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

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Disclosure of speaker's interests

Investigator initiated study

(Potential) conflict of interest	See below
Potentially relevant company relationships in connection with event	none
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• Fee or other (financial) payment • Shareholder • Other relationship, i.e. …	• none • none • none

Background

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

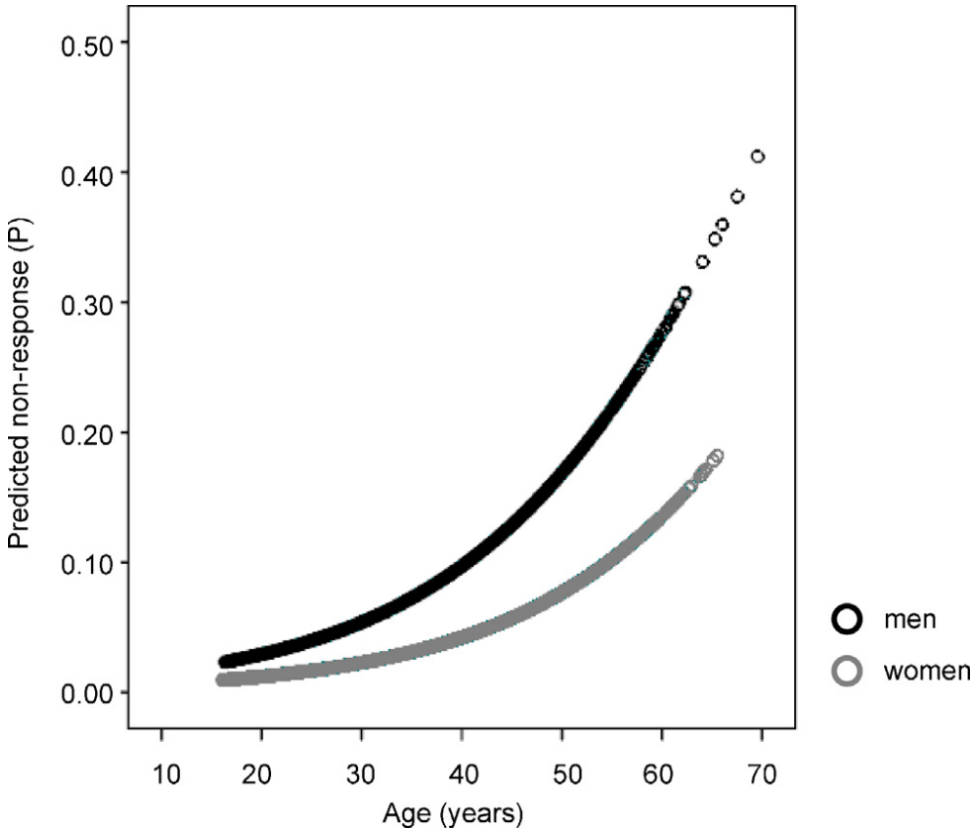

Figure: Predicted non-response to hepatitis B vaccination

[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

Heininger et al. Human Vaccines, 2010

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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.

Management option	Number of studies	Total (*N*)	Seroconversion rate % (95% CI)			
			1st additional dose	2nd additional dose	3rd additional dose	4th additional dose
IM-20	9	833	62% (41–83%)	68% (61–100%)	81% (61–100%)	Not available
IM-40	3	161	60% (23–97%)	50% (33–67%)	53% (36–70%)	Not available
ID-5	3	50	54% (39–69%)	77% (65–89%)	85% (75–95%)	89% (80–98%)
ID-20	1	23	61% (47–75%)	90% (78–100%)	Not available	Not available
Total	16	1067				

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

David et al. Vaccine 2015

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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

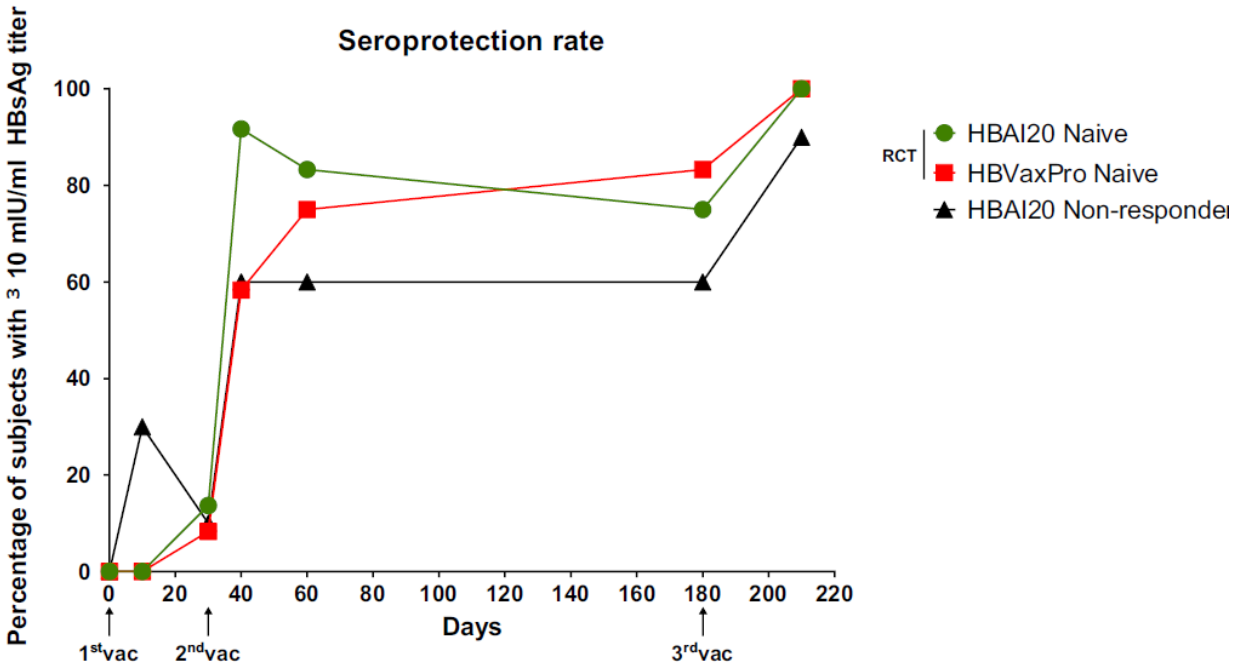
Strategies to improve response: different adjuvants

