

WHO Policy Statement: Multi-dose Vial Policy (MDVP)

Revision 2014

HANDLING OF MULTI-DOSE VACCINE VIALS AFTER OPENING



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SUMMARY OF WHO MULTI-DOSE VIAL POLICY (MDVP), 2014

All opened WHO-prequalified multi-dose 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 all four of the criteria listed below. If the vaccine meets the four criteria, the opened vial can be kept and used for up to 28 days after opening. The criteria are as follows.

1. The vaccine is currently prequalified by WHO.
2. The vaccine is approved for use for up to 28 days after opening the vial, as determined by WHO.†
3. The expiry date of the vaccine has not passed.
4. The vaccine vial has been, and will continue to be, stored at WHO- or manufacturer-recommended temperatures; furthermore, the vaccine vial monitor, if one is attached, is visible on the vaccine label and is not past its discard point, and the vaccine has not been damaged by freezing.

For vaccines that are not prequalified by WHO, independent determinations on preservative efficacy, sterility, presentation and stability may not have been made by a functional national regulatory authority. Consequently, this could mean that the vaccine does not meet the WHO requirements on safety and efficacy, which form the minimum recommended standard for keeping multi-dose vaccine vials opened for more than six hours. Therefore, WHO recommends using non WHO-prequalified vaccines as soon as possible after opening, and respecting the time limit for using opened vials as indicated by the manufacturer's instructions in the package insert. If this information is not indicated in the package insert, WHO recommends discarding all non WHO-prequalified vaccine products within six hours after opening or at the end of the immunization session, whichever comes first.

This policy statement further outlines conditions under which the MDVP can be implemented safely, including, but not limited to, adherence to good immunization practices.

† Consult each individual vaccine product sheet at the WHO prequalification website, referencing the description "*Handling of opened multi-dose vials*" http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/index.html.

Intended audience

This document is designed to provide guidance to national and senior-level programme managers on the proper handling of multi-dose vaccine vials once opened. Aide memoires and job aides should be developed for use at district and facility level to provide more practical guidance on how to implement the policy safely.

How to use this document

The intention of this policy brief is to define the conditions that must be followed to safely handle opened multi-dose vaccine vials, enabling vaccinators to understand which opened vaccine vials should be discarded within six hours after opening and which can be kept for use in subsequent immunization sessions for up to 28 days.

This document describes the policy, including its scope and the limitations on its use, outlines the scientific rationale upon which the policy is based and discusses the operational implications for implementing the policy.

The policy brief revises and replaces *WHO Policy Statement: The use of opened multi-dose vials of vaccine in subsequent immunization sessions (WHO/N&B/00.09)* issued in 2000 (1).

Context

As vaccines increase in price, wastage is a growing concern for many immunization programmes. It is therefore important to ensure that countries have information on which multi-dose vials of vaccines can be kept open for extended periods of time, to minimize vaccine wastage while at the same time ensuring vaccine safety. The policy statement on the use of multi-dose vials issued in 2000 (1), which this document replaces, has allowed immunization programme managers to reduce wastage of vaccine doses in opened vials, while ensuring that the vaccines are safe for use (2).

However, today's vaccines are different from previous vaccine products, making application of the original multi-dose vial policy (MDVP) more challenging. The original policy separated vaccines by type and specified that liquid vaccines could be kept open for re-use for up to 28 days, while lyophilized vaccines were to be discarded at the end of the immunization session or six hours after opening, whichever came first.

Since 2000, many new vaccines have been developed, many of which have already been included in the Expanded Programme on Immunization (EPI). Today, there are more than 30 types of vaccines that are prequalified by WHO, comprising over 120 different products. Due to the complexities of these new vaccine formulations, not all vaccines in use today fit into the simple '*liquid = keep for 28 days*' or '*lyophilized = discard within six hours*' categories as previously recommended. Such vaccines include liquid vaccines in presentations of greater than one dose that do not contain preservatives, or those that contain preservatives which do not meet the required standard of preservative efficacy. Vaccines with preservatives that do not meet these minimum standards may not be able to be kept safely for up to 28 days without risking bacterial growth; opened vials must therefore be discarded at the end of an immunization session or within six hours after opening, whichever comes first.

