



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

**TECHNOLOGIES & LOGISTICS ADVISORY  
COMMITTEE (TLAC)  
22 - 23 September 2009**

TLAC Members present: Dr B.G. Weniger (chair) Dr O. Benes 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
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**Meeting report and recommendations**

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## **Opening and introduction**

The third meeting of the Technologies and Logistics Advisory Committee (TLAC)<sup>a</sup> was held at World Health Organization (WHO) Headquarters in Geneva on 22-23 September 2009. Eleven TLAC members and approximately 35 observers and presenters from WHO Headquarters, WHO Regional Offices, UNICEF Headquarters, UNICEF Supply Division, PATH, and industry were present.

Dr Jean-Marie Okwo-Bele, the Director of Immunizations, Vaccines and Biologicals (IVB), opened the meeting by welcoming and thanking the TLAC committee members for their commitment to serve on this advisory committee. The Director explained the IVB plans to discontinue TLAC after the current meeting and to replace it with a future advisory body with a wider scope of work, looking at immunization practices broader than but including the focus of TLAC in technology and logistics.

## **Feedback from the SAGE Meetings in April 2009 and June 2009**

Dr Rudi Eggers summarized the meeting in Geneva in April and June 2009 of the [Strategic Advisory Group of Experts \(SAGE\)](#). The meeting included reports from the WHO regions and the other advisory committees formed by IVB, as well as presentations and discussion on polio eradication, immunization schedules, and policy regarding vaccines for H5N1 influenza virus, human papillomavirus (HPV), measles, rotavirus, and hepatitis B. An extraordinary SAGE meeting took place on July 7, 2009 that focused on potential role of vaccines in mitigating pandemic to reduce morbidity and mortality, to protect the integrity of the health care system and the country's critical infrastructure, to reduce the transmission of the pandemic virus within community. SAGE made recommendations on the deployment of pandemic A (H1N1) vaccine by advising countries to immunize health care workers as a first priority (1-2% of population), and then by stepwise approach to vaccinate particular groups in priority order based on individual country-specific conditions.

## **Use of vaccines out of the cold chain (OCC)**

The session objectives were to review OCC subgroup activities and discussions since the March 2009 TLAC meeting, to discuss the "cool chain" concept paper and proposed research agenda for storing vaccines in suitable domestic refrigerators and/or at controlled ambient temperatures higher than the standard +2°C to +8°C range, to be updated about ongoing WHO-sponsored studies of hepatitis B vaccines at higher temperatures, to inform TLAC of WHO plans for new OCC terminology and future consideration of OCC programmatic issues, and for TLAC to consider and promulgate its findings, conclusions, and/or recommendations on OCC.

### **1.1 Moving to a "cool chain"**

Mr Søren Spanner and Mr. Mogens Munck delivered a joint presentation and led the discussion on moving to a "Cool Chain" at service delivery levels.

#### ***1.1.1 Use of domestic refrigerators at the Healthcare Centre Level***

Mr Spanner suggested the use of conventional, inexpensive, domestic refrigerators pre-set to higher temperatures -- well away from freezing -- to store vaccines, say +5°C to +15°C. Such a range may be used at the healthcare facility level to reduce freeze damage and expand capacity of the cold chain. Such refrigerators should be modified to switch off the cooling of the refrigerator compartment when the temperature drops to +5°C and to switch on the cooling mechanism at no warmer than +15°C, in contrast to the usual + 2°C to + 8°C cycling

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a. [http://www.who.int/immunization\\_delivery/systems\\_policy/tlac/en/](http://www.who.int/immunization_delivery/systems_policy/tlac/en/).

range in specialized cold-chain refrigerators. The modification should prevent the end-user from adjusting the refrigerator section any colder, as this may result in freeze damage.

Such refrigerators have two doors, one for the freezer compartment above and one for the refrigeration compartment below. The freezer section can be used for freezing ice packs for lyophilized vaccines and for transporting OPV, as well as for storing the OPV itself. The refrigerator section that is set to cycle between +5°C and +15°C could be used for freeze-sensitive vaccines and for making cool [water] packs to transport these vaccines. The water packs could also be made in existing ice-lined, cold-chain refrigerators.

The introduction of new vaccines and the use of cool packs to prevent freezing during transport requires major and difficult expansion of the existing cold chain which would require up to a ten-fold increase in storage capacity. This alternative method could help achieve that expansion in an economical way. The cost of specialized ice-lined refrigerators (ILRs) is between €500 and €2,900 for typical 200 litre capacities). The cost of the domestic refrigerator units proposed, including both refrigeration section and freezer, would be approximately €300.

The use of upright refrigerators has an additional advantage over the chest type, as it is much easier to keep the vaccines neatly stored and to have an easy overview of the stock.

### ***1.1.2 Use of cool rooms at healthcare facility level***

Mr Mogens Munck presented a proposal to address the storage needs for the growing availability and introduction of new and improved vaccines which pose huge challenges to existing immunization programs to find space for them within their already-full cold chains of cold rooms, freezers, refrigerators, and cold boxes. New paradigms and strategies are needed to overcome these limitations. The proposal envisions "relaxing" the cold chain at the peripheral health level to store most vaccines "Out of the Cold Chain (OCC)" for short periods in "cool rooms".

His draft document presented multi-faceted initiatives to help reduce this shortage of refrigeration capacity through research and expected policy changes. A key rationale is that the stability of most vaccines is such that they may safely be kept at +20°C to +25°C for up to one month without significant loss of potency.

The proposed cool rooms are walk-in rooms with thick, strong, well-insulated, shaded walls, ceilings, and floors, but with neither whole-room refrigeration equipment outside of them, nor traditional refrigerators or freezers within them. Instead, one or two conventional air conditioners of about 1000-watt size each may be installed. Such cool rooms would be much less costly than typical refrigerated cold rooms, perhaps by half or even less.

Mr Munck believed that such cool rooms will at low cost provide not only sufficient hold-over time, but also safe and secure vaccine storage. In his experience, many health centre buildings are currently in a poor state of repair, and these solid cool rooms could provide good shelter, and in addition give protection against theft, which is important with increasingly expensive vaccines. Many health centres currently lack secure storage for their vaccines and medicines, which a properly-locked cool room could provide.

Health centres without sufficient building space for establishing an indoor cool room might build a separate one outside. These are available at reasonable cost in prefabricated modules, which most workers can erect on-site after a demonstration. These cool rooms could be large enough to store vaccines as well other essential medicines at health centres with a monthly delivery schedule. Filling unneeded volume in the cool room with water or eutectic salt packs can create a "cool sink" to maintain hold-over temperatures, even when electricity to the air conditioners is interrupted.

### **1.1.3 Use of eutectic packs to avoid freezing**

Eutectic salt solutions are a mix of salts and water designed to freeze and melt at positive temperatures above 0°C. Mr Munck proposed that greater use be made of these in both the existing cold chain and suggested cool chain, in order to reduce the risks of freezing adjacent vaccines.

Eutectic packs can be frozen/solidified in refrigerators, because temperatures of 0°C and lower are not required. Commercial eutectics packs are available, but are expensive. He said that inexpensive "Glaubers" salts, containing fly ash, can be made on site or under contract, and thus reduce costs, which are mainly for the labour of mixing and filling.

### **1.1.4 TLAC Findings, Conclusions, and Recommendations on the "Cool Chain"**

1. Cool Chain: The "Cool Chain" concept proposals should be pursued with appropriate discussion, debate, research, and demonstration projects by WHO, as well as other stakeholders in the global immunization community.
2. Pilot projects: Pilot projects, as detailed in a separate draft document, should be undertaken in various countries. These should be conducted according to carefully written protocols and under the guidance of a designated project director. Reports on the results of the projects should be used to persuade national regulatory agencies to approve relaxation of the present temperature storage indications for specific vaccines. WHO has valuable experience in conducting these kinds of pilot projects. Well-known examples include the "WHO cool water pack study" and the "WHO/PATH cold chain study".
3. These pilot projects should ideally:
  - Demonstrate the technical feasibility of keeping vaccines cool at the higher temperature ranges of the proposed cool rooms (+20°C to +25°C) and domestic refrigerators (+5°C to +15°C).
  - Identify training needs with regard to moving to cool chain at Health Centre level.
  - Lead to the design of various and appropriate strategies for implementing relaxation of the present temperature range in a country.
  - Identify alternative practical approaches to handle vaccines in a cool chain, such as packing in cold boxes and vaccine carriers, the use of cool water and eutectic packs, storage in refrigerators and cool rooms etc. The most appropriate approaches should be identified.
4. Training: Significant attention should be paid to training to accompany the cool chain implementation:
  - Design training curricula using the experience gained from conducting field pilot projects.
  - Prepare educational materials for both participants and trainers.
  - Obtain financial support from donors, such as the GAVI Alliance, international and bilateral agencies, etc. GAVI is already supporting the introduction of new vaccines by providing GAVI Introduction Grants.
  - Conduct courses using professional trainers, avoiding very inefficient cascade training (students at one level become trainers at the next lower level).
5. Eutectics: A range of commercial and non-commercial eutectics are available, and most have already been evaluated by UNICEF and/or PATH. TLAC recommends identification of the most appropriate eutectic cold-pack materials in regard to cost and performance for use in immunization programs.
6. Communication plan: A communications plan should be developed for each of the pilot elements and for overall changes in practice they may demonstrate.

