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

World Health Organization

Session 6

Hepatitis B vaccination

and

prevention of mother to child transmission (PMTCT)

World Health Organization

Learning objectives

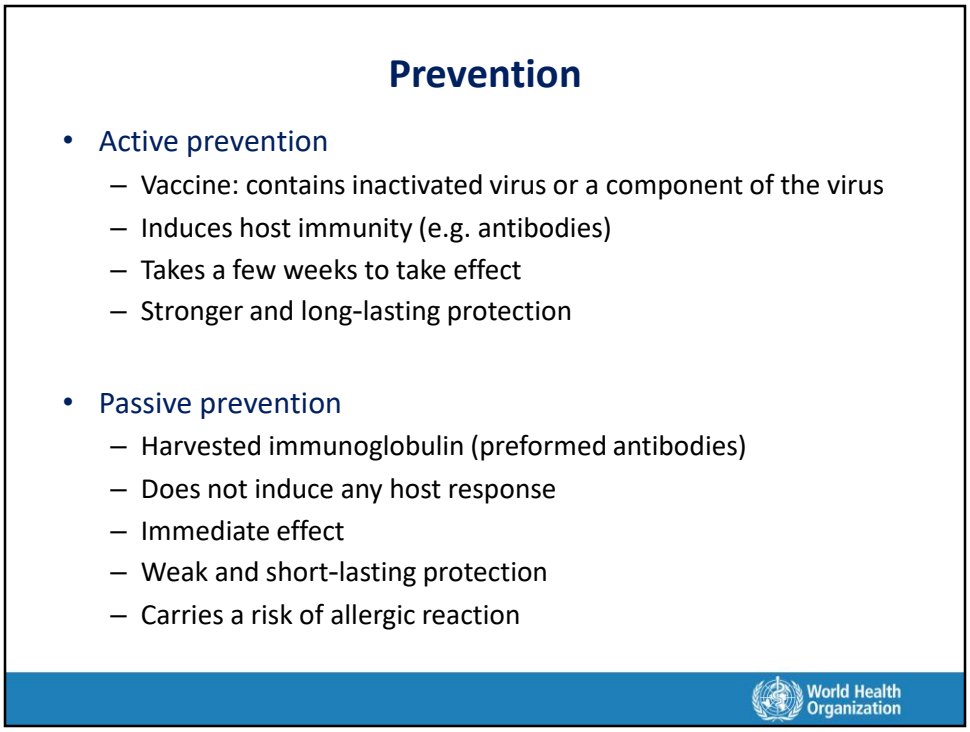
At the end of this session, participants will know the following

- 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

World Health Organization

At the end of this session, participants will understand 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
- 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 induced 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.

Hepatitis B vaccine

- Contains a viral protein: HBsAg = hepatitis B surface antigen
- Originally produced from plasma of persons with chronic HBV infection, but now only recombinant protein is used

- Recombinant vaccine
  - 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

World Health Organization

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

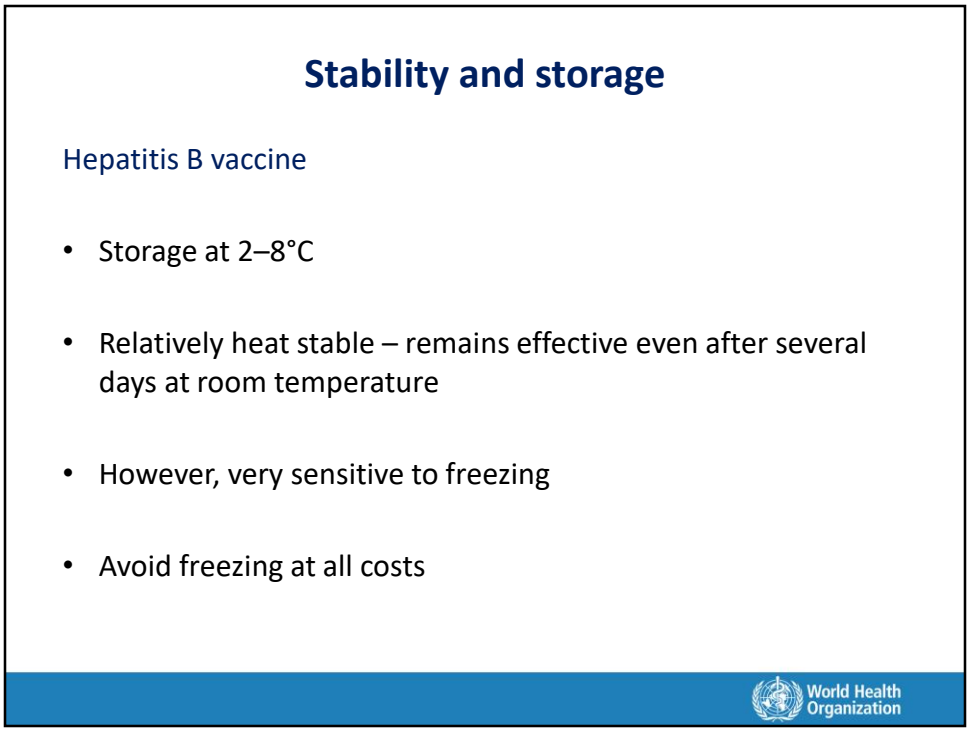
Recombinant vaccine is prepared as follows.