It is thus necessary to revise the multi-dose vial policy and the present policy brief outlines these changes.

I. WHO POLICY STATEMENT: HANDLING OF MULTI-DOSE VACCINE VIALS AFTER OPENING

A. Details of the policy

In general, most vaccine vials should be discarded within six hours after opening. However, WHO has defined four criteria which, if fully met, allow opened vaccine vials to be kept with assurance of vaccine safety and efficacy for up to 28 days after opening. These criteria, and their implications, are as follows.

- 1. The vaccine is currently prequalified by WHO.** In order for a vaccine to be prequalified, WHO independently evaluates data on vaccine quality, safety and efficacy. This evaluation includes examining the effectiveness of preservatives, as well as the stability of the vaccine under different temperature conditions. In addition, the prequalification programme assesses such things as the quality of vials, stoppers, caps and labels. Taken together, these allow the safety and efficacy of the vaccine to be assured, particularly after opening. If WHO does not have adequate information to determine the behaviour of the vaccine after the vials have been opened, the vaccine is not prequalified.
- 2. The vaccine is approved for use for up to 28 days after opening the vial, as determined by WHO.** For injectable vaccines, this means that the vaccine contains appropriate type and amount of preservative. Multi-dose vials of oral vaccines may not contain preservative but, nevertheless, may be kept and used for up to 28 days after opening the vial, unless otherwise indicated. Each WHO prequalified vaccine has a vaccine product page on the WHO website with the specific reference, "*Handling of opened multi-dose vials*"(3). This description provides information to programme managers and national immunization officials on the proper handling of multi-dose vials for each available presentation. The same information will also be found in the WHO-approved package insert for all prequalified vaccines.
- 3. The expiry date of the vaccine has not passed.** This condition is part of immunization best practice and is included here to emphasize the importance of not using a vaccine vial after the product has expired. The expiry date may be reached over the course of the 28 days so, in line with good practice, the expiry dates of all opened vials should be checked prior to every use.
- 4. The vaccine vial has been, and will continue to be, stored at WHO- or manufacturer-recommended temperatures.** All vaccines, with the exception of those approved for use in a controlled temperature chain (CTC), should be stored according to WHO- or manufacturer-recommended temperatures, normally between +2°C to +8°C, and should be protected from freezing and sunlight where relevant. Prior to use, the vaccine vial monitor (VVM) should be consulted to ensure it has not reached its discard point; if it has, the efficacy of the vaccine has been compromised by excessive heat exposure and the vaccine should be discarded (4). If a vaccine vial is labelled as freeze-sensitive and is suspected of having been frozen, or a temperature alarm indicates exposure to sub-zero temperatures, the shake test should be performed to assess if there has been damage to the product and the vaccine should be handled accordingly (5,6).

B. Application to special strategies

This section describes provisions for the handling of opened multi-dose vials in outreach and campaign situations, and when a CTC is being used.

- Campaign and outreach situations.** Provided that vaccines meet the four criteria, defined above, for keeping opened multi-dose vials for up to 28 days, and as long as appropriate handling procedures are followed to diminish the risk of vial contamination, opened vials can be used in subsequent immunization sessions, in different sites, for up to 28 days. National immunization programmes are encouraged to adapt their policy in these settings, as appropriate. However, in order to implement the MDVP safely, opened vaccine vials must continue to be kept at the recommended temperatures after opening. In particular, it is important to keep opened multi-dose vaccine vials that do not contain preservative — whether lyophilized or liquid — cooled at temperatures between +2°C and +8°C during the immunization session, or within six hours after opening, whichever comes first. Keeping these opened vials cool will reduce the risk associated with growth from microorganisms that may have been introduced into the vial.
- Use in a controlled temperature chain (CTC).** WHO has recently defined a CTC (7), whereby specific vaccines are prequalified for use at temperatures of up to 40°C for limited periods of time, as appropriate to the stability of the antigen. For vaccines approved for use in a CTC, specific guidance on how to maintain the correct temperature range and adhere to other pre-defined CTC conditions, is available from WHO. Application of the MDVP in CTC settings may vary by vaccine. Please consult the product insert and the WHO website (3) on how to apply the MDVP for each CTC vaccine.

