Training workshop on screening, diagnosis and treatment of hepatitis B and C
Session 6

Hepatitis B vaccination
and
prevention of mother to child transmission
(PMTCT)
Learning objectives

At the end of this session, participants will know the following

- Active and passive prevention of hepatitis B virus infection
- Dose and schedule of hepatitis B vaccination
- Effectiveness of hepatitis B vaccine
- Protective levels of anti-HBs titre
- Role of booster dose
- Role of birth-dose hepatitis B vaccine in prevention of mother-to-child transmission of hepatitis B

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- Active and passive prevention of hepatitis B virus infection
- Dose and schedule of hepatitis B vaccination
- Effectiveness of hepatitis B vaccine
- Protective levels of anti-HBs titre
- Role of booster dose
- Role of birth-dose hepatitis B vaccine in prevention of mother-to-child transmission of hepatitis B
- Evolving new evidence, strategy and guidance in HBV prevention and control
In general, there are two ways to prevent HBV infection: the first is active prevention; and second is passive prevention.

Active prevention is provided by the vaccine, which contains inactivated virus or a component of the virus. Vaccination induces host immunity and enables stronger and long-lasting protection, but it takes a few weeks to take effect.

On the other hand, passive prevention is induced by administration of harvested immunoglobulin. Immunoglobulin does not induce any host response, and its effect is weaker and shorter than that of the vaccine. However, it works immediately after administration. Because of homogeneous harvesting, immunoglobulin carries a risk of an allergic reaction.
We need to spend some time while discussing hepatitis B vaccine to understand it well.

Hepatitis B vaccine contains a viral protein of hepatitis B surface antigen - originally produced from the plasma of persons with chronic HBV infection, but now only recombinant protein is used.

Recombinant vaccine is prepared as follows.

- Gene for HBsAg is inserted into yeast or mammalian cells.
- The cells are cultured to produce an excess of protein.
- The protein is purified and adsorbed on the surface of an adjuvant (alum).
- Used as intramuscular injection.
Stability and storage

Hepatitis B vaccine

• Storage at 2–8°C

• Relatively heat stable – remains effective even after several days at room temperature

• However, very sensitive to freezing

• Avoid freezing at all costs

About the stability and storage, it is recommended that hepatitis B vaccine be stored at 2–8°C.

Relatively heat stable – remains effective even after several days at room temperature

However, the vaccine is very sensitive to freezing, and you must avoid freezing at all costs.
Hepatitis B vaccine: Dosage

- Most of the manufacturers supply the vaccine in a dosage of 0.5 mL each. Most contain 20 μg/dose, but some have 10 μg/dose.

- Recommended dosages
  - Newborns, infants, children, adolescents (≤18 y) 0.5 mL
  - Adults 1.0 mL
  - Haemodialysis/immunocompromised state 2.0 mL

Most of the manufactures supply the vaccine in a dosage of 0.5 mL containing 20 μg/dose, but we must pay attention to the dose because some have 10 μg/dose. Recommended dosages are as follows:

- Newborns, infants, children, and adolescents at 18 years of age or younger 0.5 mL
- Dosage of adults is 1.0 mL
- Dosage for adults on haemodialysis or immunocompromised hosts is 2.0 mL
# Hepatitis B vaccine: Schedule

<table>
<thead>
<tr>
<th>For</th>
<th>Recommendation</th>
<th>Dosing schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>Standard</td>
<td>0, 1, 6 months</td>
</tr>
<tr>
<td></td>
<td>Rapid induction of immunity</td>
<td>0, 1, 2 months + 12 months</td>
</tr>
<tr>
<td>Infants and children</td>
<td>Standard (primary immunization)</td>
<td>Birth dose (timely ≤24 hours, TBD), followed by 2 or 3 doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Countries usually have one of two schedules:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a) 3-dose schedule of HBV: TBD + 2 + 3 (monovalent or combined vaccine) given at</td>
</tr>
<tr>
<td></td>
<td></td>
<td>the same time as the first and third doses of diphtheria, pertussis (whooping</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cough), and tetanus (DTP) vaccine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) a 4-dose schedule, where a monovalent birth dose is followed by three</td>
</tr>
<tr>
<td></td>
<td></td>
<td>monovalent or combined vaccine doses, usually given with other routine infant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>vaccines.</td>
</tr>
</tbody>
</table>