Reference	Vaccine 1	Vaccine 2	Inclusion criteria	Schedule	Participants	Response ≥ 10 IU/l	Response ≥ 100 IU/l
2002, Jacques et al, Vaccine	Fendrix 40 µg	Engerix-B 20 µg	≥ 4 doses recombinant HB vaccine	3-IM (0,1,5)	Healthcare NR 1: N=58 2: N=57	1: 98%* 2:68%	1: 90% 2: 46%
2013, Halperin et al, Human Vac & Immunothera-peutics	HBsAg-1018‡ 20µg	Engerix-B 20 µg	3 doses recombinant HB vaccine	1-IM	Healthy adults NR 1: N=19 2: N 16	1 53% 2 38%	1:21% 2:13%

‡ 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.*

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Strategies to improve response: different antigens

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

Reference	Vaccine 1	Vaccine 2	Inclusion criteria	Schedule	Participants	Response ≥ 10 IU/l	Response ≥ 100 IU/l
2006, Rendi-Wagner et al, Vaccine	PreS1/PreS2 /S vaccine	Engerix-B 20	≥4 recombinant vaccine <10 IU/l (NR) (<100 IU/l (LR)	1-2 IM (0-3)	1:226 2:108	1:82%* 2:49%	1:36%* 2:21%
2014, Krawczyk et al, Vaccine	PreS1/PreS2 /S vaccine	N.A.	≥3 conventional vaccine <10 IU/l (NR) <100 IU/l (LR)	3 IM (0-1-6)	1a: 15 NR 1b: 6: LR	1a:93%	1a:80% 1b:100%

NR: non-responder, anti-HBs < 10IU/l
LW: low-responder, anti-HBs < 100 IU/l

Strategies to improve respons: HBsAg combined with other antigens/ immunostimulatory substances

HBsAg combined with hepatitis A antigen

reference	Vaccine 1	Vaccine 2	Inclusion criteria	Schedule	Participants	Response ≥ 10 IU/l	Response ≥ 100 IU/l
Cardell et al. 2008 J Infect Dis	Twinrix 2 ml 40 µg HBsAg	N.A.	4 ID Engerix	3 IM	Healthcare NR N 44	95%	80%

GM-CSF

Reference	Vaccine 1	Vaccine 2	Inclusion criteria	Schedule	Participants	Response ≥ 10 IU/l	Response ≥ 100 IU/l
2010, Lin C et al, J Infect.	Engerix-B + GM-CSF 150 µg	Engerix-B 20	≥ 3 Engerix-B	3 IM (0-1-6)	general population, NR 1: n=34 2: n= 33	1: 82% 2: 75%	1: 65%* 2: 39%

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 ≥ 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

