What vaccine product attributes do immunization program stakeholders value? Results from interviews in six low- and middle-income countries

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Abstract

This study attempts to capture the opinions of stakeholders working in immunization programs in low- and middle-income countries to understand how vaccine products could be improved to better meet their needs and to obtain feedback on specific vaccine product attributes including the number of doses per container and ease of preparing a dose for administration. We also reviewed how procurement decisions are made within immunization programs. Semi-structured interviews were undertaken with 158 immunization stakeholders in Brazil, China, India, Peru, the Philippines, and Tanzania. Interviewees included national decision-makers and advisors involved in vaccine-purchasing decisions (n=30), national Expanded Programme on Immunization managers (n=6), and health and logistics personnel at national, subnational, and health-facility levels (n=122).

Immunization stakeholders at all levels of the supply chain valued vaccine product attributes that prevent heat damage, decrease vaccine wastage, and simplify delivery. Minimizing the time required to prepare a dose is especially valued by those closest to the work of actually administering vaccines. Respondents appreciated the benefits of lower-multidose presentations on reducing wastage but seemed to prefer single-dose vials even more. They also expressed concern about the need for training and the potential for confusion and vial contamination if opened vials of liquid preservative-free vaccines are not handled properly. Procurement decision-making processes varied widely between countries, though most relied heavily on international agencies and vaccine manufacturers for information.

Keywords

Vaccine product presentation, immunization program, low- and middle-income country, supply chain, multidose, preservative

1. Introduction

The logistical and infrastructure challenges faced by national immunization programs in low- and middle-income countries are well documented [1–5]. Certain vaccine product attributes can help to mitigate these challenges, yet limited data exist on the attributes of greatest interest to immunization program stakeholders and the decision process used for weighing the trade-offs when selecting particular vaccine products for procurement. Such attributes include the number of doses per vial, use of preservatives, thermostability, packaging volume, and time required to prepare a dose.

Despite best efforts to design vaccine products that will meet the needs of end users, industry may lack insight into how product presentation attributes will affect immunization programs in low- and middle-income countries [6]. Likewise, procurement agencies and national decision-makers may be unaware of the priorities and on-the-ground realities of stakeholders at lower levels of immunization programs. National decision-makers, especially in countries transitioning off of support from Gavi, the Vaccine Alliance, must weigh the pros and cons of specific product attributes along with budget constraints when making choices about which vaccines to purchase and introduce.

One aim of this study was to illuminate which vaccine attributes are most important to stakeholders at different levels of country vaccine supply chains, as well as where priorities diverge. We also describe how vaccine procurement decisions are made in six countries, who is involved in those decisions, and where the countries are turning for information. These findings may help to influence attributes of future vaccine products and inform decision-making around product selection.

2. Methods

This was a qualitative research study. The opinions of 158 immunization stakeholders in Brazil, China, India, Peru, the Philippines, and Tanzania (both mainland and Zanzibar) were sought via semi-structured, one-on-one interviews between October 2011 and March 2012. Countries were selected to represent demographic, geographic, and economic diversity. Interview sites and participants were chosen in

collaboration with the Expanded Programme on Immunization (EPI) manager (or equivalent) in each country using a purposive sampling methodology inclusive of all levels of the supply chain and of low and high rates of third dose of diphtheria-tetanus-pertussis combination vaccine coverage. A summary of study participants is presented in Table 1.

Table 1

Overview of study participants.

	Brazil	China	India	Peru	Philippines	Tanzania	Zanzibar ^d	Total
Country information								
Economic classification ^a	UMIC	UMIC	LMIC	UMIC	LMIC	LIC	LIC	
Gavi-eligible (at time of study) ^b	No	No	Yes	No	No	Yes	Yes	
Distribution of participants by role (and supply chain level)^c								
Decision-makers and advisors (national)	7	1	7	3	9	3	0	30
EPI managers (national)	1	0	1	1	1	1	1	6
Health and logistics personnel^e								
National level	0	0	0	1	2	1	1	5
Regional/provincial level	3	3	3	7	4	6	2	28
Municipal/district level	4	5	6	9	16	6	4	50
Facility level	4	2	7	6	13	4	3	39
Total number of participants	19	11	24	27	45	21	11	158

Notes:

^a Country classification according to World Bank categories: LIC, low-income country; LMIC, lower-middle-income country; UMIC, upper-middle-income country. Source: <http://data.worldbank.org/country>.

