“New “ Hepatitis B Vaccines for Non-responders to Conventional Vaccination

Daniel Shouval
Liver Unit
Hadassah-Hebrew University Hospital
Jerusalem, Israel

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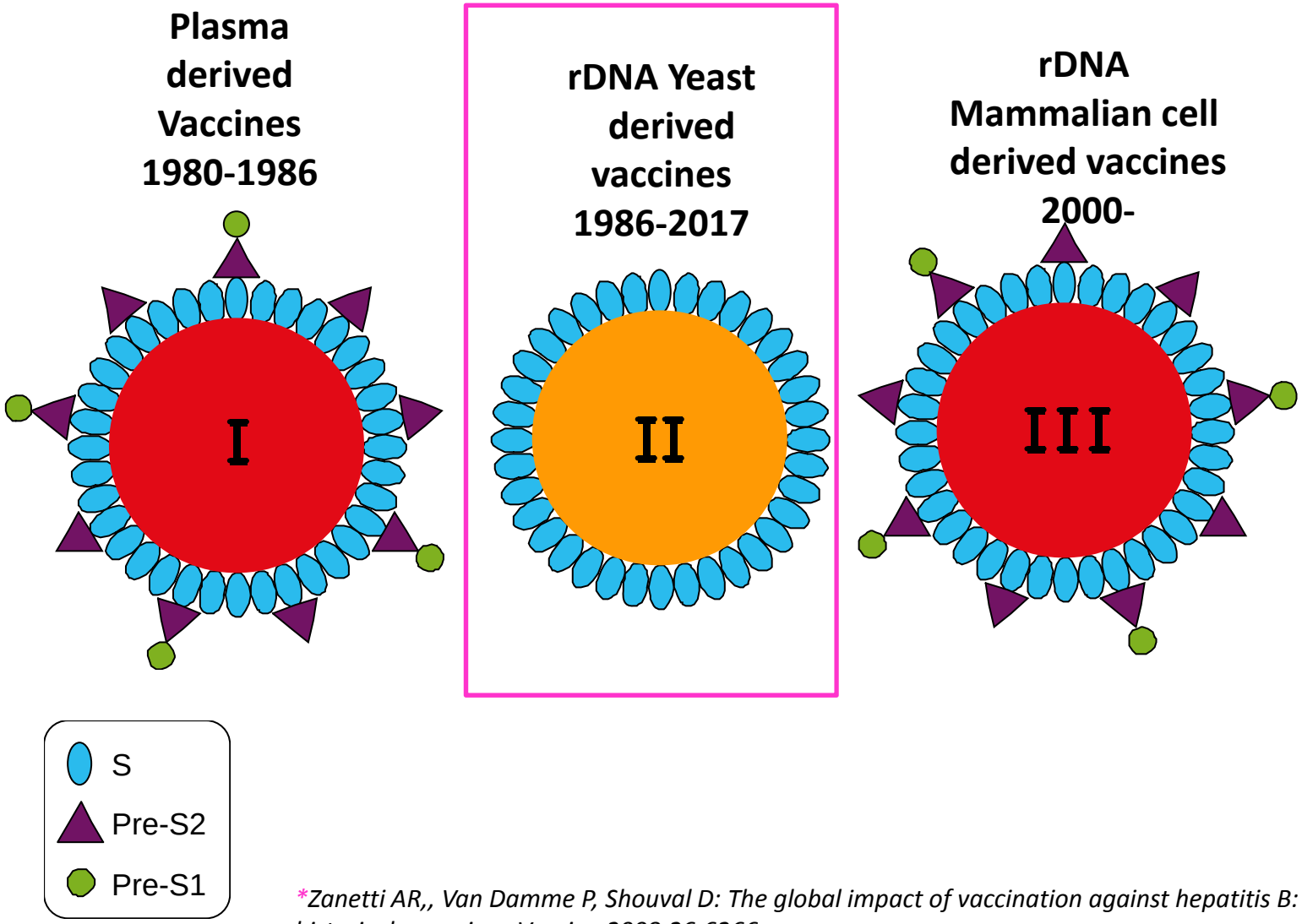
Disclosure

- Speaking engagements - GSK
- Consultant -VBI

What is the rational for developing new HBV vaccines with enhanced immunogenicity?

- Non–response to conventional HBV vaccines in populations at risk
- Low compliance with the 3 dose regimen of conventional HBV vaccines
- Faster induction of immunity to HBV after the first/second dose in defined populations
- Transition to a safe, affordable, life-long immunogenic two or even single dose immunization stimulating persistent CD4&CD8 responses
- Emerging evidence of waning of post vaccination immune memory 20 years post primary immunization
- Possible protection against HBV envelope mutant(s)
- Hypothethical: Blocking the NTCP receptor in HBV carriers

Three generations of HBV vaccines



*Zanetti AR,, Van Damme P, Shouval D: The global impact of vaccination against hepatitis B: A historical over view. Vaccine 2008;26:6266

History of of HBV vaccines*

I. 1981-1982 : Plasma derived vaccines

II. **1986 : Recombinant HBV DNA vaccine expressed in yeasts**

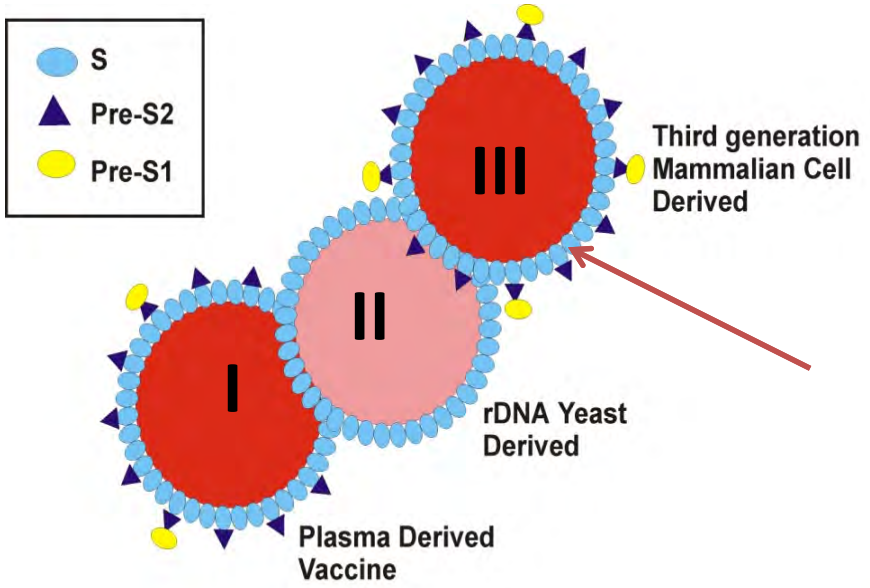
III. 1988 : Recombinant Pre-S/S vaccines expressed in mammalian cells

IV. Recombinant HBV vaccines with unique adjuvants:

-ASO4 (exp)

-CpG (licensed in the US)

-MF59 (exp)



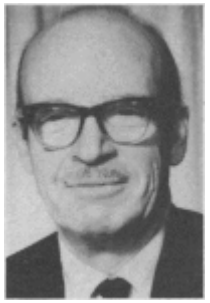
V. **Other experimental HBV vaccines :**

- DNA vaccines
- HBsAg-Anti-HBs Immune complex vaccine (IC)
- Nasal vaccines HBsAg +/- HBcAg :
  - #Chitosan Nanoparticle/DNA Complexes (non-viral transfection)
  - # CIGB, Havana, Cuba
- Recombinant HBsAg expressed in plants
- Therapeutic vaccines

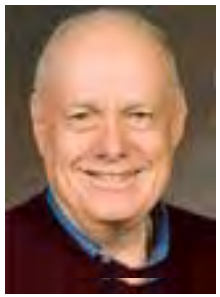
- Zanetti AR,, Van Damme P, Shouval D: The global impact of vaccination against hepatitis B: A historical over view. Vaccine 2008;6:6266,
- (No author) -A Two-Dose Hepatitis B Vaccine for Adults (Heplisav-B). JAMA 2018;319:822.
- Michel ML[1], Bourgine M, Fontaine H, Pol S .Therapeutic vaccines in treating chronic hepatitis B: the end of the beginning or the beginning of the end? Med Microbiol Immunol. 2015;204:121-9.
- Wen YM, et al. Hepatitis B vaccine and anti-HBs complex as approach for vaccine therapy. Lancet. 1995 Jun 17;34
- Nasal vaccines against hepatitis B: An Update. Almeida MS, et al.. Cur Pharm Biotechnol. 2015;16:882-90
- Al Mahtab M et al. Treatment of chronic hepatitis B naïve patients with a therapeutic vaccine containing HBs and HBc antigens (a randomized, open and treatment controlled phase III clinical trial).PLoS One. 2018 Aug 22;13(8):e0201236.
- Betancourt AA et al. Phase I clinical trial in healthy adults of a nasal vaccine candidate containing recombinant hepatitis B surface and core antigens . Int J Infect Dis. 2007 ;11:394-401.

