

Prevention and control of hepatitis B with combined vaccines and timely birth dose vaccination

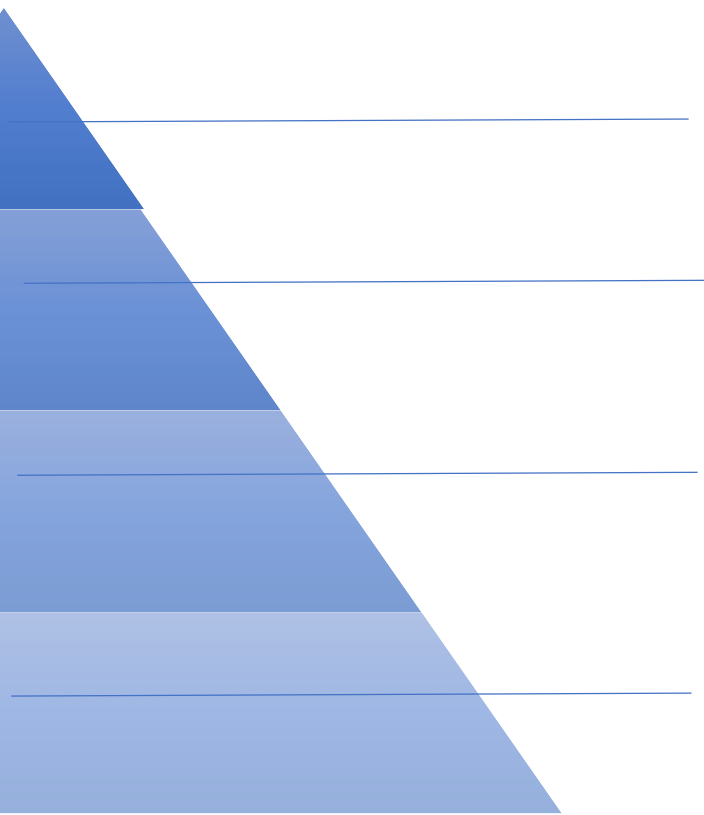
Hanoi, Vietnam

25-26 July 2018



Why this meeting?

Incremental Approach to Prevention in mother-to-child transmission of HBV - WHO

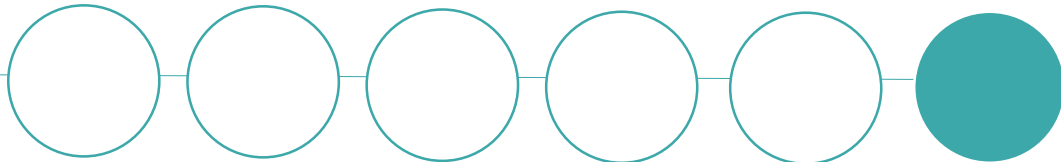


Finally, Antiviral treatment (high viral load)

3rd HBIg for children born to HBsAg+ mothers

2nd HBsAg testing, linkage-to-care, follow of infants

1st At least 3 doses of hepatitis B vaccine including a timely birth dose within 24 hours

