



## Using oral polio vaccine beyond the cold chain: A feasibility study conducted during the national immunization campaign in Mali

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### ABSTRACT

We conducted the first systematic documentation of using oral polio vaccine (OPV) out of the cold chain during national immunization day (NID) campaigns in Mali. Using a crossover intervention design, vaccinators compared the transport of OPV in vaccine carriers with or without ice packs. Vaccine integrity was assured through monitoring vaccine vial monitor (VVM) status. Despite ambient temperatures up to 40 °C, none of the VVMs on any of the vials used ( $n=956$ ) reached their discard point. Over 90% of vaccinators and supervisors preferred conducting NIDs without ice packs. In addition, using OPV out of the cold chain reduced vaccine wastage resulting from melting ice packs causing labels to detach from the vial.

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### 1. Introduction

Vaccines included in the Expanded Programme on Immunization (EPI) are sensitive to heat and lose their potency if exposed to high temperatures over long time. Therefore, it is recommended to keep them in a temperature-controlled supply chain (between 2 and 8 °C) [1]. Maintaining this cold chain under field conditions is frequently challenging where there is a lack of fridges, ice packs, electricity and efficient transport infrastructure. The effort to assuring cold chain conditions can be a major factor limiting the flexibility for the vaccination teams and their access to the entire population [2,3].

Vaccine vial monitors (VVMs) are small heat- and time-sensitive stickers attached to each individual vial of WHO-prequalified vaccines [4]. They gradually change colour as a vial's cumulative exposure to heat increases. Once the vial has been exposed to so much heat that the vaccine's potency can no longer be assured, the inner square on the VVM changes to a dark colour. When the inner square achieves the same colour as the outer circle, the VVM endpoint is reached and the vaccine should be discarded. VVMs allow

users to know whether the vaccine in a given vial remains sufficiently potent such that it should be used, even in situations where the cold chain cannot be guaranteed [5,6]. Fig. 1a illustrates the VVM standard classification. Previous studies have demonstrated the correlation between the degree of colour change in the VVM and the potency (i.e. level of content of active ingredient, attenuated poliovirus) of the vaccine [7–9].





Different types of VVMs are manufactured in order to match the varying stability profiles of vaccines. Oral Polio Vaccine (OPV) is the most heat-sensitive of the EPI vaccines and is equipped with a VVM2, which reaches its endpoint after a cumulative exposure to 37 °C for up to 2 days [6].

National immunization days (NIDs) are organised as part of the global goal of poliomyelitis eradication, targeting all children under 5 years of age [10].

Ideally, during vaccination activities, the vaccinators should use cool boxes with ice packs for transporting the OPV to prevent the vaccine's exposure to heat. Countries where polio transmission and import still occur often face challenges in securing enough vaccine carriers and ice packs to support the campaign outreach activities. In this situation, WHO and UNICEF recommend flexible polio vaccine management and guidance for this approach has been published [6,11]. These guidelines outline the procedures for storing OPV so as to ensure potency and quality when maintaining the standard 2–8 °C is not possible. Although these

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## a. Standard VVM classification illustration, stages 1 to 4:

Symbol	Explanation	Stage
	The inner square is lighter than the outer circle. If the expiry date has not passed, <b>USE</b> the vaccine.	I
	As time passes the inner square is still lighter than the outer circle. If the expiry date has not passed, <b>USE</b> the vaccine.	II
	<b>Discard point:</b> the color of the inner square matches that of the outer circle. <b>DO NOT USE</b> the vaccine.	III
	Beyond the discard point: inner square is darker than the outer circle. <b>DO NOT USE</b> the vaccine.	IV

Stage III corresponds to **endpoint**

From WHO (www.who.int).

At stage 3, when colour of the inner square matches that of the outer circle, the VVM has reached the endpoint and should no longer be used.

## b. VVM classification gradation colour scale conceived for the study:



Vaccine vials can be used up to the 90% gradation, and while the inner square is still lighter and differentiable from the outer circle.

The 100% stage corresponds to stage III above and the endpoint.

Fig. 1. (a) and (b) Illustrations for classification of vaccine vial monitor (VVM) stages.

guidelines were published in 2000 and are being applied in the field, there is no systematic published documentation about their feasibility and acceptability. Only one peer-reviewed publication mentions that the practice was used by field vaccination teams [12].

