Coverage, Cost, and Safety Impacts of Primary Container Choice

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INTRODUCTION

A single decision on the size and type of a vaccine container can have significant implications on the safety, affordability, and coverage of vaccination in routine and campaign settings. Choosing a single dose vial instead of a multi dose container or a pre-filled syringe, for example, affects a wide variety of stakeholders: the vaccine recipients who benefit from the vaccine's protection; the governments and organizations that buy, transport, and store them; the health workers who administer and dispose of them; and manufacturers who make vaccines.

Given the scarcity of data on the broader effects of container choice, decisions are often based on readily quantifiable criteria with clear short-term implications; procurement price or storage volume are common decision drivers. These criteria provide a helpful starting point for decision-making; however, container choices have additional complex impacts on safety, affordability, and coverage—particularly in low-resource, last-mile settings.

While these concepts might seem abstract, they have already had very real effects, in terms of both dollars spent and lives saved. In the early stages of pneumococcal conjugate vaccine (PCV) introduction, manufacturers developed a two dose presentation as a response to global health community requests for low storage-volume options. However, unlike other multi dose liquid vaccines used in routine immunization, the two dose PCV vial was preservative-free, with new handling requirements to ensure safe, effective administration. The resulting need for training at the country level was extensive, and—in the absence of systematic communication between countries, agencies, and manufacturers—largely unanticipated. As a result, introduction was delayed in several countries, increasing costs and leaving children unvaccinated.

The upcoming transition from oral to inactivated polio vaccine (IPV), an injectable, provides another example of these tradeoffs in action—for instance, in the short-term, standalone IPV may be the most viable option, but with how many doses per vial? Many countries prefer multi dose vials due to space constraints and price, but it's currently unclear which presentations will be available and prequalified, and whether multi dose vial policy will apply.

Furthermore, countries may want more than one option for different situations. In areas where session sizes are small, single, or low dose options may make the most sense. Further into the future, decisions will center around combination vaccines, such as hexavalent diphtheria, tetanus, pertussis, hepatitis b, haemophilus influenzae type b, and IPV vaccine. This approach avoids extra shots but requires a preservative-free one or two dose container. Low dose options often come at a higher price and increase cold chain burden, but they also reduce wastage. In cases of limited resources or uncertain supply, the fear of wastage puts health care workers in a difficult position: with a multi dose vial and a small session size, do they open the vial and waste the unused doses, or do they wait for another day when there is a larger session size, avoiding wastage but leaving today's eligible children unvaccinated? The "best" answer isn't clear, and might be different from one place to another—but getting the answer right from the start could mean the difference between successful polio eradication or an ongoing battle against the disease.

WHY NOW FOR PRIMARY CONTAINER WORK?

- New vaccine introductions are ramping up. If we help manufacturers understand priorities early, these can be addressed in product development to produce the greatest health value and deliver savings down the line.
- For eradication, almost isn't good enough. Polio eradication is within reach, but only if vaccines can make it all the way to the last child at the end of the last mile. Measles eradication efforts may be next, and will face the same difficulty. Container choice could be the small but crucial difference between eradication and continued transmission.
- Many new vaccines cost more than traditional vaccines, making high wastage rates even more costly. With traditional vaccines, which are generally pennies per dose, wastage is less costly, with an increasing number of new, expensive vaccines, costs due to wastage could increase substantially. A more in-depth look is needed to understand the full cost implications of a new vaccine introduction, factoring in issues of wastage, cold chain, health worker training, and the often hidden costs of adverse events following immunization.
- Demand-side issues are likely to become more important. There are important discussions going on in other container-impacted areas, such as the rise in public and environmental concerns about thimerosal in multi dose vial vaccines.
HOW DO PRIMARY CONTAINER DECISIONS AFFECT COVERAGE, AFFORDABILITY, AND SAFETY?

COVERAGE
As with safety, the pathways from container choice to coverage outcomes are complicated, and have not been well studied. To the extent that multi dose containers reduce storage and transport burdens, they may increase coverage by reducing space bottlenecks which may prevent vaccines from reaching the places they need to reach. However, they can also affect health care worker behavior. If a health worker has three children at a session, but the needed vaccine is in a ten or twenty dose vial, the health worker may have a dilemma. If the vaccine does not qualify for the multi dose vial policy (MDVP)* or the MDVP is not followed, they may waste a lot of doses and possibly not have enough for children who come in later sessions; or, they may inappropriately use the vaccine, potentially putting children at risk. Outreach to use the remaining doses is also an option, particularly with presentations such as prefilled syringes or oral droppers, but the associated time and logistics required could be a significant challenge.