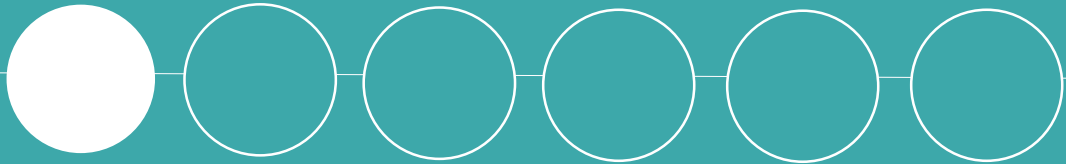


Session 1: Workshop Objectives

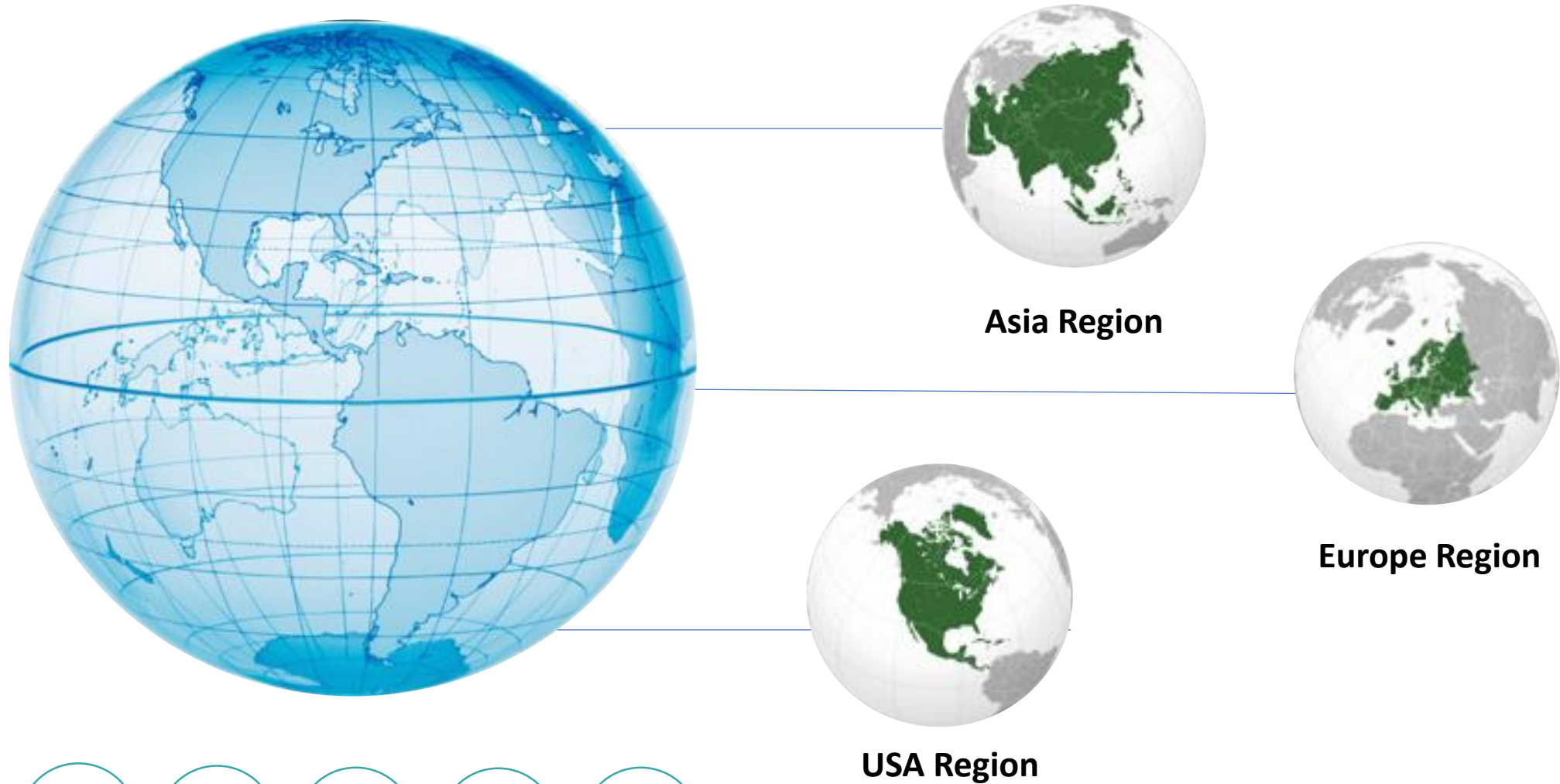
Workshop objectives:

- Take stock of the currently available/licensed combined hepatitis B vaccines in the different Asian Countries.
- Review the data on the hexavalent HB-Hib-DTPa-IPV vaccines: safety, immunogenicity, license, and availability in Asia.
- Discuss the composition and clinical evidence for efficacy of the combined vaccines.
- Evaluate the combination of birth dose vaccination and combined vaccines in the universal immunization policy of a country; practical and public health issues.
- Lessons learnt from countries who introduced already combined vaccines including hepatitis B in their immunization policy.
- Discuss the added value of combined hepatitis B vaccines in a global perspective of elimination of hepatitis B, taking into account WHO's global and regional strategic goals.

Universal Coverage



Global Elimination of Hepatitis B: The WHO Goal



Universal Coverage: Asia Region

Progress and accomplishments of Hepatitis B control through immunization in Asian region :

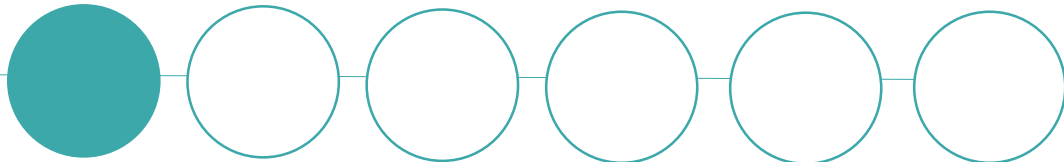
- Prevalence of HBV – WHO WPRO ¹ comprises 45% of the global HBV cases
- Clear WPRO regional controls and targets starting in 2003
 - Reached reduction target in 2017 (HBsAg prevalence <1% in 2020) in 5 yrs-olds and achieved HBsAg prevalence of 0.93% (2017)
 - 93% for 3-dose hep B vaccine (target 95%) in 2017; 85% HBV PMTCT (HepB-BD) against 95% target
 - National Policy for vaccinating healthcare workers (50% in 2017) against target of >80%
 - Encouraging health facility delivery – 89% rate throughout region
- New WPRO regional goals but advocate member states still need to adopt proposed 2018-2025 regional targets³, including:
 - All countries reduce HBsAg prevalence to <1% in 5-year-old children by 2025.
 - Countries that have reduced HBsAg prevalence to <1% in 5-year-olds further reduce HBsAg seroprevalence to <0.5% by 2025
 - Address vaccine hesitancy in Healthcare Providers and training of HCP
- SEARO regional goals⁴ (since 2016) similar as global WHO goals
 - >= 90% for 3-dose hep B vaccine by 2020
 - <= 1% HBsAg among children aged 5 years by 2020
 - No goals defined for Birth dose vaccination
- There is still in some Asian countries (WPRO/SEARO) a residual prevalence in vaccinated cohorts² due to low coverage or untimely birth dose.

