STATE MEDICAL AND PHARMACEUTICAL UNIVERSITY
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EPIDEMIOLOGY DEPARTMENT

Angela PARASCHIV

IMMUNOPROPHYLAXIS OF INFECTIOUS DISEASES

Methodical guide for medical students

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This guide is written according to analytical program in Epidemiology for medical students from General and Dentistry faculty. It is contains basic knowledge that has to know medical student about the immunoprophylaxis of infectious diseases. An important issue is practical assignments where students will be able to solve real situation with infectious diseases. Each topic has questions to check student's skills in this domain. The guide is designated for students from General Medicine of 6th year and Dentistry of 4th year. The author considers that this guide will be a useful source of university practical skills.

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IMMUNOPROPHYLAXIS OF INFECTIOUS DISEASES

Introduction

Specific immunoprophylaxis is one of the most effective measures influencing the evolution of infectious diseases. Because of it was eradicated smallpox, reduced morbidity experienced by polio, diphtheria, mumps, tuberculosis, measles, tetanus, etc. In recent years the rate of decreased morbidity was reduced in some infections controlled by immunoprophylaxis, at some of them are even registering an increase in morbidity. It is explained by bad organization and control of immunoprophylaxis of infectious diseases.

In order, to organize and perform an effective prophylaxis of infectious diseases, with maximum epidemiological result, medical staff, employed in realization of immunoprophylaxis in practice, must have wide knowledge and skills in organization, performing and effectiveness evaluation of undertaken measures.

Goal of practical lesson

This lesson is directed to study the means used in immunoprophylaxis, methods of it application, to learn how to organize immunoprophylaxis in medical practice.

Lesson Plan

1. Quiz of initial knowledge.
2. Study of immune remedy used in immunoprophylaxis, conditions of keeping (Cold Chain) and method of its using.
3. Determination of epidemiological indications for immune-biological remedies.
4. Discussions about organization policy and immunoprophylaxis methods.
5. Practical assignments.
6. Vaccination department work.

Material support

The study is organized at the Epidemiology and Vaccination Department. Immuno-biological remedy (vaccines, serum, immunoglobulin's, etc.). Recording and report forms.

Student has to know

1. The role of immunoprophylaxis.
2. Classification of remedies used in specific immunoprophylaxis.
3. Principles of obtaining and comparative characteristics of immune-biological remedies.
4. Request for immune-biological remedies.
5. Methods of using of immune-biological remedies. Technical means.
6. Indications and contraindications for vaccination.
7. Vaccination schedule.
8. Reactions and complications after vaccination. Risk factors.
9. Factors that determine the effectiveness of vaccination.
10. Organization policy of immunoprophylaxis (planning, performing, evidence, report, methods of effectiveness evaluation).

Student must be able to:

1. Determine the validity of immune-biological remedies.
2. To elaborate plan of vaccination and to calculate necessary vaccines dose.
3. To determine indications and contraindications for vaccination.
4. To estimate the effectiveness of vaccination.
5. To fill in forms for evidence and report about vaccination.

Informative material

Immunoprophylaxis is an antiepidemic measure (of public health) taken in order to prevent the spreading of infectious diseases via immunization of the susceptible groups of the population. At the moment, there are over 30 infectious diseases that can be prevented by vaccination: smallpox, diphtheria, tetanus, pertussis, polio, measles, mumps, chikenpox, Haemophilus influenzae type b infection, VHA, VHB, TB, meningococcic infection, pneumococcic infection, influenza, typhoid fever, cholera, rabies, tick encephalitis, anthrax, yellow fever, rotaviral infection, tularemia etc. Infectious diseases in the prevention of which immunoprophylaxis holds the main role are called **vaccine preventable diseases.** Immunoprophylaxis can be used as an individual protection agains rabies, yellow fever etc.

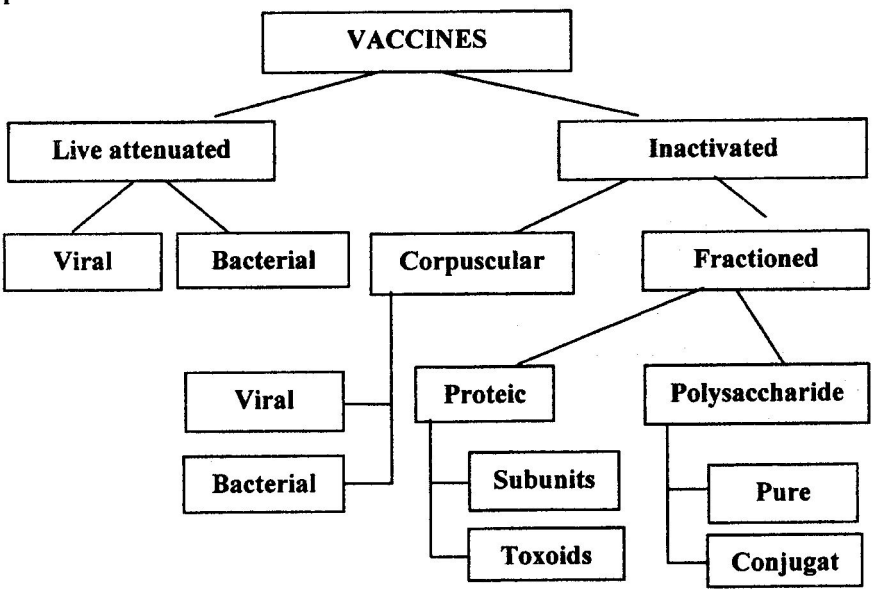
Biological remedies used in immunoprophylaxis of infectious diseases can be divided in groups:

1. Preparations that led to formation of active immunity (vaccines).

2. Preparations that led to formation of passive immunity (serum, immunoglobulin's).

3. Biological preparations inhibit the multiplication of the causative agent in the organism (phages, interferon).

In order, to develop artificial active immunity in epidemiological practice is used vaccines:



Live attenuated vaccines – suspension of live microorganisms. The main peculiarities of live vaccines is loosing of capacity to develop disease, but keeping in the same time antigenic and multiplication peculiarities in human or animal organism, increasing their immunity.

It can be produced form pathogen microorganisms (bacteria, viruses, etc) attenuated by following methods:

- Treated by temperature, chemical substances (alcohol, acetone, formaline), or biological substances;
- Cultivating in multiple mediums;
- Biotechnological methods.

Live vaccines have following peculiarities:

- Develop long and stable immunity;
- It is enough one administration of vaccine;

– Is possible to administrate via different methods (coetaneous, subcutaneous, per os, intranasal).

Disadvantages of live vaccines consists in short period of keeping that determine the necessity of following strict rules of transportation, using, keeping (cold chain), because of live microorganisms that are sensitive to external factors, especially to temperature changes. From this point of view, in order to extend the period of vaccine administration is necessary to dissolve it in physiological substance. Keeping and transportation of live vaccines must be not higher than +2+8°C degrees. Minus degrees do not have negative effects on vaccine immunogenity. Air and humidity penetration of vaccines led to inactivation of preparation. Live vaccines do not contain preservatives, that why after the opening the preparation and dissolving it is necessary to follow very strictly aseptic conditions and period of its using. Also, is forbidden the contact of vaccines with disinfectants.

In case of live vaccines, is necessary to exclude antibiotics, sulphanilamides and immunoglobulin's using 2 days before and 1–2 weeks after the vaccination because they can reduce the effectiveness of vaccination.

Live vaccines are: against tuberculosis (BCG), polio, measles, mumps, smallpox, tularemia, plague, brucellosis, anthrax, rabies, yellow fever, etc.

