Influencing factors on long-term protection of hepatitis B after infant vaccination

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The Gambia: Keneba-Manduar & GHIS cohorts
Long term protection

- Long term: high-risk periods
  - Early childhood (horizontal transmission)
  - Adolescence & Adulthood (sexual transmission)
  - Occupational exposure
  - Travel

- Protection
  - Response to vaccination (sAb)
  - (Transient) infection (cAb)
  - Chronic infection (sAg/eAg, DNA)
  - Clinical outcomes (cirrhosis, HCC)
Long term protection

- Response to vaccination (sAb):
  - Vaccin: type of vaccin, route of administration, number of doses, amount of Ag, adjuvant, interaction other vaccines, other infections
  - Vaccinee: age, sex, BMI, immunocompetence, smoking, genetics
  - Virus: genotype, mutant
  - Maternal status: VL, eAg

- Outcome:
  - Seroconversion y/n ($\geq 10iU/L$)
  - Peak sAb titre
Long term protection

- Response to vaccination (sAb)
  - type of vaccin, route of administration, number of doses, amount of Ag, adjuvant, interaction other vaccines, other infections
  - age, sex, BMI, immunocompetence, smoking, genetics
  - genotype, mutant
  - VL, eAg
- (Transient) infection (cAb)
  - Peak sAb
  - Time since last dose
- Chronic infection (sAg/eAg, DNA)
- Clinical outcomes (cirrhosis, HCC)
Probability of remaining uninfected (anti-HBcore neg) by time since infant vaccination by peak anti-HBs response

van der Sande et al, JID 2006
Vaccine efficacy against anti-HBcore infection by age by peak bleed anti-HBs category among primary responders

van der Sande et al, JID 2007

van der Sande et al, JID 2006
Long term protection

- Response to vaccination (sAb):
  - type of vaccin, route of administration, number of doses, amount of Ag, adjuvant, interaction other vaccines, other infections
  - age, sex, BMI, immunocompetence, smoking, genetics
  - genotype, mutant
  - VL, eAg
- (Transient) infection (cAb)
  - Peak sAb
  - Time since last dose
- Chronic infection (sAg/eAg, DNA)
  - Age at time of acquisition
- Clinical outcomes (cirrhosis, HCC)
Long term protection

- (peak)sAb:
  - >95% primary response (≥100 U/L)
  - decline over time:
    - 1/3-2/3 detectable sAb after 15-20 years
    - GMT ↓
  - Environment: natural boosting due to exposure
  - Primary responders 2x as likely to have anamnestic response when boosted
- (Transient) infection (cAb)
  - 5-20% BTI after 15-20 years
- Chronic infection (sAg/eAg, DNA)
  - <1% after 15-20 years
- Clinical outcomes (cirrhosis, HCC)
  - ?
Number of doses

- HBV vaccination combined in infant hexavalent vaccination
  - Move towards 2+1 rather than 3+1
- Immunological theory and mathematical modelling suggest 2 (or even 1 dose) could offer similar protection:
  - If memory develops indirectly through effector cell activation: more doses would confer better protection
  - If memory develops following clonal expansion, independent of number of doses: no benefit from additional doses
- Several studies among adults and adolescents have shown similar long-term protection after 2 (or 1 dose) as with 3 doses
- Non-responders = slow responders?
Do we need 3 doses? Van der Sande et al PLoS One 2007

- Observational study within Keneba Manduar open cohort
- All infants born 1984 onwards were scheduled to receive at least 3 doses (1-2-4 months of age), but some only received 2 doses
  - Travel, migration, death
- At 11 months of age peak antibody levels measured
- Different vaccins, different schedules in use since 1984
- Follow up every 4 years (sAb, cAb)
### Do we need 3 doses?  
**Van der Sande et al PLoS One 2007**

<table>
<thead>
<tr>
<th></th>
<th>2 doses</th>
<th>3 doses</th>
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<tbody>
<tr>
<td>n</td>
<td>89</td>
<td>575</td>
<td></td>
</tr>
<tr>
<td>Median age (wks) 1st dose</td>
<td>8.3</td>
<td>4.1</td>
<td>0.01</td>
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<tr>
<td>Median age (wks) last dose</td>
<td>16.4</td>
<td>16.9</td>
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<td>GMT peak sAb</td>
<td>158</td>
<td>491</td>
<td>0.03</td>
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<tr>
<td>Median age (yrs) follow up</td>
<td>7.0</td>
<td>4.3</td>
<td>0.02</td>
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<td>Undetectable sAb (%) follow up</td>
<td>32</td>
<td>33</td>
<td>0.4</td>
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<tr>
<td>GMT follow up sAb</td>
<td>175</td>
<td>102</td>
<td>0.3</td>
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Do we need 3 doses?  

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<table>
<thead>
<tr>
<th></th>
<th>Infected (cAb)</th>
<th>VE infection</th>
<th>Chronic infection (sAg)</th>
<th>VE chronic</th>
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<tbody>
<tr>
<td>prevaccination</td>
<td>61%</td>
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<td>20%</td>
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<tr>
<td>1 dose</td>
<td>19%</td>
<td>69%</td>
<td>0%</td>
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<tr>
<td>2 dose</td>
<td>8%</td>
<td>86%</td>
<td>1.6%</td>
<td>92%</td>
</tr>
<tr>
<td>3 dose</td>
<td>7%</td>
<td>88%</td>
<td>1.7%</td>
<td>92%</td>
</tr>
<tr>
<td>4 dose</td>
<td>9%</td>
<td>85%</td>
<td>0.9%</td>
<td>86%</td>
</tr>
</tbody>
</table>
Discussion

- sAb wanes, but boosting mostly produces rapid response
- Risk of infection increases with time since vaccination, chronic infections (still) rare
- 2 doses might be as effective as 3 doses to achieve primary response /protection against infection
- How much does lasting protection depend on ongoing natural boosting?
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