# Hepatitis B dalam Kehamilan

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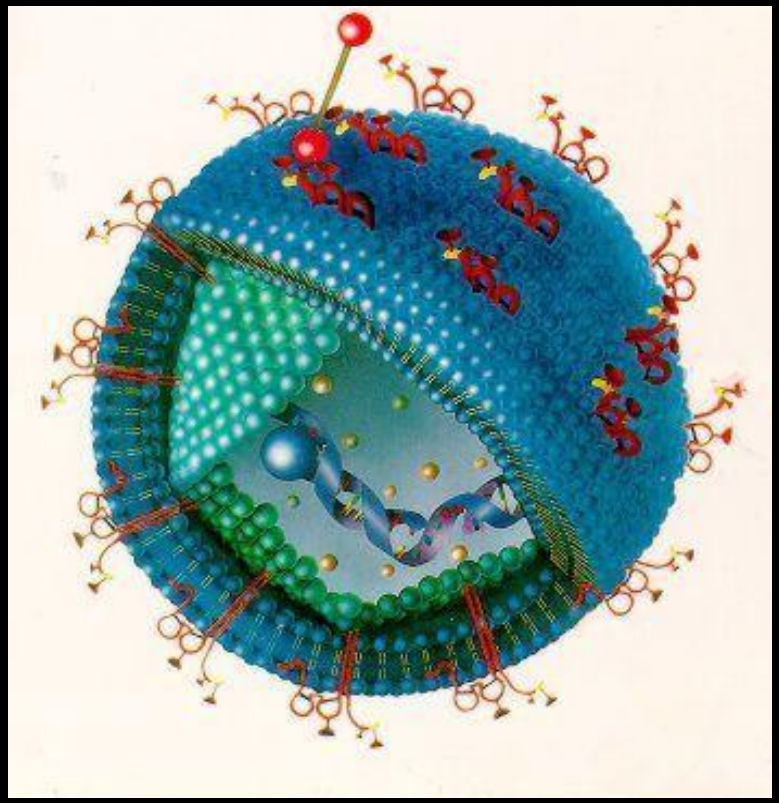
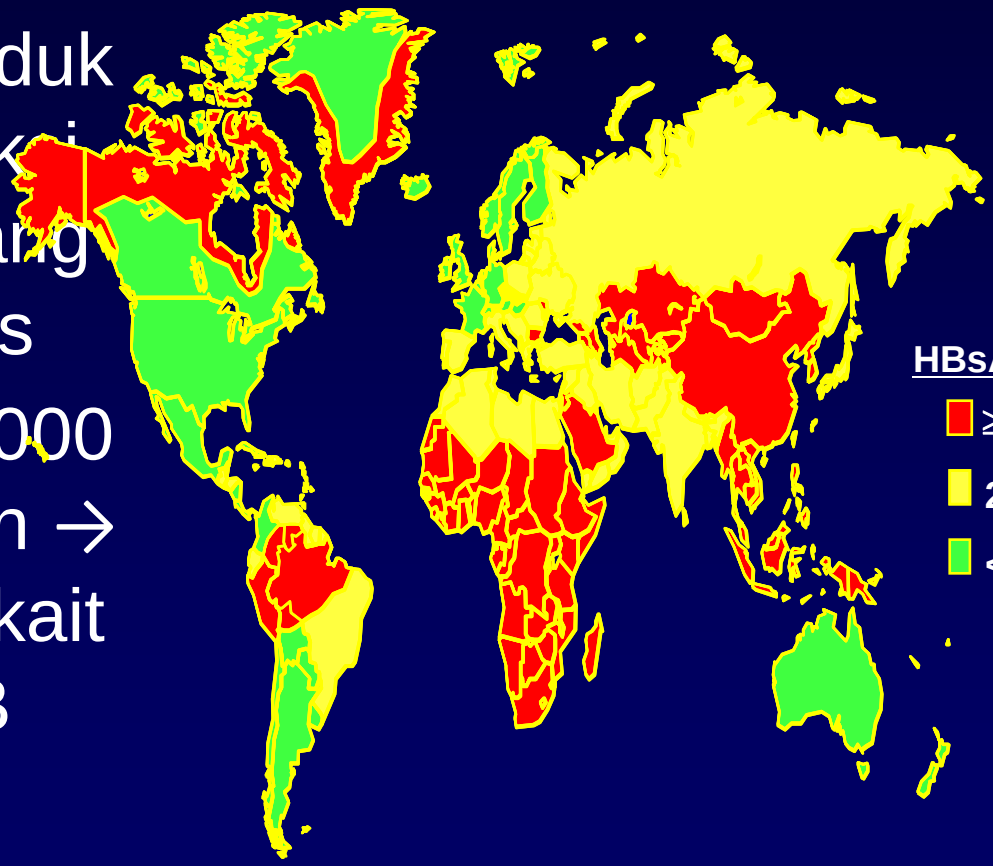
# Definisi

- Hepatitis B merupakan infeksi menular serius pada hati yang disebabkan oleh virus hepatitis B.
- Infeksi akut dapat terjadi pada saat tubuh terinfeksi untuk pertama kalinya. Infeksi akut ini dapat berubah menjadi kronis setelah beberapa bulan sejak infeksi pertama kali



# Infeksi virus hepatitis B (VHB) masalah utama kesehatan masyarakat di seluruh dunia

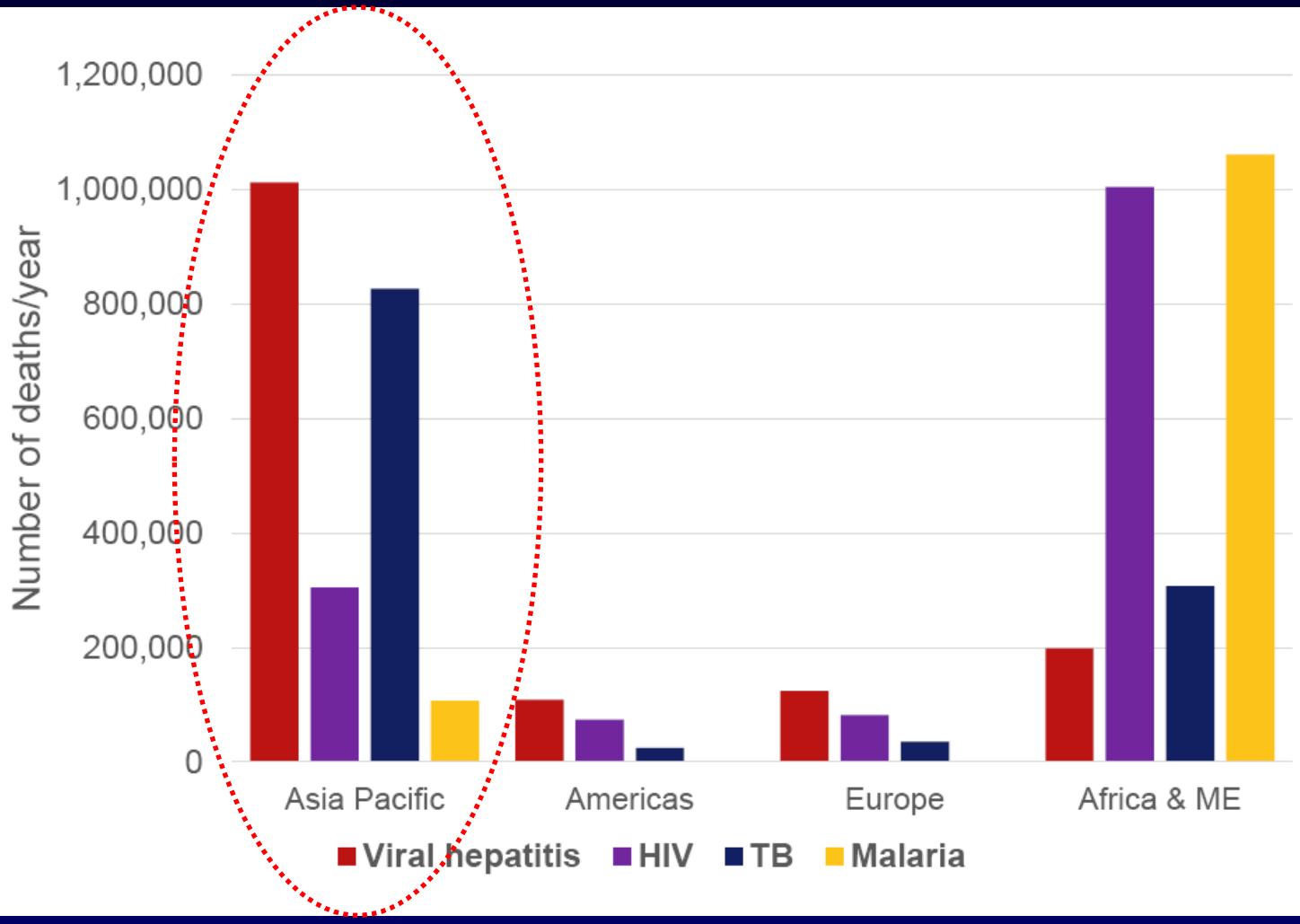
- 2 miliar penduduk dunia terinfeksi →240 juta orang infeksi kronis
- Dunia → 780.000 kematian/tahun → komplikasi terkait infeksi VHB




World Health Organization
Centers for Disease Control and Prevention.

