WHO/V&B/02.16
ORIGINAL: ENGLISH

Vaccines and Biologicals

Ensuring the quality of vaccines at country level

Guidelines for health staff

World Health Organization

WHO

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Access to Technologies team
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(comments and suggestions for improvement are welcome and should be send to att@who.int)

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www.who.int/vaccines-documents/

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Contents

Abbreviations

AD	auto-disable (syringe)
ATT	Access to Technologies team (WHO)
BCG	bacilli Calmette-Guérin (vaccine)
CCM	cold chain monitor
DT	diphtheria–tetanus (vaccine)
DTP	diphtheria–tetanus–pertussis (vaccine)
EPI	Expanded Programme on Immunization
HepB	hepatitis B (vaccine)
Hib	*Haemophilus influenzae* type b (vaccine)
MMR	measles–mumps–rubella (vaccine)
NRA	national regulatory authority
OPV	oral polio vaccine
PAHO	Pan American Health Organization
Td	tetanus–diphtheria (vaccine)
TT	tetanus toxoid (vaccine)
UN	United Nations
UNICEF	United Nations Children's Fund
V&B	Department of Vaccines and Biologicals (WHO)
VVM	vaccine vial monitor
WHO	World Health Organization

Acknowledgement

The present document was produced with the generous assistance and cooperation of many members of staff in ministries of health, field offices and health facilities throughout the European Region, the Eastern Mediterranean Region and the South-East Asia Region of the World Health Organization. The authors thank all concerned for their time, understanding and patience. Special thanks are extended to Dr Aye Aye Aung, Dr Margarita Balsanian and Dr Mohamed Koalise.

Introduction

WHO conducted a series of field surveys in order to obtained an improved understanding of typical procedures for the receipt, storage, distribution, handling and administration of vaccines in countries where UNICEF-procured vaccines are used. The aim was to identify factors that might adversely affect vaccine quality at country level, with a view to suggesting changes in procedures, which might correct or avoid these factors. The most common problems observed are listed in Table 1. The surveys clearly indicated a need for guidance on all procedures for managing vaccines, diluents and injection equipment, including shipping, receiving, quality control, release, storage, distribution and administration.

Table 1: Commonly observed problems that can damage the quality of vaccines

Shipments: inadequate advance notice, route deviations, delays *en route*, breaks in the cold chain.
• ***Receipt/acceptance:*** the quantity received is checked but the quality is not always systematically checked.
• ***Storage:*** cold chain failures, inadequate recording and/or stock control system.
• ***Release for use:*** release certificates from NRAs of producing countries are not always checked; often, no formal release system is in place.
• ***Distribution:*** freeze-dried vaccines are frequently not distributed with diluents in matching quantities; cold chain failures or interruptions.
• ***Point of use:*** problems with storage, reconstitution, administration and disposal of vaccines.

The present guidelines have been prepared specifically for countries procuring their vaccines through UNICEF, and are aimed at all programme and regulatory authority personnel at country level, UNICEF and WHO country staff as well as staff of partner and support agencies, and all who handle, store and use vaccines. They describe the procedures necessary for ensuring vaccine quality from the moment when production starts until the time of administration. Some of the procedures described can be applied to any country, wherever they obtain their vaccines, while others are specific to UNICEF vaccine supply procedures.

Part 1 describes the procedures for ensuring that vaccine production is maintained at a high standard. This is mainly the role of WHO, working closely with manufacturers and regulatory authorities.

Part 2 describes the procedures for ensuring safe and efficient shipping to the country of destination. This is mainly the role of UNICEF, working with airline agencies and forwarding agents.

Part 3 describes both the control mechanisms needed by receiving countries so that only high-quality shipments are accepted, and the systems of storage, handling, reconstitution and administration needed to ensure that the quality of vaccines is maintained until the moment of use. This is mainly the role of health ministries and immunization service staff.

Part I

1. Ensuring the quality of vaccines supplied through UN agencies

UN purchasing agencies rely on WHO technical advice to ensure that, in principle, vaccines are acceptable for purchase. They also rely on WHO to conduct investigations if the quality of vaccines supplied is questioned by receiving countries or if adverse events following immunization are reported.

In giving advice to UN agencies on the quality of candidate vaccines or on the continuing quality of vaccines already being purchased, WHO follows a procedure, detailed in document WHO/VSQ/97.06, for evaluating the acceptability in principle of vaccines for purchase. It consists of the following steps.

1) Any vaccine producer wishing to supply vaccine to UN purchasing agencies must submit a product summary file to WHO for detailed review.
2) In order to verify the consistency of final product characteristics, five consecutive vaccine lots must be independently tested by laboratories contracted by WHO.
3) The NRA of the producing country must be assessed by WHO in order to ensure that it is capable of effectively overseeing the quality of vaccines produced in that country.
4) Manufacturing facilities must be audited by a WHO team whose members have expertise in the relevant procedures, accompanied by representatives of the local NRA.

Step 1. Review of the product summary file

The product summary file contains general information on the company and its personnel, premises and equipment, copies of the national or regional licences as appropriate, information on the composition of the vaccine, presentations offered, immunization schedules recommended, production methods, quality control procedures, specifications of intermediate and final products, and data on the stability, shelf-life, clinical efficacy and safety of the vaccine.

The product summary file is reviewed by a group of experts selected by WHO, who give their opinion on the adequacy of the information provided, the quality, safety and efficacy of the vaccine, and whether WHO requirements and UN tender specifications are met.

Step 2. Testing for consistency of final product characteristics

In addition to reviewing the information on the vaccine and its characteristics in the product summary file, vaccine samples from different lots are tested in order to ensure that the vaccine consistently meets WHO requirements and UN tender specifications of relevance to immunization services.

Step 3. Assessment of the NRA

WHO cannot routinely oversee the quality of vaccines in every producing country that exports through the UN system. Consequently, reliance is placed on NRAs in this matter, and they are assessed in order to ensure that this is justified.

The six critical regulatory functions that must be performed by an NRA to ensure the quality of the vaccines they regulate are shown in Table 2. As part of the prequalification procedure for a candidate vaccine, WHO carries out an assessment of the performance of the NRA in the producing country in each of these critical areas.

Table 2: Critical functions of an NRA

• Published set of requirements for licensing
• Surveillance of vaccine performance in the field (postmarketing surveillance)
• System of lot release
• Use of laboratory when needed
• Regular inspections for good manufacturing practices
• Evaluation of clinical performance

For carrying out such assessments of NRA performance, WHO has developed a series of indicators that measure the level achieved for each of the six critical functions (document reference WHO/V&B/99.10). Any producing country applying to supply vaccines to UN agencies is automatically required to have an NRA assessment as part of the prequalification process.

Step 4. Manufacturing facility audit

WHO arranges for a team of experts to assess the adequacy of processes and procedures for the production and control of the vaccine or vaccines under evaluation. The team includes specialists on good manufacturing practices, vaccine production and quality control, and a representative or representatives of the local NRA who may choose to be an official part of the team or to act only as an observer or observers. This audit is extremely important, as it provides an insight into the good manufacturing practices and quality standards of the manufacturer. It also helps to verify the level of enforcement of good manufacturing practices by the local NRA.

Outcome of evaluation of vaccines for purchase

Once the four steps described above have been satisfactorily completed, WHO must reach an agreement with the local NRA on activities to be performed in connection with vaccines intended for exportation. These activities include the following.

a) The NRA should agree to release all lots for export on the basis of a review of lot summary protocols. The testing of selected lots for specific parameters is highly encouraged.

b) The release certificate for UN agencies should follow the recommended model (Annex 1).

c) The NRA should agree to communicate to WHO all reports of serious adverse events following immunization with vaccines supplied through UN agencies.

d) The NRA should agree to inform WHO of critical deficiencies in good manufacturing practice, which are identified during its inspections.

e) The NRA should agree to inform WHO of any recalls or licence withdrawals related to any vaccine supplied through UN agencies.

If all the steps of this procedure are accomplished to the satisfaction of WHO, UN purchasing agencies are advised to include the candidate vaccine in their list of acceptable sources for purchase. WHO publishes a list of prequalified vaccines at: *http://www.who.int/vaccines-access/vaccines/Vaccine_Quality/UN_Prequalified/UN_Prequalified_producers.htm*. The list is updated monthly.

2. Continued monitoring of the quality of prequalified vaccines

Once the initial evaluation is completed, the quality of vaccines shipped to countries is monitored through ***rounds of random testing*** performed at six-monthly intervals. This is to ensure continuing compliance with WHO requirements and tender specifications. In addition, a ***full re-evaluation*** of all prequalified vaccines takes place every two years. This is known as the reassessment process and basically covers the same steps as the initial evaluation described above, as follows.

1) Submission by manufacturers of an updated product summary file.

2) Testing of vaccine samples.

3) Meeting with the appropriate NRA.

4) Site visit to the manufacturing facility.

For reassessments however, the waiving of site visits may be considered on a case-by-case basis if certain criteria are met and at least one WHO site visit to the manufacturer has taken place within the previous five years.

3. List of WHO-prequalified vaccines

The fact that a vaccine is listed by WHO as acceptable in principle for purchase by UN agencies does not necessarily mean that the vaccine is available to the UN system. In some cases, producers may wish to obtain WHO-prequalified status because this gives them a commercial advantage. Countries that procure vaccines directly often require a producer to have WHO-prequalified status as a condition of licensing and/or tendering. It is important to note that countries purchasing vaccines directly, even from prequalified sources, may not necessarily obtain products under the same conditions as UN agencies (e.g. vaccines officially released by the NRA of the producing country) unless they specifically mention these conditions in their tender documents.

Part II

1. Tender requirements for the shipping of vaccines

Tenders for vaccines supplied through UN agencies include detailed terms and conditions for the various components of the shipping process. The purpose of these conditions is to ensure that the cold chain is maintained between the point of vaccine manufacture and that of delivery in the recipient country, and to guarantee that the recipient country receives vaccines of assured quality.

