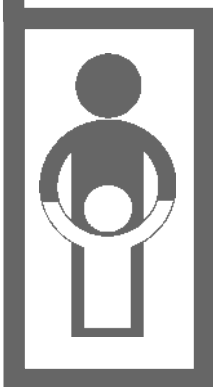


Testing the correlation between vaccine vial monitor and vaccine potency



DEPARTMENT OF VACCINES AND OTHER BIOLOGICALS



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Glossary

Vaccine vial monitor (VVM)	A vaccine vial monitor is a label made from a heat-sensitive chemical material that is placed on a vaccine vial label or cap to register cumulative heat exposure over time. The combined effects of time and temperature cause the monitor to change colour gradually and irreversibly.
Discard point	The phase of a vaccine vial monitor in which the inner square is the same colour or darker than the colour of the outer circle. Vaccine in vials with such VVMs must not be used.
Total virus content	The virus titre of the trivalent polio vaccine in the absence of antibody neutralization.
National control laboratory	An entity that performs tests on vaccines and other biological products to provide information to the national regulatory authority on the safety, efficacy, and quality of those products for their intended use.
Significant potency drop	For trivalent polio vaccine, $\geq 0.6 \log_{10}$ when the mean potency of the heated vial is subtracted from the mean potency of control unheated vials.

Introduction

The purpose of this document is to provide information on a test for examining the correlation between vaccine vial monitors (VVMs) and the vaccine in the vials to which they are attached. The test was developed by an internationally recognized laboratory and tried out on the VVMs of the four manufacturers that currently supply United Nations (UN) agency needs for oral poliovirus vaccine (OPV). The vaccines of those manufacturers meet WHO specifications. Now, the test is ready for field testing by qualified national control laboratories.

Description of the test

Vaccine vial monitors were introduced for use on OPV vials in 1996 to enable health workers to assess whether vaccine in individual vials has been exposed to too much heat over too much time. VVMs have assured health workers that the vaccines they use are good and that the vaccines they discard have, in fact, been exposed to heat for such a period of time that they are likely to have lost their potency.

Despite testing by manufacturers, concerns are still sometimes raised that VVMs might not accurately reflect the status of the OPV to which they are attached, for example, where OPV is directly procured or locally produced or where breaks in the cold chain are suspected. In such cases, national procurement agencies and immunization managers may request assurances through testing by national laboratories.

This kind of test for oral poliovirus vaccine (OPV) has been designed and evaluated for the World Health Organization (WHO) by D.J. Wood of the National Institute for Biological Standards and Control (NIBSC) in the United Kingdom. The test is described in detail in the Annex.

Summary of the correlation study

In March 1998, D. J. Wood prepared a report of the NIBSC study of vaccine vial monitors and oral poliovirus vaccine potency for the Technet Consultation meeting in Copenhagen (See WHO/EPI/TECHNET.98/BK.15).

The study showed that there was good correlation between vaccine potency and VVM change for vaccines produced by all four manufacturers that provide OPV to UN agencies. The results are shown in Tables 1 and 2 and Figures 1-4 beginning on page 4.

Conclusions of the NIBSC correlation study include:

1. Simple visual inspection of VVMs against the standard scale that measures change in colour is a realistic test for widespread application.
2. Assay of total virus content, using the standard WHO methodology, is simple, effective, and suitable for widespread application.
3. The test can identify two problems, that is, 1) VVMs reaching the discard point significantly before vaccines lose their potency; and 2) the reverse, vaccines losing their potency significantly before VVMs reach the discard point.

When VVMs expire too quickly relative to the thermal stability of the vaccine, vaccine will be discarded while still potent, adding to the problem of vaccine wastage. When they expire too slowly, there is a risk that sub-potent vaccine will be administered.

Note: As shown in Table 1 above, the test identified VVMs from Manufacturer C that expired too quickly relative to the thermal stability of the vaccine. Subsequent inquiry revealed that the vaccine manufacturer had used VVM specifications that did not meet WHO specifications. The manufacturer now uses WHO specifications.

