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Assessing the potency of oral polio vaccine kept outside of the cold chain during a national immunization campaign in Chad

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ABSTRACT

This study is the first systematic documentation of the potency of monovalent oral polio vaccine type 3 (mOPV3) kept at ambient temperatures during a polio immunization campaign in Chad. During the study test vials were exposed to temperatures of up to 47.1 °C, and kept outside of the 2–8 °C range for a maximum of 86.9 hours. Post-campaign laboratory testing confirmed that the test vials were still potent, and in conformity with the defined release specifications. Further, the Vaccine Vial Monitors performed as expected, giving an early warning indication of when cumulative exposure to heat reached levels that may have negatively affected the vaccine's potency. This study provides proof-of-concept evidence that certain types of OPV remain potent and thus can be kept, for limited periods of time, as well as administered at ambient temperatures.

1. Introduction

Oral polio vaccine (OPV) is the least stable of the vaccines commonly used in the Expanded Programme on Immunization (EPI) [1]. It is therefore recommended that OPV be kept in suitable cold chain conditions, ideally at −20 °C. However, if the vaccine cannot be kept at −20 °C, it can be kept between 2 and 8 °C for a maximum of 6 months, or for a period defined by the manufacturer based on real time stability data. Laboratory studies have demonstrated the correlation between exposure to heat and loss of vaccine potency [1].

Maintaining the cold chain under field conditions is frequently problematic, sometimes impossible and can be a major factor limiting the ability of immunization services to reach the entire population [2,3]. This is especially true during campaign activities, such as national or sub-national immunization days (NIDs or sNIDs). These NIDs, which aim to vaccinate all children under five, form a cornerstone of the global polio eradication strategy in both in endemic countries as well as for outbreak control in countries where the Polio virus can re-emerge [4]. Ideally, during campaign outreach activities, vaccinators should use vaccine carriers with frozen ice packs to prevent exposure to heat when transporting the vaccines. In Chad, as is the case in many other countries, polio immunization campaigns are faced with a limited availability of cold chain equipment and a limited ice and icepack production capacity. This makes maintaining OPV within the manufacturer recommended temperature range during campaign activities a challenge.

OPV vials, as with most other vaccines used in developing countries, are affixed with a vaccine vial monitor (VVM), in accordance with the joint WHO–UNICEF policy statement [5]. VVMs are small adhesive labels that gradually change colour as the vial's cumulative exposure to heat increases over time.

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When the vial has been exposed to cumulative heat levels at which the vaccine's potency can no longer be assured, the inner square on the VVM becomes darker than the outer reference ring. This allows health care workers to know whether the vaccine can safely be used even in situations where the cold chain cannot be guaranteed, or should unexpected cold chain breaks occur.

The vaccines that are part of the Expanded Programme on Immunization (EPI) have different sensitivities to heat. In order to account for this, there are several different types of VVMs. These are assigned to vaccines depending on the time (in days) that the potency of the vaccine remains above the WHO release specification at a temperature of 37 °C: VVM 2, 7, 14, and 30. OPV, which is the most heat sensitive of the EPI vaccines, is equipped with a VVM 2. This means the VVM of OPV reaches its endpoint after a cumulative exposure to 37 °C for two days [6] and/or 225 days when stored at +5 °C, with a 25% safety margin [7].

The rate at which the VVMs change colour has been proven in laboratory settings to be a reliable warning indicator of when heat exposure is likely to have negatively affected potency [8,9]. However, to-date these findings have not been systematically researched using vaccines exposed to field conditions.

2. Objectives

This study aims to investigate whether the potency of the OPV used during the campaign in Chad, and exposed to ambient temperatures while applying the WHO flexible cold chain management guidelines for OPV [10], is still within the acceptable potency range as measured in post-campaign laboratory testing. The study also aims to assess the relationships between the potency of the OPV, its assigned VVM and its exposure to heat.