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).

Finally, it is used as an intramuscular injection.



- 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

World Health Organization

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

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

Source: WHO 2017 position paper on hepatitis B vaccines

World Health Organization

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.

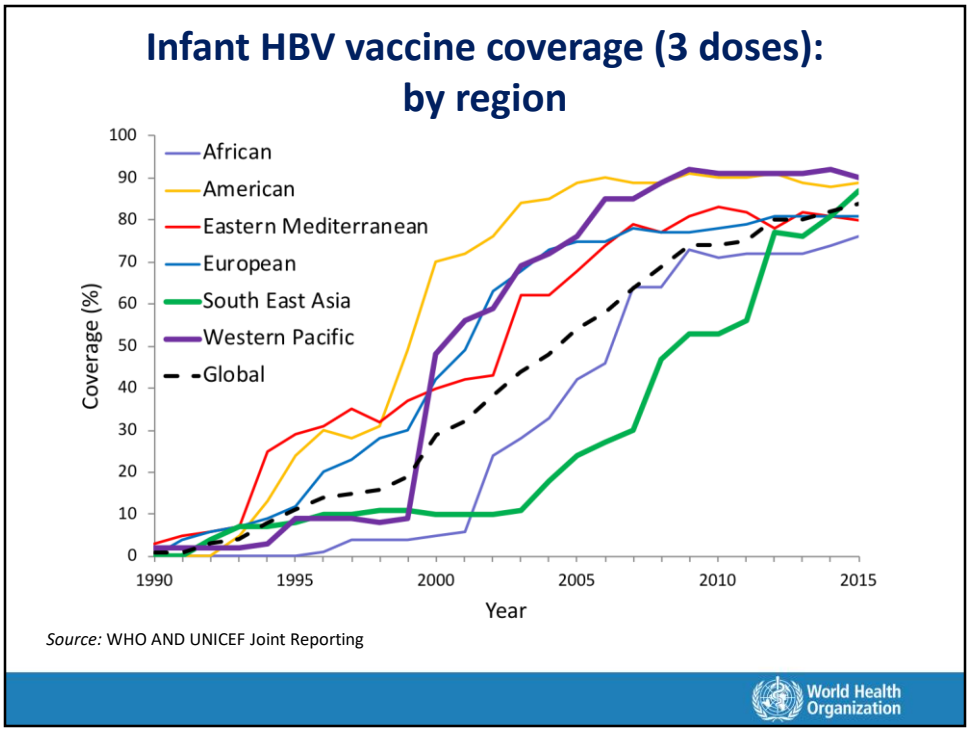
Global Health Sector Strategy on Viral Hepatitis

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

PMTCT: prevention of mother-to-child transmission (universal birth dose or other approaches)
PWID: person who injects drugs
Source: Global Hepatitis Progress 2017