Inactivated Vaccines – bacteria or viruses species inactivated through physical (temperature, radiation) or chemical agents (formaline, acetone, alchool). Inactivated vaccines are more stable to environmental changes because there are produced in liquid form. Keeping and transportation of these vaccines is necessary to be till +10°C. Frozen vaccine has less immunogenity than live vaccines and its defrosting led phizicochimical changes of vaccine. Disadvantages of inactivated vaccines consists of lower immunological activity compare with live vaccines, determining repeated administration in order to, develop the necessary level of immunity.

In this group of vaccines are included: vaccines against typhoid fever, pertussis, tick-born encephalitis, cholera, leptospirosis.

Chemical vaccines – represents a variety of inactivated vaccines; by chemical methods is extracted only antigenic part or antigenic fraction. These are organic complex – polysaccharide, proteic, purify lipids. From chemical vaccines are taken out non-imunogenic substance of

microorganism (cellular protein and nucleic acides) that make vaccin less reactogenic compair with attenuated vaccine. Chemical vaccines can be used against: typhoid fever, meningococal infection, endemic tythus, hepatitis B, etc.

Toxoids – vaccines prepared from bacteria toxin detoxified through formalin (0,3–0,4% sol. of formalin at temperature of 37–40°C). After purification, toxoids can be used for increasing the immunological effect as well, attaching on absorbance, usually ammonium sulphate. Toxoids led to develop of long and stable immunity, acting not directly on pathogen agent.

In medical practice are used toxoids in prevention of diphtheria, tetanus, botulism, staphylococcus infection, cholera, etc.

Vaccines that contains antigen of one type of microorganism are called **monovaccine.**

Vaccines that contains antigen of different species of microorganisms are called **associated,** e.g Diphtheria+Pertusis+Tetanus.

Artificial vaccines (synthetic) – novel immunogene preparations produced by chemical syntheses method which consists of artificial reproduction of antigenic determinants with similar peculiarities as natural one. By this method was prepared vaccine against Hepatis B, which contains synthetic polypeptides similar with superficial antigen in hepatits B.

Another group that assures a quick immunity developing is immune serums, and immunoglobulins. These preparations are used in emergency prophylaxis of infectious diseases. After it administration is developed passive immunity which last for 2–4 weeks.

Immunoglobulin's and serums can be divided in two groups: homologous and heterologous. Homologous preparations are prepared from human blood (from donors, placental bortion), and heterologous – from hiperimunizated animal with different antigens.

Homologous preparations are not foreign for human organism, practically do not have reactions, and after administration flow 4–5 weeks in the body. Heterologous preparations are foreign to human organism, is administrated with major precautions through fractionated method.

In medical practice serums and immunoglobulines are used against tetanus, botulism, measles, smallpox, rabies, anthrax, influenza, tick-born encephalitis, etc.

In prevention of infectious diseases can be used preparations which have inhibits effect or killing of pathogen agent. In this group are: phages, and interferon.

Phages are viruses which parasite bacteria contributing to its lyses. In order, to prevent and for treatment as well phages are used against typhoid fever, cholera, dysentery, staphylococcus infection.

Interferon represents micro molecular proteins which brakes multiplication of viruses. It is produced from leucocytes or fibroblast. This preparation is used to prevent and treat influenza, hepatitis etc. Its action is lasting a short period of time. Positive effect has been seen at the onset of disease as a result of blockage of virus penetration into the cell. In recent years, more often is used analog of this preparation – reoferon prepared through geno-engineering methods.

Requests for immunological preparations:

Immunological preparations must correspond to following request:

- To be immunogenic and safe for human;
- To not have foreign microorganisms;
- To have a standard of production, for transportation, keeping and using.

Immunologic preparations are packed in ampoules or bottles with different volume. On each ampoules or bottles is mandatory to have a label with following data:

1. Produced enterprises;
2. Vaccine name;
3. Volume and dose;
4. Vaccine content (if it is multivaccine);
5. Series number;
6. Control number;
7. Data of production and overdue.

Preparations with broken wrapping, without label, or incomplete data on it, without instructions or overdue data are forbidden for administration. Also, are not available preparations which changes their physical aspects (color, opalescence, with nor characteristic sedimentation). Immunological preparations are produced in liquid or solid form. The contents of solid form have to repeat the pack form. In case of incorrect keeping or overdue it acquires a balloon or dust form. In case of liquid form is allowed to have sediment. But on the bottle has to be a

inscription „shake it before using". If this instruction is not on the bottle preparation has to be transparent and without sediment.

Methods of vaccine administration

Immunization effectiveness in main part is determined by administration method of vaccines in organism. The majority preparations are administrated subcutaneous, intracutaneous, intramuscular, or intravenous. For some live vaccines is characteristic coetaneous, per os, intranasal administration as well.

In order, to produce a maximum immunogenic effect, inactivated vaccines are administrated repeatedly. From this point of view, vaccine administration has to be performed at the requested period of time, which corresponds with optimal period of reconstruction of organism. Any deviation from immunization schedule slows production of antibodies.

Oral polio vaccine (OPV)

The vaccine most commonly used is made from a LIVE ATTENUATED POLIO VIRUS, which is administered orally as a liquid. The vaccine is quickly destroyed by temperatures above +8o C and of the commonly used childhood vaccines, OPV is the most sensitive to heat. It is not damaged by freezing however, and can be safely frozen, thawed and re-frozen any number of times without damage. The vaccine should not be refrozen or used, however, if the Vaccine Vial Monitor indicates that the vaccine is at the discard point.

Administration: Vaccine is given orally (NEVER give by injection)

Doses needed: 4 doses to complete primary immunization (before 1 year)

Storage conditions: –15 to – 25°C (central, oblast and rayon levels) 0 to +8°C (health facility levels).

Measles vaccine

Measles vaccine is made from a LIVE ATTENUATED MEASLES VIRUS. It is a freeze dried powder, which must be reconstituted before use. Reconstitution is **only** with diluent from the manufacturer of the vaccine in use. Administration is by subcutaneous injection. The dry frozen vaccine remains potent for a long period if stored under frozen conditions. Like OPV, it can be safely frozen, thawed and re-frozen any number of times without damage. The diluent however, must never be

frozen. After re-constitution, the vaccine becomes very heat-sensitive, with rapid loss of potency so it must be used within 6 hours. This is also very important because this vaccine does not contain a preservative to prevent contamination.

Administration: Vaccine is given by subcutaneous injection

Doses needed: 1 dose to complete primary immunization (before 1 year, or older if national immunization schedule specifies).

Storage conditions: – 15 to – 25°C (central, oblast and rayon levels) 0 to +8°C (heath facility levels).

DPT vaccine

DPT, sometimes called a "triple" vaccine, contains 3 components, DIPHTHERIA TOXOID, inactivated PERTUSSIS VACCINE and TETANUS TOXOID. It is a liquid vaccine, which is administered by deep intramuscular injection. The vaccine is heat-sensitive, although to a lesser extent than OPV and measles, but is immediately destroyed by freezing. The freezing temperature is approximately –3°C, so storage temperatures should never be less than 0°C to allow a margin for safety. When DPT is at rest the liquid is clear, with a white sediment forming at the bottom of the vial. Shaking of the vial makes the vaccine a white, uniformly turbid liquid, with no granules.

Administration: Vaccine is given by deep intramuscular injection in the thigh;

do NOT give DPT in the buttock.

Doses needed: 4 doses to complete primary immunization; 3 doses before one year and the 4th dose at 16–18 months.

Storage conditions: 0 to +8°C (at all levels of the cold chain).