C. Scientific rationale for the policy

There are both economic and operational advantages in applying the MDVP, but there are also risks if the policy is not applied correctly. This section covers the scientific bases for overcoming these risks.

- Assuring safety and efficacy.** There are two critical considerations in the use of vaccines: their safety and their efficacy. Both of these characteristics can be affected by improper vaccine handling. The WHO prequalification team reviews vaccine data provided by manufacturers, to assess both parameters in the context of their field use.

To determine safety, WHO reviews the preservative efficacy of the vaccine to determine whether the opened vaccine vial can be kept and re-used safely for a period of up to 28 days. Injectable vaccines that can be kept for this length of time contain sufficient levels of preservative (traditionally thiomersal) (8,9,10) to prevent growth of bacterial contamination. If the contents of the vial become contaminated, the action of the preservative prevents any increase in bacterial or fungal growth over time, and actually decreases the level of contamination.

WHO also assesses the stability of the vaccine at different temperatures, to ensure that the dose given will be effective and that the vaccine efficacy will not be decreased by thermal damage. Based on this information, a VVM is assigned to the vaccine vial. If the VVM is attached, it allows vaccinators to know at-a-glance whether the vaccine has been exposed to cumulative levels of heat that may have decreased its efficacy. For vaccines sensitive to freezing, WHO provides information on how to decrease the risk of freeze damage, as well as how to assess vials that may have been exposed to freezing temperatures, and subsequently damaged.

For vaccines that are not prequalified by WHO, independent determinations on preservative efficacy, sterility, presentation and stability may not have been made by a functional national regulatory authority. Consequently, this could mean that the vaccine does not meet WHO requirements on safety and efficacy, as outlined above, which form the minimum recommended standard for keeping multi-dose vaccine vials opened for more than six hours. Therefore, WHO recommends using non WHO-prequalified vaccines as soon as possible after opening, and respecting the time limit for using opened vials as indicated by the manufacturer's instructions in the package insert. If this information is not indicated in the package insert, WHO recommends discarding all non WHO-prequalified vaccine products within six hours after opening or at the end of the immunization session, whichever comes first.

- 2. Time limits for keeping opened multi-dose vials.** If the vaccine does not contain an effective preservative, and if there is no evidence that data on preservative efficacy have been rigorously reviewed, opened multi-dose vaccine vials should be discarded at the end of the immunization session, or within six hours after opening, whichever comes first. The six hour time-limit corresponds to the average time frame over which an immunization session is ordinarily conducted.

The rationale for the 28-day limit is based on the assumption that, at the lowest periphery, stock is replenished once a month. The 28-day limit is not indicative of the maximum performance of the preservative.

- 3. New vaccines and presentations, including fractional doses.** The MDVP described here can be applied to all multi-dose vials of vaccines for which WHO has defined recommendations for use, and can also be applied to newer vaccines as they become WHO prequalified.

However, it should be noted that some vaccines are provided as a single-dose presentation, but can be used as a multi-dose presentation if delivered as a fractional dose (e.g. one-half or one-fifth of a full dose). Examples are: the potential for delivery of a fractional dose of rabies vaccine using intradermal administration; or for administering a half-dose of influenza vaccine for younger age groups, making a one-dose vial for children or adults effectively a two-dose vial when used for infants. If used in this manner, these single-dose presentations are to be treated as multi-dose vials. As such single-dose vaccines are unlikely to contain preservative, the six hour time-limit described above should be applied. Consequently, these vaccine presentations require special vigilance and training in their handling after opening, to minimize programme errors.