3. Methodology

During a recent polio campaign in N'djamena, conducted as part of the Africa-wide Polio National Immunization Days (NID), 20 test vials were sent along with vaccinators while they conducted their regularly scheduled activities. These test vials were exposed to ambient temperatures while vaccination activities were conducted, but remained closed and unused throughout the study. The expiry dates of the vaccines were verified, and the temperatures to which these vials were exposed as well as their VVM status, were recorded at specified points throughout the day.

At the end of the campaign in N'djamena, the vials were transported to the Belgian National Control Laboratory in order to confirm that the correlations between VVMs and vaccine potency previously documented in laboratories hold true under field conditions.

For the purposes of this study, the same batch of vaccine that was used by Ministry of Health in Chad for its immunization campaign, monovalent oral poliomyelitis vaccine type 3 in 20 dose vials, was used. At the start of the study, 22 vials were selected at random: 20 'test vials' that would be exposed to ambient temperatures, and 2 'control vials' that would remain at the central cold store. All vials came from the same batch produced by a single manufacturer. These vials had travelled to Chad as part of the regular shipment for the NID, directly from the manufacturer to the central cold store in N'djamena. Once the vaccines were received at the central store by the Ministry of Health in Chad, they were kept in the central level freezer room, where temperatures were between −10 and −20 °C until the campaign.

3.1. Vial preparation

Prior to the start of the study, the 20 test vials were labelled T1 through T20, and a Libero PDF datalogger was attached to each. The Libero PDF datalogger, manufactured by ELPRO, is able to record 16,000 data points/device, and have proven reliable between −35 °C and +70 °C (accurate to ±0.5 °C). In addition, Liberos feature a visual temperature display, which allowed for periodic recording and verification of the temperatures during the study [11]. The two control vials, labelled C1 and C2 respectively were each assigned a digital LogTag temperature monitor, manufactured by LogTag Recorders Ltd., to continuously record their temperature exposure at all times [12].

In addition to continuous temperature monitoring, VVM status of the test and control vials were checked and recorded at the start of the study at the central store. The visual percentage-based colour intensity classification scale was used to conduct these readings, which had previously been used successfully in Mali [13] (Fig. 1). VVMs were deemed to have reached their discard point when the inner square reached the same colour as or was darker than the outer control ring, which, based on the scale used, is 100%. Both the ambient temperature and the VVM status were recorded on the tracking sheet that accompanied each vial.

3.2. Vial distribution

The 20 test vials were equally divided into two groups: one-day vials and two-day vials. One-day vials were, as indicated by their name, exposed to one day of campaign activities at ambient temperatures; two-day vials were exposed to a second day of campaign activities at ambient temperatures.

These vials were distributed amongst four health centres, selected purposively to represent a mix of urban, peri-urban and village settings. Attention was paid to ensuring each health centre received a mix of both types (one-day and two-day) of vials. These health centres were a mix of city centre (Polyclinic), outer city limits (Goudji) and those servicing small villages (Hele Houdjaj and Ardeptimane).

The test vials were stored and packed alongside the regular campaign vaccines at the central store and were transported to their respective health centres along with the regular campaign vaccines one to two days prior to the campaign. Upon arrival at the health centre, the VVM status and the temperature inside the vaccine carrier on arrival were recorded in each vial's record sheet. Once at the health centre, the test vaccines were kept alongside the regular campaign vaccines. This resulted in exposure to various storage conditions, as per the availability of cold chain space and equipment and the length of time until the start of the campaign activities. Vaccines were kept either in refrigerators (city centre Polyclinic) or in cold boxes with frozen icepacks (Goudji) or in a mix of both (Hele Houdjaj and Ardeptimane).

3.3. Vaccinator training and survey

On the day prior to the campaign, vaccinators were trained on conducting VVM visual reading using the percentage-based scale, given an overview of the Libero PDF datalogger and shown how to complete the study data collection form. A refresher session was conducted the morning the vaccination activities took place. A supervisor reviewed the first recording of the day to ensure there were no remaining questions. In addition, at the end of the days' activities, a supervisor validated the VVM and temperature readings upon return to the health centre. On return to the health centre, vaccinators were also asked to complete a quick survey on their views on the controlled temperature chain (CTC) practice.

