HEPATITIS B

Pregnancy

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Hepatitis B and Pregnancy

HBsAg screening of pregnant women is essential: AASLD and EASL

- First trimester of each pregnancy or whenever they present
- Pregnant women not immune to HBV and with risk factors for infection should be vaccinated against HBV – **SAFE IN PREGNANCY**
- HBsAg positive women should be referred for additional testing, screening of partners and medical management

Management Decisions in HBsAg positive pregnant women

- Does she need treatment for chronic hepatitis B ?
  - Cirrhosis irrespective of ALT, HBeAg status and HBV DNA levels
  - Chronic hepatitis B – Immune clearance or immune escape phase
- Does she need treatment to prevent HBV MTCT ?
- Hepatitis B may flare in first 3-6 months post delivery if not on antiviral treatment or if antivirals stopped - close monitoring post delivery

Hepatology 2009 50(3):661; J Hepatol 2012;57(1):167

HBV Perinatal transmission

- Occurs mainly at birth
- In-utero transmission is rare
- Increased risk with HBV DNA levels >200 000 IU/ml
- Transmission through breast milk is controversial

Risk of chronic HBV infection at 6 months in absence of intervention

- 70-90% in babies born to HBeAg-positive women
- <10% in babies born to HBeAg-negative women (immune control)

Risk of transmission from women acutely infected in the first or second trimester is low

- Increases to 60%, if acute infection occurs in 3rd trimester

Maternal HIV/HBV co-infection increases risk of MTCT up to 2.5 fold:

- Pregnant women 3x more likely to test positive for HBV DNA, higher HBV DNA levels
- Twice as likely to test positive for HBeAg

Prevention of HBV MTCT

- **Identify:** Maternal HBsAg screening
  - Not policy in South Africa
- **Assess the need for Tenofovir in 3rd trimester of pregnancy**
  - Most women are immune tolerant or immune control phase - not candidates for treatment
  - Risk of MTCT if HBV DNA >200 000 IU/ml
  - HBIG and HepB-BD: 80-95 % effective in preventing MTCT
  - HBIG expensive and not routinely available
- **Incorporate Birth dose HBV vaccine into EPI schedule**
  - Administration within 24 hours of delivery
- **Ensure full HBV3 vaccine coverage**

Prevention of Mother to Child Transmission

China: 5 geographic regions – *Pan et al, NEJM 2016;374:2324*

- HBeAg-positive mothers HBV DNA >200 000 IU/ml
- 300 mg TDF: 30 to 32 weeks of gestation until postpartum week 4
- ***Infants***: 200 IU HBIG & 10ug HBV vaccine within 12hrs, HBV vaccine & HBIG repeated at 1 month and HBV vaccine at 6 months
- ***All mother–infant dyads:*** evaluated at postpartum weeks 4, 12, 24 & 28
- *68% TDF-treated mothers (66/97) vs 2% (2/100) - target HBV DNA level < 200 000 IU/ml at delivery*
- Week 28, rate of MTCT (HBV DNA >20 IU/ml or HBsAg positive at 28 wks)
  - **ITT analysis: 5% infants (5/97) in TDF vs. 18% (18/100), p= 0.007**
  - Per-protocol analysis 0% infants in TDF vs. 7% (6/88), p= 0.01
  - No difference in maternal HBV serological outcomes
- **No difference in birth defects - 2% (2/95) vs 1% (1/88)**

Prevention of Mother to Child Transmission

Third trimester antiviral prophylaxis

- AASLD now suggest Tenofovir 300mg daily at 28-32 weeks of pregnancy if HBV DNA >200 000 IU/ml to further reduce risk of perinatal transmission
- EASL suggests antiviral therapy in 3rd trimester if HBV DNA >10^{6-7} IU/ml
- WHO: no formal recommendation: under review

Tenofovir can be stopped 3 months post delivery if only required for prevention of HBV MTCT

- Need to discuss the mother's future pregnancy plans re remaining on Tenofovir until completes family

J Hepatol 2012;57(1):167-85; J Hepatol 2012;57: 167

Case Study 1

24 year old woman known to your clinic with Chronic Hepatitis B (immune tolerant) presents 3 months pregnant at her routine follow-up visit (G1P0)

