Pentavalent and Hexavalent Vaccines

Cold Chain Equipment

The freeze indicator is used to warn of freezing and is packed with vaccines that are sensitive to freezing temperatures: DTP, TT, DT, Td (freezing point of -6.5°C), hepatitis B (-0.5°C), liquid Hib and their combinations (DTP-HepB, and DTP-HepB+Hib vaccines) and JE. Every refrigerator storing vaccines should have a freeze indicator (Freeze Watch™). It is strongly recommended that one freeze indicator be placed in each cold box during vaccine transport and distribution. This is critical in places subject to low temperatures.

Vaccine Handling

The recommended conditions for storing vaccines used in immunization programmes are shown in Appendix 81_1. This diagram also indicates the maximum times and temperatures in each case. At the higher levels of the cold chain, i.e., at national (primary), and regional or province level, OPV must be kept frozen between -15°C and -25°C. Freeze-dried vaccines (i.e., BCG, measles, MMR and yellow fever) may also be kept frozen at -15°C to -25°C if cold chain space permits, but this is neither essential nor recommended. At other levels of the cold chain (intermediate vaccine stores and health facilities), these vaccines should be stored between +2°C and +8°C. All other vaccines should be stored at between +2°C and +8°C at all levels of the cold chain. Liquid formulations of vaccines containing diphtheria, pertussis, tetanus, hepatitis B, Haemophilus influenzae type b, IPV and their combinations should not be frozen.

Check the freeze indicator in the refrigerator. If it warns of freezing or you suspect that a freeze-sensitive vaccine (DTP, DT, TT, HepB, DTP-HepB, liquid Hib and DTP-HepB+Hib vaccines) has been frozen, you should perform the shake test.
**Pentavalent and Hexavalent Vaccines**

The currently available pentavalent vaccine requires the reconstitution of lyophilized Hib conjugate vaccine with liquid DTP-hepatitis B vaccine. In this instance, the Hib vaccine should be reconstituted only with the DTP-hepatitis B vaccine produced by the same manufacturer.

Similarly, there is at least one DTP-Hib combination that requires the reconstitution of the lyophilized Hib conjugate vaccine with liquid DTP vaccine, and the Hib vaccine should be reconstituted only with the DTP vaccine produced by the same manufacturer.

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The quadrivalent and pentavalent DTP+Hib and DTP-HepB+Hib formulations with lyophilized Hib are supplied in two separate vials (liquid DTP-HepB and lyophilized Hib) that are not packaged together. Lyophilized Hib vaccine can be stored either frozen at -20°C or refrigerated between 2°C and 8°C; however, liquid DTP or DTP-HepB vaccine MUST NOT BE FROZEN. To ensure that Hib is correctly reconstituted with DTP-HepB it is recommended that both vials of the pentavalent DTP-HepB+Hib formulation are stored together between 2°C and 8°C, and both vials should be shipped and distributed together.

*Introduction of Haemophilus influenzae type b vaccine into immunization programmes*  
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Reconstituted monovalent Hib vaccine or reconstituted Hib vaccine combined with other vaccines (DTP, DTPHB, or DTP-IPV) should be destroyed after an immunization session or within six hours.

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Multi-dose Open Vials

The WHO multi-dose vial policy applies to Hib vaccines as follows:
- All liquid formulations of Hib vaccine contain a preservative and can be used in subsequent immunization sessions.
- The freeze-dried formulation (lyophilized) contains no preservatives, and after being reconstituted with a diluent with no preservatives, must be discarded at the end of the session or within six hours, whichever comes first (the same as for BCG, measles, and yellow fever).
- Certain formulations of lyophilized Hib vaccine are supplied with DTP (or DTP/HepB) liquid vaccine or diluent containing preservatives. These reconstituted vaccines can be used safely over an extended period. However, the application of the multidose vial policy with DTP-HepB+Hib vaccine is recommended only if specific supervision and training activities are conducted in order to ensure appropriate implementation.

Schedule

(Considerations for hepatitis B vaccine schedule:)
- A determination of the role of perinatal transmission (useful for birth dose considerations) can be made based on the overall seroprevalence of HBsAg, age-specific prevalence of HBsAg, and the prevalence of the HBeAg in pregnant women.
- Combination products may not be used at birth; therefore, programmes including the birth dose will need to include monovalent HepB vaccine in the supply.
Only monovalent HepB vaccine should be used as a birth dose, the dose given within the first week of life. Combination vaccines should not be used at birth, but may be used in subsequent doses.

Do not use DTP-HepB+Hib as a birth dose. You may use the vaccine for subsequent doses.

When immunizing against HBV at birth, only monovalent hepatitis B vaccine should be used: the other antigens found in combination vaccines are currently not approved for use at birth (DTwP, DTaP, Hib, hepatitis A and IPV.)
**Pentavalent and Hexavalent Vaccines**

Monovalent hepatitis B vaccine MUST BE USED for the birth dose.
- Combination vaccines that include hepatitis B vaccine MUST NOT BE USED to give the birth dose of hepatitis B vaccine because DTP and Hib vaccines should not be administered at birth.
- Either monovalent hepatitis B vaccine or combination vaccines may be used for later doses in the hepatitis B vaccine schedule. Combination vaccines can be given whenever all the antigens in the vaccines are indicated.

**Vaccine Administration**

Administration summary: HepB vaccine and Administration summary: DTP-HepB combination vaccine (see Appendix 2_12.)

- Hepatitis B vaccine SHOULD NOT be given in the buttock as this route of administration has been associated with decreased protective antibody levels, probably because of inadvertent subcutaneous injection or injection into deep fat tissue. In addition there may be a risk of injury to the sciatic nerve.
- Hepatitis B vaccine SHOULD NOT be administered intradermally because this route of administration does not produce an adequate antibody response in children.
- Hepatitis B vaccine SHOULD NOT be mixed in the same syringe with other vaccines unless specifically recommended by the manufacturer. (Note: pentavalent DTP-HepB+Hib vaccine is supplied in two separate vials, one containing DTP-HepB vaccine (liquid), the other containing Hib vaccine (lyophilized). The manufacturer recommends mixing the contents of the two vials and giving DTP-HepB+Hib vaccine in the same syringe.)
Adverse Event

GACVS concluded that (available) data are inconsistent with any association between hexavalent (diphtheria, tetanus, acellular pertussis, Haemophilus influenzae type b, poliovirus and hepatitis B (DTaP-Hib-IPV-HepB combination)) vaccines and SID (sudden infant death) or SUD (sudden unexplained death.)

Global Advisory Committee on Vaccine Safety, 9–10 June 2005

Research

On the basis of all the available data, GACVS concluded that there is no evidence to support a causal association between the administration of hexavalent (DTaP-Hib-IPV-HepB) vaccines and SUD (sudden unexplained death.) In response to the potential signal observed in the second year of life, the Committee encouraged studies to be conducted that are designed to provide more powerful evidence on the presence or absence of an association.

Global Advisory Committee on Vaccine Safety, 2–3 December 2004