The Impact on Wastage for Different Vaccine Vial Sizes

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HPV Vaccination Session Size: The Impact on Wastage for Different Vaccine Vial Sizes

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Acknowledgments

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Introduction

Cervical cancer accounts for the deaths of over 270,000 women worldwide per year.1 Of these, nearly 85 percent occur in the developing world.1 In recent years, two vaccines for cervical cancer, Gardasil® and Cervarix®, became available. These vaccines are effective against the two strains of the human papillomavirus (HPV) that account for roughly 70 percent of all cervical cancer.2–4 Each vaccine regimen requires three doses, given through a variety of optional schedules over six months. The primary targets for these vaccines are young adolescent girls.

The World Health Organization (WHO) recently pre-qualified both vaccines,5,6 making it possible for United Nations agencies to procure and supply them to interested countries. This also made the vaccines eligible for inclusion in the Global Alliance for Vaccines and Immunization’s (GAVI) portfolio of subsidized vaccines subject to GAVI Board determination. The vaccines are now available in single-dose presentations without preservative, and WHO has given conditional approval to a multi-dose (2-dose) presentation without preservative for Cervarix®. As of this writing, HPV vaccines in a single-dose presentation have been delivered in a limited number of public-sector, developing-world immunization programs for demonstration purposes. The single-dose presentation may or may not be ideal for developing-country markets. Most vaccines for public distribution programs in developing countries are packaged in multi-dose vials containing 2 to 20 doses per vial,7 and most multi-dose liquid injectable vaccines used in developing countries contain a preservative.8 These multi-dose presentations work well for liquid vaccines with preservative because they minimize space required in the cold chain and in the medical waste disposal system on a per-dose basis. The preservative means that the vaccine can be used for more than one session—even up to 30 days—in accordance with the current Multi-Dose Vial Policy of WHO. Because the two existing HPV vaccines have not been formulated with preservative, a multi-dose preservative-free presentation is a potential future option, and a 2-dose product is already available. However, a liquid, multi-dose HPV vaccine without preservative would represent a new type of product for developing-country immunization programs as it could not be used for more than one session. Wastage rates of this expensive vaccine would therefore be expected to increase. Other potential options include multi-dose packaging with preservative and prefilled syringes.

Background

The determination for packaging of any vaccine is a delicate balance. At issue are potential vaccine wastage due to unused doses and the resultant lost financial investment; safety considerations (e.g., potential contamination of vaccines without preservative if kept longer than a single immunization session); willingness of vaccine suppliers to produce different products for different markets; cold chain volume capacity requirements in generally limited and outdated cold chain infrastructure;8,9 and per-dose cost to the purchaser or government involved. Newer vaccines, such as those for pneumococcus and HPV, are currently associated with high per-dose costs, single-dose or low multi-dose presentation, and correspondingly relatively large cold chain requirements.7,9–11 Additionally, newer vaccines are often manufactured with reduced or no preservative.11 While these characteristics may be suitable for resource-intensive immunization
programs in industrialized countries, they may not align with the realities of low-resource settings.

The opportunity exists now to influence the development of new HPV vaccine presentation options. Given that the profile of the second generation of the vaccine is not yet determined, this represents an ideal time for the public sector to provide input to manufacturers on packaging and appropriate vial presentations for different settings based on programmatic and economic factors. If multi-dose packaging reduces per-dose cost, this option becomes more appealing to user governments. Multi-dose packaging can also be much more appropriate for resource-limited Expanded Programs on Immunization (EPI) dealing with constrained cold chain infrastructure and other vaccines competing for simultaneous distribution. Multi-dose vials without preservative are believed, however, to result in greater wastage and may not be recommended for expensive vaccines such as HPV if excessive programmatic wastage would be a by-product of such a presentation.\textsuperscript{7,12} Wastage from unopened vials caused by expiry, heat/freezing damage, or inadequate handling is generally static, but opened vial wastage is not. While opened vials are a major cause of wastage,\textsuperscript{13} this programmatic wastage may be addressed by manipulating session characteristics, training health workers, or changing vial sizes to match session size.

With billions of dollars committed to global immunization programs by GAVI Alliance and UNICEF, it is worthy of mention that there is a paucity of published data on determining optimum vial size/vaccine presentations for newer vaccines and those in the development pipeline.\textsuperscript{7} The Vaccine Presentation Assessment Tool being developed at PATH is beginning to augment the body of literature around this topic for specific vaccines\textsuperscript{14,15} using estimations for wastage rates; however, more discussion is needed. There exist many studies on the cost-effectiveness of vaccination programs, though very few examine vaccine vial presentation as a key factor in wastage and cost.\textsuperscript{16–19}

Consideration of myriad factors is involved in determining an optimum presentation for the next generation of HPV vaccines. Discussions will need to include the future of delivery strategies, cost-effectiveness calculations, cold chain systems and thermostability, issues surrounding preservative versus non-preservative presentations, attainable effective coverage rates, wastage, as well as other factors. An examination of this complex web of factors is beyond the scope of this analysis. This report presents an analysis of the impact of vaccination session sizes on wastage for different vaccine vial sizes.