^b Gavi eligibility is based on support for pentavalent vaccine. Source: <http://www.gavialliance.org/results/countries-approved-for-support/>.

^c In some countries, we were unable to interview certain categories of participants.

^d Zanzibar is assumed to be treated as part of Tanzania in terms of Gavi eligibility, although it has a separate EPI manager and ministry of health team.

^e Health and logistics personnel include cold chain managers, logisticians, and health workers.

Three different semi-structured questionnaires were used for the interviews, tailored to the roles of the interviewees as follows: 1) national decision-makers and advisors involved in vaccine-purchasing decisions, 2) national EPI managers, and 3) health and logistics personnel, including subnational EPI managers, logisticians, physicians, and nurses. The questionnaires were developed in English, translated into the local language where necessary, and pilot tested. A local immunization expert and a translator, if

needed, were present at the time of the interviews to ensure questions and responses were clearly articulated and accurately transcribed into the questionnaire forms.

The survey questions reported in this article focus on desired vaccine product attributes and the processes by which the countries made vaccine procurement decisions. * Survey responses were translated (if needed), aggregated, and analyzed using Microsoft Excel.

3. Results

3.1. Vaccine product presentations

3.1.1. Desired product attributes

All survey participants were asked to name ways that vaccine products could be improved to better meet their immunization program's needs. Participants offered the responses presented in Table 2. The most frequent response was better heat stability (n=56/155 respondents). There was also a strong interest in prefilled, single-dose, and easy-to-use products (n=99/155 mentioned one or more of these attributes).

Table 2

Participants' suggested improvements to vaccine products.

Suggested improvements	Number of participants	Percent of participants
Heat stable	56	36%
Prefilled	50	32%
Single-dose	49	32%
Easy to use and understand; standardized	32	21%
Low-dose vial (2 or 5 doses)	21	14%
Combined antigens (fewer immunizations)	15	10%
Small packaging	13	8%
Fully liquid presentation (not lyophilized)	12	8%
No need to store in cold chain	11	7%
Freeze stable	10	6%

*This article concerns a subset of the survey questions. Other results are reported in: Kristensen D, Lorenson T, Bartholomew K, Villadiego S. Can thermostable vaccines help address cold-chain challenges? Results from stakeholder interviews in six low- and middle-income countries. *Vaccine*. 2015;34(7):899–904.

Suggested improvements	Number of participants	Percent of participants
Oral presentation/no injection	9	6%
Multidose vial (10+)	9	6%
Reduced doses per fully immunized child	9	6%
Vaccine with preservative	8	5%
Vaccine without preservative	4	3%
No ampoules	3	2%
Vaccine vials with freeze indicators	1	1%

However, these results varied by country. For example, 70% of participants in the Philippines stated that prefilled syringes would be the biggest improvement for meeting their country's needs. Meanwhile, the top request in Tanzania was for single-dose presentations (45%). In Peru, heat stability was equally as popular as single-dose presentations (both 44%). Heat stability was also the top attribute in Brazil, where it was desired by 47% of respondents.

In general, these responses did not vary significantly by individual level of responsibility or a country's economic classification. One exception was the desire for prefilled syringes; 49% of facility-level participants mentioned this attribute, compared to just 22% at the national level and 21% at the regional/provincial level. Likewise, single-dose presentation was suggested by only 15% of national-level participants, whereas it was more popular (36–38%) at all other levels. When comparing Gavi-eligible to non-eligible countries in our sample, the non-eligible countries (Brazil, China, Peru, and the Philippines) had a much greater preference for prefilled syringes (45%) than Gavi-eligible countries, where only 7% of participants mentioned this preference. Some participants gave reasons such as reduced vaccine wastage, less chance of human error during dilution and administration, and ease of use.