## 1.2 Hepatitis B studies at higher temperatures

### 1.2.1 Feedback from visit by TLAC/OCC subgroup leader to NIBSC

Dr Shelley Deeks reported on her visit in May 2009 to the National Institute for Biological Standards and Control (NIBSC) in London with the objective to familiarize TLAC with laboratory aspects of the hepatitis B vaccine study being conducted by Dr Morag Ferguson. According to earlier written materials about the study, its public health importance was clear: intending for its data to be provided to manufacturers for them to request a temperature variance for storage and transport out of the cold chain for a limited period. In Dr Deeks' opinion, it remained to be seen whether the data obtained from this study will be sufficient to conclude the matter, or whether further studies will be needed.

She found that there existed no detailed protocol for the study, although vaccine samples had already been shipped and received (including some that were at the end of their shelf life or already expired) from six manufacturers. She also learned that the project's stage 1 work was about to begin [vaccine/VVM incubations began in June, 2009]. An agreement had been reached to prepare a detailed summary to include logistics and an analysis plan, including the total number of data points at each temperature for each assay, the use of blinded investigators, and the continued involvement of Dr Ferguson after her pending retirement.

No data currently existed regarding at what temperature/time exposure Hepatitis B vaccine denatures, although it was said that data from the field suggested that vaccine that had been heated to  $>+60^{\circ}\text{C}$  did not lose full potency. Consequently, it was believed that the vaccines in this study would not denature at the intended temperatures to be studied. Dr Deeks pointed out that if potency loss of the vaccines at high ambient temperatures did not follow an Arrhenius equation [nor correspond with that describing VVM conversion], then VVMs might not predict vaccine potency.

All vials within a manufacturer's production lot were assumed to be equivalent -- this was stated as standard practice in such studies. As vaccines remain potent beyond their shelf life, Dr Ferguson indicated that time delays prior to expiry should not impact potency, and thus recently-expired vaccines were not excluded from the study. Such variation between lots and manufacturers in the age of their vaccines lots tested was a cause of concern for Dr Deeks.

Dr Deeks was uncertain about the criteria that the manufacturers used to select their vaccine lots for the study and about the potential for bias this may have introduced. Also, the reasons why vaccines at different stages of their shelf lives (including some already expired) were [to be] used in the study remained unclear and is a potential confounder and source of complication for interpreting study results. It was uncertain how the binary outcomes for VVMs (converted or not) would be related to the non-binary, continuous outcomes of potency measurements.

After the visit in London, Dr Deeks and Dr Piyani prepared a template listing key study components, details, and parameters from an epidemiologic perspective that should be prepared by the investigators and provided, along with preliminary results, to the study's National Regulatory Authority (NRA) Advisory Group and to any future advisory committee reviewing it.

### Discussion

Mr Davis asked how many vaccines were being studied, and their status. Dr. Milstien replied that a total of six WHO-prequalified hepatitis B vaccines were in the study, five of which were available internationally for purchase through the UNICEF system (among eight listed hepatitis B vaccines in all), and one of which was used (out of the cold chain) only in its country of manufacture.

### **1.2.2 Update on OCC protocol, advisory group, interim results and status of studies of hepatitis B vaccines at NIBSC**

Dr Julie Milstien presented an update on the *in-vitro* potency studies on hepatitis B vaccines. She stated the objectives of this study were to determine whether six different prequalified, recombinant, monovalent hepatitis B vaccines follow Arrhenius kinetics at temperatures up to +45°C, and whether the loss in potency for these vaccines correlates with the colour change of their VVM30.

According to Dr Milstien, the six vaccines (one of which is already licensed for out-of-the-cold-chain use in its country of manufacture) were being studied in this first stage. In the first quarter of 2009, five of the six manufacturers shipped to NIBSC vials from three lots (batches) of their product, selected across its entire dating period (one manufacturer provided only a single lot, which had already reached its expiration date). Three vials of each of the 16 lots (and their attached VVM-equipped labels) were held at +37°C and +45°C. The VVMs on the labels were examined daily by human visual inspection until all [three] VVMs on the vials of each lot in the +45°C water bath had darkened to endpoint. At that time, all [six] vials of that lot at both temperatures were immediately transferred to storage at +2°C to +8°C until potency assays could be performed. The observed times until the VVMs on the vaccine vials reached endpoint at +45°C ranged from 5 to 9 days.

Separately, an unspecified number of "naïve" VVMs shipped frozen to NIBSC from their manufacturer, the Temptime Corporation, were also incubated at +37°C and +45°C for ten days and measured daily by densitometer for time until endpoint conversion. These fresh, unattached VVMs yielded a reproducible conversion time around 9 days.

After incubation, samples were tested using three different potency tests (Murex HBsAg version 3, a modified GSK inhibition assay, and the Abbott Auszyme), along with control vaccine stored at +2°C to +8°C, as well as vaccine frozen at -20°C to serve as negative controls for the assays on the assumption such freezing would destroy potency.

Of the three potency tests used, only one was able to differentiate frozen vaccine as non-potent, as well as to provide consistent results for the test samples. The vaccine supplied in only a single lot by the one manufacturer producing it for out-of-cold-chain use was found non-potent even though stored upon arrival at +2° to +8°C and never incubated. Its results are being excluded from analysis. Dr Milstien stated that their preliminary results indicated that the lots are not losing their potency after heat exposure and that the VVM can thus show when vaccine is no longer utilizable, with a built-in margin of safety.

She indicated that final results from this stage 1 of the study would be ready in three months, requiring one month to finish the testing of the samples, one month for statistical review, and one month to convene the study's Advisory Group to review the data. Because of the range of test kits used, some of which were not necessarily validated for each vaccine, she proposed that the next stage 2 of the project go ahead so that the vaccines would be tested by their own manufacturers using the assay kits specifically validated for them.

Dr Milstien finished by discussing various questions and issues for future consideration about the overall study, including (1) whether vaccines with less than a specified potency at +45°C should progress to *in vivo* assays in the study's stage 2; (2) whether vaccines with "acceptable" *in vitro* results should progress to *in vivo* mice immunogenicity studies, even with wide confidence intervals; (3) whether products and processes of a manufacturer whose product is found to be sub-potent in its validated tests should be re-evaluated in regard to prequalification; (4) whether the underlying OCC strategy being pursued should be abandoned if any of the monovalent hepatitis B vaccines at high ambient temperatures is found sub-potent on *in vitro* assay, because the public sector treats them all as generic and an OCC policy must apply to all; (5) in such case, would mouse immunogenicity studies better demonstrate "functionality" of the vaccine; (6) whether TLAC agrees that the NRA Advisory Group should make such determinations.

## Contemporaneous discussion

TLAC asked about the “standard procedures” for “such kinds of testing” that were mentioned in Dr Milstien’s report which might explain the specific methods used in the study and whether TLAC could be provided with them. Dr Milstien replied that these standard operating procedures (SOPs) used at NIBSC were based on [general] requirements elaborated by the WHO Expert Committee on Biological Standardization (ECBS), as well as the instructions from the manufacturers that came with each kit for how to conduct each potency assay. There would be no one place one could find them, she said.

Concern was raised that two of the three assays were unable to demonstrate loss of potency from vaccines frozen to serve as negative controls with presumed zero potency. Dr Zaffran acknowledged that no one had been aware that freezing would not destroy potency in these *in vitro* assays. Dr Steve Wiersma commented that while freezing may disassociate the antigen from the alum adjuvant on which it is adsorbed, the vaccine may still test “potent” by a particular assay, even if it is no longer immunogenic in people. He suggested that a better negative control for such a study would have been to boil the vaccine in order to fully denature its antigen.

Other questions were raised about the difficulty in interpreting and comparing results because vaccines tested came from batches with different expiry dates, some early in their dating period, some late, and some already expired. The wide confidence limits of such testing were raised, particularly for future *in vivo* studies, with the suggestion that increasing sample sizes might help narrow them.

Another issue raised was that in the absence of a full and complete protocol, the methods and results provided to date were still insufficient to interpret and draw conclusions about results, much less to respond to the questions Dr Milstien formally posed to TLAC. There were discrepancies among and between written documents, verbal descriptions, and PowerPoint® presentations about the work provided to TLAC.<sup>b, c, d</sup>

In the discussion, it was pointed out that the fundamental purpose of the OCC studies should be to determine whether a vaccine kept out-of-cold-chain at elevated temperatures for which its VVM has not yet converted would still be potent to use. For that reason, it was suggested that the time point when potency assays should be performed should be determined only after studying a much larger sample of VVMs and selecting the time, at any given temperature, when 97.5% -- or nearly all of them -- have converted. It was suggested that it makes no sense to study potency at 8 days, say, on the basis of observing conversions of only two or three VVMs, if due to variation in color darkening and health worker interpretation there will be a number of VVMs at 9 days indicating that it is still okay to use the vaccine. Another day of incubation before performing potency assays might be added as a margin of safety.

