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Review

Doses per vaccine vial container: An understated and underestimated driver of performance that needs more evidence

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ABSTRACT

The widespread use of multidose vaccine containers in low and middle income countries' immunization programs is assumed to have multiple benefits and efficiencies for health systems, yet the broader impacts on immunization coverage, costs, and safety are not well understood. To document what is known on this topic, how it has been studied, and confirm the gaps in evidence that allow us to assess the complex system interactions, the authors undertook a review of published literature that explored the relationship between doses per container and immunization systems. The relationships examined in this study are organized within a systems framework consisting of operational costs, timely coverage, safety, product costs/wastage, and policy/correct use, with the idea that a change in dose per container affects all of them, and the optimal solution will depend on what is prioritized and used to measure performance.

Studies on this topic are limited and largely rely on modeling to assess the relationship between doses per container and other aspects of immunization systems. Very few studies attempt to look at how a change in doses per container affects vaccination coverage rates and other systems components simultaneously. This article summarizes the published knowledge on this topic to date and suggests areas of current and future research to ultimately improve decision making around vaccine doses per container and increase understanding of how this decision relates to other program goals.

Contents

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1. Introduction

In low- and middle-income countries, public sector immunization programs, particularly those supported by UNICEF and Gavi, tend to rely on multidose vials or, more broadly, multidose containers (MDCs) of vaccines (which typically range in capacity from 2 to 20 vaccine doses),[1] whereas upper-income countries predominantly opt for single-dose containers due to safety concerns, different financing, and fewer supply system constraints. The reliance on MDCs in much of the world is a result of the global effort to reach more children within existing resource and infrastructure constraints—MDCs offer lower prices per purchased dose and minimize cold chain storage and distribution requirements. The assumption is that the resulting cost savings allow donors and countries to purchase more vaccines to reach more children.

There is another assumption, however, that healthcare workers (HCWs) can anticipate session sizes and optimize MDC use to minimize wastage, mitigate safety risks, and meet coverage targets, and thus, the burden of cost efficiency is shifted from the purchaser or program manager to HCWs. Based on anecdotal reports, there is concern that in order to achieve maximum utilization of every dose in a container, HCWs need to be strategic about when to open a container, diligent about how they care for open containers, and proactive with communication and community outreach to ensure optimal attendance and timely vaccination of every child during a vaccination session. This calculation and effort may reduce a HCW's willingness to open a container for every eligible child they see (if, for example, some doses will go unused because not enough children are present to use up all the doses in the container before it needs to be discarded), despite training and higher level guidance from the World Health Organization (WHO) instructing health care workers to open a vial for every child.[2] Thus, the number of doses per container may have unintended consequences on a country's ability to achieve goals of timely, safe, and equitable vaccination coverage.

This dose per container (DPC) issue has received little formal research and analysis, yet is generally understood to require an analysis of trade-offs. However, there are limited data around the above assumptions, and evidence-based guidance for policy and decision making for product selection in light of this trade-off analysis is negligible. Accordingly, in early 2015, the authors of this paper began an effort to summarize the existing evidence of the effect of DPC on immunization systems and program goals, and to highlight key pieces of missing evidence. The intent was to gather and synthesize data to better inform a tradeoff analysis of DPC-related costs versus impacts and improve vaccine product selection for global stakeholders and country programs. The first phase of this process was a literature review and analysis to summarize stakeholder perspectives, followed by a meeting of global stakeholders to agree on missing evidence and ways forward. This paper highlights the outputs of those efforts and introduces the second phase of work currently under way to address the evidence gaps.

2. Methodology

2.1. A systems impact framework for evaluation

Evaluating the effect of a programmatic decision on number of doses per vaccine container may be straightforward if a person is only looking at one relationship (e.g., cold chain storage and distribution requirements). But the reality is that this decision affects multiple components and costs of a vaccination system (e.g., cold chain capacity, safety, wastage, cost per administered dose, and coverage) and possibly in different directions (positive/negative) and therefore must be considered as a trade-off analysis. It also requires policy makers to define performance and determine which aspect they choose to prioritize. If program performance is measured in relation to WHO Global Vaccine Action Plan targets for timely coverage, a DPC choice may be different than if the performance target is to minimize system costs and cold chain utilization. Some of these inputs are easily quantifiable (e.g., purchase price), whereas the relationship between DPC and coverage is mediated through HCW behavior, which is much more difficult to quantify. These complex relationships and interactions make it difficult to anticipate the impact of a DPC decision.