*Source: WHO 2017 position paper on hepatitis B vaccines*

We need to administer at least 3 doses of the vaccine to infants for sufficient efficacy. It should be made clear to health workers that the birth dose, which is given within 24 hours of birth, is in addition to the routine three-dose vaccination.
## Global Health Sector Strategy on Viral Hepatitis

<table>
<thead>
<tr>
<th>Type of target</th>
<th>Intervention</th>
<th>Western Pacific Region, 2015</th>
<th>South-East Asia Region, 2015</th>
<th>2020 target</th>
<th>2030 target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Service coverage</td>
<td>3-dose hepatitis B vaccine</td>
<td>93% (2016)</td>
<td>87%</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>HBV PMTCT</td>
<td>83% (2016)</td>
<td>34%</td>
<td>50%</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>Blood safety (% donations screened)</td>
<td>98%</td>
<td>85%</td>
<td>95%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Injection safety (% unsafe injections)</td>
<td>3.2%</td>
<td>5.2%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Harm reduction (injection sets/PWID)</td>
<td>57</td>
<td>29</td>
<td>200</td>
<td>300</td>
</tr>
<tr>
<td>Impact</td>
<td>HBV incidence: HBsAg +ve in 5 year olds</td>
<td>0.93% (2016)</td>
<td>0.7% (2015)</td>
<td>~30% (~1%)</td>
<td>~90% (0.1%)</td>
</tr>
<tr>
<td></td>
<td>HCV incidence</td>
<td>6 per 100 000</td>
<td>14.8 per 100 000</td>
<td>~30%</td>
<td>~90%</td>
</tr>
</tbody>
</table>

PMTCT: prevention of mother-to-child transmission (universal birth dose or other approaches)

PWID: person who injects drugs

Source: Global Hepatitis Progress 2017

Coverage with three doses of hepatitis B vaccine is one of the WHO targets (90%) by 2030.
The global coverage of hepatitis B vaccination has seen major progress since 2000. About 84% of infants were vaccinated with three doses of hepatitis B vaccine in 2015. WPR had an estimated 90% coverage in 2015 and 93% in 2016.
In WPR, coverage with the birth dose of hepatitis B vaccine has been slightly lower than that of the 3rd dose of hepatitis B vaccine.

Birth dose vaccination coverage has reached around 80% in WPR.
The slide shows the impact of universal childhood hepatitis B vaccination on the prevalence of chronic hepatitis B in 22 of 36 countries where the vaccine was introduced in 1990.

In these countries, the HBV prevalence before the introduction of vaccination was 8%, which has dramatically reduced to below 1% after the successful implementation of universal childhood hepatitis B vaccination.
Hepatitis B vaccine

Site of administration
Infants          Anterolateral aspect of thigh
Others           Deltoid

Not to be given in gluteal muscles (buttock)
  Lower efficacy
  Risk of sciatic nerve injury

We should administer HBV vaccine intramuscularly on the anterolateral aspect of the thigh in infants and deltoid for others.

We must not administer HBV vaccine in the gluteal muscles because vaccination at this has been shown to have lower efficacy and a definitive risk of sciatic nerve injury.
## Protection of infants by hepatitis B vaccination

<table>
<thead>
<tr>
<th>Number of doses</th>
<th>Protection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16–40</td>
</tr>
<tr>
<td>2</td>
<td>80–95</td>
</tr>
<tr>
<td>3</td>
<td>98–100</td>
</tr>
</tbody>
</table>

*Note: Preterm infants <2 kg may less often have a successful response.*


The efficacy of hepatitis B vaccine is defined by the presence of an anti-HBs antibody titre of 10 mIU/mL or higher. The proportion of infants that achieves this protective level of anti-HBs titre after one, two or three doses of the vaccine gradually increases.

