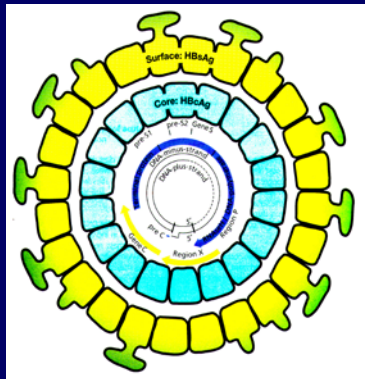


Impact of natural boosting on long-term protection against hepatitis B after newborn (HBsAg + mothers) vaccination



Roznovsky Ludek



Department of Infectious Diseases
University Hospital Ostrava, Czech Republic

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)

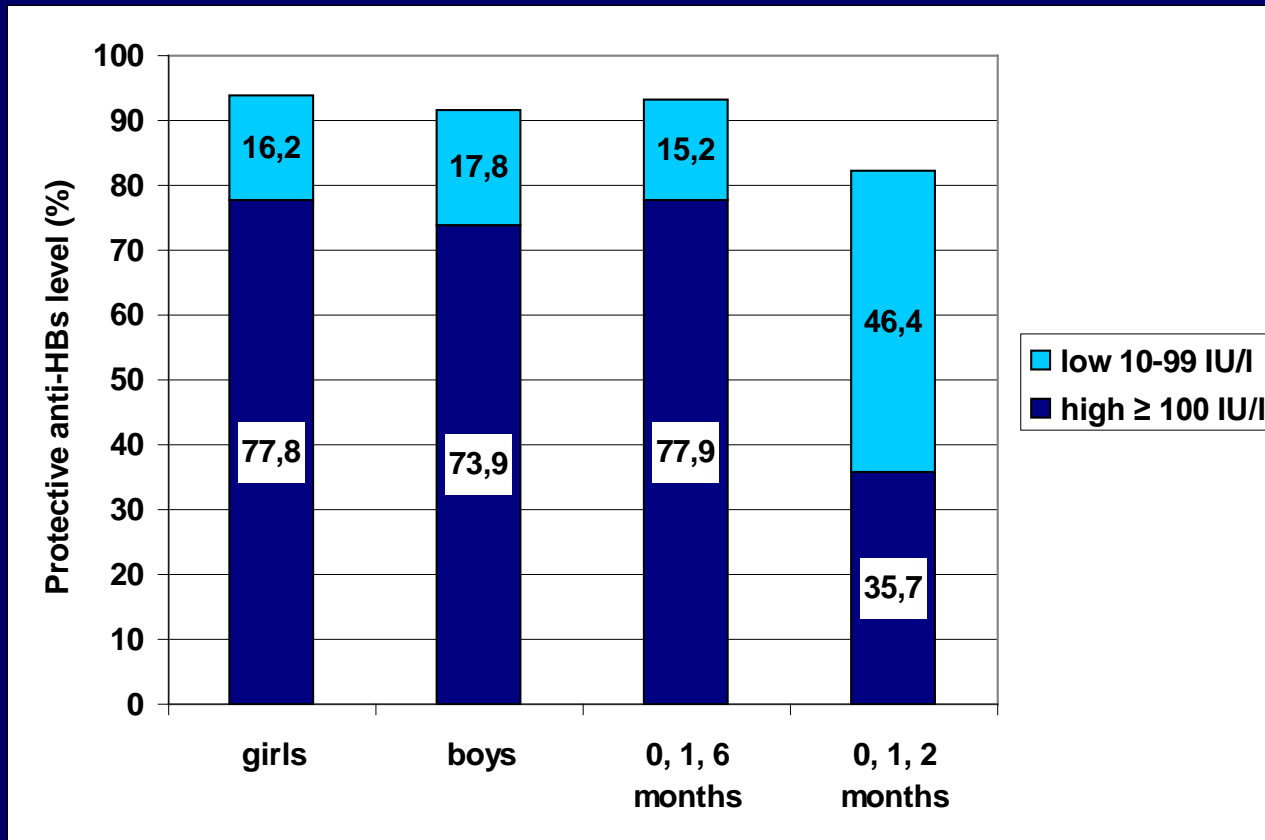
Investigation of children

- 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%)