We designed a study to show that storing OPV outside of the cold chain (OCC) during a campaign is feasible, advantageous and poses no additional risk to the potency of the vaccine. This was done in Mali during the third round of the 2009 intercountry West African NIDs (Ivory Coast, Mali, Niger, Benin, Togo, Ghana and Burkina Faso).

Our specific objectives were as follows:

- To show that using OPV outside of the cold chain does not put the patient at greater risk of being vaccinated with a vaccine that is no longer potent, as determined by its VVM having reached its discard point.
- To assess the benefits of transporting and storing OPV under OCC conditions for the time period during vaccination activities as perceived by both vaccinators and supervisors.

- To determine whether vaccine wastage varies between the two practices, namely OCC conditions or adherence to traditional cold chain procedures.

## 2. Methods

We conducted an intervention study during the third round of the national immunization days (NID) in Mali, which were held May 29th to June 1st 2009. The study was carried out in four of the six zones of Sélingué district in the Sikasso region: Kangaré, Binko, Tagan and Faraba. Their selection was based on convenience (proximity to each other), as well as on reported past challenges with maintaining the cold chain. Each zone had between 6 and 16 vaccination teams, with two vaccinators per team.

Outside of the cold chain (OCC) was defined as the absence of ice packs in the vaccine carriers during each day's vaccination activities. Twenty dose vial trivalent OPV was used to vaccinate the estimated target population of children under 5 years.

The OPV vials for each vaccination day were extracted from cold storage in the morning. Full vials that were not used at the end

**Table 1**

Number and proportion of VVMs (on the OPV vials) by colour change progression (in %) aggregated over the course of the NID at three daily points in time during vaccination activities, for OCC and CC days.

VVM status (in %)	Out of the cold chain			Cold chain		
	Departure no. (%)	First dose no. (%)	Last dose no. (%)	Departure no. (%)	First dose no. (%)	Last dose no. (%)
0	510(99.6)	420(97.4)	348(91.1)	438(99.8)	361(99.2)	325(97.3)
20	2(0.4)	9(2.1)	24(6.3)	1(0.2)	3(0.8)	7(2.1)
40	0(0)	0(0)	2(0.5)	0(0)	0(0)	0(0)
60	0(0)	2(0.5)	8(2.1)	0(0)	0(0)	2(0.6)
80	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
100	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
120	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)

of the day were reintroduced into the same cold storage until the following day. Vaccine vials that were opened but not emptied in the course of a vaccination day were discarded at the team's return to the health post.

To enable the vaccinators to make a direct comparison between OCC and traditional cold chain (CC) procedures, the study was conducted using a crossover design. All the teams followed the usual procedures by using the ice packs on 2 of the 4 days. On the remaining 2 days, OCC procedures were followed and ice packs were not used.

The study was cleared by the National Health Directorate and regional and district health authorities.

The potency of the OPV being administered during the NID was monitored through VVMs. Each vaccine vial carried by the vaccination teams was numbered to ensure individual vial tracking and follow-up. The vaccination teams were asked to classify the VVMs and note down their stages at four specific times during the day: departure from the health post in the morning (all vials at the same time), first dose of the vial (each vial individually), last dose of the vial (each vial individually), and return to health post in the afternoon (all vials at the same time). The first three registrations were done during vaccination activities. A colour intensity scale model was created to aid classification of the VVM stages. The different gradations were defined by the percentage of colour intensity as shown in Fig. 1b.

Data collection was done through questionnaires that were administered to vaccination teams and supervisors. A daily questionnaire was used to monitor the VVM status of each OPV vial. In addition, it gathered information on the number of children vaccinated, as well as details about the immunization practices that were followed. A second questionnaire was administered at the end of the NID to ascertain how vaccinators and supervisors perceived the OCC procedure.

In order to assess the temperatures that OPV was exposed to during the vaccination activities we used LogTag® recorders (<http://www.logtagrecorders.com>) in one of the four vaccination areas to collect continuous minute-by-minute temperature records. We selected the zone of Kangaré as it includes a wide spectrum of immunization delivery settings – from vaccinating in markets to house-to-house delivery to bicycle outreach. The recorders were placed inside the vaccine carriers together with the OPV vials each day. During the last two NID days, three additional recorders were attached to the outside of three selected vaccine carriers. This allowed us to capture a more accurate measurement of the ambient temperature the vaccine carriers were exposed to.