The conditions on packaging and shipping which are included in a tender and in any resulting contracts must follow the *Guidelines on the international packaging and shipping of vaccines* (unpublished document WHO/V&B/01.05).

The guidelines provide standards for insulated packaging, storage volumes, labelling, packing and shipping procedures. Some important points in these standards are indicated below.

- **Insulated packaging**

  Packaging must be designed to assure safe temperatures during transportation, appropriate to the thermostability of the vaccine concerned. Insulated boxes are used for this purpose, and WHO-validated cold chain monitor cards or manufacturer-validated temperature monitoring devices, and in some cases freeze-watch indicators, must be included with shipments as detailed in the guidelines.

  The packaging must be able to maintain the correct storage temperatures for at least 48 hours, this period being long enough to cover most vaccine shipments. If the time for transportation to the destination is expected to exceed 48 hours, provision must be made to assure maintenance of the cold chain at transit points, or, preferably, the period for which the packaging is able to ensure the desired temperatures must be extended. This is of special importance for OPV shipments.

- **Storage volume standards, labelling and packaging**

  Manufacturers are required to indicate packed volumes and weights of vaccines offered. Recommendations for maximum packed volumes per dose for all commonly used vaccines are given in WHO guidelines (WHO/V&B/01.05).

  All containers must show expiry dates and the batch number for the vaccine shipped and the storage temperatures that must be maintained. The labelling must also indicate that consignments are vaccine shipments containing

temperature-sensitive materials. A suitable label must be fixed to each shipping box. The text used for all labelling must be in a language appropriate for the country of destination.

- **Standard shipping procedures**:

  The arrival of vaccines in country, their subsequent clearance through customs and their transportation to the central vaccine store are the most critical stages in the shipment of a vaccine. This is often the stage at which mistakes are made and delays occur, with consequent damage to the shipment.

  The smooth arrival and handling of vaccine shipments depends on the manner in which each element in the delivery process is performed. Because numerous parties are involved (UNICEF Supplies Division, the manufacturer, the forwarder, the airline, the UNICEF field office, customs authorities, clearing agents, the national immunization service, etc.), and because of the need to communicate accurate, time-sensitive information, it is essential to have strict guidelines for determining and assigning responsibilities for every step of the process. These are described in the terms and conditions of the tender documents and are further detailed in individual contracts. The specific conditions depend on the country of destination.

The essential elements of the process are as follows.

1.1 Route and arrival dates

Shipments of vaccines are arranged through freight forwarders designated by UNICEF or are sent directly by the manufacturers. Details of consignee contact information, route and acceptable arrival dates are included in the contracts between UNICEF and the designated freight forwarders and/or manufacturers and determine how shipments are organized.

Instructions to forwarders include a requirement to use a direct route wherever possible and to avoid transhipments in airports without cold storage facilities. If specific transit points have to be avoided *en route* to the country of destination, they must be indicated to the purchasing agency for inclusion in the purchase orders.

As business days and official holidays vary from country to country, specific arrival dates that have to be avoided must be also indicated.

1.2 Advance notice of arrival and advance shipping documents

Advance notification of a vaccine delivery **must be sent to the consignee and the local UNICEF office *well ahead*** of the arrival of the shipment. This is ***essential*** in order to allow sufficient time for officials to prepare for receipt of the vaccine and to make arrangements such as initiating clearance procedures and preparing for vaccine storage. If other advance shipping documents are ready they may be sent together with the advance notification. If not, they should be sent separately, but in either case they ***must not delay*** the sending of the advance notification, which always has the top priority.

The amount of advance notification needed for a shipment varies from five working days to two weeks before arrival, depending on the country of destination. The shipping documents may not have to be received quite as early, but the time required must be specified in the purchase order. Only in special circumstances, and after agreement by all parties, can the time be shortened after the order has been placed.

The **advance notification** may be sent by fax or email. It must include the following information:

- type of vaccine;
- PO reference
- total number of vials or ampoules and number of doses in each vial or ampoule;
- number of cartons;
- gross weight of shipment (kg);
- value of shipment (US$);
- flight number, date and expected time of arrival at final destination;
- airway bill number;
- Instructions for collection, e.g. "Please arrange immediate collection or fax/telephone immediately if vaccine does not arrive".

Other advance shipping documents required by the consignee and the UNICEF office are:

- advance copy of invoice or *pro forma* invoice;
- advance copy of packing list;
- advance copy of airway bill;
- advance copy of release certificates and test protocols (**Note**: if these documents are required for clearing the consignment this must be indicated in the purchase order).

The airway bill must contain the consignee's name, address and telephone number, and instructions to give the consignee notification of arrival and information on handling. The data must be accurate. Most problems with vaccine shipments arise from failures in shipping notification. Typical examples of such failures are given below.

a) The consignee does not know that the shipment is coming because:

   i) the forwarder has forgotten to notify him/her of changes in the arrival date/time; or

   ii) The notification has not reached the consignee.

   Result: loss of vaccine if adequate and appropriate cold storage is not available at the airport. Demurrage charges are payable in either case.

b) The set of documents received by the consignee is incomplete.

   Result: delays in customs clearance until the correct documents are received. Demurrage charges are payable.

c) The number of vials and/or the value of the shipment do not correspond with the shipping documents.

Result: delays in customs clearance until the correct documents are issued and sent. Demurrage charges are payable.

d) Failure by the airline/forwarder to give notification of short-shipments or part-shipments as compared to the total order.

Result: confusion and anxiety for the consignee and/or the programme manager. Additional work has to be undertaken on clearing the short-shipment or part-shipment, and work has to be duplicated when the missing balance is eventually delivered.

Improvements in the process of shipping notification and in shipment arrival/clearance procedures can be made only through the combined efforts of **ALL** the partners responsible for one or more steps in the process. Two key elements are:

a) systematic reporting mechanisms from UNICEF offices and recipient governments for documenting the processes and identifying problems related to vaccine shipments;

b) Adequate monitoring aimed at improvement of the shipping component of vaccine contracts by the purchasing agency.

1.3 Documents that accompany shipments

When a vaccine shipment is sent the following essential documents must accompany the consignment:

- the original airway bill;
- a copy of the invoice with a detailed packing list;
- the release certificate or certificates from the NRA of the producing country;
- A copy of the vaccine arrival report.

These documents are usually sent inside the vaccine shipment, often in the vaccine box labelled "number 1". The box containing the documents should be clearly labelled with the words "**containing vaccine shipping documents**".

1.4 Vaccine arrival report

The vaccine arrival report (Annex 2) is a means of monitoring international shipments of vaccines in order to ensure that shipping guidelines are followed and that vaccine quality is maintained by encouraging increased ownership of the procurement process by all the parties involved. UNICEF or WHO officers should collaborate with recipient governments so as to ensure that the vaccine arrival report is duly completed and forwarded.

Part III

1. Checking vaccine shipments on arrival

The integrity of vaccines on arrival in the country of destination must be checked by:

a) verifying that the cold chain has been properly maintained throughout the period of transportation as confirmed by adequate temperature-monitoring devices contained in the shipment;

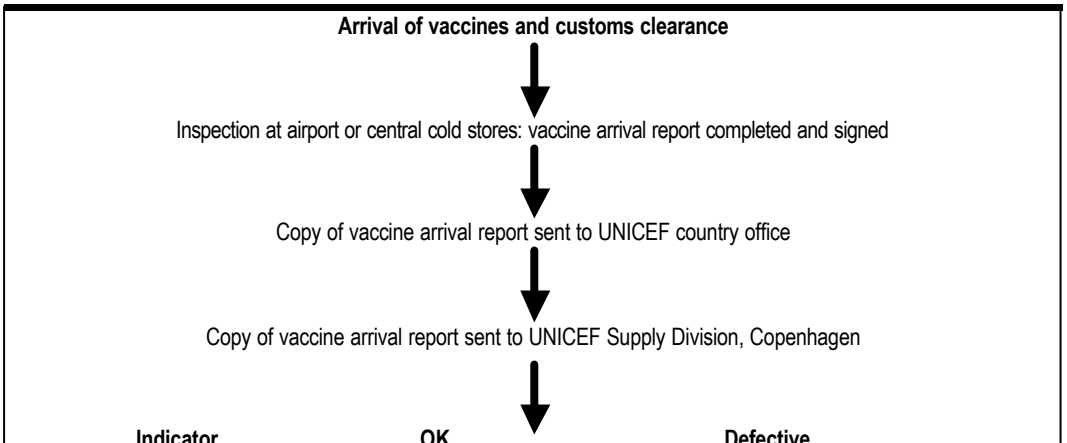
b) Ensuring that the relevant lot release certificates/test protocols from the regulatory authority in the producing country are included with the shipment.

Only vaccine shipments for which these two conditions are satisfied should be accepted by recipient agencies or governments. This requirement applies to all vaccine shipments, whether supplied through UN agencies or obtained from any other source.

The vaccine arrival report provides a means of indicating inadequacies in the shipping process and problems relating to the condition of vaccines at the time of delivery. It can thus form the basis for documenting claims or demands for corrective action.

The following procedure is recommended.

Procedure for reporting vaccine arrivals



Indicator	OK	Defective
Advance notification	Recorded	UNICEF Supply Division to follow up with forwarder
Vaccine type/expiry	Recorded	UNICEF Supply Division to follow up with manufacturer Report to WHO/V&B for further investigation if necessary
Shipping documents	Recorded	UNICEF Supply Division to follow up with forwarder or manufacturer Report to WHO/V&B on problems related to release certificate
Quantities received	Recorded	UNICEF Supply Division to follow up with forwarder or manufacturer
Status of temperature indicators	Recorded	UNICEF Supply Division to report to WHO/V&B; investigation to be carried out

Any defect in the process can lead to compensation claims and/or rejection of a shipment. Each individual situation is investigated and dealt with by all involved parties.

2. Procedure for release of vaccine lots for use

Every country receiving vaccines from UN sources should preferably ensure that each vaccine is ***licensed for use in the country*** and that field performance, i.e. the efficacy and safety of the vaccine, is monitored through an appropriate ***postmarketing surveillance system.*** In countries where NRAs are not fully developed, however, a simplified, abbreviated licensing procedure may be used for vaccines supplied by UN agencies, since all such products have already been fully assessed and prequalified by WHO.

