



**WORLD HEALTH ORGANIZATION
DEPT: IMMUNIZATIONS, VACCINES AND BIOLOGICALS**

**TECHNOLOGIES & LOGISTICS ADVISORY COMMITTEE
(TLAC)**

3 - 4 September 2008

Meeting report and recommendations

1	Introduction and background	1
2	Meeting agenda for policy and information	1
3	Use of vaccines out of the cold chain (OCC)	2
4	Revision of the multi-dose vial policy (MDVP)	7
5	Vaccine vial monitors (VVMs)	10
6	Update on jet injectors.....	10
7	Administrative issues	11

1 Introduction and background

The first meeting of the [Technologies and Logistics Advisory Committee \(TLAC\)](#) was held at World Health Organization (WHO) Headquarters in Geneva on 3-4 September 2008. TLAC represents the most recent component of WHO's policymaking apparatus for vaccines and immunization, as set forth by the [Strategic Plan 2006-2009](#) from its [Immunization, Vaccines and Biologicals Programme](#), its [Global Immunization Vision and Strategy 2006-2015](#), and [other policy statements](#).

TLAC Members present:

Dr B.G. Weniger (chair)
Prof J. Colton
Mr. R Davis
Dr S. Deeks
Prof G. Hammond
Mr M. Munck
Ms D. Phillips
Dr Piyanit T.
Mr S. Spanner
Mr R. Steinglass

Dr Thomas Cherian, on behalf of the Director: Immunizations, Vaccines and Biologicals (IVB), opened the meeting of the TLAC, welcoming and thanking the TLAC committee members for their commitment to serve on this advisory committee.

Dr Rudi Eggers, WHO/IVB staff member, described the Terms of Reference and the planned *modus operandi* of the TLAC, as well as its relationship to other related bodies such as the [TechNet e-forum](#) and community, the [Vaccine Presentation and Packaging Advisory Group \(VPPAG\)](#), and [Project Optimize](#). The remit of TLAC is to advise the IVB Director on gaps and constraints and recommend strategies and policies regarding field operations, logistics, cold chain systems, and technological innovations to help strengthen immunization programmes and facilitate new vaccine introduction. WHO expects that 80% of TLAC recommendations would be at the level of programme operations and implementation and would be made directly to the Director: IVB, while broader strategic recommendations might comprise 20% and would be presented to the WHO [Strategic Advisory Group of Experts \(SAGE\)](#) for endorsement.

Additional informational briefings provided the committee members an overview of WHO's policymaking infrastructure for vaccines and immunization. These included a presentation by Dr Phillipe Duclos, IVB staff member, on other vaccine and immunization-related advisory bodies in WHO, and the interactions of these and TLAC with the SAGE.

2 Meeting agenda for policy and information

Two major policy matters were put before the committee for consideration: One was the use of vaccines out of the cold chain (OCC) and the advantages, risks, and research plans for changes to such practice. The other was the revision of the multi-dose vial policy (MDVP) of

WHO for handling vaccines after their primary containers are opened, and potential changes thereto. In a further informational session, the TLAC was updated on progress in the field of needle-free jet injectors.

In this document, the sections below entitled "Presentations" are a summary of information provided to the TLAC, for which any statements and conclusions therein do not necessarily reflect the official views of the TLAC itself.

3 Use of vaccines out of the cold chain (OCC)

3.1 Presentations by WHO and others to the committee

Mr Michel Zaffran, WHO/IVB staff member and leader of the new Project Optimize, opened discussion on the potential use of vaccines out of the cold chain (OCC) by presenting an overview of the challenges, benefits, and risks involved in such an innovation. Project Optimize, a collaboration between WHO and PATH (Seattle, USA), was established to develop and propose a long-term vision in cold chain and health logistics and to work in partnership with industry and lower- and middle-income countries to generate necessary evidence, build consensus, and promote mechanisms and policies on optimal health logistics and technologies.

Mr. Zaffran indicated that some reasons for pursuing the possibility of using selected vaccines OCC include:

- To protect more children living beyond the geographic reach of the existing cold chain
- To be able to administer birth doses on time
- To reduce/eliminate the risk of freezing within the cold chain
- To limit the need to increase cold storage and transport volumes for new, future vaccines
- To limit the growth in cooling energy and its related carbon burden

With the expected heat stability of newer vaccines, and the availability of VVMs for nearly all vaccines pre-qualified by WHO and procured by UNICEF, developing and applying a new, formal policy on OCC is a potential means to overcome these challenges.

