Hepatitis B vaccination: VHPB lessons learnt, the challenges and the way forward

VHPB Budapest meeting

Oct 2019

(Siófok, Hungary from 6 to 9 October 1996).

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FEATURES OF HEPATITIS B VACCINE

- Available since 1982 (plasma); 1986 (recombinant); recent
  Third generation vaccines: mammalian cell derived recombinant vaccines (HBsAg/S, preS1, preS2 antigens), with enhanced immunogenicity – other under development
- Monovalent or in combination with other vaccines
- Schedule is flexible
- High immunogenicity (three dose, 95-99%)
- Long-term protection
  - Antibody concentration declines over time, but clinically significant breakthrough infections are rare (> 30 years of follow up)
  - Immunological memory can outlast the antibody detection providing long-term protection
- Good safety profile
  “One of the most studied vaccines”
GOOD SAFETY PROFILE

- More than 1,000,000 people studied in the clinical trials
- 30% of adults and < 10% of children have sore arm and/or local induration
- One of the safest vaccines ever developed
- > 2,500 million doses used worldwide since 1982
- Pain and tenderness in 15% (3%-29%) of vaccinations, fever > 37.7°C in 1%-6%, erythema, swelling and headache 3%
- Fewer reactions in children
  - Fever, headache, muscle aches, nausea, vomiting, loss of appetite, and fatigue occur at same rate as in placebo

Ref: see also Esposito et al. Clin Microbiol & Inf - 2014
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.
Challenge 5: raise the global hepB infant coverage

Number of countries having introduced Hepatitis B vaccine and global infant coverage for Hepatitis B 3rd dose (HepB3), 1989-2017

'91 global advisory group
EPI sets 1997 as target for integrating HBV in national immuniation programmes www.

'92 adherence by WHO and WHA (resolution 45.27)

In 2010, MS re-iterated the 1992 resolution and adopted resolution 63.18, which called WHO to draft a comprehensive viral hepatitis prevention and control strategy

Number of countries introduced HepB
HepB3 coverage

2012: introduced in 181 countries
2013: introduced in 183 countries
2014: introduced in 184 countries

2017: excluding 3 countries where HepB administered for adolescents

3-DOSE HEPATITIS B VACCINE: 84% COVERAGE:

Source: WHO AND UNICEF
STATUS OF HEPATITIS B, 2015

Cumulated incidence of chronic infection:
Prevalence of HBV infection in children under 5 reduced from 4.7% to 1.3% (immunization)

Prevalence:
257 million people living with HBV
* 68% in Africa/Western Pacific
HEPATITIS B IMMUNIZATION POLICY, WHO EUROPEAN REGION

- Universal newborn vaccination (26 countries)
- Universal childhood vaccination (20 countries)
- Universal children/adolescents (3 countries)
- Risk groups vaccination (3 countries)
- Risk groups / universal newborn vaccination (1 country)

Source: WHO/UNICEF JRF
IS THERE AN IMPACT AFTER ALL THIS YEARS OF HEPATITIS B VACCINATION

EXAMPLES
VHPB Country meetings < 2018
Tassi di incidenza \((x\ 100.000)\) dell'epatite B per età ed anno di notifica. SEIEVA 1985-2016.
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
HBV immunized (acurnal) and acute (ОГВ) and chronic (ХГВ) HBV cases, registered in 2000-2017

- In 2015-2017, Russia immunized against HBV annually over 3 000 000, including over 1 500 000 children.
- Total immunized since campaign start is about 100 MM.
THE NATURAL HISTORY OF VIRAL HEPATITIS B INFECTION IN ROMANIA 1989 - 2016

Incidence rate of Hepatitis B in Romania 1986 - 2017

Vaccination implemented 1995
Cases of acute hepatitis B in children under 18 years, 1986 – 2014, Latvia

New-borne vaccination programme

Catch-up vaccination programme

Number of cases

1986
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
Acute HepB incidence in Estonia, 1990-2014
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
DO WE STILL NEED TO TALK ABOUT HBV VACCINATION

- Despite the availability of safe and effective HBV vaccines since more than 35 years
- Global burden of disease is still substantial
World Hepatitis Day – July 28

Over 90% of new hepatitis B infections occur through mother-to-child transmission and during early childhood. But other groups are also at higher risk of both hepatitis B and C, including people who inject drugs; men who have sex with men; people who have had tattoos or acupuncture; partners of people living with hepatitis B; and health care workers.