¹ Ref: Progress and accomplishments of hepatitis B control through immunization in WH WPRO region Nihal Singh (WHO Country Office in Viet Nam)

²Ref: 4.2% new cases continue to occur in under 5yrs in Indonesia

³re fhttp://iris.wpro.who.int/bitstream/handle/10665.1/13601/RS-2017-GE-23-PHL-eng.pdf?ua=1

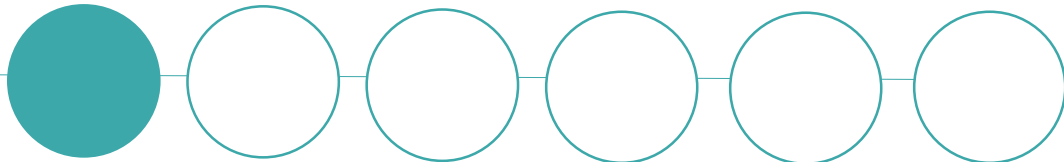
⁴ SEARO Goals:http://apps.who.int/iris/bitstream/handle/10665/272397/9789290225812-eng.pdf?sequence=1&isAllowed=y



Universal Coverage: Asia Region (cont.)

Progress and accomplishments of Hepatitis B control through in Asian region

- Perinatal transmission is the major driver
- Significant variation in geography (e.g.: large no. islands) & home vs hospital births = impact on coverage and timeliness
- Universal immunization programmes have achieved better results than targeted programmes
- Scaling up outside cold chain in countries with a restricted access to cold storage to improve BD coverage (securing reliable supply)
- Now focusing on triple elimination for HIV, Hep B and Syphilis (WHO)

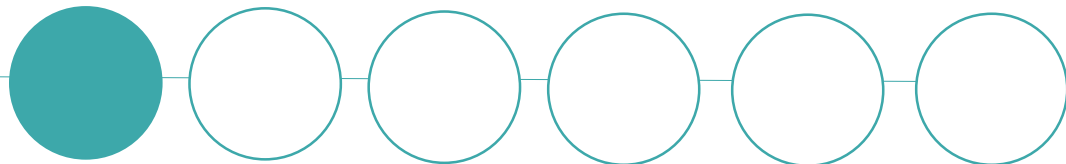


¹ Ref: Progress and accomplishments of hepatitis B control through immunization in WH WPRO region Nihal Singh (WHO Country Office in Viet Nam)

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Universal Coverage: Asia Region

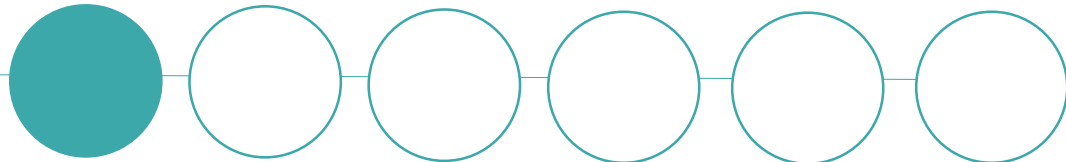
Country	Universal Vaccine Programme	Coverage HVB3 & HepB-BD (Year)	Monovalent vs Combined	Dosing (MThs)
Taiwan	Since 1984	97.8% & 98.6% ()	• Monovalent at 0, 1 & 6	0, 1 & 6
Indonesia	Since 1997	95% & 85% (2014)	• Monovalent at birth dose and Combined (Pentavalen DTP-Hib-HepB) recently	0, 2, 3 and 4
Thailand	Since 1992 (all newborns)	99.9% & 99,4	• Monovalent at birth plus Combined 2, 4 & 6 mths (started 2008)	0, 2, 4 & 6 (plus extra for HBsAg+ at 1mth)
India	Since 2002 (BD 2008)	88% & 53% (most recent data)	• Combined but unclear degree of usage and combined with BD	
Philippines	Since 1992	65.89% & 51% (2017)	• Monovalent 0. and Combined at 6, 10 & 14	0, 6, 10 & 14
Malaysia	Since 1989	98% 88.1% (2016)	• Monovalent at 0, 1, 6 mths & Combined maybe offered after PCV is introduced	0, 1 & 6



^a Note: Serious medical errors experienced in 2013 that significantly impacted on HepB-BD coverage