- 4. Vaccine preservatives.** The WHO policy position is that thiomersal has been proven safe and effective and that there is no scientific justification to remove its presence from vaccines. In addition, many countries rely on the use of thiomersal in multi-dose vials to allow opened vials to be kept for up to 28 days, thus reducing cold-chain capacity and cost constraints, and thereby assuring a sufficient supply of safe vaccines (9,10,11). While a global ban on mercury and mercury-derived products was agreed to, in 2012, by the Intergovernmental Negotiating Committee convened by the United Nations Environmental Programme, the convention grants countries the right to continue to use thiomersal in vaccines, in recognition of its safety record and importance for immunization programmes, both for humans and animals (12).

II. HOW TO IMPLEMENT THE POLICY SAFELY

A. Use of visual triggers

A VVM can be found on nearly all vaccine vials supplied to national immunization programmes and procured through UNICEF (13). The WHO vaccine prequalification programme has worked with vaccine manufacturers to define VVM placement guidelines so that the VVM, if attached to the vial, can serve as a visual trigger to assist a health worker in properly applying the MDVP. There are two different locations for VVMs and each is associated with specific guidance for handling opened multi-dose vials of vaccine.

1. *WHO-prequalified vaccines where the **VVM, if attached, is on the label of the vaccine.*** The vaccine vial, once opened, can be kept for subsequent immunization sessions for up to 28 days, regardless of the formulation of the product (liquid or lyophilized).
2. *WHO-prequalified vaccines where the **VVM is attached in a different location than on the label (e.g. cap or neck of ampoule).*** In this instance, the vaccine vial, once opened, must be discarded at the end of the immunization session or within six hours of opening, whichever comes first. This is regardless of the formulation of the product (liquid or lyophilized) and would apply, for example, to a reconstituted product of which the vaccine vial cap, which has a VVM attached, has been discarded after opening.

B. Check WHO prequalification website

The range of vaccines prequalified by WHO regularly expands and changes. As a result, WHO routinely updates the individual vaccine product sheets available on the WHO prequalification website (3). To ensure that a specific vaccine is approved for use for up to 28 days after opening the vial, these individual vaccine product sheets on the website should be consulted, referencing the description “*Handling of opened multi-dose vials.*”

C. Good immunization practice

Proper implementation of the MDVP requires reinforcement of good immunization and vaccine-handling principles. Detailed information on vaccine-handling practices can be found in WHO guidance materials, such as the *Immunization in Practice* or *Mid-level Managers* modules. Areas where good practice is especially important are outlined below.

1. **Appropriate storage and transport conditions.** In order to implement the MDVP safely, vaccines must continue to be kept at the recommended temperatures.

When national immunization programmes were first established, the six EPI vaccines — bacille Calmette-Guérin (BCG), measles, tetanus, diphtheria, pertussis and oral polio vaccine (OPV) — were then considered to be very heat sensitive, so that ensuring storage at temperatures between +2°C to +8°C was critical. However, many of the newer vaccines are actually more heat stable than many of the traditional EPI vaccines — but are sensitive to freezing. With this change, protection of vaccines from freezing has become a more important issue in many programmes than protection from heat

exposure (14–18). Additionally, the risk of freezing has increased with the use of equipment that can reach very low freezing temperatures, and the wider use of cold boxes and vaccine carriers with improved insulation. Currently, in addition to avoiding excessive heat exposure, country programmes are using strategies to avoid vaccine freezing and to take advantage of the inherent thermal stability of many traditional vaccines which impacts standard cold-chain practice (19–23).

At service-delivery level, WHO recommends that most vaccines continue to be kept at between +2°C to +8°C. The VVM, if attached, indicates whether the individual vial has been exposed to cumulative levels of heat over time such that the vaccine's potency may be compromised and its stability diminished. This means that vaccines can be used reliably if the VVM has not passed its discard point, even if there have been short breaks in the cold chain, and provided that the expiry date has not passed. However, it is important to note that current VVMs do not necessarily reflect short 'peak' exposures of vaccines to extremely high temperatures (i.e. 45°C or above). Therefore, care should be taken to avoid these situations, especially during transport. For further information on VVMs, please consult *Getting started with VVMs* and other WHO training videos available at <https://vimeo.com/channels/evvm> (4).