Paving the road for development of HBV vaccines

Zanetti AR, Van Damme P, Shouval D. Vaccine. 2008 ;26:6266



FO MacCallum



PR Beasley

S Krugman

BS Blumberg

RH Purcell

M Hilleman

F. Andre

H Alter

H Prince

P Maupas

Expression systems for HBV antigens

- **Yeasts:**
  - Ease of transfection,
  - Ease of up-scaling
  - low cost of production
  - History of failure to express Pre-S antigens

- **Mammalian cells (CHO, mouse cell line):**
  - Glycosylation & increased immunogenicity
  - Improved expression of PreS antigens compared to yeasts
  - Higher cost of production

Different Routes of Vaccine Administration

- Intra-muscular
- Intra-dermal
- Nasal
- Oral

Selected monovalent HBV vaccines

Brand Name	Source/ Expression in	Envelope Protein(s)	Manufacturer	Country
Engerix B	Yeast	S	GSK	Belgium
Hepatavax-B	Yeast	S	MSD	US
Recombivax HB	Yeast	S	MSD	US
Heberbiovac	Yeast	S	Centro D.I.G Biotecnologia	Cuba
GenHevac B	CHO	S/Pre-S2*	Pasteur-M	France
Sci B Vac	CHO	S/PreS-1/PreS-2*	Scigen	Israel
Heplisav HB**	Yeast	S	Dynavax	US/G
???	CHO	S	Huabei	China

**Glycosylated* ***CpG adjuvant*

Selected Hepatitis B Monovalent Vaccines Prequalified by the WHO

Manufacturer	Country	Brand name
Sanofi Pasteur	France	?
GSK	Belgium	Engerix B
MSD	US	Recombivax
Center for genetic enj. and biotechnology	Cuba	Heberbiovac HB
Berna Biotech/Crucell	Korea	Hepavax-Gene
LG life Sciences ltd	Korea	Euvax B
Bio Farma	Indonesia	Hepatitis B
Serum Inst of India	India	Hepatitis B rDNA vaccine
Shantha Biotechnics Private ltd	India	Shanvac B

*Modified from Plotkin et al, 7th edition 2018

Definition of Protection

Seroconversion: anti-HBs(+) >2.1 mIU/ml

Seroprotection: anti-HBs(+) >10 mIU/ml*

Non-responder: anti-HBs(–) < 2.ml

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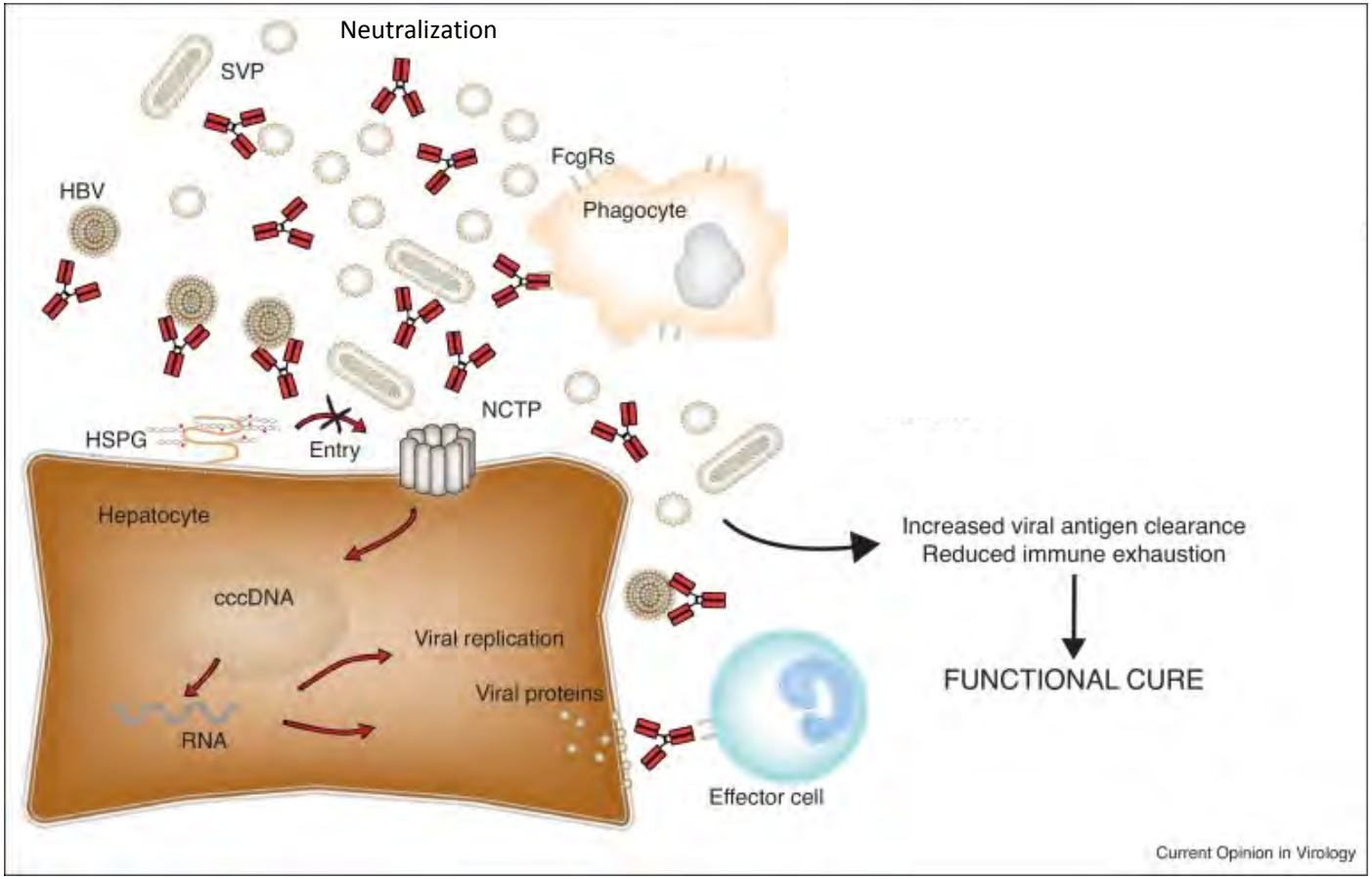
* UK ≥100 mIU/ml

Mechanisms of action of envelope-specific antibodies

Schematic representation of the various interacting mechanisms for envelope-specific, mediating viral entry blockade, antigen clearance, antibody-dependent antiviral effector actions and neutralization



Corti D, Benigni F,Shouval D. Viral envelope-specific antibodies in chronic hepatitis B virus infection Current Opinion in Virology, 2018;30: 48 (Modified-)

Two Classes of HBV Neutralizing anti-HBs antibodies

- The first class comprises a fraction of antibodies targeting specific sites in the antigenic loop of HBsAg and neutralize viral entry, blocking the interaction with the pre-receptor heparan sulphate proteoglycans (HSPG).
- The second class comprises antibodies targeting the receptor binding "site" of the PreS1 domain and block the interaction of virions with the sodium taurocholate co-transporting polypeptide (NTCP) receptor on hepatocytes .