*World Health Organization. Fact Sheet #204. 2015*
*Lozano et al. Global Burden of Disease Study 2010. Lancet. 2012; 380*

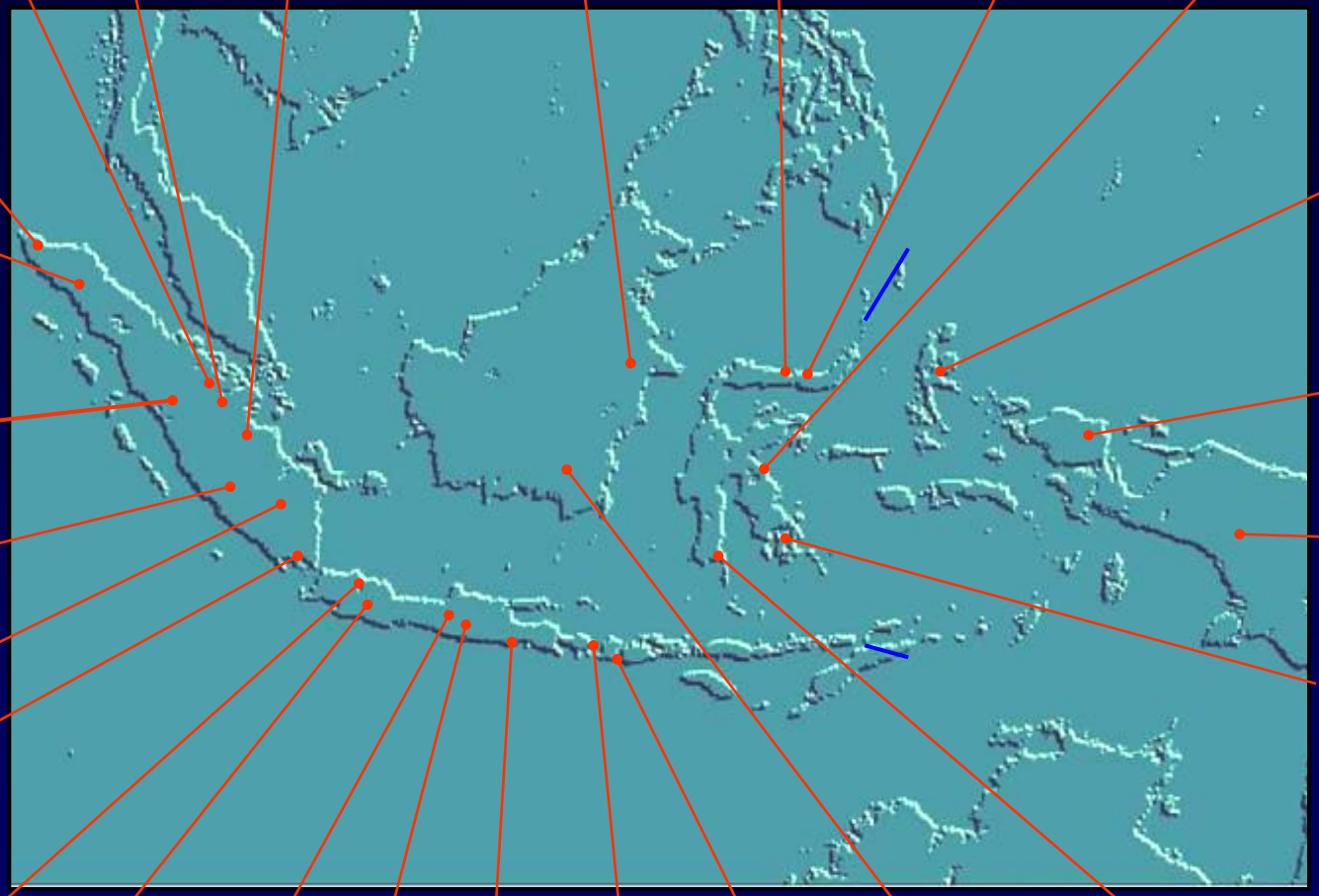
# Estimated annual deaths from selected causes by region, 2010




Lozano et al. Lancet. Vol 380. 2012

*Courtesy of IHME – Global Burden of Disease Study*

# Prevalence of HBsAg in Indonesia: 3-9.4% #



RIAU 2.4%
JAMBI 8.3%
BANGKA BELITUNG 4.4%
E. KALIMANTAN 6.4%
GORONTALO 13.0%
N. SULAWESI
C. SULAWESI
NAD 12.8%
N. SUMATRA 11.7%
MOLUCCAS
W. IRIAN JAYA
W. SUMATRA 15.1%
BENGKULU 19.3%
PAPUA
S. SUMATRA 9.7%
S.E. SULAWESI
LAMPUNG 17.0%
JAKARTA 5.9%
W. JAVA 8.2%
C. JAVA 6.7%
JOGJA 2.5%
E. JAVA 10.1%
BALI 5.6%
W. NUSA TENGGARA 5.5%
S KALIMANTAN 6.6%
S. SULAWESI 13.4%

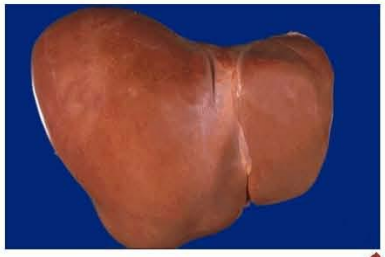
# Provisional data

# CHB – an often 'silent' progressive disease

60%

Liver stays normal for many years

Normal liver



Liver damage = the result of unsuccessful attempts to clear infected hepatocytes in the immunoclearance stage of disease

