ALTERNATIVE VACCINATION STRATEGIES FOR PRIMARY NON-RESPONDERS ON HEPATITIS B VACCINATION

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**Disclosure of speaker’s interests**

**Investigator initiated study**

<table>
<thead>
<tr>
<th>(Potential) conflict of interest</th>
<th>See below</th>
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</thead>
<tbody>
<tr>
<td>Potentially relevant company relationships in connection with event</td>
<td>none</td>
</tr>
<tr>
<td>• Sponsorship or research funding</td>
<td>• this study was supported by the National Institute of Public Health and the Environment [RIVM programmabudget]</td>
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<tr>
<td>• Fee or other (financial) payment</td>
<td>• vaccines used in this study were provided by GlaxoSmithKline and Merck Sharp &amp; Dome</td>
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<td>• Shareholder</td>
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</table>
Background

5 – 30%\textsuperscript{1} healthy adults fail to develop a protective anti-Hbs titre non-responder: anti-HBs titre < 10 IU/l

\textsuperscript{1}Vermeiren et al. Journal of Clinical Virology 2013
Strategies to improve response

- Additional doses of antigen HBsAg
- Higher dose of antigen HBsAg
- alternative routes of administration (intradermal)
- Different adjuvants
- Different antigens
- HBsAg combined with other antigens
- HBsAg combined with other immunostimulatory substances
Strategies to improve response: additional doses

- ‘Proof of principle’ trial
- N=12 healthcare workers, anti-HBs < 10 IU/l
- Mean age 35 years
- Further booster doses until the threshold has been reached

- mean 7.8 (range 4-11) doses ≥ 10 IU/l
- mean 10.3 (range 8-14) doses ≥ 100 IU/l
Strategies to improve response

- Additional doses of antigen HBsAg
- Higher dose of antigen HBsAg
- alternative routes of administration (intradermal)
- Different adjuvants
- Different antigens
- HBsAg combined with other antigens
- HBsAg combined with other immunostimulatory substances
Strategies to improve response:

- Management options in healthy non-responding adults
- Comparing different antigen doses, route of administration and additional doses
- 16 studies included in the systematic review and meta-analysis

Pooled seroconversion rates by management option and number of additional doses.

<table>
<thead>
<tr>
<th>Management option</th>
<th>Number of studies</th>
<th>Total (N)</th>
<th>Seroconversion rate % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1st additional dose</td>
</tr>
<tr>
<td>IM-20</td>
<td>9</td>
<td>833</td>
<td>62% (41–83%)</td>
</tr>
<tr>
<td>IM-40</td>
<td>3</td>
<td>161</td>
<td>60% (23–97%)</td>
</tr>
<tr>
<td>ID-5</td>
<td>3</td>
<td>50</td>
<td>54% (39–69%)</td>
</tr>
<tr>
<td>ID-20</td>
<td>1</td>
<td>23</td>
<td>61% (47–75%)</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>1067</td>
<td></td>
</tr>
</tbody>
</table>

- Heterogeneity $I^2 > 90$
- Classification by antigen dose
- Need for more evidence-based approaches (RCT)

David et al. Vaccine 2015
Strategies to improve response

- Additional doses of antigen HBsAg
- Higher dose of antigen HBsAg
- Alternative routes of administration (intradermal)
- **Different adjuvants**
- Different antigens
- HBsAg combined with other antigens
- HBsAg combined with other immunostimulatory substances
Strategies to improve response: different adjuvants

Registered vaccine
- AS04 (MPL*+ alum**) TLR-4 (Fendrix)
- immunostimulatory sequences TLR-9 HepB-CpG (Heplisav-B)

Pre-clinical/phase 1
- δ inulin (Advax)
- AI20: 20 µg recombinant human IL-2 + alum (experimental vaccine)

* MPL: monophosphoryl lipid A
** Alum: aluminium salt-based adjuvants
# Strategies to improve response: different adjuvants

<table>
<thead>
<tr>
<th>Reference</th>
<th>Vaccine 1</th>
<th>Vaccine 2</th>
<th>Inclusion criteria</th>
<th>Schedule</th>
<th>Participants</th>
<th>Response ≥ 10 IU/l</th>
<th>Response ≥ 100 IU/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002, Jacques et al, Vaccine</td>
<td>Fendrix 40 µg</td>
<td>Engerix-B 20 µg</td>
<td>≥ 4 doses recombinant HB vaccine</td>
<td>3-IM (0,1,5)</td>
<td>Healthcare NR 1: N=58 2: N=57</td>
<td>1: 98%*</td>
<td>1: 90%</td>
</tr>
<tr>
<td>2013, Halperin et al, Human Vac &amp; Immunotherapeutics</td>
<td>HBsAg-1018‡ 20µg</td>
<td>Engerix-B 20 µg</td>
<td>3 doses recombinant HB vaccine</td>
<td>1-IM</td>
<td>Healthy adults NR 1: N=19 2: N 16</td>
<td>1 53%</td>
<td>1:21%</td>
</tr>
</tbody>
</table>

‡ HepB-CpG (Heplisav)
Strategies to improve response: different adjuvants

- Phase 1, open-label in true non-responders
- Aggregated IL-2 to alum

Koc et al. 2018 *J Viral Hepat.*
Strategies to improve response

- Additional doses of antigen HBsAg
- Higher doses of antigen HBsAg
- alternative routes of administration (intradermal)
- Different adjuvants
- Different antigens
- HBsAg combined with other antigens
- HBsAg combined with other immunostimulatory substances
### Strategies to improve response: different antigens