**Methods**

**Study design**

PATH is currently collaborating with the governments of Peru, Uganda, and Vietnam to implement HPV vaccine demonstration projects in low-resource settings. HPV vaccinations were given in each country in three doses to girls between 10 and 13 years of age according to the approved schedule for the vaccine used. Uganda and Vietnam conducted vaccinations through two different strategies (school and community). Peru utilized only a school-based delivery strategy. For a summary description of program strategies, refer to each country’s case study.
below. Data for vaccination sessions were available for 90 percent of doses delivered in Uganda and Vietnam but for only 70 percent of doses delivered in Peru (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>Doses delivered</th>
<th>Doses analyzed</th>
<th>% Doses analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uganda</td>
<td>15,860</td>
<td>14,272</td>
<td>90%</td>
</tr>
<tr>
<td>Peru</td>
<td>27,320</td>
<td>18,653</td>
<td>68%</td>
</tr>
<tr>
<td>Vietnam</td>
<td>10,273</td>
<td>9,143</td>
<td>89%</td>
</tr>
</tbody>
</table>

These data constitute a convenience sample based on availability of tally sheets and not a statistically viable random sample. Also, the sessions presented may not be representative of all vaccination sessions in the HPV demonstration projects. Using these routinely collected immunization data, or tally sheets, an opportunistic, secondary analysis was conducted to calculate average vaccination session sizes and estimate vaccine wastage for a variety of vial sizes based on one year of data.

**Data collection**

Data on vaccination session size were collected via tally sheets used by EPI personnel to track administration of HPV vaccine. The tally sheets conformed to those used for other routinely administered childhood vaccines in each country. The sheets were completed by health workers at the time of vaccination and tracked, at a minimum, the date, location, and number of doses administered. Additional variables on the sheets that were unique to individual programs were not used for this analysis. Inclusion criteria for analysis were forms that contained the location and number of girls vaccinated. Illegible tally sheets or those that lacked either the vaccination site or the number of girls vaccinated were excluded. This represented a very small number of the total (six discarded tally sheets out of 3,663 vaccination sessions). An independent validator checked 10 percent of the tally sheets entered for quality assurance purposes. Less than 5 percent error was observed by tally sheet, which correlates to less than 1 percent error by vaccination session.

**Data analysis**

Given the uniqueness of each country in implementation of the demonstration project, coupled with geographic and cultural variations, a cross-country comparative analysis was not possible and a “case study” approach was used.

Vaccination session sizes calculated for each country were manipulated to perform various sub-analyses. Data were analyzed across variables of dose sequence (first, second, third), delivery strategy, location of vaccination (school, health post, outreach, home), and geographic classification (rural or urban) for the primary definition of session size (see Definitions below). All primary and secondary analyses included all vaccination session data obtained from the tally sheets.
To determine average session sizes, the number of girls vaccinated at each vaccination session was totaled, and tabulations were generated for mean, median, frequency, and range across all variables. Results were rounded to the nearest integer.

Wastage projections for potential alternative vial presentations, including 2-dose, 5-dose, and 10-dose vials without preservative, were calculated from session sizes based on the assumption that opened vials (and thus unused doses) would have to be discarded at the end of a session. For example, a session consisting of 5 girls would need three 2-dose vials and have one wasted dose. Wastage projections do not include wastage due to expiry, heat/freezing damage, or handling errors. Percentages were rounded to the nearest one-tenth of 1 percent. Due to limited data on the length of vaccine sessions and the ability of immunization programs to transfer open vials of vaccines between sites, it was not possible to project wastage rates for multi-dose vials with preservative.

Observed wastage was taken from PATH’s in-house demonstration project reports. The data were collected by ministry of health staff during routine vaccination; these figures include doses lost due to breakage, contamination, handling error, or other loss during the course of the demonstration projects. Analysis was performed in Microsoft Excel v11 and freely available data analysis plug-ins, including the Analysis Toolpak and SSCStat V2.12.

Definitions
Many terms may be used in this report outside their conventional definition. For purposes of clarity, such terms are defined below:

- Dose: the volume of vaccine intended for injection into a single recipient.
- Rural: any location designated “rural,” or variations thereof, by a country’s national statistical bureau.
- Urban: any location designated “urban,” or variations thereof, by a country’s national statistical bureau.
- Vaccinator: the individual health worker who injects vaccine.
- Vaccination session:
  - Primary definition: all vaccination activity taking place in a discrete location on one calendar day (the majority of sessions involved one location per day).
  - Alternate definition: all vaccination activity (multiple locations) by one or a team of vaccinators on one calendar day (used for secondary analysis).
- Vaccination site or, simply, “site”: the physical discrete location of the vaccination activity. Examples of a vaccination site include a school, a health post, or a home.
- Vaccination team: a distinct group of vaccinators who work together on one calendar day at one or more sites.
Results

The results are presented as three independent case studies. Even though some tables present the data from all three countries, comparisons between countries should not be made (see Limitations below).

Uganda

The HPV vaccine demonstration project in Uganda targeted 6,400 girls annually in the two districts of Nakasongola and Ibanda. Each district implemented a different strategy. In Ibanda, a school-based strategy targeted all girls enrolled in Primary 5 (P5) and out-of-school girls who were 10 years old. In Nakasongola, a community-based approach was used whereby all 10-year-old girls were vaccinated in schools in conjunction with Uganda’s Child Days Plus (CDP) events for doses one and three, and special outreach to schools was undertaken to cover dose two. The CDP program is a mechanism the government uses semiannually to deliver services such as Vitamin A supplementation and deworming medications and to maintain and advance child health and nutrition.