Project Optimize proposes to focus initially on Hepatitis B vaccine (HBV) as a pioneer antigen to define the regulatory and programmatic pathway for approvals of an OCC strategy for this vaccine, which may then serve as an example for other vaccines to follow.

WHO staff member Dr Modibo Dicko reviewed for TLAC the status of VVMs, showing their different stages to indicate heat exposure. Four different versions of VVMs are currently in use – named VVM2, VVM7, VVM14, and VVM30 according to the number of days when kept at +37° C at which they reach their visual endpoint indicating the associated vaccine should be discarded. The thermostability of the vaccine determines which VVM should be applied to it. For example, very heat-sensitive oral polio vaccine (OPV) is assigned a VVM2 for discard after only 2 days at +37° C. The first VVMs were introduced on OPV vials in 1996, resulting in a recommendation by the TechNet meeting in 1998 that all vaccines should have a VVM as soon as possible. WHO and UNICEF issued statements to promote their use in 1999 and again in 2007. In 2008, almost all WHO-prequalified and UNICEF-procured vaccines are supplied with VVMs.

Dr Dicko pointed out that only one company in the world ([TempTime Corporation](#)) now manufactures VVMs. It has a production capacity of 7 billion units per year, and offers a price to vaccine manufacturers (approximately US\$0.05 per vial label), which provides little economic incentive for other manufacturers to try to enter this market.

Dr Dicko reported that WHO works with the remaining vaccine manufacturers of WHO-pre-qualified vaccines who do not apply VVMs, and those about to be qualified, to encourage their use. VVMs constitute a vaccine management tool that can help decrease vaccine wastage,

identify cold chain problems, facilitate outreach, and increase access. In pilot studies using cool water packs (as opposed to frozen ice packs) in cold-boxes to prevent inadvertent vaccine freezing, VVMs have allowed for greater confidence in the potency of the vaccine. He explained that correct usage of VVMs by health workers varies by world region. To illustrate this point, he cited Vaccine Management Assessments conducted in several countries which indicated an average "correct knowledge of VVM" score of 70% in the African Region and 40% in the Eastern Mediterranean Region.^{1,2} (VVMs are not used in the Americas, per Pan American Health Organization policy).

Ms Anne McArthur, of PATH, reviewed eight studies in the literature (references were available at the meeting) and summarized experience with use of vaccines OCC. Four of these studies were conducted with plasma-derived HBV, three with recombinant HBV, and one was of conjugated meningococcal serotype C vaccine. All studies found no significant serological differences in the immune responses between those vaccinated by products kept in the cold chain and comparable vaccines handled OCC, indicating that both were protective. One study showed higher seroconversion for the vaccine kept OCC; it was postulated that the comparator kept in the cold chain may have suffered freeze damage and consequent loss of potency. Ms McArthur reported that reactogenicity did not appear to be altered by handling OCC. She indicated that plasma-derived HBV products are sufficiently thermostable to enable their use OCC, which may increase coverage especially in rural and hard-to-reach areas. But VVMs would be critical tools to accompany any such use OCC.

Dr Carmelia Basri, staff member of the Indonesian Ministry of Health, described the pioneering experience of the national immunization programme in Indonesia with vaccine usage OCC, which began in 1996 upon the advent of VVMs. The Indonesian rationale for use of VVMs and OCC was because of a highly-dispersed rural population, a home birth-delivery rate of >80%, a non-existent cold chain beyond the health centre (sub-district) level, and medium-to-high hepatitis B endemicity with a high proportion resulting from vertical transmission at birth. She pointed out that the single-dose, prefilled, non-reusable injection device known as the [Uniject™](#) also helped make possible the use of HBV OCC by village-based midwives and vaccinators in the field.

Dr. Basri said that the lessons learned in Indonesia include fundamental changes in vaccine handling policy that demand much time to institute and are accompanied by the reluctance of health workers to trust vaccine potency when transported and stored OCC. The Indonesian Technical Advisory Group finally became supportive of OCC use after several conclusive studies. She stated that Indonesia confirmed the critical importance of accurate reading of VVMs by health workers as a prerequisite for promoting OCC use.