An additional antiviral mechanism described for antibodies directed to the antigenic loop of HBsAg involves the FcRn-mediated endocytosis and the consequent intracellular blocking of HBV and HBsAg subviral particles release from infected hepatocytes

Corti D, Benigni F, Shouval D. Curr Opin Virol 2018;30:48

Distinction

Between:

- Primary Non-Response to 3+3 HBV vaccine doses (anti-HBs <10mIU/ml)
- Fading (waning) anti-HBs sero-positivity over time after 3 vaccine doses (with or without breakthrough infection)
- Low-hypo-responders post 3 vaccine doses (anti-HBs between 10-100 mIU/ml)
- Neutralizing Vs. non-neutralizing anti-HBs

Non-response to conventional vaccination against HBV

Protective efficacy of yeast derived HBV vaccines: 95-100% in young-healthy recipients decreasing to 60-75% in individuals> 60y old*

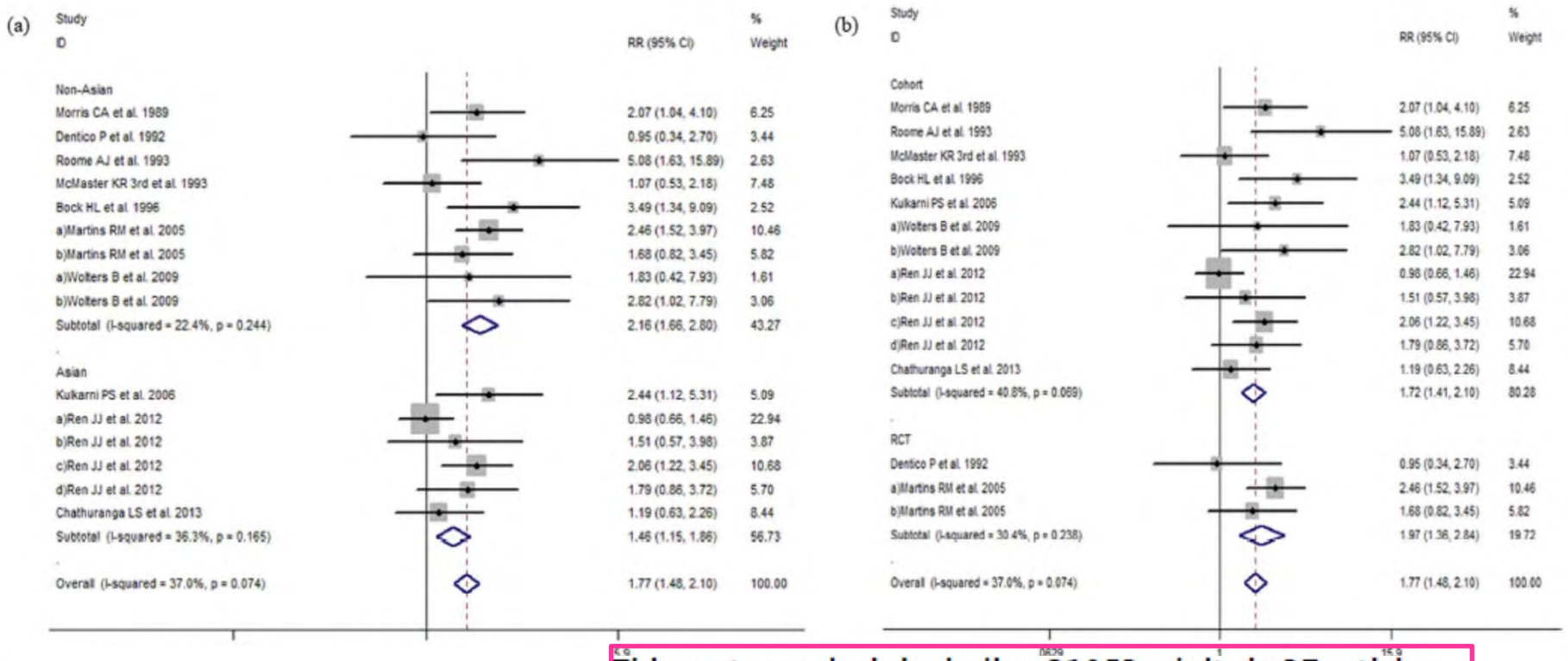
*Leroux-Roels G. 2015;204:69-78
Fishman DN et al.2002;35:1368

The Unmet Need: High-Risk Populations of Non-Responders & Low Responders to Conventional HBV Vaccination

SEROPROTECTION RATES:

- Cancer patients (children) ~57%
- Patients with chronic liver disease ~50%
- Chronic renal failure & dialysis 34-81%
- Acute lymphocytic leukemia ~10%
- Bone marrow /stem cell transplant recipients 15-68%
- Pre-transplantation candidates 28-36%
- Post-transplantation patients ~10%
- HIV (children & adolescents) ~30%
- Miscellaneous (i.e. older healthcare workers engaged in exposure prone procedures; genetically determined non-responders, celiac disease, IBD)

Meta-analysis of Studies Investigating Response to HBV Vaccines*



This meta-analysis including 21053 adults in 37 articles showed that a significantly decreased response to hepatitis B vaccine appeared in adults (age $\geq$ 40) (RR:1.86, 95% CI:1.55–2.23), male adults (RR:1.40, 95% CI:1.22–1.61), BMI $\geq$ 25 adults (RR:1.56, 95% CI:1.12–2.17), smoker (RR:1.53, 95% CI:1.21–1.93), and adults with concomitant disease (RR:1.39, 95% CI:1.04–1.86). Meanwhile, we further found a decreased response to hepatitis B vaccine appeare in adults (age $\geq$ 30) (RR:1.77, 95% CI:1.48–2.10), and adults (age $\geq$ 60) (RR:1.30, 95% CI:1.01–1.68).

**Yang S et al, Scientific Reports 2016;6:27251*

Absolute and RR of Non-Response to HBV Vaccines by Subgroup and Quality*

Comparator	Intervention	Illustrative comparative risks*(per 1000, 95% CI)		Relative risk of non-response (95% CI)	Number of Participants (studies)	Quality of the evidence (GRADE)
		Assumed risk with comparator	Corresponding risk with intervention			
Age < 40	Age ≥ 40	105	195 (163 to 233)	1.85 (1.55 to 2.21)	10233 (19 studies)	⊕⊕⊕⊕ high
Age < 30	Age ≥ 30	58	99 (81 to 121)	1.72 (1.41 to 2.1)	5372 (13 studies)	⊕⊕⊕⊖ moderate
Age < 60	Age ≥ 60	284	370 (287 to 478)	1.30 (1.01 to 1.68)	480 (5 studies)	⊕⊕⊕⊖ moderate
Female	Male	124	176 (149 to 209)	1.42 (1.2 to 1.68)	10118 (20 studies)	⊕⊕⊕⊕ high
BMI < 25	BMI ≥ 25	125	186 (134 to 255)	1.48 (1.07 to 2.03)	5807 (10 studies)	⊕⊕⊕⊖ moderate
Non-smoker	Smoker	132	195 (152 to 248)	1.47 (1.15 to 1.87)	6935 (13 studies)	⊕⊕⊕⊕ high
Non-alcoholic	Alcoholic	50	43 (29 to 63)	0.86 (0.58 to 1.26)	2381 (5 studies)	⊕⊕⊕⊖ moderate
Healthy	Concomitant diseases	100	140 (104 to 187)	1.39 (1.04 to 1.86)	4386 (12 studies)	⊕⊕⊕⊕ high
Vaccine at 0-1-6 months	Vaccine at 0-1-12 months	32	45 (12 to 192)	1.39 (0.41 to 4.67)	2433 (4 studies)	⊕⊖⊖⊖ very low

Yang S et al, Scientific Reports 2016;6:27251

Table 1 Factors determining the immune response to HB vaccine

Reduced response is correlated with	References
Subject characteristics	
Male gender	[12, 54]
Older age	[20, 21]
Obesity (BMI $\geq$ 30)	[12, 55]
Malnutrition	[56]
Lifestyle	
Smoking	[12, 54]
Drug abuse	[57]
Genetic non-response	
HLA haplotype (DPB1*02 or 1101, DRB1*03, 1302, 14, DQA1*0301, DQB1*02**, 0401, 0604)	Reviewed in [58]
Health/disease status	
Chronic kidney disease	[59, 60]
Haemodialysis	[61, 62]
Diabetes	[63]
HIV	[64, 65]
Hematopoietic stem cell recipients	[66]
Pre-existing hepatitis C infection	[67, 68]