3.1.2. *Doses per vial and the multidose vial policy*[†]

All participants were asked if their country has a policy to keep open vials of multidose liquid vaccines with preservative when all doses are not used in one immunization session (for example, keep the open vial for up to 28 days in a refrigerator) [7]. To this question of keeping open vials, 88% (n=139/158) responded yes, 6% (n=9) responded no, and 6% (n=10) said they did not know.

National immunization program respondents in India stated that the practice of keeping multidose vials of liquid vaccines with preservative for more than one session was not currently in effect but was under consideration for the introduction of pentavalent vaccine. That said, half of the health workers and logisticians in India reported that they did keep opened multidose vials of liquid vaccines with preservative. Several participants from the Philippines and one from China also mentioned that multidose vials of liquid vaccine with preservative were not kept for more than one day after opening. In the Philippines, the majority of participants (n=38/45) said that their country does have such a policy, though some reported discarding these vaccines after one session. This was also the case in Brazil, where several respondents stated that they follow instructions on the product insert. In Peru, the WHO multidose vial policy was well understood; nearly all participants stated that opened reconstituted multidose vaccines can be kept for only 6 hours, and liquid multidose vaccines for up to 4 weeks. Similarly, in both Tanzania and Zanzibar, all respondents said they follow such a policy, and nearly all understood appropriate handling of specific types of vaccines.

To further understand how multidose vials were actually managed at facilities, we also asked these follow-up questions: “How long do you typically keep reconstituted multidose vaccines?” and “How long do you typically keep liquid multidose vaccines after opening?” Individuals were aware of the need to

[†] A WHO policy specifying that all opened WHO-prequalified multidose vials of vaccines should be discarded at the end of the immunization session, or within six hours of opening, whichever comes first, unless the vaccine meets four specific criteria (prequalification by WHO, approval for use up to 28 days after opening the vial, not expired, and stored at appropriate temperatures) in which case the opened vial can be kept and used for up to 28 days after opening.

dispose of lyophilized vaccines within 4–6 hours after reconstitution; some reported discarding within 30 minutes of opening. Health workers also reported keeping liquid vaccines with preservative for up to 1 month after opening; however, several participants mentioned that opened liquid vaccines remaining after an outreach setting were discarded; only open vials used in the facility setting, with frequent immunization sessions and reliable cold chain, were kept for up to 4 weeks.

Since improper vaccine management (e.g., incorrect reconstitution or handling of vaccines after opening) can be a factor in adverse events, all participants were also asked if adverse events had been reported in their immunization program that may be related to improper vaccine management, and if so to describe those events. Thirty percent of participants (n=47/158) reported adverse events had been linked to vaccination; 63% reported no adverse events (n=99) and 8% (n=12) did not know. Of those reporting that adverse events had occurred, 60% reported rashes, fever, or swelling at the injection site or other less acute reactions to immunization. The remaining 23% of participants, all of which were from India or Peru, reported severe adverse events related to vaccine management. Nine participants reported cases of reconstitution with improper diluent or contamination due to keeping a vaccine without preservative longer than recommended. Two of three Peruvian participants reported historical cases of Nicolau syndrome.

Until recently, all multidose liquid vaccines have contained preservative. We informed participants that a 2-dose liquid vaccine without preservative was now available. Since the vaccine does not contain preservative, a partially used vial needs to be kept between 2°C and 8°C, and the second dose must be discarded within 6 hours of opening if unused [8]. We asked stakeholders how a 2- or 5-dose liquid vial of vaccine without preservative might impact their immunization program.

Figure 1 summarizes the perceived impacts of lower-multidose liquid vaccines without preservative. When compared to 10-dose vials, 39% and 19% of participants appreciated a 2-dose or 5-dose vial,

respectfully, without preservative because it would cause less wastage and fewer missed vaccination opportunities.