Universal Coverage: Asia Region

Country	Universal Vaccine Programme	Coverage HVB3 & HepB-BD (Year)	Monovalent vs Combined	Dosing (MThs)
Korea	Since 1995	99% & 93%	• Monovalent 0, 1, 6	0, 1 & 6
Singapore	Since 1987	96% & xxx	• Monovalent 0, 1 & 6 mths; some Combined at 3 rd dose (private)	0, 1 & 6
Vietnam	Since 2003	98% (tbc) & 76.6% (2017) ^a	• Monovalent 0, 2 & 4 & C. (0), 2, 3 & 4	0, 2, 3 & 4 (tbc)
Japan	Since 2016	ND: baby born to HBsAg neg. mother (will get in 2018-2019) 99.9%: baby born to HBsAg pos. mother	• Monovalent 2, 3 & 7-8 mths (baby born to HBsAg neg. mother) since 2016 • Monovalent 0(<12hours), 1 & 6 mths. (baby born to HBsAg pos. mother) with HBIG, since 1986	• 2, 3 & 7-8 • 0, 1 & 6 (baby born to HBsAg pos. mother)
Cambodia	Since 2005: nationally (piloted in one province in 2001)	83%(2016) : National hepatitis B birth dose coverage (<24 hours)	• Monovalent 0. and Combined(DPT-HepB-Hib) at 6, 10 & 14	0, 6, 10 & 14



^a Note: Serious medical errors experienced in 2013 that significantly impacted on HepB-BD coverage

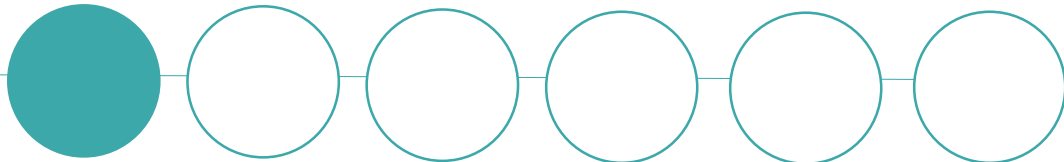
Universal Coverage: Lessons Learnt

WHO European Region (universal infant/childhood programmes)³

- 48/53 countries have implemented a universal HepB programme
- different approach between countries. Universal newborn, infant, childhood and 5 without universal programmes- risk group vaccination; prevention of horizontal or/and perinatal transmission
- Since 2015
WHO EURO regional Hep B control target and action plan ((European Vaccine Action plan 2015-2020):
 - sustainable universal programme in all countries with 95% coverage (with 3 doses);
 - universal newborn immunization (within 24hrs after birth) or effective universal screening of pregnant women, and
 - prevalence of HBsAg <0.5% in vaccinated cohort
- European experience shows flexibility of schedules
- Outcome evaluation of an universal Hep B immunization programme: acute disease surveillance, sero-surveys, immunization coverage surveys, monitoring adverse events and quality controls
- Complexity of combined vaccine might cause production issues, which requires contingency planning in the event of vaccine shortages

USA Region (experience of combined vaccine)⁴

- Combination vaccines are recommended and well accepted
- Improved coverage and compliance rates and timeliness and benefits in shipment and storage
- Well accepted by providers and parents
- No Hexavalent vaccines available

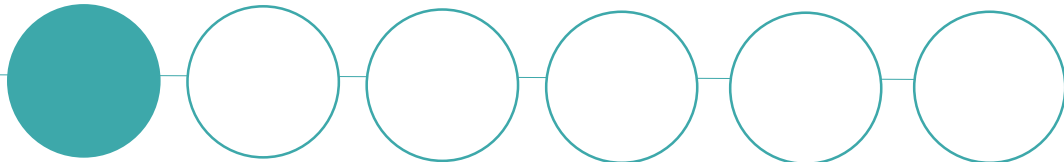


³ Ref: Lessons learnt in Europe, Johannes Hallauer (VHPB, Germany)

⁴Ref: Lessons learnt in USA, John Ward (VHPB, CDC, USA)

Universal Coverage: Surveillance & Monitoring Framework

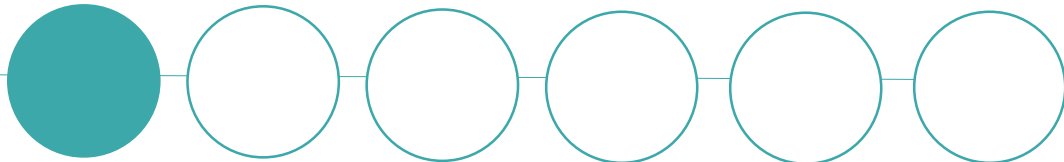
- Global elimination has been established in 2016 as a WHO priority; Immunization or targeted HBV immunization of infants in place since 1980s
- WHO targets and core indicators:
 - Incidence: Reduce new cases of HBV infections, AND;
 - Mortality: Reduce deaths related to HBV (from hepatocellular carcinoma, cirrhosis and chronic liver disease attributed to HBV & HCV infections)
- Monitoring and research is missing to evaluate **long term impact of HBV immunization programmes**, both globally, regionally and sometimes even nationally⁵
- Challenges: difficult to measure impact due to⁵:
 - Highly heterogeneous occurrence
 - Hard to repeat and compare with same population groups
 - Difficulties if collect data from the same source, with the same inclusion criteria and same type of recumbent methodology
 - Consistent and evaluating 'like with like' populations