Leroux-roels G 2015; Med Microbiol Immunol 204;69

Potential Vaccine Candidates for Bypass of Non-response to Conventional Vaccination

Table 2 Strategies to improve protection elicited by hepatitis B vaccination

Strategy	Product name (manufacturer)	References
Novel vaccine antigens		
PreS2-S	GenHevac-B (Pasteur)	[69]
PreS1–PreS2-S	SCI-B-Vac (SciGen)	[22, 57]
PreS1–PreS2-S	Hepagene (PowderJect)	[70]
Increased antigen dose		
40 µg	HBVAXPRO (Sanofi Pasteur MSD)	[71, 72]
Vaccination schedule		
Accelerated schedules		[73]
Alternative administration route		
Intradermal		[74, 75]
Adjuvants		
AS04	FENDrix (GSK Vaccines)	[33]
Immunostimulatory DNA sequences (ISS 1018)	HEPLISAV-B™ (Dynavax Technologies)	[49]

Leroux-roels G 2015; Med Microbiol Immunol 204;69

Enhancement of Immunogenicity of HBV Vaccines

- New adjuvants* :
  - Fendrix GSK™ (MPL /A&QS21)
  - **Heplisav, Dynavax® (CpG ODNs TLR 9)**
  - MF 59 (oil in water)
  - AgB/RC 529 (MPL ,Corixa, Berna Biotech)
  - Cytokines (*GM-CSF, IL-2, IL-4, IL-12, IFN a, TLR 9 ag*)
  - Miscellaneous *(Cationic lipid, Virosomes ,HBcAg)*

- Double or Triple antigen vaccines(Pre-S_1/Pre-S_2/S (with alum hydroxide)**:
  - **GenHevac B™ - France (Discontinued)**
  - **Hepagene™ - UK (Discontinued)**
  - **BioHep B/ HepImmune/ Sci B Vac® (licensed in Israel)**

Leroux-roels G 2015; Med Microbiol Immunol 204;69
Wen Y et al. Emerging Microbes and Inf 2016 , 5,e25
***Shouval D et al. Med Microbiol Immunol. 2015;204:57*

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Leroux-roels G 2015; Med Microbiol Immunol 204;69

Adjuvants

Table 3 Adjuvants and adjuvant systems used in combination with recombinant HBsAg

Adjuvant system	Al-salt (mg/dose)	MPL (µg/dose)	QS21	Excipients	HBsAg (µg/dose)	Volume (mL/dose)	Reference or product name[a]
AS01B		50	50	Liposome	20	0.5	[38]
AS01E		25	25	Liposome (half dose)	20	0.5	[44]
AS02A[b]		50	50	O/W emulsion (full dose)	20[b]	0.25	[24]
AS02B		100	100	O/W emulsion (full dose)	20	0.5	[38]
AS02V		50	50	O/W emulsion (reduced dose)	20	0.5	[38]
AS04	0.5 Phosphate	50		NaCl, water		0.5	FENDrix
–	0.5 Hydroxide			NaCl, water		1.0	Engerix-B

[a] Product names of commercially available hepatitis B vaccines

[b] The effect of AS02A is studied with SL* instead of HBsAg (S-only protein) as the vaccine antigen

Leroux-Roels G 2015; Med Microbiol Immunol 204;69

New Adjuvant ASO4

Table 4
Seropositivity, seroprotection rates and GMTs at months 1, 2, 6 and 7 in the HB-AS04 and comparator groups

Month	N	Percentage seropositivity (%)	Percentage seroprotection (%)	GMT (mIU/ml)
HB-AS04 (0, 6 month)				
1	639	76.8	34.1	10.2
2	634	87.5	45.9	10.8
6	633	92.1	63.8	18.2
7	631	99.7	98.6	7831.5
Comparator (0, 1, 6 month)				
1	314	37.3	13.1	6.9
2	312	87.8	60.6	23.7
6	307	94.8	84.7	72.5
7	309	98.7	96.8	3725.8

Table 2
Incidence of solicited local symptoms per subject

Local symptoms		Number of subjects[a] (%)	
		HB-AS04 ($N = 816$)	Comparator ($N = 410$)
Pain	Any	715 (87.6%)	247 (60.2%)
	Grade 3	120 (14.7%)	21 (5.1%)
Redness	Any	295 (36.2%)	107 (26.1%)
	Grade 3	6 (0.7%)	0 (0.0%)
Swelling	Any	206 (25.2%)	62 (15.1%)
	Grade 3	9 (1.1%)	2 (0.5%)

Grade 3 pain: spontaneously painful; grade 3 redness/swelling >50 mm.
[a] Number of subjects for whom at least one solicited symptom was documented.

Boland G et al. 2004;23:316

Heplisav^{R*}

- HepB-CpG contains 20μg yeast-derived, r-HBsAg in combination with a new synthetic adjuvant CpG (X2 dose inj)
- CpG is a synthetic immuno-stimulatory cytidine - phosphate-guanosine oligodeoxynucleotide (CpG-ODN) motifs (1018 adjuvant)**.
- The 1018 adjuvant binds to Toll-like receptor 9 to stimulate a directed immune response to HBsAg
- HepB-CpG is available in single-dose 0.5 mL vials.
- Each dose contains 20 μg of HBsAg and 3,000 μg of 1018 adjuvant without preservatives for IM inj.

*ACIP recommendations MMWR 2018;67:455-458•

** Eng FE et al . Human vaccine&Immunother 2013 (Adjuvant Review)

Heplisav^{R}

- Two doses , HEPLISAV-B is indicated for prevention of HBV in healthy recipients, >18y old, Comparative phase III trials against Engerix B^{R} (X3 doses)conducted in Germany and Canada

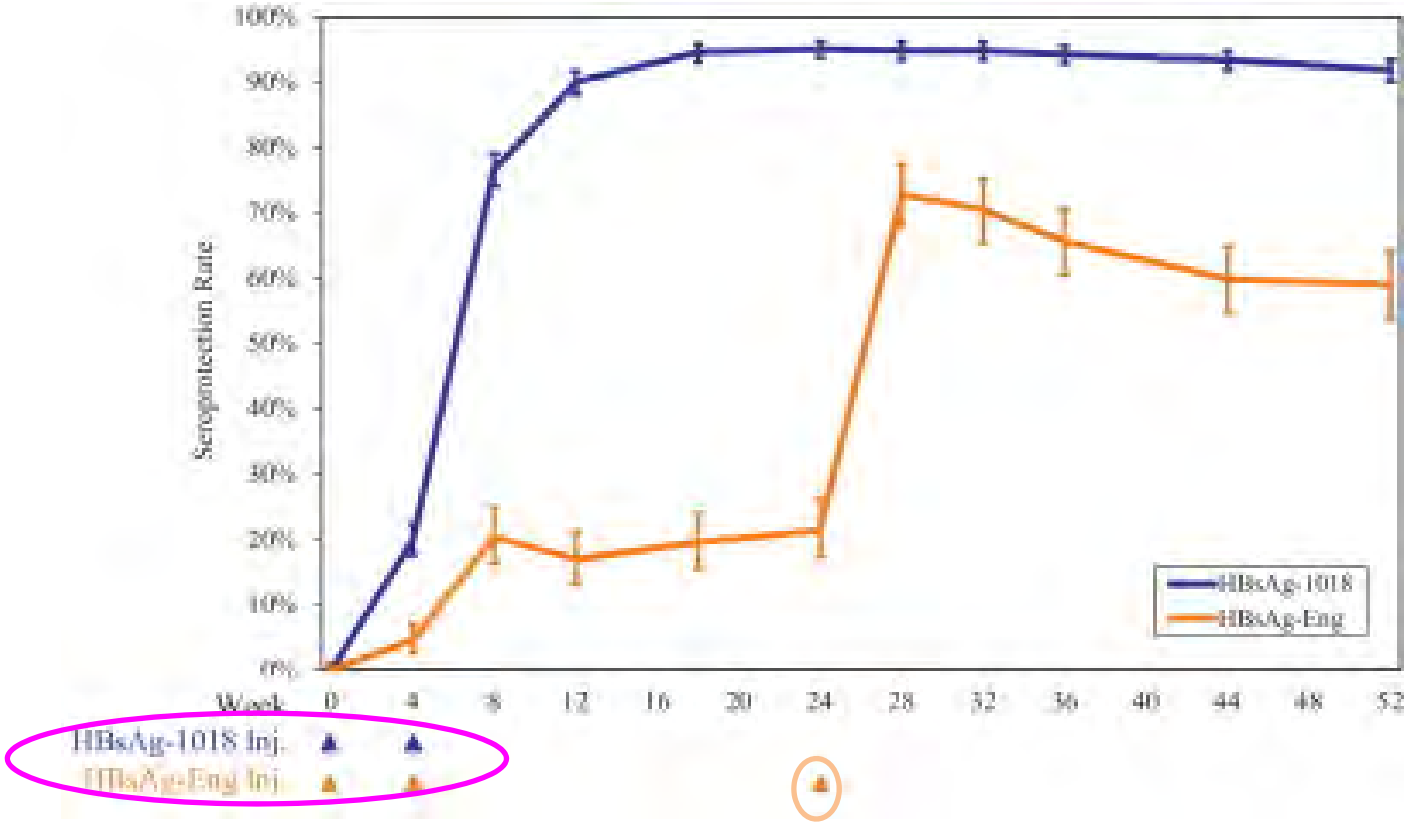
- N= 1810 subjects receiving Heplisav^{TM} Vs 605 recipient of Engerix B^{R}