Even a single dose of vaccine induces a small degree of protective immunity, which ranges from 16% to 40%.

The second dose markedly enhances the proportion of children developing protective immunity. The third dose of the vaccine works more like a booster dose and it has three effects: first, it slightly increases the proportion of children that develop protective immunity to 95%; second, it increases the level of antibody titre in those who develop immunity; and third, it better sustains the antibody titre.
Hepatitis B vaccine response rates

• A 3-dose series induces protective antibody concentrations in >95% of healthy infants, children and young adults (<40 years)

• Lower response rates in older adults (>40 years), obese individuals, smokers, those with chronic systemic illnesses

• Seroprotection rates following vaccination in older persons

  40–49 years >90%
  50–59 years >80%

A 3-dose series induces protective antibody concentrations in >95% of healthy infants, children and young adults (<40 years).

Lower response rates are seen in older adults (>40 years), obese individuals, smokers and those with chronic systemic illnesses.
Vaccine non-responders

- 5–10% of people may not respond to the 3-dose schedule
- Most of the non-responders respond to an additional 3-dose vaccination series
- Alternative options for non-responders
  - Double dose
  - Four-dose schedule
  - Intradermal administration
  - Newer vaccines

Though we have highly potent hepatitis B vaccine available with us, about 5–10% of people may not respond to the 3-dose schedule and they are called vaccine non-responders.

We have a few alternatives for these non-responders, such as the following:
- About 50% of non-responders may respond to an additional 3-dose vaccination series.
- Alternative options for non-responders are
  - repeating the three- or four-dose schedule using double the usual dose
  - administering the vaccine intradermally
  - using experimental newer vaccines
Anti-HBs titre

• Serum level ≥10 mIU/mL is protective

• This titre is used as a cut-off to define the vaccine response

• Over 90% (74–100%) of vaccine responders remain protected for at least 30 years, irrespective of whether anti-HBs antibody remains detectable or not (because they have immune memory and kick up antibodies quickly on exposure)

• Hence, booster doses of hepatitis B vaccine are not needed

As discussed earlier, the protective efficacy of hepatitis B vaccine is assessed by the serum levels of anti-HBs antibody titre.

In general, serum anti-HBs level ≥10 mIU/mL is considered to be protective.

It is important to mention that, once the anti-HBs titre has reached the protective level, over 90% of individuals will remain protected for over 20 years, irrespective of whether the anti-HBs antibody remains detectable or not.

WHO does not recommend either booster vaccination after the 3-dose vaccination schedule or repeated anti-HBs titre estimation once its protective level has been achieved.
Mild adverse events of HBV vaccine have been reported at a low frequency. Overall, hepatitis B vaccine is extremely safe and serious adverse effects are very uncommon.
Currently used hepatitis B vaccines are subunit vaccines and hence they are safe in high-risk populations such as immunocompromised people, low-birth-weight baby, and preterm babies.

There is no mutual interference on co-administration with other childhood or adult vaccines.
In this section we will learn about the method of preventing mother-to-child transmission of hepatitis B, which is one of the most common routes of hepatitis B transmission in developing countries in Asia and Africa.
The natural history of HBV infection depends upon the age of the host at the time of infection. There is an inverse relationship between the risk of developing acute hepatitis and its progression to chronic infection and the age of the host. Infections during infancy remain asymptomatic and carry more than 90% chance of progressing to chronic infection.

By the age of 5 years, about 20% develop chronic infection.

After the age of 5 years and particularly in adults, more than 90% develop acute hepatitis and clear the virus within six months.
What is a timely birth dose?

• Administration of the first dose of hepatitis B vaccine within 24 hours of birth
• To prevent transmission during perinatal period and early infancy
• Birth dose followed by at least two doses: effectively prevents MTCT in ~90%

• As early as possible after birth, but ideally within 24 hours

WHO recommends a timely birth dose within 24 hours of birth. As far as possible, all birth doses should be given within 24 hours of delivery but if birth dose administration delayed, due to any reason, it should NOT be refused. This message should be passed on to health-care workers.