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b. For example, previous documents furnished TLAC summarizing the study indicated either 4 or 6 vials of each vaccine would be examined at each temperature (e.g., 3-page document “A” dated 21 January 2009 entitled “*Outline study protocol to assess the potency of hepatitis B vaccines following storage at +37° and 45°C*” [n=4, page 1]), and 15-page document “B” distributed for this September 2009 meeting entitled “*Vaccines Out of the Cold Chain (OCC) – studies on prequalified monovalent recombinant hepatitis B vaccines*” [n=6, page 5]. But the verbal presentation to TLAC on 21 September and a 3-page results document “C” also provided at the meeting (entitled “*Optimize study vaccines – exposure to +37° and +45°C at NIBSC, Morag Ferguson, Updated 11 August 2009*”) reported only 3 vials of each had been held at +45°C and examined daily (except weekends) by visual (eye) inspection for endpoint conversion.

c. Another ambiguity was whether the incubations at elevated temperatures were aborted for each vaccine type after “any” of the VVMs on their labels converted (as stated on page 5 of Document B), or only when “all” had done so (as stated to TLAC around 48:00 minutes into the OCC discussion [cf. *TLAC3-Day1-LS100010.wma* recording]).

d. Document A (page 8) indicated that VVM readings were performed on weekdays only during the incubations, not daily [no Saturdays and Sundays], although Figures 1 and 2 of “naive” VVMs (page 7) illustrated 11 days of consecutive data.

TLAC was requested to use the succeeding weeks to provide feedback to the WHO Secretariat about the OCC studies and the questions posed by Dr Milstien. A few TLAC members expressed support for proceeding to the *in vivo* potency assays in mice as proposed in the OCC strategy as stage 2.

### Post-meeting discussion and feedback

In response to the request for subsequent feedback, TLAC members commented on the OCC study design and work presented to date in subsequent communications among them. It was stated that two temperatures alone (+37°C and +45°C) are insufficient for the OCC studies to "demonstrate Arrhenius kinetics" of biological degradation at the elevated temperatures under consideration. A minimum of three is technically required (to demonstrate a straight line on semi-logarithmic *shelf life plot*). Five are desirable according to a leading expert in this field who consulted for TLAC at its March 2009 meeting, Prof Ted Labuza.<sup>e</sup> If +45°C is the expected peak temperature to which OCC vaccines might be exposed (for which a TLAC member expressed some doubt from field experience in Yemen and elsewhere), a higher temperature should be studied as well (e.g., +50°C). This would permit interpolation to verify that the vaccine potency will indeed degrade as predicted if exposed to, say, +46°C.

The daily intervals at which the VVMs were examined for the stage 1 results reported to date (excluding intervening weekends when no observations were made) were too infrequent for the rapid endpoint conversions at such elevated temperatures. With observed endpoint conversions ranging from 5 to 9 days, the results may be unreliable because of such gaps in observation (e.g., endpoints detected on a Monday might actually have occurred more than 2½ days earlier). These might have been performed every 12 hours, or even 8 hours, including Saturdays and Sundays, in order to more reliably establish the corresponding incubation time point for potency assays to be performed.

Technical and scientific oversight: According to a telephone conversation by the TLAC chair with Dr Michael Pfeleiderer in the summer of 2009, the NRA Advisory Group for the OCC studies<sup>f</sup> referred to by Dr Milstien had never had a face-to-face meeting of its members, nor a teleconference call. He reported its communications were solely by email. No report or minutes of its deliberations, nor copies of its e-mail correspondence and discussions, had ever been provided to TLAC or its OCC subgroup, even after TLAC's Dr Deeks and Dr Piyanit were formally joined to this Advisory Group in March 2009. The level of oversight should be reviewed and an appropriate level assured.

Given the issues raised concerning the findings from *in vitro* potency testing already completed, and the predicted wide confidence limits in planned "stage 2" *in vivo* studies in mice, there is a question whether the results are likely to lead to strong enough evidence to persuade vaccine manufacturers to invest in similar research, to allow NRAs to approve label indications for storage at such elevated temperatures, or to justify a major change in WHO recommendations for OCC practice for hepatitis B. Uncertainties will remain for the relevance at such high temperatures of *in vitro* and *in vivo* hepatitis B potency assays, which may never have been validated for same. The results of clinical trials of immune response among volunteers receiving hepatitis B vaccines stored at various elevated temperatures would provide the most convincing evidence.

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e. Labuza T. *Application of chemical kinetics to deterioration of foods*. J Chem Educ 1984;61(4):348-358.

f. As reported to TLAC at its March 2008 meeting, the NRA Advisory Group for the OCC study was comprised by Dr Michael Pfeleiderer of the Paul Ehrlich Institute, Germany, and Chair of the Vaccine Working Party of the Committee for Human Proprietary Medicines of the European Medicines Agency; Ms Teeranart Jivapaisarnpong, Director of the Division of Biological Products of the Thailand NRA, and Dr Sang Ja Ban, Director of the Viral Vaccines Department of the Biologics Headquarters of the South Korea NRA.

### **1.2.3 TLAC Findings, Conclusions, and Recommendations on OCC for Hepatitis B**

#### **Background**

It is recognized that one of the main constraints for lower-income countries to achieve immunization targets is maintaining the cold chain. Some studies suggest an out-of-the-cold-chain (OCC) strategy for heat-stable vaccines may have the potential for increasing immunization coverage by allowing short-term transport of these vaccines OCC. This strategy also may avoid problems of freezing which have been increasingly recognized as a problem threatening the potency of certain freeze-sensitive vaccines. Cold chains also are challenged by increasing numbers of vaccines that must be stored despite limited refrigeration capacity.

Criteria were developed and presented to the Technologies and Logistics Advisory Committee (TLAC) to assist in identifying other suitable candidate vaccines among those used in the Expanded Programme on Immunization (EPI) to be taken out of the cold chain.

Alternative or complementary approaches to the OCC strategy for meeting the challenge of an overburdened cold chain might also be pursued, including the following:

- Collaboration of immunization programs with the Essential Drugs programs on sharing of cold chain space and other complementarities;
- New or expanded use of existing technologies for improving thermostability;
- Improvements in programmatic efficiencies; and
- Consideration of other options such as a "cool chain" (see separate recommendations)

The WHO-sponsored study on hepatitis B vaccines for the OCC strategy takes advantage of the important ability of vaccine vial monitors (VVMs) to monitor for excessive heat exposure when vaccines are taken out of the cold chain. The study is examining the potency of six different recombinant monovalent hepatitis B vaccines at the elevated temperatures of +37°C and +45°C after relatively short periods of time before one or more of their attached VVM30 time-temperature integrators changes colour.

Data on vaccine stability at elevated temperatures could have public health importance in contributing to an evidence base on which national regulatory authorities might approve manufacturer requests for storage and transport of specific vaccines out of the cold chain for limited periods. This would allow flexibility from the rigid +2°C to +8°C cold chain requirements. Whether the specific study design and its resulting data will be sufficient for this purpose, or whether additional studies will be needed, remains to be seen.

This study was presented and discussed at TLAC meetings in September 2008, and in March and September 2009. In addition, two TLAC/OCC subgroup members, Dr Piyanit Tharmaphornpilas and Dr Shelley Deeks, were invited at the March 2009 TLAC meeting to join the separate NRA Advisory Group for this study (although neither prior nor subsequent face-to-face meetings nor teleconferences of this group had ever occurred through mid-September 2009).

Preliminary summaries of study results were shared with TLAC. Dr Morag Ferguson, the study coordinator, prepared a brief protocol of the study (Document "B", footnote b), which was provided to TLAC at the September 2009 meeting. It had been hoped that there would also have been a teleconference of the Advisory Group prior to the September 2009 TLAC meeting; unfortunately, this never occurred. However, Dr Milstien stated that the NRA Advisory Group of this Hepatitis B study will meet to review the results as they become available and make recommendations at study completion. These results should also be presented to an independent outside advisory body such as TLAC.

#### **Lessons Learned**

One challenge faced by TLAC was that a position designated for a member with expertise in regulatory affairs and science remained vacant for the 13 months of TLAC's existence. This

made essential but difficult the education of TLAC members on the application, interpretation, and significance of potency assays for the OCC study strategy.

WHO-sponsored studies on which global immunization program policies, recommendations, and practices might be based should proceed only after the development and independent review of a comprehensive protocol. Each study protocol and process should include detailed methodological and statistical considerations. Where possible, such studies should follow current Good Laboratory Practice (GLP) or Good Clinical Practice (GCP) guidelines. These include identifying a "Study Director" to have overall responsibility for the nature, design, quality, and implementation of the study worldwide, as well as designated "Principal Investigators" at each study location.

Further, WHO should continue to engage independent, multi-disciplinary, and subject-qualified advisory groups to review protocols for such studies. Such groups should meet regularly during key stages of protocol design and study analysis to provide technical oversight and advice. Both of these processes would help ensure scientific rigor and credibility of results.