- Study design : Two doses of Heplisav at month 0 and 1 and a placebo inj. at months 6Vs three doses of Engerix B^{R} at 0,1 and 6 months

- Licensure approved by FDA (2018),based on data in 9597 vaccinees, age 18-70, receiving at least 1 dose

https://heplisavb.com/assets/pdfs/HEPLISAV-B-Prescribing-Information.pdf

Immunogenicity of an hepatitis B vaccine with a Toll-like receptor 9 hepatitis B *agonist adjuvant (HBsAg-1018) compared to a licensed vaccine in healthy adults 40–70 years of age



Vaccine 2013,;31, 2013, 5300 - William L. Heyward WL et al.
Exp Opin Biol Ther 200;:131 BarryM Cooper C,

Table 2. Results of Heplisav-B Seroprotection Studies

	Heplisav-B	Engerix-B	SPR Difference (95% CI)
Study 1[a]: Patients 18-55 y old (n = 2032)			
Time point	12 weeks	28 weeks	
SPR	95.0%	81.3%	13.7% (10.4, 17.5)
Study 2[b]: Patients 40-70 y old (n = 1474)			
Time point	12 weeks	32 weeks	
SPR	90.1%	70.5%	19.6% (14.7, 24.8)
Study 3[c]: Patients 18-70 y old (n = 6665)			
Time point	24 weeks	28 weeks	
SPR	95.4%	81.3%	14.2% (12.5, 15.9)
Study 3[c]: Patients 18-70 y old with type 2 diabetes (n = 961)			
Time point	28 weeks	28 weeks	
SPR	90.0%	65.1%	24.9% (19.3, 30.7)

Reproduced from JAMA 2018;319:822

Table 3. Seroprotection Rate by Age Group (Study 3)[a]

Age Group (yrs)	Heplisav-B	Engerix-B
18-29	100%	93.9%
30-39	98.9%	92.0%
40-49	97.2%	84.2%
50-59	95.2%	79.7%
60-70	91.6%	72.6%

[a] Jackson S et al. Vaccine 2017 Dec 27 (epub).

Reproduced from JAMA 2018;319:822

Heplisav

- The most common local reaction was injection site pain (23%- 39%).
- The most common systemic reactions were fatigue (11% - 17%) and headache (8% - 17%)

Comparable AEs

Table 3
Overview of solicited post-injection reactions after all active injections and unsolicited adverse events and medically-attended adverse events.

Type of event (Study)	HBsAg-1018	HBsAg-Eng
Post-injection reactions (HBV-10 and HBV-16), N	3762	1084
Any PIR,% (n)	55.1 (2071)	57.1 (619)
Local PIRs,% (n)	42.8 (1612)	41.1 (445)
Systemic PIRs,% (n)	32.3 (1215)	37.4 (405)
AEs (HBV-10 and HBV-16), N	3778	1086
Any AE,% (n)	55.3 (2089)	58.1 (631)
Discontinuation of treatment due to AE,% (n)	0.5 (19)	0.4 (4)
Related,% (n)	6.2 (234)	6.0 (65)
MAEs (HBV-23), N	5587	2781
Any MAE,% (n)	46.0 (2569)	46.2 (1286)
Discontinuation of treatment due to MAE,% (n)	0.6 (32)	0.5 (15)
Related,% (n)	1.0 (58)	1.6 (45)
Safety population (HBV-10, HBV-16, HBV-23)	9365	3867
New-onset immune-mediated AESIs	0.17 (16)	0.13 (5)
Bell's palsy,% (n)	0.06 (6)	0.05 (2)
AESI excluding Bell's palsy,% (n)	0.11 (10)	0.08 (3)
Death,% (n)	0.28 (26)	0.21 (8)
Serious AE,% (n)	4.8 (449)	4.8 (184)
Related,% (n)	0.04 (4)	0.1 (5)

Hyer R et al. Vaccine 2018;36:2604

Table 4
Participants with new-onset adverse event of special interest excluding Bell's palsy by days since last active dose (HBV-10, HBV-16, and HBV-23 Safety Population).

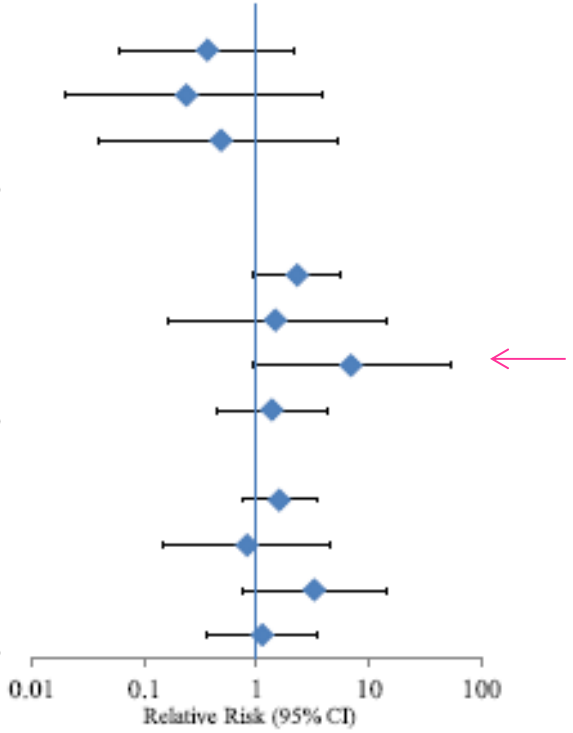
Trial	Age	Sex	Preferred term	Last active dose	Days since last active dose	Immune classification[a]
HBsAg-1018						
HBV-16	69	M	Vitiligo	2	2	Classical autoimmune
HBV-16	62	M	Erythema Nodosum	2	20	Innate immune mediated
HBV-10	48	F	Lichen Planus	2	26	Innate immune mediated
HBV-10	41	F	Basedow's (Grave's) Disease	2	44	Classical autoimmune
HBV-10	54	F	Granulomatosis with Polyangiitis	2	73	Classical autoimmune
HBV-10	35	F	Guillain-Barré Syndrome	2	111	Molecular mimicry
HBV-23	46	F	Colitis Ulcerative	2	221	Intermediate disease MHC-class I
HBV-23	52	F	Alopecia Areata	2	229	Innate immune mediated
HBV-23	68	M	Polymyalgia Rheumatica	2	292	Innate immune mediated
HBV-16	68	M	Cavernous Sinus Syndrome[b]	2	292	Unknown
HBsAg-Eng						
HBV-10	46	M	Raynaud's Phenomenon	3	33	Vasospasm
HBV-10	30	F	Basedow's (Grave's) Disease	2	78	Classical autoimmune
HBV-10	44	F	ANCA Positive Vasculitis	2	127	Classical autoimmune
			Scleroderma	2	127	Innate immune mediated

F = female; M = male.