[insert Figure 1 here]

3.1.3. Time required to prepare each dose

Another important characteristic that varies between vaccine products is the time required to prepare a dose of vaccine; some vaccine presentations take only seconds to prepare for administration, while other presentations can take up to two minutes. We asked participants if they thought the time required to prepare a dose of vaccine for administration is an important consideration in selection of a vaccine for purchase. The time to administer a dose of vaccine varied in importance depending on the respondent's level in the vaccine supply chain. As Figure 2 shows, 66% of facility-level participants felt that time to administer is "very important," compared to only 26% of national-level participants.

[insert Figure 2 here]

Health and logistics personnel were asked if the type of immunization delivery scenario (routine versus campaign setting) matters in relation to time needed to administer a vaccine. Of the 126 participants who responded to this question, 37% (n=46) believe time to administer vaccine is more important in campaign settings, 8% (n=10) believe time is more important in a routine immunization setting, and 56% (n=70) believe that in any vaccination environment it is important to have efficient delivery.

3.2. Vaccine procurement decision-making

3.2.1. Key decision-makers, processes, and sources of information

Another aim of our survey was to document the key decision-makers and processes used to select vaccine product presentations to purchase. We also asked national EPI managers and policy and procurement participants (n=35), "Once your country has made a decision to introduce a vaccine, where do you obtain

information on which vaccine brand and product presentation to select for your country or region?” Not surprisingly, these results varied by country. The sources of information used are summarized in Figure 3.

[insert Figure 3 here]

In Brazil, there is a general coordinating committee that makes a joint decision with the National Immunization Program. The director of the ministry of health (MOH), the Brazilian National Health Surveillance Agency, and technical groups are also involved. Product presentation is a joint discussion between the technical and scientific advisory groups. Decision-makers seek information to inform their decisions from academic societies, the pediatric association, other scientific expert groups, and manufacturers. They also gain insights from surrounding countries as well as the World Health Organization (WHO) and the Pan American Health Organization (PAHO).

The decision-making process in China involves the China Food and Drug Administration, WHO representatives in China, the national Chinese Center for Disease Control and Prevention (provides data), and the National Institutes for Food and Drug Control. In China, information on brands and product presentation is obtained from the China Food and Drug Administration and vaccine manufacturers.

In India, key decision-makers for selecting specific product presentations include the National Immunization Technical Advisory Group (NITAG), noted by most of the respondents, as well as global partners such as WHO and the United Nations Children’s Fund (UNICEF) and technical expert groups. One participant said that decisions include cabinet-level approvals, which “can have long delays because of political influences.” Two respondents referred to the role of the procurement division, though one felt that it was primarily involved in recommending the least expensive vaccines. In India, information on brands and product presentation are obtained from the NITAG, internal departments of health research, scientific expert groups, and manufacturers according to the respondents; however, the immunization specifications committee makes the final decision on product selection.

205 In Peru, the National Immunization Advisory Committee suggests the presentation and a technical
206 committee approves it and conducts cost comparisons. Then the ministries of health and finance approve
207 to provide resources for procurement. Epidemiological data, safety data, world and regional experiences,
208 prices, and acceptability by providers are taken into account if this information is available. Peruvian
209 procurement and policy participants reported obtaining information from the PAHO Revolving Fund and
210 from physicians and scientists.

211 In the Philippines, the Pediatric Infectious Disease Society of the Philippines, a subspecialty of the
212 Philippine Pediatric Society, provides technical inputs to the guidelines for all vaccines. WHO's
213 recommendations based on disease surveillance and vaccine availability are also taken into account. The
214 National Immunization Committee makes final vaccine purchase decisions. The most common sources of
215 product information used by decision-makers in the Philippines were the WHO, UNICEF, and
216 manufacturers with information obtained via meetings and these organizations' websites.