An increasing number of vaccines are freeze-sensitive — with some vaccines inactivated by an exposure to temperatures below zero degrees for even a brief period of time. This includes all vaccines that depend on the integrity of an aluminium matrix as an adjuvant, such as, for example, the Tetanus-Toxoid (TT) or Tetanus-diphtheria (Td) vaccines or the combined diphtheria, tetanus, pertussis-hepatitis B - Haemophilus influenza type B (DTP-HepB-Hib) vaccine (5,24,25,26). If the aluminium matrix is exposed to freezing temperatures, then the adjuvant may clump and the vaccine potency is diminished. This effect is permanent and cannot be reversed, even if the vaccine is later thawed.

To minimize exposure to freezing conditions that may damage vaccines, some programmes have adopted the use of cool water-packs rather than frozen water-packs for outreach activities (27). Freeze indicators should also be used during storage or transport, as recommended by WHO.

To check for freezing damage, when relevant, the shake test must be conducted (5,6,28).

Use of both the shake test and the VVMs help countries ensure that exposure to sub-zero temperatures or excessive heat conditions have been avoided during vaccine handling.

2. **Appropriately preserved.** WHO has analysed the characteristics of all prequalified injectable vaccines to determine whether their preservatives are sufficient to protect them from contamination if used according to this policy and consistent with good immunization practice. To help programme managers in setting national and local policy, the results of this analysis, for each specific vaccine presentation, are included on the WHO prequalification website under the heading "*Handling of opened multi-dose vials*" on the specific page for each vaccine product (3). These recommendations are incorporated into the WHO-approved package insert, and are emphasized by appropriate placement of the VVM.
3. **Appropriate use conditions.** Good injection practices should be followed at all times. For example, a new sterile syringe and needle should be used for each injection, and the needle should never be left inside the vial. Furthermore, the septum should not be contaminated nor have been immersed in water, and the contents of the vial should show no visible evidence of contamination. Any vaccine vial missing a label, or attached with a label that cannot be read, should never be used.

For vials that can be kept for up to 28 days after opening, national programmes are encouraged to recommend, where possible, that vaccinators record the date and month when the vial was opened. In this case, a nationally agreed standard on date format should be used, such as DD/MM (i.e. 30/06 for 30 June).

It is important to keep opened multi-dose vaccine vials that do not contain preservative — whether lyophilized or liquid — cooled at temperatures between +2°C and +8°C during the immunization session, or within six hours after opening, whichever comes first. Keeping these opened vials cool will reduce the risk associated with growth from microorganisms that may have been introduced into the vial.

D. Training

The introduction of this revised policy requires health-worker training and supervision, and provides an opportunity to reinforce good immunization practices in the field.

Because the MDVP touches on areas ranging from vaccine management, to injection safety, to antigen stability, it will be important to ensure that training is well-planned and that sufficient time is allocated to cover the topic.

Previous studies indicate that adverse events following immunization can result from improper attention to sterility of injections (29,30). Unsafe practices, such as needle and syringe re-use and leaving needles in multi-dose vials, have been documented (29), as have infant deaths following improper use of reconstituted measles vaccine after a session has ended (31,32).

In addition, lack of knowledge of recommended storage conditions for vaccines has been described in several studies (33–37). The VVM itself may not be consistently read correctly (22,38) nor is the shake test always correctly conducted.

For a revised policy such as this one, policy implementation will need to be accompanied by onsite and supportive supervision, job aids and periodic reminders, as well as integration into the standard training curriculum and supervisory checklist.

Conclusion

This policy brief provides an overview of the new MDVP policy, including information on how and when it can be used. A proper application of the MDVP can decrease vaccine wastage while ensuring safety, thereby reducing costs in field use and overcoming storage and transport constraints. This policy brief outlines best immunization practices that allow the policy to be applied in ways that ensure vaccine safety and efficacy, but it must be scrupulously followed and adequate field training, supervision and monitoring must be in place.

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