Strengthening immunisation systems and introduction of hepatitis B vaccine in Central and Eastern Europe and the Newly Independent States 3rd meeting, Kyiv, Ukraine, May 25-28, 2004

Duration of protection after hepatitis B vaccination: current status

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how long does protection last?
protection after Hep B vaccination

- *protection against infection* bound to anti-HBs-concentrations $\geq 10$ IU/l
  persistence depends on initial (peak) anti-HBs concentration
decrease of anti-HBs in 4 individuals after 3rd dose

Jilg et al, Lancet 1990; 335:173
percentage decrease of anti-HBs

202 healthy young adults after three doses of recombinant hepatitis B vaccine

Jilg et al, Infection 1989;17:70
kinetics of anti-HBs after hepatitis B vaccination

- very similar in every vaccinee *irrespective of the peak antibody level after the third vaccination*
- half-life of anti-HBs is *function of time*, being *very short initially* and *becoming longer with time* after last vaccination
- influenced by *disturbances to the immune system*, specific disorders (e.g. Down-Syndrome), certain drugs (e.g. antiepileptics)

how long does anti-HBs persist?
<table>
<thead>
<tr>
<th>Population</th>
<th>time after first vacc.</th>
<th>anti-HBs ≥10 IU/l (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alaskan natives (n=959)</td>
<td>10 yrs</td>
<td>76</td>
</tr>
<tr>
<td><em>Wainwright et al 1997</em></td>
<td></td>
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<tr>
<td>Taiwanese children (n=539)</td>
<td>10 yrs</td>
<td>85</td>
</tr>
<tr>
<td><em>Wu et al 1999</em></td>
<td></td>
<td></td>
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<tr>
<td>Italian children (n=223)</td>
<td>11-14 yrs</td>
<td>75</td>
</tr>
<tr>
<td><em>Mele et al 1999</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese children (n=52)</td>
<td>15 yrs</td>
<td>50</td>
</tr>
<tr>
<td><em>Liao et al 1999</em></td>
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</tbody>
</table>
in 10 - 50% of all successfully vaccinated individuals the anti-HBs concentration decreases below 10 IU/l within 10 years as protection against infection is bound to anti HBs concentrations above 10 IU/l these individuals are again susceptible to infection
break-through infections
10-year follow-up after Hep B vaccination in high-risk infants

972 Taiwanese children of HBsAg-positive mothers
→ HBIG at birth + vaccine at month 0, 1, 6
4 different doses of plasma-derived vaccine tested
(2.5 / 5 / 10 / 20 µg)

month 12:
805 children anti-HBs pos., HBsAg and anti-HBc neg.

after 10 years:
539 available for analysis

Wu et al JID 1999; 179: 1319
anti-HBs 10 years after HB vaccination according to anti-HBs level at 12 months (Wu et al 1999)

Wu et al JID 1999; 179: 1319
infection rate 10 yrs after HB-vaccination according to anti-HBs level at 12 months (Wu et al 1999)

Wu et al JID 1999; 179: 1319
break-through infections in successfully vaccinated individuals

<table>
<thead>
<tr>
<th>population</th>
<th>time after 1st vaccination</th>
<th>n (%) positive for anti-HBc</th>
<th>HBsAg</th>
</tr>
</thead>
<tbody>
<tr>
<td>homosex. men (n=634)</td>
<td>7-9 yrs</td>
<td>46 (7)*</td>
<td>2 (0.3)**</td>
</tr>
<tr>
<td>Hadler et al 1991</td>
<td></td>
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</tr>
<tr>
<td>eskimos in Alasca (n=1630)</td>
<td>10 yrs</td>
<td>13 (0.8)*</td>
<td>0</td>
</tr>
<tr>
<td>Wainwright et al 1997</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>children in Taiwan (n=805)</td>
<td>10 yrs</td>
<td>109 (14)*</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Wu et al 1999</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>children in Gambia (n=731)</td>
<td>14 yrs</td>
<td>79 (11)*</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Whittle et al 2002</td>
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</tbody>
</table>

* clinically silent ** HIV-positive
break-through infections after successful Hep B vaccination

- risk of hepatitis B infection is *inversely related to the maximal antibody response* to vaccine
- risk of infection *increases with declining anti-HBs*
- vast majority of infections in successfully vaccinated individuals are *clinically silent*
- protection against clinically important disease *outlasts the presence of detectable antibodies*

Hadler et al, NEJM 1986; 315: 209; Wu et al JID 1999; 179: 1319

Wainwright et al, JID 1997; 175: 674; Whittle et al BMJ 2002; 325: 569
protection after Hep B vaccination

- Protection against infection (anti-HBs > 10 IU/l)
- Protection against disease (immunologic memory)
- Protection limit

Diagram shows the decrease in degree of protection against infection and disease over time after vaccination.
protection against disease due to presence of immunologic memory

- vaccination induces B- and T-memory cells
  - rapid proliferation after contact with antigen, production of cytokines and specific antibodies („anamnestic response“)