Sometimes, small numbers of infants experience serious adverse reactions to DPT vaccine, usually due to the Pertussis component. Such infants should receive DT vaccine (i.e., Diphtheria with Tetanus vaccines only, without the "P" component) as an alternative for completing their primary series. **Minor** reactions to DPT vaccine, with local redness and mild fever, are frequent, and can occur in up to 50% of immunizations, but this subsides without treatment in one or two days.

NEVER use adult formulation Td vaccine (i.e., Tetanus vaccine with reduced Diphtheria content) as a substitute for DPT vaccine.

BCG vaccine

BCG is a LIVE BACTERIAL VACCINE. It is a freeze-dried powder which must be reconstituted before use. Reconstitution is **only** with diluent from the manufacturer of the vaccine in use. Administration is by intradermal injection. The dry frozen vaccine retains potency for a long time if stored under frozen conditions, but is readily destroyed by sunlight and is thus supplied in dark brown glass ampoules to reduce light penetration. The vaccine is not damaged by freezing and can be frozen, thawed and re-frozen without damage. The diluent however, must never be frozen. In practice however, BCG vaccine is not normally stored in the frozen state. After reconstitution, the vaccine rapidly loses potency and must be used within 6 hours. This is very important because the vaccine does not contain a preservative to prevent contamination.

Administration: Vaccine is given by intradermal injection.

Doses needed: 1 dose to complete primary immunization (before *1 year*)

Storage conditions: 0 to +8°C (at all levels of the cold chain).

Mumps vaccine

Mumps vaccine is a freeze-dried powder, which must be reconstituted with diluent before use. Reconstitution must be **only** with diluent from the manufacturer of the vaccine in use. Administration is by deep intramuscular injection. The dry frozen vaccine retains potency for a long time if stored under frozen conditions and can be frozen, thawed and re-frozen without damage. The diluent however, must never be frozen. After reconstitution, the vaccine rapidly loses potency and must be used within 6 hours.

Administration: Vaccine is given by deep intramuscular injection in the thigh; do NOT giveMumps vaccine in the buttock. Doses needed: 1 dose given between 12 and 18 months.

Storage conditions: –15 to –25 C (central, oblast and rayon levels) 0 to +8 C (health facility level)

IMPORTANT!

- Measles, BCG and mumps vaccines must be reconstituted only with the diluent provided by the manufacturer of the vaccine in use.
- Never use other diluent.
- Diluent must be cold, between 0 and 8 degrees Celsius, before being mixed with the vaccine.
- When reconstituted, the vaccine must be used within 6 hours, and any remainder discarded.

Hepatitis B vaccine

Hepatitis B Vaccine is a liquid vaccine available as a recombinant yeast or as a plasma derived preparation. It is administered in a deep intramuscular injection. The vaccine is about as sensitive to heat as DPT vaccine, and is destroyed immediately if frozen. The storage temperature should therefore never be below 0°C.

Administration: Vaccine is given by deep intramuscular injection in the thigh; do NOT give hepatitis B vaccine in the buttock.

Doses needed: 3 doses to complete primary immunization (before 1 year)

Storage conditions: 0 to +8 C (at all levels of the cold chain)

Table 2

Dosage and administration of EPI vaccines (summary)

Vaccine	No. of doses for Primary Series	Administration	Dose
OPV	4	Oral	2 drops
Measles	1	Subcutaneous	0.5 ml
DPT	4	Deep intramuscular	0.5 ml
BCG <1yr	1	Intradermal	0.05 ml
BCG >1yr	1	Intradermal	0.1ml
hepatitis B	3	Deep intramuscular	0.5 ml
Mumps	1	Deep intramuscular	0.5 ml

IMPORTANT:

- All vaccines lose potency gradually, even at correct.
- Storage temperatures – observe expiry dates.
- All vaccines suffer much faster loss of potency when exposed to temperatures above +8 degrees C.
- Any loss of vaccine potency is irreversible.
- Damage due to successive exposures to heat or light is cumulative.
- Hepatitis B, DPT, DT, Td and TT are destroyed by freezing.
- BCG and measles vaccines are damaged by exposure to strong light as well as heat.

Organization of immunoprophylaxis includes following measures groups:

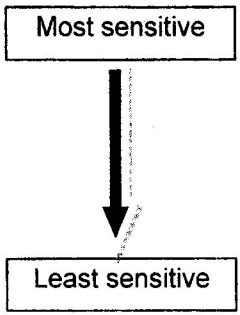
1. Preparation measures to immunization;
- Information collecting about the population number and age structure;
- Elaboration of vaccination plan and calculation of necessary doses;
- Insurance of medical institutes with necessary preparations;
- Insurance of medical institutes with technical means and devices, evidence and recording forms, shock kits;
- Organization of seminars and trainings about immunization;
- Population education about importance of vaccination.

2. Measures performed in immunization period:
- Medical examination before vaccination;
- Vaccination and its evidence in statistic forms;
- Surveillance of vaccinated persons during 1-2 hours;
- Determination of reactions frequency and its intensity;
- Inactivation of vaccine wastes and instruments sterilization.

3. Measures performed after vaccination:
- Presentation of monthly reports on performed vaccination;
- Determination of immunological and epidemiological effectiveness,
- Estimation of immunoprophylaxis effectiveness as antiepidemic measures (for one or more years).

Annual plan of immunoprophylaxis is elaborated according to complete data base about population groups and vaccinations already performed. In plan are included vaccinations of all children who live in served territory by medical institutes.

All vaccines are sensitive biological substances that progressively lose their potency (i.e., their ability to give protection against disease). This loss of potency is much faster when the vaccine is exposed to temperatures outside the recommended storage range. Once vaccine potency has been lost, returning the vaccine to correct storage condition cannot restore it. Any loss of potency is permanent and irreversible. Thus, storage of vaccines at the correct recommended temperature conditions is vitally important in order that full vaccine potency is retained up to the moment of administration. Although all vaccines are heat-sensitive, some are far more sensitive than others are. Those listed in Section 1.2 can be arranged in order of decreasing sensitivity to heat as follows:



- Live oral polio vaccine (OPV)
- Measles (Lyophilized)*
- Pertussis and Mumps (Lyophilized)
- Hepatitis B
- Adsorbed Diphtheria-Pertussis-Tetanus vaccine (DPT)
- Adsorbed Diphtheria-Tetanus vaccine (DT, Td)
- BCG (Lyophilized)*
- Tetanus Toxoid (TT)

***Note:** These vaccines become much more heat sensitive after they have been reconstituted with diluent.

Some vaccines are also highly sensitive to being cold. Such vaccines will lose their potency entirely if frozen, although others can sustain freezing without any damage whatsoever. It is therefore vitally important to know the CORRECT storage conditions for each vaccine, and to ensure that each is kept always at the recommended conditions.

Table 1

Sensitivity of vaccines to freezing

Vaccines damaged by freezing	Vaccines unaffected by freezing
DPT	BCG *
DT	OPV
Td	Measles *
TT	Mumps
Hepatitis B	

*** Note:** Vaccines freeze at temperatures just below zero.
- BCG and measles vaccines must not be frozen after reconstitution
- diluent for any vaccine must never be frozen.

In addition to being temperature-sensitive, several vaccines are also highly sensitive to strong light, and thus need to be kept in the dark as far as possible. BCG and Measles are those most affected. These vaccines must never be exposed to sunlight, and are given some protection by being supplied in vials of dark brown glass to reduce the penetration of light. This alone will not prevent light damage however, and great care must be taken to protect them during use. As with loss of potency due to heat, any loss of potency due to light is also permanent and irreversible.