Once a vaccine is licensed and is being routinely shipped to a country for use, UNICEF requires as part of the tender specifications that all shipments be accompanied by the ***lot release certificates issued by the regulatory authority of the producing country***. These documents provide the evidence that the specific lots received have been checked by the appropriate authority in the producing country. In receiving countries without an NRA for vaccines, the national immunization service manager or other responsible staff in the immunization service must ensure that the lot release certificates are included in the shipment for all the vaccine lots received. ***This should be a condition for the acceptance and distribution of the vaccine.***

In addition to the lot release certificates, producers usually include ***their own internal release documents*** with the shipping documents. At country level these documents are sometimes confused with the official lot release certificates issued by the NRA of the producing country. **Annex 3** lists the contact points for NRAs and national control laboratories in all vaccine-producing countries that supply UN agencies. Official lot release certificates for UN-supplied vaccines can ***only*** be issued by one of these bodies. National immunization sercice managers must ensure that ***all*** shipments have lot release certificates issued by the appropriate bodies in the countries of manufacture and that they correspond to the vaccine lots received.

Manufacturers' release documents and any other papers that may accompany a shipment ***do not replace*** and are ***not a substitute*** for the official lot release certificates issued by the NRA of the producing country.

Countries in which an NRA for vaccines is already established or is being developed should release each vaccine lot received. Lot release should be done by checking the release certificate from the country of origin and reviewing the lot summary protocols supplied by the manufacturer. The latter are submitted by the manufacturers on request and provide summary data on the history of each vaccine lot included in the shipment, with technical information on production steps, quality control tests and results obtained.

In some cases, manufacturers send summary lot protocols for the vaccine together with the shipping documents, whether or not the country concerned has requested them. If the receiving country does not have the expertise to review summary lot protocols, these should not be requested. If they are received without having been requested the information provided in them should be disregarded.

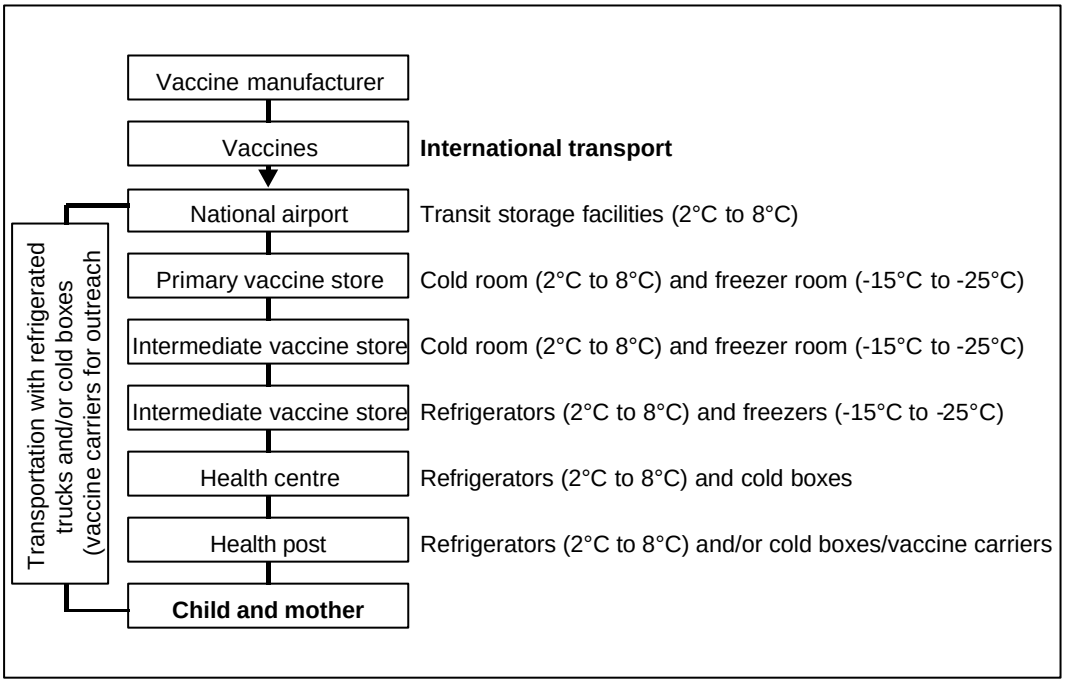
3. Storage and distribution of vaccines and diluents

All vaccines are sensitive biological substances and lose their potency, i.e. their ability to give protection against disease, with time. The rate of loss increases as vaccines are exposed to higher temperatures. In order to maintain their quality, vaccines must be continuously stored at the appropriate temperature from the time they are manufactured until the moment of use. Once potency is lost it cannot be regained or restored. Without proper care a vaccine may eventually lose its entire potency. If this occurs, the vaccine no longer provides any protection against the target disease and is useless. In some cases, heat exposure leading to loss of potency may also cause the vaccine to become more reactogenic.

The cold chain is the system for keeping and distributing vaccines in good condition. It consists of a series of storage and transport links, all of which are designed to keep the vaccine at the correct temperature until it reaches the user. A typical cold chain is shown in figure 1.

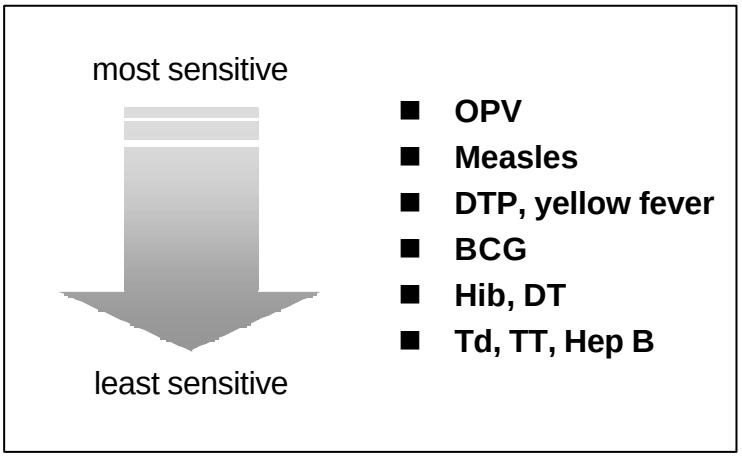
Different vaccines require different storage conditions. What is correct for one vaccine may be dangerous for another. It is therefore vital to know the **correct storage conditions** for each vaccine. Because diluents for vaccines are less sensitive to storage conditions than vaccines they are not normally kept in the cold chain. However, they **may** be kept in the cold chain under certain conditions if space permits.

Figure 1: A typical vaccine cold chain system



3.1 What are the correct conditions for storing vaccines used by national immunization services?

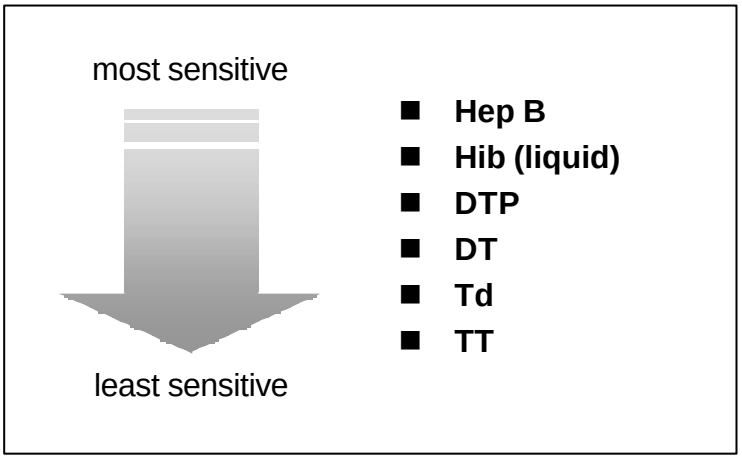
All vaccines are **sensitive to heat** but some are more so than others. The vaccines commonly used national immunization services can be ranked in order of sensitivity to heat as follows.



However, all freeze-dried vaccines become **much** more heat-sensitive after they have been reconstituted, when it is even more important that they are not exposed to heat. See Part 3, Chapter 6, on vaccine reconstitution and administration.

Some vaccines are also sensitive to low temperature: freezing or exposure to temperatures below 0°C can cause loss of potency and the vaccines become useless. It is therefore essential to protect them not only from **heat** but also from **freezing.** The vaccines that are sensitive to **freezing** as well as to heat are indicated below.

Finally, some vaccines are very sensitive to **strong light** and their exposure to ultraviolet light causes loss of potency. Consequently, they must always be protected against sunlight or fluorescent (neon) light. BCG, measles, MR, MMR and rubella vaccines are equally sensitive to light (as well as to heat). Normally, these vaccines are supplied in vials made from dark brown glass, which gives them some protection against light damage, but care must still be taken to keep them covered and protected from strong light at all times.



The recommended conditions for storing national immunization service vaccines are shown in figure 2. The maximum storage times and temperatures are indicated in each case. At the higher levels of the cold chain, i.e. at the national (central) and regional or provincial levels, OPV must be kept frozen between -15°C and -25°C. Freeze-dried vaccines, i.e. BCG, measles, MMR and yellow fever vaccines, may also be kept in this temperature range if there is sufficient space in the cold chain, but this is neither essential nor recommended. At other levels of the cold chain these vaccines should be stored between +2°C and +8°C. All other national immunization service vaccines **should be stored** between +2°C and +8°C at **all levels of the cold chain**.

Remember, if a vaccine is damaged by heat and loses some of its potency the loss can never be restored. The damage is **permanent**. Each time heat damage occurs there is an additional loss of potency. Eventually, if the cold chain is not correctly maintained, all potency is lost and the vaccine becomes useless.

Even when stored at the correct temperature, vaccines do not retain their potency indefinitely. Every vaccine has an **expiry date.** This is the date by which the vaccine must be used. It is printed on all vials and packets during manufacture and is valid only if the vaccine is properly stored and transported at all times in accordance with the guidelines shown in figure 2. If the vaccine is damaged by heat or other causes its potency is reduced **before** the expiry date shown on the vial or packet.