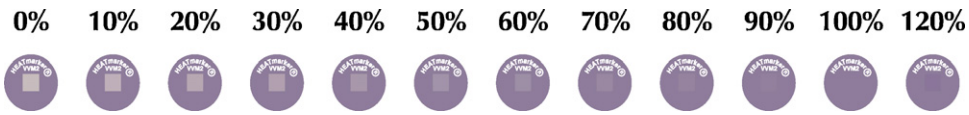


Fig. 1. VVM visual classification scale.

3.4. Campaign day

On the day of the campaign, the test vials were removed from their storage location at the health centre at the same time as the vials used in the regularly scheduled activities. The VVM status of the test vials was recorded, along with the ambient temperatures. In the more rural locations, where vaccines were distributed to villages the day before the campaign activities were scheduled to begin, ambient temperature and VVM status were recorded starting at that point.

At the start of the day's campaign activities, the test vials, along with their Libero PDF dataloggers, were taken by vaccinators and placed in a plastic bag and kept in their pockets or purses. The VVM status and temperature were recorded upon departure from the health centre, administration of the first dose of the day, administration of the last dose of the day and upon return to the health centre.

3.5. Post-campaign

As soon as the day's immunization activities ended, the one-day vials were transported back to the health centre in cold chain conditions and returned to negative temperature storage at the central store. The status of the VVM status and ambient temperature readings from the Libero PDF dataloggers were recorded upon arrival.

Two-day vials followed the same process as the one-day vials described above, however at the end of the first day's activities they were not taken to the central store and instead were kept at the health centres overnight in cold chain conditions, and then taken out again for campaign activities the following day. Temperature and VVM reading protocol mirrored that of the first day. At the end of the second day's activities, the two-day vials were transported back to the health centre in cold chain conditions and returned to the central store where they were stored between −10 and −20 °C.

At the conclusion of the campaign, all twenty test vials along with the two control vials were packed in vaccine carriers with frozen icepacks and were accompanied by study personnel from Chad to the laboratory in Brussels. Temperature loggers remained with the vials at all times.

3.6. Laboratory testing

Laboratory testing was carried out in Brussels at the Belgian Scientific Institute of Public Health, which houses the Belgian National Control Laboratory (NCL). Standard laboratory OPV lot release quality assurance testing was conducted using a standard potency assay performed routinely by the Belgium NCL for the release of their nationally produced OPV and also on the behalf of WHO as part of the prequalification random testing [14]. The tests assessed whether the titres of the mOPV3 test vials were over the threshold of $10^{5.80}$ $CCID_{50}$/dose (with a confidence interval of ±0.3 log).

The protocol tested the OPV viral activity by cell culture infection and cytopathic effect (CPE) counting. Testing was conducted by inoculation in a microtitre plate of 10 wells of each of the 4 dilutions of the virus, followed by a volume of Hep-2 (Cincinnati) line cell suspension. Further details on this testing protocol can be found in the WHO Manual of Laboratory Methods for Testing Vaccines Used in the WHO Expanded Programme on Immunization [15]. For serotype potency evaluation, CPE counting was conducted at day seven.

In addition to reading the VVMs using the visual classification scale, the VVMs were read by the Xrite Model 404 GS reflection densitometer at the laboratory in Brussels to verify the visual readings conducted in the field. A densitometer is a specialized tool that allows a technician to verify the precise change in colour of the inner VVM square, a precision that cannot be obtained by human eye alone [16]. The correlation between the visual readings and the densitometer readings was assessed using R^2 for coefficient determination.

4. Results

Over the course of the study, ambient temperatures during campaign activities ranged up to a maximum of 47.1 °C.

The length of time each vial was out of the standard 2–8 °C cold chain varied by location. For one-day vials, the times spent above 8 °C ranged from 10.7 to 24.6 hours, of that up to 4.4 hours were above 37 °C. For the two-day vials, the time spent above 8 °C ranged from 17.8 to 86.9 hours and time above 37 °C reached up to 9.7 hours (see Table 1).