In the final presentation, Dr Morag Ferguson of the National Institute for Biological Standards and Control (NIBSC) in the United Kingdom, outlined a proposed way forward for HBV as a pathfinder for OCC usage. HBV was chosen because (1) it is very susceptible to freezing damage, (2) is very heat-stable, (3) guidelines already exist for its use out of the cold chain.³ (4) its frequency of on-time delivery at birth is low (reported as 7% in one study in China⁴), and (5) all HBV products currently supplied through UNICEF now have VVM30s applied.

Dr Ferguson described a proposed collaborative study with HBV vaccines from six manufacturers to correlate hepatitis B vaccine potency and VVM status, and to test potency at +45° C for 7 days and its impact on shelf life and antigenicity. The study would be overseen by experts from four National Regulatory Authorities (NRAs). She outlined particular steps to be taken as follows:

Step 1. Constitute the *ad hoc* NRA advisory group (agreements have already been reached among NRA collaborators at NIBSC in the UK, Paul Ehrlich Institute in Germany [also

¹ [Vaccine Management Assessment \(WHO/IVB/05.02\)](#)

² [WHO-UNICEF: Effective Vaccine Store Management Initiative \(WHO/IVB/04.16-20\)](#)

³ [Preventing Mother-to-Child Transmission of Hepatitis B: Operational Field Guidelines for Delivery of the Birth Dose of Hepatitis B Vaccine \(2006\)](#)

⁴ Wang L, Li J, Chen H, Li F, Armstrong GL, Nelson C, Za W, Shapiro CN. Hepatitis B vaccination of newborn infants in rural China: Evaluation of a village-based, out-of-the cold-chain delivery strategy. [Bull World Health Org. September 2007;85\(9\):649-732.](#)

representing the EMEA], the KFDA in South Korea, and the Division of Biological Products in Thailand, following an April 2008 meeting in Seoul and a subsequent meeting in August 2008 on hepatitis B vaccine potency testing in Bangkok.

- Step 2. Agreement of relevant manufacturers for data sharing (in-principle agreements have been obtained by all manufacturers to take part in this study -- Berna/Crucell [Switzerland], Serum Institute of India, Biofarma [Indonesia], Panacea [India], Shantha [India], and LG [South Korea]).
- Step 3. Approve a study protocol, including contracting with the research laboratory and biostatistician (targeted to start by the end of December 2008).
- Step 4. Request samples from manufacturers to send the required number of samples as indicated by the target protocol (by the end of December 2008).
- Step 5. Commence study (by the end of February 2009 for 6-12 months).
- Step 6. Analysis of results by the *ad hoc* NRA Advisory Group as data become available to provide a framework for discussion at the meeting of the Expert Committee on Biological Standardization and to propose a plan for implementation.
- Step 7. Support manufacturers to seek license variances by making the data available to manufacturers to request a license variance from their respective NRA.
- Step 8. Issue a global recommendation, outlining which products meet the criteria and indicating the accepted procedure for OCC use of these products. The WHO prequalification team would need to assure oversight of ongoing stability testing if needed.

Dr Ferguson indicated that project implementation is challenged by the fact that there is no standard potency assay for all recombinant hepatitis B vaccines. The Auszyme[®] test kit used historically for this purpose is no longer available. Specifications validated by the relevant NRA for regulatory release of a batch differ for each product, and are based on a product-specific reference [assay] which is traceable to the batch(es) used in its clinical trial. Moreover, in 2005, a licensed combination vaccine with a hepatitis B component was removed from the market because it was found that vaccine recipients poorly seroconverted to the hepatitis B antigen.^{5,6,7} This problem had not been detected by its routine batch release potency assay performed by the national control laboratory. Such *in vitro* potency assays are generally used only as a measure of consistency of production. Although potency relative to its reference assay and thus acceptability for release can be determined for each product, there is no single standard against which potency measures can be compared across products.

3.2 Discussion by TLAC of OCC practice and policy

The following points were raised and discussed by TLAC members and WHO staff and others participating in the meeting, or in subsequent follow-up electronic communications and telephone conferencing.

Some vaccines currently labelled for typical storage at +2° to +8° C might potentially be labelled for storage in certain circumstances at higher temperature ranges if their actual thermostabilities were carefully studied and determined. This might greatly reduce the challenges of the cold chain and limitations on immunization practice. Were manufacturers to lack incentives, or otherwise be unwilling to pursue the necessary regulatory review of such OCC changes to their vaccine labels, future OCC recommendations might perforce remain “off label”.