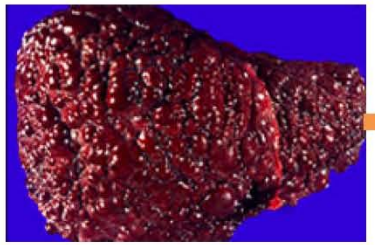
Chronic HBV infection

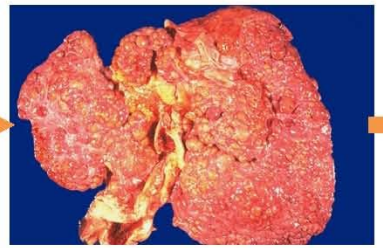
40%

CIRRHOSIS

CIRRHOSIS/ ESLD

HCC





20–30 years

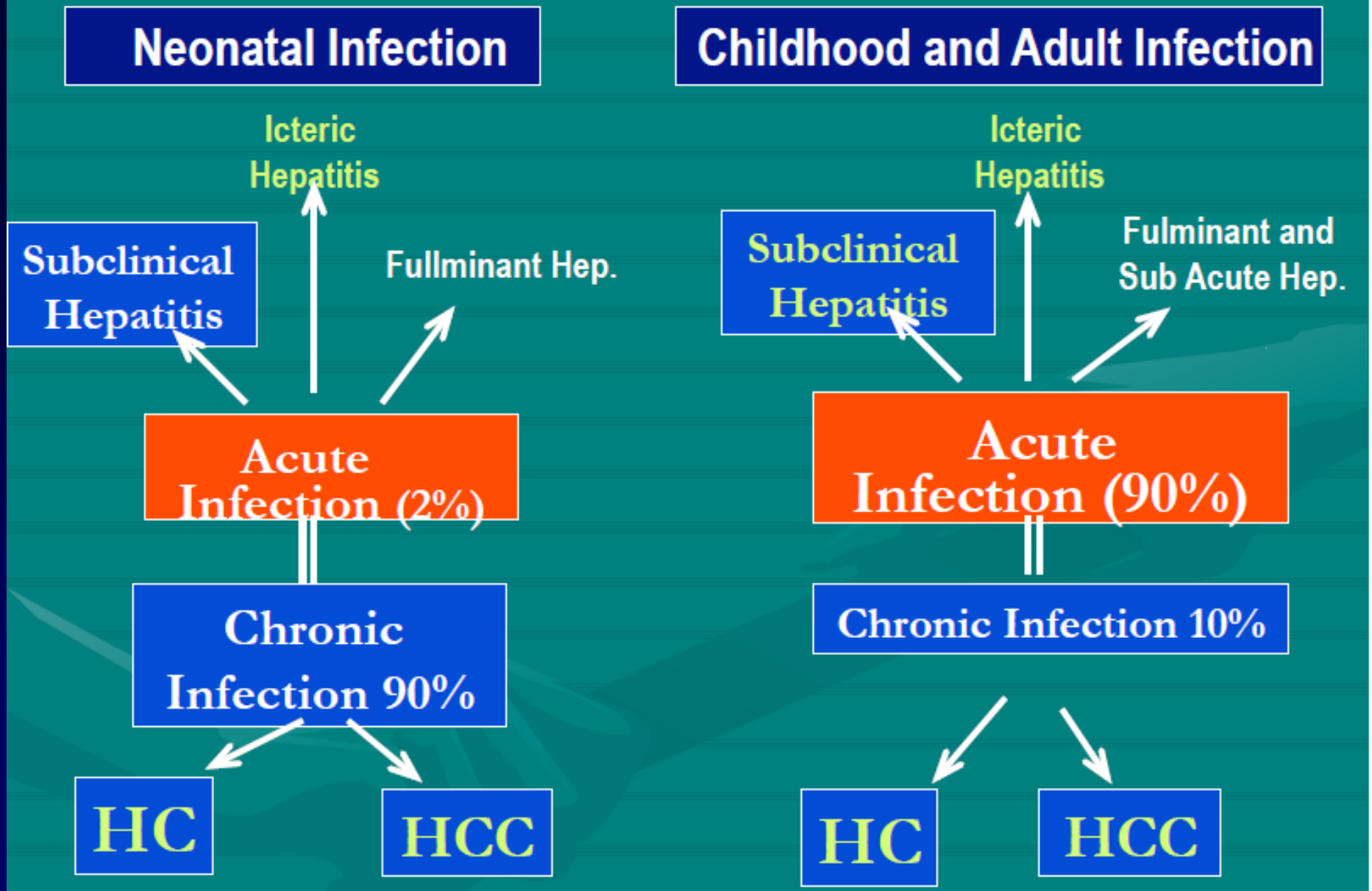
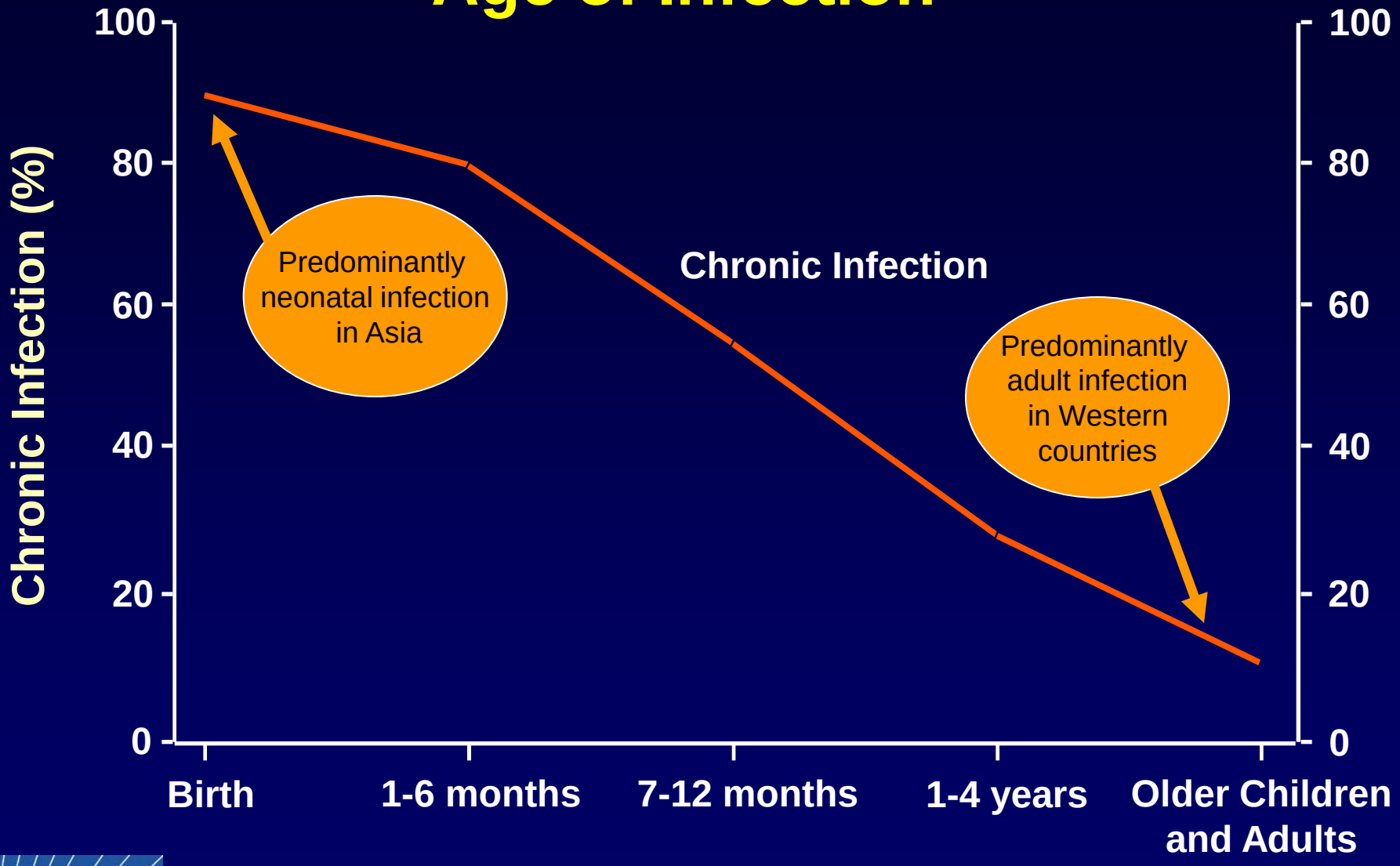



Fig. Natural history of Hepatitis B virus (HBV) infection after neonatal or adult exposure.

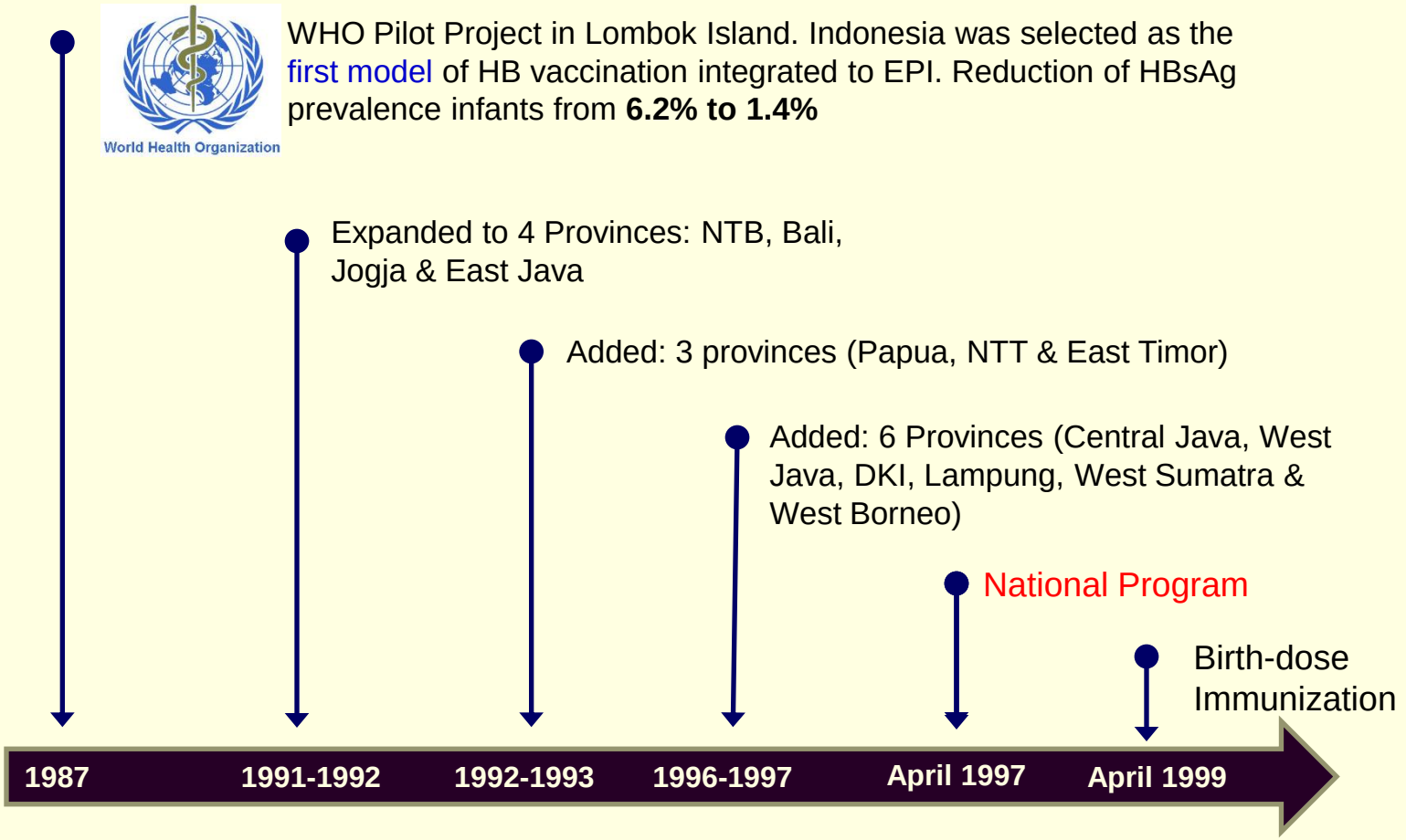
# Outcome of Hepatitis B Infection by Age of Infection

