HPV vaccine in areas of greatest need. Innovative financing solutions such as the PAHO (Pan American Health Organization) Revolving Fund for bulk purchase of vaccines that brought down the price in Latin America are needed to accelerate access to HPV vaccines in places where the cervical cancer burden is the highest.

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REFERENCES


