Humoral and cellular immune responses after hepatitis B (booster) vaccination. How long will immune memory last?

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Immune memory

cardinal feature of the *adaptive* immune system:

- ability to maintain protective level of specific antibody by *long-lived plasma cells*

- ability to mount an *accelerated* immune response upon re-exposure to the same pathogen (*anamnestic response*) due to generation of *memory* B- and T-cells
How can immune memory be demonstrated?

- epidemiologically: prevention of reinfection or disease
- persistence of specific antibodies in the protective range
- „boostability“ of specific antibodies by revaccination
- demonstration of memory T- and B-cells
Vaccination against Hepatitis B: generation of specific antibodies
Decrease of anti-HBs after hepatitis B vaccination

Course of anti-HBs in 4 vaccinees

Percentage decrease of anti-HBs (mean of 202 vaccinees)

Jilg et al, Lancet 1990; 335:173

Jilg et al, Infection 1989;17:70-76
Kinetics of specific antibodies after vaccination with protein-based vaccines

Persistence of specific antibodies above a certain limit is a function of peak concentration

Half-life depends on:
- Vaccine
- Time after immunization

Limit of protection/detection

Gesemann et al, Vaccine 1995; 13: 443-447 (Hepatitis B)
Van Herck et al, J Med Virol 2001; 63:1-7 (Hepatitis A)
Anti-HBs 10 yrs after hep B vaccination in children and young adults in Italy

children (n=1212) vaccinated as newborns

recruits (n=446) vaccinated with 12 years

Anti-HBs 8-12 yrs after hep B vaccin.
with different vaccines in children/adolescents in Bavaria

Huber, Wenzel et al. unpublished
Waning of anti-HBs according to anti-HBs after vaccination at birth

Roznovsky et al. Infection 2010;38:395-400
Persistence of Anti-HBs

- persistence of anti-HBs is a function of peak anti-HBs-level and time after vaccination

- peak anti-HBs level depends mainly on age at vaccination, vaccine and vaccine dosage and genetic factors (in immunocompetent individuals)

- after 20 years, only about 20-30% of individuals vaccinated as newborns are still anti-HBs-positive with values $\geq 10$ IU/l
Vaccination against Hepatitis B: What is an anamnestic reaction? An example

- Anti-HBs (IU/l)
- Days after booster
- Increase of Anti-HBs: 140 U/I / min

51 years old male, revaccinated 17 years after primary immunization. 9 years later, an increase of 140 U/I/min was observed.
Vaccination against Hepatitis B: criteria for an “anamnestic response”

- in anti-HBs-positive individuals (anti-HBs ≥ 10 IU/l):
  - 4fold increase of anti-HBs within 4 weeks

- in individuals with anti-HBs < 10 IU/l („anti-HBs-negative“):
  - increase of anti-HBs to ≥ 10 IU/l after 10-14 days and/or 28 days
Vaccination against Hepatitis B: What is an anamnestic reaction?

4 children were revaccinated 8-12 years after primary immunization. All showed anti-HBs below 10 IU/I before booster.

Huber, Wenzel et al unpublished
Revaccination of individuals <10 IU/l
10 years after basic course of immunisation

children (n=342)
vaccinated as infants

recruits (n=48)
vaccinated with 12 years

Revaccination of individuals <10 IU/l
10 years after basic course of immunisation

Zanetti et al Lancet 2005; 366: 1379-1384
Revaccination of individuals <10 IU/l
8-12 years after basic course of immunization/Bavaria

Huber, Wenzel et al unpublished
82 children were revaccinated 8-12 years after primary immunization. All showed anti-HBs below 10 IU/l before booster.

Huber, Wenzel et al unpublished
### Anamnestic response to revaccination 15 - 24 years after hepatitis B vaccination in newborns