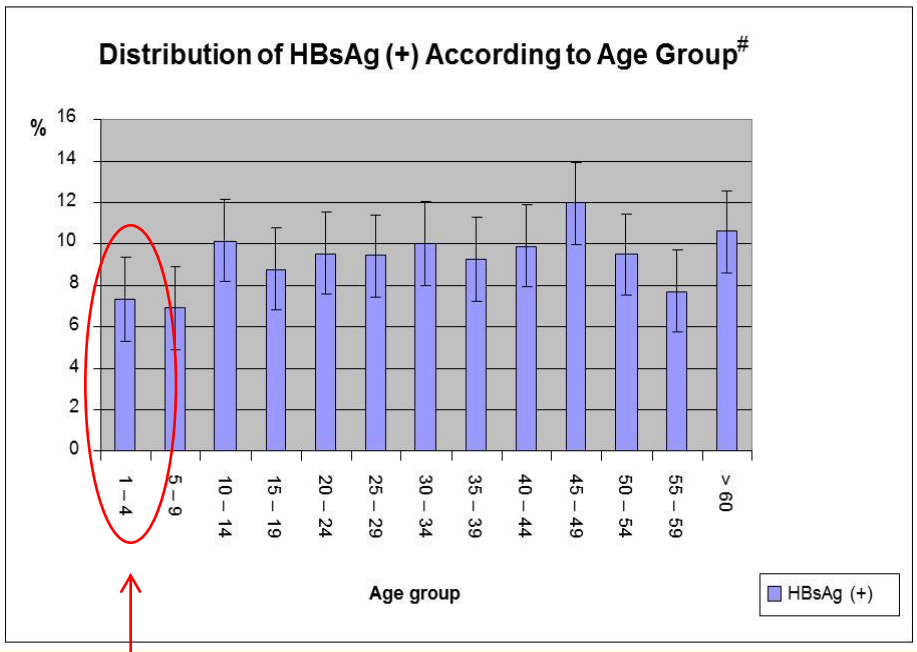



CDC
SAFER·HEALTHIER·PEOPLE™

# Immunization Program in Indonesia

## HB Vaccination in Indonesia

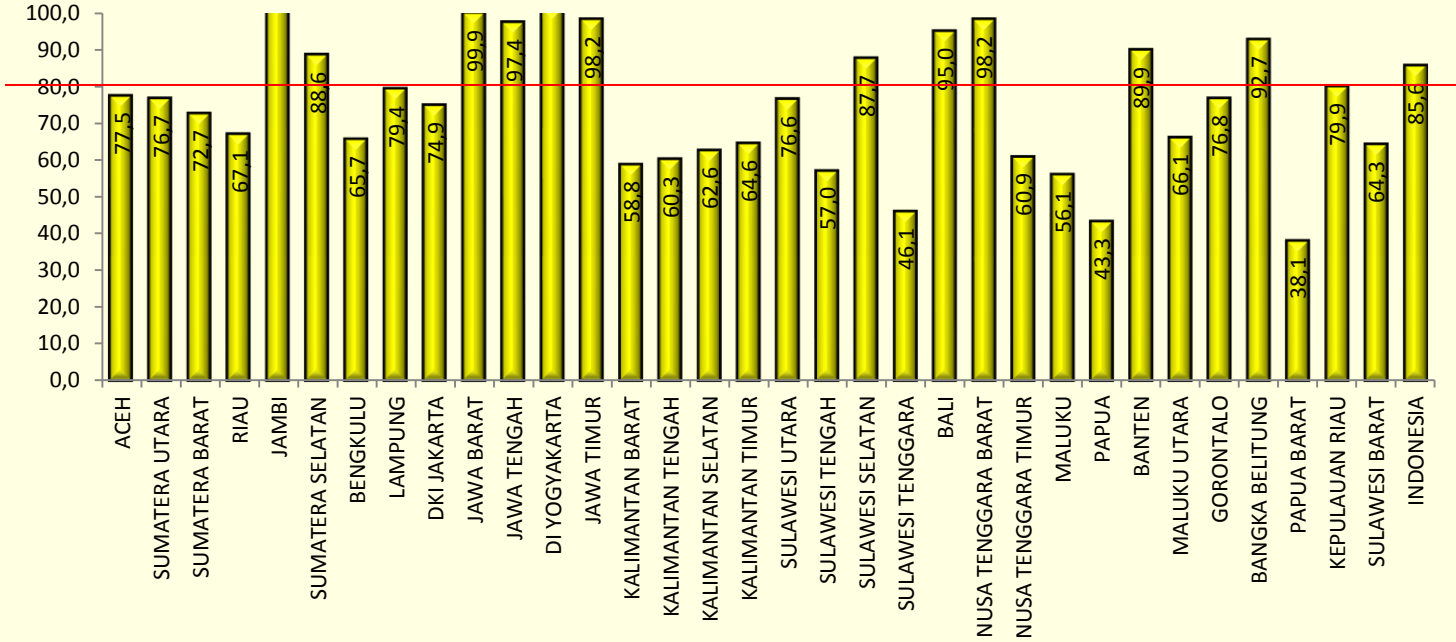




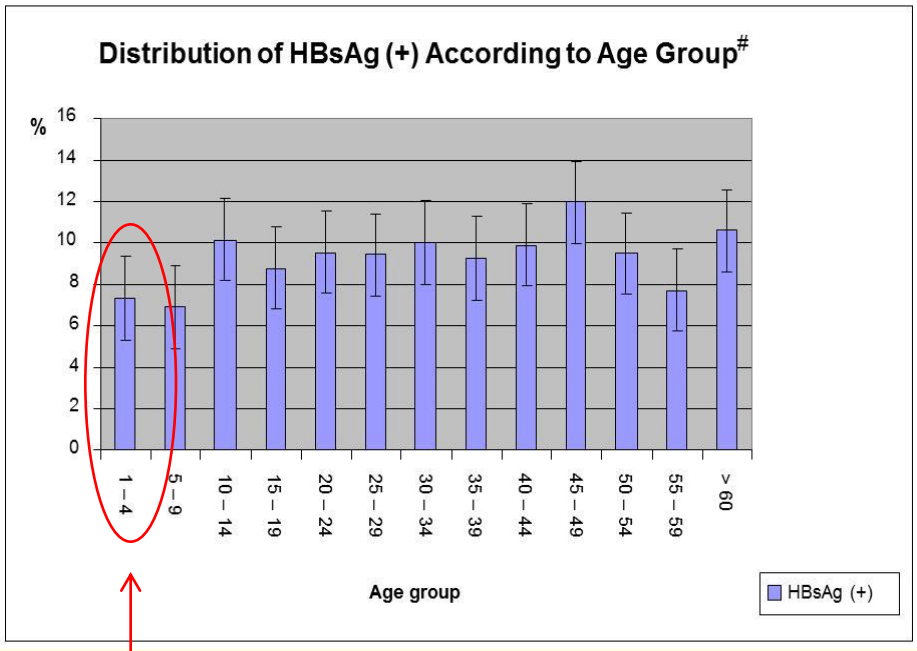

**New cases continue to occur in under-five children**

**WHY?**

**Coverage of Birth-dose Hepatitis B immunization in Indonesia 2012 (By Province)**




Possibility I:
•Low coverage in many provinces



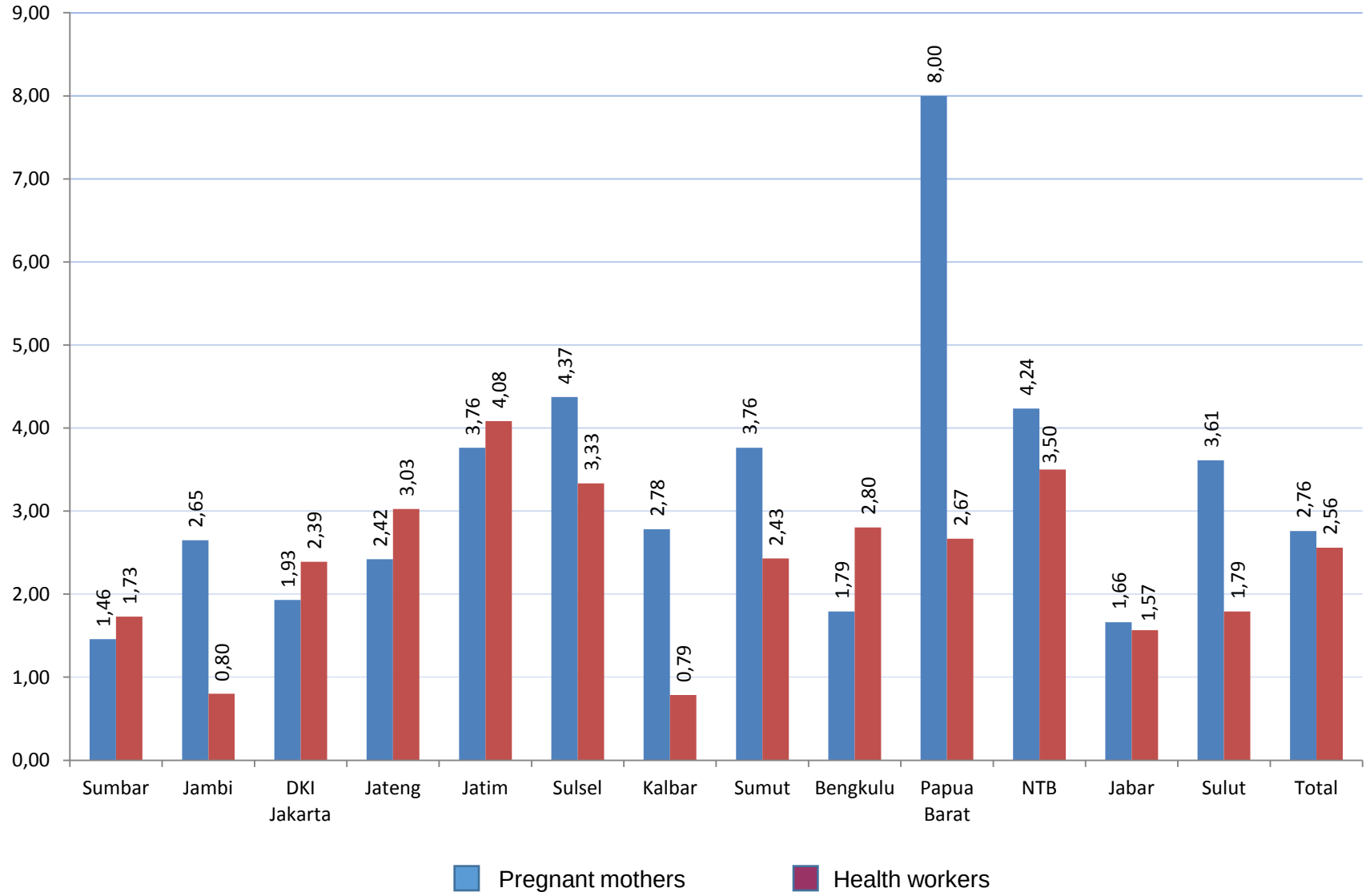

New cases continue to occur in under-five children

WHY?