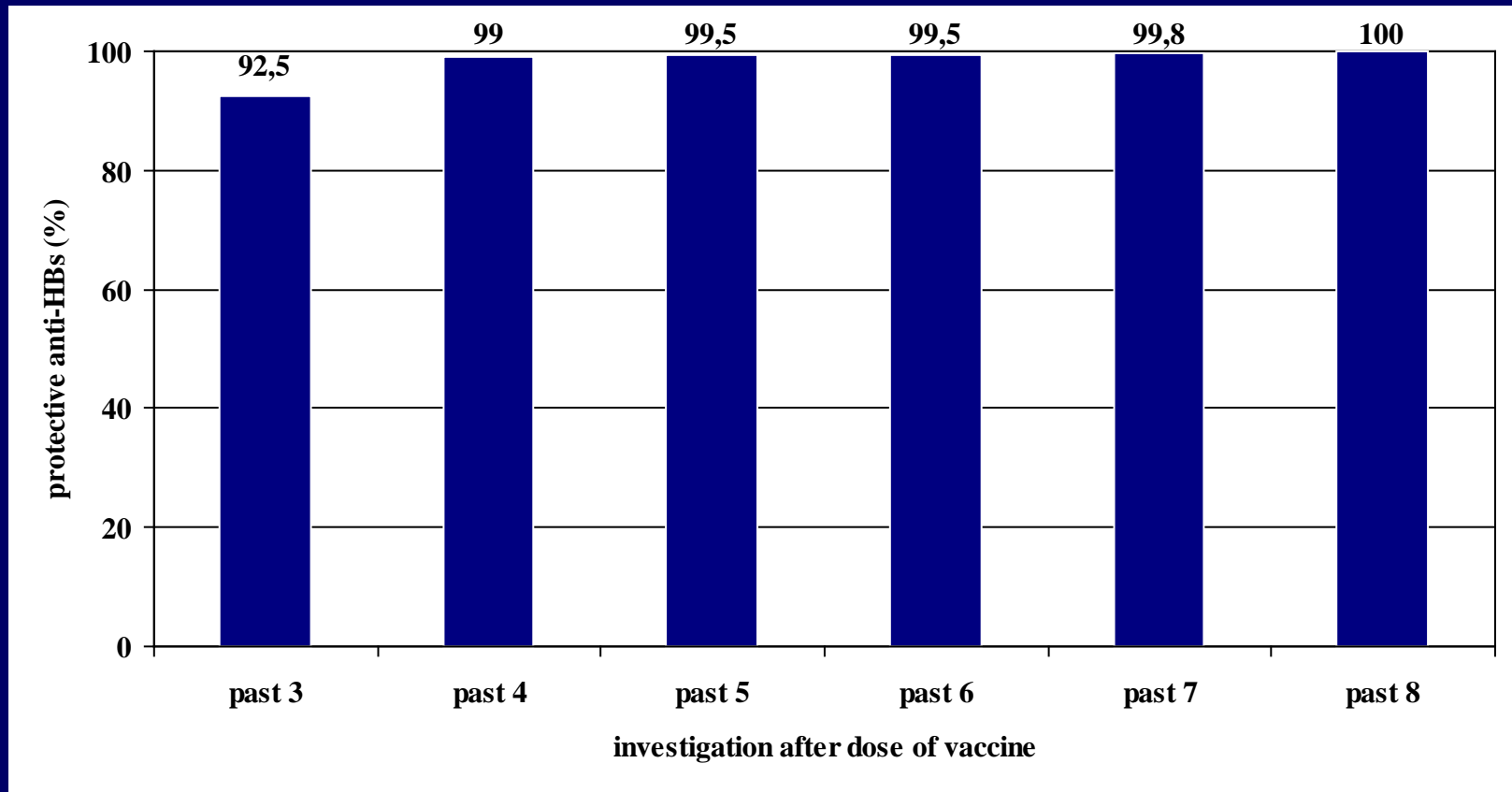
Anti-HBs after basic vaccination



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

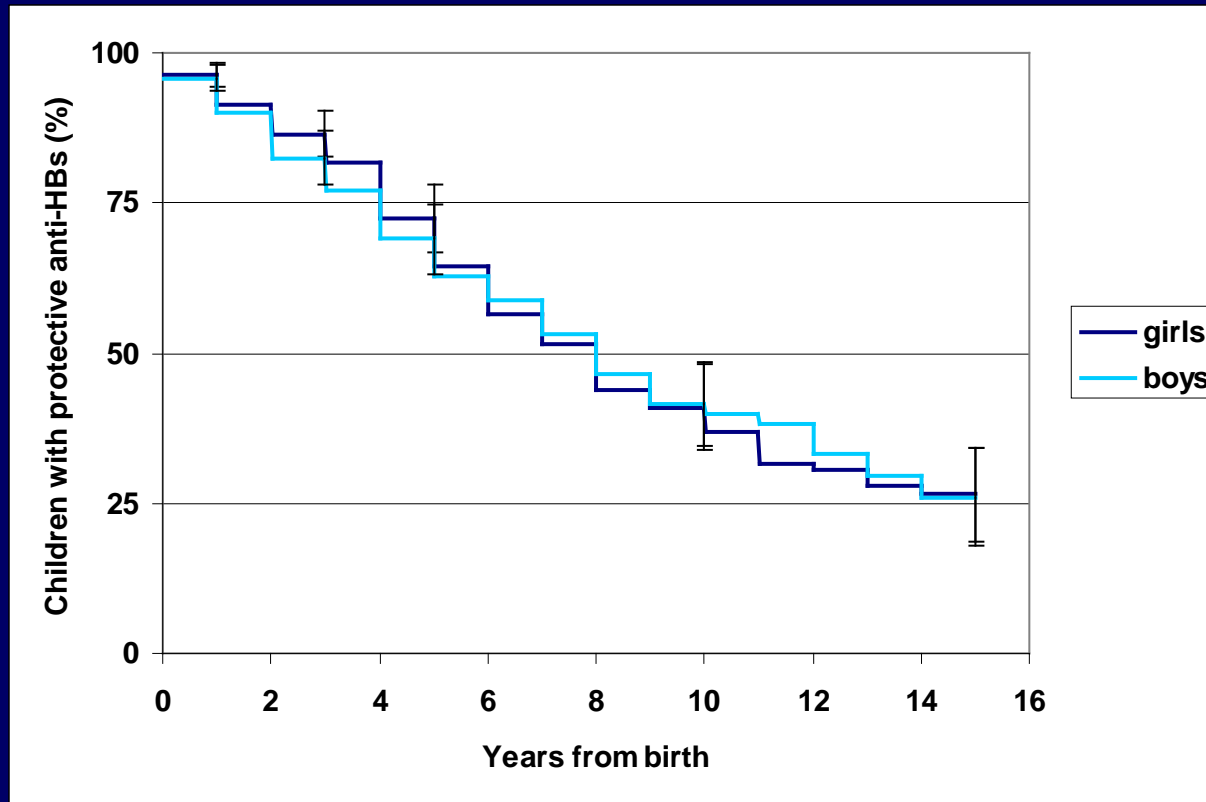
Protective anti-HBs after revaccination