All vaccination teams in the participating health zones were trained before the study started. The training included a study description, a refresher session regarding the use and classification of VVMs and to the questionnaires for data collection. During the NID, the vaccination teams received support and supervisory visits. Adverse events surveillance was conducted throughout the campaign as usual.

### 3. Results

During the third round of the 2009 NID campaign, 14,913 children were vaccinated with OPV in the four health areas included in this study. The OPV kept outside of the cold chain during the vaccination activities was used to vaccinate 7922 (53.1%) of the total number of children vaccinated.

All 39 teams vaccinating in the study area during the NID agreed to participate to the study. Ninety-seven percent of daily questionnaires were completed, and 84% of the vaccinators filled out the final questionnaires on their perception of the OCC procedure.

The most frequently used vaccination strategy was house-to-house vaccination, reported by 100% of the teams. In addition 5% of them reported vaccinating children at the market. All teams used vaccine carriers to transport the OPV – 57% of them used NID vaccine carriers made of foam, and 43% used EPI polyethylene cool boxes. The teams carried between 1 and 22 vials of OPV each day, with an average of 8 vials carried per vaccination team. The principal means of travel was by foot (83%), and some teams combined walking with bicycles or motorcycles. The daily travel distance per team ranged from 2 to 150 km with a median of 12 km. The duration of the daily vaccination activities ranged between 30 min and 12 h, with an average of 6 h 43 min.

All OPV vials used in the study area, in total 956, were monitored during the study. Most health areas chose to restrict themselves to percentage increments of 20% (0, 20, 40, 60, 80, and 100%) to ease VVM classification. None of the vials used in this NID campaign reached the stage of VVM endpoint at the time of administration. Therefore, no child was given OPV with a VVM that had reached the discard point. Consequently, there was no loss of vaccine (wastage) due to the vaccine no longer being safe to administer, as measured by the VVM having exceeded the acceptable stage and reached its endpoint. Table 1 shows the breakdown of the VVM status of the vials used during the study. As expected, the VVM progressed through its stages slightly faster during OCC days, which is due to the cumulative higher temperatures exposure under those conditions. However, despite this, at the time the last dose was administered, no VVM had surpassed the VVM stage of 60% (Fig. 1b).

Eighteen LogTag®s were used during the study by the 16 vaccination teams in Kangaré. The highest ambient temperature recorded during the vaccination activities was 40.9 °C. The average temperatures recorded inside the vaccine carriers during the OCC and CC days are summarised in Table 2. During the OCC days, the OPV was exposed to average temperatures between 27.6 and 33.3 °C. The data in Table 2 comes from recordings from all LogTag®s for which the day's start and end temperature recording at a specific time in the morning and afternoon were available. These recordings were available for 100% of the LogTag®s for the two OCC procedure days, and for 87% for the days where the cold chain was maintained through ice packs. Of these latter cold chain days not all temperature recordings were included, since not all teams could begin their activities around the same time. Five vaccination teams worked beyond the river several hours away from

**Table 2**  
Temperatures recorded inside the vaccine carriers at the start and end of immunization activities using LogTag<sup>®</sup> recorders ( $n = 16$  and  $14$  for OCC and CC, respectively).

Temperature (°C)	OCC vaccine handling procedures		CC vaccine handling procedures	
	Start	End	Start	End
Min.	24.8	30.0	2.0	3.8
Max.	29.2	36.0	10.8	10.7
Average	27.6	33.3	6.4	6.2
Median	28.0	33.9	5.6	5.5

the health post. In order to provide them with new vaccine and ice pack stocks, supervisors departed in the morning and these teams only started vaccinating later in the day.

In general, the temperature inside the vaccine carrier was less variable and lower than the outside temperature. Over the course of the day, the temperatures inside the vaccine carrier gradually increased from an average of 28–29 °C to 34–36 °C. The average temperature difference between NID vaccine carriers and EPI polyethylene cool boxes was of 2.6 °C.