⁵ Ref: Long-term impact of infant immunisation on hepatitis B prevalence: Systemic review and meta-analysis, Whitford et al. (Session 3. John M Kaldor)

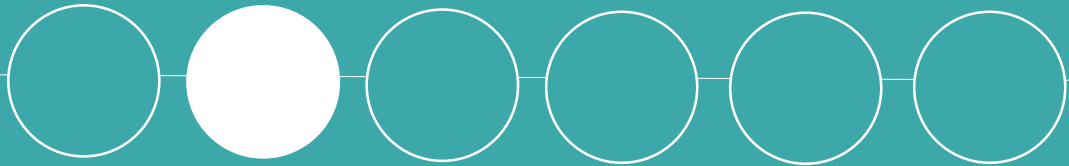
Universal Coverage: Surveillance & Monitoring Framework

- Recommendation⁵:
 - Most immediate need are surveys to prompt countries to implement birth dose and secondarily, document prevalence after vaccination - e.g. Mongoli found high prevalence with high coverage because of poor vaccine due to freezing.
 - By protecting children, the time of high risk for chronic infection - morbidity will decline.
 - Beginning planning longer term monitoring, if the global community is committed to truly elimination of HBV (and HCV)
 - Standardised protocols for monitoring and coverage information held locally in regions, as well as nationally, to ensure timely HBV-BD dosage.
 - Data is needed to guide testing and care to those already infected.



⁵ Ref: Long-term impact of infant immunisation on hepatitis B prevalence: Systemic review and meta-analysis, Whitford et al. (Session 3. John M Kaldor)

Scheduling



Scheduling: Birth Dose

Evidence Review⁶:

- High levels of seroprotection (98%) achieved from Hep B vaccine starting at birth.
- Final Seroprotection did not vary with maternal HBsAg status; HBIG administration; or vaccine schedule and dosage
- No difference between compressed schedule (including a 4th dose) and non-compressed schedule, except in earlier protection
- Several studies were presented that proves the importance of timely birth dose vaccination.

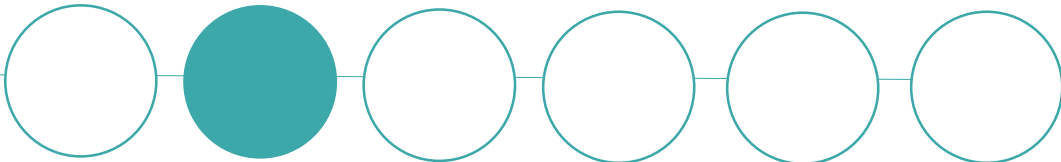
Birth Dose^{7,8}:

- A child born in a hospital or health centre, is more likely to receive a birth dose <24hr
- HBV BD must be offered by health staff and awareness needed about real and false contra-indications⁸
- In Cambodia⁷, in those who received a birth dose, overall HBsAg was 0.30%
 - If within 24hr HBsAg was 0.17%
 - If after 24hr HBsAg was 0.48%
 - Not received the birth dose >3%
- Overall HBsAg prevalence in children born at home was higher

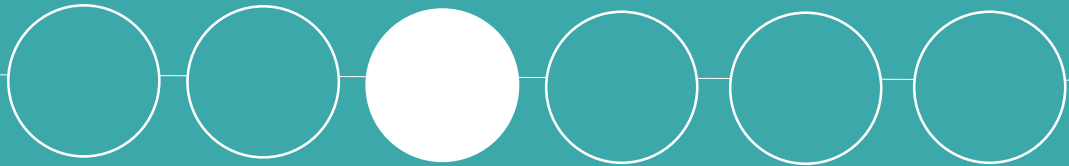
⁶ Ref: Seroprotection after hepatitis B vaccination among newborn infants: a review. Rania Tohme (CDC, USA)

⁷ Ref: The sero-epidemiological study on the prevalence of hepatitis B among children and mother in Cambodia. Junko Tanaka (Japan)

⁸ Ref: The coverage of hepatitis B birth dose vaccination and barriers to timely vaccination in the Mekong Delta in Vietnam Pierre Van Damme (VHPB, Belgium)



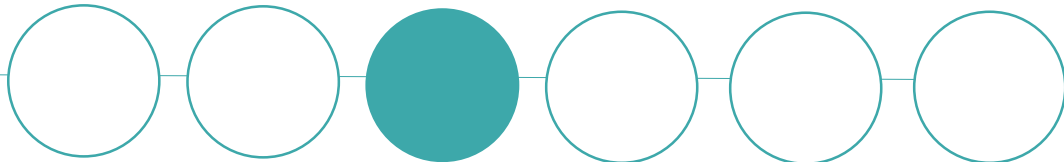
Awareness & Adherence



Education & Training

Awareness^{8, 10, 11}:

- Healthcare providers required training on both the importance of (timely) administration of infant vaccines and timely birth dose vaccination; education needed on efficacy of intervention which might influence increased adherence; and on injection techniques, safe immunization practice; cold chain, vaccine and logistics management
- Educate family (3 in 1: pregnant women, father and grandmother) and increase demand on the side of the parent, to understand the long term impact and benefit of Hep B vaccination
- HepB-BD should be part of a 'birth-bundle-approach' to create ownership and target hospital leadership
- Revise and make available written hospital policy and guidelines – on administration and update list of real contra-indications
- Public health communication material on Hep B and distributed during antenatal and postnatal care by midwives and health volunteers; and improve media communication on vaccinations
- Guidance and education need to harmonize use of combination and single antigen vaccines⁸



⁸ Ref: The coverage of hepatitis B birth dose vaccination and barriers to timely vaccination in the Mekong Delta in Vietnam Pierre Van Damme (VHPB, Belgium)

⁹ Ref: Lessons learnt in USA, John Ward (VHPB, CDC, USA)

¹⁰ Ref: Session 5: Group discussions per WHO Region: SEARO (India, Indonesia, Taiwan, Thailand)

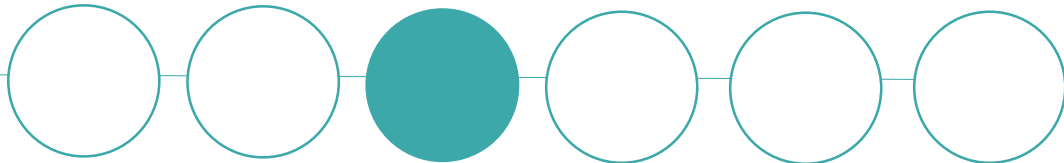
¹¹ Ref: Lessons learned from a rapid assessment to address low hepatitis B vaccine birth dose uptake in Vietnam following serious adverse events following immunization (AEFIs) - Le Thi Thanh Xuan (Vietnam)

Education & Training

- Some countries in the Asian Region experiencing growing parental concerns^{9, 10}.

Reasons for less vaccine confidence in clinicians & parents^{8, 9}:

- Number of injections; the perception that ‘Immune system overload’ and the news on adverse events and serious historical medical mistakes – immediate (pain, fever) and long term (e.g. autism-comprehensively disproven)
- Recommendations to HCP, parental support and compicance can easily evaporate: important to keep messages and programmes simple (not over-complicate)

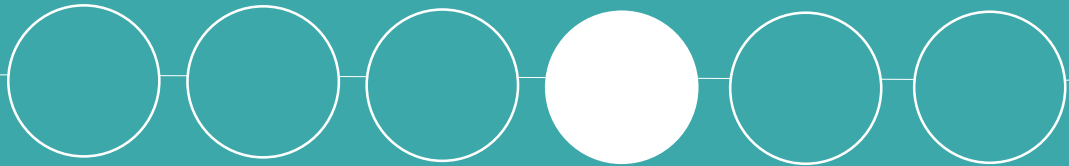


⁸ Ref: The coverage of hepatitis B birth dose vaccination and barriers to timely vaccination in the Mekong Delta in Vietnam Pierre Van Damme (VHPB, Belgium)

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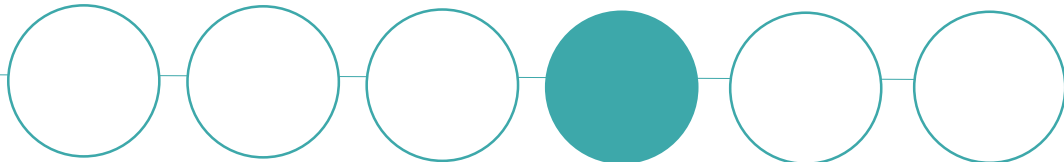
¹⁰ Ref: Session 5: Group discussions per WHO Region: SEARO (India, Indonesia, Taiwan, Thailand)

Combined Vaccines



Combined Vaccines: Immunogenicity, efficacy & Safety

- More than 15 yrs data and growing literature shows hexavalent vaccines demonstrate excellent immunogenicity, clinical efficacy, tolerability and safety profile, and can be administered in infants >6 weeks of age^{12, 13} (not used in birth dose or at the age of 4 weeks if HBV vaccine needs to be administered).
- Administration of million doses during 15 yrs (approx. 150 million doses hexavalent), shows an immunogenicity and long term protection for all antigens including HBV
- Comparison between different products are reported to be 'non-significant and comparable (non-inferior)'
- Small differences in composition and quantity of Al⁺⁺⁺ adjuvants in hexavalent vaccines¹⁴
- Can be co-administered with other pediatric routine vaccines, No interference with other vaccines (pneumococcal, rotavirus, Mening. vaccines MMR)
- Use of hexavalent vaccines guarantee better coverage of all antigens
- Some slight increase in short term adverse events (fever, redness, swelling etc.)
- Vaccine inter-change can be done, but the recommendation is to continue with same vaccine