Session size

The tally sheets available from Uganda enabled an analysis of 823 vaccination sessions representing delivery of 14,272 doses (90 percent) of HPV vaccine in Nakasongola and Ibanda districts. The resulting average session size was 17 girls vaccinated per day at a single location (Table 2). Moderate variability of session size is evidenced by a range from 1 to 88 girls at one session. The median session size is 14, indicating a skew toward smaller sessions.
Table 2. Average vaccination session size by session characteristics, Uganda, Peru, and Vietnam, PATH HPV vaccine demonstration projects, 2008–2009

<table>
<thead>
<tr>
<th></th>
<th>Uganda</th>
<th>Peru</th>
<th>Vietnam</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (range); median no. of sessions (n)</td>
<td>Mean (range); median no. of sessions (n)</td>
<td>Mean (range); median no. of sessions (n)</td>
</tr>
<tr>
<td>Overall</td>
<td>17 (1–88); 14 n = 823</td>
<td>8 (1–127); 3 n = 2,482</td>
<td>26 (1–178); 19 n = 358</td>
</tr>
<tr>
<td>By session (% of total)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 girl</td>
<td>26 (3%) n = 307</td>
<td>783 (32%) n = 795</td>
<td>37 (10%) n = 162</td>
</tr>
<tr>
<td>2 girls</td>
<td>36 (4%) n = 348</td>
<td>327 (13%) n = 812</td>
<td>22 (6%) n = 114</td>
</tr>
<tr>
<td>3–5 girls</td>
<td>87 (11%) n = 168</td>
<td>539 (22%) n = 879</td>
<td>42 (12%) n = 82</td>
</tr>
<tr>
<td>6–10 girls</td>
<td>156 (19%) n = 809</td>
<td>346 (14%) n = 1,985</td>
<td>38 (11%) n = 211</td>
</tr>
<tr>
<td>&gt; 10 girls</td>
<td>518 (63%) n = 367</td>
<td>487 (20%) n = 200</td>
<td>219 (61%) n = 323</td>
</tr>
<tr>
<td>By dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose 1</td>
<td>17 (1–77); 14 n = 113</td>
<td>8 (1–94); 3 n = 1,985</td>
<td>21 (1–129); 12 n = 114</td>
</tr>
<tr>
<td>Dose 2</td>
<td>17 (1–78); 14 n = 124</td>
<td>7 (1–121); 3 n = 812</td>
<td>30 (1–177); 22 n = 114</td>
</tr>
<tr>
<td>Dose 3</td>
<td>17 (1–88); 14 n = 135</td>
<td>8 (1–127); 3 n = 879</td>
<td>28 (1–98); 25 n = 82</td>
</tr>
<tr>
<td>By site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>School</td>
<td>17 (1–88); 14 n = 809</td>
<td>9 (1–121); 4 n = 1,985</td>
<td>31 (1–178); 20 n = 151</td>
</tr>
<tr>
<td>Health post</td>
<td>5 (2–8); 4 n = 5</td>
<td>3 (1–25); 1 n = 373</td>
<td>22 (1–98); 14 n = 211</td>
</tr>
<tr>
<td>Outreach, home</td>
<td>5 (1–10); 3 n = 9</td>
<td>2 (1–28); 1 n = 215</td>
<td>n/a</td>
</tr>
<tr>
<td>By strategy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strategy 1(^b)</td>
<td>18 (1–88); 16 n = 456</td>
<td>8 (1–127); 3 n = 2,482</td>
<td>25 (1–178); 13 n = 200</td>
</tr>
<tr>
<td>Strategy 2(^c)</td>
<td>16 (1–77); 12 n = 367</td>
<td>n/a</td>
<td>27 (1–98); 26 n = 158</td>
</tr>
<tr>
<td>By geography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>16 (1–88); 14 n = 745</td>
<td>7 (1–127); 3 n = 1,080</td>
<td>25 (1–94); 23 n = 200</td>
</tr>
<tr>
<td>Urban</td>
<td>24 (2–78); 20 n = 71</td>
<td>8 (1–105); 3 n = 1,402</td>
<td>26 (1–178); 8 n = 158</td>
</tr>
<tr>
<td>By alternative session definition(^d)</td>
<td>27 (1–153); 20 n = 494</td>
<td>9 (1–127); 4 n = 2,054</td>
<td>28 (1–178); 23 n = 323</td>
</tr>
</tbody>
</table>

Abbreviations: n, number of sessions; n/a, not applicable.
Percentages may not total 100 due to rounding.
\(^a\) Session defined as all vaccination activity at a single location (school, post, or outreach) in one day.
\(^b\) Strategy 1 defined as school-based.
\(^c\) Strategy 2 defined as combined with Child Days Plus (Uganda) or health center-based (Vietnam).
\(^d\) Alternative session defined as all activity by health worker team per day.
Histogram analysis (Figure 1) reveals 18 percent of sessions with 5 or fewer girls, and 37 percent of sessions with 10 or fewer girls. The majority of girls received vaccinations in sessions of between 11 and 30 girls (51 percent of sessions), and there were few very large sessions; only 12 percent of analyzed sessions in Uganda involved more than 30 girls.

**Figure 1.** Histogram, frequency of sessions, by session size, Uganda

Analysis of session size across the 3-dose delivery schedule (Table 2) reveals remarkable consistency between doses; all doses average a session size of 17 girls, and the median for each dose does not shift from 14. Examining the results by delivery strategy, mean session size rises to 18 for school-based sessions \((n = 456)\) and falls to 16 for the CDP-based strategy \((n = 367)\). This is correspondingly reinforced in the distribution curve for the school-based strategy, as the curve shifts slightly to the right. Figure 2 illustrates this shift. Where a leftward shift in distribution indicates a greater percentage of small sessions, a rightward shift in distribution indicates a greater percentage of larger sessions. This observed right shift notwithstanding, the school-based strategy still has 32 percent of all sessions consisting of 10 or fewer girls, while the CDP program exhibits 43 percent of sessions with 10 or fewer girls.

