Impact of natural boosting on long-term protection against hepatitis B after newborn (HBsAg + mothers) vaccination

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Hepatitis B Vaccination, Milan, 2011
Vaccination of newborn

• Vertical transmission practically interrupted
  - only rare infections (HBeAg positive mothers)

• Main questions
  - long-term protection against HBsAg carrier
  - is booster vaccination necessary?
Basic description of the group

• The Czech Republic is low endemic country with 0.56% HBsAg prevalence

• Vaccination of newborn of HBsAg positive mothers started in 1988

• Group of 665 newborns from north-eastern part with 1 million inhabitants (field experience)

• Group gradually increased till the end 2006 (hexavaccine)
Group of 665 newborns

- 334 females, 331 males

- All mothers HBsAg positive during pregnancy
  - 34 mothers also HBeAg positive

- Combine active and passive immunisation
  - first day after birth
  - standard schedules in the Czech Republic
Vaccination schedule

• Passive immunisation
  – hepatitis B immunoglobulin 50-100 I.U.

• Active immunisation: 10 μg of HBsAg
  • plasma-derived, since 1990 recombinant vaccine
  • 0, 1, 6 months in most children
  • 0, 1, 2, (12) months in 29 children (HBeAg+ mothers)
Investigation of children

• After vaccination 1-3 months, at 2 years, biennially thereafter

• HBsAg, anti-HBs, anti-HBc
  – ELISA method, commercial sets
  – approximately 5 000 samples

• HBV DNA: PCR diagnostic since 1994
  – samples positive for HBsAg or anti-HBc
Anti-HBs after basic vaccination

- Complete schedule in 640 children
- Investigation of anti-HBs in 620 children
- Protective anti-HBs in 574 of 620 children (92.5%)
Anti-HBs after basic vaccination

- Protective anti-HBs level (%)
  - Low 10-99 IU/l
  - High ≥ 100 IU/l

<table>
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<tr>
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<th>0, 1, 2 months</th>
<th>0, 1, 6 months</th>
<th>boys</th>
<th>girls</th>
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<tbody>
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<tr>
<td>High</td>
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<td>Overall</td>
<td></td>
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<td>77,8</td>
<td>77,9</td>
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Revaccination of children without protective anti-HBs after vaccination

- Revaccination of 39 children
  - one dose of vaccine
  - after 1-2 months anti-HBs
  - next revaccination without protective anti-HBs
Protective anti-HBs after revaccination

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Persistence of protective anti-HBs

- Group of 620 children with investigation of anti-HBs after 3 doses of vaccine
- Booster vaccine stopped analysis in child
- Kaplan-Meier analysis: first result without protective anti-HBs
Persistence of protective anti-HBs
($\geq 10$ IU/L)

Children with protective anti-HBs (%)

Years from birth

Hepatitis B Vaccination, Milan, 2011
Persistence of protective anti-HBs (≥ 10 IU/L)
Breakthrough infections

- HBsAg carrier status (viral hepatitis)
- Anti-HBc seroconversion

- Different definitions in studies
  - one or two positive results
  - transient (isolated) positive results
  - age dependent false positive results
    - HBsAg in umbilical blood (venous blood in infants)
    - anti-HBc until 3 years of age
Detection of HBsAg in umbilical and venous blood in our children

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Detection of anti-HBc in umbilical and venous blood in our children

Hepatitis B Vaccination, Milan, 2011
Criteria in our study

• **HBsAg carrier status**
  - at least 2 positive results
  - detection in children older than 1 month

• **Isolated HBsAg positive result**
  - one positive result
  - detection in children older than 1 month
HBsAg carrier status

• Vertical transmission in 2 children (0.3 %)
  – detection at the end of first year of life

• Boy with escape mutant
  – variant of HBsAg: substitution “a” determinant at residues 137 and 139 (Dr. Harrison et al., London)

• Girl without escape mutant
Isolated HBsAg positive result

• Detected in 3 children
  - in 13 months, 5 and 12 years of age

• Next investigations excluded infection
  - negative results of HBsAg, anti-HBc, anti-HBc IgM
  - negative result of HBV DNA in 2 children
Criteria in our study

• **Anti-HBc seroconversion**
  - at least 2 anti-HBc positive results in child with 3 or more years
  - new appearance of anti-HBc
  - long term persistence of anti-HBc

• **Isolated anti-HBc positive result**
  - one positive result in child with 3 or more years
Anti-HBc seroconversion
(new appearance of anti-HBc)

- Appearance of anti-HBc after waning of maternal anti-HBc
- Children with 3 or more years

Contact with HBV

Hepatitis B Vaccination, Milan, 2011
Anti-HBc seroconversion
(long-term persistence of anti-HBc)

- Long term persistence without negative result of anti-HBc
- Children with 3 or more years
Anti-HBc seroconversion

- Only in 10 children (1.6 %)
  - new appearance of anti-HBc in 5 children
  - long-term anti-HBc persistence in 5 children
  - from 3 to 14 years of age

- PCR diagnostic in all 10 children
  - negative HBV DNA in 8 children
  - low viraemia in 2 children
Isolated anti-HBc positive result

- Detected in 11 children
  - from 3 to 14 years of age
  - next negative result of anti-HBc
  - PCR in 6 children with negative HBV DNA
Anamnestic anti-HBs response

- Natural booster
- Revaccination (booster vaccination)

- Different criteria in studies
  - different for natural booster and revaccination
  - twofold increase, fourfold increase
  - any increase from negative level
Anamnestic anti-HBs response

- **Natural booster**
  - anti-HBs increase without revaccination

- **Revaccination**
  - anti-HBs increase after booster

- **No appearance of anti-HBc**
Criteria in our study

• Identical for natural booster or revaccination
  - twofold increase if first anti-HBs ≥100 IU/L
  - fourfold increase if first anti-HBs < 100 IU/L
  - et least 40 IU IU/l, if first anti-HBs < 10 IU/L

• Exclusion of physiological and laboratory fluctuation of anti-HBs level
Natural booster

• Observed in 38 children (6.0%)
  – two cases in one child (total 39 cases)
  – from 1 to 18 years of age

• PCR diagnostic in 8 children
  – HBV DNA negative
Lower natural increase of anti-HBs

- Twofold increase if first anti-HBs < 100 IU/L
  - detected in 35 children (5.6%)

- Any lower increase of anti-HBs
  - detected in 210 children (33.3%)
  - physiological and laboratory fluctuation
    • approximately 5 000 samples
Anamnestic response after revaccination

• Revaccination after waning of anti-HBs till 2002
  - revaccination in 159 cases
  - anamnestic response ($\geq 40$ IU/L) in 151 cases (95.0%)
  - lower increase (10-39 IU/L) in 5 cases (3.1%)
  - protective anti-HBs after second booster in 2 children and after third booster in one child

• At least short immune memory in most of children
Age distribution of breakthrough infections and natural booster
Calendar distribution of breakthrough infections and natural booster

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Conclusion: Vaccination of newborns against hepatitis B in low endemic country

- Practically interrupted vertical transmission
  - only 2 HBsAg carriers in 665 children (0.3 %)
- Long-term protection against HBsAg carrier status
  - waning of anti-HBs in 75 % of children during 15 years
  - natural booster only in 38 children (6.0%)
  - anti-HBc seroconversion only in 10 children (1.6%)
- Revaccination is not necessary at least to adolescence
  - continued follow-up is necessary
  - problem - different criteria in studies
Co-workers

- University Hospital Ostrava
  - Kabieszova
  - Sulakova
  - Dr. Zjevikova
  - Dr. Lukacova
  - Dr. Orsagova
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Thank you for your attention