Note that all losses of potency are CUMULATIVE, that is, each time a vaccine is exposed to incorrect temperature or strong light its potency will decrease. Since the vaccine may have already been exposed previously, any new exposure, however small, will increase the damage to the vaccine. Ultimately, due to cumulative damage, the vaccine may be completely destroyed, with all its potency lost. Note also that even when stored at the correct temperature vaccines do not retain potency forever. Therefore the expiry date marked on a vial or packet of vaccine must be strictly observed even when correct storage temperatures have always been maintained.

Estimation of immunoprophylaxis effectiveness

Estimation of immunoprophylaxis effectiveness is performed through immunological and epidemiological method.

Epidemiological effectiveness can be appreciated:

- By comparing of morbidity and lethality before and after vaccination;
- By studying of epidemic process indexes in dynamics before and after vaccination (periodicity, sezonality, age distribution, etc);
- By determination of epidemiological effectiveness index (K) that shows how many times the morbidity is lower among vaccinated people than non-vaccinated (B).

$$K = \frac{B}{A}$$

- By determination of epidemiological effectiveness coefficient (E) that shows with how many percents the morbidity is lower at vaccinated people compared with non-vaccinated;

$$E = \frac{B - A}{B} x100$$

- By determination of correlation coefficient between coverage indexes with vaccination of the population (or immune status indexes) (X) and morbidity (Y).

The appreciation of immunological effectiveness is performed in base of:

- Calculation of immunological effectiveness index (E):

$$E = \frac{a \times 100}{A} \text{ or } E = \frac{a \times 100}{A} - \frac{b \times 100}{B}$$

Where: a – number of vaccinated people in experimental group who have positive immunological reaction;

b – the same index among vaccinated with „placebo";

A – number of people vaccinated with vaccine;

B – number of people who received „placebo".

In case of absence of control group only the first formula is used.

In order, to appreciate immunoprophylaxis the following indexes are used:

- Vaccinal – number of vaccinated people against an infection in percent from total number of children who are at evidence at every age separately and in groups;
- Immune layer – total number of vaccinated people and of those who have infection in their history in percent from the total number of children till the age of 14 for every year separately and in groups;
- Minimal level of antibodies at certain nosological forms.

Table 2

Minimal level of antibodies which protect against some infections

Disease	Method of investigation	Minimal level of antibodies for protection
Diphtheria	PHR	0,015–0,03 IU/ml
Tetanus	PHR	0,1 IU/ml
Whooping cough	PHR	1:80
Measles	PHR	1:10
Mumps	IHR	1:10
Polio	IHR	1:4
Influenza	IHR	1:40
Rubella	IHR	1:64

The cold chain system

"Cold chain" refers to the process used to maintain optimal conditions during the transport, storage, and handling of vaccines, starting at the manufacturer and ending with the administration of the vaccine to the client. Potency over time, especially if exposed to heat, and in addition, some also lose their potency when frozen. It is obviously pointless to immunize with impotent vaccine, and efforts to reach extremely high levels of immunization coverage will be useless if the vaccine being administered has insufficient potency to give the necessary protection. Attention to maintaining correct temperatures during storage and transport of vaccine is thus a major task for health workers.

The cold chain system comprises three major elements:

- **Personnel**, who use and maintain the equipment and provide the health service;
- **Equipment** for safe storage and transportation of vaccines; and
- **Procedures** to manage the programme and control distribution and use of the vaccines.

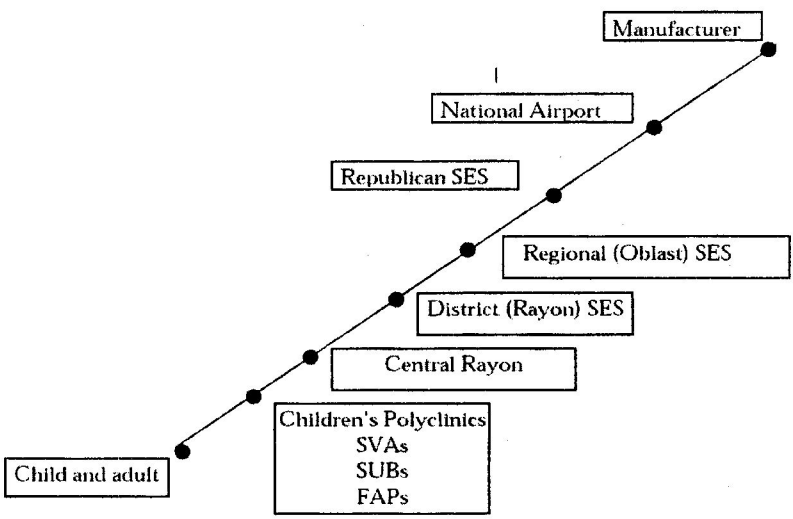


Figure 1. **A typical cold chain system**

REMEMBER:

- Even the most expensive and sophisticated equipment will not ensure an effective cold chain if not correctly used and managed by health personnel.

Competent personnel and efficient procedures are a vitally important part of the cold chain system:

Figure 1 illustrates a typical cold chain system, showing the various steps which may be involved in delivering vaccine from the manufacturer to the person being immunized. Not all countries have an identical system, but the vaccine must always be maintained at a safe temperature throughout its entire journey; – during transport, while waiting at the airport, when being kept in cold store, freezer or refrigerator, and finally, during the course of an immunization session at the health facility.

Vaccine storage

The optimum temperature for refrigerated vaccines is between +2°C and +8°C. For frozen vaccines the optimum temperature is –15°C or lower. In addition, protection from light is a necessary condition for some vaccines. Vaccines are sensitive biological products which may become less effective, or even destroyed, when exposed to temperatures outside the recommended range. Cold-sensitive vaccines experience an immediate loss of potency following freezing. Vaccines exposed to temperatures above the recommended temperature range experience some loss of potency with each episode of exposure. Repetitive exposure to heat episodes results in a cumulative loss of potency that is not reversible. Table 3 shows the maximum times and temperatures for storage of EPI vaccines at different levels of the cold chain as recommended by WHO. During transport between one level and the next, all vaccines must be maintained at a temperature between 0o and +8oC. If unopened and OPV, Measles or Mumps vaccines become unfrozen during transit, they can be safely re-frozen at the next level without any harm or loss of potency to the vaccine.

Table 3

Recommended vaccine storage temperatures/times for different levels of the cold chain

Vaccine	Republican SES (National)	Regional SES (Oblast)	District SES (Rayon)	Health Facilities
Maximum Storage time	up to 6 months	up to 3months	up to 1 month	up to 1 month
OPV	-15 to -25°C	-15 to -25°C	-15 to -25°C*	0 to +8°C
Measles	-15 to -25°C	-15 to -25°C	-15 to -25°C*	0 to +8°C
Mumps	-15 to -25°C	-15 to -25°C	-15 to -25°C*	0 to +8°C
DPT	0 to +8°C	0 to +8°C	0 to +8°C	0 to +8°C
Hep B	0 to +8°C	0 to +8°C	0 to +8°C	0 to +8°C
DT	0 to +8°C	0 to +8°C	0 to +8°C	0 to +8°C
Td	0 to +8°C	0 to +8°C	0 to +8°C	0 to +8°C
TT	0 to +8°C	0 to +8°C	0 to +8°C	0 to +8°C
BCG	0 to +8°C	0 to +8°C	0 to +8°C	0 to +8°C

Notes:

(1) If freezers are not available at rayon level these vaccines may be stored at 0° to + 8°C.

(2) This table shows maximum storage times at each level. Maximum times are based on the relative security of storage expected at each level, and together ensure that any vaccine will take at most one year to be sent through the cold chain and be used. Normally you would expect to use most vaccine stocks before the maximum time is reached.

(3) Remember to check the expiry dates of all vaccines and ensure that they will not expire during storage or before they can be distributed and used.