For this reason, a systems framework to categorize the multiple components and assess tradeoffs provides an organized way to analyze the data on relationships between DPC and other aspects of immunization programs. The framework adopted for this analysis looks at five main areas: operational costs, timely coverage, safety, product costs/wastage, and policy/correct use. The framework and the subcomponents/proxy measurements of these areas are outlined in Fig. 1.

The graph (Fig. 1) represents two hypothetical presentations of one antigen in two different doses per container presentations. This graph is illustrative of the trade-offs and relationships between the multiple components within a vaccination system and how a DPC choice can affect each. The positive and negative directions labeled on the axes are indicative of such trade-offs within a vaccination system, based on favorability of the outcome (increased safety, lower costs/wastage, lower operational costs, higher rates of timely coverage, and increased adherence to policy/correct use all considered more favorable). This is not based on actual data, but represents the type of trade-off analysis we would like evidence to enable. For example, with Presentation 1, safety, products costs / wastage, timely coverage, and policy/correct use are more favorable (positive) than Presentation 2 but operational costs are greater for Presentation 1 than Presentation 2 (negative for Presentation 1, positive for Presentation 2).

Many of these relationships are presumed in terms of direction (positive/negative) but may actually compound or contradict each other, so it is difficult to understand the net impact of DPC decisions. The importance and magnitude of these associations also depend on the specific antigen and the country context, including—

- The particular size of the presentation (both number of doses per container and volume).
- Characteristics of the vaccine (lyophilized, liquid, with or without preservative).
- Cost of the vaccine in different presentations.
- Multi-dose vial policy[3] (WHO recommended criteria to permit certain vaccines to be stored up to 28 days after opening) and adherence to it by HCWs, including any actual or perceived thresholds for opening a vial.
- Vaccination schedule and session size, which may vary within a country.
- Current state and capacity of the immunization logistics system, including transportation and cold chain storage at all levels.

Vaccine experts have hypothesized that these factors can also influence vaccine availability and ultimately timely and equitable vaccine coverage. Higher-capacity (with more doses) MDCs may

[1] WHO Strategic Advisory Group of Experts (SAGE) Meeting - 10–12 April 2012; Trends in use of multi-dose vaccine vials in UNICEF procuring countries - http://www.who.int/immunization/sage/meetings/2012/April/consultation_INC4_MDVuse_JLiu_20120401.pdf.

[2] WHO Document. Training for Mid-level Managers (MLM). I. Cold chain, vaccines and safe-injection equipment management. Geneva: World Health Organization; 2008. WHO document WHO/IVB/08.01.

[3] WHO Policy Statement: Multidose Vial Policy, 2014 Revision - http://apps.who.int/iris/bitstream/10665/135972/1/WHO_IVB_14.07_eng.pdf.

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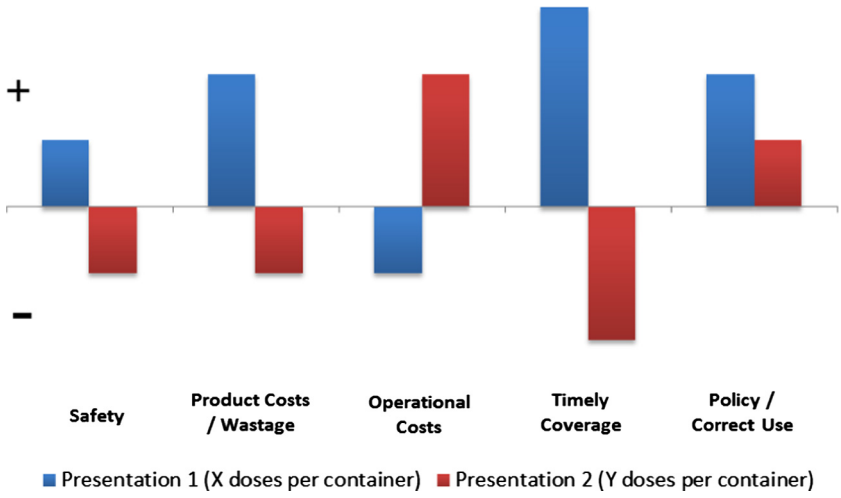

Fig. 1. Systems impact framework for assessing trade-offs of dose per container options.

result in HCWs and their supervisors trying to reduce wastage by implementing infrequent sessions or establishing thresholds for opening vials. In some settings this means they may miss opportunities to vaccinate children until enough children gather to justify opening a vial. While this practice may be reduced or eliminated by lower-capacity MDCs with fewer doses, the extra volume these vials require for handling may stress cold chain storage or transportation capacities, resulting in fewer vaccines arriving in service delivery points and thus fewer children being immunized. Without accurate, quantifiable data on these relationships, it is difficult to assess the cost and coverage implications of a vaccine presentation.