Most of the prior OCC field studies cited were of plasma-derived hepatitis B vaccines, and some caution is indicated before assuming applicability of their findings to newer recombinant hepatitis B vaccines.

⁵ European Medicines Agency Press Office. European Medicines Agency recommends suspension of Hexavac, 20 September 2005 ([EMEA/297369/2005](#)).

⁶ European Medicines Agency Press Office. Questions and Answers on the suspension of Hexavac, 20 September 2005 ([EMEA/304888/2005](#)).

⁷ Giambi C, Bella A, Barale A, et al. A cohort study to evaluate persistence of hepatitis B immunogenicity after administration of hexavalent vaccines. [BMC Infect Dis. 2008; 8: 100.](#)

Although OCC usage of hepatitis B vaccine may seem straightforward and uncomplicated when used for a limited application (such as a birth dose in remote areas), there may be unintended programmatic consequences when used more broadly in immunization programmes. Thorough thought and analysis of the positive and negative effect on programmes by such changes are needed before issuing recommendations to change current practice and policy to effect widespread OCC use.

The presenters were requested to share with TLAC members more detailed criteria and data used in selecting hepatitis B vaccine as the pathfinder. Another potential "pathfinder" vaccine mentioned for possible studies of its use OCC was tetanus toxoid (TT) which could prevent tetanus, particularly in countries in Africa where a hepatitis B birthdose is not yet part of the immunization schedule. However, there exist less data available on OCC use of TT than for HBV. WHO staff reported that pre-qualified manufacturers of TT were not currently interested in pursuing a label change for OCC use for TT.

VVMs are a key technology enabling the use of vaccines OCC. Several concerns and questions were raised about them as follows:

- a. As the product of a single manufacturer for the global market, a fire or industrial accident in a VVM manufacturing facility, or an ownership transition due to death or takeover, could threaten global VVM supplies.
- b. There appears to be a lack of control by WHO and UNICEF over usage of VVMs on vaccines not part of their pre-qualification and procurement systems. Since some immunization programs have both WHO pre-qualified/UNICEF-procured and private-market vaccines in their cold chains, health workers might incorrectly assume that all VVMs are alike, when in fact some on non-prequalified vaccines may not meet the WHO standards for selection of VVM version (e.g., VVM2, VVM7, VVM14, VVM30), accuracy, reliability, or location on the packaging.
- c. It appears the only review for efficacy and safety of this technology is that provided by the vaccine pre-qualification system at WHO and perhaps by PATH. The history of any prior independent review of this technology and approval by a respected NRA would be of interest.
- d. PAHO has opted out of the use of VVMs, preventing global application of policies dependent on this technology. TLAC requests formal briefing by PAHO to explain its rationale for this decision, and under what circumstances it would consider revision of its position on VVMs.

In pursuing the OCC strategy for HBVs, the committee felt that consideration should be given to restoring the commercial or investigational availability of the Auszyme® HBV assay, or a replacement, in order to apply and validate a standard assay against which multiple products in clinical trials could be compared directly by laboratories independent of the vaccine manufacturers.

TLAC formed a sub-group on OCC policy to more thoroughly consider the OCC issues, to monitor the proposed research described above, and to formulate formal recommendations for consideration by the plenary TLAC. The OCC sub-group point person is Dr Shelley Deeks (designated on conference call of 13 October, switching a different initial assignment). Other OCC sub-group TLAC members are Mr Søren Spanner, Ms Dianne Phillips, Mr Mogens Munck, and *ex officio* the TLAC chair, Dr Bruce G. Weniger. A WHO staff member will be designated to assist the sub-group administratively and logistically (subsequently identified as Dr. Modibo Dicko). All other TLAC members and key WHO staff will be welcome but not required to participate in sub-group discussions.

