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Vaccine Vial Monitor– Taking a Closer Look (Part II)

This is the second in a series of two articles on Vaccine Vial monitors

Effect of Light and Water

VVMs are sensitive to light, which accelerates the same polymerization reaction as does heat in increasing the Optical Density (OD) of the indicator. Exposure to light will cause endpoint conversion earlier than otherwise would occur on the basis of its cumulative temperature exposure over time. The brighter the light and the longer its exposure, the greater the effect.

According to the manufacturer, the unreacted monomer of the VVM indicator chemical is <0.1% soluble in water at room temperature and formulated in a binder that is insoluble in water. Soaking in water seemed to decelerate the color change compared to unsoaked patches.

WHO performance specifications

There have been several performance specifications issued over the years and the latest one was published in 2006.

Price, Cost and Economics

The price of a lable is likely to be in the range of 4¢ to 8¢ (calculated in US$) per label and the overall cost of VVMs might roughly be estimated by multiplying the total number of doses of vaccine procured by UNICEF in 2007 – 3.2 billion– by the cost of a lable and then dividing by10, assuming all of them were 10 dose vials. This produces a total annual global cost estimate for VVMs from $12.8 million to $25.6 million (less the baseline cost of conventional labels). This amount compares to the total $617 million value of all vaccines that UNICEF reported it procured in 2007. This is a conservative cost estimate which ignores the relatively small numbers of vials with fewer than 10 doses.

A joint WHO-UNICEF statement published in 1999 stated that “use of VVMs do not increase immunization system costs”. It claimed major cost savings from reduction in the wastage of vaccines due to cold chain failures, due to implementation of the open vial policy and savings on the cost of cold chain equipment in temperate climates.

Performance

From a regulatory perspective, a VVM is a medical device somewhat analogous to a diagnostic test. Instead of predicting the presence of a disease or condition, the VVM is intended to indicate when a vaccine has lost potency below an arbitrary level set by its manufacturer and regulatory authority, such that it may not effectively immunize the recipient.

In assessing new diagnostic tests, they are usually compared to the best available but often tedious and expensive existing test for a disease or condition – often referred to as the “gold standard”. Error rates for the new test are often quantified in terms of false positivity, false negativity and predictive values positive and negative.

These concepts can be applied to VVMs, despite their different purpose. In this review, two new terms are used to replace false positivity and false negativity as measures of error. The first is termed “wastage error”, and the other “impotency error”. Wastage error reflects when a VVM reaches its endpoint conversion and the vial must be discarded before the associated vaccine has actually lost its potency. Theoretically, in such cases, still-good vaccine is discarded.

Impotency error represents the opposite situation when the vaccine has lost its potency through exposure to heat, but the VVM has not yet reached its endpoint to indicate that it should be discarded. In such cases, recipients of that vaccine may not be protected from disease, with subsequent risks to their health and to the community’s health.

These two types of errors vary inversely with each other and thus illustrate tradeoffs in designing and setting the target time for endpoint con-

Contents	Page

version. As the endpoint is moved to an earlier point in time, wastage goes up and impotency down. Conversely, delaying the endpoint decreases wastage but increases impotency.

There are four main aspects on which the performance of VVMs may be evaluated in order to estimate their wastage and impotency errors and the resulting consequences, both financial and human:

1. How closely do VVMs satisfy their specifications to convert around a certain target day when held at their key "sentinel" temperatures?

2. How well do VVMs match the actual stability of the vaccines on which they are applied?

3. How accurately can health workers compare the VVM indicator's optical density to its reference ring when the VVM is near or at its endpoint conversion?

4. What is the actual frequency in which vaccines are discarded in ongoing immunization programs due to VVM conversion before use?