217 The decision-making process is well defined in Tanzania and Zanzibar. The EPI team, which includes
218 two national managers from Zanzibar and the mainland, two national cold chain officers, a surveillance
219 officer, a WHO focal point, and a UNICEF focal point, collectively decide on vaccines to be introduced.
220 In Tanzania, a technical working group gathers data from other experts (WHO, UNICEF, immunologists,
221 pediatricians, and other public health specialists). The EPI manager then writes a proposal and the MOH
222 approves the proposal and budget; the Interagency Coordinating Committee must also approve (even if
223 the vaccine is donated). The Tanzanian MOH procures vaccines for both the mainland and Zanzibar.
224 Tanzania and Zanzibar typically leverage UNICEF, WHO, PATH, and the US Centers for Disease
225 Control and Prevention websites, literature, or focal points to obtain specific information on products. The
226 EPI manager is the individual most responsible for determining which brand and presentation to purchase.

227 When considering a vaccine product for purchase, country decision-makers were asked if they consider
228 systems costs associated with introduction of the vaccine in addition to vaccine price. Specifically,

229 decision-makers were asked if a vaccine's impact on storage, transport, wastage, and disposal or
230 human-resources costs were taken into account when choosing a vaccine. According to the responses
231 from the 32 procurement and policy participants interviewed, the majority accounted for storage and
232 wastage in the decision-making process (Figure 4). Close to half of the participants stated that transport,
233 disposal, and general human-resource requirements were also taken into account. It should be noted that
234 the interviewers did not stress the cost component of this question; therefore, interviewees may have
235 considered these attributes from a qualitative impact perspective, and not necessarily by quantifying the
236 cost implications of the vaccine attributes on these system components.

237 **[insert Figure 4 here]**

238 We asked decision-makers if the currently available information on vaccine products meets their
239 country's or region's needs. Twenty-six of 34 (74%) decision-makers responded "yes" and nine (26%)
240 responded "no." Those that felt that the information available does not meet their needs commented that
241 more information on adverse events is desired. One participant said that "Information on vaccine delivery
242 [and] storage is very general; we would like detailed information such as how long can [a] vaccine be
243 outside of the cold chain." Participants from the Philippines commented on a "need for additional cost-
244 effectiveness information; however, this has to be obtained from a third party in order to not show bias.
245 [It is] expensive to have a third party do this; so we assume that a vaccine is cost-effective if it becomes
246 available for Gavi-eligible countries."

247 3.2.2. *Success in obtaining products with desired vaccine product attributes*

248 We then asked the 28 national-level participants who are involved in policy and procurement if their
249 country receives the vaccine product attributes that they request. Twenty-two (79%) reported that vaccine
250 product attributes requested are received. A Brazilian participant commented, "If the country is large
251 enough, manufacturers will change the attributes requested." Participants from the Philippines added a
252 caveat, though, stating, "Sometimes vaccine products requested are received; however, it depends on the

bidding process. WHO and [the Department of Health] would prefer to fulfill the priority specifications, but price is usually the strongest determinant.”

Another six participants (21%) believed products requested are not always received. A Peruvian participant commented, “The PAHO Revolving Fund is who at the end decides.” A participant from Zanzibar commented, “UNICEF projects availability of products. Sometimes we make decisions for future vaccines and then they aren’t available at the projected time. For example, we heard that all vaccines would have VVMs by a certain year, but this didn’t happen. It took some time.”

4. Discussion

4.1. Vaccine product presentations

Immunization stakeholders especially valued vaccine product attributes that prevent heat damage, decrease vaccine wastage, and simplify vaccine delivery. The WHO multidose vial policy appears to be broadly used in the countries surveyed, and most stakeholders understand the proper procedures for handling opened vials of vaccine. In the course of our research, we learned that several facilities in Peru, the Philippines, Tanzania, and Zanzibar offered reconstituted vaccines (e.g., measles and bacillus Calmette–Guérin) on fewer days per week than other vaccines to avoid vaccine wastage. Greater use of single- or low-dose vials could allow for children to be immunized more frequently and may result in increased coverage [9–11]—advantages widely recognized by our study participants.