In areas with uncertain supply, there is some evidence that health workers are hesitant to open the vial, and children miss opportunities for vaccination.

Even if a worker does open the vial, the increase in wastage reduces overall supply and can result in shortages. On the other hand, if the health center is supplied with only single dose vials, storage constraints may prevent them from keeping enough vaccine on hand to meet demand on any given day. In addition, there are reports of central managers reporting adequate supply while regional managers report shortages; these disconnects could be a result of multiple factors, but an incomplete understanding of decisions at the clinic level may contribute to communication and forecasting failures. The difficult tradeoffs in coverage demonstrate the extent to which the “best” container choice will vary by context, and highlight the importance of better data for decision-making.

Additionally, compact, pre-filled auto-disable devices (CPADs) reduce the transportation and planning burden for ensuring availability of syringes. They also offer another benefit that can not be forgotten - given that needles are already attached, there is no added risk that children will not receive vaccine due to a shortage of needles at the time of administration.

To illustrate the impact that these choices can have on coverage, see Figure 1, which shows the impact on coverage of a 10-dose vial with a 50% opening threshold. In other words, if a health care worker only opens a vial when at least half of that vial will be used, what is the impact on coverage? As the figure shows, the impact varies by session size. With larger session sizes, the coverage differences are very small. But in areas where sessions are between 1-10 children—as in many “last-mile” settings—coverage will decrease to 60% even when the needed vaccines are technically available. Even in scenarios with larger average session sizes, coverage impacts can be observed; in areas where sessions average between 11-20 children, a 50% opening threshold decreases coverage to 92%. This is still a relatively high percentage, but it also represents a best case scenario in which the needed vaccine is always available. When variations in availability combine with reluctance to open large vials, the coverage impacts will be larger.

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*MDVP states that under certain conditions, opened multi dose vials of OPV, DTP, TT, hepatitis B, and liquid formulations of Hib may be used in subsequent sessions for up to four weeks.
the coverage impacts will be larger. These impacts may be somewhat mitigated if children return to the clinic after an unsuccessful visit, but when health facilities are hard to reach, a return visit is a difficult option. For eradication campaigns and last-mile efforts, these small differences can be the difference between success and failure.

**AFFORDABILITY**

The pathways from container choice to affordability outcomes are in some ways straightforward. Stakeholders, however, do not always consider the impact of all aspects of affordability and may thus focus on one aspect—such as price per dose, or cost to add additional cold chain storage—without considering other aspects. The characteristics of the container and the market affect the price charged by a manufacturer, and the country pays that price in addition to storage, transport, disposal, and wastage costs. Taken together, all of these factors determine price per dose, cost per vaccinated child, and overall affordability of a presentation. Usually, presentations with a high number of doses in a single container lower procurement costs and require less space, reducing storage needs, transport needs, and medical waste. For this reason, multi dose vials are generally considered the least expensive option when procurement and logistics costs are considered alone. However, increased global demand for a particular presentation may help lower procurement costs; as cost to manufacturer is not directly related to price, procurement costs could be similar across presentations. Other costs, such as wastage or handling, may add considerably to the overall cost of the vaccine program. Where wastage is an issue in a country, the lower cost per dose delivered benefits of a multi dose vial may be erased as the system needs to procure more product, transport it and store it.

As an illustration, consider the hypothetical scenario illustrated in Figure 2 below. In this example, a hypothetical vaccine is priced similar to Pneumococcal Conjugate Vaccine (PCV): $3.50 for a single dose vial, $2.80 per dose in 5-dose vials, and $2.40 per dose in a 10-dose vial.