To assess the existing research on DPC issues, a literature review was conducted of peer-reviewed and grey literature. The intent was to summarize existing knowledge, not conduct a meta-analysis. Initial searches using key words "doses per container" and combinations of "coverage," "wastage," "costs," "cold chain" and "safety" yielded limited information on the topic. Despite the publication of special issues of journals dedicated to vaccines and vaccination programs, there were few relevant articles identified from the initial search.

Therefore, in order to gather data for this article a purposeful search using snowball sampling was conducted, including information found in grey literature, meeting reports and presentations. As a starting point the authors consulted the report from the Primary Container Roundtable Meeting [13], a similar effort convened in 2012 to summarize available data on the topic. The data collected and generated from that meeting provided a critical body of evidence and analysis on this topic. It has also spurred additional modeling efforts and research that this review sought to capture to build upon the initial body of information, so the authors used a forward snowballing approach to find articles citing that report or references included within it.

To be considered for this review, articles had to include a methodology to establish, or compile data to document, a relationship between vaccine presentation and one or more of the system components described earlier, namely operational costs, timely coverage, safety, product costs/wastage, or policy/correct use. Publications were limited to English-language but not limited by geographic scope or research method or design.

In total and including the meeting synthesis, 23 peer-reviewed articles were reviewed for relevant information. Of these, 10 publications analyzed the association between DPC and one of the other factors under consideration (operational costs, product costs/wastage, safety, policy/correct use, and timely coverage) and thus, qualified for the review (see Table 1). Five unpublished reports and presentations found in the grey literature which met the inclusion criteria were also consulted and, where data were included, considered for the analysis.

To complement this review, the authors also conducted key informant interviews to summarize the current understanding of the evidence and institutional perspectives on the impact of vaccine presentations and DPC choices globally. The interview results were shared at a stakeholder meeting held in July 2015 but are not included in this analysis due to the fact that the interviews were conducted in confidence and not with the intent to publish.

3. Results

Of the 10 published articles that met the inclusion criteria, four focused on the effects of vial presentation on cold chain capacity, three discussed the effects of coverage and/or vaccine availability, four discussed open vial wastage, one discussed safety, and two discussed waste disposal. Seven of these attempted to quantify the effects of vial presentations on some aspect of operational cost. The following sections summarize the studies' findings and metrics.

3.1. Operational costs

In seven of the studies, an attempt was made to quantify the effects of vial presentation selection in terms of costs for the system. Five summarized costs from all the perceived cost drivers and presented findings as cost per dose administered. In four of the studies, lower-capacity MDCs resulted in higher cost per administered dose for the different scenarios modeled in each study [1,6,9,11], taking into account the factors incorporated in the model and their effects on the modeled countries, including cold chain capacity, vaccine availability, wastage, and/or waste disposal. The fifth study modeled nine different scenarios, each modeling one antigen and DPC presentation against another presentation (both replacing higher dose per container vials with lower capacity dose per container vials and vice versa) and one scenario including a combination of changes for multiple antigens. The results showed that both higher- and lower-capacity MDCs reduced the cost per dose administered [5]. However, overall costs of the system were also included, resulting in much lower overall costs associated with lower-capacity MDCs and higher overall costs with higher-capacity MDCs, but also increased system bottlenecks and fewer doses administered. Much of this variation in

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Table 1
Summary of articles included that evaluated data related to DPC and one of the other system factors being analyzed.