(4) Rotate vaccine stock: vaccine received first should be distributed or used first ("First In, First Out") unless a Vaccine Vial Monitor (VVM) shows that another batch should be distributed or used first.

However, information on vaccine degradation is sparse and multipoint stability studies on vaccines are difficult to perform. In addition, information from manufacturers is not always available, so it can be difficult to assess the potency of a mishandled vaccine[1].

Maintaining the potency of vaccines is important for several reasons.

- There is a need to ensure that an effective product is being used. Vaccine failures caused by administration of compromised vaccine may result in the re-emergence or occurrence of vaccine preventable disease.
- Careful management of resources is important. Vaccines are expensive and can be in short supply. Loss of vaccines may result in the cancellation of immunization clinics resulting in lost opportunities to immunize.

- Revaccination of people who have received an ineffective vaccine is professionally uncomfortable and may cause a loss of public confidence in vaccines and/or the health care system.

An estimated 17% to 37% of healthcare providers expose vaccines to improper storage temperatures. Refrigerator temperatures are more commonly kept too cold rather than too warm[2,3]

When a cold chain break is identified after a vaccine has been administered, consult your local public health office or immunization program* for advice. The type of vaccine, duration and temperature of the exposure will be taken into account when assessing the situation. Serological testing or revaccination may be suggested[4].

IMPORTANT!

- Vaccine must always be transported in insulated boxes with sufficient ice to ensure it remains between 0 and +8°C. Never use un-insulated boxes, or forget the ice!

The "shake test" was one method previously used as an indicator that a liquid vaccine was inappropriately frozen. A positive shake test is the formation of granular particles which show up in the liquid upon shaking the vaccine after the vaccine was frozen and then thawed.

The shake test is not a reliable method of testing vaccine potency because a positive shake test may or may not occur after a liquid vaccine has been frozen.

Cold chain equipment and its use

Each level requires different storage equipment depending on the quantity of vaccine to be stored, the duration of storage and the temperature necessary. All equipment must be able to keep vaccines safely whatever the outside temperature, and however the climate varies at different times of the year. There are also different types of equipment designed for transporting vaccines between the various levels of the cold chain, and for use during immunization sessions. All types of cold chain equipment contain one or more of a series of organic gas compounds, used either as their working fluid, in manufacture of their insulation, or both. These gas compounds, known as CFC gases, were once considered to be ideal for cold chain purposes, but have more recently been found to have harmful effects if allowed to escape into the environment. Thus, a new range of cold chain equipment was introduced from 1996 to replace

those using CFC gases. The new equipment is described as being CFC-free equipment. The symbol shown in *Figure 2* is used on refrigerators, cold boxes and vaccine carriers to indicate that the equipment has been made using CFC-free material for the insulation and CFC- free gas for the refrigerator's cooling system. These materials are less harmful to the environment than those previously used for the manufacture of such equipment.

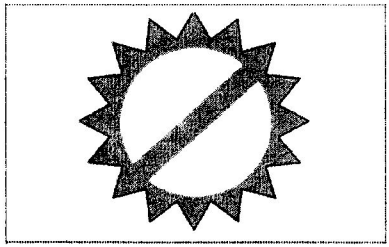


Figure 2. WHO/EPI symbol for CFC-free cold chain equipment

Equipment for vaccine transportation

All transportation links in the cold chain must be able to protect vaccines from heat and sunlight. However, in some winter conditions, when atmospheric temperatures are below 0°C, you may also have to take measures to prevent vaccines from becoming too cold. Cold boxes and vaccine carriers are designed to give the required protection.

The "cold life" of a cold box or vaccine carrier is the number of hours it will keep the vaccines at a safe temperature. According to WHO test procedures, it is the number of hours the cold box or vaccine carrier will maintain a temperature below +10°C after it has been loaded with the recommended number of frozen icepacks. The cold life of each cold box or vaccine carrier differs and depends on the following factors:

- Type of cold box or vaccine carrier, insulation material, thickness, method of construction and foaming agent used;
- mass and initial temperature of icepacks that are put into the cold box or vaccine carrier;
- the number and duration of openings; and
- the surrounding air temperature. This factor greatly affects the cold life, the lower the air temperature, the longer the cold life.

In the winter season air temperatures get extremely low in certain areas, and transport of PT, DT, Td, TT and Hepatitis B must be done

with utmost care to avoid freezing the vaccines. In this case, the cold box must protect vaccines from becoming too cold, and the "warm life" is the number of hours it will keep the vaccines above their freezing point. To protect these vaccines from freezing under winter conditions, the following measures will help:

Fill the icepacks with water from the tap, **but do not freeze them;**

- Keep DPT, DT, Td, TT and Hepatitis B in the center of the cold box or vaccine carrier, and farthest from the icepacks;
- Use a Freeze Watch Indicator in addition to the normal CCM and thermometer;
- Do not leave the cold box or vaccine carrier outdoors or in very cold rooms for longer than necessary;
- Do not leave cold box or vaccine carrier in unheated means of transport longer than necessary.

A cold box is an insulated container with a tight fitting insulated lid. The temperature inside the box is maintained by icepacks. The cold box is designed for:

- Collection and transport of large quantities of vaccine at temperatures between 0° to +8° C;
- Storage of vaccine during maintenance periods, e.g. when cleaning or defrosting a refrigerator or freezer;
- Emergency storage of vaccine, e.g., during breakdowns of cold chain equipment, power failures, and similar situations.

Different levels of the cold chain require different types and sizes of cold boxes, according to the population served. An example is shown in *Figure 3:*

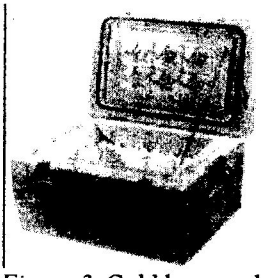


Figure 3. Cold box used in the cold chain

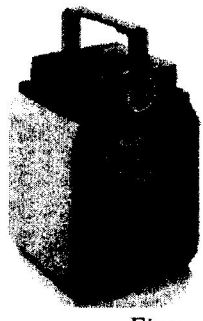


Figure 4. Vaccine carriers

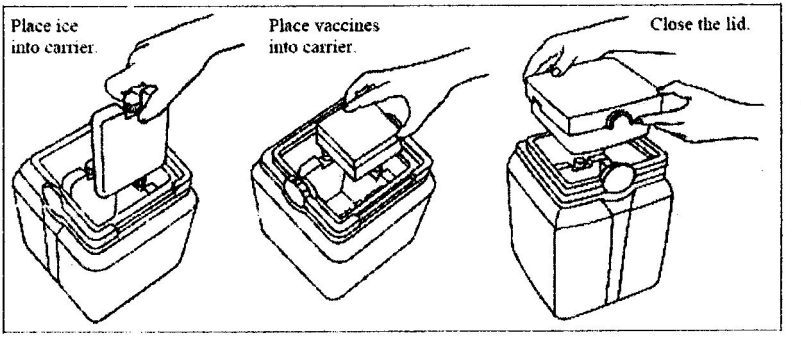


Figure 5. How to load a vaccine carrier

Icepacks are rectangular plastic containers to be filled with plain water. They come in many different sizes, although WHO recommends only two sizes:

- **0.4 liter to be used with vaccine carriers.**
- **0.6 liter to be used with cold boxes.**

The icepacks, once frozen, are used to maintain the temperature between 0 and +8°C in cold boxes and vaccine carriers.

Always have 2 sets of icepacks for each cold box or vaccine carrier – one set to be frozen while the other is being used.