Assessing Performance to Specifications

Straightforward, intuitive, pivotal assessment of the actual frequencies by day or other reasonably short interval on which VVMs reach endpoint conversion when maintained at each of their key sentinel temperatures (+5℃, +25℃, and + 37℃) would be of immense value. Such data would permit determination of point estimates (mean, median), measures of dispersion around them (standard deviations, confidence limits), demonstrate the Arrhenius decay and serve as a pillar for "bridging" with simpler and shorter lot release assays using potential surrogates like OD dispersion measured at a single time point.

One brief data summary was provided in 2009, describing studies of 6 lots of VVM 30s of differing ages from 2000 to 2002. Twenty samples from each lot were examined at either 22.5, 30, or 37 days for endpoint conversion at 37°C. A similar number were examined at 116, 193, and 270 days at +25℃. In these samples from the six lots, no VVMs were found to have converted before the early time and all were found to have converted by both the middle (target) time and the post-target time. The study design did not permit determination of mean days until conversion and confidence limits around such point estimates.

Assessing VVM Matching to Vaccine Stability

This is most intuitively illustrated and understood by simply graphing the mean time until endpoint or loss of potency for both the VVM and the associated vaccine, for a given temperature. When the vaccine curve is higher than the VVM curve, the vertical distance between the two lines represents potential premature conversion of the VVM and thus a source of wastage error. When the vaccine curve lies below the VVM curve, as in the extrapolations of the VVM lines at extremely high temperatures, the vertical distance reflects potential delayed conversion, and thus impotency error.

Vaccine manufactures themselves select from among the available VVMs the best type to purchase for their products. Since the most "heat-stable" of the available labels is the VVM30, significant wastage error can occur for vaccines with substantially greater longevity. The primary complaint was that VVMs do not reflect the actual [higher] stabilities of some of their vaccines, particularly at some temperatures.

For example, one manufacturer reported a product requiring a VVM2 because of its 37℃ stability, but at +5℃ it r etains potency for 3+ years, and is assigned a shelf life of 3 years after filling. However, as VVM2s are targeted at that temperature to "expire" at 225 days, this would result in significant wastage when properly-stored and still-potent vaccines are discarded more than 2 years before product expiration because of the VVM color change.

This apparent mismatch is found in some hepatitis B vaccines (HBV) at 37℃ and their VVM30s, which convert on or bef ore one month at that temperature. But stabilities at +37℃ from 2 to 7 months are reported for some unidentified HBV products, substantially longer than the life time of VVM30.

Assessing Accuracy of User Readability

Another potential source of wastage and impotency error in day to day use of VVMs is the degree of accuracy by which human beings actually can correctly read and interpret the VVM. Unlike densitometers used in bench assessments, human vision may have trouble distinguishing the darkness of the central indicator square and the reference ring of the VVM when the VVM is approaching endpoint.

VVM specifications describe a simple "observer perception test" to assess how well end-users can accurately read them to determine endpoint conversion. But this test only requires distinguishing between VVMs at their original day-zero OD, at an OD midway to conversion, and a converted OD. A more realistic assessment would test human perception when the OD of the indicator inner square approaches and even exceeds the OD of the reference outer circle.

In a pre-licensure study of user accuracy, a US company used a densitometer to determine the actual indicator ODs of 12 VVMs at various stages from 0.35 OD units (well-before expiration) to 0.50 (beyond expiration). A sample of 30 employees – 15 female and 15 male – were asked to judge whether or not the 12 indicators had expired.

The results have shown false-positive rates from 7% to 33% in judging not to use the product, when indeed it was still OK by densitometer measurement. The false negative rates ranged from 17% to 47%, depending on how far beyond endpoint the central indicator color had darkened.

Experience from the Field

Over a decade has passed since the gradual introduction and now universal use of VVMs procured by UNICEF for the EPI.
In 1997, WHO published a study of comparing OPV wastage between two consecutive rounds of national immunization days in 34 health centers in 12 volunteering provinces in Turkey, where the second round adopted the open vial policy with VVMs. Vaccine wastage decreased substantially in the second round.