**Figure 2. Average cost per dose administered by session size range, assuming that health care workers open vials as needed, and unused doses are wasted.**

![Graph showing average cost per dose administered by session size range.](image)

Multi dose vials are sometimes cheaper—but only for large session sizes. As an example, a hypothetical vaccine is priced similarly to possible Pneumococcal Conjugate Vaccine (PCV) pricing: $3.50 for a single dose vial, $2.80 per dose in 5-dose vials, and $2.40 per dose in a 10-dose vial. As illustrated above, cost per dose administered is higher for a multi dose vial when sessions are small, and that relationship quickly reverses as session sizes increase. This demonstrates the need to consider multiple presentations in a single country, even when affordability is the primary concern.

**ASSUMPTIONS**

- Logistics costs are calculated per vial: $1.00 for the 10-dose, $0.70 for the 5-dose, and $0.50 for the single dose. Possible economies of scale in logistics costs are not represented.
- Price per dose is $3.50 for single dose vial, $2.80 for 5-dose vial, and $2.40 for the 10-dose vial.
- Distribution of session sizes is equal; no session size is weighted to reflect a more frequent occurrence.
In this illustration, cost per dose administered is higher for a multi dose vial when sessions are small, and that relationship quickly reverses as session sizes increase. This demonstrates the need to consider multiple presentations in a single country, even when affordability is the primary concern.

Actions to keep wastage low (such as session size management or compliance with multi dose vial policies) can help keep multi dose vials affordable for small session sizes, even when cost per dose administered is considered along with procurement costs. Wastage at earlier points along the supply chain (e.g., during transport or at the central cold store) should also be considered for a comprehensive cost per dose assessment. Additionally, investing in additional cold chain options and/or reevaluating the structure of storage and delivery options may be an affordable option over the long term.

The manufacturer perspective on affordability is also important; as noted earlier, price is not a fixed characteristic of a presentation, but a function of the entire economic and technological environment. Although single dose containers generally cost more, those differences do not fully account for the disparity in pricing between presentations. Economies of scale help reduce price per dose; the greater the demand for single dose product, the lower the possible cost per unit. If that demand can be reliably predicted, it can be leveraged to reduce prices. When demand is uncertain, however, manufacturers will necessarily be less flexible in price setting, and affordability will be reduced.

SAFETY

The pathways from container choice to safety outcomes are perhaps the most difficult to quantify, and have not been well characterized to date. Essentially, increasing the doses per container increases the opportunity for user error, which may raise the likelihood of non-sterile injections and injections with expired vaccine. In turn, this increases the likelihood of infection from injection and of blood-borne disease transmission. Certain presentations may also increase the risk of accidental needle sticks, which put health workers at risk of blood-borne disease.

The presence of preservatives may reduce the likelihood of some adverse outcomes, but thimerosal, the most commonly used preservative, has been a target of concerned parents and activists due to its chemical relation to mercury. Furthermore, thimerosal may have antibacterial action, but is not effective in controlling viral contaminants.

Additionally, public opinion can have a significant impact on perceived safety of certain vaccines or the program overall; regardless of actual safety, these concerns can lower demand and thus coverage. Costs to mitigate bad publicity or restart a program after a serious adverse event can also be significant.

INTERRELATIONSHIPS BETWEEN DOMAINS

There are also safety or coverage effects that influence affordability or vice versa. For example, the health worker choosing between wasting doses or leaving children unvaccinated will affect cost per administered dose as well as coverage. If the worker opens the vial, wastage costs increase, reducing the affordability of the multi dose presentation. If the worker decides not to open the vial, the costs of wastage are averted, but there may be increased costs of illness and lost productivity from incidence of vaccine-preventable diseases in those unvaccinated children. Poor safety outcomes can increase the cost of illness (particularly at the household level) while also reducing coverage by depressing demand.

POLITICAL WILL AND DECISION-MAKING

It is important to note that the relationships illustrated above exist within and alongside a series of similarly complicated political systems. While container choice is not inherently a political issue, agencies, governments, and funders set priorities which in turn affect the range of options and willingness to prioritize different aspects of container decisions. Politics and policy are therefore key, albeit indirect, components of the primary container decision system.

SCENARIO ANALYSIS: ROUTINE IMMUNIZATION IN BENIN

In a more concrete example of the importance of health care worker decision-making, we can consider the variations in vaccine availability and cost per dose administered within a small country such as Benin. According to the Highly Extensible Resource for Modeling Event-Driven Supply Chains (HERMES) analyses (conducted after an extensive data collection and verification process), the national-level cost per dose administered, averaged across all vaccines, is $0.25. Reducing doses per vial for any vaccine in the schedule increases the cost per dose administered, and simulating a 50% opening threshold for each vial results in decreased vaccine availability.