Hyer R et al. Vaccine 2018;36:2604

Heplisav: Comparison of Observed Vs Expected Major Cardio-vascular Events

MACE	HBsAg-1018	HBsAg-Eng	Relative Risk (95% CI)	
	N=1968	N=481		
HBV-16	**n (%)**	**n (%)**		
Composite 3-point MACE	3 (0.15)	2 (0.42)	0.37	(0.06, 2.19)
Death from cardiovascular cause	1 (0.05)	1 (0.21)	0.24	(0.02, 3.9)
Myocardial infarction	2 (0.10)	1 (0.21)	0.49	(0.04, 5.38)
Stroke	0	0	N/A	
	N=5587	N=2781		
HBV-23	**n (%)**	**n (%)**		
Composite 3-point MACE	28 (0.50)	6 (0.22)	2.32	(0.96, 5.60)
Death from cardiovascular cause	3 (0.05)	1 (0.04)	1.49	(0.16, 14.35)
Myocardial infarction	14 (0.25)	1 (0.04)	6.97	(0.92, 52.97)
Stroke	11 (0.20)	4 (0.14)	1.37	(0.44, 4.30)
	N=9365	N=3867		
HBV-10, HBV-16, and HBV-23	**n (%)**	**n (%)**		
Composite 3-point MACE	31 (0.33)	8 (0.21)	1.6	(0.74, 3.48)
Death from cardiovascular cause	4 (0.04)	2 (0.05)	0.83	(0.15, 4.51)
Myocardial infarction	16 (0.17)	2 (0.05)	3.3	(0.76, 14.36)
Stroke	11 (0.12)	4 (0.10)	1.14	(0.36, 3.56)



Hyer R et al. Vaccine 2018;36:2604

Routes of vaccine administration

- Intramuscular
- Intradermal
- Nasal
- Oral

Table 1 Studies published since 1983 on vaccination against hepatitis B virus by intradermal route and percentage of positive response

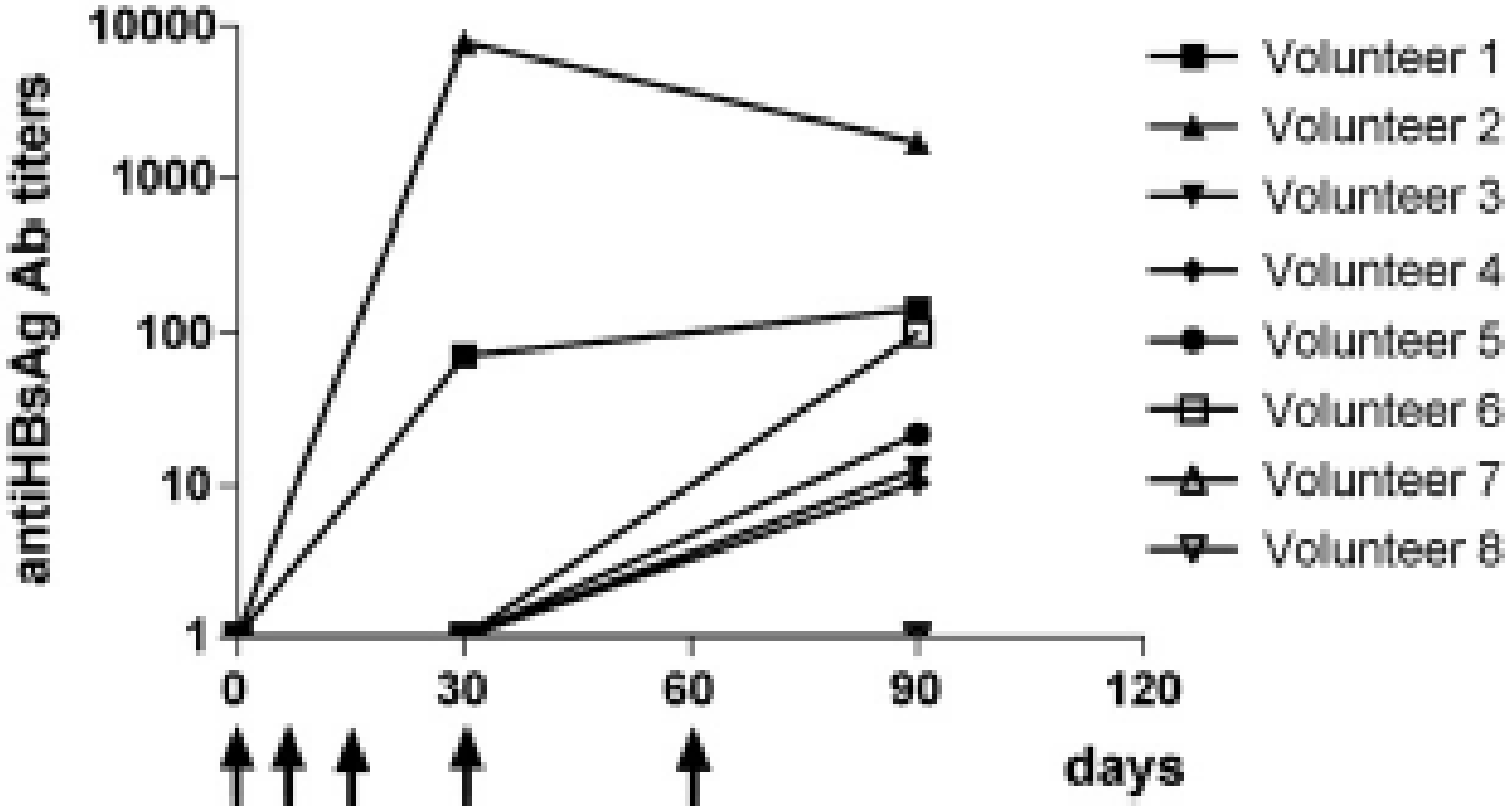
Ref.	Categories of patients	Patients (*n*)	Dose for ID administration	Positive response
Marangi *et al*[72]	Chronic kidney disease	5	5 ìg/dose until the protective titer	100%
Fabrizi *et al*[76]	Chronic kidney disease	25	16 doses of 5 ìg/dose	100%
Chanchairujira *et al*[74]	Chronic kidney disease	25	7 doses of 10 ìg/dose every 2 wk	92% at 7 mo
Barraclough *et al*[75]	Chronic kidney disease	30	10 ìg/dose every week for 8 wk	79% at 24 mo
Bunupuradah *et al*[109]	HIV- children	41	2 ìg/dose at mo 0, 2 and 6	90.2% at month 7
Launay *et al*[108]	HIV- adults	144	4 ìg × four doses at weeks 0, 4, 8, and 24	77% at week 28
Dhillon *et al*[113]	Chronic liver disease	42	40 ìg/dose maximum of three doses	69% after the third dose
Leonardi *et al*[123]	Celiac disease	20	2 ìg/dose maximum of four doses	90%
Leonardi *et al*[126]	Celiac disease	30	2 ìg/dose x four o five doses every 4 wk	90% after the third dose
Li Volti *et al*[130]	Insulin-dependent diabetes mellitus	9	3 ìg/dose at the start of the study and at two, four, and six or eight week intervals	77.7%
Leonardi *et al*[148]	Thalassaemia	54	5 ìg/dose every two weeks until the protective titer	96.4%
Ghebrehewet *et al*[142]	Healthcare workers	23	Two doses of 20 ìg	91.3% after 1 or 2 doses
Hayashi *et al*[134]	Mentally retardation	63	4 ìg/dose maximum of three doses	93.5%
Heijtink *et al*[135]	Mentally retarded patients	92	2 ìg/dose maximum of four doses	92%
Hayashi *et al*[134]	Mentally retarded patients	62	4 ìg/dose maximum of three doses	93.5%

Filippelli M et.al. WJG 2014;20:10383

Different Routes of Vaccine Administrat ion

- Intra-muscular
- Intra-dermal
- Nasal (“therapeutic”?)
- Oral

Cuba: Kinetics of anti-HBs antibody response in healthy adults nasally immunized with an HBsAg-HBcAg vaccine candidate