### **Recommendations**

1. TLAC is supportive of pursuing a potential strategy for taking specified thermostable vaccines out of the cold chain for limited periods of time at the peripheral level for transport and administration to vaccine recipients. A limited number of field studies to date support such a strategy. However, such a strategy will require further careful documentation of its scientific basis, including carefully-designed laboratory, clinical, and operational field studies, when appropriate, as well as consideration of programmatic consequences.
2. TLAC believes the most promising candidates for such OCC studies are vaccines for hepatitis B, tetanus, and human papillomavirus (HPV).
3. Future OCC recommendations should be based upon scientific evidence from studies of all generally available brands of a particular vaccine type in the EPI (e.g., all recombinant hepatitis B vaccines). UNICEF does not generally permit purchasers to specify vaccine by brand, and thus multiple products may be found in any national inventory. The inability of any one vaccine to retain potency out of the cold chain should therefore preclude an OCC recommendation for all brands of that vaccine type, to avoid health worker confusion and medical errors in applying OCC to inappropriate products.
4. Technology and programmatic gaps should be identified in pursuing OCC strategies, including the use of single, standard potency assays against which multiple products can be compared. Because of uncertainties in relying on hepatitis B potency assays for significant changes in immunization practice, serious consideration should be given to early human trials as the most definitive and convincing evidence to justify an OCC strategy.
5. VVMs should be affixed to all vaccines taken out of the cold chain under an OCC strategy.
6. WHO should encourage further research, development, and implementation of freeze monitors that could be applied directly to vials (or less desirably in each secondary carton) of freeze-sensitive vaccines [*similar cross-recommendation with OCC subgroup, section 1.9*].

### **1.3 Selecting a new term for 'OCC' work**

Mr Steve McCarney from Project Optimize presented a proposed new terminology for "OCC". WHO and Project Optimize realized that the term "Out of the Cold Chain" was problematic in describing the work currently pursued by these organizations and reviewed by TLAC. "OCC"

appeared to contradict current training messages and vaccine storage guidelines and was prone to misinterpretation.

Using a TechNet (<http://www.technet21.org>) discussion entitled "What's in a name?", the immunization community was solicited for other terms to better represent the storage and transport of vaccines outside of the standard +2°C to +8°C range. Numerous terms were suggested (listed alphabetically here):

- Briefcase vaccines,
- Controlled air conditioned storage,
- Controlled ambience limited time,
- Controlled ambient temperature storage,
- Controlled room temperature,
- Controlled temperature storage and transportation,
- Cool chain or Cool,
- Easy cold chain,
- Fast chain,
- Flexible cold chain or Flex chain,
- Heat flexible vaccine storage and transport system,
- Higher temperature storage,
- Hold chain,
- Life chain,
- Out of cold chain,
- RT (room temperature) stable,
- Safe chain,
- Storage temperature below and above +2/8° C range,
- Storage temperature limit,
- Thermostable vaccines,
- Thermolabile vaccines,
- Vaccine control chain,
- Vaccine temperature limit,
- Warm chain

Mr McCarney reviewed various definitions used by pharmacopeia and other public bodies dealing with the storage of temperature-sensitive pharmaceutical products. He indicated that temperature ranges presently used in the pharmaceutical industry and by perishable cargo transporters could be adapted to support a single term that could replace "OCC".

As a result of the process, Project Optimize and WHO proposed that the replacement term for OCC be "Controlled Temperature Chain (CTC)".

## Discussion

TLAC members discussed this new term and suggested several others, as well. One idea put forth and supported by several members was that the term might be qualified to specify the specific temperature range that it implied (e.g., "CTC/8-25"). This would allow better clarity and accuracy in communications. Indeed, the existing "cold chain" could in such new format be termed "CTC/2-8". Others favoured maintaining the term "cold chain" for the current standard storage temperatures. "CTC" would thus be applied only to conditions where vaccines were kept at temperatures above the +2 - +8°C range.

There was support to try to align the new WHO/Project Optimize terminology with existing industry standards. TLAC did not specifically endorse the new "controlled temperature chain" term. It suggested that the OCC subgroup could consider it in the weeks after the meeting, if desired.

## 1.4 WHO plans for future programmatic issues regarding OCC

Dr Modibo Dicko presented plans for how WHO might consider programmatic issues regarding OCC (to be renamed CTC). He mentioned the suggestion from a prior TLAC discussion to establish a working group to help countries prepare for OCC vaccine use once adopted by relevant bodies in WHO such as SAGE and ECBS. Such a working group would aim to better understand, define and provide guidance on the practical implementation activities and guidelines for alternate storage temperature for vaccines. This would include the advantages, risks, financial implications, and communication strategies. The outcome would be draft operational guidelines for implementation at country level.

The proposed working group will consider the following:

- The vaccines and segments of the vaccine supply chain in which alternate temperature storage could be used;
- Temperature boundaries for storing and transporting vaccines and the role of VVMs;
- Operational and financial implications, such as cost of managing multiple temperature supply chains vs. benefit of increased coverage of some vaccines;

- The criteria for establishing an additional component of the cold chain with relaxed temperature standards;
- The training plan for managers and health workers at all levels of the vaccine supply chain for OCC implementation;
- The communication and information-sharing strategies needed for various audiences, such as (a) industry, (b) regulatory authorities, (c) medical community and health workers at country level, and (d) users of immunization services for successful implementation of CTC; and
- The plan for policy introduction (guideline materials, etc.) in countries, once approved by SAGE and/or ECBS.

Dr Dicko stated the working group would meet on an *ad hoc* basis, primarily through tele/videoconferencing and virtual online meetings. Minutes, reports, and conclusions would be shared with WHO and relevant stakeholders. Project Optimize will house the secretariat of the working group and cover its operating costs (e.g., communications, report printing, face-to-face meetings, if any) for 2010, at which time the arrangement will be revisited.

## Discussion

The discussion focused primarily on how the new group's input would be translated into agreed practices and policies. The original intention had been to constitute this group as a formal sub-group within TLAC. With TLAC's dissolution, it thus would be created elsewhere within WHO, along with a new advisory body.

### **Revision of the multi-dose vial policy (MDVP) and related topics**

The objectives of this session were to review MDVP subgroup activities and discussions since the March 2009 TLAC meeting, to brief and update TLAC on the "three strands" of the effort to update WHO policy regarding when to discard opened multi-dose vials, and to consider and promulgate TLAC findings, conclusions, and/or recommendations on this subject.

Dr Rudi Eggers presented a brief overview of the progress made in the revision of the MDVP, highlighting the three questions that have to be addressed to achieve the revision. These are how one can assure ...:

- That health workers know which vaccines can be kept for subsequent sessions and which vaccines should be discarded at the end of the session (*visual cue*);
- That vaccine manufacturers, regulators, and the pre-qualification group at WHO have a common understanding of the preferred and critical characteristics of vaccines in the EPI (*preferred presentation*); and
- That there is scientific justification to support the new policy (*evidence base*).

These three areas were discussed in further detail in the specific topic sessions. Dr Eggers predicted that the revised MDVP will ultimately form one part of a broader WHO vaccine handling policy.

## **1.5 Development of a visual cue in the use of a revised MDVP**

### ***1.5.1 Update on funding and status of candidate visual cues***

Dr Eggers presented the progress made by WHO and the TLAC MDVP subgroup on the development of visual cues on vaccine vials to prompt the correct discard rules to follow for opened vials. The MDVP sub-group had conferred several times on this topic and had provided guidance on the criteria that such visual cues should meet.

He pointed out that the hoped-for timeline to decide on which icons to use had not been met, and presented a revised one. The next step was for leading candidate icons to be assessed

through a focus group methodology in several different cultures and settings. The purpose would be to find those icons that best prompt health workers to apply the correct discard policy, with the least chance for misunderstanding and confusion.

In addition to the focus groups, the candidate icons would be presented for consultation to regional and country staff, and to vaccine manufacturers. In both these consultations, the main purpose would be to judge the feasibility of the proposed icons and to elicit what challenges would be faced in the transition.

### **1.5.2 Findings, Conclusions, and Recommendations on visual cues**

Mr Robert Steinglass, leader of the MDVP subgroup of TLAC, presented the findings, conclusions and recommendations of the subgroup on visual cues (see below), and moderated the TLAC discussion.

#### **Background**

Some new vaccine presentations to be introduced will render obsolete common “rules of thumb” based on whether the products are liquid or lyophilized and will undermine old presumptions on whether or not they contain antimicrobial preservatives. In response to WHO’s request for input from TLAC for a planned revision of the current MDVP published in 2000,<sup>9</sup> TLAC recommended the development of obvious icons on vaccine labels to indicate whether an opened multidose primary container was suitable to be kept for use in subsequent immunization sessions, or whether it must be discarded at the end of the session (or after six hours, whichever is earlier).

The goal is that a vaccinator using a prequalified vaccine, simply by looking at the vial and seeing its visual cue, will be prompted to know which of two dichotomous courses of action to follow:

- a. Upon opening, the vaccine may be used until the end of that day's vaccination session or until 6 hours have passed, whichever is earlier; or
- b. Upon opening, the vaccine may be used for up to 28 days, if returned promptly to its recommended cold chain conditions when the vial is not in use and if the VVM has not reached its endpoint.

In the future, when very heat-labile vaccines might be introduced, a third indication might require discard at 3 hours, or even much earlier (such as for varicella).

#### **Purpose**

The visual cue is intended to disabuse health workers of a common, but mistaken, generalization that will become dangerous when unprecedented presentations are introduced, such as unpreserved, multidose, liquid vaccines. It is largely unknown whether field workers understand the technical rationale (i.e., absence or presence of preservative) for the differing treatment of various vaccines (e.g., same-day discard for BCG and measles on the one hand, and allowing use up to 28 days for DTP, hepatitis B and OPV on the other). It is quite likely many apply an incorrect “rule of thumb” that liquid vaccines may be kept for future days (rather than because they have preservative), while lyophilized ones must be discarded the same day (rather than because they lack preservative). Thus, a prominent, consistent, globally-standardized set of visual cues would be necessary to overcome this common misperception.