#TestTreatHepatitis
#WorldHepatitisDay
CHALLENGES FOR THE FUTURE

- challenge 1: Keep or increase vaccination coverage

Sustainability
# Hepatitis B 3 Vaccine Coverage, 2015

<table>
<thead>
<tr>
<th>Coverage (%)</th>
<th>No of countries</th>
</tr>
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<tbody>
<tr>
<td>≥ 95</td>
<td>24</td>
</tr>
<tr>
<td>94</td>
<td>8</td>
</tr>
<tr>
<td>91 – 93</td>
<td>5</td>
</tr>
<tr>
<td>80 – 90</td>
<td>6*</td>
</tr>
<tr>
<td>&lt; 80</td>
<td>2**</td>
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<td><strong>Total:</strong></td>
<td><strong>45</strong></td>
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* BiH, France, Germany, Montenegro, Romania, Slovenia
** San Marino, Ukraine

Source: WHO/UNICEF estimate
challenge 2: Non-response to conventional vaccination against HBV

Protective efficacy of yeast derived HBV vaccines: 95-100% in young-healthy recipients decreasing to 60-75% in individuals> 60y old*

*Leroux-Roels G. 2015;204:69-78
Fishman DN et al. 2002;35:1368
The Unmet Need: High-Risk Populations of Non-Responders & Low Responders to Conventional HBV Vaccination

**SEROPROTECTION RATES:**

- Cancer patients (children)  
  ~57%
- Patients with chronic liver disease  
  ~50%
- Chronic renal failure & dialysis  
  34-81%
- Acute lymphocytic leukemia  
  ~10%
- Bone marrow /stem cell transplant recipients  
  15-68%
- Pre-transplantation candidates  
  28-36%
- Post-transplantation patients  
  ~10%
- HIV (children & adolescents)  
  ~30%
- Miscellaneous (i.e. older healthcare workers engaged in exposure prone procedures; genetically determined non-responders, celiac disease, IBD)
The hepatitis B vaccine

- Three generations of hepatitis B vaccine
  - **Plasma-derived vaccines** (HBsAg) introduced in 1982 – no longer in use
  - **DNA recombinant vaccines** synthesized in yeast, since 1986. Most widely used vaccines in the world.
  - **Third generation vaccines**: mammalian cell derived recombinant vaccines (HBsAg/ S, preS1, preS2 antigens), with enhanced immunogenicity. Possible indication for non-responders at risk. So far access limited to a few countries (France, Israel, some East Asian countries).
- Hepatitis B vaccines are available as monovalent vaccine or in combination with other vaccines
Three generations of HBV vaccines

Plasma derived Vaccines 1980-1986

rDNA Yeast derived vaccines 1986-2017

rDNA Mammalian cell derived vaccines 2000-

[S, Pre-S2, Pre-S1]

Enhancement of Immunogenicity of HBV Vaccines

New adjuvants*:
- Fendrix GSK™ (MPL /A&QS21)
- Heplisav, Dynavax™ (CpG ODNs TLR 9)
- MF 59 (oil in water)
- AgB/RC 529 (MPL ,Corixa, Berna Biotech)
- Cytokines (GM-CSF, IL-2, IL-4, IL-12, IFN α, TLR 9 ag)
- Miscellaneous (Cationic lipid, Virosomes ,HBcAg)

Double or Triple antigen vaccines(Pre-S₁/Pre-S₂/S (with alum hydroxide))**:
- GenHevac B™ - France (Discontinued)
- Hepagene™ - UK (Discontinued)
- BioHep B/ HepImmune/ Sci B Vac™ (licensed in Israel)