4. The rate of vaccine potency loss differs among manufacturers. The correlation study showed that manufacturers have not taken advantage of the flexibility in WHO specifications. All have used the minimum VVM standard, and as a result, some vaccines have still been high in titres when the VVMs have reached their discard point.

Application issues for management

The test described in this document can be used for OPV after validation in local laboratories when national authorities make decisions on the following issues:

1. When and how often to conduct the test?

For vaccines supplied through UN agencies, the test is conducted initially to pre-qualify a manufacturer's product. Thereafter, the test is done on lots selected randomly every 6 to 12 months. For vaccines supplied to countries directly, the same routine should be followed. That is, the national control laboratory should pre-qualify a manufacturer's vaccines and then test randomly selected lots.

2. Who should conduct the test?

The test should be done only by those laboratories that are proficient in conducting the OPV potency test and use a validated test that is standardized against the international reference preparation for polio vaccine.

3. Does the test change anything in what health workers and others have been taught about using VVMs?

NO. See Vaccine Vial Monitor and Opened Vial Policy: Questions and Answers, WHO/EPI/LHIS/96.01, revisions in process.

4. What changes will be needed to make this test applicable for VVMs on other vaccines?

At the present time, this test can be used only with measles and yellow fever vaccines because only they have reliable potency assays that can readily be correlated with VVM performance.

Table 1: High temperature conditions that may identify VVMs that expire too quickly relative to the thermal stability of the vaccine

Heating conditions (°C/hours)	Manufacturer	Number of vials tested	Number of vials with:	
			Significant potency drop	Expired VVM
37°(±1)/24(±4)	A	5	0	0
	B	5	0	0
	C	5	0	5
	D	5	0	0
35°(±1)/24(±4)	A	5	0	0
	B	5	0	0
	C	5	0	5
	D	5	0	0

A significant potency drop is $\geq 0.6 \log_{10}$ when potency of the heated vial is subtracted from the mean potency of control unheated vials.

An expired vial is \geq grade 3 on a standard scale for visual inspection.

Table 2: High temperature conditions that may identify VVMs that expire too slowly relative to the thermal stability of the vaccine

Heating conditions (°C/hours)	Manufacturer	Number of vials tested	Number of vials with:	
			Significant potency drop	Expired VVM
37°(±1)/48(±4)	A	5	0	0
	B	5	1	0
	C	5	0	5
	D	5	0	0
37°(±1)/72(±4)	A	5	0	5
	B	5	2	5
	C	5	0	5
	D	5	0	5
35°(±1)/48(±4)	A	5	0	0
	B	5	0	0
	C	5	0	5
	D	5	0	0
35°(±1)/72(±4)	A	5	0	5
	B	5	2	5
	C	5	0	5
	D	5	0	5

A significant potency drop is $\geq 0.6 \log_{10}$ when the potency of the heated vial is subtracted from the mean potency of control unheated vials.

An expired VVM is \geq grade 3 on a standard scale for visual inspection.