Studies, brief, or summary	References	Year	Geographic scope	Operational costs	Vaccine costs/ wastage	Safety	Coverage/ availability	Policy and correct use
Study	Assi, Brown, Djibo, Norman, Rajgopal, Welling, Chen, et al.	2011	Niger	Y	Y		Y	
Study	Burton, Bigogo, Audi, Williamson, Munge, Wafula, Ouma, et al.	2015	Kenya			Y		
Summary	DeBaun	2005	U.S.A.			Y		
Summary	Drain, Nelson, Lloyd	2003	Global			Y		
Study	Haidari, Wahl, Brown, Privor-Dumm, Wallman-Stokes, et al.	2015	Benin	Y	Y		Y	Y
Study	Lee, Assi, Rookkapan, Connor, Rajgopal, Sornsrivichai, Brown, et al.	2011	Thailand	Y	Y		Y	
Study	Lee, Norman, Assi, Chen, Bailey, Rajgopal, Brown, Wiringa, Burke	2010		Y				
Study	Parmar, Baruwa, Zuber, Kone	2010	Global (WHO HQ data)	Y	Y			
Study	Pereira and Bishai	2010	USA	Y		Y		
Study	Yang, Parisi, Lahue, Uddin, Bishai	2014	Bangladesh, India, Mozambique, Uganda	Y	Y			

costs was attributed to the large variation in vaccine availability displayed in the models (ranging from 60% to 92%).

The 2010 study by Parmar et al. did not make a recommendation for a specific country and so could not quantify the costs in a country context. Instead, it attempted to create a general rule that could inform vial presentation selection of pneumococcal conjugate vaccine (PCV) in the future, dependent on the price differential between vial sizes and the anticipated reduction in open vial wastage. However, the authors concluded that the optimal DPC choice would be dependent on the country context and in countries with higher wastage rates MDCs could be a more costly option.

The 2010 study by Lee et al. also created a general rule for presentation selection by modeling data not specific to one country. In this case, a model was created to determine the greatest cost savings per vaccine by looking at the average session size within the immunization system, favoring lower-capacity MDCs for smaller session sizes and higher-capacity vials for bigger session sizes. Both the Parmar et al. and [7] studies focused primarily on wastage rates (and arrival rates to determine session size) to create models for vaccine presentation selection. The Parmar study incorporated cold chain costs but with very broad assumptions.

Two studies directly discussed the effects of waste disposal in their modeled systems [1,6]. In both cases, lower-capacity MDCs were associated with higher waste disposal costs because there were more vials and reconstitution syringes that needed disposal. In both of these cases, waste disposal was measured in terms of overall costs, using in-country information for both waste disposal costs and anticipated weight of extra waste. These costs were later incorporated in larger cost metrics.

As a component of systems costs, cold chain capacity was considered explicitly in many of the studies. Cold chain capacity was measured in several ways, most often using modeling tools to assess cold chain storage at different levels of the supply chain as well as transportation capacity between levels. Across the four studies that assessed cold chain capacity, all four made positive associations between using a lower-capacity vial and an increase in both transportation needs and cold chain storage [1,5,6,8].

In some cases, these increased demands on the cold chain were easily managed by existing equipment, as in the case in Thailand [6], while others showed an exacerbation of already overloaded transportation and cold chain storage systems [1]. In measuring supply chain demands, several different metrics were used, including the median capacity required by vaccines both in transport and storage equipment, the number or proportion of routes or facilities that had insufficient capacity, and the number of additional transportation routes that would be needed to support additional distribution.

3.2. Product costs/wastage

Wastage was largely considered in terms of open-vial wastage and was a focus of four of the studies. In all four studies, a change to a lower-capacity MDC was found or modeled to have lower wastage [1,6,8,11], and single-dose vials were modeled to eliminate all open-vial wastage [6]. For the Parmar et al. study the median wastage rates for single, 2- and 10-dose vials were 5%, 7% and 10% respectively. However wastage varied between 1–10%, 1–27% and 4–44% for single, 2- and 10-dose vials respectively. These data show that single-dose vials consistently had lower wastage rages. Parmar et al. investigated wastage data for all 72 Gavi-eligible countries in 2010 and found that only 19 had any information on wastage rates, which may indicate that many countries have not been consistently monitoring this in their systems. As newer (and generally more expensive) vaccines are being introduced and wastage becomes a more costly concern, efforts are under way to increase measurement of wastage; but it remains difficult to measure, especially estimates of subnational variations. Again, different metrics were used to measure wastage, from a proportion of all vaccines ordered [8,11] to the number of wasted doses and their associated costs [1].