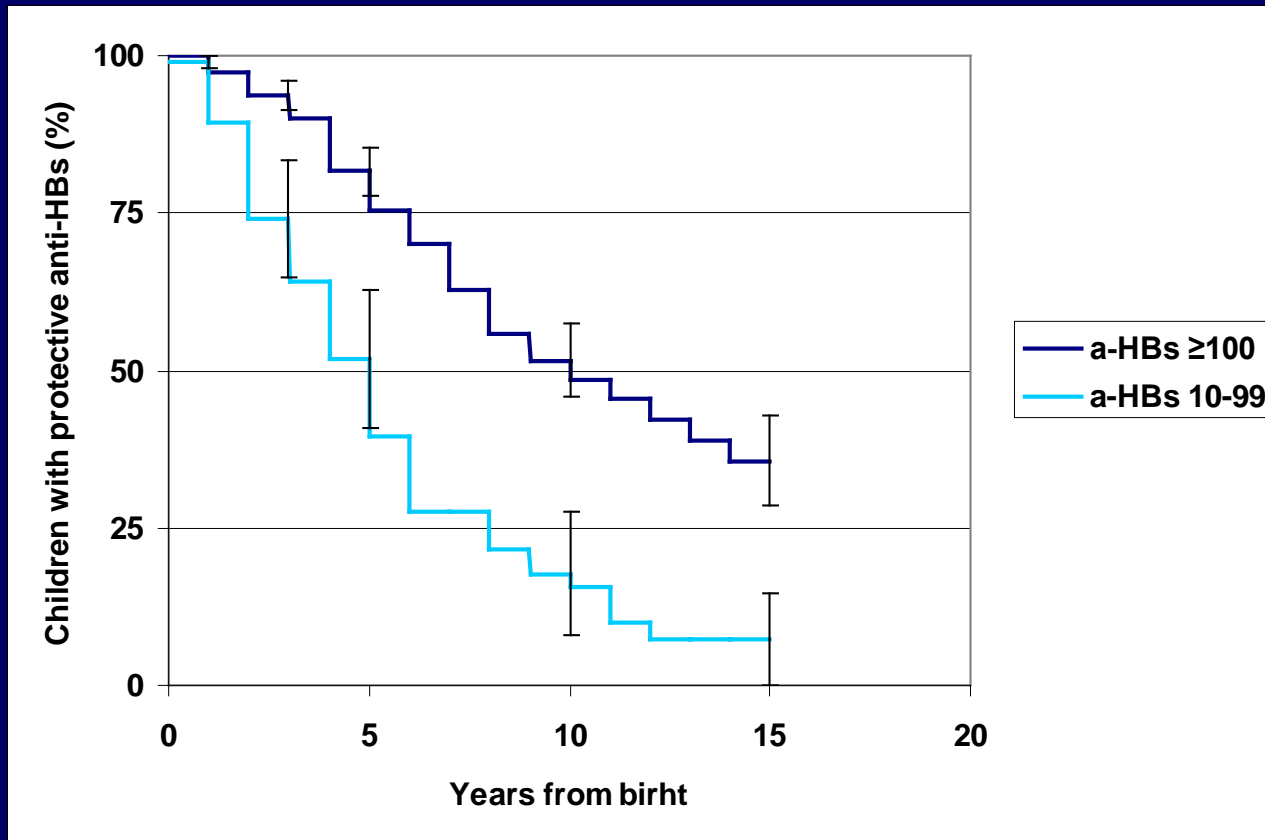
Persistence of protective anti-HBs

- 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 (≥ 10 IU/L)



Persistence of protective anti-HBs (≥ 10 IU/L)