- Completely asymptomatic
- Concerned about HBV transmission to the baby

Clinically

- Not jaundiced, mild palmar erythema
- Liver span: 11cm and no clinical signs of portal hypertension

Investigations

- Urinary dipstix normal, Creatinine 65
- **FBC:** Hb 13 WCC 5.2 Platelets 258 x 10^9 /L
- **Liver profile:** TBil 11 umol/L (0-21), CBil 5 umol/L (0-6), ALT 14 units/L (5-40), ALP 168 units/L (40-120), GGT 35 units/L (0-35), **Albumin 35 g/L** (35-52)
- **AFP:** 348 ug/l (0-7)
- **Serology:** HBsAg pos, HBeAg pos and HBeAb neg. HIV negative
- **HBV DNA:** 5 346 486 IU/ml
- **Ultrasound liver:** Normal size, contour and echogenicity. No lesions

Pregnancy in a HBV Immune Tolerant Woman

- Does she need to be started on treatment to prevent progression of her liver disease during pregnancy ?
- Are you concerned about the elevated AFP and low Albumin levels?
- What are the risks of perinatal transmission ?
- Do you need to consider HBV MTCT prophylaxis ?
  - When would you start and what antiviral would you choose ?
  - What target HBV DNA level are you aiming for?
- What other preventative modalities do you need to tell the mother ?
- If she does not require long-term HBV treatment, when can you stop antivirals ?
- How would you monitor her post delivery?

Case Study 2

28 year old woman: G1P0: Antenatal booking at 28 weeks pregnant

Completely asymptomatic, but HIV positive and CD4 count 794

Clinically:

- Increased BMI 30. Not jaundiced, mild palmar erythema
- Liver span: 13 cm with no clinical signs of portal hypertension

Investigations

- Creatinine 62
- **FBC:** Hb 12 WCC 4.8 Platelets 231 x 10^9 /L **INR** 1.1
- **Liver profile:** TBil 14 umol/L (0-21), CBil 5 umol/L (0-6), **ALT 56 units/L (5-40), AST 49 units/L (5-40),** ALP 158 units/L (40-120), GGT 40 Units/L (0-35), **Albumin 37 g/L (35-52)**
- **Serology:** HBsAg pos, HBeAg pos and HBeAb neg.
- **HBV DNA:** 7 546 493 IU/ml
- **Ultrasound liver:** Liver 13 cm, smooth contour and increased echogenicity suggestive of steatosis

Pregnancy: HIV/HBV Co-infection

- Initiated on FDC (Tenofovir/Emtricitabine/Efavirenz) per protocol
- Counseled re screening of partner for HIV and HBV
- Counseled re need for HBV birth dose vaccination
- Lifelong treatment: HIV and HBV viral suppression
- Advised re weight loss post delivery as hepatic steatosis important negative co-factor for disease progression

Efavirenz DILI *(Sonderup et al; AIDS 2016;30(9):1483)*

- "Immunoallergic" DILI leading to submassive necrosis with lymphoplasmocytic/eosinophilic inflammatory infiltrates
  - CD4 count of >350 cells/mm3 [OR, 11.1; 95% CI, 2.7-46.2, p=0.001)
  - Younger age [OR 0.87; 95% CI, 0.78-0.98, p=0.02) median age 34 yrs
  - Female gender [OR, 12.3; 95%CI, 1.5-100.1, p=0.02]
  - Median duration on ART was 20 weeks (IQR 12-24) – up to 1year
- High morbidity and mortality – usually requires steroid therapy

Conclusions : HBV and Pregnancy

- All pregnant women must be tested for HBsAg
- All neonates born to HBsAg positive mothers must receive birth dose of HBV vaccine and complete vaccine series
- Consider Tenofovir therapy in 3rd trimester to prevent MTCT
  - HBeAg positive or HBV DNA >200 000 IU/ml
- Indications for HBV therapy in pregnancy are the same as for non-pregnant women
- Close follow up for 6 months postpartum - risk of flares if not on therapy or therapy stopped during pregnancy
- Be aware of EFV DILI post partum – young women starting ART on high CD4 counts

Universal HBV Vaccination

World Health Organization (WHO) recommended its incorporation into the Expanded Programme of Immunization (EPI) in 1991