Possibility 2:
- Mother-to-child transmission (MTCT)

| Prevalence of HBsAg (+) mothers in several cities in Indonesia | | |
|---|---|---|
| Jakarta | 1985 | 4 % |
| Surabaya | 1989 | 4,6% |
| Denpasar | 1981 | 2,46% |
| Mataram | 1993 | 3,4% |
| Bali | 1996 | 5% |
| Jakarta | 2009 | 2,2% |
| Makassar | 2013 | 5.3% |
| Jakarta | 2013 | 3.5% |

# Prevalence of HBsAg (+) among Health Workers and Pregnant Women in 13 Provinces in Indonesia (2014)



# Diagnosis

- Skrining HBsAg (+) pada ibu hamil

# Hepatitis B Lab Markers

- HBsAg - Marker of current infection

- Anti-HBs - marker of resolved infection /immunity after immunization

# Hepatitis B Lab Markers

- HBeAg - marker of active replication, Identification of persons at increased risk for transmitting HBV
- Anti-HBe - Identification of person with lower risk for transmitting HBV
- HBV DNA - Viral load ; virulensi

# Hepatitis B and Pregnancy

## Mother

- Worsening of hepatitis before or during pregnancy?
- Worsening of hepatitis after delivery?
- Safer modes of delivery?

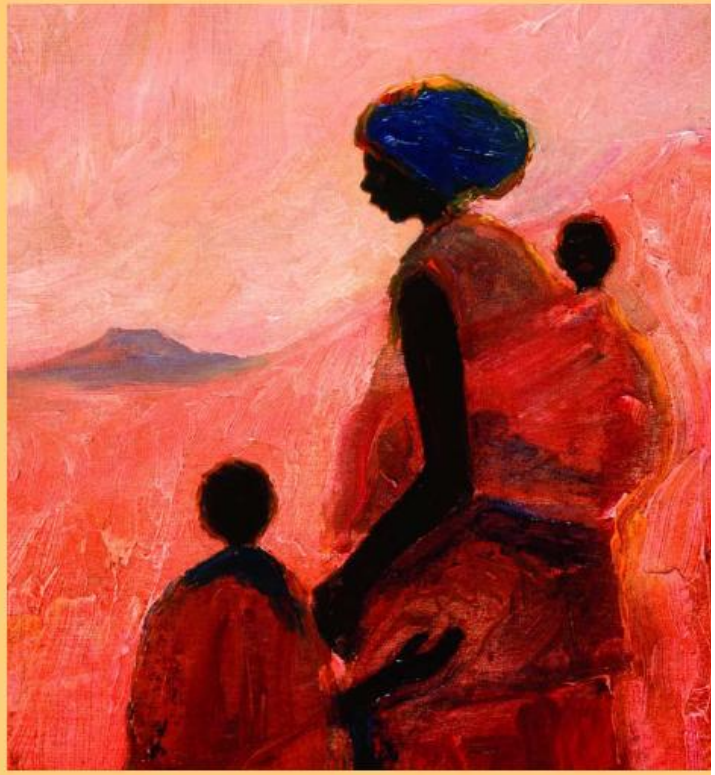
## Infant

- Transmission of HBV?
- Vaccination?
- Breast-feeding?

Göttingen International Health Network (GIHN)
Uwe Groß and Kerstin Wydra (Eds.)

# Maternal–Child Health

Interdisciplinary Aspects Within the Perspective of Global Health



Universitätsverlag Göttingen

## 19. Vertical Transmission of Hepatitis B Virus; the Role of Placental Barrier, Modes of Delivery, Viral Load & Immunoprophylaxis of Neonates

*Maisuri T. Chalid, Department of Obstetrics and Gynecology, Medical Faculty, Hasanuddin University, Makassar, Indonesia*

*David H. Muljono, Chairman of the National Committee on Viral Hepatitis and Head of Department of Hepatitis and Emerging Disease of Eijkman Institute of Molecular Biology, Jakarta, Indonesia*

### 1 Abstract

Hepatitis B virus (HBV) is a major public health problem that affects a significant proportion of the world's population. Approximately 2 billion people worldwide have been infected with the Hepatitis B virus. Globally 50 million new cases are diagnosed annually. Worldwide, 240 million people are chronically infected, comprising 5-10% adults and up to 90% of infants (World Health Organization, 2012). About 75% of them reside in the Asia-Pacific. Africa has the second largest number with 50 million chronic carriers, whereas in Europe and North America the prevalence is less than 1%. In endemic areas, where up to 20% of women at childbearing age may have HBV, vertical transmission remains the most frequent route of infection. Estimated 40-50% of chronic HBV infection originates from perinatal transmission. Factors that may contribute to vertical transmission are

# Factors associated with MTCT

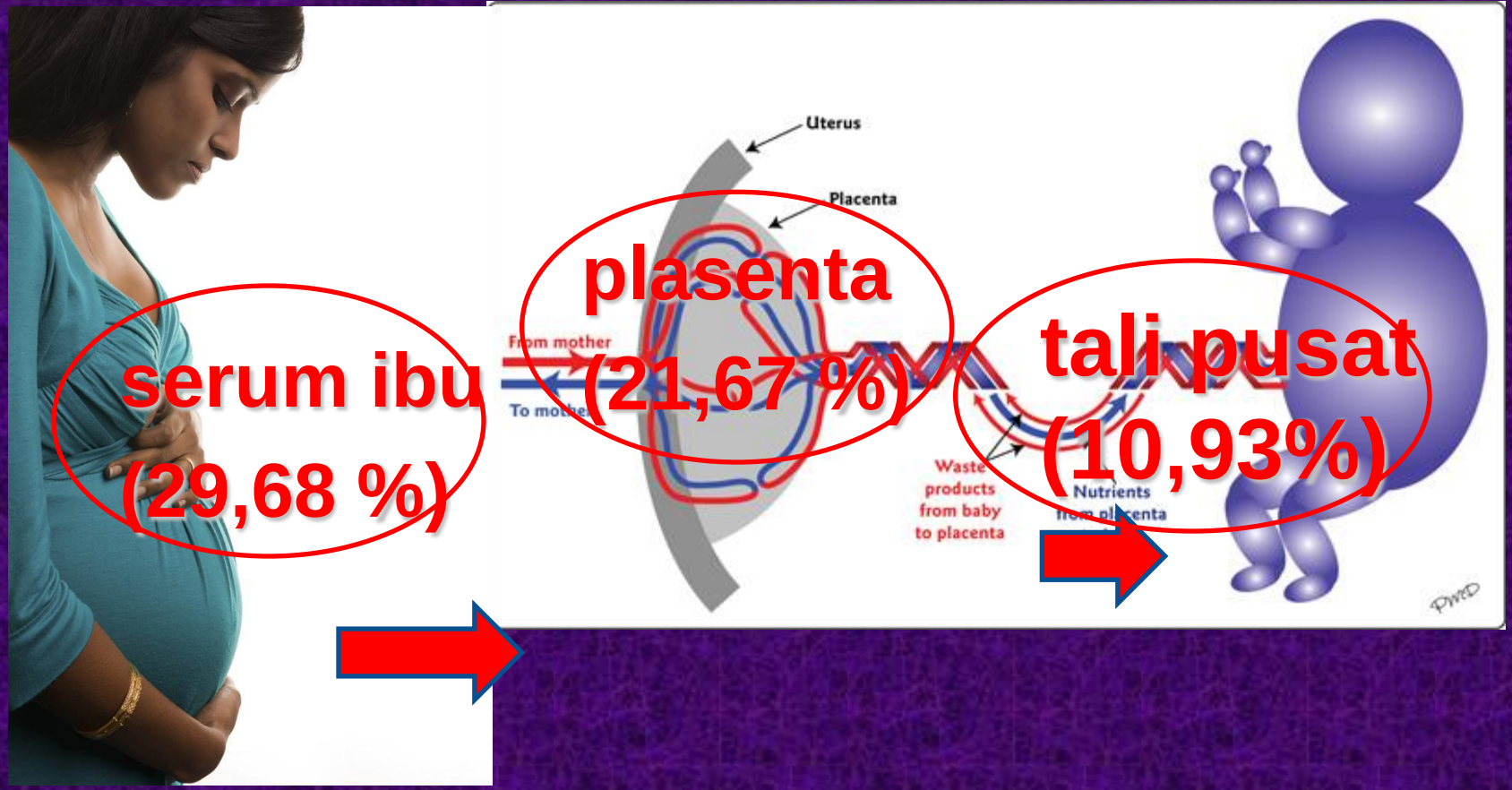
- Maternal Viral load (HBV DNA level)
- Maternal HBeAg status
- Mode of delivery
- HBV S gene variation (mutant)
- Neonatal immune deficiency

# Factors associated with MTCT

- Maternal Viral load (HBV DNA level)
  - Higher Maternal HBV DNA levels [<6, 6–6.99, 7–7.99, and ≥8 $\log_{10}$ copies/mL] → higher rates of immunoprophylaxis failure: [0%, 3.2%, 6.7%, and 7.6%, respectively];
  - antenatal HBV DNA level >6 $\log_{10}$ copies/mL (>200,000 IU/mL) is the most important predictor for MTCT.