The Yang et al. study used actual data on average session size from four countries to model the impact of a change in doses per container. The study used the median session size data and modeled the impact of a change from 10- to 5-dose vials of inactivated polio vaccine (IPV); the estimated open vial wastage rate was reduced by 56% in Bangladesh (from 0.25 to 0.11), 53% in India - Uttar Pradesh (from 0.17 to 0.08), 53% in Mozambique (from 0.13 to 0.06), and 44% in Uganda (from 0.09 to 0.04).[4] The study found that despite wide variation in session size, the estimated open-vial wastage rate for IPV was reduced with the 5-dose vial in all four settings, yet the costs per dose increased in all four locations when considering costs of procurement, cold chain requirements, and wastage [11].

3.3. Timely coverage

In three studies, vaccine availability (percent of eligible children presenting at a health facility for whom the required vaccine is in stock) was modeled to represent the proportion of anticipated visitors to health facilities with enough vaccines in stock. In effect, this measure is largely a reflection of the two previous factors: cold

[4] The reduction in wastage for Uganda reported by Yang et al. was 44%, however our recalculation based on the absolute numbers provided in the article would show that wastage was reduced by 56%.

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chain capacity and wastage. In all three cases, lower-capacity MDCs resulted in decreased vaccine availability [1,5,6]. These models found that increased cold chain burden outweighed the benefits of reduced wastage, although other system components were not fully considered.

Multi-scenario modeling on the impact of changes by antigen (alone and in combination) and with/without a vial-opening threshold showed multidirectional impact. Modeling of Benin's vaccine supply chain and analysis of multiple scenarios using aggregated national data showed that higher-capacity MDC presentations increased availability and decreased costs (logistics and cost per administered dose) and that these savings were greater when a vial-opening threshold was in place (i.e., an MDC would only be opened if at least half of the doses would be used that day) [5].

3.4. Safety

It is presumed that the more times a vial is touched or manipulated, the greater the chance for contamination. This would imply that MDCs are less safe than single-dose vials, but quantifying this risk is difficult. The case for single-dose formats to help ensure safety is supported by the following observations and assumptions [4] and per WHO guidance[5]: (1) dosing is more accurate; (2) a reconstituted lyophilized vaccine may be inappropriately used after the 6-h window; and (3) presentations that reduce the amount of handling and potential for error during preparation and administration of a vial is preferred.

Of the ten studies in the literature review, five mentioned the greater safety risk of adverse events following immunization (AEFI) associated with higher-capacity MDCs; of these one study provided a serious discussion on safety but this did not include metrics or further analysis [9]. This greater risk, which is due to risks of contamination between vaccinations, improper labeling of opened vials, and in some cases the presence of preservatives [3,4,13], is suggested but not well quantified in immunization programming. This is a difficult metric to quantify properly, as AEFI are rare, difficult to monitor, and the costs associated with them, such as surveillance and response to an AEFI, are incorporated into other activities and/or are highly contextual.

The recent study by Burton et al. in Kenya was the only one of the five that generated data on this topic. The study sought to establish the magnitude of risk of AEFI (abscess, shock, death) among children vaccinated with 10-valent PCV in a 2-dose presentation without preservative [2] using pentavalent 2-dose with preservative as the comparator due to similarities in dosing schedule and administration methods. However, during the course of the study, the comparator vaccine was changed nationally from a 2-dose to 10-dose presentation (also with preservative) of pentavalent vaccine, which affected the comparator in all study sites. In the three sites that tracked the change in comparator vaccine researchers found a 4.8-fold higher risk of abscess associated with the 10-dose pentavalent presentation compared with the 2-dose pentavalent presentation. However, this association was not statistically significant and, as it was not part of the original study design, may have been affected by sampling error or other unintended variations in the comparison groups; but the authors concluded that given the indication of potential risks, this warranted further study.

3.5. Policy and use

Many countries have set immunization days and limited days on which specific vaccines are offered, especially unpreserved lyophilized vaccines that can only be used for a short period of time after reconstitution. These lyophilized vaccines are often offered only once a week or once a month. However, data on session size are difficult to capture, and it may vary widely within a country. Further, while the national policy may be to open a vial for any eligible child, HCW behavior may reflect different priorities. While it can be difficult to quantify this for models, several studies attempted to include measures to indicate the role that policies (and potential lack of adherence thereto) or HCWs could play in affecting outcomes. This includes examples found in Burkina Faso, where immunization sessions for lyophilized vaccines such as BCG, measles, and yellow fever are offered less frequently than other vaccines and even then, a vial is only opened when the number of children is equal to or greater than half the number of doses per vial [12].

