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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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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.