Figure 2: Recommended storage conditions for national immunization service vaccines

<table>
<tr><th></th><th>Primary</th><th colspan="2">Intermediate</th><th>Health Centre</th><th>Health Post</th></tr>
<tr><td></td><td></td><td>Region</td><td>District</td><td></td><td></td></tr>
<tr><td></td><td>6 months[a]</td><td>3 months</td><td>1 month</td><td>1 month</td><td>Daily use</td></tr>
<tr><td>OPV</td><td colspan="2">-15°C to -25°C</td><td rowspan="13" colspan="3"></td></tr>
<tr><td>BCG</td><td colspan="2" rowspan="6">WHO no longer recommends that freeze-dried vaccines be stored at –20°C. Storing them at –20°C is not harmful but it is unnecessary. Instead, these vaccines should be kept in refrigeration and transported at +2°C to +8°C.</td></tr>
<tr><td>Measles</td></tr>
<tr><td>MMR</td></tr>
<tr><td>MR</td></tr>
<tr><td>Yellow Fever</td></tr>
<tr><td>Hib freeze-dried</td></tr>
<tr><td>HepB</td><td colspan="3" rowspan="7">+2°C to +8°C</td></tr>
<tr><td>DTP-HepB</td></tr>
<tr><td>Hib liquid</td></tr>
<tr><td>DTP</td></tr>
<tr><td>DT</td></tr>
<tr><td>TT</td></tr>
<tr><td>Td</td></tr>
<tr><td colspan="6">Diluent vials must NEVER be frozen. When the manufacturer supplies a freeze-dried vaccine packed together with its diluent, ALWAYS store the product at between +2°C and +8°C. Where space permits, diluents supplied separately from the vaccine may safely be stored in the cold chain at between +2°C to +8°C.
Note a. 6 months is the maximum recommended storage time at primary level. This includes the period required to obtain clearance from the national regulatory authority. Wherever possible, a 3-month storage period should be aimed for.</td></tr>
</table>

Only vaccine stocks that are fit for use should be kept in the vaccine cold chain. Any expired vials, heat-damaged vials or vials with VVMs beyond the discard point should **not** be kept in a cold store, refrigerator or freezer, as they may be confused with vaccines of good quality. If unusable vaccines have to be retained for a period before disposal, until, for example, accounting or auditing procedures have been completed, the vials should be kept outside the cold chain, separated from all usable stocks and carefully labelled in order to avoid mistaken use.

3.2 What are the correct storage conditions for diluents used with national immunization service vaccines?

Diluents for vaccines are less sensitive to storage temperatures than the vaccines with which they are used but they may be kept in the cold chain between **+2°C and +8°C** if space permits. When vaccines are reconstituted the diluent should be at same temperature as the vaccine. Sufficient diluent for daily needs should therefore be kept in the cold chain at the point of vaccine use, i.e. a health centre or a vaccination post. At other levels of the cold chain, i.e. central, provincial or district stores, it is not necessary to keep any diluent in the cold chain unless it is planned to use it for reconstituting vaccine within the next 24 hours. However, vials of diluent **must never be frozen.** This would risk cracking the glass and contaminating the contents. Consequently, vials of diluent must never be kept in a freezer or placed in contact with a frozen surface.

3.3 What are the correct conditions for distributing national immunization service vaccines?

Freeze-dried vaccines and their diluents should always be distributed **together** in matching quantities. The vaccines must be kept in the cold chain between +2°C and +8 °C at all times, or, optionally, between -15°C and -25°C **if there is sufficient space in the cold chain**. For each distribution link the cold chain normally comprises cold boxes or vaccine carriers with ice packs. The diluents do not need to be kept in the cold chain unless they are to be used for reconstituting vaccines within the next 24 hours. However, diluents must travel with the vaccine **at all times,** and the diluent must **always** be of the correct type and from the **same manufacturer** as the vaccine that it is accompanying. This is essential in order to ensure that the health worker always has equal numbers of vaccine vials and diluent vials for reconstituting them, and that he/she has the correct type of diluent for the vaccine being used.

Diluents may appear to consist only of water but in fact they usually contain a variety of additives that stabilize specific vaccines after reconstitution. Each vaccine requires a particular diluent. Consequently, diluents are **not** interchangeable. For example, a diluent made for measles vaccine must **not** be used for reconstituting BCG, yellow fever or any other type of vaccine. Moreover, diluent made by one manufacturer for use with a certain vaccine **cannot** be used for reconstituting the same type of vaccine produced by another manufacturer. This means that diluent for measles vaccine made by company "A" **cannot** be used for reconstituting measles vaccine made by company "B".

Some combination vaccines comprise a freeze-dried component, e.g. Hib that is designed to be reconstituted by a liquid vaccine, e.g. DTP or DTP-HepB, instead of a normal diluent. For such combination vaccines it is vital that **ONLY** vaccines manufactured and licensed for this purpose be combined. Furthermore, for combination vaccines in which the diluent itself is a vaccine, **ALL** components must be kept in the cold chain between +2°C and +8°C at all times. As with all other freeze-dried vaccines it is essential that this diluent travel with the vaccine **at all times**.

4. Stock control system

It is essential to keep complete and accurate stock records in order to maintain the quality of vaccines. Stock control involves the following three steps, each of which must be performed regularly, accurately and completely.

Step 1

When vaccine consignments arrive at a storage point their details are checked and recorded.

All details of each consignment must be checked and recorded in the stock register. (In the case of international shipments, see also Part 3, Chapter 1 on checking vaccine shipments on arrival.)

The details to be recorded include:

- type of vaccine;
- quantity received (**doses**);
- vaccine manufacturer;
- manufacturing batch or lot number or numbers (there may be more than one batch or lot in a consignment);
- expiry date or dates for each batch or lot;
- status of VVMs on arrival of the consignment;
- status of the CCM card on arrival of the consignment.

It is advisable to have separate books, ledger sections, or stock cards for each type of vaccine. Each book or section of a ledger should be clearly labelled with the vaccine type. Each delivery of a vaccine should be entered in the record system **on receipt**. If stock cards are used, a new card should be used for each new delivery and only one vaccine batch or lot should be recorded on each card.

In consignments of freeze-dried vaccine, each shipment should **always** arrive with the correct quantity of diluent for reconstituting the vaccine when it reaches the user. For such shipments, the following details must also be checked and recorded for the accompanying diluent:

- type of diluent (i.e. type of vaccine with which it is to be used);
- quantity received (**doses**);
- diluent manufacturer;
- expiry date or dates.

If stock ledgers or books are used, a separate section or book should be maintained and clearly labelled for each diluent, e.g. “diluent for measles vaccine”. If stock cards are used, a new card should be opened for each new delivery of diluent and clear labelling should be used to indicate the vaccine for which the diluent is intended. With regard to vaccines, only one type of diluent should be recorded on each card.

Remember, diluents must **always** be used for the vaccine for which they are manufactured. Diluents are **not** all the same, and they must **never** be interchanged.

Careful stock control and accurate records are **vital** in order to ensure that the **correct** diluent is always kept and distributed with each vaccine type and batch.

Whether using either a stock book or stock card record system, a summary should be drawn up every month or every three months showing the amount of each vaccine and diluent received. Large stores with frequent deliveries and despatches should complete summaries monthly. For smaller stores with less frequent deliveries and despatches, three-monthly summaries are probably sufficient. In either case the amount of each vaccine and diluent received must be totalled at the end of each year.

Step 2

During the time that vaccine stocks are in storage their details and conditions are checked.

All vaccines and diluents have an expiry date, after which they must not be used. All stocks must be distributed **well before** their expiry date in order to allow sufficient time for them to pass through the distribution system and reach the user. Newly arrived stocks generally have a longer period before expiry than ones that have been in storage for some time. Older stocks, therefore, should normally be distributed **first**, i.e. before any newer stocks. This ensures that there is a proper rotation of supplies and that no batch or lot remains too long in storage. All vaccines must be systematically arranged so as to facilitate a first-expiry, first-out stock management system.

During the period that vaccines remain in storage the **expiry dates** of the stock should be regularly checked in order to ensure that there are no older batches that should have been distributed before more recent arrivals. The **integrity of the stocks** should also be regularly checked by reviewing the status of the VVMs and CCM cards for each batch or lot. Any significant colour change in either type of monitor during the period the vaccines have been in storage indicates a weakness in the cold chain system. Repair or maintenance of the cold chain equipment may be needed.

Remember, only vaccine stocks that are fit for use should be included in stock records. Any expired vials, heat-damaged vials or vials with VVMs beyond the discard point should **not** appear in the available stock balance. If such vaccines have to be retained for some time, e.g. until accounting or auditing procedures have been completed, they should be recorded on a separate page or card until disposal takes place.

Step 3

When vaccine consignments leave the storage point for distribution to regions, provinces, districts and, eventually, the user, their details are checked and recorded.

The details of each consignment leaving the store should be recorded in the appropriate ledger, stock book or stock card, and the remaining balance in stock should be calculated. This should be done at **the time of distribution** in order to ensure that all details are correctly recorded. The following information is recorded for each consignment that is distributed:

- quantity distributed (**doses**);
- destination of consignment (i.e. name of region, province, district, etc);
- balance (**doses**) of each batch or lot number remaining after subtraction of the amount distributed.

All details of the vaccines and diluents being distributed should be written on the **delivery note or receipt** that accompanies the consignment to its destination. This enables the receiver of the consignment to know exactly what items are being delivered and to enter the correct details in the stock record system at the next level. All details of each vaccine and diluent should be entered on the delivery note or receipt, including:

- type of vaccine or diluent;
- quantity distributed (**doses**);
- vaccine manufacturer;
- manufacturing batch or lot number or numbers;
- expiry date or dates for each batch or lot;
- status of VVMs as the vaccine **leaves** the store;
- Status of CCM (if used) as the vaccine **leaves** the store.