Compiled by Dr. Madhava Gunasekera of the Epidemiology Unit

Source-Preliminary Review of Vaccine Vial Monitors available from

*www.who.int/entity/immunization_delivery/TLAC-Report_**2009**-03.pdf*

Table 1: Vaccine-preventable Diseases & AFP

18st – 24th August 2012 (34thWeek)

Disease	No. of Cases by Province									Number of cases during current week in 2012	Number of cases during same week in 2011	Total number of cases to date in 2012	Total number of cases to date in 2011	Difference between the number of cases to date in 2012 & 2011
	W	C	S	N	E	NW	NC	U	Sab					
Acute Flaccid Paralysis	00	00	00	00	00	00	00	00	01	01	00	52	60	- 13.3 %
Diphtheria	00	00	00	00	00	00	00	00	00		-		-	-
Measles	00	00	00	00	00	02	00	00	00	02	02	38	100	- 62.0 %
Tetanus	00	00	00	00	00	00	00	00	00	00	01	08	16	- 50.0 %
Whooping Cough	00	00	00	00	00	00	00	00	00	00	02	62	27	+ 129.6 %
Tuberculosis	42	00	13	16	15	19	13	00	24	142	313	5905	6088	- 03.0 %

Table 2: Newly Introduced Notifiable Disease

18st – 24th August 2012 (34thWeek)

Disease	No. of Cases by Province									Number of cases during current week in 2012	Number of cases during same week in 2011	Total number of cases to date in 2012	Total number of cases to date in 2011	Difference between the number of cases to date in 2012 & 2011
	W	C	S	N	E	NW	NC	U	Sab					
Chickenpox	10	10	06	02	09	08	02	02	07	56	43	3070	2953	+ 04.0 %
Meningitis	02 CB=2	03 KD=2 ML=1	00	03 VU=3	00	01 KR=1	00	00	01 KG=1	10	19	503	583	- 13.7 %
Mumps	10	13	05	00	09	07	06	04	10	64	71	3269	2134	+ 53.16 %
Leishmaniasis	00	03 ML=3	25 MT=2 HB=23	00	00	00	12 AP=6 PO=3	00	00	40	29	674	507	- 32.9 %

Key to Table 1 & 2

Provinces: **W**: Western, **C**: Central, **S**: Southern, **N**: North, **E**: East, **NC**: North Central, **NW**: North Western, **U**: Uva, **Sab**: Sabaragamuwa.

DPDHS Divisions: **CB**: Colombo, **GM**: Gampaha, **KL**: Kalutara, **KD**: Kandy, **ML**: Matale, **NE**: Nuwara Eliya, **GL**: Galle, **HB**: Hambantota, **MT**: Matara, **JF**: Jaffna, **KN**: Killinochchi, **MN**: Mannar, **VA**: Vavuniya, **MU**: Mullaitivu, **BT**: Batticaloa, **AM**: Ampara, **TR**: Trincomalee, **KM**: Kalmunai, **KR**: Kurunegala, **PU**: Puttalam, **AP**: Anuradhapura, **PO**: Polonnaruwa, **BD**: Badulla, **MO**: Moneragala, **RP**: Ratnapura, **KG**: Kegalle.

Data Sources:

Weekly Return of Communicable Diseases: Diphtheria, Measles, Tetanus, Whooping Cough, Chickenpox, Meningitis, Mumps.

Special Surveillance: Acute Flaccid Paralysis.

Leishmaniasis is notifiable only after the General Circular No: 02/102/2008 issued on 23 September 2008.

Dengue Prevention and Control Health Messages

Thoroughly clean the water collecting tanks bird baths, vases and other utensils once a week to prevent dengue mosquito breeding .