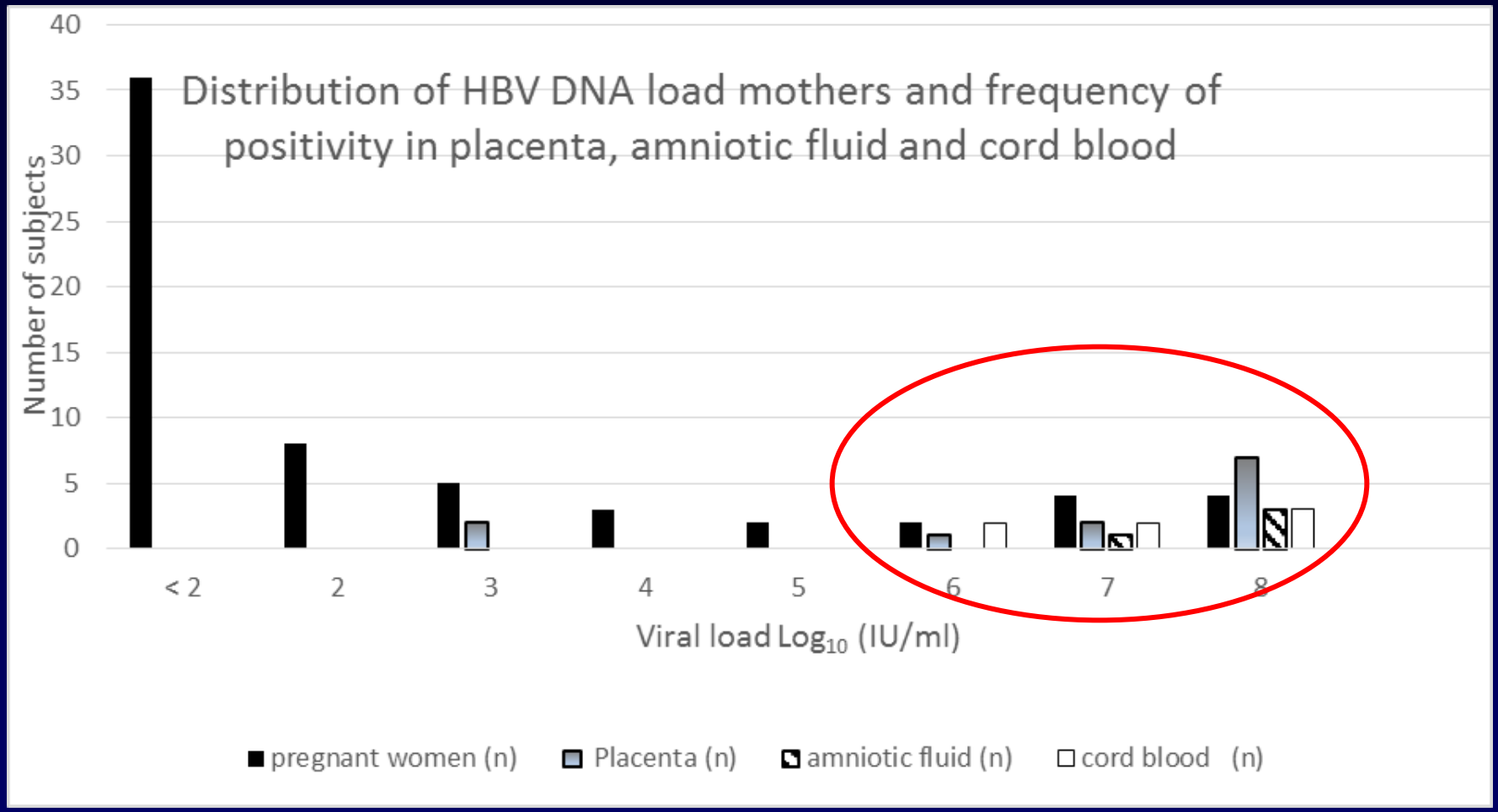
# Plasenta berperan sebagai barier

## Deteksi DNA VHB




Chalid MT et al (Makassar), The Pattern of Hepatits B vertical Transmission During Labor: Role of Viral load, Placenta and Obstetrics Contribution. The 11th Asia Pacific Congress of Maternal Fetal Medicine, Taipei, November 2015

# Factors associated with MTCT: viral load contribution




Chalid MT et al (Makassar), The Pattern of Hepatits B vertical Transmission During Labor: Role of Viral load, Placenta and Obstetrics Contribution. The 11th Asia Pacific Congress of Maternal Fetal Medicine, Taipeh, November 2015

# Factors associated with MTCT

- Maternal HBeAg status
  - Transplacental HBeAg from the mother induces a specific unresponsiveness of helper T cells to HBeAg and HBcAg in neonates born to HBeAg-positive HBsAg carrier mothers

Outcome of HBV infection in infants with different immunoprophylaxis strategies and maternal HBeAg status

| HBsAg (+) mother | Infant | | |
|---|---|---|---|
| | No vaccination | Vaccination | HBIG + vaccination |
| HBeAg (+) | >90% chronic infection | 20–25% chronic infection [30] | 10–15% chronic infection |
| HBeAg (–) | <5% chronic infection | <1% chronic infection | <1% chronic infection [31] |

# HBV Transmission: When Does It Happen?

- In utero transmission
  - Very rare (< 10%); associated with high HBV DNA levels[1]
- During amniocentesis
  - Very rare; no transmission reported in 2 case series[2,3]
- **At birth!**
  - HBeAg-positive mothers: 85%
  - HBeAg-negative mothers: 31%[4]

1. Wang Z, et al. J Med Virol. 2003;71:360-366. 2. Alexander JM, et al. Infect Dis Obstet Gynecol. 1999;7:283-286. 3. Towers CV, et al. Am J Obstet Gynecol. 2001;184:1514-1518. 4. Beasley RP, et al. Am J Epidemiol. 1977;105:94-98.

## Routes of mother-to-child HBV transmission

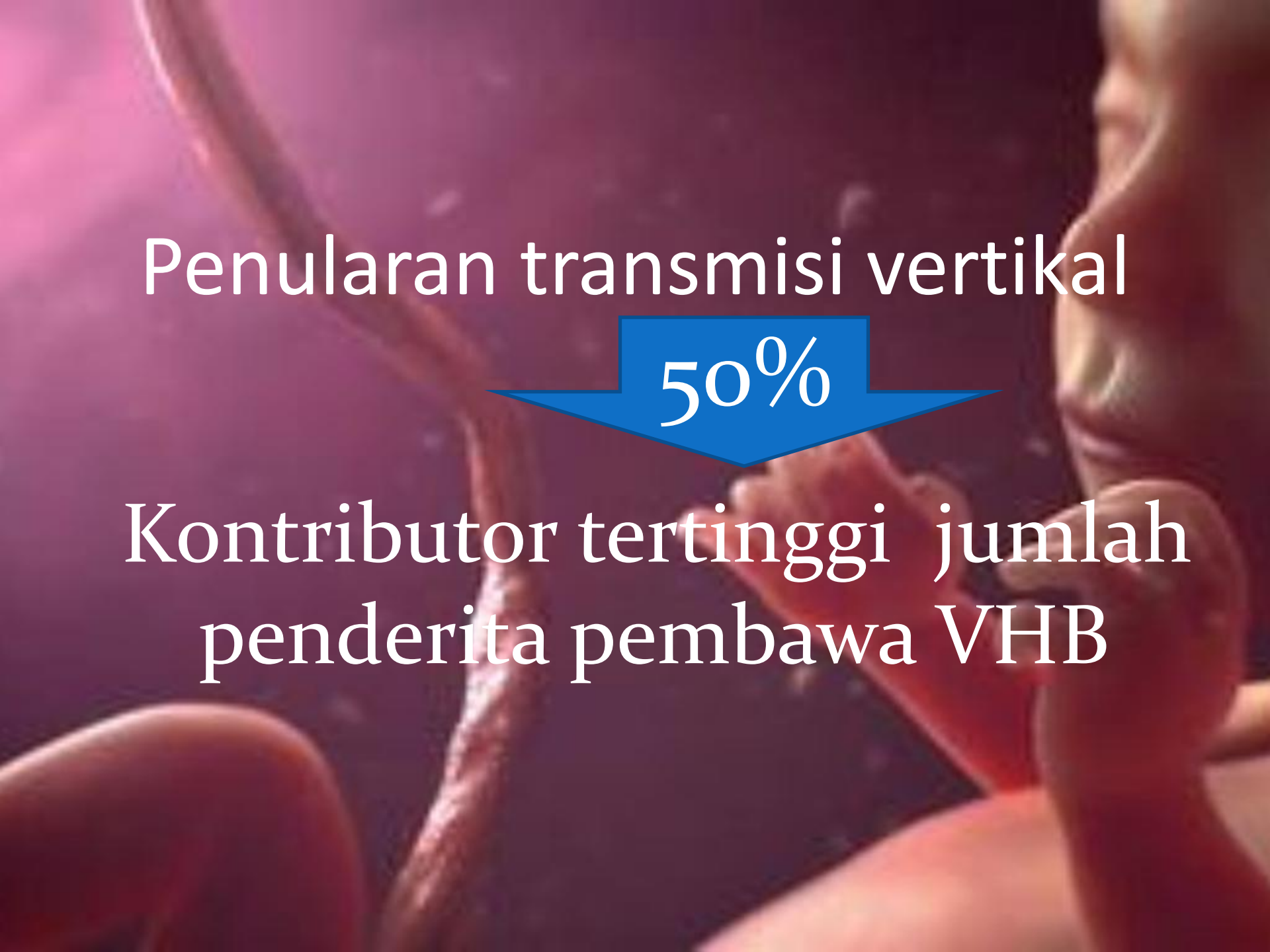
### – *Intrapartum transmission (transmission during delivery)*