Betancourt AA et al. Int J Infect Dis. 2007 Sep;11(5):394-401

Nasal HBsAg-HBcAg Vaccine-AEs

Adverse event/ group	Vaccine candidate	Placebo	Total
Total of applied doses	42	48	90
Requested adverse events			
Sneezing	14 (18.2%)	4 (5.2%)	18 (23.4%)
Rhinorrhea	5 (6.5%)	3 (3.9%)	8 (10.4%)
Nasal itching	1 (1.3%)	8 (10.4%)	9 (11.7%)
Nasal stuffiness	4 (5.2%)	2 (2.6%)	6 (7.8%)
Local pain	0	1 (1.3%)	1 (1.3%)
Epistaxis	2 (2.6%)	0	2 (2.6%)
Palate itching	4 (5.2%)	0	4 (5.2%)
Anosmia	0	2 (2.6%)	2 (2.6%)
Odynophagia	2 (2.6%)	2 (2.6%)	4 (5.2%)
Local edema	0	1 (1.3%)	1 (1.3%)
Headache	4 (5.2%)	4 (5.2%)	8 (10.4%)
Febricula	1 (1.3%)	2 (2.6%)	3 (3.9%)
Asthenia	0	5 (6.5%)	5 (6.5%)
General malaise	3 (3.9%)	2 (2.6%)	5 (6.5%)
Unsolicited adverse events			
Vasovagal syncope	1 (1.3%)	0	1 (1.3%)
Total	41 (53.2%)	36 (46.8%)	77 (100%)

Betancourt AA et al. Int J Infect Dis. 2007 Sep;11(5):394-401

Table 2 Antibody response to HBcAg–HBsAg vaccine candidate in healthy volunteers immunized by the nasal route with 50 μg HBcAg non-covalently linked to 50 μg HBsAg following the schedule 0, 7, 15, 30, and 60 days

Group/time	Vaccine candidate			Placebo		
	Day 0	Day 30	Day 90	Day 0	Day 30	Day 90
N	9	8	8	10	9	9
Anti-HBcAg seroconversion %	–	8 (100%)	8 (100%)	–	–	–
Anti-HBs seroprotection % (anti-HBs ≥10 IU/l)	–	2 (25%)	6 (75%)	–	–	–

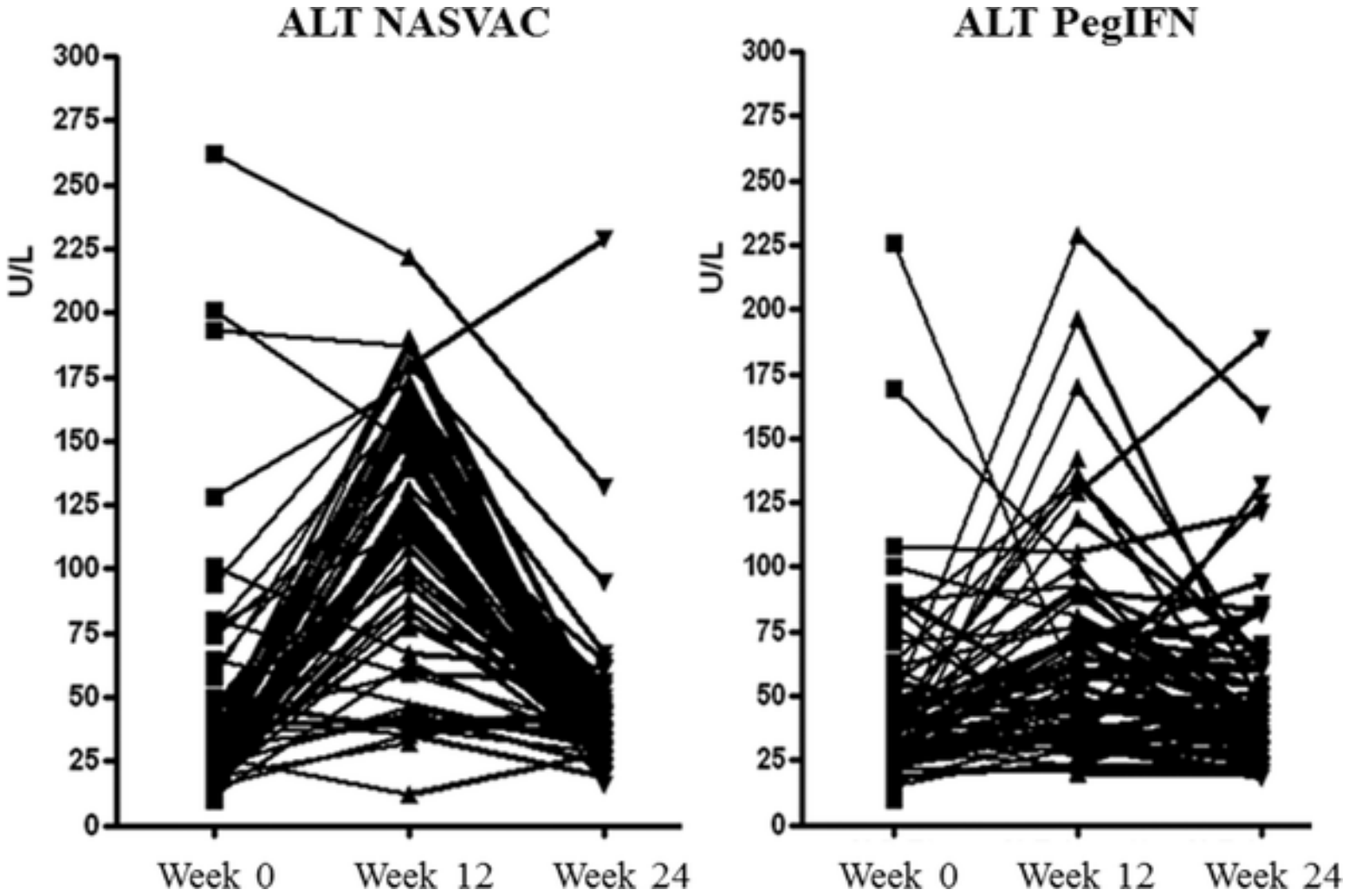
Source: data collection sheets.

Betancourt AA et al. Int J Infect Dis. 2007 Sep;11(5):394-401

Treatment of chronic hepatitis B naïve patients with a therapeutic vaccine containing HBs and HBc antigens (a randomized, open and treatment controlled phase III clinical trial (Japan and Cuba))

- Mamun Al Mahtab , et al. (Collaboration between Japanese and Cuban investigators). PLoS ONE 13(8): e0201236.

Fig 3. Changes in serum ALT levels during therapeutic vaccination.



Al Mahtab M, Akbar SMF, Aguilar JC, Guillen G, Penton E, et al. (2018) Treatment of chronic hepatitis B naïve patients with a therapeutic vaccine containing HBs and HBc antigens (a randomized, open and treatment controlled phase III clinical trial). PLOS ONE 13(8): e0201236. https://doi.org/10.1371/journal.pone.0201236
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0201236