- Most effective way to reduce global burden of HBV
- **2015:** 185/194 countries worldwide and 47 in WHO Africa region have incorporated hepatitis B vaccination into EPI
- ***Systemic review (1990-2005)***: HBV seroprevalence has decreased in many regions of the world
- **Estimated to have prevented more than 1.3 million deaths**

In 2009, WHO recommended HBV Birth dose vaccine for all countries, even those with low HBV prevalence

Vaccine 2012;30:2212; Vaccine 2013;6:206; WHO position paper on hepatitis B vaccines. Geneva, World Health Organization, 2009 (http://www.who.int/wer/2009/ wer8440.pdf).http://apps.who.int/immunization_monitoring/globalsummary;
Nature Gastro 2012; 9: 492

HBV Birth dose vaccine

MONOVALENT HEPATITIS B VACCINE MUST BE USED FOR THE BIRTH DOSE

NAME OF DOSE	TIMING OF ADMINISTRATION OF DOSE	
	3-DOSE SCHEDULE	4-DOSE SCHEDULE**
HepB-BD	As soon as possible after birth (≤24 h)	As soon as possible after birth (≤24 h)
HepB1	HepB1 is not given (i.e. not counted*)	As per combination vaccine schedule
HepB2	4 weeks minimum after HepB-BD	As per combination vaccine schedule
HepB3	4 weeks minimum after HepB2	As per combination vaccine schedule

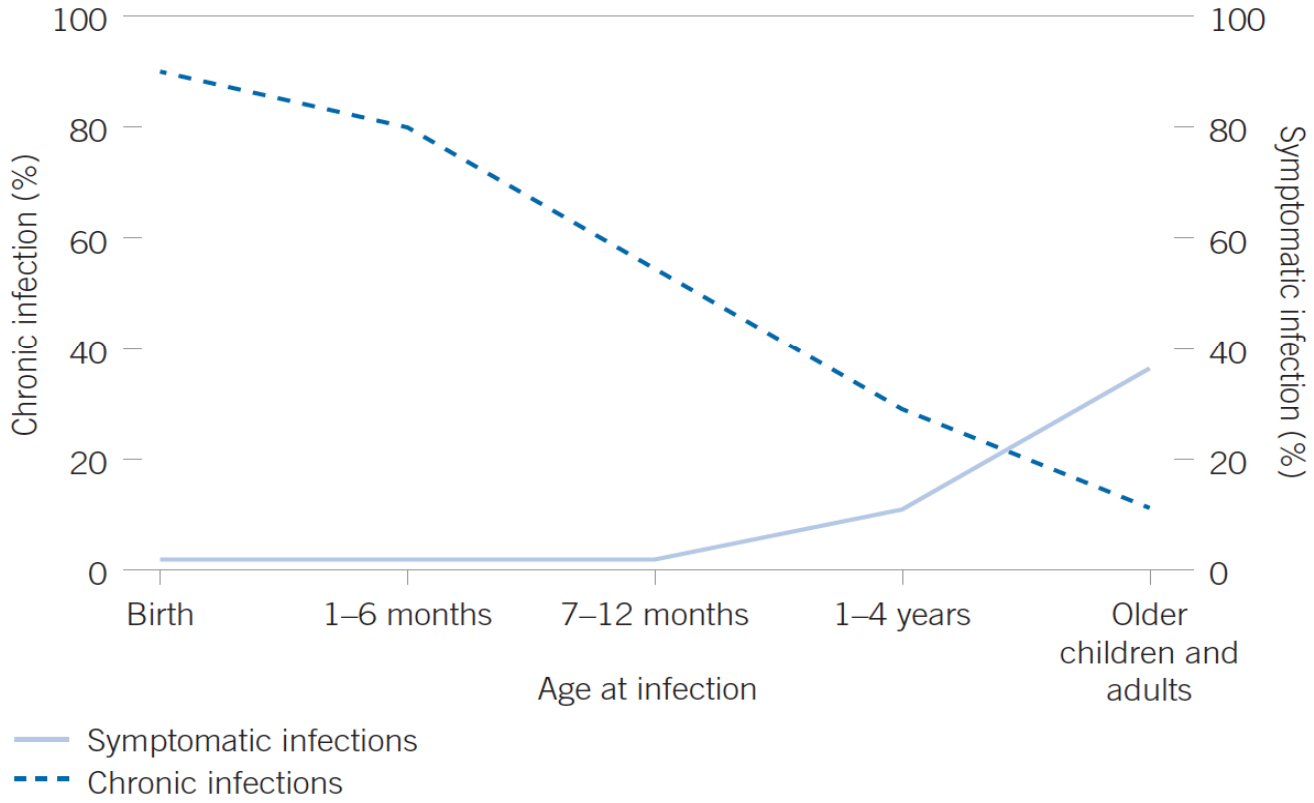
* Not counting HepB1 is recommended as a standard to allow for reporting coverage of HepB-BD and HepB3 when using a 3-dose schedule.
** In the 4-dose schedule, the second dose is still called HepB1 in order to avoid confusion with DTP1/Pentavalent1.