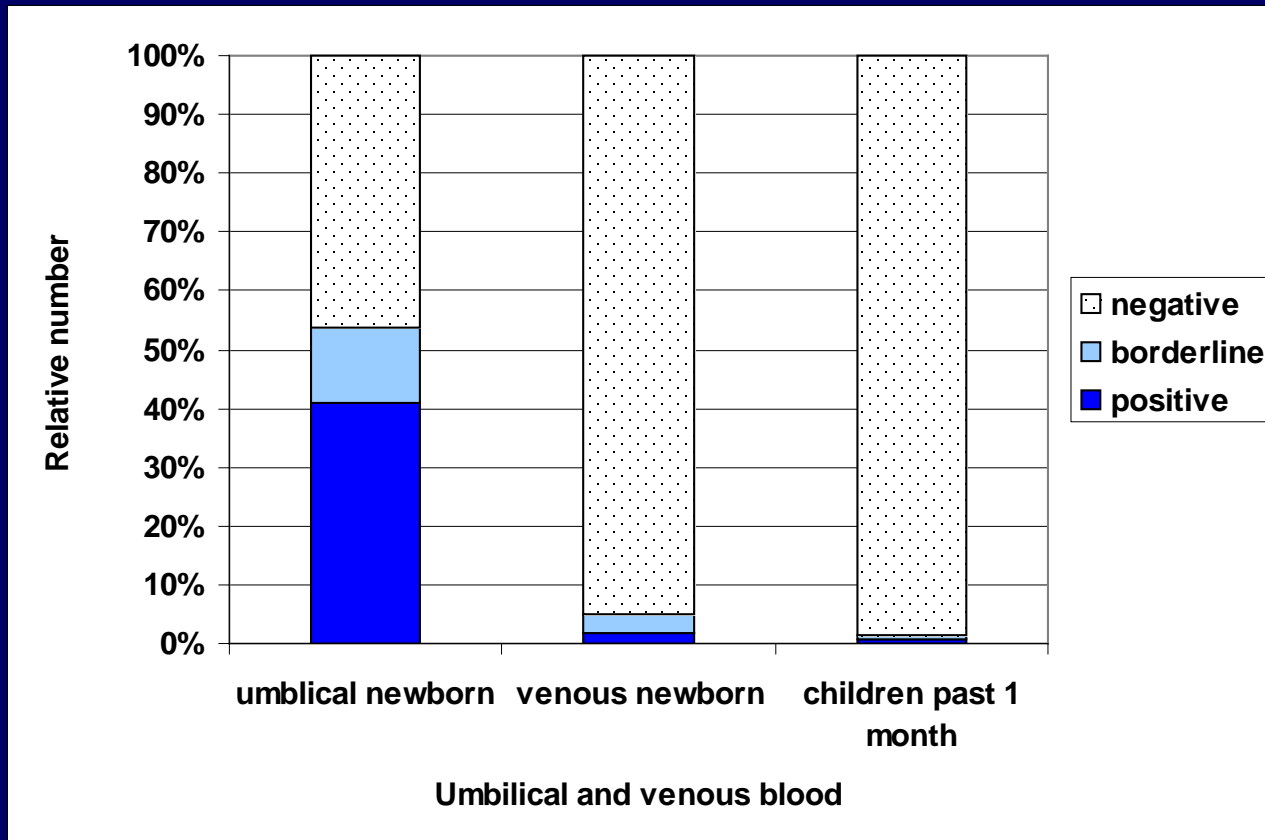


Breakthrough infections

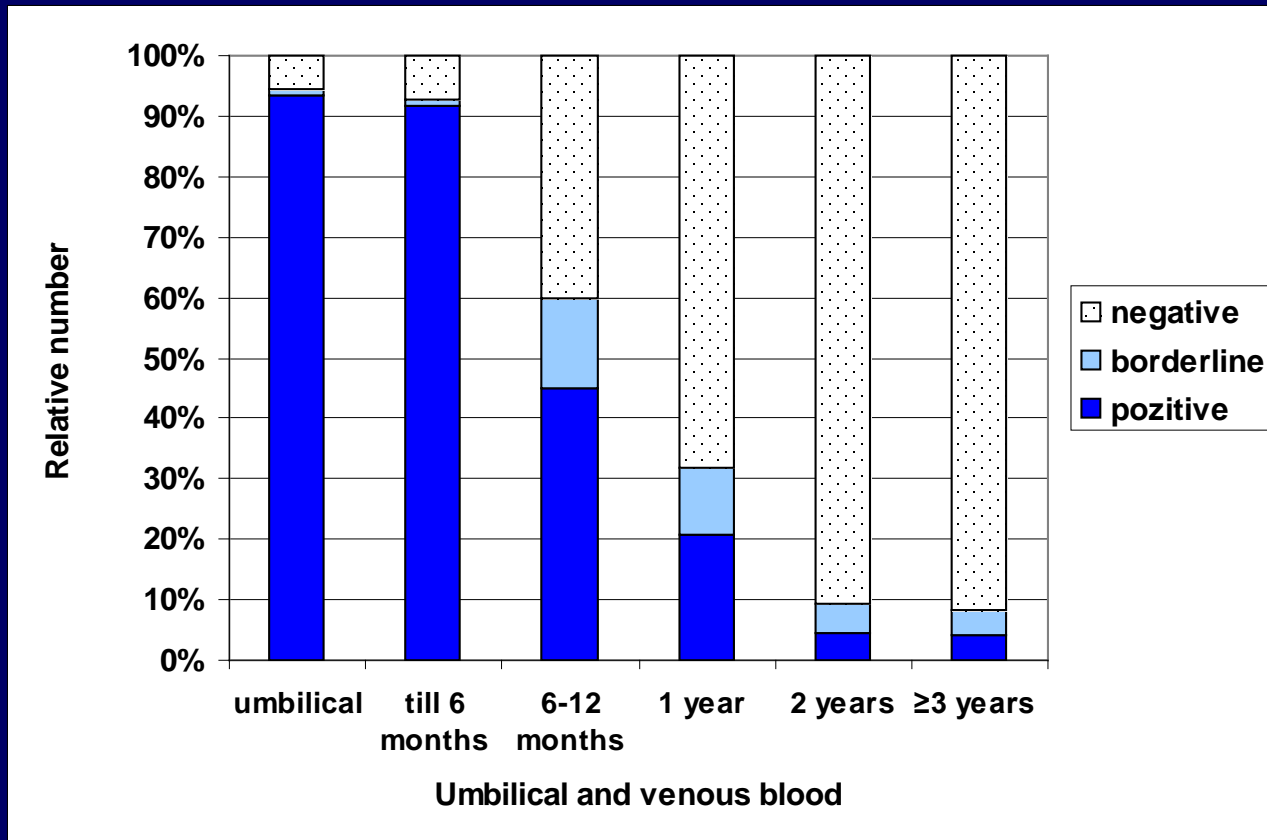
- HBsAg carrier status (viral hepatitis)
- Anti-HBc seroconversion

