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

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The Gambia: Keneba-Manduar & GHIS cohorts

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A4

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

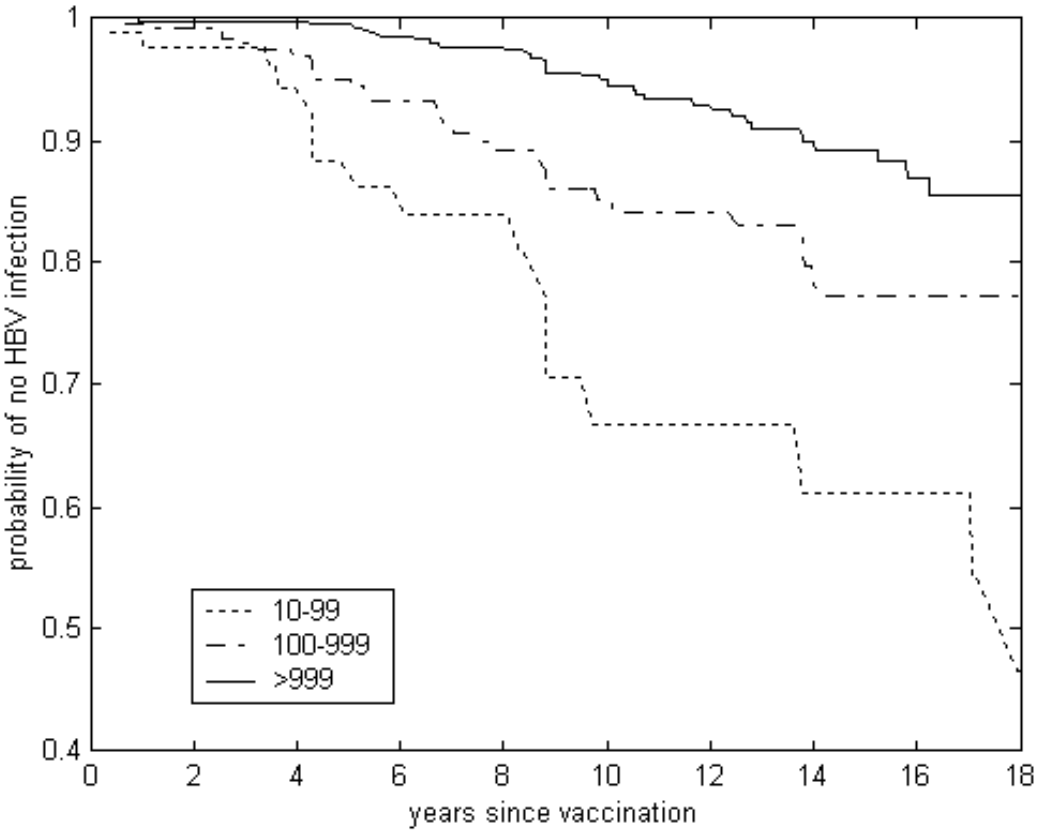
- Response to vaccination (sAb) :
  - Vaccin: type of vaccin, route of administration, number of doses, amount of Ag, adjuvant, interaction other vaccines, other infections
  - Vaccinee: age, sex, BMI, immunocompetence, smoking, genetics
  - Virus: genotype, mutant
  - Maternal status: VL, eAg

- Outcome:
  - Seroconversion y/n (≥10iU/L)
  - Peak sAb titre

Long term protection

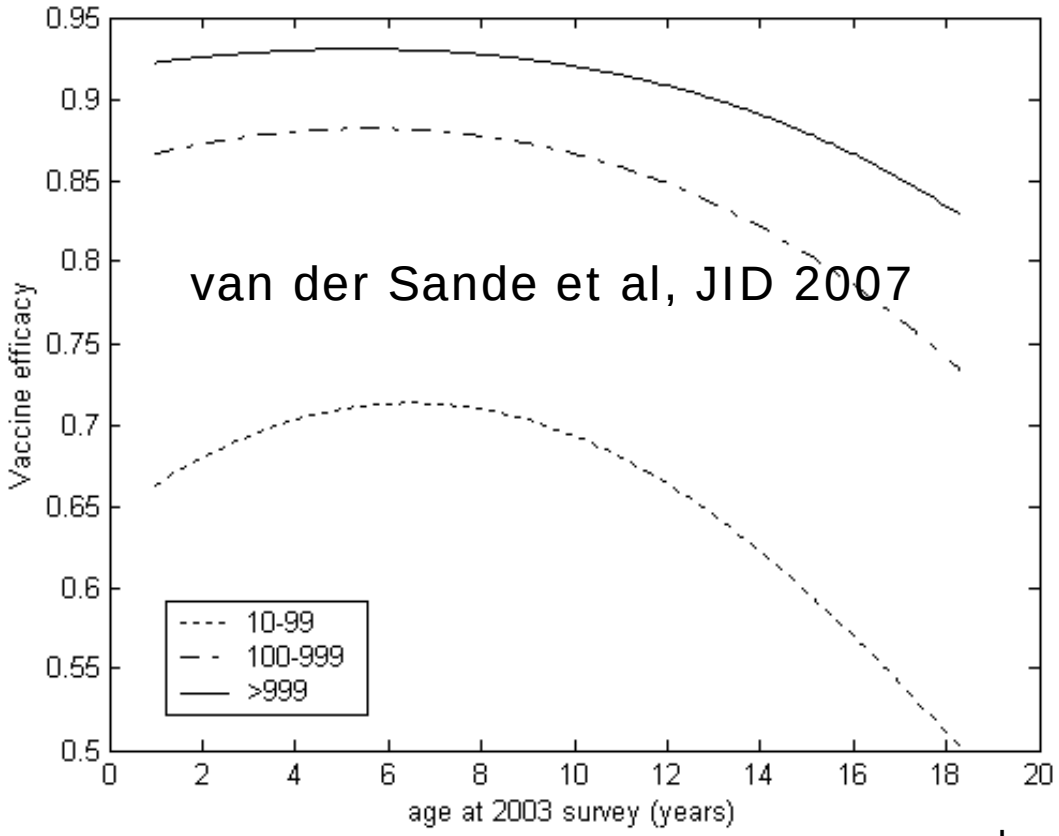
- Response to vaccination (sAb)
  - type of vaccin, route of administration, number of doses, amount of Ag, adjuvant, interaction other vaccines, other infections
  - age, sex, BMI, immunocompetence, smoking, genetics
  - genotype, mutant
  - VL, eAg
- **(Transient) infection (cAb)**
  - **Peak sAb**
  - **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 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 (≥10iU/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*

	2 doses	3 doses	p
n	89	575	
Median age (wks) 1st dose	**8.3**	**4.1**	**0.01**
Median age (wks) last dose	16.4	16.9	0.3
GMT peak sAb	**158**	**491**	**0.03**
Median age (yrs) follow up	**7.0**	**4.3**	**0.02**
Undetectable sAb (%) follow up	32	33	0.4
GMT follow up sAb	175	102	0.3

Do we need 3 doses?

Van der Sande *et al PLoS One 2007*

	Infected (cAb)	VE infection	Chronic infection (sAg)	VE chronic
prevaccination	61%		20%	
1 dose	19%	69%	0%	
2 dose	8%	86%	1.6%	92%
3 dose	7%	88%	1.7%	92%
4 dose	9%	85%	0.9%	86%

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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