These variations in exposure temperatures and durations reflect the different vaccine handling procedures required at various vaccination sites. For example, the health centre in centre of the city had functioning refrigerators in which to store the vials, and a reliable energy source to power it; whereas those health centres in more rural areas packed the vaccines into vaccine carriers immediately upon receipt, with one or two ice packs, depending on availability. In addition, in sites where vaccination activities were scheduled to start early in the morning (5h00 or earlier) and where cold chain space was limited (Goudji), or where the vaccination sites were located far from the health care centre (Hele Houdjaj), the vaccines were packed into vaccine carriers with an ice pack or two the night before campaign activities. This procedure, although not common, has also been seen in other countries where cold chain capacity is limited, and where distances between health centres and the population make same day distribution and vaccination operationally extremely challenging. Given the high ambient temperatures, the one or two ice packs placed in the vaccine carrier did not stay frozen overnight, which meant that vaccines were exposed to temperatures above 8 °C earlier than expected.

Two of the two-day vials were exposed to temperatures above 8 °C for over 80 hours. These vials were kept in a refrigerator in a health centre prior to the start of the campaign, and in between the first and second day of use. Because of electricity outages and malfunction of the refrigerator, these vials were exposed to higher temperatures than would have been expected, despite the efforts of the health care workers to keep them between 2 and 8 °C conditions.

The Vaccine Arrival Report, completed by the central store at the time of receipt of the international vaccine shipment, confirmed the condition of the vaccines on arrival, on the basis of VVM readings as well as temperature recorders included in the shipment [17]. In addition, at the start of the study, the VVM status of all test vials was checked and recorded at the central store in N'djamena.

At the end of the first day of vaccination activities, only one of the twenty test vials had a VVM that had reached its endpoint. By the end of second day a further five vials had VVMs that had reached their end point. These readings were conducted visually, based on

Table 1
Summary results table.

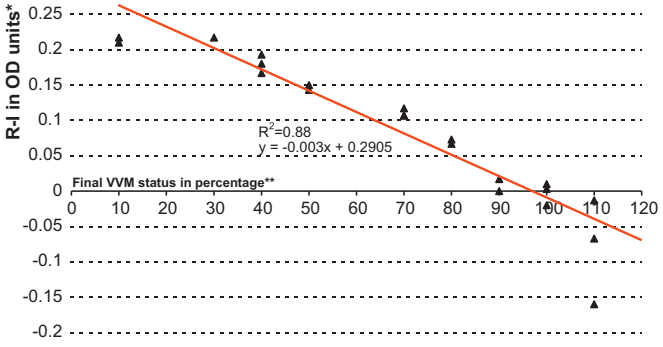
Location/type of vial	# of vials	Maximum temp °C average (min–max)	Hours >8 °C average (min–max)	Hours >37 °C average (min–max)	Potency (±0.3)[a] average (10_{xx} $CCID_{50}$/dose) (min–max)	Initial VVM reading[b] average (min–max)	Final VVM reading[c] average (min–max)
Polyclinic							
1-day	1	36.6	6.9	0	5.9	10%	50%
2-day	1	39.6	25.8	1.3	6.4	10%	30%
Goudji							
1-day	3	38 (37.2–40.2)	21 (20.5–21.2)	0.7 (0.0–0.1)	6.0 (5.9–6.2)	10% (10–10%)	60% (40–80%)
2-day	3	39 (36.7–40.7)	75 (44.0–86.9)	1.3 (0.0–2.9)	6.0 (5.9–6.1)	10% (10–10%)	90% (70–100%)
Ardeptimane							
1-day	3	40 (37.7–43.3)	21 (15–24.6)	1 (0.8–1.3)	6.2 (6.2–6.3)	10% (10–10%)	60% (40–80%)
2-day	3	41 (39.3–43.0)	29 (21.5–32.5)	5 (4.4–5.5)	6.1 (6.1–6.2)	10% (10–10%)	80% (70–110%)
Hele Houdjaj							
1-day	3	42 (40.0–43.8)	13 (10.7–17.9)	4 (3.3–4.4)	5.8 (5.6–5.9)	10% (10–10%)	60% (40–70%)
2-day	3	44 (42.4–47.1)	21 (17.8–25.5)	9 (7.1–9.7)	6.0 (5.8–6.2)	10% (10–10%)	100% (90–110%)