In the models developed by Haidari et al., they incorporated a proxy to measure HCW behavior by implementing a vial-opening threshold. This was meant to show instances when HCWs would not open a vial unless enough children were present to vaccinate (in this case, equal to half of the number of doses in the vial). The other studies/models presumed a correct adherence to the MDC Policy when it applied.

Additional findings from measles outbreak studies have identified reluctance by HCWs to open vials of measles vaccine, though not the frequency or prevalence of this attitude [4]. The unpublished WHO investigation report of the 2014 measles outbreak in Ethiopia concluded that two of the major contributors to the outbreak were (1) the measles vaccine was opened only when 6 or 7 eligible children were present to minimize wastage and (2) some health facilities inappropriately vaccinated children before the age of 9 months to justify opening the vial, leading to invalid doses [16]. Similarly, an unpublished investigation report of a measles outbreak in Zanzibar in 2011 concluded that one of the drivers of low vaccination rates was HCWs not opening vials because they were concerned about wastage [15].

4. Discussion

The studies reviewed here acknowledged the complexity of these analyses and recognized that choices would vary depending on what is prioritized. It was also acknowledged that variations within a country (population, logistics, etc.) could mean that a single presentation (one dose-per-vial option) may not meet the needs of the entire country/program and multiple presentations may be warranted [5].

Further, much of the research and analysis has focused on the ability of a country to adjust session schedules and policies to accommodate the lower systems costs associated with higher-capacity MDC presentations. Studies and models to date have focused on lowering systems costs and placed limited emphasis on vaccination coverage and HCW behavior. Remarkably, given the current emphasis on equity and reaching every child, no study attempted to look at the relationship between DPC presentation and actual vaccine coverage rates at any level of the system or for different uses (e.g. fixed sites compared to outreach). While vaccine availability may serve as a proxy of vaccine coverage, there are several factors (like policy or pressure to reduce wastage that make a HCW unwilling to open a vial) that can create a large discrepancy between vaccine availability and coverage. Focusing on availability alone fails to fully assess and understand the relationship between availability, policies, and HCW perceptions of wastage rates and session sizes, and ultimately, HCW behavior. For instance, availability does not mean that a HCW will open a vaccine for any eligible child that is present. Alternatively, if inventory management policies are not adjusted to ensure sufficient buf-

[5] WHO Assessing the Programmatic Suitability of Vaccine Candidates for WHO Prequalification (Revision 2014).

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fer stock with a change in DPC, this may affect availability but not be a function of the actual presentation.

Finally, there is still a need to include assessment of costs related to human resources, missed opportunities, safety, and uneven adherence to MDC policies to assess impact on timely and equitable coverage.

The findings from published literature and key informant interviews were summarized and shared with immunization program experts at a stakeholders meeting in July 2015. Through this process, it was clear that while people agreed on the need to better understand and quantify the tradeoffs related to DPC, stakeholders have varying mandates and would optimize a tradeoff analysis using different factors. Participants agreed with the summary, but also stated that the initial evidence was insufficient and there were some critical gaps in data which made it difficult for countries, normative bodies such as the WHO, and manufacturers to understand how DPC choice can affect program goals and their ability to provide adequate policy guidance related to product selection.

Notably, there was no consensus on how countries currently assess DPC options beyond price and cold chain impact, the most easily quantifiable components. This led participants to conclude that there was a lack of information on the interest or potential demand for lower-capacity DPC and limited feedback loops for that demand to be expressed in such a way that action would be taken. Specifically, it was not clear how alternative DPC presentations would fit into a country's decision making process (forecasting and procurement) and how potential demand would be communicated to procurement agencies or manufacturers in a timely manner so that different DPC options would be offered and available to countries when desired [10].

Stakeholder discussions emphasized the strong need to broaden DPC considerations to include timely and equitable coverage and other key factors that are hard to measure—vaccine safety, session size, and HCW behavior are three such factors. The consensus at the global stakeholder meeting was that there is a need for country research focused on these factors. If the data are present, reviews of historical changes in several country and antigen contexts can provide insight into the DPC selection process and the effects of switching product presentations on the immunization system. Where such data are lacking, studies on the ground might also capture this information. Once these data have been collected and analyzed, it may be possible to incorporate these metrics back into computational models to more accurately describe the effects of DPC selection.