Sometimes errors occur in counting the quantities of vaccines and diluents entering or leaving stores. **Regular physical checking** is therefore essential in order to ensure that there are complete and accurate stock records of the quantities of vaccines and diluents in storage. In this way a crosscheck is provided on the running balance shown by the records. All stocks of each vaccine and diluent in storage should be counted and the totals should be compared with those shown as the running balance in the stock records. If the result of counting a stock item is different from that shown in the record, the stock should be counted again in order to ensure that there has not been a counting error. If the second count gives the same result as the first the stock record is probably incorrect and must be corrected. The correct balance should be entered on a separate line below the old balance in the stock book or card, and the person who has done the count should also enter and sign a note indicating that a physical check has confirmed the new balance. The corrected total must be used for all subsequent stock calculations.

Physical stock checks should be completed each time a monthly or three-monthly summary is drawn up in the stock book or card. Whether using either monthly or three-monthly checks, an annual physical stock check is also essential.

Figure 3 shows an example of a stock record system for vaccine. This design may be used for either the pages in a stock book or ledger or for a stock card system. It may be used at any level of a storage and distribution system (central, provincial, district or health facility). However, at the health facility level the simplified version of the record shown in figure 4 may be more appropriate. In figures 3 and 4 there are columns for each of the categories of information which must be recorded for consignments arriving at and leaving a vaccine store, and there is a column for the running balance. There is also a box for entering the results of physical stock checks and one for entering the corrected balance to be carried forward to the next page of the stock book or to the next stock card.

For lyophilized vaccines, an alternative form of the stock record system may be used, where spaces are provided for both the vaccine **and its diluent** on the same stock page or card. As already noted, consignments of freeze-dried vaccine must **always** arrive and be stored with the correct quantity of diluent for reconstituting the vaccine when it reaches the user. Recording both the vaccine and its diluent on the same record card may help to remind the storekeeper that the quantities of vaccine and diluent must be equal at all times.

This alternative form of the stock record system specifically for use with lyophilized vaccines is shown in figures 5 and 6.

Figure 3: Example of a stock record sheet or card for vaccines

Vaccine stock record

Store name: _____ **Vaccine:** _____ **Vial size:** _____

Region: _____ **Province:** _____ **District:** _____

Date	From: manufacturer supplier	To: store	Batch number	Expiry date	VVM status	Vaccine quantities			Remarks
						Received (doses)	Issued (doses)	Balance (doses)	
			Carried forward from previous sheet:-						
					Totals:				
								Physical stock check:	
								Carried forward:	

Figure 4: Simplified stock record sheet or card for use at health facility level

Vaccine stock record

Health facility: _____ **Vaccine:** _____ **Vial size:** _____

Region: _____ **Province:** _____ **District:** _____

Date	From: manufacturer supplier	Batch number	Expiry date	Vaccine quantities			Remarks
				Received (doses)	Issued (doses)	Balance (doses)	
		Carried forward from previous sheet:-					
			Totals:				
					Physical stock check:		
					Carried forward:		

Figure 5: Example of a stock record sheet or card for vaccines and diluents

Vaccine stock record

Store name: _____ **Vaccine:** _____ **Vial size:** _____

Region: _____ **Province:** _____ **District:** _____

Date	From: manufacturer supplier	To: store	Batch number	Expiry date	VVM status	Vaccine quantities			Remarks
						Received (doses)	Issued (doses)	Balance (doses)	
			Vaccine carried forward from previous sheet:-						
			Diluent carried forward from previous sheet:-						
	(vaccine)								
	(diluent)								
	(vaccine)								
	(diluent)								
	(vaccine)								
	(diluent)								
	(vaccine)								
	(diluent)								
	(vaccine)								
	(diluent)								
				Totals (vaccine):					
				Totals (diluent):					

Physical stock check (vaccine):	
Physical stock check (diluent):	
Carried forward (vaccine):	
Carried forward (diluent):	

Figure 6: Simplified stock record sheet or card for use at health facility level (vaccines and diluent)

Vaccine stock record

Store name: _____ **Vaccine:** _____ **Vial size:** _____

Region: _____ **Province:** _____ **District:** _____

Date	From: manufacturer supplier	Batch number	Expiry date	Vaccine quantities			Remarks
				Received (doses)	Issued (doses)	Balance (doses)	
		Vaccine carried forward from previous sheet:-					
		Diluent carried forward from previous sheet:-					
	(vaccine)						
	(diluent)						
	(vaccine)						
	(diluent)						
	(vaccine)						
	(diluent)						
	(vaccine)						
	(diluent)						
	(vaccine)						
	(diluent)						
		Totals (vaccine):					
		Totals (diluent):					

Physical stock check (vaccine):	
Physical stock check (diluent):	
Carried forward (vaccine):	
Carried forward (diluent):	

5. Handling of injection equipment and safety boxes

In order to ensure that health workers always have sufficient syringes, needles and safety boxes for the vaccines they use, the concept of a bundle of these items has been introduced. This concept serves to remind managers, programme staff, storekeepers, health workers and, indeed, anyone involved with immunization, that vaccines, syringes, needles and safety boxes must **always** be supplied together and that they are all **essential** for safe and effective immunization. The term "bundle" has no physical connotations, since the items cannot travel in the same containers or occupy space in the cold chain. However, in logistical terms they must **always** be treated as inseparable and every 100 doses of vaccine must always be supplied with 100 sterile syringes and needles and one safety box. If fewer than 100 doses of vaccine are distributed, one safety box must still be supplied to the immunization point. In order to ensure that there are enough safety boxes for distribution to **all** immunization points, including those needing fewer than 100 doses, a reserve factor, e.g. 10% extra, must be incorporated into all calculations of annual orders.

This principle must be observed whenever supplies are sent to a country and **also** when vaccines are distributed **within** a country at all levels of the distribution system. However, in some countries the management of syringes, needles and safety boxes, even if they are covered by the same budget, is effected by departments or units other than EPI, e.g. by the medical stores department. In such cases the bundling of vaccines with syringes, needles and safety boxes requires additional coordination in order to ensure that matching quantities of injection materials and the corresponding numbers of safety boxes are delivered to users at the same time as the vaccines.

Shipping arrangements and routes for syringes and safety boxes may differ from those of vaccines, depending on the geographical location of the country concerned. In many cases, countries receive vaccines by air, while syringes and safety boxes, because of their volume, usually travel by sea or road. Consequently there are different times of arrival. This has to be taken into consideration in the planning for bundled distribution within a country, and extra efforts have to be made to ensure coordination. The bundling of vaccines with syringes, needles and safety boxes is an important practice ensuring that a new sterile syringe and needle is available for each new dose of vaccine to be given and that a safety box is available for the disposal of **every** used syringe and needle.

Droppers for OPV must also be bundled with the vaccine with which they are to be used. They do not need to be ordered as a separate item, however, being supplied with the vaccine by the manufacturer. Some presentations of OPV come with separate droppers, while others come with droppers already attached to the vaccine vial. Droppers do not need to be kept refrigerated but if they are not attached they should be clearly marked to indicate the vaccine with which they are to be used. This makes it possible for matching quantities of droppers and vaccine to be issued during distribution.

The auto-disable (AD) syringe is recommended for all immunizations. It automatically locks and becomes unusable after delivering a single dose of vaccine. This ensures that every injection is given with a new sterile syringe and needle, and prevents the dangerous practice of reusing syringes and the consequent risk of transmitting bloodborne pathogens. Although AD syringes improve injection safety, they must,

like all other syringes, be used with special care in order to avoid the risk of needle-stick injury, contamination and spread of infectious diseases. The safety box is critical in reducing such risks, and **all** syringes, i.e. ADs as well as the standard disposable types, must be placed in a safety box **immediately** after use, without recapping.

Injection equipment, like vaccines, has an expiry date and may become contaminated. Before a syringe is used its packet must be carefully examined in order to ensure that it is intact and not pierced or damaged in any way, and that the expiry date has not been reached. If the packet is damaged in any way or if the expiry date has passed the equipment should be discarded without having been used.

6. Using opened multi-dose vials for subsequent immunization sessions

The WHO multi-dose vial policy (MDVP) previously called "open vial policy" was first introduced in 1995 and revised in 2000 based on scientific data collected on the safety and potency of vaccines recommended by the WHO for use in immunization services. ***(WHO policy statement: The use of opened multi-dose vials in subsequent immunization sessions. WHO/V&B/00.09)***. The revised policy applies only to OPV, DTP, TT, DT, hepatitis B, and liquid formulations of Hib vaccines that meet WHO requirements for potency and temperature stability; are packaged according to ISO standard 8362-2; and contain an appropriate concentration of preservative, such as thiomersal (injectable vaccines only).

The policy states "multi-dose vials of OPV, DTP, TT, DT, Td, hepatitis B, and liquid formulations of Hib vaccines from which one or more doses of vaccine have been removed during an immunization session *may be used* in subsequent immunization sessions for up to a maximum of four weeks, provided that all of the following conditions are met:

- the expiry date has not passed;
- the vaccines are stored under appropriate cold chain conditions;
- the vaccine vial septum has not been submerged in water;
- aseptic technique has been used to withdraw all doses;
- the VVM, if attached, has not reached its discard point."

The revised policy does not change recommended procedures for handling vaccines that must be reconstituted before use, that is, BCG, measles, yellow fever, and some formulations of Hib vaccines. Once they are reconstituted, vials of these vaccines *must be discarded* at the end of each immunization session or at the end of six hours, whichever comes first.

Most freeze-dried (lyophilized vaccines) do not contain preservatives and consequently must not be kept longer than the manufacturer's recommended limit and never longer than *six hours* after they are reconstituted. Liquid injectable vaccines such as DTP, TT, DT and hepatitis B contain preservatives that prevent growth of bacterial contamination. Should contamination take place within the vial, the action of these preservatives prevents any increase in bacterial growth over time and actually decreases the level of contamination.

Implementation of the MDVP requires a series of operational conditions such as proper training of personnel, use of VVMs and re-evaluation of vaccine wastage rates for vaccine forecasting. It is estimated that new wastage rates may be reduced to approximately 15-20%, but this needs to be confirmed at country level before making any radical changes to vaccine ordering policies.