All the vaccinators and supervisors were able to experience both activities with (CC) and without ice packs (OCC) during this NID campaign. A questionnaire was distributed towards the end of the NIDs to determine their impressions and preferences. The majority of vaccinators (90%) and supervisors (88%) preferred the OCC procedure. One individual of each group stated that the traditional CC procedure was preferable to OCC without providing an explanation; both reported being fully comfortable relying on VVMs. Table 3 summarizes the responses received to both the vaccinator and the supervisor questionnaires.

In Kangaré, three unfinished vials of OPV had to be disposed of during the CC days, which used ice packs and traditional cold chain procedures. This was due to the humidity generated by the ice packs inside the vaccine carrier, which caused the labels to get wet and subsequently detach from the vials, rendering them unreadable and therefore the vials unusable. Two of these vials were full.

#### 4. Discussion

Maintaining the standard cold chain during vaccination campaigns is a challenge, especially in areas where electricity, equipment and resources are scarce. This study provides evidence that flexible cold chain management procedures as outlined in the WHO document on flexible cold chain management are possible to implement [6]. We found that OPV kept outside of the cold chain during NID activities remained sufficiently potent for use as per its VVM status. No VVM reached the endpoint despite exposure to external temperatures between 25 and 40 °C during vaccination activities that lasted nearly seven hours on average. There was no OPV wastage resulting from heat exposure. The OCC procedure was easily understood and feasible for all vaccination teams that participated in the NID.

This approach provides a possible practice for overcoming the challenges of delivering vaccines in situations where the continuity of the cold chain cannot be assured. Our study was conducted in a rural context in a country with limited resources and high temperatures. In Mali, it is almost impossible to continuously maintain the cold chain in all settings. This is made even more difficult during national immunization campaigns, which strain the country's already overloaded transportation systems and storage capacities.

Some additional factors make maintaining the cold chain problematic, notably the access to an infrastructure capable of freezing ice packs, as well as the need to carry these ice packs along with the OPV to maintain the recommended 2–8 °C temperature range. This is especially true during immunization activities outside the health care posts where it results in additional weight to be carried during the outreach vaccination activities. Moreover, the moisture generated by the ice packs inside the vaccine carriers soaks the OPV labels. After a few hours, the labels often either peel off and/or become destroyed, and the vial details as well as the VVM become unreadable. If a vial has not yet been opened or finished at this point, it must be disposed of. Vaccine wastage was higher on days with CC procedures, whereas on OCC days it was zero.

The temperature data collected by the LogTag<sup>®</sup> recorders will inform programmatic guidance for controlled temperature chains.

**Table 3**  
Perceptions of vaccinators ( $n = 29$ ) and supervisors ( $n = 8$ ) on the use of OCC.

	Vaccinators ( $n = 29$ ) % of responses	Supervisors ( $n = 8$ ) % of responses
Description of the advantages		
Lower weight and easier transport	97	100
Reduced preparation time	86	100
Reduced activity time, greater speed	69	75
Less travel detour to restock with ice packs	62	75
Fewer calls to the supervisor for ice packs	62	50
Number of children vaccinated using OCC, compared to CC		
Greater than	45	50
The same	55	50
Ease of VVM classification		
Very easy	41	50
Easy	45	50
Average	14	0
Difficult	0	0
Trust in VVM		
Total	100	88
Almost always	0	13
Not much	0	0
No problems with the parents during OCC days	100	N/A <sup>a</sup>
OCC versus CC method		
Preferable	90	88
No difference	7	0
Less preferable	3	13

<sup>a</sup> Supervisors did not vaccinate children.



The aim is to develop a regulatory framework that will enable vaccines to be stored and transported at controlled temperatures outside of the standard 2–8 °C range based on their individual stability profiles. This field-level data is a key component in ensuring the policy changes and licensing sought are compatible with country needs and conditions.

Assessment of the vaccine usability was based on the status of the VVM on the OPV vials. Laboratory studies and field studies conducted mainly in India have shown good correlation between the OPV potency (level of active ingredient) and the VVM stage following exposure of the vaccine to heat [7–9]. Nevertheless, in order to obtain certainty that the vaccines delivered during these NIDs did in fact retain the assumed potency levels, a study measuring the remaining virus content levels would be required.

