HBV vaccination: Optimizing coverage and efficacy.

Alex Vorsters, Pierre Van Damme
Viral Hepatitis Prevention Board
Declaration of Interest

• Alex Vorsters is member of the scientific secretariat of the Viral Hepatitis Prevention Board (VHPB).

• The VHPB secretariat is managed within the Centre for the Evaluation of Vaccination at the University of Antwerp.

• The University of Antwerp gets financial and in-kind support from pharmaceutical industry, several universities and other institutes for the functioning of the VHPB. Additional information on www.vhpb.org
Content

- Introduction
- History
- Progress and Impact
- Challenges
- Future
Strategies to control hepatitis B infection

Infection source → Transmission → Susceptible host

Preventive measures to avoid transmission

Vaccination

Screening and treatment (suppression of HBV)

Secondary and tertiary prevention in chronic carriers

Vaccination = most effective measure to reduce global incidence of hepatitis B

Adapted from Chen DS. J Hepatol. 50 (2009): 805-816
History

- Hepatitis B vaccines have been available since early 1980’s
- First recommended in industrialized countries for high risk groups (MSM, IDU, multiple sex partners)
- In 1991, the Global Advisory Group of EPI (Expanded Programme on Immunization) set 1997 as the target for integrating the hepatitis B vaccination into national immunization programmes worldwide. Adherence by WHO and WHA (resolution 45.17) in 1992
In 2010, Member States re-iterated the 1992 resolution and adopted resolution 63.18, which called WHO to draft a comprehensive viral hepatitis prevention and control strategy, including universal hepatitis B immunization programmes and development of time-specific immunization goals.
Notable Features of Hepatitis B Vaccine

- Available since 1982 (plasma); 1986 (recombinant)
- High immunogenicity (three dose, 95-99%)
- Long-term protection
  - No infections for 25 years among vaccine responders
  - Antibody concentration declines over time, but clinically significant breakthrough infections are rare
  - Immunological memory for HBsAg can outlast the antibody detection providing long-term protection
- Good safety profile
  - “One of the most studied vaccines”
Overall description of proportions of anti-HBs $\geq 10$ mIU/ml 5 to 20 years for children vaccinated with hepatitis B vaccine in infancy. Schönberger et al PIDJ 2013
HepB vaccines prevent perinatal transmission when administrated within 24h after birth: efficacy from 90-95%

As a monovalent vaccine

If specific HBIG available, simultaneous administration, at an other injection site
  - Adds >2-3% protective efficacy

Schedules

- 0,1,6 or 0,1,2,12 month schedule
- End result is equal
- Minimal 4 weeks between 2 primary injections
- Minimal 4 months between last and first dose (in 3 dose schedule)
  - Shortest schedule: 0,1,4 month
- Schedule is very flexible
  - Adaptation to all existing infant immunization programmes
  - As many schedules as countries/regions
- 2 dose-schedule: 0-6 months (adult dose for ado’s)
  - Licensed in many countries for 11-15y. old
The use of other HBV vaccines

- **Pre-S1/Pre-S2/S vaccines**
  - Licensed in Israel, Hong-Kong, India, the Philippines and Vietnam.
  - Induce faster and higher anti-HBs response compared to yeast vaccines
  - Potential applications:
    - Provide sero-protection in non-responders or immune compromised
    - Reduce number of doses
    - (Protection against HBsAg mutant viruses) up to now not an issue.
  - High production cost limits use and availability
# Hepatitis B vaccination policy

## Risk group approach versus universal vaccination

<table>
<thead>
<tr>
<th>Risk group vaccination</th>
<th>Universal vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Individual risk perspective</td>
<td>• Global approach</td>
</tr>
<tr>
<td>• Difficulty of accessing high risk groups</td>
<td>• More easy to implement through existing structures and use of combination vaccines</td>
</tr>
<tr>
<td>• No identifiable risk among 50% of acute HBV patients in industrialized countries</td>
<td>• Protection of future risk groups</td>
</tr>
<tr>
<td>• Infections often acquired before risk is recognized</td>
<td>• Optimal coverage</td>
</tr>
<tr>
<td>• Often low completed schedule coverage</td>
<td>• Cost-effective in low to high endemic setting</td>
</tr>
<tr>
<td>• Negative social stigma</td>
<td>• Impact on HBV control and endemicity</td>
</tr>
<tr>
<td>• So far, programmes targeting risk groups failed to eliminate HBV circulation</td>
<td></td>
</tr>
</tbody>
</table>

Source: Van Damme et al. BMJ 2013;346:f4057
Global Immunization 1989-2014,
3rd dose of Hepatitis B coverage in infants
global coverage at 82% in 2014