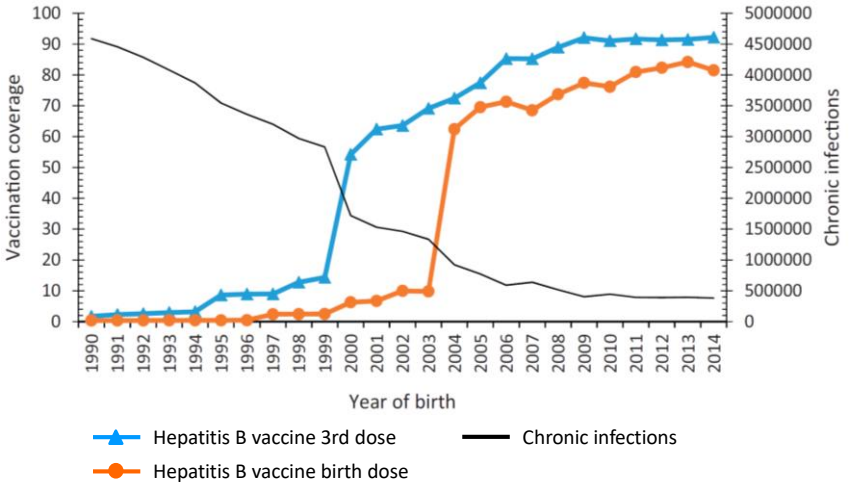
World Health Organization

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.

Impact of vaccine coverage (WPR) on HBV rate



Source: Eric Wiesen et al., Progress towards hepatitis B prevention through vaccination in the Western Pacific, 1990-2014. Vaccine 2016

World Health Organization

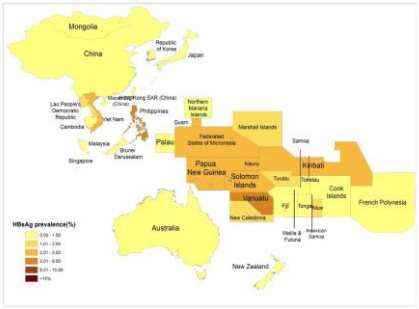
In WPR, coverage with the birth dose of hepatitis B vaccine has been slightly lower than that of the 3rd dose of hepatitis B vaccine.

Birth dose vaccination coverage has reached around 80% in WPR.

Impact of universal childhood immunization

Figure 1. Prevalence of chronic hepatitis B before vaccine introduction

Figure 2. Prevalence of chronic hepatitis B after implementation of national immunization programs



Prevalence of HBV chronic infection in the Western Pacific Region

- before vaccine introduction in 1990: ~8%
- after vaccination in 2014 ~0.93%

Source: WHO WPRO

World Health Organization

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

World Health Organization

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

Number of doses	*Protection (%)*
1	16–40
2	80–95
3	98–100

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

Adapted from Margolis et al. Hepatitis B: evolving epidemiology and implications for control. Semin Liver Dis. 1991;11:84–92.