#### **Criteria**

The TLAC MDVP subgroup indicated that candidate visual cues should be compared and selected according to the following criteria:

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g. WHO. WHO Policy Statement: The use of opened multi-dose vials of vaccine in subsequent immunization sessions. 2000. Document WHO/V&B/00.09 (<http://www.who.int/vaccines-documents/DocsPDF99/www9924.pdf>).

- Simplicity, for printing directly onto the vial label.
- Non-textual, relying on image or shape, rather than any words, letters, or text in any particular language or alphabet.
- Intuitiveness, comprehensibility, and universality in multiple cultures, regions, and linguistic groups in correctly prompting health workers to follow the corresponding policy **a.** or **b.** above.
- Legibility when reduced to a size that might be as small as 6 mm in diameter in redesigned layouts of labels already crowded with other needed text and features.
- Low marginal cost, e.g., if its colours are not already printed on the vial label.

### **VVM Location**

WHO currently requires that prequalified vaccines which may be kept according to the 28-day discard rule have their vaccine vial monitor on the label of the primary container. Vaccines that should follow the 6-hour discard rule must have their VVM placed on the vial cap or ampoule neck, so that they are separated upon opening the container. TLAC concludes that placement of the VVM should not be the principal or primary visual cue for discard policy, because it is not obvious, it is not currently mentioned in immunization training materials for peripheral health workers, of which few are likely aware of such meaning. However, there is no reason that this placement cannot continue as a secondary, reinforcing visual cue.

### **Discussion**

During the debate, it was mentioned that global buy-in on visual cues would be important from countries procuring vaccines through the UN mechanism, and that regional inputs would be critical, especially as PAHO has a separate tendering and procurement system.

Some discussants doubted that complex visual cues would be legible, because of their small size, leading them to suggest that only Xs or tick marks would be feasible. There was also some concern that health workers may ignore the visual cue, as some are said to ignore VVMs.

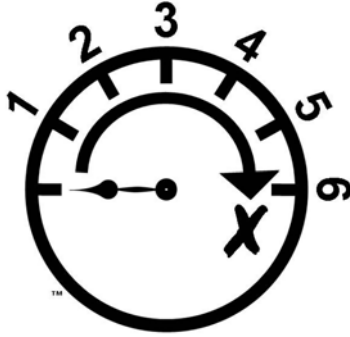
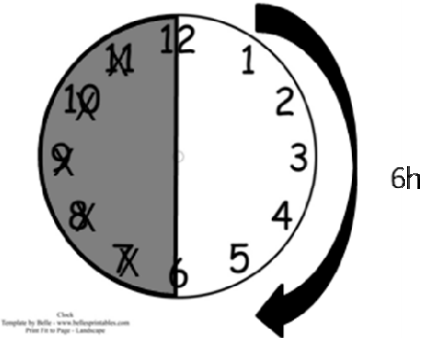
The use of any text in some of the proposed candidates was questioned. For example, although the Latin alphabet letters "d" and "h" used in some candidate icons may well be understood to mean days and hours, respectively, in countries speaking English, Spanish, and some other languages, such characters may not be understood in other settings. It was also pointed that very few health workers in the world mark vials with their dates of opening, even though this practice is recommended by many public health authorities, including in the U.S.A.

In conducting the recommended research with health workers, it was suggested that the first phase – before identifying the two discard policies that the cues are intended to prompt – should expose naïve health workers to a number of candidate visual cues (including that of the placement of the VVM) to measure their current interpretation and understanding of them.




### **Recommendations**

1. Urgency. WHO and partners should speed up the pace to implement the recommendations concerning visual cues. Because the suggested processes to select and implement visual cues for global adoption will not likely be completed before unpreserved, multidose, liquid vaccines are introduced into developing-country immunization programs, TLAC urges WHO to select a provisional icon from among the current best candidates illustrated below, and require it be placed immediately on such products. If the suggested research indicates a different icon is preferable for global adoption, it can replace the provisional one.
2. Pair of cues. A pair of new visual cues in the form of obvious icons or symbols should be developed for the two current discard rules.
3. Location. The icons should be printed on the label of the primary container (vial, ampoule, syringe, oral-instillation dispette, etc).

4. **Colouring.** The icons should be printed in black-white; gray-scale components may be less legible. The icons should avoid the use of colours to distinguish between the two discard rules, not only because of colour blindness in the population, but also to avoid any additional costs in printing.
5. **Evaluation and empirical testing.** Selection of the pair of icons to be recommended for global use should result from rigorous evaluation among the most promising competing candidates using empirical applied research and scientific methods. Field testing should be performed at the peripheral health-centre level in various cultural and linguistic settings on three continents. This work should be designed and conducted by professionals experienced in market research, product image recognition, and consumer assessment.
6. **Training.** WHO should begin immediately to develop “rollout” introduction plans and associated training materials. Once the pair of icons is selected, wide-scale pilot testing and monitoring of such introduction should be conducted before scale-up to global implementation on all UNICEF-supplied vaccines.
7. TLAC considers the following icons as the most promising candidates to date for evaluation as the visual cues:<sup>h</sup>

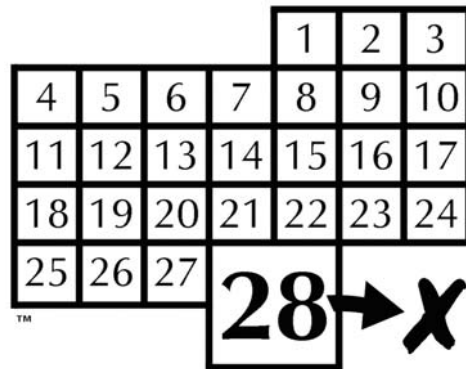
<b>6-HOUR DISCARD ICONS</b>	
<b>1. “Watch face X”</b>	
<b>2. “Clock face half moon”</b>	

<sup>h</sup> All symbols shown are copyrighted / trademarked by their respective sources (WHO, M|e|o).

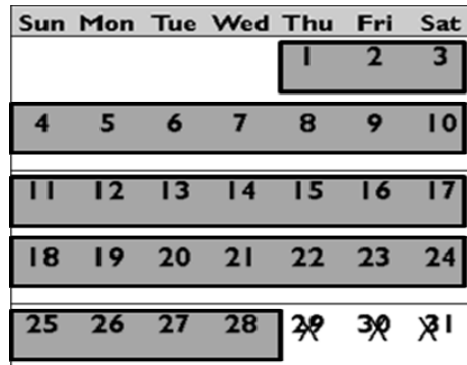
<p>3. "Watch band 6h"</p>	
<p>4. "Man &amp; Trashcan 6h"</p>	
<p>5. "Vial &amp; Trashcan 6h"</p>	

# 28-DAY DISCARD ICONS

6. "Calendar 28 X"


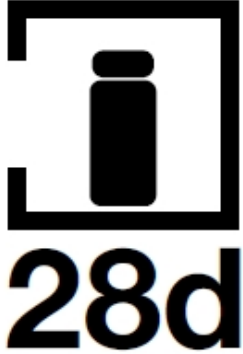


7. "Greyed Calendar "



8. "Flip Calendar 28d"



<p>9. "Person &amp; Shelf 28d"</p>	
<p>10. "Vial in Box 28d"</p>	

## 1.6 Development of a Generic Preferred Product Profile (gPPP) for vaccines

### 1.6.1 VPPAG development of the gPPP

Dr Osman Mansoor, of UNICEF HQ, and Dr Souleymane Kone, of WHO HQ, presented the document entitled "*Generic Preferred Product Profile (gPPP) for Vaccines: Recommendations and Work Programme*" (gPPP) that was prepared by the Vaccine Presentation and Packaging Advisory Group (VPPAG).<sup>i</sup> The document sets forth recommendations for vaccine producers and developers on the presentation and packaging of new vaccines for use by public-sector programmes in developing countries. The VPPAG was established in 2007 by the GAVI Alliance to provide a unique forum for representatives of agencies and experts involved in public sector delivery of vaccines, along with industry representatives – both the International Federation of Pharmaceutical Manufacturers Association (IFPMA) and DCVMN (Developing Country Manufacturer's Network).

The initial focus was to respond to an industry request regarding pneumococcal conjugate vaccine (PCV) and rotavirus vaccine (RV). For PCV, VPPAG provided input for a WHO target product profile (TPP) for the Advance Market Commitment (AMC). VPPAG advised on a range of aspects for packaging and presentation, and most of its recommendations were included in the TPP.

<sup>i</sup> <http://sites.google.com/site/vppagp/Home>

In 2008, WHO assumed the role of convening the VPPAG, together with the Project Optimize, as the mandate of the group was extended beyond GAVI supported vaccines. It needs to develop a more generic approach to address presentation and packaging issues for the range of potential new vaccines. The VPPAG developed the initial consultation draft of the gPPP in June 2009, and an updated version (2.1) was released in August. It contains recommendations generally supported by both public and private sector representatives based on existing evidence. For other issues, a work programme is proposed to collect the evidence needed to develop a future recommendation for the evolving gPPP, which is considered a living document to be updated as the work programme is implemented over time.