Subnationally, however, the picture varies. Simulating a 50% opening threshold—a rule that vials are only opened when 50% or more of the doses will be immediately used—yields differing results across the areas analyzed. In Natitingou and Kandi, two of the three areas with the lowest vaccine availability, a 50% opening threshold results in slight increases in vaccine availability and reductions in cost per dose administered. This may indicate that current large vial sizes are reducing overall availability due to open vial wastage. In the higher performing areas, applying a 50% opening threshold had the opposite effect, increasing cost per dose administered and decreasing availability.
In terms of threshold changes, the increases and decreases of the largest magnitude were observed in the areas with the highest baseline vaccine availability. However, variations in cost and coverage as a result of vial size changes were much smaller in the high availability areas, perhaps indicating a greater ability to adapt to changes in the system. Interestingly, variations in the number of health post trips needed as a result of vial size changes follow the same pattern in both high-availability and low-availability areas; as expected, reducing the doses per vial increases the number of trips necessary. However, the trips themselves are cheaper in high-availability areas, reducing the cost impact of the additional logistics burden.

WHAT IS THE CURRENT STATE OF PRIMARY CONTAINER DECISION-MAKING?

There is no comprehensive set of guidelines weighing the trade-offs of affordability, safety, and coverage. Decision makers from different sectors or regions will naturally have differing priorities, which may lead them to a focus on certain aspects over others. The resources available to a given decision-maker vary widely as well. In resource-limited settings, up-front costs, and current system capacity are very often the determining factors in container choice at the country level. Costs are most easily compared in terms of procurement prices. While price differences are certainly not trivial, changes in vaccine presentations can change other outcomes, such as wastage, that in turn change the cost per vaccinated child—even when price per dose procured remains the same.\(^{19, 20}\) On the flip side, choosing a presentation with a high volume per dose (such as a single dose vial) can lead to increased cold chain, transport, and personnel needs and costs.\(^{21}\) While container choice almost certainly affects safety,\(^{22}\) there is little concrete evidence quantifying these effects; the lack of data often excludes safety concerns from explicit consideration in container decisions.

Simulating a 50% opening threshold—a rule that vials are only opened when 50% or more of the doses will be immediately used—yields differing results in different areas of Benin. In Natitingou and Kandi, two of the three areas with the lowest vaccine availability at baseline, a 50% opening threshold results in slight increases in vaccine availability and reductions in cost per dose administered. This may indicate that current large vial sizes are reducing overall availability due to open vial wastage. In the higher performing areas, applying a 50% opening threshold had the opposite effect, increasing cost per dose administered and decreasing availability.
The most consistent source of guidance is the WHO prequalification process, an established procedure used by WHO for the evaluation of candidate vaccines. Prequalification provides a set of standards for health products, including vaccines; a vaccine that has achieved WHO prequalification is eligible for purchase by UNICEF and other UN agencies. Prequalification requires that vaccine efficacy data and studies are relevant to the target population, and that vaccines meet specific criteria in terms of potency, thermostability, presentation, labeling, shipping conditions, and more. The prequalification process is enormously helpful in setting baselines and facilitating dialogue between manufacturers and global agencies. However, it cannot serve as a comprehensive analysis of all the issues surrounding introduction in a particular country; prequalification processes are necessarily operating at the global level, and they are focused on efficacy and supply, rather than behavioral, policy, or demand-side impacts of introduction.

There is a need to balance country and global perspectives. A one-size-fits-all, global approach commonly seen in low income countries can lead to programs or policies that don’t meet the needs of specific countries, or that don’t fit the needs of certain regions within a country. For instance, a country with limited cold storage may need to prioritize low volume above all other considerations, regardless of international recommendations. Countries may also find that session sizes in urban locations vary drastically from those in hard to reach areas, thus necessitating different size containers. And in some cases, the initial investment of funding and human resources necessary to set up—and maintain—an improved cold chain may be out of reach, even if the investment case itself is clear. Cold chain investments are not always as high as they may seem initially, however, and are often a cost-effective way to ensure that other priorities of coverage and safety are considered. This decision, therefore, should be taken with those objectives in mind, also taking into account that capacity may need to be added anyway to prepare for future vaccine introductions.