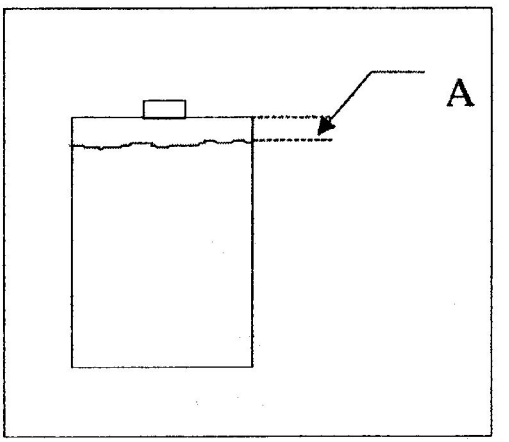


Figure 6. How to fill an icepack

CONTROL AND MONITORING OF TEMPERATURES

Maintaining correct temperatures during storage and transport of vaccines is a critical task for the health worker. Temperatures must be regularly measured and recorded in order to:

- ensure storage of all vaccines at the correct temperature conditions, and
- ensure the correct operation of your cold chain equipment.

Monitoring of temperatures should be a routine activity, and a task that is carried out at the start and end of each working day. There are a number of different types of monitoring devices to help you measure, control and record storage temperatures.

Every piece of cold chain equipment must be fitted with a thermometer to measure the internal temperature at any given moment. If the refrigerator, freezer or cold box is not fitted with a thermometer, there is no way of telling if the vaccine is being stored at the right temperature and is maintaining its potency. The following types of thermometer are commonly used in the cold chain system to measure temperatures.

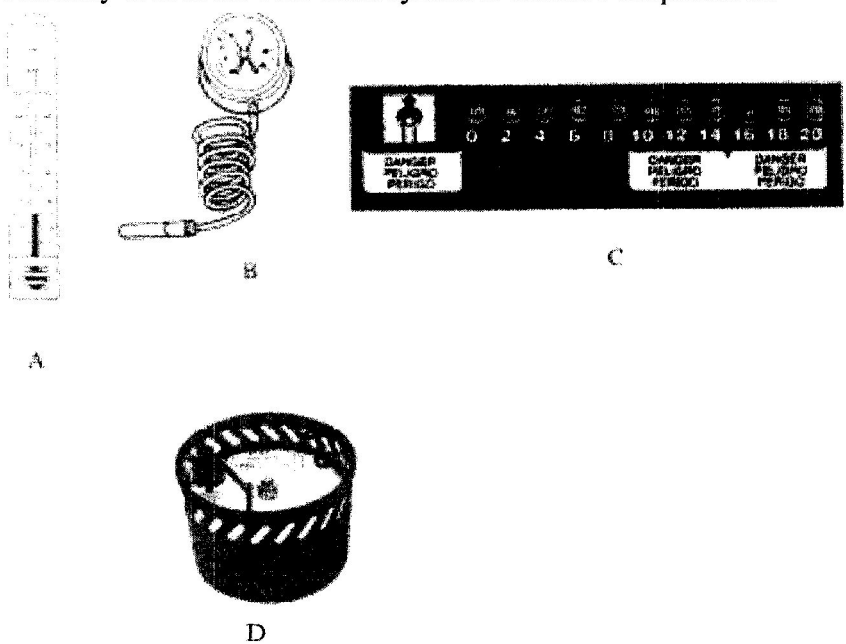


Figure 7. Common thermometer types.

A. Alcohol or mercury thermometer: Shows precise temperatures in the immediate area of the sensing bulb. This is the recommended type for use with refrigerators or freezers.

B. Dial thermometer: shows the current temperature; a max/min version also shows the maximum and minimum temperatures since the previous resetting of the hands.

C. Liquid-crystal thermometer: Comprises a row of temperature-sensitive indicator spots; the spot corresponding to the current temperature changes to a bright green colour. This type of thermometer is suitable only for indicating the temperatures in cold boxes but is not for use in refrigerators.

D. Recording thermometer: This type records the temperature continuously on a paper chart, each chart typically recording for a period of 7 days. Recording thermometers are used mainly for cold rooms and freezing rooms. Note the date on each chart when it is fitted, and when you remove/change the chart, keep the old charts as a permanent record of store performance.

Cold chain monitor card

A cold chain monitor card (CCM) is designed to follow the vaccines from the point of manufacturer to the end user. Throughout the journey the CCM monitors the temperature and will keep a record of vaccine exposures that have been experienced. The monitor is activated by removing a small protective strip, and after activation the indicator will show an irreversible colour change in one of the 4 "windows" if storage temperature rises above a certain level. (For imported vaccines, the CCM is activated by the vaccine manufacturer).

The first three windows of the indicator (A, B and C) will change gradually and irreversibly from white to blue when temperatures are above 10°C. First A will change, then B and then C.

The A, B and C indicators change relatively slowly, for instance, at a temperature of 21° C window A changes its colour entirely in 2 days; window B, in 6 days and window C, in 11 days. If the temperature exceeds 34° C, window D changes in colour from white to blue also.

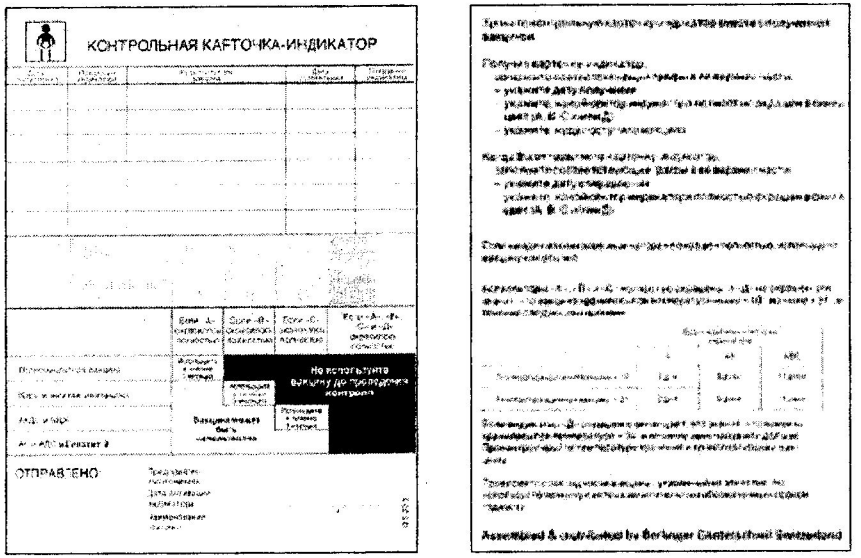


Figure 8. Cold chain monitor card, front and back.

How to interpret the CCM:

- If windows A, B, C and D are all white, use vaccines normally.
- If windows A only, A and B, or A, B and C are completely blue, but window D is still white it means that the vaccine has been exposed to a temperature above +10°C but below 34°C for the number of days shown in *Table 5*.
- Follow instructions on card before using the vaccines.
- If window D is blue it means that there has been a break in the cold chain of a temperature higher than 34°C for a period of at least two hours. This would indicate a serious cold chain failure has occurred, and an immediate investigation is needed.