The gPPP provides both a summary and details of key characteristics that are preferred in vaccines for the developing country markets in relation to:

- Vaccine formulation: mixing lyophilized products versus “ready-to-use” liquid ones, heat stability, freeze stability, and presence of antimicrobial preservatives;
- Vaccine presentation: product format, optimal number of doses per primary container, prefilled injection devices;
- Labelling: product labelling and package insert, vaccine vial monitors (VVMs), freeze indicators, and the visual cue regarding discard policy;
- Packaging: product bundling, maximum packed volume, packaging materials, including the primary container

### ***1.6.2 Role of operational and programmatic considerations in WHO prequalification of vaccines***

Dr. Nora Dellepiane, WHO HQ, presented on the subject of operational and programmatic considerations in WHO’s prequalification of vaccines. She focused on the pre-requisites, the evaluation procedures, the challenges, and the programmatic considerations.

The WHO prequalification system tries to ensure that all vaccines used in all national immunization programmes are of assured quality, in accordance with six specified functions defined by WHO. This is meant as a service, especially to countries that may not have sufficient capacity to provide the necessary regulatory functions.

The pre-requisite for WHO prequalification is that the responsible National Regulatory Authority (usually of the producing country) has to be independent and functional. It should meet all the critical indicators required for prequalification purposes following an independent WHO assessment. The status of the NRA is reassessed at regular intervals.

The evaluation procedure for pre-qualification includes obtaining a general understanding of production process and quality control methods, clinical data relevant for the target population of the recommended schedules, production consistency at commercial scale (assessed by testing of samples of final product), compliance with current good manufacturing practice (cGMP), compliance with WHO recommendations and UN tender specifications, including labels, inserts, and - importantly - the suitability of the presentation to immunization programs.

Guidance documents for pre-qualification have been produced; these focus on strengthening quality assurance systems (e.g., SOPs, checklists, instructions). A provision for a fast-track procedure in case of high-priority vaccines has been instituted, and is currently being used for seasonal and pandemic virus influenza vaccines. The expedited procedure includes parallel evaluation with the NRA and increased human resources by WHO.

To ascertain programmatic components of pre-qualification, the following issues are considered:

- suitability for the target population;
- compatibility with existing EPI schedules;

- stability profile: understanding of the cold chain requirements / suitability for use under field conditions, VVM category requirements;
- packaging: presentation/primary packaging suitability, open-vial-policy applicability;
- information on inserts: adequacy, clarity, reflection of product characteristics, required languages; and
- validity of transport boxes for international shipments.

Pre-qualified vaccines are currently sourced from 13 industrialized-country manufacturers and six developing-country manufacturers (total 24). They supply 86 pre-qualified vaccines used in 112 countries.

### **1.6.3 Translating the VPPAG gPPP into programmatic inputs for pre-qualification**

Dr Rudi Eggers, WHO HQ, elaborated on a proposed new approach for consideration of programmatic suitability in regard to prequalification. He reiterated that a main purpose of pre-qualification is to assure the quality, safety, and standards of vaccines for countries procuring them through the UN system, and which may not have the capacity to conduct the licensing process themselves.

Current assessment of programmatic suitability of the vaccines is made on a case-by-case basis, in consultation with programme components of WHO and in countries, and also based on precedent. He said it would be important for the new approach to better define the components of programmatic feasibility, so as to clearly state the preferred vaccine characteristics and to judge programmatic feasibility against them. Although such a new “rules based” approach would provide general guidance, a final “human” decision must be made by the pre-qualification team and their advisors in order to take into account nuances and complexities.

This approach may require a “grandfather clause”, exempting for the time being vaccines currently pre-qualified. Products departing from the preferred presentation as an exception will require further public health, programmatic, or supply justifications to achieve pre-qualification. Further clarification of the relationship with the UNICEF Supply Division and with the PAHO Revolving Fund tendering processes will be sought.

In judging the programmatic feasibility of a vaccine submitted for prequalification, certain vaccine characteristics will be considered (among others that may be considered and reviewed):

- *Critical* – i.e., the product departs in some essential way from programmatic feasibility which is likely to prevent pre-qualification (although the final decision is made by appropriate authority)
- *Preferred* – i.e., vaccines with these characteristics will be preferred to vaccines that do not have them

Dr Eggers said the next steps for implementing the gPPP include drafting a document to reflect these proposals and current thinking, followed by consultations with regions and countries, with vaccine manufacturers, and with the WHO pre-qualification team. He concluded by estimating this process will lead to a review of the pre-qualification process in the first quarter of 2010.

### **Discussion**

Participants commented that there might be some incentives for conforming to the gPPP, such as faster processing through prequalification, or an exception to requirements for manufacturers to conduct further studies. This potentially might provide some incentive to comply with the preferred presentation. It was suggested suppliers of preferred presentation products receive some market advantage.

Another factor proposed for gPPP preference involved some advantage to vials and devices that are easier to dispose safely. It was also pointed out that there may sometimes be a tradeoff between ensuring that vaccines satisfy safety criteria and making lifesaving ones rapidly available for mass use in emergencies. The UNICEF Supply Division representatives said the agency prefers having multiple prequalified manufacturers, and looks at price and other considerations when making the awards.

#### **1.6.4 TLAC Findings, Conclusions, and Recommendations on VPPAG and gPPP**

Mr Robert Steinglass, leader of the MDVP subgroup of TLAC, presented the findings, conclusions and recommendations of the subgroup on the VPPAG and gPPP, and moderated the TLAC discussion.

#### **Background**

TLAC expressed that the VPPAG is a unique body of multilateral and industry representatives to provide guidance to the pharmaceutical industry and other groups involved in vaccine development on preferred formulations (e.g., liquid, lyophilized, frozen, with preservative or without, etc.) and presentations and packaging (e.g., single-dose, multi-dose, vials, prefilled syringes, unique prefills such as Uniject<sup>®j</sup> etc.) for products intended for public sector use in developing countries. TLAC considers that “presentation and packaging” comprises more than the obvious physical characteristics described above. It also includes certain programmatic features and characteristics of vaccines that can greatly affect its safe and effective use.

A principal purpose of VPPAG is to ensure that vaccine producers are aware of the needs, circumstances, and constraints of this previously-ignored market so that their products will best serve their intended purpose to prevent disease and be successful from the perspective of both customers and manufacturers. TLAC recognizes and appreciates the foresight of the GAVI Alliance for having created VPPAG in 2007, the energy of UNICEF in chairing it, and the responsibility now assumed by WHO in hosting and convening it to provide focused leadership to advance its aims.

The VPPAG document gPPP has important implications for the ongoing revision of the 2000 WHO Multi-Dose Vial Policy (MDVP),<sup>k</sup> which provides guidance to health workers on how long they may safely keep and administer a vaccine once its vial has been opened. TLAC welcomes the thoughtful, methodical, open and consultative manner in which VPPAG has developed the gPPP, and generally supports its overall conclusions and programme of work to answer unresolved issues. However, the process by which WHO will assume this leadership and pursue the work remains undefined.

Implementation of the recommendations of the gPPP will be difficult. Industry requires consistent messages, operates with long lead times, and expects secured funding in order to undertake expensive changes in vaccine formulations and presentations.

#### **Mitigating the dangers of unusual presentations**

Trends in the developed world, such as North America and Europe, raise obstacles for the safe and practical introduction of vaccines used there into the developing world. For example, developed-world vaccine manufacturers are increasingly avoiding preservatives such as mercury-based thimerosal (also known as thiomersal) because of unsubstantiated allegations against their safety. To do so usually requires single-dose presentations which avoid the danger of bacterial overgrowth between doses. However, single-dose syringes, often in pre-filled syringes with elaborate packaging, require larger volumes for the cold chain to store. In contrast, most developing country vaccine manufacturers are inclined to continue to use

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<sup>j</sup> <http://www.path.org/projects/uniject.php>

<sup>k</sup> WHO. WHO Policy Statement: The use of opened multi-dose vials of vaccine in subsequent immunization sessions. 2000. Document WHO/V&B/00.09 (<http://www.who.int/vaccines-documents/DocsPDF99/www9924.pdf>).

preservatives for economical multi-dose vials, which take up less space within the crowded vaccine refrigerators found in developing countries.

For many years, live vaccines for injection (e.g., measles, BCG for tuberculosis, yellow fever) were presented in lyophilized (dry powder) format, without any preservative which would kill the antigen and render it useless. Once reconstituted with diluent, such vaccines must be administered within a few hours, before the organism dies and before overgrowth can occur of potentially harmful contaminating bacteria introduced after opening. Thus, health workers around the world have likely associated dry powder vaccines with the requirement to discard them at the end of that day's vaccination session, or within 6 hours, whichever comes first.

Similarly, all liquid vaccines heretofore in the developing world have been predominantly in multidose vials, and have contained preservative to kill any contaminating bacteria, permitting the vaccine to be used safely on subsequent days if kept refrigerated. This avoids wastage of remaining doses in such vials. Thus, health workers likely consider that after opening liquid vaccines in multidose vials, these can be returned to the refrigerator for re-use.