- 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



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



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

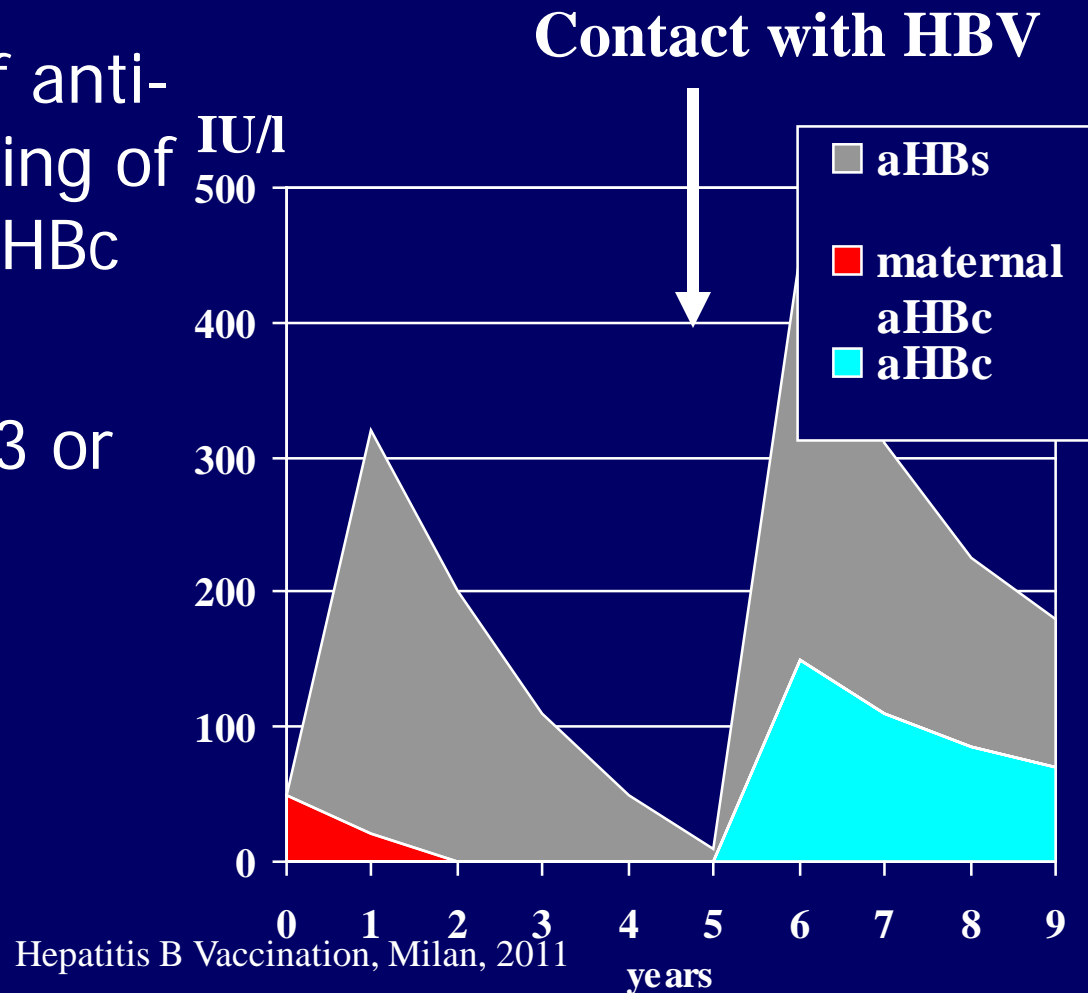
- Detected in 3 children
 - in 13 months, 5 and 12 years of age
- Next investigations excluded infection
 - negative results of HBsAg, anti-HBc, anti-HBc IgM
 - negative result of HBV DNA in 2 children