Table 5

Time-temperature exposure of CCM card

	Index		
Windows completely blue	A	AB	ABC
At a temperature of 12°C	3 days	8 days	14 days
At a temperature of 21°C	2 days	6 days	11 days

An example of a CCM card for a vaccine batch part way along the distribution system is shown in *Figure 9.*

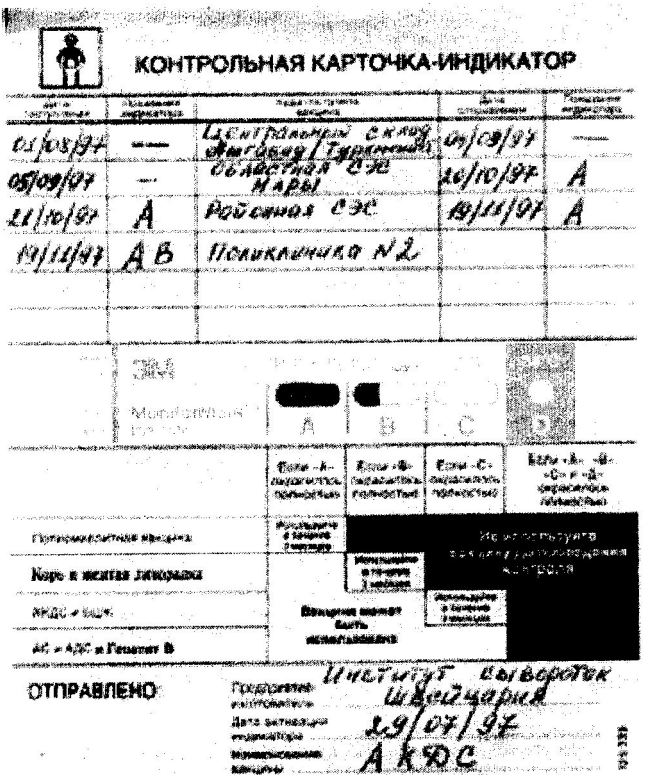


Figure 9. Example of exposed CCM card.

In this example, Index A and B are all blue, C and D are still white. That means that the Polio must be tested before use, the measles must be used within 3 months DPT & BCG and TT & DT can be used as normal. The card also tells you that there is something wrong with the cold chain at the Pruta SES. The temperature has been e.g. 12°C for 8 days.

REMEMBER!

- The CCM must always be kept with the vaccines with which it came.
- Follow your manager's instruction on what to do with the CCM after the vaccines that it came with have been used.

Vaccine vial monitor

The vaccine vial monitor (VVM) is a new type of monitor device applied directly to each vaccine vial by the manufacturer. It enables the health worker to verify at the time of use, whether vaccine is in useable condition and has not lost its potency and efficacy due to temperature exposure. The VVM progressively changes colour with heat exposure, and gives a visual indication when exposure has occurred. The vaccine itself of course, exhibits no visible change with heat exposure. At present VVMs are only used on foreign-manufactured OPV, but similar monitors are under development for other vaccines. All OPV supplied through UNICEF has been fitted with VVMs since mid-1996.

Note that VVMs are not a substitute for CCMs; they are an additional device to use in conjunction with other monitors.

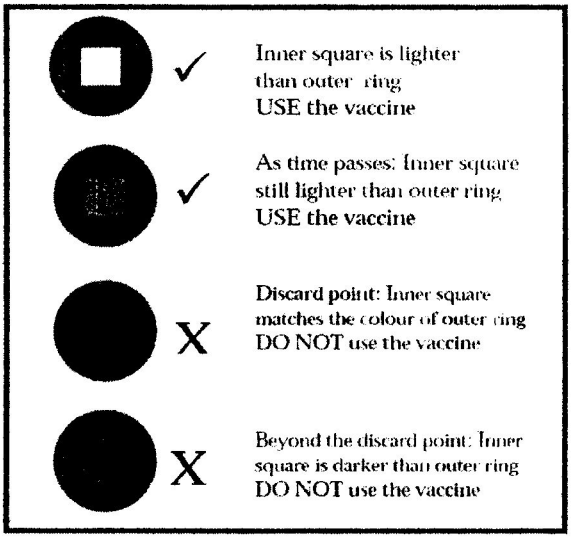


Figure 10. How to read the VVM

How to read the VVM:

The only important point is the colour of the inner square relative to the outer circle:

- If the inner square is lighter than the outer circle, the vaccine may be used.
- If the inner square is the same colour or darker than the outer circle, the vaccine must not be used.

A simple glance at the monitor will be enough to show whether the vaccine can be used or not.

Table 6

Times recorded for a VVM attached to a vial of OPV

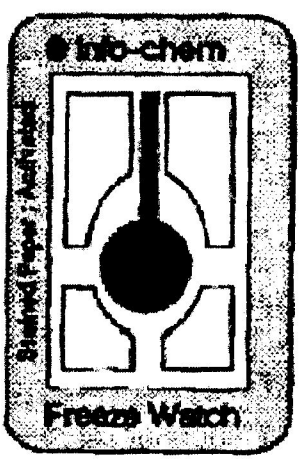
Constant temperature, day and night	Time for VVM to reach "discard point"
At room temperature: +25°C	8 days
At room temperature: +20°C	20 days
In a refrigerator: +4°C	180 days
In a freezer: –20 C	over 2 years

Questions

FreezeWatch indicator

The FreezeWatch indicator is an irreversible temperature indicator, which shows if vaccines have been exposed to temperatures below 0°C. It consists of a white backing card with a small vial of red liquid, all contained in a plastic casing. If the indicator is exposed to temperatures below 0°C for more than one hour, the vial will burst and release the red

Before freezing



After freezing

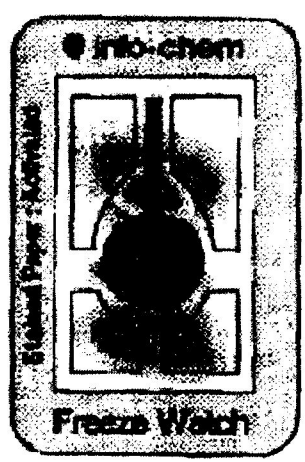


Figure 11. FreezeWatch indicators inactivated and activated

WARNING!

- If a FreezeWatch indicator has burst, the vaccines it accompanied should be checked before use.

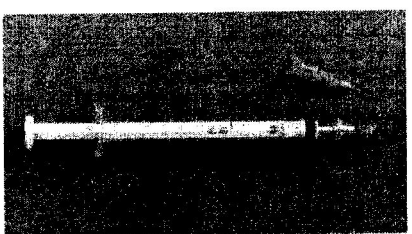
liquid. The indicator is used to monitor the storage conditions of DPT, DT, Td, TT and Hep. B. vaccines that lose their potency if frozen. (FreezeWatch indicators supplied before 1997 burst at –4°C; the design was changed because Hepatitis B vaccine freezes at –0.5°C) *Figure 11*, on the left image, shows the indicator with an intact vial, and the right image shows the indicator with a burst vial. Changes in the colour of the paper are irreversible and will be clearly seen.

Syringes, needles and sterilisation

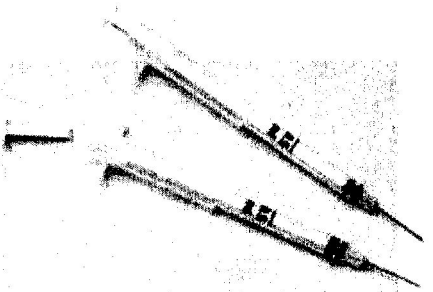
Ensuring safe immunizations extends right to the place and time that the vaccine is administered during an immunization session. Correct use and care of injection equipment is therefore just as important as safe vaccine handling and maintaining the cold chain.