Improved market forecasting could spur product development. Mismatches between available presentations and country needs can create shortages or unnecessary burdens; when countries receive products that are not compatible with their systems, additional or unplanned investments may be required for successful introduction. Manufacturers are willing to develop new presentations in response to global health community requests. Historically, however, communication around desired characteristics has not been systematic or consistent, leaving manufacturers hesitant to invest in new product development. Accurate and transparent forecasting is needed to restore private sector confidence in the health community’s decisions.

Space reduction does not always equate to lowest cost. Many EPI managers will avoid adding cold chain capacity wherever possible. The cost of new refrigerators and incremental operational costs, are often lower than the wastage seen for multi dose vials. Adding cold chain space may become a necessity anyway given the number of new antigens introduced in the coming years. Additional space needed from single dose vials may have insignificant cost compared to the wastage savings and other benefits of safety and coverage that could be seen assuming the country has the capacity to handle the product.

Stakeholder perspectives are complex and diverse. Decision-makers have different needs, priorities, and resources, even within a particular stakeholder group. For instance, an EPI manager within a country may want multi dose vials to minimize cold chain burdens, but a health worker in the same country may have concerns about opening a multi dose vial for a small session size and wasting doses, particularly if there’s uncertainty about the ability to restock in a timely manner. In addition, constraints differ between campaign settings and routine administration; some vaccines must fit in both contexts, as they are administered in both settings or transitioned to routine after an initial campaign period.

High-priority data gaps have not been identified and addressed. Important information such as wastage rates, cold chain capacity, session sizes, safety outcomes, and cost per administered dose can be very difficult to pin down, particularly at subnational levels. The lack of data, particularly on safety, hinders evidence-based decision-making, and there is little ability to prioritize within existing data gaps. Additional data on safety are needed for countries, manufacturers, and donors to make better decisions; these data should be incorporated into available tools such as HERMES to facilitate decisions based on all factors that should be considered.
HOW CAN PRIMARY CONTAINER DECISIONS BE IMPROVED?

The public health community will be facing some very important decisions in the near future, which have implications not only for countries that introduce new vaccines, but for manufacturers who supply new product and countries, and donors who fund the process. Introduction of inactivated polio vaccine (IPV), recently recommended by SAGE\textsuperscript{30}, and other new vaccines that will significantly expand countries’ immunization programs will have significant implications for all stakeholders. Individual decisions, made on the basis of up-front indicators such as cost or cold chain expense, have the potential to work against the long-term needs of disease reduction and eradication effort in hard to reach locations. If multi dose vials are used in hard-to-reach areas with small session sizes, potential impacts include high wastage levels, potentially resulting in insufficient supply; containers unopened and children turned away if a sufficient number of children are not in a session; a health worker spending additional time in outreach, which has direct costs and opportunity costs; or the retention of open multi dose vials, risking contamination. Single or low dose vials avoid those particular pitfalls, but they too come with downsides. Some have suggested that perhaps a five dose vial is a solution, but it is important to evaluate whether that will in fact address the issues that are to be solved. Further, both global and country guidance will need to be vaccine specific, taking into account price of vaccine, safety implications, how it is used, and other factors. More data are needed to understand the risks to enable all stakeholders to make fully informed decisions.

It is clear that there is no “one size fits all” solution; answers will be very context specific, and some trade-offs will be unavoidable. However, running scenarios and modeling the impact in multiple ways may help answer some important questions and allow for more informed decision-making. Tools such as HERMES and other models can help provide detailed and dynamic simulations of country supply chains,\textsuperscript{31} and be adapted to evaluate coverage and safety implications. In addition, a comprehensive approach makes it possible to identify and evaluate innovative opportunities, such as regional procurement or multiple presentations within a single country. Also, the manufacturers’ perspective will need to be considered as economies of scale derived from focus on a small number of product presentations can be important.

Having the data to support decisions could then result in policies that can be evaluated in the context of the complex and dynamic environment that exists today. Although there may still be trade-offs, the decision to select for instance a single dose vial in some countries or a ten dose container for the majority of a country and single, two or five dose container for the hard to reach areas will help in making better informed decisions to meet coverage goals, and in turn protect more children from vaccine-preventable diseases.