3.3 Preliminary TLAC Recommendations on OCC pending sub-group deliberations

1. Once thorough and careful documentation exists for the scientific basis and programmatic consequences of moving thermostable vaccines out of the cold chain (OCC), there would be a strong rationale and high priority to do so at the peripheral level for transport and administration to vaccine recipients. This might help overcome the limitations of volume capacity by reserving space in the cold chain for thermosensitive antigens. It might enhance outreach programs to remote areas beyond the geographic extent of refrigeration equipment. It might reduce the risk of damage to vaccines inadvertently frozen within the cold chain. Ideally, all vaccines will someday be sufficiently thermostable to avoid the cold chain completely between their manufacture and their administration to the recipient.
2. TLAC generally supports the concept of additional bench, clinical, and programmatic [field feasibility] studies that would be needed to justify new OCC recommendations. However, the committee requests copies of the specific detailed protocols and other methodologic documentation for the proposed collaborative HBV vaccine potency and related OCC studies described in section 3.1 above before it would consider endorsing the suitability of any particular studies as a basis for future OCC recommendations.
3. TLAC appreciates background documents provided,⁸ but in addition requests the WHO Secretariat to furnish the committee with compilations of existing potency and stability data, and to be updated with new data that arise, relevant to identifying specific vaccines for future OCC recommendations among those currently in use or considered for future use in the Expanded Programme on Immunization (EPI).
 - Most useful would be comparative data in tabular matrix form to permit side-by-side comparisons among candidate vaccines for OCC.
 - TLAC also welcomes reports evaluating programmatic aspects, successes, failures, and lessons learned from the past field trials of OCC, which may require documentation from or interviews with investigators and participating health workers from past studies.
4. There is no presumption that a future OCC recommendation for a particular vaccine type and brand could be applied generically among competing brands of a particular vaccine type (e.g., all plasma-derived hepatitis B vaccines [HBV], or all recombinant HBV). In the absence of a scientific basis for such generic performance, each vaccine formulation will need independent justification for OCC by relevant studies.
5. Notwithstanding the above caveats, various HBVs currently have the most stability and clinical/field data from the Southeast Asia and Western Pacific regions towards justifying OCC, and should be the first focus of an OCC initiative. Some data suggest tetanus toxoid vaccines are also a promising candidate for OCC in the African region and elsewhere, and should be studied preliminarily for OCC.
6. Alternative or complementary approaches to OCC for meeting the challenge of an overburdened cold chain might also be pursued:
 - Collaboration of immunization programs with Essential Drugs programs on sharing cold chain space and other complementarities
 - New or expanded use of existing technologies for improving thermostability
 - Improvement in programmatic efficiencies

⁸ Temperature Sensitivity of Vaccines ([WHO/IVB/06.10](http://www.who.int/ivb/06.10))

4 Revision of the multi-dose vial policy (MDVP)

4.1 Presentations to the committee

Mr Soulemane Kone, WHO staff member, reported on the current status and the experience with the current multi-dose vial policy (MDVP) of WHO/UNICEF from 2000,⁹ which applied to the liquid vaccines available at that time. The current MDVP allows for opened vials of vaccines shipped and stored as liquids to be kept in the cold chain for up to 4 weeks if certain storage conditions are maintained (expiry date not passed; stored in cold chain; vial septum not submerged in water; aseptic technique used to withdraw prior doses, VVM -- if attached -- has not reached discard point). However, lyophilized vaccines are to be discarded 6 hours after reconstitution with diluent, or at the end of the vaccination session, whichever comes first.

Mr Kone pointed out that the MDVP is a simple message for health workers, for which understanding and implementation are not difficult. An example of the MDVP impact was seen in Tunisia, where despite greatly increased provision of primary health care (PHC) from 1986 to 2007, and despite falling birth rates, no increase in DPT consumption was seen. This avoidance of wastage was attributed both to changing from 20-dose to 10-dose vials and, since 2005, to the MDVP. Experience from many countries has shown that it takes many years to effectively implement the MDVP at the periphery; for this reason a revision needs to be as comprehensive as possible.

Mr Kone explained that challenges to relevance and application of the MDVP are increasing. VVMs are absent on vaccines in some middle income countries, some world regions, and in countries that procure vaccines themselves. Inadequate cold chain at service delivery may create a problem of storing opened vials for reuse. Some service providers perceive the reuse of opened vials of liquid vaccine as being "poor quality" service. Vaccine product inserts are not uniform regarding MDVP and often give contrary information. Different vaccines of the same type may have different instructions for use. Misunderstandings continue, such as applying the MDVP to some newer liquid vaccines, even though the 2000 policy was not designed to deal with them. New vaccines often come in single or low multi-dose vials (1 to 5 doses), some containing reduced or no preservative. New combinations are being produced, including both liquid-liquid and lyophilized-liquid combinations in which the liquid component may contain preservative. Thus, the relatively simple instruction to discard re-constituted vaccine after 6 hours, and to keep liquid vaccines for up to 4 weeks has become confusing and potentially wasteful or dangerous. Mr Kone indicated a great need to update and clarify the MDVP message, while somehow maintaining its simplicity, continuity, and universality.