At present, WHO allows prequalification of 1- and 2-dose vials, but not higher doses per vial, of liquid injectable vaccine without preservative. Countries receiving the 2-dose vials must undergo a programmatic readiness assessment before they are able to procure these vaccines from UNICEF [12]. The most frequently mentioned issue from stakeholders interviewed concerning new liquid low-dose vials of vaccine without preservative (e.g., 2-dose vials of pneumococcal vaccine) was vaccine wastage, with respondents preferring single-dose to low-dose and preferring low-dose to 10-dose vials to minimize wastage and improve coverage. Other impacts of preservative-free, low-dose vials mentioned were the

need for training, risk of vial contamination, and greater cold chain space required (in comparison to larger multidose vials; though larger multidose vials are not currently available for these vaccines). Benefits mentioned were fewer missed opportunities for vaccination (in comparison to larger multidose vials) and the fact that the vaccines were preservative free. A few individuals implied that the lower-dose vials would result in fewer adverse events, though the rationale for this is unclear.

Improving immunization efficiency by decreasing the time required to prepare a dose was valued more highly by those closest to the actual work of administering vaccines. Recent immunization system cost analyses find that human resources are among the most costly component of immunization programs [13–15], making this perception especially noteworthy for those who are concerned about overall immunization program budgets. Finding means to ensure that procurement decision-makers and advisors are fully aware of the systems costs of different product presentations as well as the impacts on those handling and administering vaccines is important to improve immunization efficiency, cost-effectiveness, and coverage.

4.2. Vaccine procurement decision-making

There is great diversity in the procurement decision-making processes between countries. The majority of national-level respondents felt that they currently receive vaccines with the attributes they request and that the information available to them is adequate for their needs. Those individuals who are tasked with making procurement decisions for their national immunization programs are relying primarily on international agencies and vaccine manufacturers to provide the information they require to make decisions. Qualitative assessment of the impacts of different vaccine presentations on storage, transport, wastage, disposal, and human resources seems to be taken into account. Assistance to countries with access to product information and systems analyses to better quantitatively assess these impacts and other factors could be useful going forward—especially as more vaccines are introduced and more countries become self-sufficient in their vaccine procurement. Countries, especially large ones, can serve as important vaccine product attribute influencers if they are willing and able.

4.3. Limitations

The study only surveyed a small number of individuals in a few countries and should not be considered a representative sample. The findings presented are designed to illuminate the opinions of stakeholders with a variety of diverse perspectives and priorities.

5. Conclusions

Immunization stakeholders at all levels in the countries surveyed value vaccine product attributes that prevent heat damage, decrease vaccine wastage, and simplify vaccine delivery. Minimizing the time required to prepare a dose of vaccine is especially valued by those closest to the work of actually administering vaccines. Survey respondents valued the benefits of lower-multidose presentations on wastage, but seemed to prefer single-dose vials even more. They also expressed concern about the need for training and potential for confusion and vial contamination if opened vials or preservative-free vaccines are not handled properly. Procurement decision-making processes varied widely between countries, though most relied heavily on international agencies and vaccine manufacturers for their sources of information and are satisfied with the information available. Additionally, the study revealed that some countries rely on international agencies to define which products are most cost-effective. For this reason, it is especially important that such organizations take product attributes, such as those described above, into account when making recommendations.

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Fig. 1. Perceived impacts of a lower-multidose (2- or 5-dose) liquid vaccine without preservative.

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337 Abbreviation: EPI, Expanded Programme on Immunization.

338 **Fig. 2.** Importance of time required to prepare a dose of vaccine for administration, by participant role.

Abbreviations: PAHO, Pan American Health Organization; UNICEF, United Nations Children's Fund; WHO, World Health Organization.

Fig. 3. Sources of information on vaccine product brand and presentations utilized by each country.

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Fig. 4. Systems cost factors considered in vaccine procurement decision-making.