The sample selection was based on convenience, taking into account the logistical and practical constraints of organising the study. Nevertheless, the four health areas that participated are a likely good representation of the six areas of the Sélingué district selected for the investigation. They cover more than half of the geographical area and inhabitants of the district.

During this study, teams had the opportunity to use and experience both methods. This way, each vaccination team performed as its own comparison group for the two procedures that were applied, preventing a potential systematic difference between OCC/CC groups. The teams were therefore aware of the purpose and objective of investigation. Consequently, it is possible that there was a systematic difference in the perceptions of the participants concerning the new method introduced. The risk of respondent bias, i.e. participants responding what they think will please the interviewers, was reduced by a neutral and independent approach to data collection [13]. Questions were phrased and administered in an impartial way, and there was no judgement or incentive related to responses. Furthermore, the weight reduction through the OCC procedure, which was the main reason for vaccinators to prefer this procedure, is undisputable. Nevertheless, a small element of respondent bias in this more qualitative part of the study cannot be fully excluded.

One of the main concerns in planning the study was ensuring that none of the vaccines administered had an expired VVM. To prevent this from happening, prior training was conducted and supervision during the vaccination activities was assured. Further, the teams only used the polio vials kept outside of the cold chain for one day at a time (whereas stability data indicate that OPV can remain stable at 37 °C for 2 days). These precautions proved effective, as evidenced by the fact that at the time the last dose of each vial was administered the VVM stage was always reported to be acceptable.

The VVMs were read and classified by the vaccinators, and not by a densitometer, which theoretically provides room for human error. The study's colour intensity method for assessing VVM progression presented a few difficulties: the concept of percentage gradation was new and not intuitive for everybody; moreover, the differentiation of the stages (in %) was not easy for all vaccinators and was not standardised between individuals. In one of the health areas (Binko), due to the classification problems described and in order to preserve the quality of the results, it was decided that instead of using the new colour intensity scale model, the classical method of classifying VVMs by the four stages would be used (Fig. 1a). However, past studies have shown VVMs to be a reliable, easy to read tool that allows health care workers to clearly assess if a vaccine should be used [14–17]. These findings were confirmed in our study through the vaccinators' responses to the questionnaire, with 89% of respondents classifying the VVM's colour progression as 'easy' or 'very easy' to interpret.

The vaccination teams involved in the study were composed of volunteers without any specific health care training, who showed

commitment to the study protocol and its implementation. Most of them had previously participated in other NIDs. The majority of vaccinators (90%) and supervisors (88%) interviewed preferred the OCC procedures. Following OCC procedures meant they had less weight to carry, the process of preparing for the outreach visits was easier and quicker, and, finally, the costs incurred were reduced.

To our knowledge, this is the first systematic documentation of Oral Polio Vaccine kept outside of the cold chain during vaccination activities in the field. As previously stated, OCC can be a useful alternative in specific contexts, where maintaining the cold chain poses a challenge. This includes campaigns such as the polio NIDs, where large-scale outreach activities are conducted. Use of this approach provides an opportunity to expand coverage, which is essential to achieving elimination and eradication targets. Moreover, as the number of vaccines included in the EPI programme continues to increase, the same approach can be considered as a way to address the cold chain capacity limitations experienced by many countries. However, it is essential to note that using vaccines outside of the cold chain can only be considered if the vaccine has a VVM and if adequate training of the vaccinators precedes the introduction of OCC practices.

OCC practices have been under discussion within the immunization community and have been in use in several countries for many years [18–22]. Nonetheless thus far, the implementation of and programmatic implications of these practices have not been studied scientifically. It is important to increase the evidence available on this approach, which has a great potential for facilitating expanded vaccination activities and increasing the flexibility of vaccination practices.

Given the increasing pressures on the supply chain with the introduction of new vaccines, there is growing support for moving to more flexible vaccine management, using a Controlled Temperature Chain (CTC) broader than 2–8 °C in order to take advantage of the true stability of the vaccines. The findings of this study add to the body of evidence showing the feasibility of the CTC approach.

We recommend further studies be conducted in order to better document and understand the potential benefits and challenges of using OPV outside of the cold chain in various settings. Repeating this study in another campaign situation or adapting it for a routine vaccination context using other antigens in addition to OPV would be the logical next step. The collection of more data and evidence is essential before generalized recommendations can be made.

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