This mistaken generalization that all liquid vaccine contains preservative and thus can be kept for another day now represents a threat. An unprecedented vaccine presentation is on track for introduction – multidose vials of liquid vaccine without preservative – as philanthropy, governments, and international organizations admirably extend to millions of children in the developing world access to the same vaccines as children in rich countries. Unless and until health workers in developing countries can be adequately warned and trained that such products must be discarded six hours after opening, there is a substantial risk that recipient children may suffer serious adverse events as a result of bacterial overgrowth in such vials.

In many countries, the training and supervision of health workers are weak. The interval between training activities is often long, their content outdated, and the pedagogical methods ineffective. New staff members enter the workforce without sufficient orientation, and existing staff are assigned new responsibilities without relevant training. In this situation, it is not sufficient to simply call for "training" as an all-purpose bromide that will automatically reduce the risks of serious iatrogenic injury.

TLAC expresses serious reservations about the potential harm in poorer countries of multidose liquid vaccines without preservative, which may undermine public confidence in the safety of vaccines.

## **Recommendations**

1. Prioritizing within the gPPP. TLAC encourages WHO and its partners in VPPAG to continue to review and prioritize from among the many proposed suggestions for work and action within the gPPP document, and then to advocate for the required human and financial resources to carry this important programme forward.
2. Monitoring of the vaccine R&D pipeline and advocacy. TLAC recommends that WHO track the research and development pipeline in which vaccines move from the bench to the field, with particular focus on those vaccines relevant to global immunization programs. WHO should maintain listings of such vaccines and their likely presentations and formulations. WHO should exert pro-active leadership upstream in the pipeline to advocate for products, presentations and packaging relevant to global immunization programmes in diverse settings.
3. Operational and programmatic factors for pre-qualification. TLAC urges the WHO prequalification unit (Quality, Safety, and Standards team [QSS]) to elaborate further and to disseminate the operational and programmatic factors to consider in assessing the safety of vaccines and in weighing their risks and benefits. When indicated, WHO should require extraordinary product labelling and/or set geographic or other marketing limitations to mitigate risk. WHO should articulate and disseminate a formal process of

providing operational and programmatic guidance to GAVI and UNICEF for safe use of individual vaccine products.

4. Printed icons on high-risk vaccines. In the case of unpreserved, multidose liquid presentations, TLAC recommends that WHO ensure the label of each vial is imprinted with a prominent icon reminding health workers to dispose it within six hours of opening (or earlier, if indicated by the particular vaccine profile) (*see related recommendations above on "visual cues", section 1.5.2*).
5. Immediate steps for unpreserved, multidose, liquid presentations. In the interim period until candidates for such visual cues can be scientifically evaluated, tested, and recommended for general global use, one of the candidate icons described elsewhere in this report (section 1.5.2) should be required for immediate application onto unpreserved, multidose, liquid presentations. The site of placement of the VVM on the vial should not be considered a substitute for an obvious printed icon.
6. Separate stickers for preprinted label stock. If label stock for unpreserved, multidose, liquid presentations has already been produced – or vials filled – without such an icon, then safety warnings should be added onto all vials sold under the UNICEF procurement system.
7. Additional labelling in certain countries. WHO should determine which countries have a weaker infrastructure for the rollout of new vaccines that are programmatically problematic to use (such as unpreserved, multidose, liquid presentations). In such locations, WHO should urge the ministries of health to take special precautions to alert health workers with the required information on the safe use of such new products.
8. Rollout plans. WHO should provide clear guidelines to countries contemplating introduction of new vaccine products that are likely to be programmatically difficult to use.
9. Advocacy with GAVI and other partners. TLAC recommends that WHO advocate with the GAVI Alliance and other partners to mitigate the risk of unusual vaccine presentations. This includes urging (i) well-defined safety plans for training and risk reduction before granting financial support to countries planning introduction of unusual vaccine presentations with high iatrogenic risk; (ii) GAVI Independent Review Committees to consider criteria in determining readiness of individual countries to introduce unpreserved, liquid, multi-dose vaccine presentations; and (iii) GAVI increasing grant amounts for readiness to introduce such vaccines.
10. Vaccine handling. WHO should begin the process of preparing comprehensive vaccine handling guidelines for adoption at country level.

## 1.7 Creating an evidence base for MDVP revision

Dr Rudi Eggers presented on the third component of the work to revise the MDVP, namely the collection of the necessary scientific evidence to support various revisions to the MDVP. This component had not yet been addressed in detail by the MDVP subgroup, nor implemented by the WHO.

He indicated that the necessary studies may investigate the following:

- Level of preservative considered adequate for use in EPI
  - Determining minimum preservative concentration levels and their effect
  - Effect of temperature of preservative effectiveness
  - Determining to what extent contamination reduces efficacy
- Use of alternative preservatives, including mercury-free ones

- Operational risk for contamination of the septum by submersion in water (to support the current rule),<sup>9</sup> as well as by sneezing or handling with unwashed hands
- The duration unpreserved vials can be safely be kept (can it exceed the current 6-hours limit?)
- The duration preserved vaccines can be safely kept (can it be longer than the current 28 days?)
- Wastage rates in different settings, and detailed knowledge of session sizes
- Cost comparison between vial size, cold-chain requirements, and wastage
- Efficacy of reduced or fractional doses (such as for intradermal delivery), and the consequences of multiple entries into nominal single-dose vials without preservative
- Risk of various injection practices, including reusable syringes, UniJect<sup>®</sup> prefills, and jet injectors

In the interim until such new data are forthcoming, Dr Eggers said that the following criteria are being used for vaccines now submitted for prequalification:

- Vaccines containing standard amounts of thiomersal (thimerosal) (50 to 100 µg/mL) can be kept beyond the end of the session;
- Vaccines containing no preservative have to be discarded at the end of the session or within 6 hours, whichever comes first; and
- Vaccines containing reduced amounts of thiomersal, or alternative preservatives, require decision-making on a case-by-case basis

To facilitate decision making for vaccines containing reduced amounts of thiomersal or alternative preservatives, he reported the following criteria are used:

- The manufacturer has shown that vaccine meets criterion C when tested in the preservative efficacy test (single challenge) of the European Pharmacopoeia;
- The manufacturer has conducted multiple challenge tests with microorganisms specified by the EU Pharmacopoeia in comparison with control vaccines containing standard amounts of thiomersal and control vaccines without any preservative; and
- The manufacturer has demonstrated that the preservative efficacy of the vaccine is comparable to that of vaccine containing standard concentrations of thiomersal for all microorganisms tested

### **Open issues on other topics in TLAC portfolio**

Several issues covered at prior TLAC meetings did not fall within the domain of any existing TLAC subgroup. These were presented by Dr Bruce Weniger, TLAC chair.

#### **1.8 Injection safety – spring-loaded syringes for EPI**

As presented by Dr Selma Khamassi, WHO HQ, at TLAC's March 2009 meeting, and discussed there, some spring-loaded syringes prequalified by WHO for vaccination use do not meet the letter or the spirit of the ISO standard for fixed-dose, auto-disabling syringes, which requires that they be rendered non-reusable *passively* and *automatically*,<sup>1</sup> to prevent health workers from intentionally defeating the auto-disabling feature.

Dr Weniger demonstrated how one such 0.5 mL syringe could intentionally be used unsterile multiple times by simply not pushing the plunger the final 2 millimetres at the end of its stroke,

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1. International Organization for Standardization. Sterile hypodermic syringes for single use - Part 3: Auto-disable syringes for fixed-dose immunization. First edition 2005-03-01. International standard ISO 7886-3 ([http://www.iso.org/iso/iso\\_catalogue/catalogue\\_tc/catalogue\\_detail.htm?csnumber=36742](http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=36742)).

which is required to trigger the spring to shoot the needle back into the syringe barrel. Overfilling the device a compensatory 2 mm beyond its fiducial line would allow full doses to be given repeatedly from the same unsterile syringe. At the March meeting, TLAC requested a report from WHO on the status and resolution of this problem.

WHO reported at the September 2009 meeting that this subject would be addressed at a meeting in Geneva on 5 December 2009 of its immunization partners and manufacturers in order to develop a "roadmap" in which all syringes prequalified as auto-disabling must render the syringe non-reusable at the beginning of the injection, thus preventing defeat of the auto-disabling feature as demonstrated.

WHO staff stated that the risk of intentional re-use of such devices was theoretical and field studies would be needed to document its occurrence. WHO stated that certain manufacturers might need only minor modifications to satisfy this specification, while others – such as the spring-loaded syringe makers – may require substantial reengineering work.

A UNICEF representative reported that its Supply Division was aware of this aspect of such prequalified syringes, and was avoiding their purchase for global immunization until the problem was solved. They were currently giving preference to syringes with truly passive and automatic disabling features.

## 1.9 Freeze damage to vaccines

### Background

An increasingly-recognized problem in immunization programs is freeze damage within the cold chain to some vaccines -- particularly alum-adsjuvanted ones like hepatitis B (HBV), diphtheria-tetanus-pertussis (DTP), and others.<sup>m, n</sup> Freezing may render them impotent to afford protection to the children that receive them. The causes of freezing are various: poorly-maintained refrigerators, improper cold-chain practices, cold climates, and inadequate training of health workers. Avoiding such freeze damage is a contributing reason for proposed initiatives to take some vaccines out of the standard cold chain of +2°C to +8°C at the peripheral level.