Haemophilus influenzae type b vaccine (Hib), now in use in the immunization services of a number of countries, is available in different formulations and combinations, including liquid single antigen, liquid combined with other antigens, and freeze-dried for reconstitution with a diluent or with another liquid vaccine (DTP, DTP-HepB). All liquid formulations of Hib vaccine contain a preservative and can be used in subsequent immunization sessions. The freeze-dried formulation contains no preservative however, and after being reconstituted with a diluent, must be discarded at the end of the session or within 6 hours, whichever comes first (the same as for BCG, measles, and yellow fever). Certain formulations of lyophilized Hib vaccine are supplied with DTP liquid vaccine. However, although these can be used safely over an extended period, implementing a decision to use them requires additional management and supervision activities, and is not therefore recommended in the absence of specific training of personnel.

7. Vaccine reconstitution and administration

Vaccines are produced in two different forms: as liquids, which are ready to administer, or as freeze-dried powders that must be mixed with a liquid in a process known as reconstitution before they can be used. The reconstitution of a freeze-dried vaccine must be carried out by using a sterile syringe and needle for each vial of diluent. The process of reconstitution requires careful attention and the use of the **correct diluent** for each type and batch of vaccine in order to ensure adequate potency, safety and sterility of the resulting mixture.

The reconstitution process

The reconstitution of freeze-dried vaccine **must** be carried out using **only** the specific diluent provided by the manufacturer for each type and batch of vaccine. Diluents are specifically designed for the needs of each vaccine and are **not interchangeable**. Diluents may appear to consist only of water but in fact they usually contain various additives. These may include :

- stabilizers to improve the heat stability of the vaccine;
- bactericides to maintain sterility after reconstitution;
- chemicals that help to dissolve the vaccine;
- buffers to ensure the correct acidic balance of the mixture.

Special attention should be paid when opening diluent ampoules and freeze-dried vaccine vials in order to avoid any loss of either the liquid diluent or the freeze-dried powder. Reconstitution should be performed away from direct sunlight so as to protect the vaccine from exposure to harmful ultraviolet light. Although vaccines that are sensitive to light are usually supplied in dark brown glass vials they must nevertheless be protected from exposure to sunlight during reconstitution and subsequent use.

Reconstitution involves drawing the diluent into a sterile syringe and injecting it into the vaccine vial. The **whole amount** of diluent provided for reconstitution is used in order to obtain the correct number of doses and the proper concentration of vaccine in the vial. The vial is shaken gently to ensure proper mixing of the liquid diluent and the dry powder. This continues until all the powder has dissolved. After reconstitution the vaccine vial should be kept in the foam pad of a vaccine carrier or wrapped in dark paper or foil and maintained in the cold chain during use. The syringe and needle used for reconstitution should immediately be dropped into a safety box or a safe container without recapping. The needle used for reconstitution must **not** be left in the rubber stopper of the vaccine vial. This would provide a route for pathogens to enter the vial and would thus expose the vaccine to serious risk of contamination.

A new sterile syringe and needle must be used to draw the necessary dose for each immunization injection. All vials of reconstituted vaccine must be discarded at the end of each immunization session or within six hours, whichever is earlier. Such vials must **not** be kept for use in subsequent sessions. **Unlike many multi-dose liquid vaccines, reconstituted vaccines do NOT contain a preservative and thus present an ideal environment for the growth of dangerous organisms.** This is why the maximum period for using reconstituted vaccine is the duration of one immunization session or six hours, whichever is shorter. Remember to avoid any risk of introducing contamination. A vial of reconstituted vaccine should never be allowed to become wet or submerged in water. If a vial is kept in a vaccine carrier during an immunization session it **must** be inserted in a slit in the foam pad of the carrier and must not be allowed to contact any water that may collect in the bottom of the carrier.

For freeze-dried vaccines, a VVM is placed on a part of the vial or ampoule, which is removed during the reconstitution process, e.g. on the metal cap of a vial or the neck of an ampoule. VVMs must be checked before reconstitution to ensure that the vaccine has not been exposed to excessive heat. After reconstitution, when the part where the VVM is located has been removed, the VVM cannot and should not be referred to because it no longer gives valid information.

10 critical steps for safe reconstitution of a vaccine

1. Read the label on the diluent to confirm that it is the correct diluent provided by the manufacturer for the specific vaccine and vial size.
2. Check that the expiry date has not been reached.
3. Check the status of the VVM to make sure that it is not at or beyond the discard point and discard the VVM during the reconstitution process.
4. Cool the diluent to below +8°C, preferably a day before use.
5. Draw the entire content of the diluent into a new sterile mixing syringe and empty the entire contents of the diluent into the vaccine vial.
6. Discard the used mixing syringe and needle into a safety box without recapping.
7. Do not leave the mixing needle in the vaccine vial.
8. After reconstitution, wrap the vaccine vial in dark paper or foil or insert it in a foam pad of a vaccine carrier. **Never** allow the vial to become wet or immersed in water.
9. **Discard all reconstituted vaccine at the end of each session or within six hours, whichever is earlier.**
10. Use a new sterile syringe and needle to withdraw each dose of the vaccine and use the same needle and syringe for injecting the vaccine. After giving the injection, drop the used syringe and needle into the safety box without recapping.

Vaccine administration – avoiding programme errors

Many of the reported adverse events following immunization are caused by programme error, especially by unsafe reconstitution and administration of freeze-dried vaccines. Freeze-dried vaccines require special care during reconstitution and administration. Safe immunization injection practices must be followed with all vaccines, including freeze-dried vaccines. A new sterile syringe and needle must be used for every dose given, and the correct route and dosage must be used for each type of vaccine.

Some frequently observed programme errors are indicated below:

- too much or too little vaccine in one dose;
- immunizations given in wrong part of body;
- syringes and needles improperly sterilized;
- used needles handled carelessly;
- vaccines reconstituted with incorrect diluent;
- wrong amounts of diluent used;
- vaccines prepared incorrectly;

- drugs substituted for vaccine or diluent;
- vaccines or diluents contaminated;
- vaccines stored incorrectly;
- contraindications ignored, e.g. when a child who has had a severe reaction to a previous dose of DTP is immunized again with the same vaccine;
- reconstituted vaccine not discarded at end of immunization session but kept for use in a subsequent session.

Of the above errors, incorrect practices affecting freeze-dried vaccines usually have the more serious consequences, sometimes involving the death of a child.

Wrong diluents

The distribution of vaccines and diluents separately or in non-matching quantities can lead to severe problems. For example, a very dangerous situation may arise if a health facility receives consignments of a vaccine from one manufacturer and subsequently receives diluent for another type of vaccine or from another manufacturer. This may lead to a vaccine being mixed with the wrong diluent and to serious or fatal consequences.

Potentially dangerous medications are sometimes inappropriately stored with vaccines in the same refrigerator. Such medications may be packed in vials or ampoules similar to those containing vaccines or their diluents, and consequently may easily be used by mistake when freeze-dried vaccines are being reconstituted. Missing or illegible vial labels can lead to the use of incorrect substances as diluents. Many examples of such mistakes have been documented, and some of them have caused serious illnesses or fatalities.

It is therefore extremely important to check each diluent before reconstitution in order to ensure that it is the one specifically provided by the manufacturer for the vaccine in question.

Toxic shock

Reconstituted vaccines must be discarded at the end of each immunization session or within six hours, whichever occurs first. Remember, **reconstituted vaccines do NOT contain a preservative,** and contamination can occur very easily. Keeping the vaccine for a subsequent immunization session would be extremely dangerous, as contamination with *Staphylococcus* or another toxic organism could occur. Once established, such organisms grow extremely rapidly and produce a toxin in the vaccine, which causes the toxic shock syndrome. If this syndrome occurs, programme managers should investigate the following possibilities:

a) non-sterile reconstitution or injection technique;

b) failure to discard reconstituted vaccines within six hours.

Need for training

Many cases of improper handling of diluents during and after reconstitution have been recorded, involving not only inexperienced health workers but also more experienced personnel, who sometimes pay less attention and care to this critical process than they should. The training and retraining of all health staff involved in reconstitution and the handling of diluents is therefore extremely important so that programme errors of this type can be avoided.

8. Package inserts

A package insert is small information sheet packed with a vaccine. It carries a description of the vaccine, instructions on the mode of administration, the recommended immunization schedule, and information on side effects, contraindications, storage conditions and available presentations. For UNICEF-supplied vaccines, inserts must be written in English, French, Portuguese and Russian, Spanish being optional, while for vaccines supplied through WHO/PAHO for countries in the Americas, inserts must be written in English, French, Portuguese and Spanish.

Intermediate packing boxes are supplied with a number of copies of package inserts, and these are intended to provide information useful for national immunization service managers and other senior staff centrally and at the higher levels of the distribution system. Inserts do not usually continue to accompany vaccines to the lowest levels of the distribution system, e.g. below the district level, mainly because of the smaller numbers of vials distributed and the consequent lack of sufficient inserts. Furthermore, the languages used on inserts are often not understood by health staff at the facility level. Even if the languages are understood the information on the inserts may not be useful at this level because it is intended for managers and decision-makers.

It is therefore important that senior staff responsible for immunization services review the information provided in package inserts for the vaccines used and conveys all important points to operational staff **in the local language** through training sessions, posters or other appropriate means. All information that is essential for health staff who give immunizations, on the use of polio droppers, the interpretation of VVMs, dose size, storage conditions required, and so on, must be made readily available through staff training.