- Monovalent HBV birth dose improves immunogenicity of penta/hexavalent vaccines
- **4 dose schedule** does not immunologically compromise infants who do not access Hep-BD - **add on to the usual 6, 10 and 14 week schedule**
- **Risk of chronic HBV infection, despite HepB-BD, is 3.74x higher if interval between 1st and 2nd vaccine dose >10 weeks**

Vaccine 2009;27:6110–6115

Age at Acquisition and Chronicity

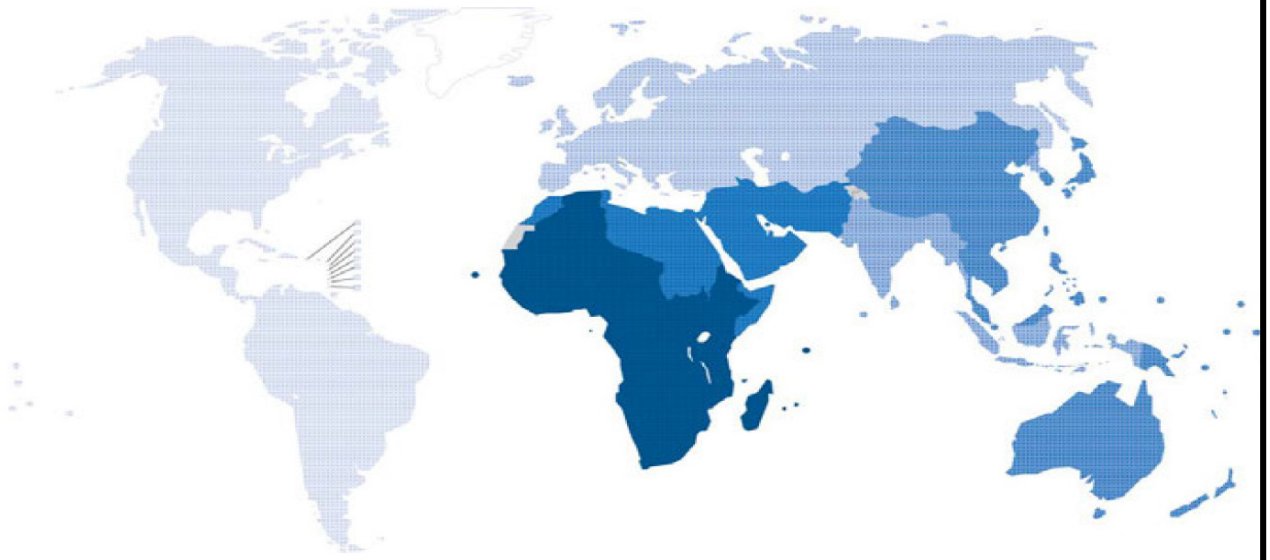
FIGURE 3.1 Outcome of hepatitis B infection by age at infection



2015 WHO Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection

Global Hepatitis B Epidemiology (Children <5yrs) : 2015

Table 1 (with map). Cumulated incidence of chronic HBV infection, 2015 (prevalence of HBsAg in children under 5 years) after the use of the vaccine by WHO region: about 1.3% of under-5 children have developed chronic HBV infection



		Prevalence of HBsAg (%)		
			Uncertainty intervals	
WHO region	Map key	Best	Lower	Higher
African Region		3.0	2.0	4.7
Region of the Americas		0.2	0.1	0.5
Eastern Mediterranean Region		1.6	1.2	2.1
European Region		0.4	0.2	0.8
South-East Asia Region		0.7	0.5	1.6
Western Pacific Region		0.9	0.6	1.3
Total		**1.3**	**0.9**	**2.2**