This dose is given in addition to the routine vaccination schedule.
Follow-up vaccination after birth dose

The birth dose is followed by one of the following schedules

**A three-dose schedule**
Two more doses (monovalent or combined vaccine) given at the same time as the 1st and 3rd doses of diphtheria–tetanus–pertussis (DTP)

**A four-dose schedule**
Three more doses (monovalent or combined vaccine) given with other routine infant vaccines

If combined vaccines (e.g. DPT–HepB–Hib) used, then the 4-dose schedule is more practical

The birth dose of HBV should not be counted as a the first dose of the routine childhood vaccination schedule prevailing in the country. Rather, the birth dose should be considered as an extra dose administered in addition to the routine vaccination schedule.
Birth dose coverage

- WHO advocated for universal administration of hepatitis B birth dose in 2009

- Globally, the birth dose coverage was 38% in 2014 and 43% in 2017, with wide variability among countries and regions
That other intervention is the birth dose. On the slide, you can see the coverage of the birth dose of hepatitis B vaccine between 2000 and 2015 for selected regions. We have had success stories in the Western Pacific region where perinatal transmission was a major problem. In the Americas, coverage tremendously increased also. However, global coverage (as a dashed black line) is still low at 39% and in the African region which is highly endemic for hepatitis B, the coverage of the timely birth dose is only 10%.

Source: WHO AND UNICEF Joint Reporting
Mother-to-child transmission (MTCT)

In many endemic countries, the majority of the HBV burden is related to mother-to-child transmission at birth or due to other exposure during early infancy

- High birth rates
- Poor antenatal care
- Poor birth hygiene
- Poor coverage of hepatitis B birth dose
- High population density
- Excess use of injections for minor childhood illnesses

*Birth dose helps to better prevent such early (chronic) infections.*

In several resource-poor countries, HBV is transmitted during infancy. This transmission happens either from the mother or from the surroundings due to the reasons mentioned above. The birth dose is effective in preventing HBV infection during infancy.
## Precaution when used with immunoglobulin

- Addition of hepatitis B immunoglobulin (HBIG) to the birth-dose vaccine improves the efficacy of MTCT

- However, HBIG has challenges
  - High cost
  - Refrigeration needed
  - Limited availability

- If HBIG is also administered, then the vaccine and HBIG should be administered at different locations (contralateral limbs) and using separate syringes.

At many places, HBIG is also administered as a part of the HBV prophylaxis strategy to prevent MTCT. We must know that in a public health setting, HBIG is costly, needs timely administration and facilities for storage and transport. The benefits of the additional use of HBIG is limited. If HBIG and HBV vaccine are both given; they should be given simultaneously intramuscularly in different thighs.
Not a contraindication for the birth dose

Hepatitis B vaccine birth dose is safe even in the following situations:

- Prematurity
- Low birth weight
- Small for gestational age baby
- HIV infection of mother or infant
- Jaundice

HBV vaccine has been shown to be effective and safe in the above-mentioned high-risk group babies.
The triple elimination framework has a clear vision, goals and targets to be achieved. This framework piggybacks on the existing dual elimination, with HBV elimination added on.

The ultimate target for HBV elimination is 0.1% prevalence among children by 2030.
In pragmatic terms, using the maternal neonatal and child health care platform, universal testing for HIV, syphilis and hepatitis is offered. If positive, interventions are provided. For HBV-positive pregnant women, a set of additional interventions can include antiviral drug use for prevention of mother-to-child transmission, and among infants, post-vaccination serological testing to know their infection status.
Incremental approach from birth and in the first years of life

The interventions at the base of the pyramid benefit the largest number and are necessary for those at the top of the pyramid to be effective

Opportunities and challenges

- Antiviral treatment can make a difference for the few women with a high viral load.
- HBIG is recommended in many high-income countries, but there are supply issues (quantity, quality) in middle- and low-income countries.
- A strong system to test and link to care is the foundation for more interventions. It also allows impact monitoring.
- Universal administration of a timely birth dose is the first line of defence against perinatal infection for all infants.
- Three-dose vaccination is the foundation for reducing incidence and ensuring the effectiveness of interventions at birth.