**Figure 2.** Session size as a cumulative percentage of all sessions, by delivery strategy, Uganda
Examination of session size by site characteristic is less illustrative due to the predominance of school-based data (n = 809); both the school-based and CDP-based strategies utilized schools as the primary vaccination site. Very few sessions took place at the health post (n = 5) or through outreach sessions (n = 9). Urban sessions (n = 71) have a significant increase over the mean at 24 and a shift toward the right in the distribution curve as well, indicated by a median of 20. As the median approaches and surpasses the mean, distribution of session sizes tends toward a greater percentage of large sessions and the previously mentioned rightward shift in the distribution. That said, urban sessions show the same percentage of sessions with fewer than 5 girls, although less than half the number (~10 percent versus ~20 percent) of sessions of between 5 and 10 girls.

Uganda is the only demonstration project in which considerably different results are found when the definition of “vaccination session” is changed to “all activity by a team of health workers per day, regardless of the number of locations serviced.” The alternate definition provides a significantly higher mean, at 27 (versus 17 for our standard definition), and a higher median at 20. This is a larger variance between the median and mean, which points to greater incidence of outliers at the peak of the range further evidenced by 10 percent of sessions with this definition involving more than 60 girls. The bottom of the range has not shifted. Also, 10 percent of all sessions are still 5 or fewer girls, and 25 percent are 10 or fewer girls.

Wastage

Observed wastage for the demonstration project, which used single-dose vials, was 0.7 percent. Table 4 displays projected wastage rates for Uganda for 2-, 5-, and 10-dose presentations of HPV vaccine without preservative. Examining hypothetical vial presentations, wastage climbs with near-linearity proportional to the number of doses per vial. Wastage of 2.8 percent is projected for 2-dose vials without preservative. Each dose added to the vial adds between 2 percent and 3 percent wastage. Thus, a 3-dose vial without preservative would have 5.6 percent wastage, 4-dose 8.1 percent, 5-dose 10.7 percent, 6-dose 13.0 percent, etc. As vial size reaches 20 doses or more, the increase dips down below 2 percent per dose added to the vial, on average.

Examining wastage by dose and strategy mirrors the effects on mean session size and session-size distribution. For example, the per-dose wastage rates stay nearly static across doses one, two, and three in Uganda, paralleling the tightly correlated distribution of mean session size across those variables. Those cofactors skew the distribution curve toward the right, resulting in increased numbers of larger sessions, higher mean session sizes, and a decrease in wastage rates. The analysis by strategy shows that the CDP strategy, which has a lower mean and median session size than the school-based strategy, has higher wastage rates than the school-based program at all standardized proposed vial presentations (2, 5, and 10 doses per vial) (Table 4). Differences by strategy are 0.5 percent for a 2-dose vial, increasing to a 3 percentage point difference for 10-dose vials (23.7 percent versus 20.6 percent). Examining wastage using the alternate definition of session size (all activity by vaccination team per day) shows a significant reduction in projected wastage by more than 30 percent at all proposed vial presentations.

Vietnam

PATH’s demonstration project in Vietnam targeted 4,650 girls per year in two provinces: Thanh Hoa in the north and Can Tho in the south. To represent the diverse geographical and
sociocultural considerations in Vietnam, two districts in each province were selected. As in Uganda, two different vaccine delivery strategies were carried out: a school-based program targeting all girls in grade 6 along with out-of-school, 11-year-old girls vaccinated at the local health post, and a facility-based approach targeting all 11-year-old girls.

Session size

The tally sheets available from Vietnam enabled an analysis of 358 vaccination sessions representing delivery of 9,143 doses (89 percent) of HPV vaccine in Can Tho and Thanh Hoa provinces. Of the three countries, Vietnam has the highest overall mean number of girls per session at 26 girls and the largest variability in session size, with anywhere from 1 to 178 girls in one session. A median session size of 19 indicates a leftward skew of the session-size distribution—a larger proportion of sessions with small sizes than a normal distribution would imply, reinforced by 28 percent of sessions overall numbering 5 or fewer girls. Half of all sessions fell between 11 and 60 girls, and 10.6 percent of sessions had more than 60 girls. Figure 3 illustrates this distribution.

![Figure 3. Histogram, frequency of sessions, by session size, Vietnam](image)

Vietnam evidences variability across each of the three doses, with a progressive decrease in the variance between median and mean. Dose two has the highest mean at 30, though dose three has the least difference between mean and median (mean 28 versus median 24). The two delivery strategies also present differences; the school-based strategy (n = 200) has a mean of 25, and the facility-based strategy (n = 158) has a mean of 27. The distribution of sessions across strategies also shows clear differences; the facility-based strategy has only 19.8 percent of sessions with 5 or fewer girls, whereas the school-based strategy shows 35 percent of similarly small sessions. Figure 4 indicates the differences in this distribution. The health center-based strategy distribution is shifted rightward of the school-based strategy, with a greater percentage of sessions containing 40 or more girls.
**Figure 4.** Session size as a cumulative percentage of all sessions, by delivery strategy, Vietnam

![Graph showing session size distribution by delivery strategy](image)

Schools in Vietnam have a much higher average session size at 31 than their health-post counterparts at 22. While urban and rural locations have very similar means (25 rural, 26 urban), their medians are vastly different: median of 23 girls in rural sites and 8 girls in urban ones. This correlates with their proportion of “small” sessions, where nearly 40 percent of urban sessions involved fewer than 5 girls, compared to just below 20 percent for rural sessions.