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

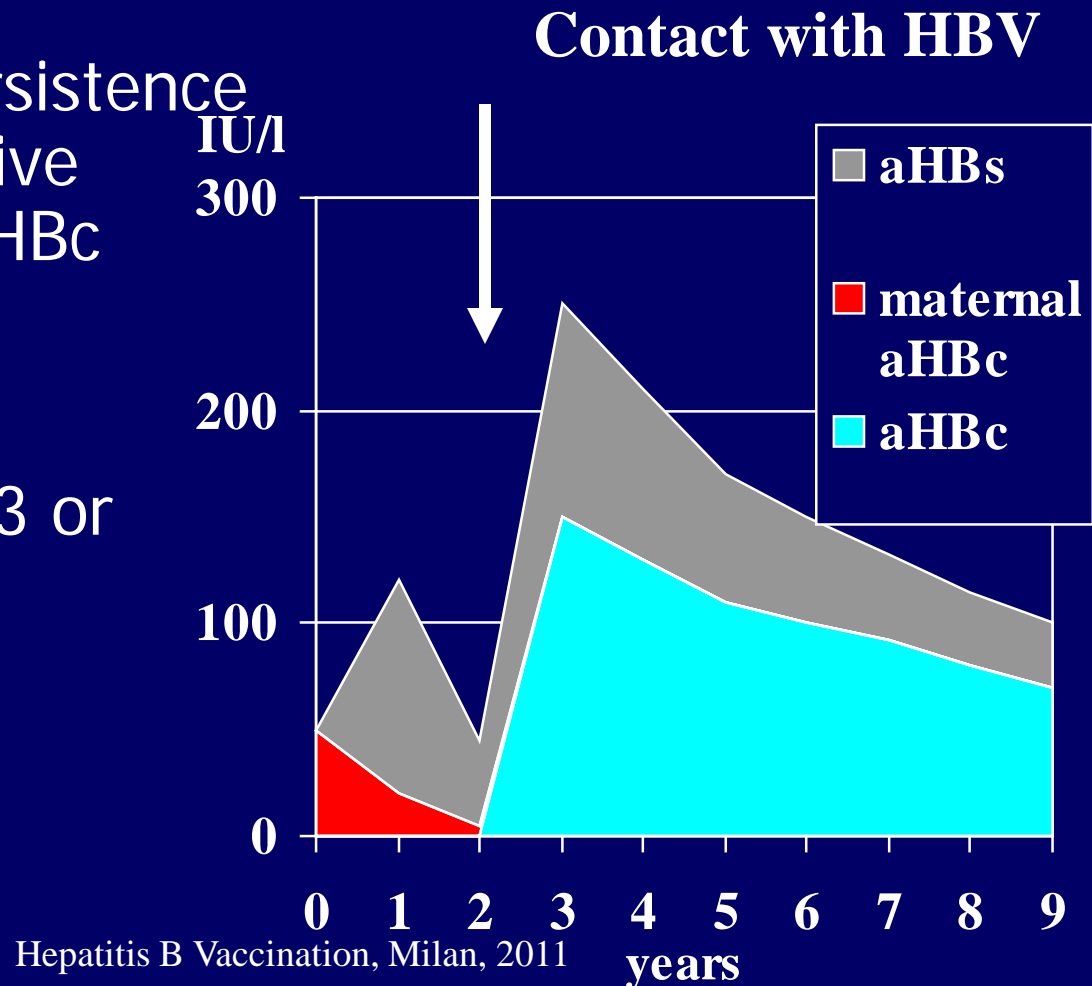
Anti-HBc seroconversion (new appearance of anti-HBc)