Figure 1: Comparison of drop in potency for OPV and VVM at 35°C – Manufacturer B

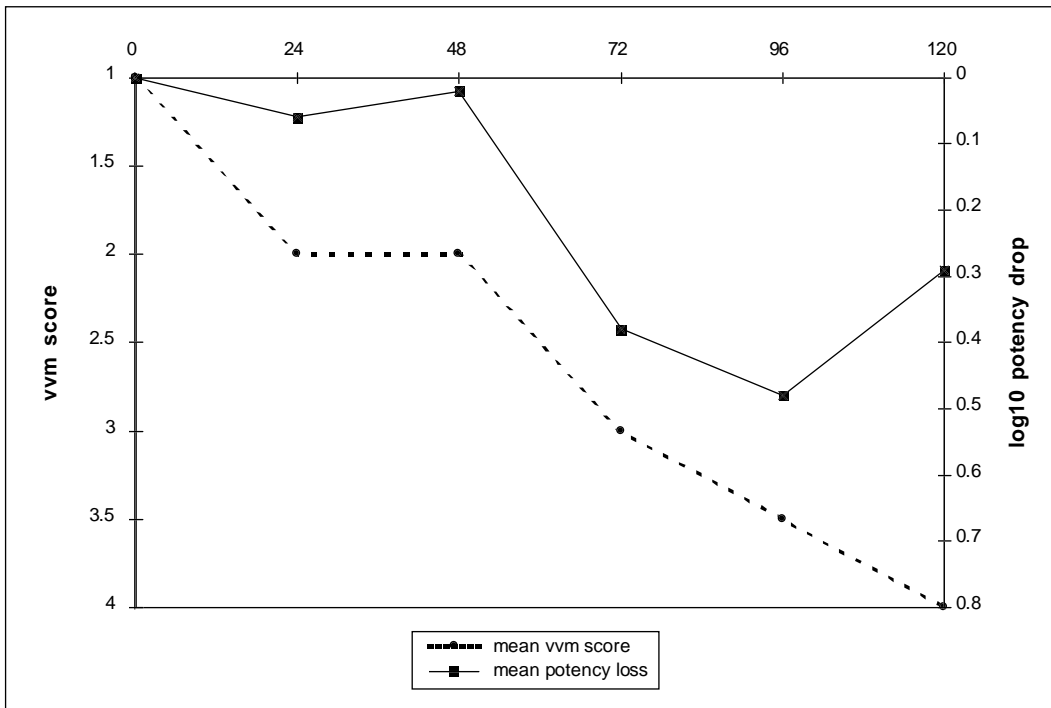
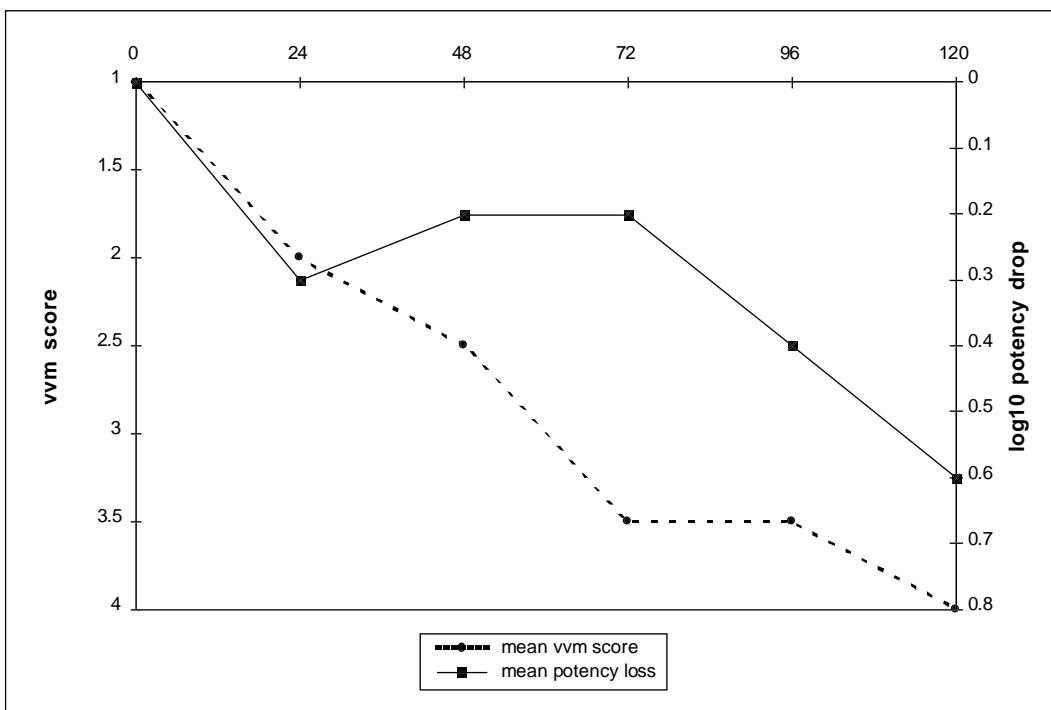