[a] *Note:* Potency release threshold is 105.80 $CCID_{50}$/dose (±0.3 CI).
[b] *Note:* VVM readings read using a percentage scale, intervals of 10%, where 100% indicates the VVM has reached its endpoint.
[c] *Note:* Final VVM readings validated by Densitometer at lab in Brussels.

the percentage scale validated in Mali [13]. Readings conducted in the field by vaccinators were verified upon return to the health care centre, and again upon deposit at the central store and on arrival at the laboratory in Brussels. The vaccinators surveyed indicated they were comfortable administering OPV that had a valid VVM, even if it had been kept at ambient temperatures.

There was no change in VVM status between the visual classification conducted at the central cold room in N'djamena and upon arrival at the Laboratory in Brussels. These readings were conducted by the same person, without referencing the previous reading. The reflection densitometer readings of the difference between the reference ring and the active surface (indicator) of the VVM highly correlated ($R^2 = 0.88$) to visual readings performed on arrival at the laboratory in Brussels (Fig. 2).

Laboratory testing showed that the study vials conformed to the release specifications (Table 1). All twenty vials tested at the laboratory fell within the batch release specifications for monovalent OPV type 3 of $10^{5.80}$ $CCID_{50}$/dose, with a confidence interval lower or equal to ±0.3 log $CCID_{50}$ ($p = 0.95$) for the estimated virus concentration of the reference preparation for the three replicates combined. The vials ranged in potency from $10^{5.60}$ $CCID_{50}$ to $10^{6.40}$ $CCID_{50}$/dose. 17 of the vials tested above at $10^{5.80}$ $CCID_{50}$/dose, 2 tested at $10^{5.80}$ $CCID_{50}$/dose, and 1 tested at $10^{5.60}$ $CCID_{50}$/dose, which although below the specification of $10^{5.80}$ $CCID_{50}$/dose, when considered with the CI of ±0.3 log cannot conclusively be determined to be outside the acceptable limits of the release specification or as lacking the potency to result in seroconversion.



** Difference between the reflection densitometer readings of the reference ring (R) and active indicator surface (I) in optical density (OD) units*
*** Final VVM status visual reading conducted on arrival at the laboratory in Brussels*

Fig. 2. Correlation between visual VVM readings and reflection densitometer readings.

5. Discussion

Given the public health importance of national immunization days, and the logistical and infrastructure challenges faced by many countries in conducting them, the use of a more flexible temperature chain in these situations is often unavoidable. Although vaccines are heat sensitive and must be handled with care, this study provides field-level evidence to support the WHO guidelines on OPV which encourage countries to take advantage of the stability of the vaccine to use a CTC rather than missing vaccination opportunities altogether. The inclusion of a VVM on each vial is essential for this practice.

This study highlights the challenges of keeping vaccines in the 2–8 °C range in field conditions, especially during campaign activities. Even at points in the study where it was thought that the vaccine was being stored within a 2–8 °C range, data from the temperature loggers revealed cold chain breaks.

VVMs are designed to give health care workers an indication of when a vaccine has been exposed to such levels of heat that its potency may have been compromised. Designed as an early warning signal, all VVMs, including the VVM2 used on OPV, are designed to reach their endpoint early, in order to avoid using vaccine that would potentially not be potent. The VVMs in this study behaved as expected; the VVMs on several vials exposed to extremely high ambient temperatures reached their endpoints even though subsequent testing indicated that the vaccine was still potent. Strong correlation was also found between the reflection densitometer readings and visual VVM readings in the field. These results are inline with VVMs performance specifications [7], to err on the side of caution so as to ensure children are not being given an inactive vaccine.