Taking the incremental approach, and building from the foundation of the immunization programme, work upwards through improving access to testing, linkage to care and follow up, and antiviral drug use for women who have a high viral load – so as to work towards an “almost zero infection” status
Additional interventions to prevent HBV mother-to-child transmission - 1: HBIG

- WHO recommendation: addition of hepatitis B immunoglobulin (HBlg) to birth-dose vaccine improves the efficacy of prevention of mother-to-child transmission

- However, HBlg has challenges
  - High cost
  - Refrigeration required
  - Limited availability

- If HBlg also administered, then vaccine and HBlg should be administered at different locations (contralateral limbs) and using separate syringes.

WHO also recommends that addition of hepatitis B immunoglobulin to birth-dose vaccine improves the efficacy of prevention of mother-to-child transmission.

However, HBlg has some challenges, including high cost, need for refrigeration and limited availability.

If HBlg is available, the vaccine and HBlg should be given at the same time but at different sites using separate syringes.
Additional interventions to prevent HBV mother-to-child transmission

*Guidance evolving, given the increasing evidence on use of antiviral drugs for PMTCT of hepatitis B*

- Antiviral drug of choice: tenofovir
- HBsAg+ mothers should be categorized for transmission risk (high HBV DNA and/or HBeAg-positive)
- New WHO guidelines on antiviral use during pregnancy for HBV prevention of mother to child transmission (for launch in 2020)

Another additional intervention is antiviral drugs.

It has been reported that the transmission rate of HBV was suppressed by the administration of tenofovir to high-risk women with HBeAg positivity and high viral load of HBV.

Although there are some ongoing discussion points, antiviral drugs may become a useful option for PMTCT of HBV, given the increasing evidence.
Vaccination of adults at high risk

• Groups considered at high risk:
  – patients who frequently require blood or blood products
  – patients on dialysis, patients with diabetes
  – recipients of solid organ transplantation
  – persons with chronic liver disease, including those with hepatitis C
  – persons with HIV infection
  – persons interned in prisons
  – persons who inject drugs
  – household and sexual contacts of persons with chronic HBV infection
  – men who have sex with men
  – persons with multiple sexual partners
  – Health-care workers and others who may be exposed to blood, blood products or other potentially infectious body fluids during their work.

WHO also recommends vaccination for adults at high risk such as the following:

• patients who frequently require blood or blood products
• Patients on dialysis, patients with diabetes
• recipients of solid organ transplantation
• persons with chronic liver disease, including those with hepatitis C
• persons with HIV infection
• persons interned in prisons
• persons who inject drugs
• household and sexual contacts of persons with chronic HBV infection
• men who have sex with men
• persons with multiple sexual partners
• Health-care workers and others who may be exposed to blood, blood products or other potentially infectious body fluids during their work.
Vaccination among adults: optimizing the immune response to vaccination

- **HIV-positive individuals** should be vaccinated as early as possible in the course of the HIV infection.
- **In immunocompromised individuals**, including patients with chronic renal failure, chronic liver disease, coeliac disease and diabetes, the immune response following vaccination is often reduced.
- Hepatitis B vaccine can be administered safely to **pregnant and lactating women**.

Among them,

- **HIV-positive individuals** should be vaccinated as early as possible during the course of the HIV infection.
- **In immunocompromised individuals**, including patients with chronic renal failure, chronic liver disease, coeliac disease, and diabetes, the immune response following vaccination is often reduced.
- Hepatitis B vaccine can be administered safely to **pregnant and lactating women**.
Summary

- Recombinant hepatitis B vaccines are highly safe, easy to administer and effective.

- Recommended three-dose schedule provides good protection in 95% of recipients.

- Anti-HBs titre ≥10 mIU/mL indicates adequate protection.

- Birth dose provides additional protection against mother-to-child transmission (MTCT) of hepatitis B.

- Birth dose followed by two additional doses has 90% efficacy in preventing MTCT of hepatitis B.

- Booster doses of hepatitis B vaccine are not needed in the general population.