Mr Darin Zehring of PATH pointed out additional problems with the current MDVP in regard to dose sparing and intradermal delivery of vaccines. Some new liquid vaccine production processes eliminate the need for anti-microbial/preservatives during production. Conversely, certain liquid vaccines do not contain nutrients that would support microbial growth (as opposed to lyophilized vaccines, i.e. measles). With dose-sparing, nominal single dose vials (almost always without preservatives) become, in effect, multi-dose vials when used for intradermal delivery, for example. Future MDVP modification will in some cases help influence manufacturer decisions on vaccine presentation (e.g., shifting to single-dose vials to allow for both full IM or reduced-dose ID delivery – without preservative – if a valid MDVP was formulated to cover this scenario). Thus, any new MDVP should take into account alternative routes of delivery and the potential use of liquid, single-dose vials of vaccine, without preservative, that may be labeled or recommended for dual indications of both ID delivery and standard target tissue and dose.

WHO Staffer Dr. Nora Dellapiane described the implementation and challenges to the current MDVP: Liquid vaccines with or without a label VVM may be kept for ongoing use provided cold

⁹ WHO Policy Statement: The use of opened multi-dose vials of vaccine in subsequent immunization sessions ([WHO/V&B/00.09](http://www.who.int/vaccines/bulletin/00.09)).

chain and sterility criteria are met. But lyophilized (freeze-dried) vaccines with or without a VVM on the cap must be discarded at the end of the immunization session. In revising the current MDVP, two distinct situations must be considered:

- A safety hazard arises when vaccines that are not adequately preserved are kept for 4 weeks because they happen to be liquid formulations. This may occur when:
 - multi-dose liquid vaccines contain reduced amounts of thiomersal;
 - alternative preservatives are used that may not meet the requirements of the MDVP;
 - no preservative is contained in some novel vaccines, like 2-dose vials of pneumococcal and human papilloma virus in liquid formulations; or
 - the intradermal route is adopted, rendering single-dose vials into *de facto* 5-dose ones.
- Unnecessary wastage may occur when a freeze-dried vaccine is reconstituted with a liquid vaccine that contains adequate antimicrobial preservative for both antigens. Current MDVP would require discarding after 6 hours, even if a much longer period were justified. For example:
 - A DTP-HBV+Hib combination vaccine is formulated with its freeze-dried component (Hib) to be reconstituted with a liquid DTP-HBV component containing suitable preservative in adequate amounts to protect the entire reconstituted combination for several weeks.

Dr Dellapiane suggested a possible method to indicate the longevity of opened vaccine vials would be to control and vary the placement of the VVM. For example, regardless of whether the vaccine is liquid or freeze-dried, a VVM on the cap might signify a vaccine that should be discarded after 6 hours, whereas a VVM on the vial itself would signify a vaccine that could be kept for subsequent sessions.

4.2 Discussion by TLAC of MDVP issues

The following points were raised and discussed by TLAC members and WHO staff and others participating in the meeting, or in subsequent follow-up electronic communications and telephone conferencing.

TLAC agreed that the wave of new vaccines entering immunization programs and the various new ways they are being formulated and packaged has rendered the 2000 MDVP nearly obsolete and potentially wasteful and/or dangerous.

Several caveats were raised about the proposal that the location of the VVM on the vaccine vial carry a secondary meaning for how long doses within an opened vaccine vial may be administered to patients:

- Neither WHO nor UNICEF appear to control the potential use and placement of VVMs on private sector vaccines that may enter a health center's vaccine formulary side-by-side with WHO-pre-qualified vaccines. Nor does any NRA appear to regulate VVMs on vaccine vials. Uncontrolled, unregulated placement could result in patient harm or vaccine wastage were the position of the VVM on the vial to be attributed such significance inappropriately by the health worker.
- VVMs were developed, designed, and validated for a specific purpose – to indicate when exposure to temperatures over time relative to the vaccine's thermostability characteristics have rendered it unsuitable for use. VVMs were not designed to indicate whether bacterial contamination and overgrowth have rendered a vaccine unsafe, nor for how long an opened vial may be used safely. Trying to add such separate meanings to the location of the VVM on vaccine vials may lead to confusion, particularly

for newer combination vaccines shipped with components in separate vials for mixing by the end-user before administration.