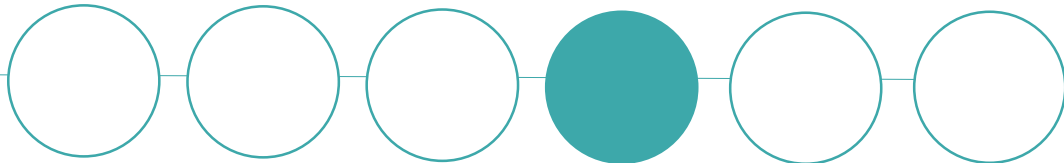
¹² Immunogenicity and safety of combined hepatitis B vaccines, European experience, Vana Papaevangelou (VHPB, Greece)

¹³ Immunogenicity and safety of a fully liquid hexavalent vaccine compared with the standard of care in infants in the Republic of Korea. Yae-Jean KIM (Republic of Korea)

¹⁴ Ref: Hexavalent vaccines: Hepatitis B antibody response and co-administration with other vaccines, Timo Vesikari (Finland)

Combined Vaccines: Immunogenicity, efficacy & Safety

- Benefits^{15, 16}:
 - Co-administrated with other pediatric routine vaccines, increase compliance and vaccine coverage
 - Improve vaccination documentation, reduce overall costs of campaigns, reduce storage, reduce doctors visits and number of injections
 - Some flexibility in vaccine schedules possible, but timely vaccination is essential
 - Although schedule may incorporate pentavalent vaccines to reduce the number of HB vaccines doses administered (especially in areas with birth dose), it is recommended to use one product (hexavalent) and keep schedules simple, to avoid errors.
- Challenges¹⁶:
 - Longer term data on newly available hexavalent vaccines;



¹⁵ Ref: Lessons learnt in Europe, Johannes Hallauer (VHPB, Germany)

¹⁶ Ref: Lessons learnt in USA, John Ward (VHPB, CDC, USA)

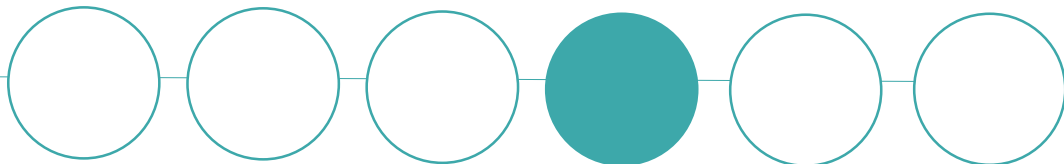
Combined Vaccines: Issues & Opportunities

Issues¹⁷:

- Logistical and budget issues
- Address anti-vaccine attitudes (e.g.: SAE fears) when new or changes to vaccine programmes occur
- Level of country-specific evidence to support adoption of new regimes
- Potential delay in switching to combined vaccinations and impact on well-embedded vaccination programmes
- Lack of awareness and knowledge of parents and healthcare professional
- Lack of availability of combination vaccinations in public sector

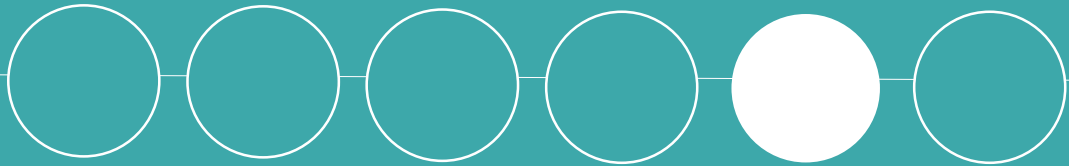
Opportunities¹⁷:

- Introduction of new vaccine could help decision makers to go for a simplified immunisation schedule with combined vaccines
- Easy to administration and fewer injections



¹⁷. Ref: Session 5: Group discussions per WHO Region: WPRO (Cambodia, Korea, Laos, Malaysia, Philippines, Singapore, Vietnam) & SEARO (India, Indonesia, Taiwan, Thailand)

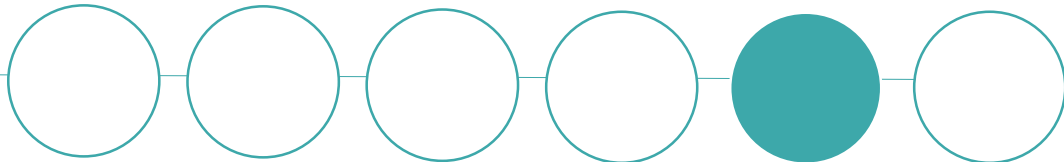
Flexible Vaccination Delivery Model



Flexible Vaccination Delivery Model

Strengthen community outreach and linkage with hospitals¹⁸:

- Health Care Providers and VHV (village health volunteers) to regularly meet : update registers, immediate report home deliveries to health facility staff (can increase BD coverage: 81% to 93%)
- Receive education, training and supervision on Hep B and vaccination from local health facilities
- Improvement in vaccine storage conditions, available information on storage, stock and data management
- Vaccine availability plays a big role in vaccine coverage