World Health Organization

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

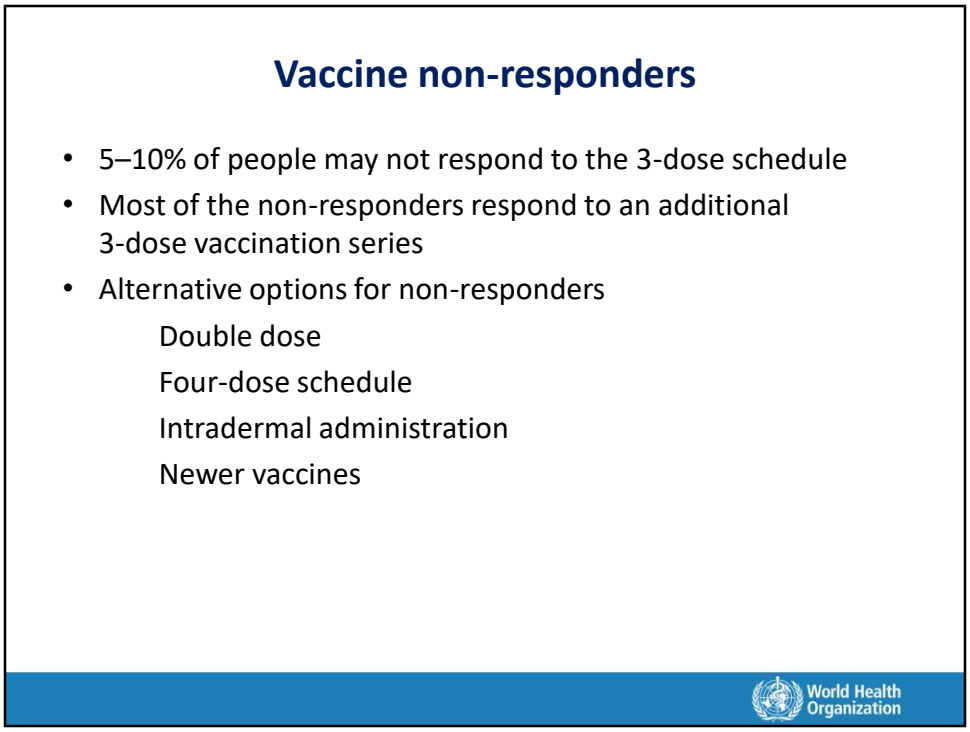
- A 3-dose series induces protective antibody concentrations in >95% of healthy infants, children and young adults (<40 years)
- Lower response rates in older adults (>40 years), obese individuals, smokers, those with chronic systemic illnesses
- Seroprotection rates following vaccination in older persons

40–49 years	>90%
50–59 years	>80%

World Health Organization

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 .



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

World Health Organization

- 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.

HBV vaccines: Adverse events

Nature of adverse event	Description	Frequency (rate / doses)
Mild	Local reactions	
	Pain	3–29 per 100
	Erythema	3 per 100
	Swelling	3 per 100
	Generalized reactions	
	Temperature >37.7°C	1–6 per 100
	Headache	3 per 100
Severe	Anaphylaxis	1.1 per million

World Health Organization

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.

HBV vaccine: Other considerations

- A subunit vaccine (no live virus). Hence, safe even in persons with immunodeficiency
- No mutual interference when co-administered with other childhood or adult vaccines

World Health Organization

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.

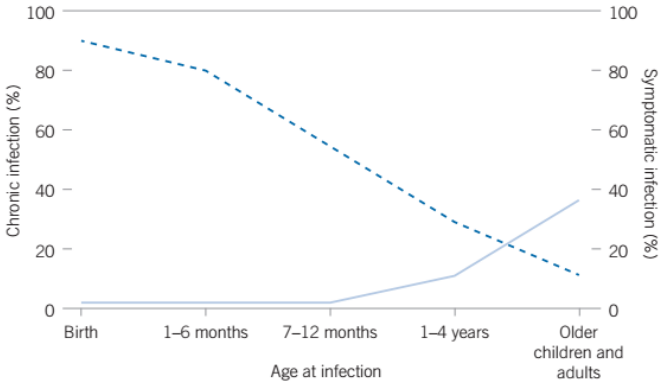
There is no mutual interference on co-administration with other childhood or adult vaccines.

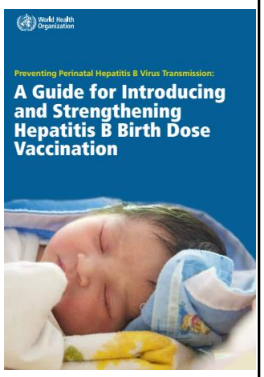
Birth dose and mother-to-child transmission (MTCT)

World Health Organization

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.

Why is timely birth dose important?





Early infection → → greater risk of chronic infection

we need to prevent early (mother-to-child)/perinatal infections

World Health Organization

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***

World Health Organization

WHO recommends a timely birth dose within 24hours 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

World Health Organization

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.