While studies have shown that the intermittent freeze/thaw conditions have no impact on VVM performance [18] studies conducted by TempTime, the manufacturer of VVMs, have confirmed that exposure to sunlight accelerates the rate at which VVMs reach their endpoint [19]. TempTime's study also showed that the effect of sunlight on VVMs is most pronounced with VVM2, the VVM used for OPV. This may have been a contributing factor to the findings that 6 of the VVMs had reached their endpoint even though they had only been exposed to temperatures of above 8 °C for a period of 24 h. Several solutions for addressing this, including a small plastic cover on top of the VVM, are proposed by TempTime. Should the use of OPV in a CTC become a widespread practice, this issue may warrant further discussion. However, given the extreme temperatures these vials were exposed to, and the predicted performance of the VVM under such circumstances, along with the vial handling

procedures, the impact of sunlight on the VVM rate of progression in this study is likely extremely minimal.

The inclusion of VVMs on vaccine vials is imperative for implementing a CTC strategy; there is no safe way to utilize a CTC approach without them. Not only does the use of a CTC-based strategy allow for vaccination to be undertaken in areas where there is no reliable cold chain, but it also presents several other logistical and operational advantages. These include saving icepack freezing capacity, allowing teams to split up to cover markets or bus/train stations without requiring additional equipment, and to visit homes in both the early morning and late afternoon to reach children who are absent during the normal working day. After one day of CTC activities, only one of the 20 test vials had a VVM that had reached its endpoint. However after the second day of CTC activities, a further five VVMs had reached their endpoint. Therefore, in considering a CTC strategy that spans longer than one day, the extent of vaccine wastage due to heat exposure must be assessed. In situations where ice packs or a cold chain are not available, a higher wastage rate may be preferable to not conducting vaccination activities at all.

This study did not allow for a detailed correlation to be drawn between the length of time and temperature exposure and vaccine potency reached and VVMs. This is due in part to the lack of specificity in the standard assays used in the lab, to the small sample size as well as to the fact that only one type of OPV vaccine, from a single batch produced by a one manufacturer was studied. Further and larger studies including studies with various types of OPV from a variety of manufacturers would be required to provide definitive field-evidence to support the correlations shown in the laboratory.

Health care workers surveyed during this campaign, like those in other studies [13] have indicated that they are comfortable using OPV kept in a CTC if the VVM has not yet reached its endpoint. However, anecdotal evidence in N'djamena indicates that this may not be acceptable to the parents of those being vaccinated. Owing to a lack of cold chain equipment, (including vaccine carriers and icepacks), polio campaigns carried out in the southern part of N'djamena asked vaccinators to carry the vaccine in a plastic bag for a few hours while they vaccinated in the urban area close to the health centre. Several vaccinators reported parents refusing to have their children vaccinated with a vaccine that was not 'kept properly with ice'. This is important to note, as should the conduct of NIDs using CTC practices be implemented, the use of a thermos or other vaccine carrier, even without ice packs, along with a clear communication and education strategy aimed at parents should be considered.

This study provides field-level evidence that mOPV3 can be safely kept, for limited periods of time, outside of the 2–8 °C cold chain, following WHO's flexible cold chain guidelines for OPV, and using the VVM as an indicator of when exposure to heat is at such levels that the vaccine's potency may be negatively affected. However, given the fact that all vials used in the campaign originated from the same manufacturer and were of the same batch, it is not possible to generalize these findings to other types of oral polio vaccine or even other manufacturers' monovalent type 3 oral polio vaccine. In order to generalize these findings, additional studies using various batches and OPV from multiple manufacturers' would be required.

Nonetheless, this study provides field generated evidence that even certain types of OPV, the most heat sensitive of all EPI vaccines, could be used in a controlled temperature chain. The OPV specifications require that the drop of potency when the vaccine is exposed to 37 °C for 48 h [1] does not exceed 0.5 log $CCID_{50}$/dose. This study showed that even under field conditions, including extreme and cycling temperatures, the vaccine retains its potency within the required specifications. Thus, when the vaccine is equipped with a VVM, the lack of a reliable cold chain should not be seen as a reason not to pursue immunization, provided vaccinators are trained in the interpretation of the VVM and appropriate guidelines are followed.

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