Finally, changing to the alternate definition (i.e., incorporating multiple sites visited by a vaccinator or vaccination team in one day) results in a limited increase in the number of girls vaccinated. Where 26 girls on average can be vaccinated per location per day, the mean rises slightly to 28 girls when the analysis is performed by team activity per day.

**Wastage**

Vietnam had an observed wastage rate of 0.8 percent during Year 1 of the demonstration project (Table 3). This wastage is based on the single-dose vials used. When session data are analyzed to project wastage at potential alternative-dose presentations, 2-dose vials without preservative, if used, would generate 1.9 percent wastage; 5-dose vials 7.8 percent wastage; and 10-dose vials without preservative 17.1 percent wastage (Table 4). As vial sizes increase, wastage increases from 0.6 to 2.5 percentage points per dose added to the vial. As with Uganda, the factors that elevate the mean and shift distribution to the right, consistent with increasing the proportion of sessions with many girls, generally decrease wastage. Projected wastage in the facility-based delivery strategy at all hypothetical vial sizes is consistently less than that of the school-based strategy, but not to a great degree. An improvement of 0.5 to 1.9 percentage points is seen for the facility-based strategy.

Altering the definition to incorporate multiple sites per day visited by a single health worker team does not greatly reduce projected wastage. Only a marginal gain is observed at each alternative vial size, mirroring the marginal gain seen in average session size when using the alternate definition.
### Table 3. Reported vaccine wastage, PATH HPV vaccination demonstration projects, Uganda, Peru, and Vietnam, 2008–2009

<table>
<thead>
<tr>
<th></th>
<th>Uganda</th>
<th>Peru</th>
<th>Vietnam</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15,860 doses delivered</td>
<td>27,320 doses delivered</td>
<td>10,273 doses delivered</td>
</tr>
<tr>
<td>Reported wastage</td>
<td>Doses wasted</td>
<td>Percent wastage</td>
<td>Doses wasted</td>
</tr>
<tr>
<td>1-dose vial</td>
<td>116</td>
<td>0.7%</td>
<td>25</td>
</tr>
</tbody>
</table>

### Table 4. Estimations\(^a\) of projected vaccine wastage for alternative vial sizes without preservative, by delivery strategy and session definition, PATH HPV vaccination demonstration projects, Uganda, Peru, and Vietnam, 2008–2009

<table>
<thead>
<tr>
<th></th>
<th>Uganda (n = 14,013)</th>
<th>Peru (n = 18,653)</th>
<th>Vietnam (n = 9,143)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>2-dose vial 399 2.8%</td>
<td>1,513 7.5%</td>
<td>175 1.9%</td>
</tr>
<tr>
<td></td>
<td>5-dose vial 1,687 10.8%</td>
<td>6,647 26.3%</td>
<td>772 7.8%</td>
</tr>
<tr>
<td></td>
<td>10-dose vial 3,927 21.9%</td>
<td>16,177 46.5%</td>
<td>1,887 17.1%</td>
</tr>
</tbody>
</table>

By strategy

<table>
<thead>
<tr>
<th></th>
<th>Strategy 1(^b)</th>
<th>Strategy 2(^c)</th>
<th>Strategy 1(^b)</th>
<th>Strategy 2(^c)</th>
<th>Strategy 1(^b)</th>
<th>Strategy 2(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>2-dose vial 2.6% 3.1%</td>
<td>7.5% 3.1%</td>
<td>n/a 2.1%</td>
<td>n/a 1.6%</td>
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</tr>
<tr>
<td></td>
<td>5-dose vial 9.9% 11.9%</td>
<td>26.3% 26.3%</td>
<td>8.1% 7.5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10-dose vial 20.6% 23.7%</td>
<td>46.4% 46.4%</td>
<td>18.0% 16.1%</td>
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</table>

By alternative session definitions

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<th>Location/day(^d)</th>
<th>Team/day(^e)</th>
<th>Location/day(^d)</th>
<th>Team/day(^e)</th>
<th>Location/day(^d)</th>
<th>Team/day(^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>2-dose vial 2.8% 1.7%</td>
<td>7.5% 1.7%</td>
<td>6.1% 1.9%</td>
<td>1.6%</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>5-dose vial 10.8% 7.0%</td>
<td>26.3% 22.3%</td>
<td>7.8% 6.9%</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>10-dose vial 21.9% 14.7%</td>
<td>46.4% 40.6%</td>
<td>17.1% 15.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: n, number of doses delivered; n/a, not applicable.

\(^a\) Estimations include data only from vaccination sessions reported on daily tally sheets which can be classified. Data for estimations do not reflect all vaccinations performed during the demonstration projects.

\(^b\) Strategy 1 defined as school-based.

\(^c\) Strategy 2 defined as combined with Child Days Plus (Uganda) or health center-based (Vietnam).

\(^d\) Session defined as all vaccination activity at a single location (school, post, or outreach) in one day.

\(^e\) Session defined as all vaccination activity by health worker team per day.
Peru

Peru’s demonstration project sought to provide evidence of the effectiveness of school-based delivery programs for HPV vaccine in areas representing three diverse ecological regions. The project delivered over 27,000 doses of HPV vaccine to all girls in grade 5 of primary school (P5) in the states of Ayacucho (highland), Ucayali (jungle), and Piura (coastal); 68 percent of doses delivered in Peru were available for analysis.