Existing vaccine vial monitors (VVMs) provide valuable guidance about exposure to heat: After lapses of uncertain degree or duration in the cold chain, VVMs can indicate that the vaccine is probably still potent and thus avoid wastage by having to discard it on precautionary grounds. When they do convert, VVMs can prevent the administration of impotent vaccine that will not protect the child. But VVMs do not reveal anything about exposure to freezing temperatures that may also damage the vaccine. In many cases, health workers may not notice the changed appearance of frozen vaccine after thawing and may inadvertently administer ineffective product.

A variety of freeze indicators have been developed over the years, for which a number have been and remain pre-qualified by WHO for sale under UNICEF procurement.<sup>o, p</sup> But for

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**m.** PATH. Evidence of Vaccine Freezing in the Cold Chain: Literature Review. Program for Appropriate Technology for Health, Seattle, WA, unpublished document ([http://www.path.org/files/TS\\_cc\\_evidence.pdf](http://www.path.org/files/TS_cc_evidence.pdf)).

**n.** Matthias DM, Robertson J, Garrison MM, Newland S, Nelson C. Freezing temperatures in the vaccine cold chain: A systematic literature review. *Vaccine*. 2007;25(20):3980-3986 (<http://dx.doi.org/10.1016/j.vaccine.2007.02.052>).

**o.** WHO. E06: Temperature monitoring devices performance specifications and verification protocols [webpage]. Geneva, Switzerland: World Health Organization ([http://www.who.int/immunization\\_standards/vaccine\\_quality/pqs\\_e6\\_temp\\_monitoring/en/index.html](http://www.who.int/immunization_standards/vaccine_quality/pqs_e6_temp_monitoring/en/index.html)).

**p.** WHO. Performance, Quality and Safety (PQS): Prequalified devices [webpage]. Geneva, Switzerland: World Health Organization ([http://www.who.int/immunization\\_standards/vaccine\\_quality/pqs\\_prequalified\\_devices\\_e06/en/index.html](http://www.who.int/immunization_standards/vaccine_quality/pqs_prequalified_devices_e06/en/index.html)).

reasons of size or cost these have not yet been practical for attachment to individual vaccine primary containers (vials) as are VVMs, or for inclusion in or attachment to secondary cartons. A new generation of much smaller or less-expensive indicators is in development, for which prototypes were shown to TLAC at its March, 2009 meeting<sup>q</sup> by Prof Ted Labuza of the University of Minnesota, an expert who has researched and developed such devices for vaccines and foods.

## Recommendations

TLAC encourages WHO as a high priority to pursue the research, development, and implementation of freeze monitors that could be applied directly to vials (or less desirably in each secondary carton) of freeze-sensitive vaccines [*similar cross-recommendation with OCC subgroup, section 1.2.3*].

### 1.10 VVMs for highly thermostable new vaccines

#### Background

Several new vaccines in the “pipeline” for introduction into immunization programs in the developing world have been reported to have relatively high stability to maintain potency during prolonged heat exposure, such as vaccines for meningococcal disease<sup>r</sup> and human papillomavirus (HPV).<sup>s, t</sup> One HPV vaccine was found at +25°C to be stable for periods of 130 months (~11 years) or longer, and at temperatures of +37°C to +42°C to maintain more than 50 percent of initial potency for “several months”.<sup>s</sup> There may also be existing vaccines with relatively high thermostability, such as some for hepatitis B.<sup>u, v</sup>

Many of these vaccines are likely to have shelf-life plots that substantially exceed and diverge from that of the most heat-stable VVM version now available, the VVM30. This version is designed at +37°C to “convert” (indicate discard) just before 30 days, and at +25°C at ~193 days (~6 months). In such cases, the existing VVM30 may not provide a suitable match to the vaccine’s shelf life; it would convert to indicate discard well before the vaccine actually loses acceptable potency.<sup>w</sup> As these new products will likely cost many times more than most vaccines currently in developing-country immunization schedules, such mismatching may result in expensive wastage when these vaccines are discarded prematurely because of VVM conversion.

Since the initial application of VVMs to oral polio vaccines (OPV) in the late 1990s, and their eventual application in the early 2000s to all vaccines as a condition for WHO-prequalification, there has yet been no “post-marketing surveillance” on the frequencies by which health

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q. TLAC. Meeting Report and Recommendations, 11-12 March 2009. Geneva, Switzerland: WHO Technologies and Logistics Advisory Committee ([http://www.who.int/immunization\\_delivery/systems\\_policy/tlac/en/](http://www.who.int/immunization_delivery/systems_policy/tlac/en/)).

r. Schöndorf I, Banzhoff A, Nicolay U, Diaz-Mitoma F. Overcoming the need for a cold chain with conjugated meningococcal Group C vaccine: A controlled, randomized, double-blind study in toddlers on the safety and immunogenicity of Menjugate®, stored at room temperature for 6 months. *Vaccine* 2007; 25: 1175-1182 (<http://dx.doi.org/10.1016/j.vaccine.2006.10.022>).

s. Shank-Retzlaff ML, Zhao Q, Anderson C, et al. Evaluation of the thermal stability of Gardasil®. *Human Vaccines* 2006; 2(4): 147-154 (<http://www.landesbioscience.com/journals/13/article/2989/>).

t. Le Tallec D, Doucet D, Elouahabi A, Harvengt P, Deschuyteneer M, Deschamps M. Cervarix™, the GSK HPV-16/HPV-18 AS04-adjuvanted cervical cancer vaccine, demonstrates stability upon long-term storage and under simulated cold chain break conditions. *Human Vaccines* 2009; 5(7): 467-474 (<http://www.landesbioscience.com/journals/13/article/8485/>).

u. Van Damme P, Cramm M, Safary A, et al. Heat stability of a recombinant DNA hepatitis B vaccine. *Vaccine* 1992; 10: 366-367.

v. Galazka A, Milstien J, Zaffran M. Thermostability of vaccines. World Health Organization document WHO/GPV/98.07, 1998, pp. 1-64 ([http://whqlibdoc.who.int/hq/1998/WHO\\_GPV\\_98.07.pdf](http://whqlibdoc.who.int/hq/1998/WHO_GPV_98.07.pdf)).

w. TLAC. Preliminary Review of Vaccine Vial Monitors (ver. 10, 9 March 2009). Geneva, Switzerland: WHO Technologies and Logistics Advisory Committee ([http://siamlotus.com/Pubs/TLAC\\_VVM\\_Review\\_V10-2009Mar9.pdf](http://siamlotus.com/Pubs/TLAC_VVM_Review_V10-2009Mar9.pdf)).

workers are discovering converted VVMs and properly disposing of presumed impotent vaccine before it is administered. Such data would be essential for rigorous economic analyses and modeling to weigh the estimated annual expenditure of US\$13 million to \$26 million for such VVMs (as a component of manufacturers' cost of goods passed on to vaccine purchasers) against VVM benefits and savings.<sup>w</sup> Such studies will be of growing interest as newer, more expensive vaccines of high thermostability are introduced.

### 1.11 Recommendations

TLAC urges WHO to work with the manufacturer of VVMs, the Temptime Corporation (<http://www.temptimecorp.com>), and any other potential vendors, to pursue the research and development of additional versions of VVMs that would have significantly longer stability profiles than currently available in order to better match future and perhaps existing vaccines.

TLAC recommends the commissioning of high-quality, quantitative surveillance of the "incidence" or "prevalence" of VVM conversion in field use by researchers independent of the developers, manufacturer, or advocates of this technology. Such efforts might be based on existing reporting, if any, of the frequency of vaccine wastage by cause (including VVM conversion) in routine immunization programs or special immunization campaigns. If unavailable, *ad hoc* prospective studies may be required in sentinel health centers and other levels of the cold chain.

### Closing

Dr Jean Marie Okwo-Bele thanked the TLAC members for their service on the committee and for their accomplishments over the 13 months since its creation. On behalf of TLAC members, Dr Weniger expressed the honour of members in their selection to serve on such a prestigious advisory committee, despite the hard work and long hours involved. He indicated that TLAC members recognized and appreciated the many challenges that the WHO faces, with limited resources and staff, in fulfilling its mission with no easy solutions and often difficult trade offs.

Among informal closing comments by others, the WHO was urged to minimize short-term *ad hoc* arrangements and to try moving towards development and adoption of long-term systems and policies. It was acknowledged that the immunization world is becoming increasingly complex. Nevertheless, the importance was stated of reaching out to other institutions to share experience from programmes with less sophisticated logistics.

TLAC members specifically thanked Dr Rudi Eggers for his tireless efforts as the point of contact for TLAC with the various parts of the WHO, as well as Claire Jouan for her logistical and administrative assistance getting TLAC members to meetings, and were grateful to other WHO staff who provided assistance.

The WHO indicated that the work started by TLAC will be continued and expected former TLAC members would be able to contribute in the future to the mission of the Department of Immunization, Vaccines, and Biologicals. Dr Okwo-Bele then recognized the individual members of the advisory committees by awarding them certificates of appreciation as tokens of WHO's gratitude for their hard work, time, effort, and service.

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### Disclaimer

This report reflects the discussions and recommendations made by the Technologies and Logistics Advisory Committee to WHO, but do not necessarily reflect WHO position, unless specifically stated.