- Is the main route of MTCT of HBV infection
- Association with duration of the first stage of labour lasting >9 hours.
- Occurs through:
  - Exposure of baby to HBV-containing maternal body fluids when passing through the birth canal
  - Partial placental leakage due to uterine contractions or instrumentation trauma during labour

# THE PREDISPOSING FACTORS OF PERINATAL INFECTION

- Viral Titers (> 3,5 pg/ml)* or more than $10^6$ copies of HBV-DNA**
- HBeAg (+)
- Acute HBV infection in the 3rd trimester of preg.
- Vaccine escaped mutations :

  Infant HBsAg & Anti HBs positive (10 - 20%)
- Prolong delivery


Penularan transmisi vertikal
50%
Kontributor tertinggi jumlah penderita pembawa VHB

**Perlu diperhatikan:**

Bayi terinfeksi vertikal:

- berisiko tinggi menderita hepatitis kronis sepanjang hidupnya → sirosis hepatis atau kanker hati (Karsinoma Hepatoselluler) dan kematian pada usia dewasa muda
- Sumber penularan

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journal homepage: www.elsevier.com/locate/ijid

# Chronic hepatitis B in pregnant women: is hepatitis B surface antigen quantification useful for viral load prediction?

Masita Fujiko [a,1], Maisuri T. Chalid [a,1], Turyadi [b], Susan I. Ie [b], Maghfira [a], Syafri [a], Ridha Wahyuni [a], Martono Roni [b], Ilhamjaya Patellongi [a], M. Nasrum Massi [a], David H. Muljono [a,b,c,*]

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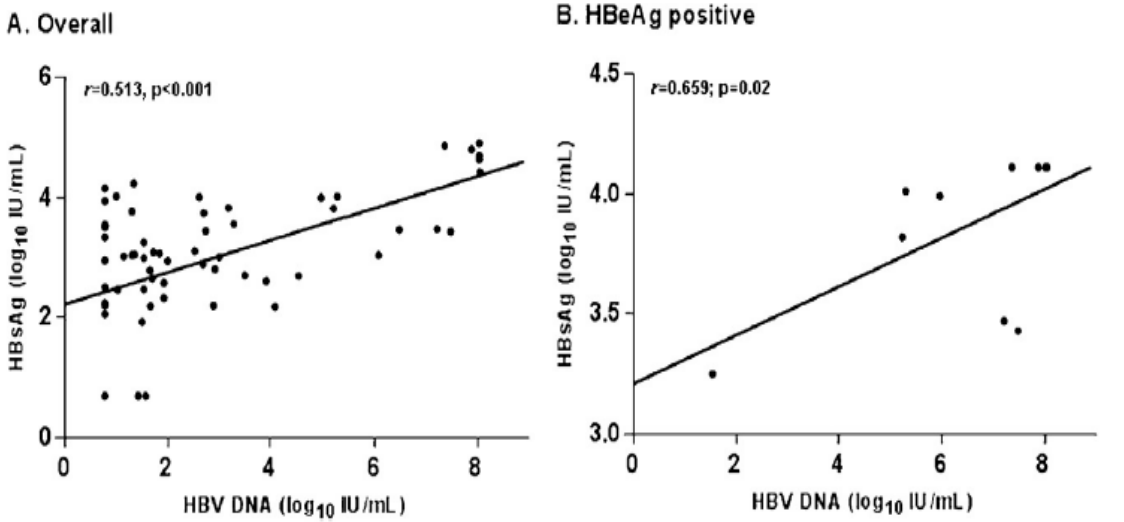
[b] Eijkman Institute for Molecular Biology, Jl. Diponegoro 69, Jakarta Pusat 10430, DKI Jakarta, Indonesia
[c] Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia



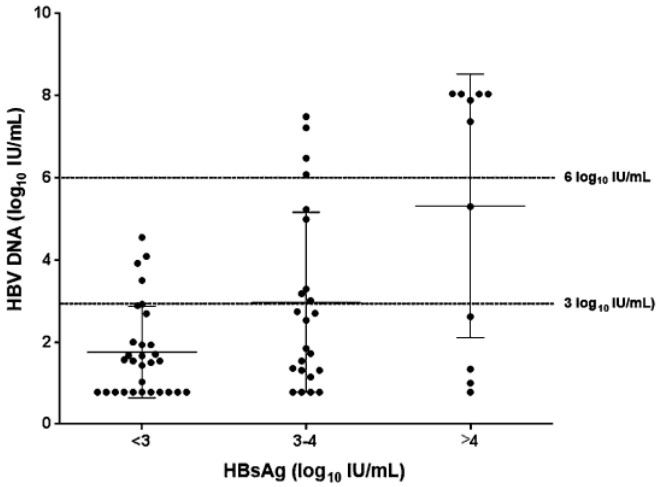
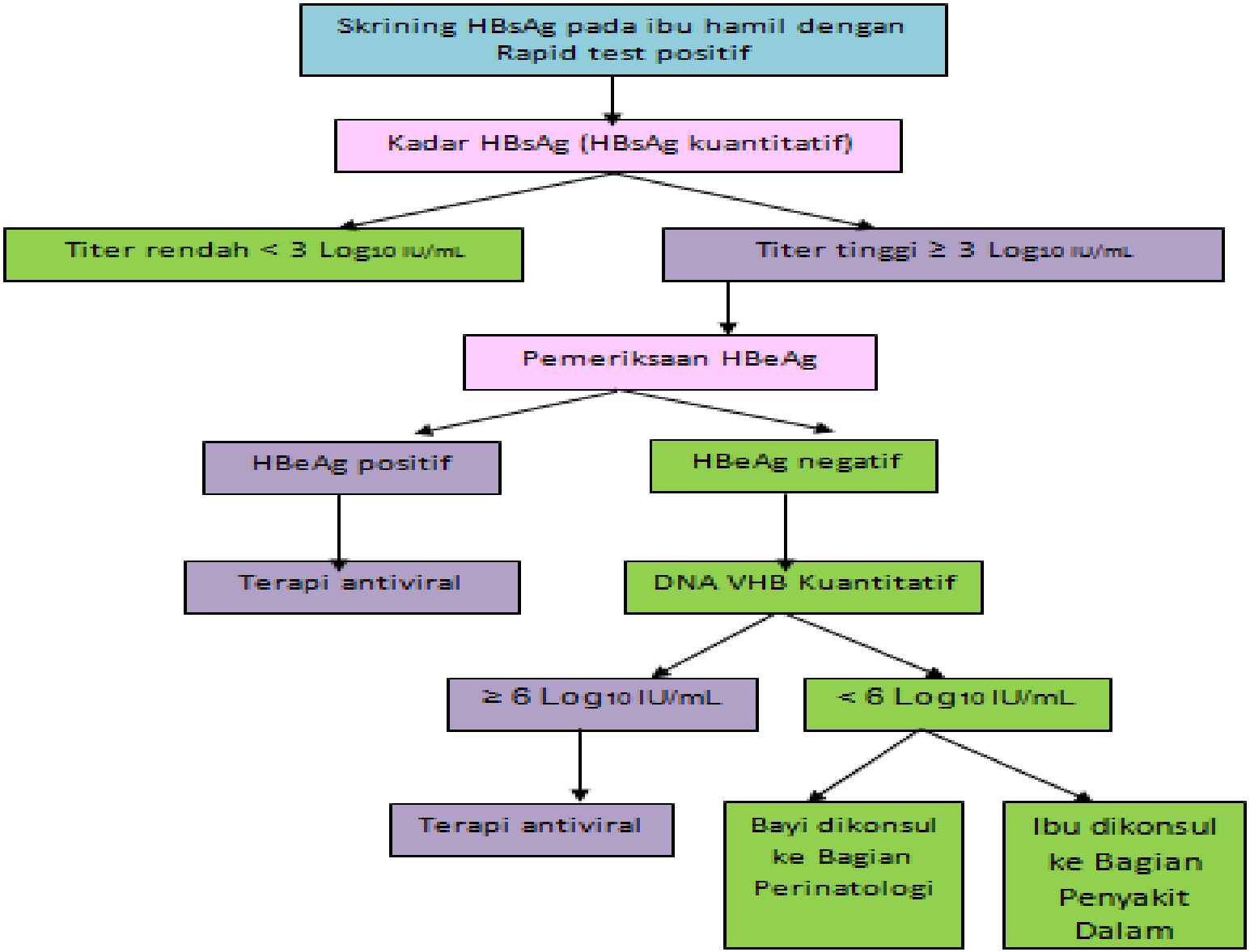




**Figure 3.** Distribution of HBV DNA levels among pregnant women according to HBsAg levels. In most cases, low levels of HBsAg were associated with low levels of HBV DNA; HBsAg levels $<3.0$ $\log_{10}$ IU/ml were significantly correlated to HBV DNA levels $<3.0$ $\log_{10}$ IU/ml ($r = 0.363$; $p = 0.003$) and to HBV DNA levels $<6.0$ $\log_{10}$ IU/ml ($r = 0.404$; $p = 0.001$). No subjects with HBsAg levels $<3.0$ $\log_{10}$ IU/ml had HBV DNA $\geq 6.0$ $\log_{10}$ IU/ml.