Figure 2: Comparison of drop in potency for OPV and VVM at 37°C – Manufacturer D



References

1. D.J. Wood Report of a study of Vaccine Vial Monitors and oral poliovirus vaccine potency, WHO/TECHNET.98/BK.15.
2. *WHO Technical Report Series 800, Annex 1, 1990.*
3. **Manual of Laboratory Methods for Testing of Vaccines used in the WHO Expanded Programme on Immunization, WHO/VSQ/97.04.**

Annex:

VVM-OPV correlation test

The test described below is further discussed in D.J. Wood *Report of a study of Vaccine Vial Monitors and oral poliovirus vaccine potency*.

1. Selection of sample

- Check that all vials from which the sample is to be taken are frozen on receipt.
- Randomly select a sample of vaccines. Generally, five vials should be selected for each time and temperature point.
- Immediately place samples in -70°C storage, and keep them there until testing begins.

2. Exposure to heat

Place the samples of vaccine with VVM attached in sealed plastic bags inside an airtight container and submerge them in a water bath maintained at 37°C .

- **Temperature:** The temperature 37°C recommended by WHO is the standard temperature used in thermal stability tests for OPV and other vaccines.
Temperatures should remain within $\pm 1^{\circ}\text{C}$ of the target.
- **Duration of exposure to heat.** WHO recommends that, in addition to the required duration of 48 hours, incubation periods include 24, 72, and 96 hours.
Time tolerances can be within ± 4 hours of the target.

Note: Temperatures and times need to be monitored closely if, in addition to the correlation test, the laboratory is ensuring that the vaccines meet the WHO stability requirement (<0.5 log loss after 48 hours at 37°C).





3. Examination of VVMs

As soon as the vials are removed from the water bath, visually inspect each VVM and give it a score. Use the scale in Figure 1 on the next page to assess VVM colour change and select a score.

If the square matches the circle or is darker than the circle, the score will be 3 or higher which indicates that the VVM has reached the discard point. (In the field, the health worker would discard the vaccine when the VVM changed colour in this way.)

Calculate a mean VVM score for each temperature/time combination. After scoring the VVMs, store the vials at -70°C until the test for vaccine potency (step 4 below) is carried out.

Figure 1

VVM appearance	VVM grade
	1 - 1.5
	2 - 2.5
	3 - 3.5
	4

4. Assay of vaccine potency

- The potency test on all samples in a study should be conducted at the same time.
- The vaccines in all vials subjected to the water bath should be tested for potency, whether or not the VVM has changed.

Test the potency of the vaccine by assaying the total poliovirus content of each vial in Hep2C cells in microtitre plates, using the standard methodology described in the WHO documents named at the end of this annex and summarized below.

- 4.1 Inoculate eight replicates per dilution, and use half-log dilution steps.
- 4.2 Incubate the plates at 35°C , and stain after 7 days.
- 4.3 Read the plates. Calculate titres by probit analysis.

Assays are valid only if a concurrently tested in-house reference preparation is within specification and the fiducial limits for each individual titration are not more than $0.5 \log_{10}$.

- 4.4 For each time point (and each temperature, if temperatures in addition to 37°C are used), assay five heated vials of a batch concurrently with five vials of the same batch that have been stored continuously at -70°C .
- 4.5 Subtract the mean of the heated vials from the mean of concurrently tested unheated vials to obtain the potency change of a vaccine.

A significant potency drop is $^3 0.6 \log_{10}$ when the mean potency of the heated vials is subtracted from the mean potency of unheated vials.

Note: This assay of total poliovirus content does not provide an estimate of potency for the three serotypes present in OPV, so if potency is shown to have been reduced, it is not possible to state which of the three serotypes is out of specification.

5. Correlation of VVM discard point and vaccine potency change

Vaccine vial monitors should reach discard point just before significant vaccine potency loss occurs.

Compare VVM scores with vaccine potency in the same vials to determine whether VVMs have changed too quickly or too slowly relative to changes in the vaccine. In either event, the manufacturer should be contacted.