- Without a mandate that every vaccine have a VVM, it becomes impractical to recommend vaccine handling according to placement of a VVM which may be entirely absent.

The committee considered that separate icons or symbols might be created, trademarked, and controlled by WHO and/or UNICEF specifically to indicate proper longevity of the vaccine after opening, and to encourage the time or date of opening to be recorded on the vial.

Clarification was sought on the time limitations in the current MDVP, which states that liquid vaccines could be kept "for 4 weeks" if cold chain and sterility requirements are met. Earlier versions of the MDVP indicated the open vaccine could be used "until the next vaccine delivery arrived." This earlier policy was considered too open-ended, prompting introduction and rationale of the 28-day limit in the current MDVP. Looking forward, it was suggested that, with supporting data, opened vaccines might be labeled for longer or shorter longevities than the 6 hours and 28 days of the existing MDVP.

Compliance with current policy is not known, and the characteristics of future vaccines are unclear. Before TLAC considers a change to the MDVP, a document should be prepared to discuss the ramifications and issues regarding all existing and likely future EPI vaccines which may qualify for MDVP.

During the discussion it became evident that there were three characteristics of any vaccine that needed to be distinguished and addressed separately:

- Exposure to inappropriate elevated temperatures over time - this is covered by VVMs (an additional "freeze-VVM" would be helpful for freeze-sensitive products)
- Quality assurance - the status as a WHO-pre-qualified vaccine is not indicated in any way on the vials (e.g., similar to a quality mark on food products, or a CE mark on medical devices). The presence of such a mark could avoid mistaken application of an MDVP to unsuitable products. The mark might consist of a copyrighted or trademarked variation of the square-in-circle shape of the current VVM. Any future MDVP might specifically indicate its applicability only to vaccines thus marked.
- Ability to keep - the resistance of the opened vial to microbial overgrowth or to entry of other contaminants that might harm patients (e.g., pieces of the stopper released by excessive needle entries). Current MDVP advises how long an opened vaccine may be kept solely according to its liquid vs. lyophilized formulation, which may be inapplicable for newer vaccines and formulations.

TLAC members agreed that the existing MDVP is rapidly becoming obsolete. Specific suggested changes to it, along with their ramifications and consequences, should be more precisely compiled, organized, and presented to the TLAC sub-group or plenary session for future deliberation. TLAC formed a sub-group on MDVP to more thoroughly consider its issues and ramifications, and to formulate formal recommendations for consideration by the plenary TLAC. The sub-group point person is Mr Robert Steinglass (designated on conference call of 13 October, switching a different initial assignment). Other sub-group TLAC members are Prof Jonathan Colton, Mr Robert Davis, and *ex officio* TLAC chair, Dr Bruce G. Weniger. WHO staff will be designated to assist the sub-group administratively and logistically (subsequently identified as Souleymane Kone and Drew Meek). All other TLAC members and key WHO staff will be welcome but not required to participate in sub-group discussions.

4.3 Preliminary TLAC Recommendations on MDVP pending sub-group deliberations

1. Existing policy of WHO on the proper handling of multi-dose vials after opening is rapidly becoming obsolete. The WHO Secretariat should undertake or commission a more

thorough review of the issues, problems, and various possible solutions in updating the policy, and present them to the TLAC sub-group for further deliberation and then TLAC plenary action.

5 Vaccine vial monitors (VVMs)

Existing and contemplated recommendations by WHO and its partners for OCC and MDVP rely heavily on the validity, accuracy, and regulation of the revolutionary technology of temperature-and-time exposure indicators known as "vaccine vial monitors" (VVMs). These are chemical and ink imprints on vaccine vial labels designed to change colour to indicate to health workers which vaccines have (and have not) experienced exposures to temperature and time that would affect their potency and thus provide reduced or no disease protection to their recipients.