9. Reporting of adverse events following immunization

Sometimes a suspicion arises that adverse events are related to a vaccine or a particular lot of vaccine. It must be stressed that the likelihood of this is extremely remote. If such a suspicion does occur, however, the **response by health ministry staff** and, when necessary**, UNICEF staff** must be **immediate and effective** in order to ensure that a thorough investigation is conducted and that corrective measures are taken if required. The investigation may uncover programmatic errors that can be corrected. Whenever a severe vaccine-related adverse event is suspected, it is therefore essential that the **UNICEF country office immediately advise the Chief of Immunization, UNICEF Supply Division**, and that a copy be sent to the Regional Office. The reason for alerting the UNICEF Supply Division is that the contract with the vaccine supplier is the key to rapid identification of the source of the vaccine and to information on the production batch that may be implicated. The following factors should be borne in mind.

a) Immediate notification of the entire group of countries and immunization services that might be affected can only be achieved by immediately notifying UNICEF Supply Division. Vaccines are normally used soon after receipt. If the report of an adverse event is delayed, and in the unlikely case that it is related to vaccine quality, millions of children could be unnecessarily exposed to risk.

b) If it becomes necessary to involve the health ministries in other countries that have received the implicated vaccine, the Chief of Immunization, UNICEF Supply Division, contacts the corresponding UNICEF country office and explains the circumstances.

c) In order to ensure a correct and rapid response to the report, UNICEF Supply Division simultaneously notifies the following bodies.

- ***WHO Geneva***

  WHO immediately contacts the vaccine supplier and the appropriate regulatory authority in order to check whether similar cases have been reported elsewhere, and conducts a full batch documentation review. If it is deemed necessary, WHO audits the manufacturing facilities, assists the affected country or countries to conduct case investigations, and arranges vaccine testing. All correspondence to and from WHO is copied to the UNICEF country office and the WHO regional office and country representative.

- ***UNICEF Programme Division***

  In coordination with regional offices and WHO, UNICEF Programme Division assists the UNICEF field office to assess the programmatic impact of the event on the country in question and on any other countries subsequently found to be affected.

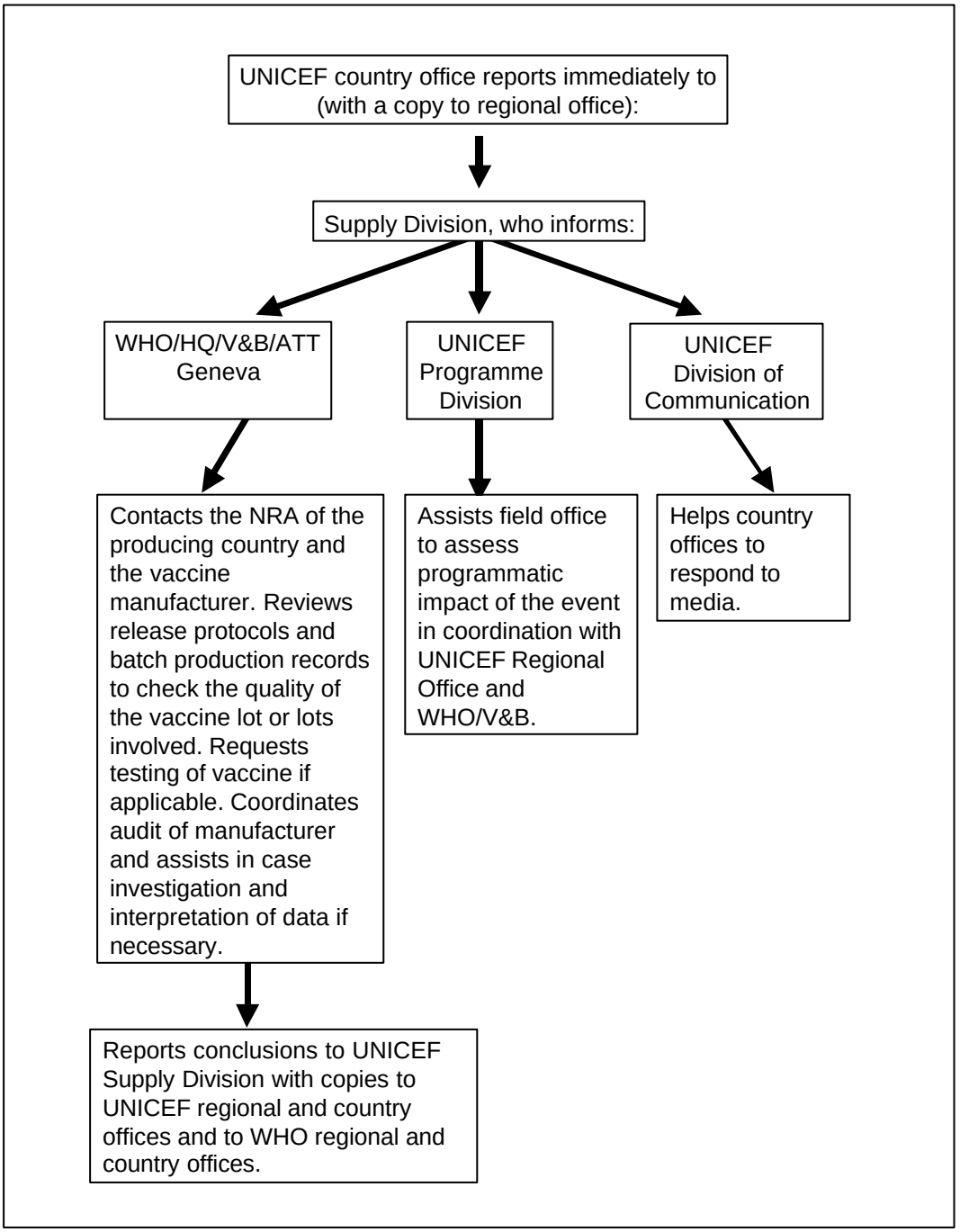
- ***UNICEF Division Of Communication***

  Vaccine-related adverse events are sometimes reported in the press and media in a sensational manner. Biased or misleading press reports may seriously damage country or regional immunization services. A report of an infant severely disabled, injured or dying following immunization may cause

widespread damage to the full range of programme activities. It is therefore essential that the field office be supported in responding to questions from the media. The Division of Communication is experienced in responding to such questions and is in the best position to assist field offices to deal with them effectively and openly.

Figure 7 indicates the reporting steps that are necessary when a suspected adverse event following immunization occurs.

Figure 7: Procedure for reporting a suspected adverse event following immunization



Summary

The present guidelines describe the steps and procedures necessary for ensuring the maintenance of vaccine quality from the point of manufacture to the moment of use at country level. These measures include correct manufacturing procedures under appropriate conditions and with adequate quality controls and certification, safe and efficient shipping procedures in accordance with international guidelines, prompt collection with safe handling and storage in the country of destination, careful distribution and the provision of an adequate cold chain system through all the administrative levels until final injection of the child or mother at the point of use.

Each of the steps and procedures described must be correctly and consistently followed in order to ensure that every child and mother receives vaccine of high quality which gives the required level of protection. Any break in the chain of quality would result in weakened or ineffective vaccine and a reduction in the impact of immunization efforts and of health services as a whole.

The roles and activities of the main groups of partners who help to ensure vaccine quality are as follows.

a) Ensuring that manufacturing procedures are maintained at a high standard is mainly the role of WHO, working closely with manufacturers and regulatory authorities.

b) Ensuring safe and efficient shipping to the countries of destination is mainly the role of UNICEF, working together with manufacturers, airline agencies and transport forwarders.

c) Ensuring vaccine quality once shipments arrive in countries is the responsibility of health ministries and immunization service staff. Experience shows that this stage is the most critical for the maintenance of vaccine quality and the one at which failures are most likely to occur. National immunization service staff therefore have a vital role to play in ensuring that THEIR responsibilities and activities do not allow any break in the chain of vaccine quality and contribute to the fulfilment of a safe, effective and efficient service.

Documents and other useful information

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies. Geneva, 2002 (unpublished document WHO/V&B/02.08; available from Vaccines and Biologicals, World Health Organization, 1211 Geneva 27, Switzerland and on the Internet at http://www.who.int/vaccines-documents/DocsPDF02/www675.pdf).

Regulation of vaccines: building on existing drug regulatory authorities. Geneva, 1990 (unpublished document WHO/V&B/99.10; available from Vaccines and Biologicals, World Health Organization, 1211 Geneva 27, Switzerland and on the Internet at http://www.who.int/vaccines-documents/DocsPDF99/www9918.pdf).

Guidelines on the international packaging and shipping of vaccines. Geneva, 2001 (unpublished document WHO/V&B/01.05; available from Vaccines and Biologicals, World Health Organization, 1211 Geneva 27, Switzerland and on the Internet at http://www.who.int/vaccines-documents/DocsPDF99/www9942.pdf).

Address of WHO/Access to Technologies Internet web site, which gives a list of prequalified vaccines, details of producers and other information:

http://www.who.int/vaccines-access/vaccines/Vaccine_Quality/UN_Prequalified/UN_Prequalified_producers.htm

Annex 1:

Model certificate for the release of vaccines acquired by United Nations agencies

(Revised 1988)

(To be completed by the national control authority of the country where the vaccines have been manufactured, and to be sent by the vaccine manufacturer to UNICEF.)

The following lots of ……[1] vaccine produced by ……[2] in ……,[3] whose numbers appear on the labels of the final containers, meet all national requirements.[4] Part A[5] of Requirements for Biological Substances No. ……[6] (Requirements for ……[1], published in 19……. [if applicable, revised 19……, addendum 19…….]) and Requirements for Biological Substances No. 1 (General Requirements for Manufacturing Establishments and Control Laboratories, published in 1959; revised 19……).[7]

Lot No.	Expiry date	Lot No.	Expiry date
.....	.....	.....	.....
.....	.....	.....	.....
.....	.....	.....	.....
.....	.....	.....	.....

As a minimum, this certificate is based on examination of the manufacturing protocol. The Director of the National Control Laboratory (or Authority as appropriate)[8]

Name (typed) .....

Signature .....

Date .....

1 Indicate type of vaccine (measles, oral poliomyelitis, tetanus, diphtheria-tetanus, diphtheria-pertussis-tetanus, BCG).

2 Name of manufacturer.

3 Country.

4 If any national requirements are not met, specify which one(s) and indicate why release of the lot(s) has nevertheless been authorized by the national control authority.

5 With the exception of the provisions on shipping, which the national control authority may not be in a position to control.