Immunization Vaccines and Biologicals, (IVB), World Health Organization.
194 WHO Member States. Date of slide: 24 July 2015.
Immunization coverage with 3rd dose of HepB vaccines in infants, 2014

Date of slide: 16 July 2015
Example of Bulgaria

Cumulative number of newborns immunized with HBV vaccine and hepatitis B incidence (per 100,000) in children and young adults, Bulgaria, 1983-2010

Source: National Centre of Infectious and Parasitic Diseases, Bulgaria

Update January 2014
Prevalence of Chronic Hepatitis B Virus Infection Among Children Before and After HepB Vaccine Introduction

- **Taiwan**
- **Shanghai**
- **Rural China**
- **Gambia**
- **Alaska**
- **Thailand**

**HBsAg prevalence**

- **Children born before hepB introduction**
- **Children born after hepB introduction**

---

**Legend:**
- Blue bar: Children born before hepB introduction
- Red bar: Children born after hepB introduction
China, Qidong, cross sectional surveys in 1996-2000 and 2008-2012:
Incidence of PLC and mortality of end stage liver disease significantly lower in vaccinees versus controls

Chunfeng Qu, PLOS Medicine, 2014
Modes of HBV Transmission in Neonates and Early Childhood

1) Transmission from infected mother to infant during delivery or before

2) Transmission from infected household contacts to infant or child

➢ The hepatitis B vaccine administered shortly after birth serves 2 functions: as post-exposure prophylaxis following exposure and as protection for future exposures
Perinatal transmission: most efficient!

- **HBsAg-positive**
  - HBeAg-positive
    - Transmission Rate: 70-90%
    - Neonate Evolution to Carrier: 90%
  - HBeAg-negative
    - Transmission Rate: 10%
    - Neonate Evolution to Carrier: 10-15%

- **HBsAg-negative**
Outcome of HBV Infection According to Age at Time of Infection

WHO 2001
Table 2  Proportion of future hepatitis B-related deaths without vaccination by age at acquisition of infection, hepatitis B disease burden model

<table>
<thead>
<tr>
<th>Region</th>
<th>Age at acquisition of HBV infection</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Perinatal (%)</td>
<td>Early childhood (%)</td>
<td>Late (%)</td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td>18</td>
<td>52</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Americas</td>
<td>23</td>
<td>37</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>13</td>
<td>47</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>16</td>
<td>40</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>17</td>
<td>48</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Western Pacific</td>
<td>26</td>
<td>47</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Global</td>
<td>21</td>
<td>48</td>
<td>31</td>
<td></td>
</tr>
</tbody>
</table>

Percent of infants born in countries with universal HBV birth dose policy, by WHO region

- WPRO: [90%]
- AMRO: [88%]
- SEARO: [87%]
- EURO: [63%]
- EMRO: [30%]
- AFRO: [23%]
Countries Using Hepatitis B Birth Dose Vaccine in their National Immunization Schedule, 2010

- No (7 countries [of which 3 given at adolescence] or 4%)
- No (but HepB in schedule) (87 countries or 45%)
- Yes (Birth dose) (91 countries or 47%)
- Yes (Birth dose in parts of the country) (1 country or 1%)
- No (but HepB in schedule for risk groups) (7 countries or 4%)
Situation in industrialized countries for prevention of perinatal transmission 1)

• Some countries have a very efficient screening program for pregnant women, followed by targeted immunization of the exposed newborn:
  • Denmark: 96% of exposed newborn receive first dose (Harder et al, Vaccine, 2011)
  • UK, audit in Norfolk & Suffolk:
    • In exposed newborns: 99.4% 1° dose – 83.4% 4° dose
    • Testing at 12m = issue (Keeble et al, Hum Vacc Immunother, 2015)
Situation in industrialized countries for prevention of perinatal transmission 2)

• Challenges in some countries:
  • Italy (Spada, J of Infection, 2011): screening of pregnant women for HBsAg related to
    • geographical location of the hospital (South (-)),
    • foreign origin of the women (-),
    • delivery in public (-) versus private hospital (+).
  • Belgium, Antwerp Region (De Vrieze, J du Médecin, 2014)
    • Screening related to
      • Complicated pregnancy (+)
      • Foreign origin of the women (+)
      • Number of health providers (-)
<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 (Hospital X) De Paep &amp; De Vrieze, 2014 (14)</th>
<th>Cohort 2 (Hospital Y) De Roeck &amp; Dockx, 2012 (15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children’s year of birth</td>
<td>2010</td>
<td>2006 and 2007</td>
</tr>
<tr>
<td>Number of women</td>
<td>2852</td>
<td>2964</td>
</tr>
<tr>
<td>Number of women with an accessible screening result for HBsAg</td>
<td>795 (28%)</td>
<td>1617 (55%)</td>
</tr>
<tr>
<td>- Hospital laboratory</td>
<td>795</td>
<td>693</td>
</tr>
<tr>
<td>- Private laboratory</td>
<td>(Not included in methodology)</td>
<td>924</td>
</tr>
<tr>
<td>Expected number of HBsAg seropositive women according to a seroprevalence of 0.66% (11)</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Number of identified HBsAg seropositive mothers</td>
<td>9 (47%)</td>
<td>17 (85%)</td>
</tr>
<tr>
<td>Number of children born to identified HBsAg seropositive mothers</td>
<td>10</td>
<td>18</td>
</tr>
</tbody>
</table>
### Table 2