Given this key role for VVMs, TLAC members indicated that they would like to review the scientific data relating to the efficacy, validity, and regulatory status of VVM technology and the underlying fundamental research methods and results. TLAC member Prof Colton was designated to serve as point person to gather and organize for member review the necessary technical information – published or proprietary, confidential or otherwise – about VVMs from its manufacturer, from the scientific literature, from any National Regulatory Authorities (NRAs) which may have registered/licensed this technology as a medical device or combination biological/device product, and from the WHO vaccine/device prequalification program upon which many NRAs rely.

5.1 Recommendations on VVMs

1. Vaccine Vial Monitors (VVMs) represent a potential "insurance policy" or "failsafe" mechanism relevant to both OCC and MDVP implementation or revision. Therefore:
 - For the existing VVM2, VVM7, VVM14, and VVM30 versions, TLAC requests copies of documentation illustrating the individual data points and frequencies for each replicate in VVM validation studies for the exact temperatures studied and the exact days when the replicate VVM labels were deemed to change colour to indicate their endpoints (this would be the underlying, empirical data which gave rise to the fitted, straight-line estimates shown to the committee in a figure labelled "Current TTI Categories – Feb 2006").
 - TLAC requests data on the effect on VVM performance when the VVM label is frozen, wetted, or otherwise stressed or abused.
 - TLAC requests a definitive briefing on the regulatory history and status of any licensure/registration by recognized and respected NRAs of VVMs as medical devices applied to vaccine vials and thus duly regulated as a "combination" medical device/biological product.
2. A VVM-type freeze indicator should be explored and pursued.
3. As newer vaccine products become available, new VVMs that match the specific vaccine's thermostability characteristics should be developed.

6 Update on jet injectors

The session on jet injectors was for information purposes only to provide an update on the progress of this technology. No policy recommendations were sought.

Mr. Darin Zehrung, representing PATH, provided an overview of the jet injector technology, outlining the basic functioning and types of jet injectors. He provided a brief history from its beginnings in the 19th century to the withdrawal of jet injectors due to the fear of cross contamination. Subsequently, disposable technology has been developed that prevents cross contamination, making it again a feasible delivery technology. Various models of cartridge type jet injectors were shown and their pros and cons outlined.

In a second presentation, he also described to the committee a new initiative funded by the Bill and Melinda Gates Foundation to research, develop, and evaluate a new generation of safer, disposable-syringe jet injectors (DSJIs) and their potential to overcome the dangers and drawbacks of the needle-syringe in routine and special immunization programs in developing countries. This PATH project also includes a focus on the DSJI potential for easier and dose-sparing intradermal (ID) delivery.

7 Administrative issues

The committee also suggested modifications in meeting format and committee function, listed in no specific order:

- TLAC materials (e.g., agenda, background documents, and PowerPoint presentation slides) should be distributed to members at least two weeks before any meeting.
- In "deliberation" sessions where TLAC members are expected to formulate a collective recommendation, time should be allocated for members to formulate their positions; opinion from non-member attendees should be reserved until the appropriate time later in the discussion. Always welcome, of course, would be prompt correction of factual errors and responses to information requests. Except in rare cases to protect confidential information, it is expected that all TLAC sessions would be open to WHO staff and other observers. In "information" sessions, full discussion by all participants would be welcomed.
- The TLAC chair should be permitted to designate different members as session moderators, so as to reduce the administrative burden on the chair.
- Between face-to-face TLAC meetings in Geneva and plenary telephone conference calls, the TLAC sub-groups should take the initiative in investigating and preparing agenda topics (in conjunction with the WHO staff point persons), and presenting them to the plenary TLAC.
- A secure, password-protected website should be created by WHO for sharing among TLAC members of background materials, drafts of TLAC reports, and other information.
- To assure "committee memory", the length of second terms for initial TLAC members, or the terms of replacements, might be shortened to stagger membership rotations. Also to the same end, a position of *emeritus* member might be considered.
- TLAC should interface with the [Safe Injection Global Network \(SIGN\)](#), including sending a TLAC member representative to its annual meeting.

The next TLAC face-to-face meeting will be held in Geneva on 10-12 March 2009. Between face-to-face plenary meetings, the TLAC sub-groups and its VVM review process will confer by email exchanges and teleconferencing.

TLAC members were informed of the WHO TechNet Consultation to be held in Tunisia from 2 - 4 December 2008. The TLAC chair requested TLAC member Mr Robert Steinglass to represent TLAC at this meeting, which he consented to do, and for which WHO concurred.

--- 000 ---