6 Indicate the reference number of the relevant Requirements for Biological Substances published by WHO.

7 These requirements were revised in 1965; a further revision is in preparation for consideration by the WHO Expert Committee on Biological Standardization in 1989.

8 Or his or her representative.

Annex 2:
Vaccine arrival report (VAR)

Vaccine arrival report

RETURN TO (agency) COUNTRY OFFICE
FOR FORWARDING TO (supplying agency)

Country			
report No		Date of report	

Place of inspection	Date and time	Name of cold store, date and time vaccines entered into cold store

PART I - ADVANCE NOTICE

Date received by consignee	Copy airwaybill (AWB)	Copy of packing list	Copy of invoice	Copy of release certificate	
		Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐

Other documents (if requested)	

PART II - FLIGHT ARRIVAL DETAILS

AWB number	Airport of destination	Flight No.	ETA as per notification		Actual time of arrival	
			Day	Time	Day	Time

Name of clearing agent: _____ On behalf of: _____

PART III - DETAILS OF VACCINE SHIPMENT

Procurement agency	Purchase order No.	Consignee	Vaccine description (Type and doses/vial)	Manufacturer	Country

Vaccine				Diluent/droppers			
Lot number	Number of boxes	Number of vials	Expiry date	Lot number	Number of boxes	Number of units	Expiry date

(Please continue overleaf if necessary)

	Yes	No	Comments
Was quantity received as per shipping notification?			
If not, were details of short-shipment provided prior to vaccine arrival?			

PART IV - DOCUMENTS ACCOMPANYING THE SHIPMENT

Copy of invoice with packing list	Copy of release certificate	Vaccine arrival report	Other
Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	

PART V - STATUS OF SHIPPING INDICATORS (list only No. of boxes inspected, coolant and any problems noted)

Total number of boxes inspected:		Coolant type:	Dry ice ☐	Ice packs ☐	None ☐

Box No. (boxes with problems only)	Lot No.	VVM (1,2,3,4)	Cold chain monitor card index (A,B,C,D)	Freeze watch indicator (DTP, DT,TT,HEP B,HIB liq)	Date/time of inspection

(please continue overleaf if necessary)

Temperature recorder (if available, attach copy of record)	Box No.	Model	Serial No.

PART VI - GENERAL CONDITIONS OF SHIPMENT

What was the condition of boxes on arrival?	
Were necessary labels attached to shipping boxes?	
Other comments: (continue overleaf if necessary)	

PART VII - NAME AND SIGNATURE

Authorized inspection supervisor	Date	Central store or immunization services manager	Date

RETURN TO (agency) COUNTRY OFFICE
FOR FORWARDING TO (supplying agency)

Guidelines for completing vaccine arrival report (VAR)

The purpose of the VAR is to monitor cold chain conditions during transport, compliance /deviations with shipping instructions and ensure adequate record keeping of information related to vaccines. It can also serve as the basis for documenting claims or initiating corrective action if problems occur.

Recipient governments, UNICEF Country Offices and UNICEF Supply Division are responsible for the implementation of the vaccine arrival report, and for taking corrective action as necessary.

Components of the report:

Use one for each shipment and for each vaccine in the shipment. In the case of short-shipments (part of the original quantities not delivered), one report should be filled for each part of the delivery.

The heading of the report is for the name of recipient country, report number and details of place and date of inspection and storage. The report number is an internal number for organizing records, for which the format COUNTRY CODE-YEAR-REPORT NUMBER (e.g. BUR-2002-001) is suggested. In the case of short-shipments, the numbers for the different deliveries (for one vaccine type only) would be BUR-2002-001.1, BUR-2002-001.2 etc.

Part I – ADVANCE NOTICE: Indicate dates and details of documents received in advance of the vaccine shipment.

Part II – FLIGHT ARRIVAL DETAILS: Fill details of expected and actual arrival times for the shipment, as well as name of clearing agent and for whom they act (i.e., MoH/UNICEF, etc).

Part III – DETAILS OF VACCINE SHIPMENT: Fill details of the order (i.e. procurement agency, purchase order number, consignee, vaccine description etc). For **each batch of vaccine** included in the shipment, indicate the number of **shipping boxes, vials and expiry date**. The same applies to diluent/droppers when present. **Diluents for freeze-dried vaccine and droppers for OPV should be considered as integral parts of the vaccine, and always reported on the same form. Separate deliveries should be considered as short-shipments.** The figures entered in the "number of boxes" column should always match the number shown in the packing list. If it does not, indicate if advance notice of such change in the quantity sent was provided.

Counting of the number of individual vaccine boxes in each shipping box is not required in the report.

Part IV – DOCUMENTS ACCOMPANYING THE SHIPMENT: The box containing the shipment documents should be indicated in the packing list (often these will be in box number 1). Verify that all necessary documents are present and fill the form accordingly.

PART V – STATUS OF SHIPPING INDICATORS: Inspection of the temperature indicators is an essential part of the report. The temperature monitors should be checked **in all boxes** before vaccines are put into cold storage. In case of very large shipments, or when immediate storage in the shipping boxes is required, a representative number of boxes should be checked prior to placing the shipment in the cold store. Complete inspection of all boxes the next day, or as soon as possible thereafter, indicating date and time when the complete inspection took place.

Indicate the number of boxes inspected (this should equal the total number in the shipment), the type of coolant used and details of any temperature exposure if detected. **Only boxes in which temperature indicators show a change of colour should be reported on this report form.**

If temperature recorders are included, indicate the box(es) in which recorder was shipped, model and serial number(s). Attach photocopy of chart to vaccine arrival report.

PART VI – GENERAL CONDITIONS OF SHIPMENT: Indicate if the shipping boxes were received in good condition.

PART VII – NAME AND SIGNATURE: The form should be signed by the authorized person responsible for the inspection and by the central store manager or the manager of immunization services.

Once completed, a copy of the report should be sent to the procuring agency country office, to be forwarded to the agency responsible for the report. Any problems reported will be taken to the appropiate levels (i.e. manufacturer, forwarder, WHO, etc.) for necessary action and correction.

If necessary, enter additional information on the shipment here:

Vaccine				Diluent/droppers			
Lot number	Number of boxes	Number of vials	Expiry date	Lot number	Number of boxes	Number of units	Expiry date

Total number of boxes inspected:		Coolant type:	Dry ice ☐	Ice packs ☐	None ☐

Box No. (boxes with problems only	Lot No.	VVM (1,2,3,4)	Cold chain monitor card index (A,B,C,D)	Freeze watch indicator (DTP, DT,TT,HepB,HIB liq.)	Date/time of inspection

Annex 3:

List of contact points for NRAs (countries with vaccine producers supplying to UN agencies)

NRAs in North America

Therapeutic Products Directorate
Bureau of Biologics and Radiopharmaceuticals
Tunney's Pasture
0603C Ottawa (Ontario) K1A OL2
Canada

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike, Suite 2000
Rockville, MD 20852
USA

NRAs in Europe

Scientific Institute of Public Health – Louis Pasteur *
Juliette Wytsmanstraat, 14
B-1050 Brussels
Belgium

National Drug Institute
26 Yanko Sakazov Boulevard
1504 Sofia
Bulgaria

Danish Medicines Agency
378, Frederikssundsvej
DK-2700 Brønshøj
Denmark

Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS)
Direction des Laboratoires et des Contrôles
321, Avenue Jean-Jaurès
F-69007 Lyon
France

National Institute of Public Health
1097 Budapest, Gyáli út.2-6
H-1966 Budapest Pf. (P.O. Box) 64
Hungary

Ministero della Sanità *
Istituto Superiore di Sanità
Viale Regina Elena, 299
I-00161 Roma
Italy

Paul Ehrlich Institut
Paul Ehrlich strasse 5l-59
Postfach 1740
D-63225 Langen
Germany

Swiss Federal Office of Public Health
Schwarzenburgstrasse 165
CH-3097 Liebefeld
Switzerland

National Institute for Biological Standards and Control *
Blanche Lane, South Mimms
GB-Potters Bar
EN6 3QG
United Kingdom

NRAs in Oceania

Therapeutic Goods Administration
Commonwealth Department of Health and Family Services
PO Box 100
Woden ACT 2606
Australia

NRAs in Asia

Central Drugs Laboratory *
Central Research Institute
Kasauli 173204
India

Directorate General of Food and Drug Control
JI. Percetakan Negara 23
Jakarta 10560
Indonesia

National Institute of Infectious Diseases *
1-23-1 Toyama Shinjuku-ku
Tokyo 162
Japan

Ministry of Health and Welfare
Bureau of Pharmaceutical Affairs
Seoul
Republic of Korea

***** National control laboratories with officially delegated responsibility for issuing release certificates for vaccines.

The Department of Vaccines and Biologicals was established by the World Health Organization in 1998 to operate within the Cluster of Health Technologies and Pharmaceuticals. The Department's major goal is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases.

Five groups implement its strategy, which starts with the establishment and maintenance of norms and standards, focusing on major vaccine and technology issues, and ends with implementation and guidance for immunization services. The work of the groups is outlined below.

The *Quality Assurance and Safety of Biologicals team* team ensures the quality and safety of vaccines and other biological medicines through the development and establishment of global norms and standards.

The *Initiative for Vaccine Research* and its three teams involved in viral, bacterial and parasitic diseases coordinate and facilitate research and development of new vaccines and immunization-related technologies.

The *Vaccine Assessment and Monitoring team* assesses strategies and activities for reducing morbidity and mortality caused by vaccine-preventable diseases.

The *Access to Technologies team* endeavours to reduce financial and technical barriers to the introduction of new and established vaccines and immunization-related technologies.

The *Expanded Programme on Immunization* develops policies and strategies for maximizing the use of vaccines of public health importance and their delivery. It supports the WHO regions and countries in acquiring the skills, competence and infrastructure needed for implementing these policies and strategies and for achieving disease control and/or elimination and eradication objectives.

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World Health Organization
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Email: vaccines@who.int
or visit our web site at: http://www.who.int/vaccines-documents

WHO

unicef