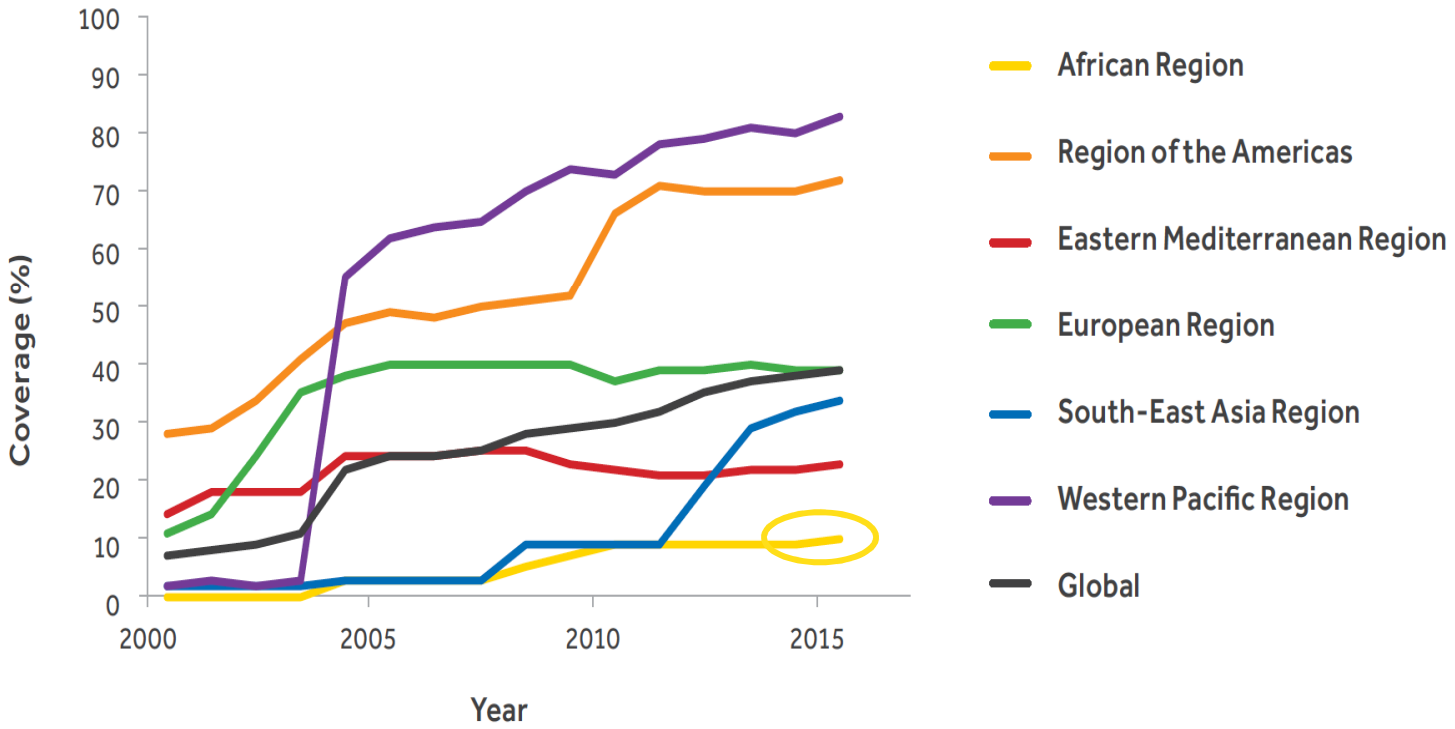
HBV endemicity is established in early childhood (under age of 5 years)