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



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

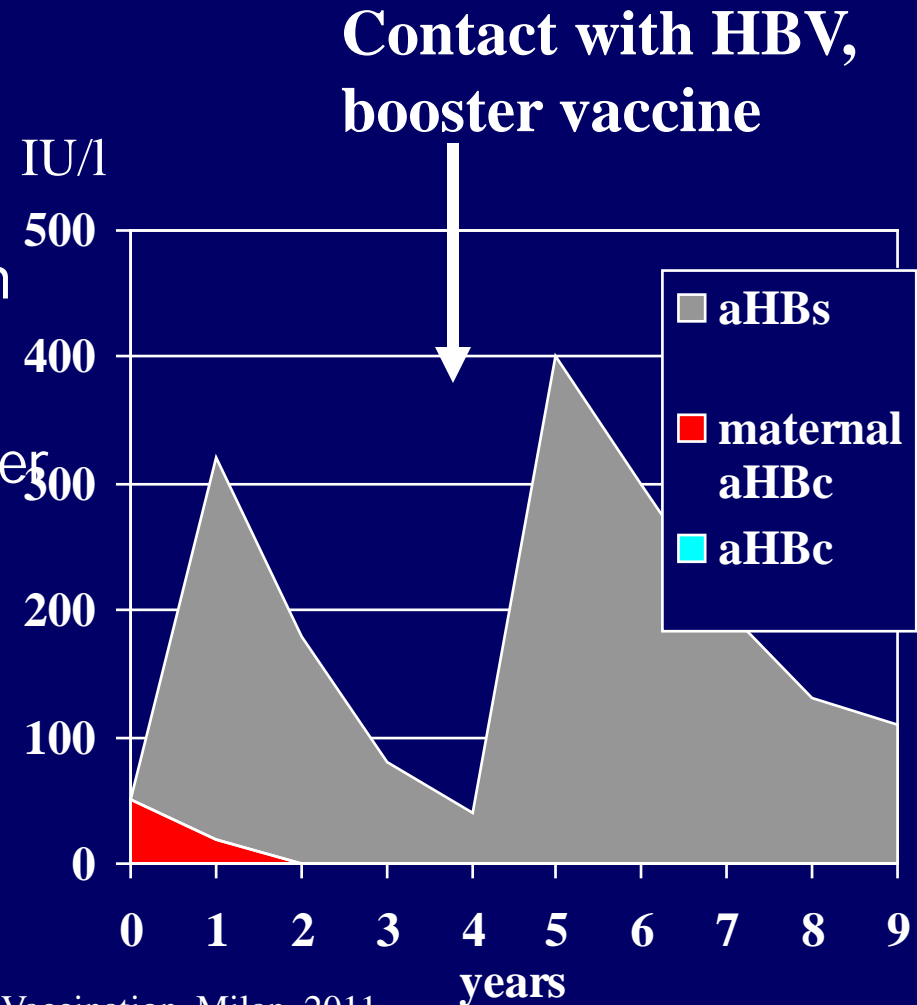
- Detected in 11 children
 - from 3 to 14 years of age
 - next negative result of anti-HBc
 - PCR in 6 children with negative HBV DNA

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
 - at 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