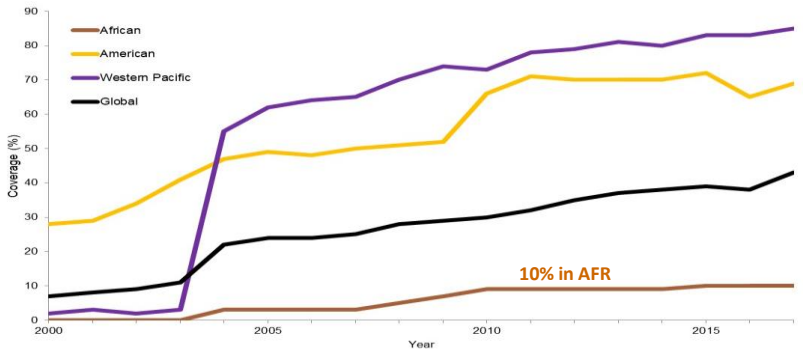
Birth dose coverage

- 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

World Health Organization

Coverage of hepatitis B birth dose, 2017

- From 38% in 2015 to 43% coverage in 2017



No progress	Incomplete, minor actions	**Incomplete, but major actions**	On track, gaps	On track, minor gaps

Source: WHO AND UNICEF Joint Reporting

World Health Organization

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%.

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.

World Health Organization

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.

World Health Organization

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

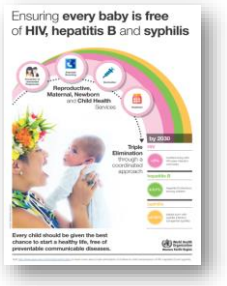
Hepatitis B vaccine birth dose is safe even in the following situations:

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

World Health Organization

HBV vaccine has been shown to be effective and safe in the above-mentioned high-risk group babies.

Triple elimination of mother-to-child transmission (EMTCT) of HIV, hepatitis B and syphilis in Asia and the Pacific 2018–2030



Vision
Every infant free of HIV, hepatitis B and syphilis

Goal
Achieve and sustain EMTCT of HIV, hepatitis B and syphilis and achieve better health for women, children and their families through a coordinated approach and efforts by 2030

Pillar 1: Policy
Coordinated national policy and strategy

Pillar 2: Service delivery
Seamless quality care for women, newborns, children and their families

Pillar 3: M&E
Coordinated monitoring and evaluation of elimination

HIV ≤50 new paediatric HIV infections per 100 000 live births; transmission rate of <5% (breastfeeding) or <2% (non-breastfeeding) by 2020

Syphilis ≤50 cases congenital syphilis per 100 000 live births by 2030

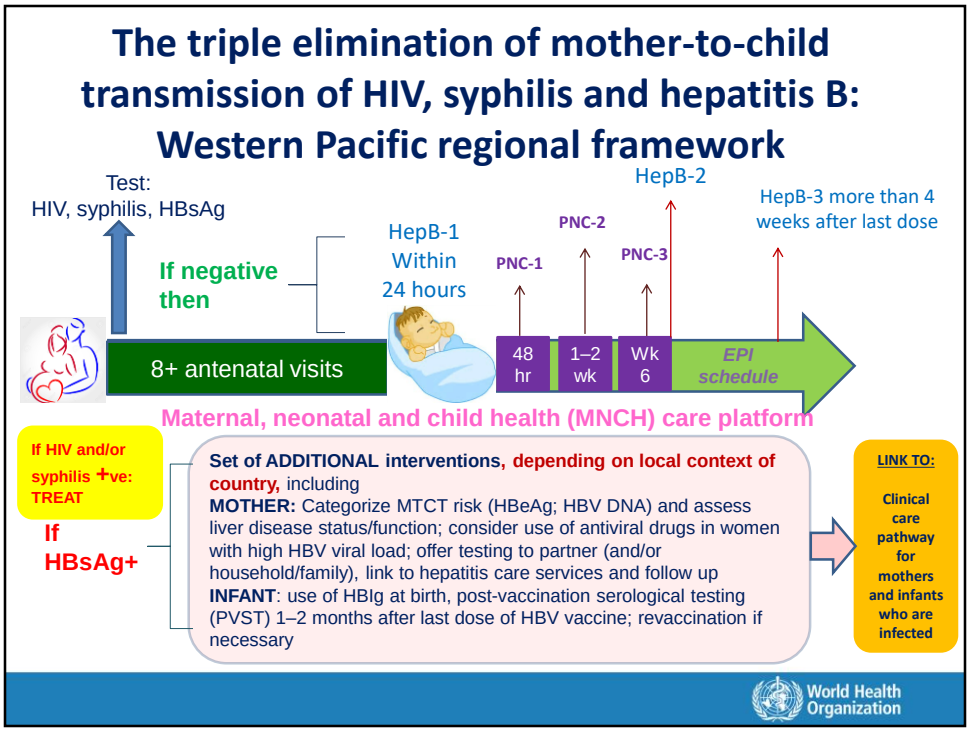
Hepatitis B ≤0.1% prevalence of HBsAg among children by 2030

World Health Organization

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.

