Hepatitis B

Vaccination
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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

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The hepatitis B vaccine

- Three generations of hepatitis B vaccine
  - Plasma-derived vaccines (HBsAg) introduced in 1982
  - 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

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Vaccination schedule

- Different vaccination schedules possible, three (0, 1, 6 months) or four doses (0,1,2,12 months)
- Flexibility → adaptable to existing infant immunization programs
- Neonatal schedule: first dose (monovalent vaccine) at birth (within 24 hours) recommended for all countries by WHO. Industrialized countries might start later if screening program for pregnant women. Some countries recommend the addition of HB specific immunoglobulins.
- Minimum interval of 4 weeks between 2 primary injections
- No booster dose (with current knowledge)

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Efficacy

- Complete vaccination induces protective antibody levels close to 100% in infants, children and young adults, less in older age groups
- Indication of protection: anti-HBs $\geq$ 10mIU/ml 1-3 months after last dose of primary vaccination series
- Duration of protection at least 20-23 years and probably lifelong\(^1\)

1. Leuridan & Van Damme. CID 2011
# Vaccine response

## Protection (anti-HBs ≥ 10 mIU/ml) by age group and dose

<table>
<thead>
<tr>
<th>Dose</th>
<th>Infants</th>
<th>Adults*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16-40%</td>
<td>20-30%</td>
</tr>
<tr>
<td>2</td>
<td>80-95%</td>
<td>75-80%</td>
</tr>
<tr>
<td>3</td>
<td>98-100%</td>
<td>90-95%</td>
</tr>
</tbody>
</table>

* Factors that may lower vaccine response rate in adults are: ≥ 40 years, male gender, smoking, obesity, immune deficiency


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How safe is the B vaccine?

- More than 200,000 people studied in clinical trials
- More than 1,000 million doses used worldwide since 1982
- Very good safety profile and well tolerated:
  - local pain and tenderness in 15% (3%-29%) of vaccinations, fever > 37.7°C in 1%-6%, erythema, swelling and headache in 3%. Fewer reactions in children
  - no evidence of serious adverse events that have been causally linked to hepatitis B vaccination

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# 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

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Current WHO recommendations

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.
Worldwide use of hepatitis B vaccine

- In 2012, 181 countries out of the 194 introduced newborn or infant hepatitis B vaccination, compared to 23 in 1989

- Europe WHO Region (53 countries):
  - universal infant and/or adolescent immunization program in 47 countries, except 6 (Denmark, Finland, Iceland, Norway, Sweden and UK)
  - risk group immunization
  - screening pregnant women and neonatal immunization

- Infant vaccination coverage in Europe is generally high (> 80-90%), except for France and Ukraine

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Number of countries having introduced HepB vaccine* and global infant HepB3 coverage 1989-2012


* Excluding 3 countries where HepB administered for adolescence

Date of slide: 22 July 2013

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Reported hepatitis B vaccination coverage rate in infants of one to two years

Source: ECDC. Surveillance and prevention of Hepatitis B & C in Europe. 2010

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## Vaccination of risk groups in Europe

### Risk group vaccination programs in 30 European countries*, 2012

<table>
<thead>
<tr>
<th>Risk group programme</th>
<th>Nb of countries (N=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Household contacts of HBV carriers</td>
<td>24 (80%)</td>
</tr>
<tr>
<td>Injecting drug users</td>
<td>19 (63%)</td>
</tr>
<tr>
<td>Men who have sex with men</td>
<td>9 (30%)</td>
</tr>
<tr>
<td>Commercial sex workers</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Health care workers</td>
<td>28 (93%)</td>
</tr>
<tr>
<td>Prison population</td>
<td>16 (53%)</td>
</tr>
</tbody>
</table>

* EU27 + Croatia, Norway and Switzerland

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Source: ELPA. Euro Hepatitis Care Index. [http://www.hep-index.eu](http://www.hep-index.eu)
Impact of vaccination

- Vaccination = most effective measure to reduce global incidence of hepatitis B
- First European countries with universal infant vaccination: Cyprus (1990, infants), Bulgaria (1991, newborns), Italy (1991, newborns and adolescents), Spain (autonomous region of Catalonia, 1991, pre-adolescents) and Israel (1992, newborns + catch-up children and adolescents), resulting in dramatic decline in HBV infections rate
- Effectiveness of protection from HBsAg carriage after hepatitis B vaccination in Asia varied between 61.1 and 100% and in Africa between 63.6 and 89.5%¹

¹ Chen. J Hepatol. 2009 Apr;50(4):805-16
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
Hepatitis B incidence (per 100,000) by age group, Italy, 1985-2010

Total incidence decreased from 12 per 100,000 in 1985 to 0.9 in 2010
Example of Spain

Hepatitis B incidence (per 100,000) by age group, Catalonia, 1992-2002

Total incidence decreased from 5 per 100,000 in 1992 to 1.2 in 2002

Source: Salleras et al. Vaccine 23 (2005) 2181-2184
Example of Israel

Acute hepatitis B incidence (per 100,000) by population groups, Israel, 1992-2012

Total incidence decreased from 2.2 per 100,000 in 1992 to 0.5 in 2012

Source: Anis E. Division of Epidemiology, Ministry of Health, Israel. Presented at the VHPB meeting March 2013

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Other indicators of impact

Estimated reduction in future HBV-related death with increasing hepatitis B vaccination and birth dose coverage