<table>
<thead>
<tr>
<th>Factors</th>
<th>Factor categories</th>
<th>Surveyed number (N)</th>
<th>HBsAg prevalence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth dose vaccination</td>
<td>Day</td>
<td>1946</td>
<td>1.52</td>
</tr>
<tr>
<td></td>
<td>2–7 days</td>
<td>418</td>
<td>2.80</td>
</tr>
<tr>
<td></td>
<td>&gt;7 days</td>
<td>4558</td>
<td>3.20</td>
</tr>
<tr>
<td>Vaccination status(^{b})</td>
<td>Zero doses</td>
<td>1639</td>
<td>3.47</td>
</tr>
<tr>
<td></td>
<td>1–2 total doses</td>
<td>211</td>
<td>2.11</td>
</tr>
<tr>
<td></td>
<td>No BD and 3+ total doses</td>
<td>2764</td>
<td>2.98</td>
</tr>
<tr>
<td></td>
<td>BD and 3+ total doses</td>
<td>2305</td>
<td>1.75</td>
</tr>
</tbody>
</table>

### Table 4
Hepatitis B vaccination coverage by birth cohort group.

<table>
<thead>
<tr>
<th>Birth cohort</th>
<th>Total children</th>
<th>Hepatitis B vaccine birth dose coverage(^{b})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>%</td>
</tr>
<tr>
<td>2000–2003</td>
<td>1740</td>
<td>22.0</td>
</tr>
<tr>
<td>2004–2006</td>
<td>1783</td>
<td>52.7</td>
</tr>
<tr>
<td>2007–2008</td>
<td>3426</td>
<td>30.4</td>
</tr>
</tbody>
</table>

\(^{a}\) Counting birth dose vaccination.

\(^{b}\) Hepatitis B vaccination within 7 days of birth.
Tremendous progress since 1990

Hepatitis B

81% Global coverage of infants in with three doses of hepatitis B vaccine in 2013

1% Global coverage of infants in with three doses of hepatitis B vaccine in 1990

Global coverage of infants with birth doses of hepatitis B vaccine in 2013: 38%
Challenges in achieving elimination include:

- Setting of national goals for hepatitis B control
- Provision of a HBV vaccine birth dose including children born outside health facilities
- Vaccination of all persons at high risks
- Building and sustaining support for existing hepatitis B vaccination policies and programmes.
Challenges for the future

- Increasing number of immigrants from mid and high endemic countries moving to Europe, leading to changes in hepatitis B epidemiology of low endemic countries → surveillance!

- Transmission is not confined within the immigrant communities but has been reported to spread horizontally or sexually beyond, creating new dynamics of infectious disease transmission\(^1\)

- With availability of new drugs for treatment of hepatitis C, focus (and financial resources) is moving from prevention to treatment, with risk of decreasing vaccination coverage hepatitis B vaccination

---

Global Health Sector Strategy on viral hepatitis, 2016-2021 [Circulating Draft]

• The Vision: A world where viral hepatitis is stopped and everyone living with hepatitis has access to safe, affordable and effective care and treatment

• The Goal: Eliminate viral hepatitis as a major public health problem

WHO Global Hepatitis targets at-a-glance.

<table>
<thead>
<tr>
<th>Expand and enhance services</th>
<th>2020</th>
<th>2030</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV vaccination</td>
<td>&gt;90% coverage in infants</td>
<td>90% coverage in healthcare workers</td>
</tr>
<tr>
<td></td>
<td>50% coverage in healthcare workers</td>
<td></td>
</tr>
<tr>
<td>HBV birth dose vaccination</td>
<td>80% coverage</td>
<td></td>
</tr>
</tbody>
</table>
Vision: All Children in the WHO European Region will be Hepatitis B free

- Overall goal is zero prevalence and no transmission
- First Milestone: Prevalence of HBsAg in children 5-10 yrs 0.5% or lower by serosurvey by 2020
- Universal sustainable immunization in all countries with 95% HB-3 coverage at national level
- Universal newborn immunization (<24 hours of birth) or effective universal screening of pregnant women and post exposure prophylaxis of carrier children