<table>
<thead>
<tr>
<th>Population</th>
<th>Vaccine</th>
<th>Follow up years</th>
<th>anti-HBs ≥10 IU/l (%)</th>
<th>Response to booster</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micronesian</td>
<td>recombinant 5 / 2.5 / 2.5</td>
<td>18</td>
<td>7</td>
<td>39/ 90</td>
<td>43%*</td>
</tr>
<tr>
<td>(n=105)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>plasma 4x10(Pasteur)</td>
<td>15-18</td>
<td>37</td>
<td>393/551</td>
<td>71%**</td>
</tr>
<tr>
<td>(n=5981)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>plasma 4x10(Pasteur)</td>
<td>18-23</td>
<td>-</td>
<td>26-96/127</td>
<td>21-76%*,**</td>
</tr>
<tr>
<td>(n=127)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>plasma 3x5 (Merck)</td>
<td>24</td>
<td>30</td>
<td>45-55/ 63#</td>
<td>71-87%*,**</td>
</tr>
<tr>
<td>(n=404)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>58-80%*,**</td>
</tr>
</tbody>
</table>

* % at day 10-14  ** % at day 28  # anti-HBs+ at year 5  ## anti-HBs- at year 5

378 children and adolescents vaccinated at birth with different vaccines/doses were revaccinated at the age of 5-14 years. 292 had anti-HBs-levels below 10 IU/l before booster.
Persistence of „boostability“

- boostability shows the presence of immune memory
- it outlasts the presence of anti-HBs
- it can be demonstrated in the vast majority of vaccinees for at least 10 years
- loss of “boostability” shown in recent reports indicates that immune memory may wane with time
- waning immune memory seems to be more frequent in individuals vaccinated at birth and/or with low doses of vaccine
Demonstration of HBsAg-specific memory T- and B- cells

- demonstration of **HBsAg-specific T-cells**
  - proliferation assays
  - cytokine secreting cells (ELI-spot)
  - intracellular cytokines (FACS-analysis)

- demonstration of **anti-HBs-secreting B-cells** in vitro (ELI-spot)
Demonstration of memory T-and B-cells in 15 vaccinated individuals after loss of anti-HBs

Bauer, Jilg, Vaccine 2006;24:572-7
HBsAg-specific T-memory/-effector cells before and after booster vaccination

$T_M$: memory T cells
CD4+/CD45R0+

$T_E$: effector T cells
CD4+/CD45RA+

Bauer, Jilg, Vaccine 2006;24:572-7
## T-cell memory

**IFN\(\gamma\) / IL2 secreting cells before / after booster vaccination**

<table>
<thead>
<tr>
<th>Response category</th>
<th>IFN-(\gamma)</th>
<th>IL-5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before booster</td>
<td>After booster</td>
</tr>
<tr>
<td>&lt;1 SFCs/10(^6) PBMCs</td>
<td>76 (82.6)</td>
<td>63 (68.5)</td>
</tr>
<tr>
<td>&gt;1–5 SFCs/10(^6) PBMCs</td>
<td>16 (17.4)</td>
<td>13 (14.1)</td>
</tr>
<tr>
<td>&gt;5–10 SFCs/10(^6) PBMCs</td>
<td>0</td>
<td>9 (9.8)</td>
</tr>
<tr>
<td>&gt;10–100 SFCs/10(^6) PBMCs</td>
<td>0</td>
<td>5 (5.4)</td>
</tr>
<tr>
<td>&gt;100 SFCs/10(^6) PBMCs</td>
<td>0</td>
<td>2 (2.2)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of subjects.

*Lu et al. J Infect Dis 2008;197:1419-26*
Demonstration of HBsAg-specific memory T- and B- cells

- important research method, but at present not very well suited for the determination of the duration of immune memory, as the tests are
  - technically demanding, tedious and expensive
  - influenced by the need of not standardized biological reagents as HBsAg, peptides, human sera, therefore results from different laboratories hardly comparable
  - difficult to interprete, as only 5-8% of lymphocytes in the peripheral blood

- determination of „boostability“ probably more sensitive!
Summary and conclusion I
How long does memory last?

● presence of anti-HBs depends on maximal value after primary course of vaccination – in individuals vaccinated in infancy, after 10 years 50-60%, after 20 years only 20-30% still positive (more when vaccinated as adolescents?)

● ability to mount an anamnestic response („boostability“) outlasts presence of anti-HBs, will be maintained for at least 10 years in vast majority of vaccinees. Waning of boostability with time seen especially in individuals with low initial anti-HBs-titers
Summary and conclusion II

Are boosters needed?

- at least in individuals vaccinated in infancy booster doses might be considered for individual protection

- in this case, booster doses should be given as long as memory is present, i.e. after 10-15 years (e.g. in 12-14 years old, before risk of sexual transmission starts)