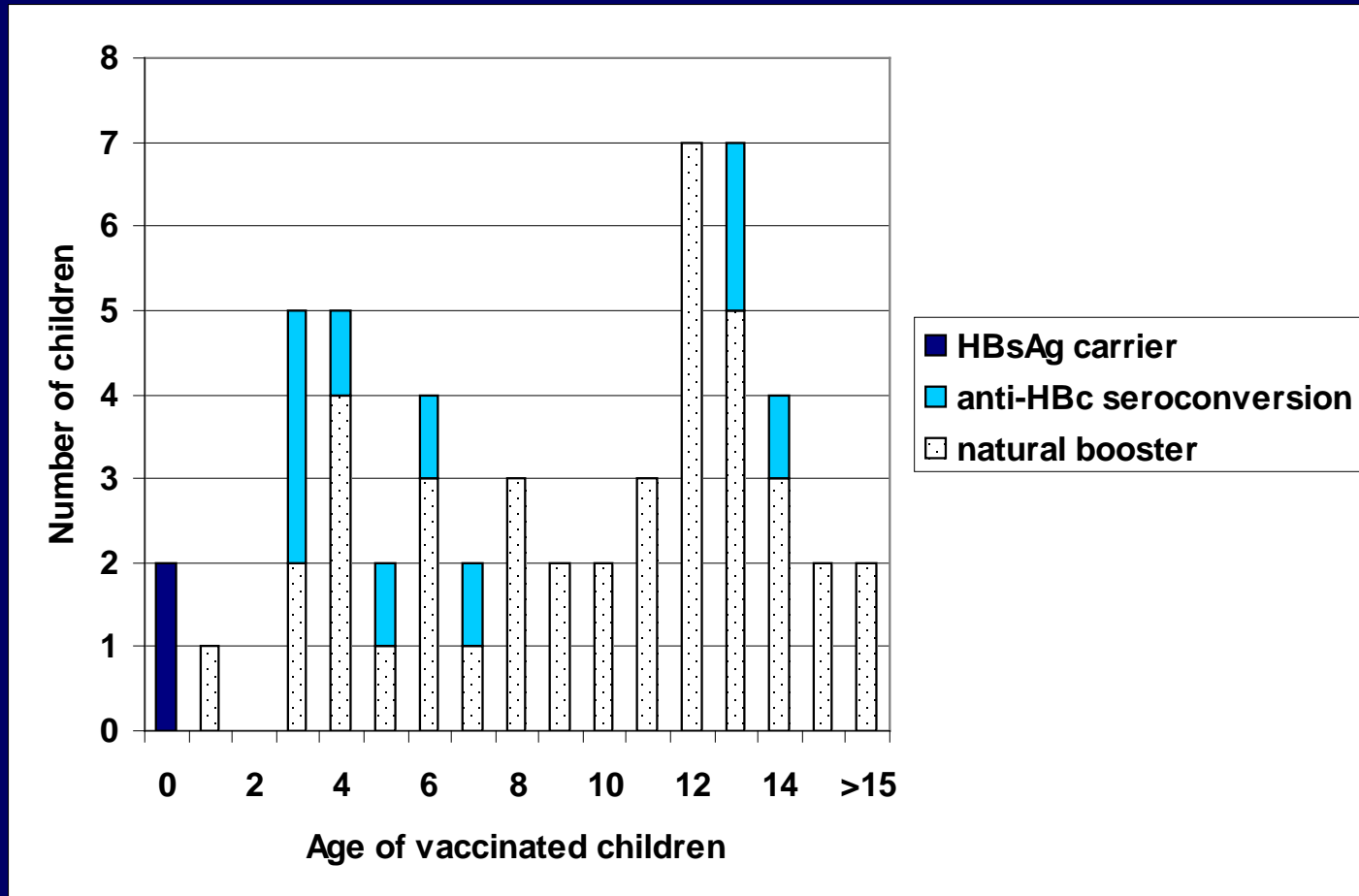
Lower natural increase of anti-HBs

- 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

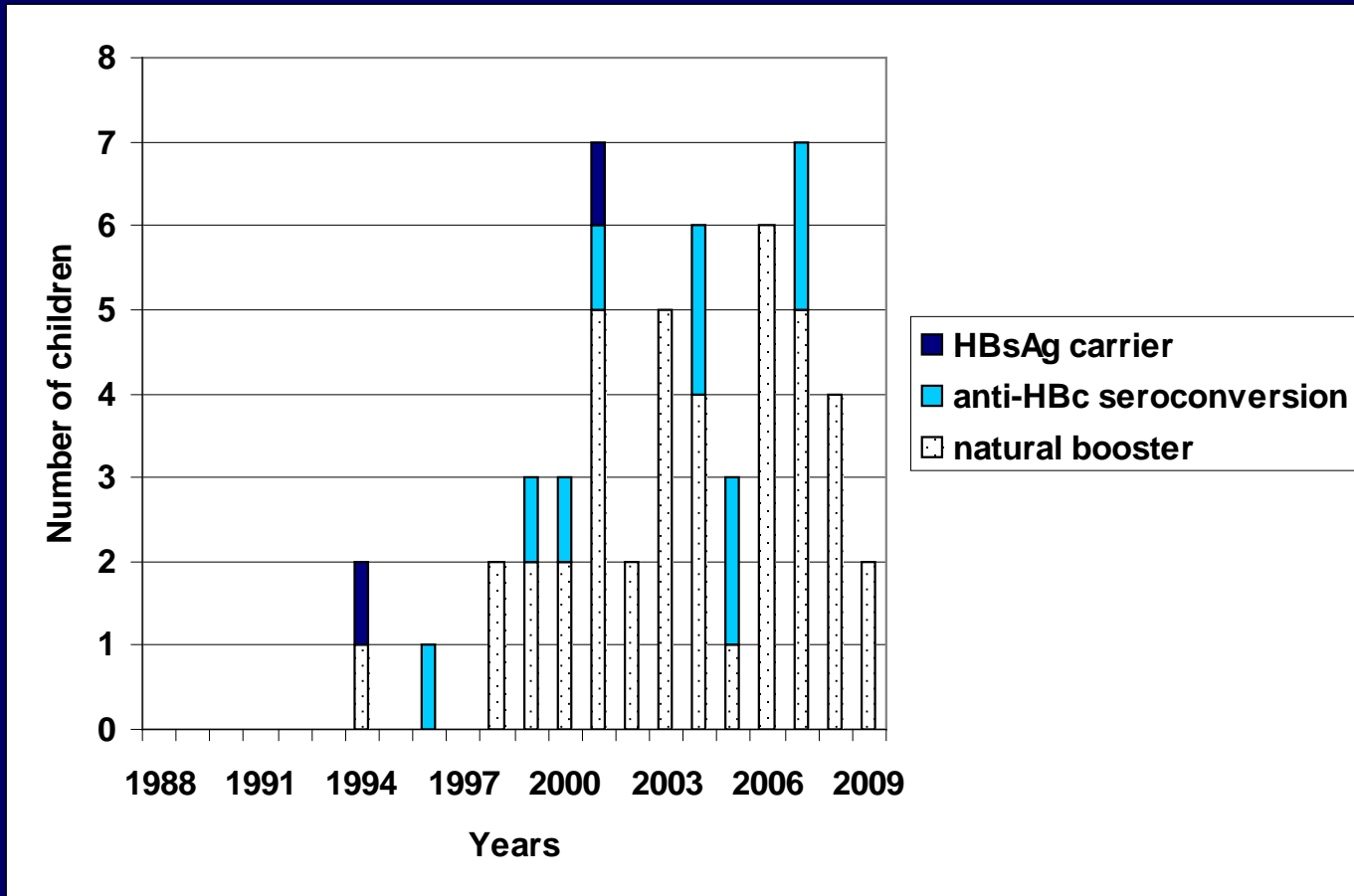
Anamnestic response after revaccination

- Revaccination after waning of anti-HBs till 2002
 - revaccination in 159 cases
 - anamnestic response (≥ 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



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
- Svarovsky - programmer
- University of Ostrava
- Tvrdik – statistical analysis
- Grant support:
- Ministry of Health, Czech Republic
- Reg. Institute of Hygiene Ostrava
- Dr. Lochman
- Dr. Kloudova
- Mgr. Mrazek
- University Hospital Hr. Kralove
- Dr. Pliskova
- Royal Free Hospital in London
- Dr. Harrison
- Dr. Fang
- Dr. Ling

Thank you for your attention