Efforts to achieve a better understanding of DPC-related issues include a recent Gavi study in Kenya on mixed vial presentations (results forthcoming); another study of introducing multiple DPC options of the same antigen is proposed in Ethiopia. In a 2011 UNICEF survey of 71 countries (36 responding) on measles/measles rubella (MR) vaccines, responses indicated that only in 55% of the countries did HCWs open a vial for any child who presented, despite the widespread policy that any eligible child should be vaccinated.[6] Of the 34 countries responding on preferences for measles vaccine, 35% indicated potential interest in a 5-dose vial compared to the 10-dose vial in widespread use, indicating unrecognized interest in lower capacity MDCs than what is currently offered.[7] In addition, recent modeling by WHO on wastage rates and session sizes will help improve tools to ensure wastage estimates are accurate and that vaccines are ordered in sufficient quantities given expected session sizes. Efforts such as these have been useful to generate some evidence on the relationship between DPC and other systems components, but review of the data and stakeholder perspectives both indicate that gaps remain, providing a solid path forward for further research.

The studies included in this literature review provide important insights and varied perspectives into DPC issues; however, there are some notable limitations. First, there are only a small number of studies specifically looking at relationships between DPC and program outcomes, and there is only a small group of researchers focusing on this topic. This likely indicates that the topic is underrepresented in the literature and not well appreciated.

Of the seven studies in the literature review, only one (Pereira and Bishai) included data on vaccine presentations being used in a real-life setting. The remaining studies relied on models to simulate supply chains, such as the HERMES model,[8] and concluded that higher-capacity MDCs are sometimes less expensive when considering cost per administered dose, but only when session sizes are larger. This does not take into account the effect of uneven distribution of session sizes. Ideally, models would allow different subnational inputs/assumptions to incorporate variability within a system. The absence of real-life data to inform the assumptions make the modeling results subject to great uncertainty.

While some of the most impactful factors in DPC selection are thoroughly incorporated in these models and studies, several are not. Factors such as vaccine safety, HCW behavior (particularly hesitancy to open a vial), and session size are widely recognized as important but were generally not included. More recent modeling efforts have tried to simulate HCW behavior to control wastage rates by applying a vial-opening threshold but assumed just one scenario, while HCW behavior may vary widely by geography, antigen, catchment area, population concentration, total vaccine supply, and vaccination delivery strategy.

Many of the country model studies indicated that with lower-capacity MDCs, increased systems costs had a larger impact on overall cost than the savings from reduced wastage. However, some of the broader modeling reinforced the importance of wastage reduction in presentation selection. Further research into these conflicting factors, possibly in the context of actual presentation switches in a country, may provide more information to reconcile these conflicting conclusions.

5. A next step

The authors of this report are undertaking a second phase of work in partnership with a consortium of organizations to fill in DPC evidence gaps identified here and help ensure that DPC considerations are part of decision-making for immunization systems. The partnership will assess program issues such as procurement costs, systems costs, cold chain footprint, safety, human resources, coverage rates, and HCW behaviors, perceptions, and preferences. Quantitative and qualitative prospective implementation research will be undertaken in one country, with a new presentation of one vaccine introduced in select geographies and program data collected to compare the new presentation with the existing presentation. Observational research is planned for another two countries to generate evidence around DPC for several antigens and identify those antigens for which a change in DPC would most likely improve key immunization program indicators. These activities will study the effects of vaccine presentation on equitable, timely coverage, open-vial wastage, session size and frequency, storage and distribution capacity, cost, and HCW behavior, with the intent

[6] WHO Document. Training for Mid-level Managers (MLM). I. Cold chain, vaccines and safe-injection equipment management. Geneva: World Health Organization; 2008. WHO document WHO/IVB/08.01.

[7] [14]. Unpublished. Meeting Presentation at Global Measles Rubella Management Meeting; Geneva, March 2011.

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of better understanding the relationships of a DPC decision on the components included in the systems framework. The partnership will document and assess country-specific DPC policies and decision making processes to better understand and align country demand with vaccine contracting and procurement. The evidence gathered should help identify use scenarios where various DPC presentations might be recommended while providing tools and guidance for decision makers to understand the DPC-related tradeoffs between costs and health impacts. As more metrics are quantified, these tradeoffs can be better predicted and total systems costs and outcomes better measured.

Conflict of interest

The authors of this article confirm that they have no conflicts of interest.

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