Session size

Analysis of 18,653 doses delivered in 2,482 vaccination sessions resulted in an overall mean of 8 girls for Peru’s three regions. Sessions ranged in size between 1 and 127 girls. A median of 3 girls indicates a highly skewed distribution, further demonstrated by 32 percent of all sessions consisting of only a single girl, and 66 percent of all sessions consisting of 5 or fewer girls. Figure 5 illustrates this skewed session distribution for all doses analyzed. Roughly 5 percent of all sessions consisted of more than 30 girls.

Across the three doses, there is little variability in mean session size; doses one and three exhibit means of 8 girls and dose two a mean of 7 girls, though variation is largely due to rounding (Table 2). All three doses also have greater than 65 percent of all sessions containing 5 or fewer girls and 80 percent of sessions with 10 or fewer girls. Comparing by site, the mean for delivery in schools (n = 1,985) is close to the overall mean at 9 girls. The health post (n = 373) and home visit (n = 215) sessions means are 3 and 2 girls, respectively. These include mop-up sessions, as it is not possible to separate primary versus mop-up sessions for the analysis. Upon examination of rural versus urban sessions, rural sessions (n = 1,080) are below the overall mean at 7 and urban sessions (n = 1,402) are at 8. Slightly more urban sessions are of only 1 girl (32.6 percent) than their rural counterparts (30.3 percent), but both maintain over 60 percent of sessions with 5 or fewer girls.

Finally, Peru displays little shift in mean session size when the definition is altered to incorporate multiple sites per day by a single vaccination team; the mean increases from 8 to 9 girls after rounding (Table 2). A median shift from 3 to 4 girls accompanies a slight rightward shift in the

Figure 5: Histogram, frequency of sessions, by session size, Peru
distribution curve, indicating a decrease in the number of small sessions. While some teams of vaccinators were able to visit more than one site per day, the data indicate that the majority of teams were able to visit only a single site per day and vaccinate relatively few girls when able to visit multiple sites.

**Wastage**

Peru’s three demonstration locations delivered 27,320 doses with 0.1 percent wastage (25 doses) (Table 3). Projected wastage for multi-dose formulations based on session-size distribution results in 7.5 percent programmatic wastage with a 2-dose vial without preservative, 26.3 percent with a 5-dose vial without preservative, and over 46 percent with a similar 10-dose vial (Table 4). Consistent with little variability across mean session sizes for the three vaccine doses, the wastage rates across the doses are largely equivalent. There is little difference between urban and rural session wastage; this is consistent with the small shift seen in their means and distributions, respectively. Changing the functional definition of a vaccination session for Peru reduces projected wastage by a full percentage point for the 2-dose vial, up to more than 5 percentage points for the 10-dose vial.

**Discussion**

**Session sizes**

The mean session-size analysis described in this report highlights several issues that are worthy of discussion. While the variability of any single factor in the analysis informs deliberations around the selection of an alternative presentation of the HPV vaccine, the lack of variability across a factor in the analysis can be equally informative. Also, given that the sessions are not normally distributed in any of the countries, means may not be the most useful measure for interpretation. Medians are also informative indicators.

**Summary of findings**

While it is important to retain the independence of the data across each country and not compare results, it is significant that no country’s results show a normal distribution of session size. Each country has its own modal (sometimes bimodal) distribution, but largely they are all skewed toward session sizes to the left of the continuum, indicating a high proportion of sessions with few participants. In all countries, at least 35 percent of all sessions had 10 or fewer girls.

Peru exhibits the lowest mean session size of the three countries and, coincidently, the largest proportion of vaccination sessions (greater than 30 percent) attended by only 1 girl, and 66 percent of vaccination sessions with 5 or fewer girls. This is likely due to ministry of health initiatives to ensure maximum possible coverage during the demonstration project, including “active follow-up” for missed second and third doses. Peru and Uganda both display striking similarity in consistency in mean session size across each of the three doses, whereas Vietnam has modest variability between doses. Peru’s uniformity in mean session sizes across the three doses is unsurprising given the vaccination activities did not vary between doses. In Uganda, the previously noted per-dose uniformity is surprising given differences in delivery strategy. It was expected that there would be a leftward skew in overall dose-two delivery as the CDP strategy involved an “off schedule” mobilization of resources solely for HPV vaccination. In Uganda, the
session-size distribution within each strategy also remained largely consistent from dose one to
dose three. Schools were the main venue for vaccination of all three doses in both delivery
strategies, which may explain the consistency across doses. Vietnam displays increasing mean
session size and flattening distribution curve from dose one to dose three. The improvement
across doses appears to indicate increased efficiencies across doses and a decreased need for
“mop-ups” to catch missing girls. This is interesting, as generally one expects to see a drop-off
across doses as subjects drop out or are lost to follow-up.

Another interesting finding is that the Uganda and Vietnam data countered our expectation that a
school-based delivery program solely for HPV vaccine would result in much larger session sizes,
on average, than a community-based strategy, based on the premise that schools offer
consistently larger captive audiences and no division of attention for other health care needs. In
Uganda, the difference between strategies is only 2 girls per session, on average, and the medians
are moderately close to their means. The difference observed between strategies is likely a result
of the difference in characteristics of the districts selected for the demonstration projects. The
CDP strategy was implemented in a more rural district with fewer numbers of eligible girls in
schools. Also, it is important to note that the school-based strategy in Ibanda involved
vaccinating a cohort of girls in grade 5 and thus a range of ages potentially from 10 to 18 years,
while the CDP strategy involved targeted vaccination only of 10-year-old girls; a broader or
more easily applicable selection criterion may have allowed for greater session sizes.