Injection equipment can be divided into four categories:

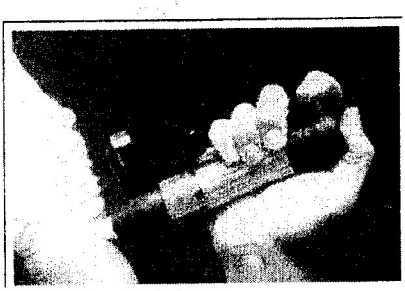
- reusable syringes and needles
- disposable syringes and needles
- single use syringes (the "auto destruct" system)
- syringes without needles (jet injectors)



Reusable syringes and needles



Disposable syringes and needles



Jet injector gun

"Auto-destruct" syringe

Vial size and doses/vial for EPI vaccines

OPV	Foreign vaccine* (10 and 20 dose vials)	2 drops/dose
	Russian vaccine (50 dose/5ml vials)	2 drops/dose
	Russian vaccine (25 dose/5ml vials)	4 drops/dose
	Russian vaccine (10 dose/2ml vials)	2 drops/dose
MEASLES	Foreign vaccine (10 dose vials)	0.5 ml/dose
	Russian vaccine (10 dose vials)	0.5 ml/dose
	Russian vaccine (5 dose vials)	0.5 ml/dose
	Russian vaccine (1 dose vials)	0.5 ml/dose
DPT	Foreign vaccine (10 and 20 dose vials)	0.5 ml/dose
	Russian vaccine (20 dose vials)	0.5 ml/dose
	Russian vaccine (3 dose vials)	0.5 ml/dose
	Russian vaccine (1 dose vials)	0.5 ml/dose
BCG	Foreign vaccine (20 dose ampoules)	0.05 ml/dose
(Infants < 1yr)	Russian vaccine (10 & 20 dose ampoules)	0.1 ml/dose
BCG	Foreign vaccine (20 dose ampoules)	0.1 ml/dose
(Children > 1yr)	Russian vaccine (10 & 20 dose ampoules)	0.1 ml/dose
BCG – m	Russian vaccine (10 & 20 dose ampoules)	0.1 ml/dose
HEPATITIS B VACCINE		
	Foreign vaccine (10 and 20 dose vials)	0.5 ml/dose
	Foreign vaccine (1 dose vials)	1.0 ml/dose
	Russian vaccine (20 dose vials)	0.5 ml/dose
MUMPS VACCINE		
	Foreign vaccine (10 and 20 dose vials)	0.5 ml/dose
	Russian vaccine (20 dose vials)	0.5 ml/dose

* Foreign vaccines used in immunization programmes are usually supplied in 10 or 20 dose vials. However, foreign vaccine manufacturers can also provide almost any vial size ordered.

Annex 2

Vaccine stock record

Store Name: _____ Vaccine: _____ Vial Size: _____

Region: _____ Province: _____ District: _____

Date	From: Manufacturer/ Supplier	To: Store/ Health Unit	Batch Number	Expiry Date	Vaccine Quantities Received (doses)	Issued (doses)	Balance (doses)	Remarks
-	-	-	Carried	forward	from	previous	sheet	-
				Totals:				
				Physical	Stock	Check:		
					Carried	Forward:		

Annex 3

Monthly temperature recording sheet (sample)

Name of facility:.....
Type of equipment: .....
Date: .....
Signature: .....

Date / Temp	1		2		3		4		5		6		7		8		9		10		11		12		13		14	
	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A
20																												
18																												
16																												
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-16																												
-18																												
-20																												
-22																												
-24																												
-26																												

SAFE ZONE FOR ALL VACCINES

SAFE ZONE FOR POLIO, MEASLES AND MUMPS

Annex 4

Annual temperature recording sheet (sample)

Headings: facility, refrigerator etc.

Month	1	2	3	4	5	6	7	8	9	etc															
J m																									
a																									
F m																									
a																									
M m																									
a																									
A																									
M																									
J																									
J																									
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D																									

Adverse events following immunization

Causes related to practice

(from WHO investigations in various countries, reported in *Weekly Epidemiological Record* no.32, August 1996)

- Too much vaccine given in one dose
- Improper immunization site or route
- Syringes and needles improperly sterilized
- Vaccine reconstituted with incorrect diluent
- Wrong amount of diluent used
- Drug substituted for vaccine or diluent
- Vaccine prepared incorrectly for use
- Vaccine or diluent contaminated
- Vaccine stored incorrectly
- Contraindications ignored
- Reconstituted vaccines not discarded at end of immunization session, and used at subsequent one

QIZ QUESTIONS

1. What is active immunization? Indicate preparations used for active immunization.
2. What is passive immunization? Indicate preparations used for passive immunization.
3. What request are for immunological preparations?
4. What methods are used in administration of the vaccines?
5. List the indications and contraindications to vaccination.
6. What kind of preparations groups led to artificial active immunization (comparative characteristics)?
7. What preparations can be used in emergency prophylaxis (their characteristics)?
8. What methods are used in appreciation of immunoprophylaxis effecttiveness?

PRACTICAL ASIGNMENTS

1. From the proposed list select preparations for:
   I. active immunization;
   II. passive immunization:

a) Live vaccine, b) inactivated vaccine, c) phages, d) heterologous serum, e) homologous serum, f) toxoids, g) immunoglobulin, interferon.

2. Select indications for administration:
   I. Vaccine; II. Serum and immunoglobulin:
   a) planned vaccination according to the age;
   b) risk or epidemic spreading in the region;
   c) complications after vaccine administration;
   d) contact with a contagious person;
   e) treatment of person with acute infectious diseases;
   f) travel to endemic zone.

3) Indicate the possible way of developing:
   I. artificial active immunity;
   II. natural active immunity:

a) Typical form of infection;
b) Rudimentary form;
c) Live vaccine administration;
d) Inactivated vaccine administration;
e) Prophylaxis with serum;
f) Entering into the organism of little doses of pathogenic agent during the contact with source of infection.
g) Immunization with the toxoids.

4) At the trauma department came 2 people. One of them was bitten by neighbor's dog. The dog is tied and is healthy. The second person was bitten by hand and shoulder. He was bitten by wolf. Determine the necessity of vaccination against rabies and rules for performing of its.

4) Indicate the method of administration of the medicine in the body:

Preparation	Per os	Intracutaneous	Subcutaneous	Intramuscular	Skin scarification
Measles vaccin					
DTP					
OPV					
IPV					
MMR					
Hepatitis B vaccine					
Measles immuniglobulin					
Hepatitis A immunoglobulin					

5) Work out a plan for vaccination against diphtheria, tetanus, and pertussis in community C.

The age structure of the population (children) is: under 1 year – 1700, 1 year – 1900, 2 years – 2003, 3 years – 1500, 4 years – 1870, 5 years – 1920, 6 years – 1940, 7 years – 2100, 13 years – 1905, 14 years – 1780, 15 years – 1960, 16 years – 1895, 17 years – 1864, 18 years – 1921, 19 years – 1904, 20 years – 1891, 21 years – 1875, 22 years – 1908, 23 years – 1903, 24 years – 1892, 25 years – 1907 and 26 years – 892 persons.

Indicate the necessity vaccines and their quantity.

6) In refrigerator where are immunological medicines the temperature decreased till –20°C. What medicines can be used (I), and what medicines are forbidden for using (II).

a) Serum against tetanus;
b) Diphtheria toxoid;
c) Vaccine BCG;
d) Measles vaccine.

7) In the bottle with chemical (inactivated) vaccine, nurse saw porous sediment. What she has to do?

a) To take the content into the syringe?
b) To shake it before using?
c) To inactivate it?

8) What preparations listed below are administrated fractionate?

a) Measles immunoglobulin;
b) Rabies immunoglobulin;
c) Tetanus immunoglobulin;
d) Tetanus serum;
e) Cl.botulini serum.

9) List the recording forms used for vaccination evidence performed to children (a) and adults (b).

10) In the following statements decide on the indications or contraindications to vaccination:

I. – Diphtheria; II. – Rabies.

a) Medical nurse, 26 years old, 5th month of pregnancy;
b) Worker, reinforcement department, diabetes;
c) Student, 22 years old, 3 months ago had flu;
d) Engineer, 36 years old, one month ago was vaccinated against tetanus;
e) Lab technician, 18 years old, light symptoms of rhinitis.

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