- in case of infection the anamnestic response prevents its further spread, downregulates viral replication and finally eliminates the virus
  - prevents disease and chronic infection
how can we prove the presence of an immunologic memory?
methods to demonstrate immunologic memory after hepatitis B vaccination

- **anamnestic anti-HBs response** after revaccination
anamnestic response 17 years after HepB vacc.

within 8 days anti-HBs increases from 80 IU/l to 25 000 IU/l

>300 fold increase in anti-HBs

mean increase of 130 IU per hour or 2 IU per min
### anamnestic response to revaccination of 203 individuals ≥10 years after first Hep B-vaccination

<table>
<thead>
<tr>
<th>Group</th>
<th>Time after first vaccination</th>
<th>Anamnestic response at (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italian children (n = 147*)</td>
<td>10 years</td>
<td>96</td>
</tr>
<tr>
<td>Da Villa et al 1996</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italian children (n = 17*)</td>
<td>10 years</td>
<td>100</td>
</tr>
<tr>
<td>Resti et al 1997</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US children (n = 14)</td>
<td>12 years</td>
<td>100</td>
</tr>
<tr>
<td>West et al 1994</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US children/adults (n = 25**)</td>
<td>13 years</td>
<td>100</td>
</tr>
<tr>
<td>Watson et al 2001</td>
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</tbody>
</table>

* all anti-HBs neg.  
** 5 anti-HBs neg.
anamnestic response to booster doses with 2.5 or 10 µg HBsAg in previously immunized HCW (n=59)

Baseline anti-HBs: <10 IU/l

Baseline anti-HBs: 10-50 IU/l

Williams et al. Vaccine 2001;19:4081
revaccination of 131 individuals 2-6 years after basic immunization

anamnestic response to revaccination is correlated to primary response but on a higher level

Jilg et al in Coursaget, Progress in Hepatitis B immunization 1990;p 419
anamnestic response to administration of non-absorbed HBsAg in responders to HB vacc. after loss of anti-HBs

Dentico et al Vaccine 2002;20:3725
anamnestic anti-HBs response after revaccination

- present in >95% of vaccinees for at least 10 years after basic immunization
- correlated with primary response
- strength of response depends on antigen dose
methods to demonstrate immunologic memory after hepatitis B vaccination

- **anamnestic anti-HBs response** after revaccination
- demonstration of **anti-HBs-secreting B-cells** in vitro (ELI-spot)
in vitro anti-HBs production by B cells after vaccination against hepatitis B (n=51)

van Hattum et al. in Hollinger, Viral Hepatitis and Liver disease; 1990; p 774
methods to demonstrate immunologic memory after hepatitis B vaccination

- *anamnestic anti-HBs response* after revaccination
- demonstration of *anti-HBs-secreting B-cells* in vitro (ELI-spot)
- demonstration of *HBsAg-specific T-cells*
  - proliferation assays
  - cytokine secreting cells (ELI-spot)
  - intracellular cytokines (FACS-analysis)
T cell proliferative response to HBsAg in 31 HCW vaccinated 3-12 years before against hepatitis B
T cell proliferation positive individuals

![Graph showing T cell proliferation positive percentage by anti-HBs-titer at analysis.](image)

T cell proliferative response to HBsAg in 31 HCW vaccinated 3-12 years before against hepatitis B
T cell proliferation: mean counts per minute

Wang et al  World J Gastroenterol 2004;10:260
demonstration of T-and B-memory-cells in 15 vaccinated individuals after disappearance of anti-HBs

- preparation of CD4/CD45RO-positive T cells (T memory cells) and B-cells from peripheral blood
- determination of IFN-γ-secretion (T cells) and anti-HBs-production (B cells + T cells) using ELI-spot-assays after stimulation with HBsAg
demonstration of T- and B-memory-cells in 15 vaccinated individuals after disappearance of anti-HBs
demonstration of anamnestic response to revaccination in 15 vaccinees after disappearance of anti-HBs
Immunologic memory after Hep B vaccination

- presence of HBsAg specific T- and B-cell memory in successfully vaccinated individuals documented for at least 10 years
- primary immune response seems to be a good predictor for the quality of immunologic memory

* Banatvala et al, Vaccine 2001: 19: 877
**Hepatitis B vaccination - how long does protection last?**


“Memory seems to last for at least 15 years in immunocompetent individuals. To date there are no data to support the need for booster doses of HB vaccine in immunocompetent individuals who have responded to a primary course.”
Hepatitis B vaccination - how long does protection last?

however....

question about long term protection can finally only be answered by future long term follow-up studies looking for break-through infections and investigating the humoral and cellular basis for immunologic memory
difficulties in determining the length of protection

- follow-up studies with an observation time of >>10 years still rare
- number of vaccinees available for follow up decreases with time - data become less significant
- in low endemicity countries risk of hepatitis B very low - clinically significant break-through-infections (as sign of vaning immunity) will be rare
- immunologic memory so far mainly demonstrated by anamnestic response to revaccination - reliable and sensitive cellular tests only seldom used