Table 4: Selected notifiable diseases reported by Medical Officers of Health

18st – 24th August 2012 (34thWeek)

DPDHS Division	Dengue Fever / DHF*		Dysentery		Encephalitis		Enteric Fever		Food Poisoning		Leptospirosis		Typhus Fever		Viral Hepatitis		Human Rabies		Returns Received
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	%
Colombo	152	6707	1	96	0	8	5	141	0	31	3	125	0	3	0	80	0	3	**69**
Gampaha	73	5294	1	62	0	10	0	43	0	23	1	157	0	15	0	226	0	0	**47**
Kalutara	25	1809	1	68	0	2	3	31	0	26	0	161	0	3	1	26	0	2	**54**
Kandy	55	1756	2	77	1	2	1	17	0	54	0	51	2	89	2	53	0	0	**74**
Matale	21	360	1	65	0	5	0	8	0	7	1	32	0	3	1	32	0	0	**58**
Nuwara	5	245	4	140	0	3	0	21	0	8	2	30	1	52	0	16	0	1	**62**
Galle	34	1109	1	90	0	6	0	10	0	17	4	90	7	48	0	2	0	0	**68**
Hambantota	13	411	0	26	0	2	0	5	0	25	1	62	2	36	0	14	0	0	**67**
Matara	26	1124	0	49	0	8	0	15	0	19	1	102	4	59	1	85	0	0	**82**
Jaffna	7	314	7	131	0	13	9	290	1	69	0	2	1	250	0	11	0	0	**83**
Kilinochchi	1	63	1	10	0	2	0	27	0	40	0	4	0	29	0	4	0	1	**50**
Mannar	0	118	0	49	0	4	0	21	0	14	0	18	0	42	0	2	0	0	**40**
Vavuniya	6	48	2	22	0	21	2	8	0	15	1	18	0	2	0	1	0	0	**100**
Mullaitivu	0	17	0	11	0	1	0	6	0	2	0	3	0	5	0	0	0	0	**25**
Batticaloa	2	595	6	145	0	2	0	14	0	304	0	8	0	0	0	6	0	4	**64**
Ampara	0	104	1	64	0	2	0	5	0	8	1	23	0	0	0	2	0	0	**43**
Trincomalee	1	121	1	117	0	2	0	16	1	9	0	36	0	14	0	4	0	0	**58**
Kurunegala	46	1615	3	127	0	14	1	75	1	33	2	114	1	23	1	106	1	4	**73**
Puttalam	46	743	3	36	0	6	0	10	0	1	4	26	0	13	0	3	0	1	**58**
Anuradhapu	8	250	2	52	0	6	0	11	0	16	0	71	0	21	1	50	0	1	**42**
Polonnaruw	4	173	0	34	0	0	0	2	0	1	0	42	0	2	0	34	0	1	**29**
Badulla	4	244	2	87	0	3	0	45	0	3	0	31	3	79	0	34	0	0	**71**
Monaragala	3	184	0	48	0	4	0	17	0	7	1	55	1	63	5	147	0	2	**45**
Ratnapura	57	2665	1	154	0	25	1	42	0	11	4	213	1	33	2	82	0	1	**72**
Kegalle	58	2063	0	45	0	9	1	20	0	10	3	137	1	46	18	417	0	0	**91**
Kalmune	0	170	1	192	0	1	0	5	0	76	0	2	0	0	0	7	0	3	**38**
SRI LANKA	**647**	**28302**	**41**	**1997**	**01**	**161**	**23**	**905**	**03**	**829**	**29**	**1613**	**24**	**930**	**32**	**1444**	**01**	**24**	**63**

Source: Weekly Returns of Communicable Diseases WRCD).
***Dengue Fever / DHF** refers to Dengue Fever / Dengue Haemorrhagic Fever.
****Timely** refers to returns received on or before 27thAugust, 2012 Total number of reporting units 329. Number of reporting units data provided for the current week: 209
A = Cases reported during the current week. **B** = Cumulative cases for the year.

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Comments and contributions for publication in the WER Sri Lanka are welcome. However, the editor reserves the right to accept or reject items for publication. All correspondence should be mailed to The Editor, WER Sri Lanka, Epidemiological Unit, P.O. Box 1567, Colombo or sent by E-mail to **chepid@sltnet.lk.**

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