S, PreS1 and PreS2 antigens: third generation PreS/S vaccine (Sci-B-Vac)

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<tr>
<th>Reference</th>
<th>Vaccine 1</th>
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<th>Schedule</th>
<th>Participants</th>
<th>Response ≥ 10 IU/l</th>
<th>Response ≥ 100 IU/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006, Rendi-Wagner et al, Vaccine</td>
<td>PreS1/PreS2/S vaccine</td>
<td>Engerix-B20</td>
<td>≥4 recombinant vaccine &lt;10 IU/l (NR) &lt;100 IU/l (LR)</td>
<td>1-2 IM (0-3)</td>
<td>1:226</td>
<td>1:82%*</td>
<td>1:36%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2:108</td>
<td></td>
<td>2:49%</td>
<td>2:21%</td>
</tr>
<tr>
<td>2014, Krawczyk et al, Vaccine</td>
<td>PreS1/PreS2/S vaccine</td>
<td>N.A.</td>
<td>≥3 conventional vaccine &lt;10 IU/l (NR) &lt;100 IU/l (LR)</td>
<td>3 IM (0-1-6)</td>
<td>1a: 15 NR</td>
<td>1a:93%</td>
<td>1a:80%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1b: 6: LR</td>
<td></td>
<td>1b:100%</td>
<td></td>
</tr>
</tbody>
</table>

NR: non-responder, anti-HBs < 10IU/l  
LW: low-responder, anti-HBs < 100 IU/l
Strategies to improve response: HBsAg combined with other antigens/immunostimulatory substances

### HBsAg combined with hepatitis A antigen

<table>
<thead>
<tr>
<th>Reference</th>
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<th>Inclusion criteria</th>
<th>Schedule</th>
<th>Participants</th>
<th>Response ≥ 10 IU/l</th>
<th>Response ≥ 100 IU/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardell et al. 2008 J Infect Dis</td>
<td>Twinrix 2 ml 40 µg HBsAg</td>
<td>N.A.</td>
<td>4 ID Engerix</td>
<td>3 IM</td>
<td>Healthcare NR N 44</td>
<td>95%</td>
<td>80%</td>
</tr>
</tbody>
</table>

### GM-CSF

<table>
<thead>
<tr>
<th>Reference</th>
<th>Vaccine 1</th>
<th>Vaccine 2</th>
<th>Inclusion criteria</th>
<th>Schedule</th>
<th>Participant s</th>
<th>Response ≥ 10 IU/l</th>
<th>Response ≥ 100 IU/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010, Lin C et al, J Infect.</td>
<td>Engerix-B + GM-CSF 150 µg</td>
<td>Engerix-B 20</td>
<td>≥ 3 Engerix-B</td>
<td>3 IM (0-1-6)</td>
<td>general population, NR 1: n=34 2: n=33</td>
<td>1: 82%</td>
<td>1: 65%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2: 75%</td>
<td>2: 39%</td>
</tr>
</tbody>
</table>
Aim of the study

To determine the immunogenicity of three different hepatitis B revaccination series:

- HBVaxPro-40 alum, higher antigen dose (40 μg)
- Fendrix MPL + alum (20 μg)
- Twinrix alum + HAV adjuvant (20 μg)

Compared to a standard revaccination series of three Engerix-B (20 μg) or HBVaxPro-10 (10 μg)
Outcomes

Primary outcome:
Seroconversion rate; percentage of participants with a protective anti-HBs titre \( \geq 10 \) IU/l

Secondary outcome:
• Adverse events (7 days) after vaccination
• Seroconversion rate stratified by baseline titre (< 1 IU/l vs > 1-9 IU/l)
Study design / population

parallel-group, multi-centre, randomised, controlled trial
Allocation ratio of 1:1:1:1, stratified by site and using a fixed block size of 4

HBV non-responders: anti-HBs titre < 10 IU/l after three HBV vaccinations (0,1, and 6)

Inclusion criteria
- age: 18-80 years
- immunocompetent
- no pregnancy
- no mixed primary schedule
- no markers of previous or current HBV infection
Data collection

- Hepatitis B vaccination
- Blood sample
- Side effects diary
Outcome analysis

Anti-HBs measurement:

- four blood samples
- stored until study completion at minus 20 °
- Central laboratory, Leiden UMC
- ARCHITECT assay (Abbott Laboratories)

• Intention-to-vaccinate (ITV) analysis
• Last observation carried forward for missing variables
Approximately 640 screened for eligibility

25% declined to participate*

480 randomised

- 114 assigned HBVaxPro-40
  - 109 completed 3rd vaccination

- 118 assigned Twinrix
  - 114 completed 3rd vaccination

- 124 assigned Fendrix
  - 119 completed 3rd vaccination

- 124 assigned control-group
  - 117 completed 3rd vaccination

* Based on centres responsible for 1/3 of inclusion
Conclusion & recommendations

Many strategies available to overcome non-responsiveness

Revaccination with Fendrix or HBVaxPro-40 resulted in significantly better seroconversion rates and titre heights and should be considered over standard revaccination schemes.

Fendrix showed some higher reactogenicity compared to the other vaccines.

Role of the primary antibody titre between the ‘zero-responder’ and ‘poor-responder’ group should be studied in future research.
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• LUMC
• UMCU