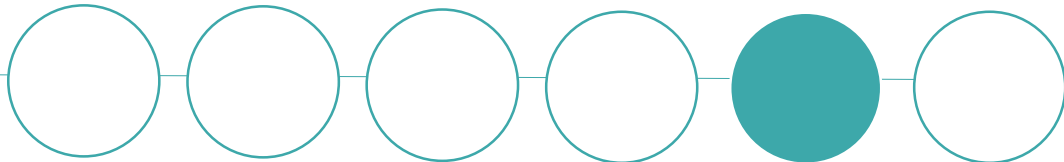


¹⁸ Ref: Birth dose improvement projects in the Western Pacific Region - Makiko Iijima (WHO Country Office in Vietnam)

Flexible Delivery Model

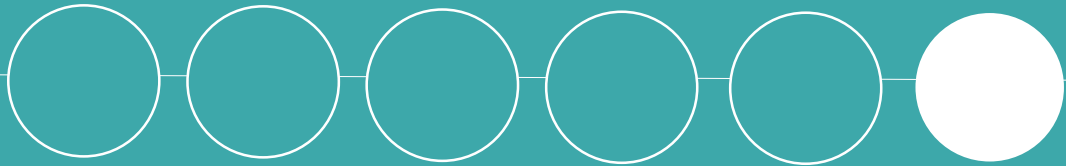
Improve coverage in hard to reach communities:

- Consider mobile clinics or VHV to provide HepB-BD to hard to reach populations
- Consider out of cold chain (OCC) introduction¹⁹
 - HepB vaccine is extremely heat stable vaccine and maintains safety and immunogenicity profile
 - Significant experience in the Asia Region and studies have demonstrated 'no difference in anti-HBs level and GMT' even after storage up to 37° for 28-30 days
 - Timely HepB-BD coverage increased by using vaccine OCC especially for home births
 - Health workers and mothers accepted use of HepB-BD OCC
 - VHV proved competent at providing vaccination with Uniject
 - Strong support and promotion for OCC to increase HepB-BD (WHO-WPRO guidelines)
 - Challenges: Reluctance to scale-up use of HepB-BD OCC (off-label use); Lack of manufacturer interest to re-label for CTC (controlled temperature chain) use (potential increase in pricing)



¹⁹ Ref: Improving timely hepatitis B birth dose vaccination through use of the vaccine outside the cold chain: The Asia Pacific experience. Rania Tohme (CDC, USA)

Eliminating Hepatitis B



Key Messages: Prevention & Elimination Of Hepatitis B

Universal Coverage:
Asia Region



Timely Birth Dose

management of
HBV+ mothers and
infected newborns

Combined
vaccinations
+ flexible but timely
delivery

Catch up
vaccination and
care for HBV
infected

Elimination of
Hepatitis B

Eliminating Hepatitis B: VHPB Asia Workshop

Workshop Recommendations:

- First priority to make the universal immunisation programme a success in the Region (with high level of sero-protection (98%) achieved starting with BD and reduces HBsAg prevalence^{21, 23}.
- Timely administration of the HBV BD is utmost important to control perinatal transmission as soon as possible
- Education of healthcare providers and families on vaccine (safety and efficacy), administration, disease transmission and burden is key²² including communication tools to cope with vaccine hesitancy arguments
- Combination vaccines are both safe, well tolerated and have good immunogenicity profiles and should be used to enable improved coverage²³
- Need longer term data on use of combined vaccines²³
- Birth dose within 24hr of birth targets should be prioritised and use of OCC to enable timely first home birth dose. ²⁴
- Need for standardized methodology and population –based data to document progress towards and achievement of elimination targets²⁵
- Once the universal programmes have been fully implemented and benefits being realised, the need to look forward at monitoring impact on burden of illness in adults^{24,25} Next order of business is to avert mortality among the 257 million who were not in a time or place to be vaccinated
- The significant achievements of the WPRO and member countries in controlling hepatitis B was emphasized, and their experienced and lessons learnt should be shared with member countries of the SEARO region to improve the hepatitis B vaccination coverage including timely hepatitis B birth dose vaccination

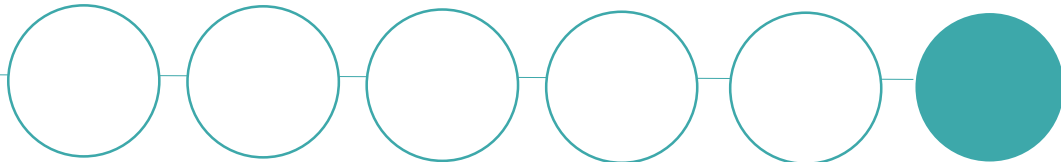
²¹ Ref: Long-term impact of infant hepatitis B immunization on Hepatitis B prevalence: a systematic review and meta-analysis John M Kaldor (Australia)

²² Ref: Birth dose improvement projects in the Western Pacific Region - Makiko Iijima (WHO Country Office in Vietnam)

²³ Ref: Lessons learnt in USA, John Ward (VHPB, CDC, USA)

^{23a} Ref: Seroprotection after hepatitis B vaccination among newborn infants: a review. Rania Tohme (CDC, USA)

²⁵ Ref: Long-term impact of infant immunisation on hepatitis B prevalence: Systemic review and meta-analysis, Whitford et al. (Session 3. John M Kaldor)



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