*Leroux-roels G 2015; Med Microbiol Immunol  204;69
Wen Y et al. Emerging Microbes and Inf 2016 , 5,e25
**Shouval D et al. Med Microbiol Immunol. 2015;204:57
Immunogenicity of an hepatitis B vaccine with a Toll-like receptor 9 hepatitis B *agonist adjuvant (HBsAg-1018) compared to a licensed vaccine in healthy adults 40–70 years of age.
Challenge 3: How long does hepB vaccine-induced protection last?
Figure 1. Levels of antibody to hepatitis B surface antigen (anti-HBs) decline over 35 years among those who received no follow-up serologic testing, Alaska.
Persistence of immunity up to 20 years after HBV vaccination

Five independent long-term follow-up clinical trials have assessed the antibody persistence and the response to a challenge dose 5 to 20 years after a 3-dose vaccination course of Engerix-B.

Circulating anti-HBs antibodies decline over time (orange bars).

In contrast, the ability to mount an anamnestic response upon receipt of a challenge dose (blue bars) remains >95% even 20 years after vaccination, demonstrating the persistence of immune memory beyond the presence of circulating antibodies.

Challenge 4: can we prevent perinatal transmission?

No

Can we prevent perinatal HBV infection?

Yes
Challenge: timely birth dose!

Proportion of fully immunized children (FIC) and HepB BD within 24 hours among children 12-23 months in different cities/ provinces
**BCG & Hep B Vaccine within 24 hours of birth:**
N=526 infants participated (2015-2016)

<table>
<thead>
<tr>
<th>BCG vaccine</th>
<th>Freq</th>
<th>%</th>
<th>HBV</th>
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<tr>
<td>≤ 24 hours after birth</td>
<td>234</td>
<td>44.5</td>
<td>46.6%</td>
</tr>
<tr>
<td>2 – 7 days</td>
<td>136</td>
<td>25.9</td>
<td>16.5%</td>
</tr>
<tr>
<td>&gt;7 days</td>
<td>149</td>
<td>28.3</td>
<td>36.9%</td>
</tr>
<tr>
<td>Not given</td>
<td>7</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>526</td>
<td>100</td>
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HEPATITIS B BIRTH DOSE: 39% COVERAGE: IMPACT ON CHRONIC LIVER DISEASES

Source: WHO AND UNICEF
Hepatitis B vaccines
WHO recommendations October 2009

- All infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours.

- The birth dose is crucial in areas of high hepatitis B endemicity, but important even in intermediate and low endemicity areas.

- To complete the primary series the birth dose should be followed by 2 doses, spaced by ≥ 4 weeks, e.g. at the time of the first and third doses of DTP vaccine, or, if programmatic more convenient, by 3 doses coinciding with DTP or other routine infant vaccines.

- There is no evidence to support the need for a booster dose following 3 (or 4) doses of hepatitis B vaccine in routine immunization programmes.
SAGE reemphasized the importance of the birth dose and urged all countries to introduce the universal birth dose without further delay.

All infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours.
CHALLENGES FOR THE FUTURE

- Challenge 5: Cope with vaccine issues and increase vaccine confidence
LEARN FROM PAST TO COPE WITH THE FUTURE

In the past hepatitis B vaccination programmes were several times damaged by unsubstantiated rumors:

- Hepatitis B derived vaccine from plasma, linked with HIV
- HepB can be sexually transmitted
- Safety concerns
  - HepB vaccine was linked to Multiple Sclerosis, Autism, …
  - Picked up by anti-vaccine
  - Although no causal link with vaccine
  - Communication of rational arguments did not seem to have impact
Tremendous progress since 1990!

- But ....

- A number of challenges:
  - Guarantee high coverage in neonates and infants
  - Guarantee timely birth dose administration
  - Reach the target groups (“access”)
  - Address the non-responders
  - Understand longterm protection & boostability
  - Integrate hepB vaccination in a control and elimination plan with therapy
  - Political will is needed!
Website and social media:

- Newsletters
- Renewed membership of Vaccine Safety Network
- Twitter