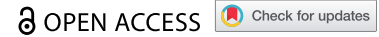



COMMENTARY



## Multi-dose vials versus single-dose vials for vaccination: perspectives from lower-middle income countries

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### ABSTRACT

The choice of the vaccine packaging type either as single- or multi-dose vial is a crucial determinant of vaccine coverage. The experience of vaccination strategies in lower-middle-income countries suggests that multi-dose vaccine vials translate into greater economic-logistic advantages due to lower packaging and storage costs with significant environmental benefits accrued from reduced medical waste generation. However, the use of multi-dose vials is associated with a theoretical risk of contamination particularly from human error. Moreover, the overall economic advantage of multi-dose vials is contingent on the reduction of the extent of vaccine wastage associated with their use. Robust data collection for monitoring of vaccine wastage rates and adverse effects following immunization is therefore needed to understand the extent of economic benefit and risks involved with multi-dose vial use.

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### Introduction

Vaccination is considered as the most cost-effective public health intervention in reducing morbidity and mortality from various diseases by providing direct protection to the vaccinated individuals and indirect protection through herd immunity to the unvaccinated individuals.<sup>1,2</sup> Immunization is an essential prerequisite to achieve the sustainable development goal<sup>3</sup> to ensure healthy lives and promote well-being for all ages by saving lives, promoting global health security, and inhibiting antimicrobial resistance.<sup>3</sup> It is estimated that vaccination of ten high burden pathogens is likely to avert 69 million deaths between 2000 and 2030 in 98 lower-middle-income countries (LMICs).<sup>4</sup>

Global initiatives led by the World Health Organization's Expanded Program on Immunization (EPI) and the Global Alliance, Vaccines (GAVI) have made enormous contributions in promoting vaccine equity and access for all those at risk.<sup>5,6</sup> However, despite the increasing availability of newer vaccines against existing diseases which are of public health concern, an estimated 20 million infants, mostly in the developing world, do not receive basic vaccines, while 13 million failed to receive even a single dose of any vaccine.<sup>7</sup> Furthermore, vaccination among older adults has been neglected in most developing countries.<sup>8</sup>

The developing countries are still struggling in achieving optimal vaccine coverage among susceptible children, which is influenced by multiple factors related to individual and societal perspectives like stigma, resistance, concern, affordability, accessibility, etc. as well as those related to health system perspective like antigen variety, skilled human resources, cold chain logistics, and universal coverage.<sup>9</sup>

The choice of the vaccine packaging type either as single- or multi-dose vial is a crucial determinant of vaccine coverage as it is associated with the extent of vaccine wastage, cost-effectiveness, logistics, cold chain, and potential safety concerns.<sup>10,11</sup> Multi-dose vaccine (MDV) vials are available in multiple sizes ranging from 2 to 20 doses, and for childhood immunizations, constitute 5, 10, or 20 doses for both the liquid and lyophilized vaccines. More than 80% of the global vaccines and nearly universally in the public sector of the developing world is supplied through MDVs.<sup>10</sup>

We explore the economic, logistic, safety, coverage, and ethical issues related with the use of single vs MDV vials especially in context of the developing world.

### Economic issues

The economic costs of single versus MDV vials are related to the differential vaccine manufacturing costs, vaccine wastage rates, and cold chain logistics. Vaccine manufacturing costs for MDV vials are lower than single-dose vials because of comparatively lower filling costs, overfill adjustment, and reduced costs of packaging.<sup>10</sup> Similarly, higher volume of single-dose vials escalates their cold chain distribution costs compared to MDV vials although single-dose vials ease vaccine tracking and inventory logistics. Nevertheless, newer technology-assisted solutions such as the Electronic Vaccine Intelligence Network (eVIN) in India enable real-time technology-assisted tracking of vaccine stock and storage temperatures negating any competitive logistic advantage in using single-dose vials instead.<sup>12</sup>

Vaccine wastage is defined as the “sum of the vaccines discarded, lost, damaged or destroyed” (WHO: 2019) that is estimated as the proportion of vaccine doses discarded without administration to the intended beneficiaries.<sup>11</sup> The escalation

of vaccine-related costs for child immunization can undermine efforts in accelerating vaccine coverage of existing vaccines and delay the introduction of newer vaccines against other infectious pathogens in the immunization programs of LMICs.<sup>13</sup> Globally, high vaccine wastage rates have been observed with nearly half of all vaccines being wasted necessitating the advancement of strategies for lowering vaccine wastage rates.<sup>14</sup>

The use of MDV vials causes considerably greater vaccine wastage, estimated to be five to ten higher compared to open vials during routine immunization sessions.<sup>10</sup> Events of vaccine wastage during the utilization of both unopened and opened vials are manifold higher for MDV vials compared to single-dose vials. Consequently, for some vaccines with lower requirement such as Hepatitis B dose in children or anti-rabies vaccines in adults, it is estimated that single-dose vials may be administered at a similar price point compared to multi-dose vials.<sup>15,16</sup>

To retain and maximize the economic advantage of MDV vials, vaccination staff need to minimize vaccine wastage requiring them to ensure the utilization of all vaccine doses in a vial. The open vial policy (OVP) recommended by the WHO prequalifies certain liquid vaccines for use up to 28 d after opening the vial if the expiry date has not been met, the vaccine being stored at the recommended temperature without freezing, and the vaccine vial monitor having not reached discard point.<sup>11</sup> Additionally, to avoid contamination, the vaccine vials should not get submerged in water anytime during transport or conduct of the immunization sessions, while the vial septum should be maintained clean and dry.<sup>17</sup> A higher degree of technical proficiency is therefore needed by the vaccination staff when using MDV vials with potential failure to adhere to OVP requirements translating into the loss of vaccine effectiveness for the beneficiaries.