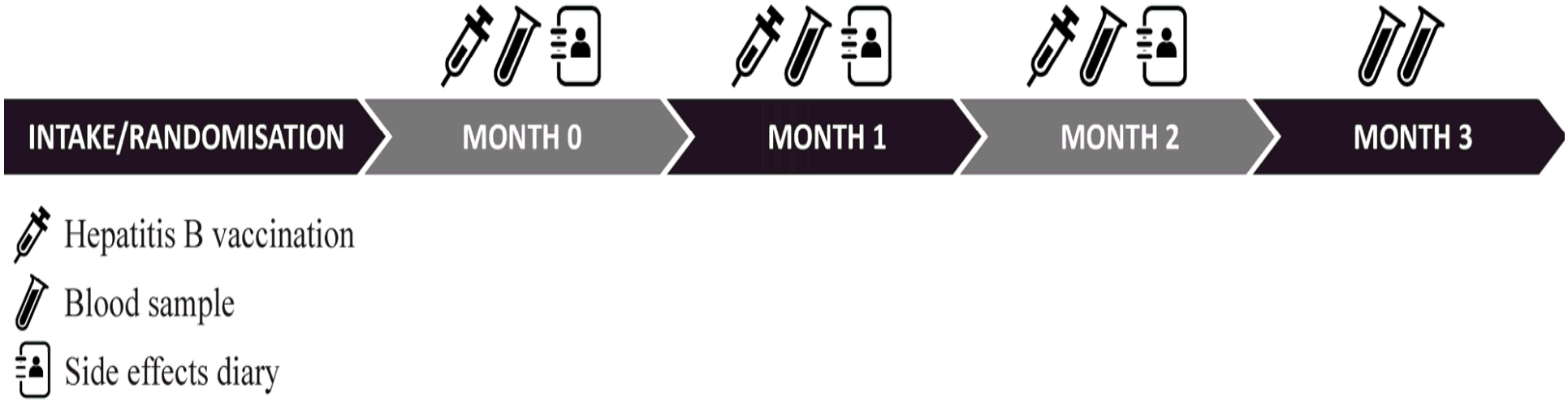
Allocation ratio of 1:1:1:1, stratified by site and using a fixed block size of 4

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

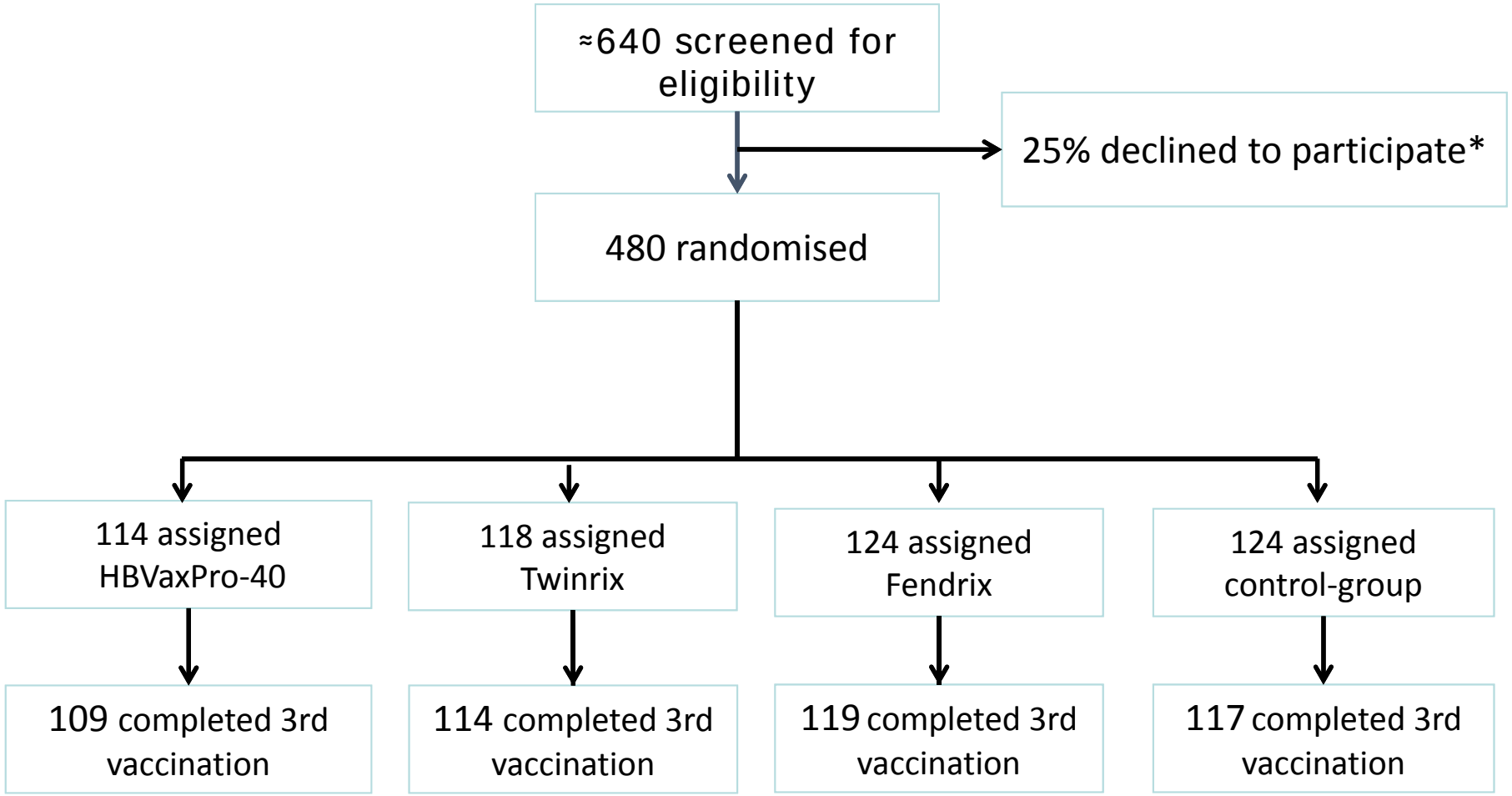


Outcome analysis

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



* 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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