Globally, with HBV vaccination: HBsAg 4.7% → 1.3%

WHO Global Hepatitis 2017 report

2015: Global HepB-BD vaccine coverage

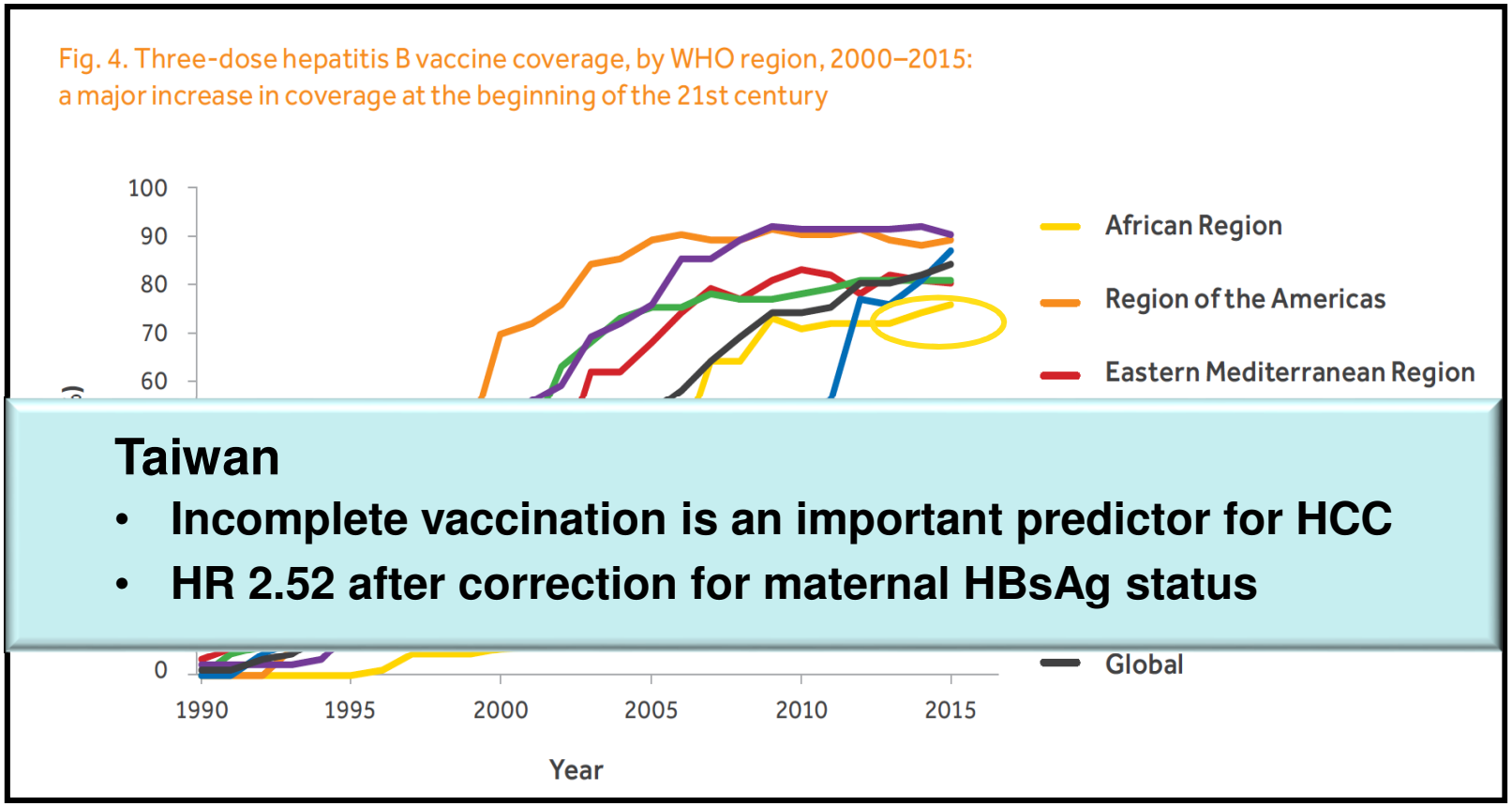
Fig. 5. Hepatitis B birth dose coverage, by WHO region, 2000–2015: good progress in the Region of the Americas and Western Pacific Region



2015: HepB-BD vaccine as part national EPI: 39% globally

- **<38% of babies born worldwide received HepB-BD within 24 hours after birth**
- **Africa Region only 10% HepB-BD coverage – Not yet adopted in South Africa**

Global and regional infant vaccination rates



WHO/UNICEF estimates of third dose of HBV vaccine coverage 1990-2015

- Global coverage: 84%
- **Africa region: 77%**

WHO 2017 Global Viral Hepatitis Report