In Vietnam, differences in average session sizes between the two strategies are similarly small.
The school-based delivery strategy displays a slightly smaller mean than the facility-based
strategy. However, there is a large difference in medians (13 versus 26) which indicates a
significant presence of “small” sessions for the school-based delivery strategy. These two
characteristics—smaller mean and larger delta from mean to median for the school-based
strategy—are likely an artifact of the program design. Largely speaking, 11-year-old girls are in
the 6th grade (the first year of secondary school) in Vietnam; however, some may still be in 5th
grade (the last year of primary school). These few girls required vaccination in separate schools
in the school-based program, often in sessions of no more than 1 or 2 girls. For the alternate
definition, given that in most areas vaccination activity occurred at only one site per day by a
team of vaccinators, the collapsing of two school sessions in these areas into a single day-long
session likely accounts for the limited increase in mean session size observed. For the health
center-based vaccination program, all girls were mobilized to be vaccinated at the same site, and
vaccination occurred only in a single location.

Analysis by site is less illustrative. As expected, any site that was designated as solely “mop-up”
by the program design saw greatly reduced mean session sizes; these sites included health posts
and outreach events for Uganda, health posts and home visits for Peru, and health posts for
Vietnam’s school-based strategies. All display markedly lower means than their corresponding
country average, though they all represent a relatively small portion of the total delivery.
Unfortunately, the tally sheets data did not allow for a systematic separation of mop-up activities
from primary vaccinations in any of the countries. However, there is tenuous support for the
theory that mop-up efforts account for the bulk of the small sessions; this may be particularly
true for Vietnam as stragglers from the school-based program are represented in the health-post
session numbers, thereby skewing the results for Vietnam toward smaller session sizes in health.
centers when analyzing by site. Supporting this idea are anecdotal reports from Vietnam indicating a longer mop-up period in selected urban areas due to low initial coverage for the first dose. Though, again, it was not possible to conclusively separate out the mop-up sessions using the available information.

In all three countries, urban/rural distinctions fall roughly as expected: rural sessions are generally smaller than urban sessions on average, possibly due to population densities involved. In Peru and Vietnam, this difference is quite small, less than 1 girl on average before rounding. In Vietnam, however, the distribution of session sizes is much more skewed toward smaller sessions in urban areas (median 8 urban versus 23 rural). Urban sites had twice as many sessions, proportionally, with 10 or fewer girls, than their rural equivalents. It may be that the unique administrative structure of Vietnam is a factor in this regard. In Vietnam, a rural commune may not have its own school if the population is too low; girls may attend school in a neighboring commune, resulting in a larger rural session. Conversely, the density of students in urban areas may be sufficient to support multiple schools having smaller class sizes. As such, class sizes in rural communes may be larger than their urban counterparts. Also, in some urban areas the mop-up period was longer, thereby enabling the opportunity for 1 or a few girls at a time to be vaccinated at the health post.

**Wastage**

As expected, projected wastage rate trends appear to mirror their respective session-size trends. Thus, factors in each country that increase mean session size and skew the distribution rightward reduce wastage rates at all proposed vial sizes. Examples include the school-based strategy having less wastage than the CDP strategy in Uganda, generally urban areas having lower wastage than rural ones, and dose-three wastage rates being lower than dose-one wastage rates in Vietnam due to greater efficiencies achieved and less mop-up needed.

A second key point is that projected wastage rates seem to increase linearly, specific to the country involved, when doses-per-vial increase. This is found in the relatively continuous increase in projected wastage calculated from session-size data subjected to 2-, 5-, and 10-dose presentations without preservative. None of the variables examined radically countered this trend, indicating that wastage with multiple vial presentations of vaccine without preservative would be essentially fixed in these demonstrations.

Of note are the remarkably low actual wastage rates observed in these country demonstration projects. Anecdotal accounts from the field during the demonstration projects related stories of how much money each vial is worth—in some cases, a single vial may be worth more than the average citizen makes in a month. This, coupled with the heightened vigilance around vaccine tracking and control for the demonstration projects, may have contributed to these low observed wastage rates; rates may be higher in more routine programs.

**Alternate definition of “vaccination session”**

The largest variation in session size of any of the analyses is observed in Uganda’s data when the definition of “vaccination session” is modified to incorporate all activity undertaken by a single vaccination team per day, regardless of the number of locations involved. This modification accounts for a 60 percent increase in mean session size and a 30 percent reduction in potential
wastage at all proposed vial sizes. The alternate definition improves Peru’s figures as well, though to a lesser extent. A 50 percent increase in mean session size is paired with a 15 to 25 percent decrease in wastage projections for Peru. This trend is not mirrored in Vietnam, where only a modest increase at best is observed in mean session size or wastage rate as a result of “allowing” the teams to hypothetically visit more than one location per day.

Uganda’s project involved very active micro-planning before all doses, specifically charting which schools to visit, by which vaccinator teams for each parish, in what order, and at what time. Close coordination prior to deployment allowed many vaccinator teams to make the most efficient use of their time, often visiting multiple sites per day. Geography, environment, and culture also play a role in the ability to visit multiple sites per day. Changing the definition of vaccination session, then, allows all of those visits to be considered a single activity. As a result, the mean session size increases due to reaching multiple locations, and wastage goes down.

In Peru, the data indicate a 30 percent decrease in the number of 1-girl and 2-girl vaccination sessions performed under this alternate definition. The decrease in projected wastage is largely accounted for in this improvement. The overall mean did not significantly increase, implying that sessions remained quite small overall. Where vaccination activity in Peru did not exhibit the same sort of micro-planning seen in Uganda, there was still opportunity for vaccinators to visit multiple sites in one trip, though the advantage of this opportunity was diminished by small sessions at each of these multiple sites.