Skrining HBsAg pada ibu hamil dengan Rapid test positif
Kadar HBsAg (HBsAg kuantitatif)
Titer rendah < 3 Log10 IU/mL
Titer tinggi ≥ 3 Log10 IU/mL
Pemeriksaan HBeAg
HBeAg positif
HBeAg negatif
Terapi antiviral
DNA VHB Kuantitatif
≥ 6 Log10 IU/mL
< 6 Log10 IU/mL
Terapi antiviral
Bayi dikonsul ke Bagian Perinatologi
Ibu dikonsul ke Bagian Penyakit Dalam

# Drugs already used in pregnancy

| Drug name | Drug category | Effectiveness | Remark |
|---|---|---|---|
| Lamivudine (LAM) | C | Start at week 32: Significant reduction of MTCT | Frequent resistant for long-term use (15%/year) |
| Tenovofir (TDF) | B | Effective: preferred than LAM<br>Good safety: Experience in HIV-treatment program | Better resistance profile |
| Telbivudine (LTD) | B | Given in 2nd or 3rd semester, significantly lowers MTCT than controls (0 vs 8%) | No resistance, no deeformities |

# Tatalaksana pada bayi

- Bila ibu HBs Ag(+)
  - Bayi disuntik HBIG (Imunoglobulin Hep B) 0,5 ml IM pada lengan atas segera setelah lahir (dalam 12 jam kelahiran) dan
  - Vaksin hepatitis B dengan dosis 0,5 ml (5 µg) IM pada lengan atas sisi lain pada saat yang sama kemudian pada usia 1 bulan dan 6 bulan.
  - Tidak ada perbedaan pemberian HBIG dan vaksinasi hepatitis B pada bayi prematur namun pemberian vaksinasi hepatitis B diberikan dalam 4 kali pemberian yaitu pada bulan ke-0, 1, 6, dan 8 bulan.

# Tatalaksana pada bayi

- Tidak ada larangan pemberian ASI eksklusif pada bayi dengan ibu HbsAg positif terutama bila bayi telah divaksinasi dan diberi HBIG setelah lahir
- Bila ibu HBs Ag(-)
  - Vaksin hepatitis B dengan dosis 0,5 ml (5 µg) IM pada lengan atas pada usia ke-0, 1 bulan, dan 6 bulan.

# Prevention of MTCT:
## During pregnancy

- *Screening of mothers*:
  - HBsAg: at least before the 3rd trimester
  - HBeAg (for HBsAg-positive mothers)
  - Viral load/HBV DNA level (for HBsAg-positive mothers)
- *Treatment of mothers:*
  - - Has not been a general treatment policy
  - - Indications are judged by:
    - HBV DNA level status
    - HBeAg
    - Evidence of liver injury (by alanine aminotransferase [ALT] level and/or liver histology).

# Prevention of MTCT: At delivery

- *For mothers: Caesarean section*:
  - Still controversial:
    - One study: 17.5% risk reduction of MTCT when compared with immunoprophylaxis alone
    - Other studies: elective caesarean section offers no benefit.
    - Beijing (2007-2011) from 1,409 infants born to HBsAg (+) positive mothers, with appropriate immunoprophylaxis at birth:
    - 1.4% after elective caesarean section
    - 3.4% after vaginal delivery
    - 4.2% after emergency caesarean section ($P$ <0.05).
    - When stratified according to HBV DNA levels:
      - delivery mode did not affect MTCT rates for HBV DNA levels <6 log copies/ ml).

# Prevention of MTCT: At delivery

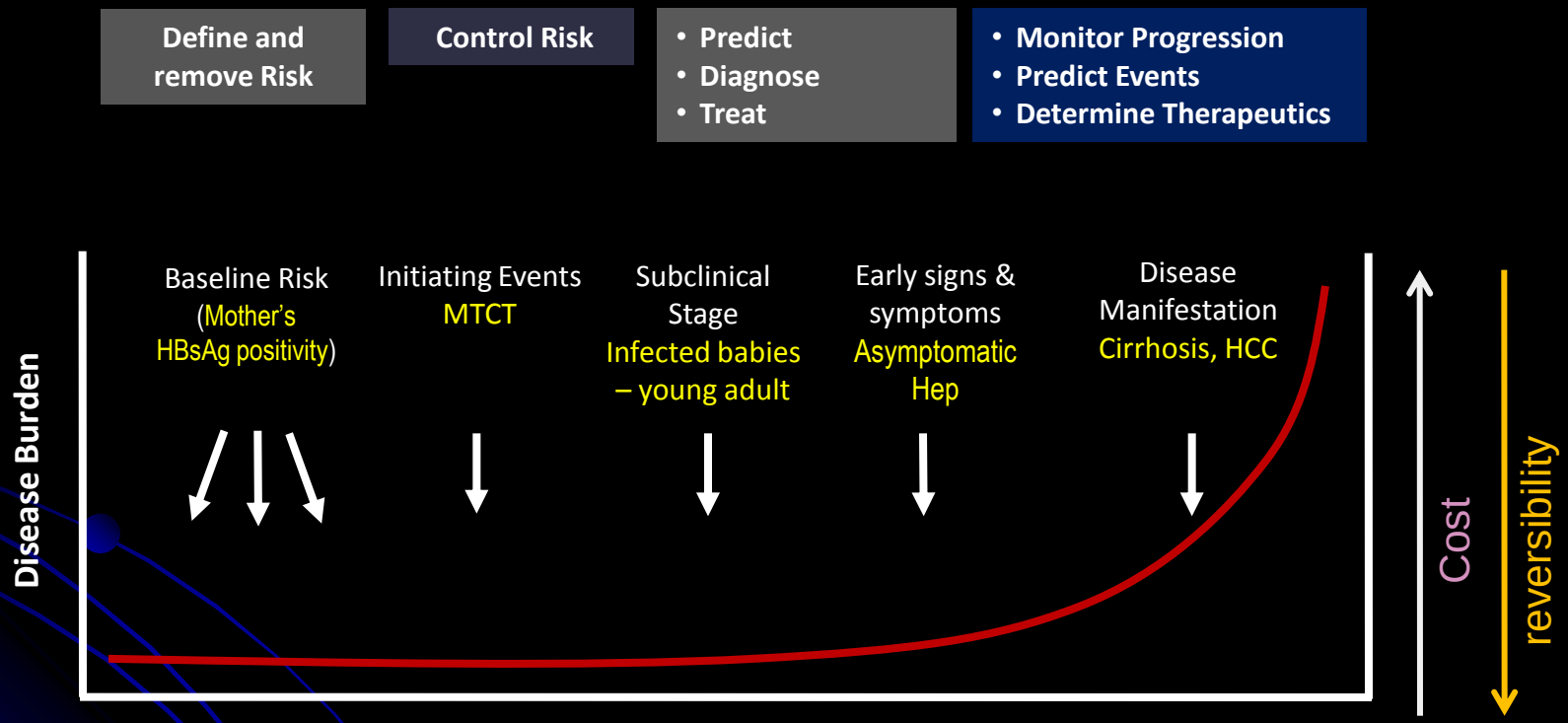
2. *For babies: Immunoprophylaxis*

- *Active immunization: 2 strategies*
  - 3-dose schedule
    - 1st dose (birth dose) – monovalent vaccine
    - 2nd and 3rd doses together with other vaccination
  - 4 dose schedule:
    - 1st dose (birth dose) – monovalent
    - 2nd, 3rd, 4th doses together with other vaccines.
- *Passive immunization:*
  - Hepatitis B immune globulin (HBIG): in 12 hours after birth (Provides temporary protection for 3 to 6 months).

# Conclusion

- HBV MTCT deserves full attention.
- Screening women for HBV infection, HBV birth dose vaccine, increasing overall coverage of vaccine are all feasible.
- Antiviral therapy for HBV-infected mothers need to be discussed and considered by relevant associations of experts.
- Urgent needs: Roles of health providers, political commitment and financial investment, to the elimination of HBV MTCT in Indonesia

# Disease development: From baseline risk to disease manifestation




**Control of hepatitis should start from the mothers**

Prevention of HBV by immunization means prevention of HC and HCC

**IMPROVE THE QUALITY OF LIFE OF THE NEW GENERATION**