On the other hand, lyophilized vaccines without preservatives such as BCG, Measles-containing vaccines, and Rotavirus vaccines must be discarded within 6 h of opening of the vial rendering them susceptible to higher wastage. This apprehension of vaccine wastage may translate into missed opportunities for vaccination particularly in resource-limited settings by nudging vaccine staff to refuse some eligible beneficiaries during an immunization session.<sup>18</sup> In most LMICs, the coverage of the second dose of MCV is substantially lower than first dose since often the number of beneficiaries required for near-complete of the doses in a MDV may be lacking during the routine immunization sessions.<sup>19</sup> A mixed-method study in Zambia observed that health workers were more willing to open a 5-dose Measles Rubella MDV compared to a 10-dose Measles Rubella MDV translating into increased vaccine coverage and reduced wastage at the district level.<sup>20</sup> This barrier can be overcome by the facilitation for increased vaccination through support driven by the network of community and frontline health workers who play a key role in bridging the communication gap between the community and health systems. They also serve as a knowledge link to the community by providing vaccine information, alleviating all concerns related to vaccination and their potential side effects. Consequently, adequate community mobilization through frontline workers improves vaccine accessibility for vulnerable communities and enables optimal resource utilization by minimizing vaccine

wastage.<sup>21</sup> Furthermore, timely conduct of sessions, as a result of adequate mobilization, directly or indirectly are likely to lower the incidence of product-related reactions in view of timely utilization of all the vaccine doses from the MDVs. Finally, behavior change communication for health workers can potentially reduce vaccine wastage rates suggestive of the need for scaling-up.<sup>22</sup>

## Safety issues

Community acceptability of vaccines especially for children is subject to their perceived safety and efficacy.<sup>23</sup> Although perception of disease lethality is a factor known to determine vaccine acceptability, primary health systems in developing countries have obtained high routine vaccination coverage rates despite low awareness of vaccines in the general population signifying how public trust can mediate vaccine confidence.<sup>24</sup>

Several reports have indicated that medical treatment involving multi-dose vials can occasionally transmit infectious organisms especially on the failure of compliance to stringent infection control measures. Gosbell et al. from a review of literature identified 13 infectious disease outbreaks globally that occurred for purposes other than immunizations while two reports of bacterial contamination of immunization vials have been reported.<sup>25</sup> Nevertheless, mass vaccination campaigns have not reported any significant outbreaks resulting from contamination by any infectious agents till date even as millions of children have been vaccinated with multi-dose vials in the global south. Universal adult vaccination with billions of vaccine doses during the Covid-19 pandemic was conducted mostly using multi-dose vials globally and there are no reported outbreaks resulting from vial contamination which indicate the negligible risk involved in their use. The safety of thiomersal, used as a preservative against bacterial contamination in MDVs, has also been established in previous studies.<sup>26,27</sup> However, the immunization safety monitoring in developing countries is suboptimal and as of 2019, less than one in four countries reported adverse effect following immunization (AEFI) data, some of which could be possibly linked to MDV contamination.<sup>28</sup>

## Ethical issues

It has been argued that the use of multi-dose vials in immunization programs must be accompanied with disclosure to the beneficiaries of the additional but small risk of disease transmission associated with MDVs as part of the informed consent process.<sup>29</sup> However, from a biomedical perspective, it can be argued that incorporating client autonomy by disclosing the negligible higher risk of MDVs during immunization purposes can be counterproductive as it may have the potential to promote vaccine hesitancy in communities.

The tenet of justice in this context warrants the use of MDVs in the developing world when considering the economics of scale and limited resource availability in terms of cold chain logistics and infrastructure required for achieving universal vaccination and healthcare through government-funded immunization and health programmes. Additionally, the

significantly higher volume of medical waste generated per dose by single-dose vials compared to MDVs is a major global environmental concern particularly when considering the counterfactual position.<sup>10,30</sup> The focus on technological and eco-friendly innovations to reduce the medical waste generated in this process for reduction of the environmental impact is, therefore, an ethical imperative for those countries which continue to predominantly vaccinate their population with single-dose vials.

## Conclusion

The experience of vaccination strategies in LMICs suggests that MDV vials translate into greater economic-logistic advantages due to lower packaging and storage costs with significant environmental benefits accrued from reduced medical waste generation. However, the use of multi-dose vials is associated with a theoretical risk of contamination particularly from human error. Moreover, the overall economic advantage of MDVs is contingent on the reduction of vaccine wastage associated with their use. Robust data collection for monitoring of vaccine wastage rates and AEFIs is needed to understand the extent of economic benefit and risks involved with MDV use.

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