This contrasts with Vietnam’s commune-based administrative structure, which generally consists of only one eligible site (a health post or school) within the territory of a single vaccination team. Few opportunities exist for Vietnam’s vaccination teams to visit multiple delivery sites per day; thus, limited change is seen in their results.

Current WHO multiple-dose vial policy is formulated around vials that contain preservative. It should be noted, again, that the current generation of HPV vaccine does not contain preservative. As a result, hypothetical multi-dose preservative-free HPV vaccine vials, once opened, would have to be discarded within 4 to 6 hours of first use, and transportation between vaccination sites may be difficult, if not prohibitive.

**Limitations**

Even though the results uncover some significant trends, there are several limitations to the work that warrant consideration. Given the unique elements of each country’s demonstration project and the type and quantity of data available, a case-study approach to analyze the implications of vaccination session-size distributions is the only feasible option. This methodology prevents a cross-country comparison of results and, consequently, each analysis must stand on its own. The authors do feel that the countries examined provide a diverse analytical environment to explore, with each having unique sociocultural, geographic, health system, political, and economic considerations. However, relationships across the same variable can not be construed through this analysis.
The analysis was secondary and based on data made available from the three HPV vaccine demonstration projects. Thus, these data constitute a convenience sample based on availability of tally sheets and not a statistically viable random sample. The sessions presented may not be representative of all vaccination sessions done for HPV. In addition, due to the timing of vaccine delivery, data representing dose three in the Ugandan district of Nakasongola (2,700 doses) and the Vietnamese district of Ninh Kieu (1,500 doses) were not available for analysis. Because 30 percent of the data were missing from Peru, those results should be interpreted with caution. It is unknown whether missing data were a function of session size or of another factor. Given the characteristics of the delivery strategies for Nakasongola and Ninh Kieu, it is believed the results would mirror those for doses one and two.

Data on which vaccinators specifically composed a single team were unavailable for Uganda and Vietnam. Each Ugandan tally sheet clearly designates a “Post-in-charge” of the vaccination session, as well as the number of health workers present, but the precise composition of teams is unknown. It is possible the composition of any team changed between locations, or that the Post-in-charge directed more than one team per parish. For Vietnam, it was assumed that only one team of vaccinators worked in any one commune, based on anecdotal knowledge of demonstration-project implementation.

Finally, tally sheets were examined by hand and contents were, where necessary, interpreted by the responsible staff. Mathematical inconsistencies, when found, were not corrected, and the data were entered precisely as indicated on the tally sheets.

**Conclusion**

**Implications for packaging and presentation considerations**

Balancing vaccine cost and the operational costs related to immunization with cold chain consumption, effective vaccine coverage, and wastage may be challenging. A determination of the optimal vial size for HPV vaccine, in light of these inherent complexities, is outside the scope of this analysis. This notwithstanding, session size is an important factor in determining optimal vial size. As expected, we found that session size and wastage of preservative-free vaccine have a tightly correlated inverse relationship. This is independent of administrative wastage and contingency stores. As described in this report, session size varies in each country depending on many factors. Furthermore, not one of the proposed multi-dose vial sizes “outperforms” across the countries in terms of wastage projections. Judging by the varied results of potential wastage, there may not be a “one vial size fits all” option.

This indicates that vaccine wastage may be best controlled if different vial sizes are used for different strategies. Two distinct presentations may be required to meet the varied strategic and environmental needs for a particular program. The flexibility to match a multiple-dose vial to large vaccination campaigns or organized primary activities, combined with a single-dose vial available to accommodate catch-up or opportunistic sessions, would likely generate the most favorable scenario in regard to wastage and cold chain costs. As others have noted, immunization programs may need to communicate their own specific programmatic needs to manufacturers to maintain low wastage rates.
Implications for countries

It has been noted that open-vial discards are one of the major causes of vaccine wastage.\textsuperscript{13} Vaccination session size is an important determinant of potential vaccine wastage and, therefore, is relevant to the discussion of the optimal number of doses per vial. Generally speaking, the trend illustrates that an increase in average session size reduces the wastage, even if the distribution curve is skewed toward a large proportion of small sessions. By the same token, taking a left-skewed distribution and “normalizing” it or shifting it rightward also reduces open-vial wastage. Therefore, these results suggest if reduced wastage is desired for a multiple-dose presentation without preservative, program managers should facilitate larger session sizes and reduce the prevalence of small sessions. It is likely that developing-country programs will deliver most HPV vaccine in school and other settings using a campaign-style approach, producing relatively large session sizes, and that planned mop-up sessions will not be part of the vaccine-delivery strategy in a routine program. In areas with some clustering of vaccination sites, further evidence indicates that detailed micro-planning may improve wastage rates through more efficiently implemented vaccination programs; however, there may be limitations resulting in higher wastage for multi-dose, preservative-free vaccines.

In summary, the overarching concerns of wastage, cost, and cold chain will inform decisions about possible future presentations of HPV vaccine. Locally driven programmatic changes appear to have some impact, but wastage appears to be most influenced by the relationship of session size to doses per vial. Larger sessions or vials containing fewer doses contribute to lower wastage. The best possible solution for reducing wastage appears to be active micro-planning before and during the vaccination efforts, combined with the availability of more than one vial packaging option to maximize cold chain and cost efficiency.
References