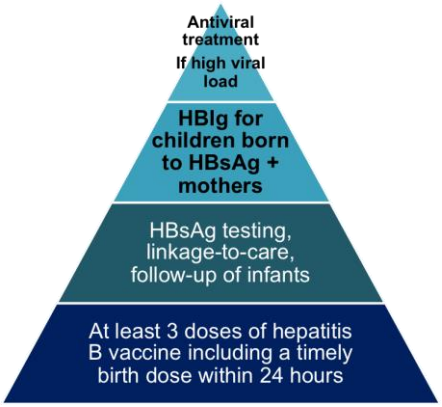
The ultimate target for HBV elimination is 0.1% prevalence among children by 2030.



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.

World Health Organization

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 (HBIg) to birth-dose vaccine improves the efficacy of prevention of mother-to-child transmission
- However, HBIg has challenges
  - High cost
  - Refrigeration required
  - Limited availability
- If HBIg also administered, then vaccine and HBIg should be administered at different locations (contralateral limbs) and using separate syringes.

World Health Organization

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

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

If HBIg is available, the vaccine and HBIg 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)

World Health Organization

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.

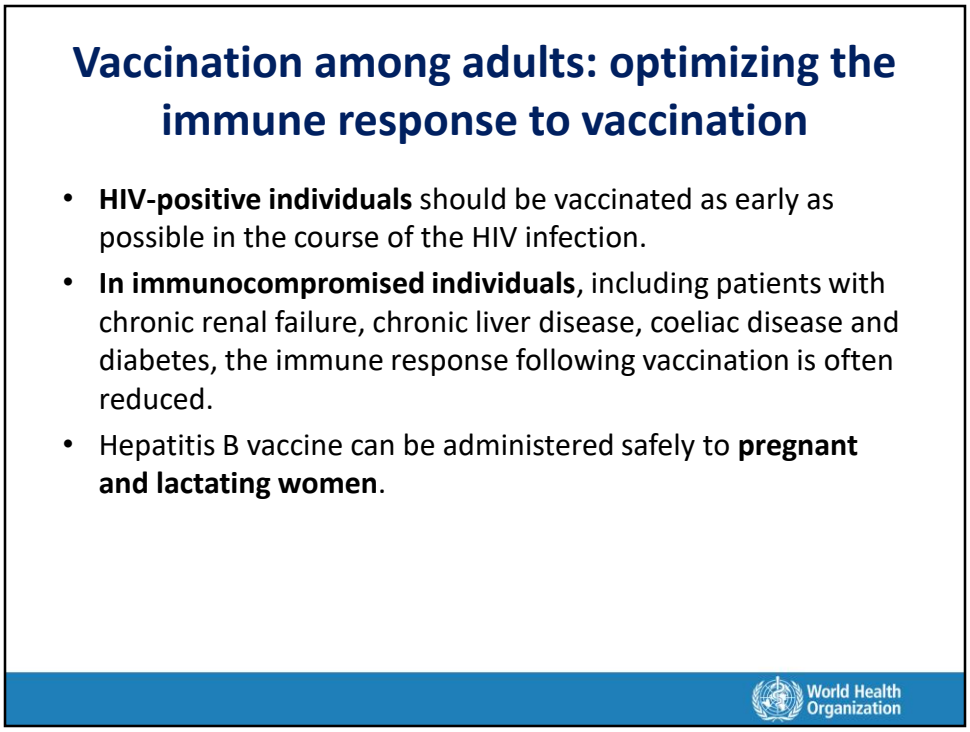
Vaccination of adults at high risk

- 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.

World Health Organization

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.



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.

World Health Organization