Table 2 Strategies to improve protection elicited by hepatitis B vaccination

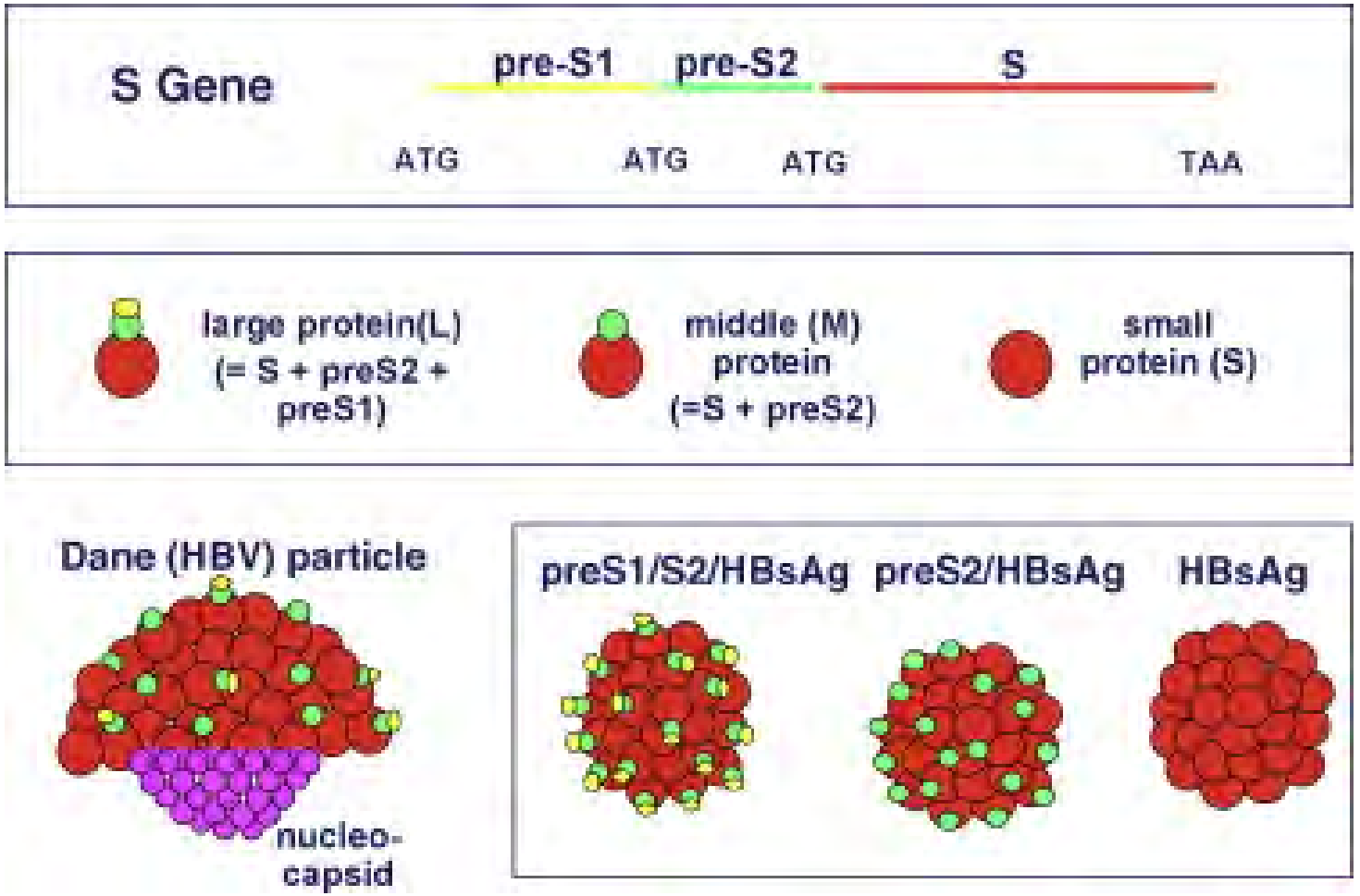
Strategy	Product name (manufacturer)	References
Novel vaccine antigens		
PreS2-S	GenHevac-B (Pasteur)	[69]
PreS1–PreS2-S	SCI-B-Vac (SciGen)	[22, 57]
PreS1–PreS2-S	Hepagene (PowderJect)	[70]
Increased antigen dose		
40 µg	HBVAXPRO (Sanofi Pasteur MSD)	[71, 72]
Vaccination schedule		
Accelerated schedules		[73]
Alternative administration route		
Intradermal		[74, 75]
Adjuvants		
AS04	FENDrix (GSK Vaccines)	[33]
Immunostimulatory DNA sequences (ISS 1018)	HEPLISAV-B™ (Dynavax Technologies)	[49]

Leroux-roels G 2015; Med Microbiol Immunol 204;69

Mammalian Cell Derived HBV Vaccines

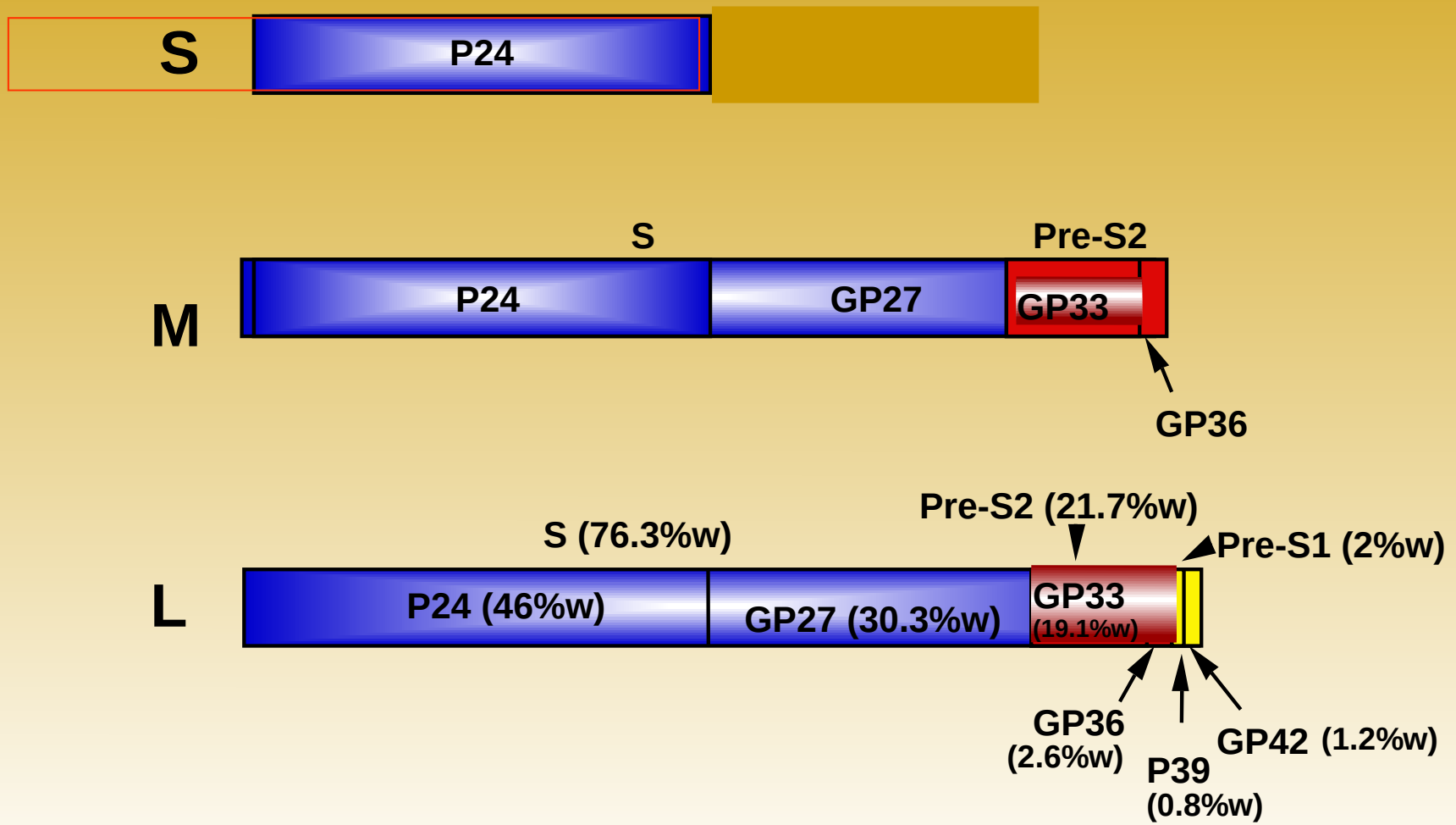
- S
  - ✓ Wang F et al.,2015 *China)
- Pre-S2/S
  - ✓ Adamovicz et al 1987- ISVHLD (France)
  - ✓ Akahane et al 1993-ISVHLD (Japan)
- Pre-S1/Pre-S2/S
  - ✓ Hemmerling et al1990 – ISVHLD (Germany)
  - ✓ Shouval et al 1990 - ISVHLD (Israel)

HBV envelope Genes Proteins and Particles



Michel ML, et al. Pathologie Biologie 2010;58:288

Peptide composition of third generation Recombinant HBV vaccines



D. Diminsky and Y. Barenholz, 1990.

A Pres1/PreS2/S mammalian cell (CHO) derived HBV vaccine

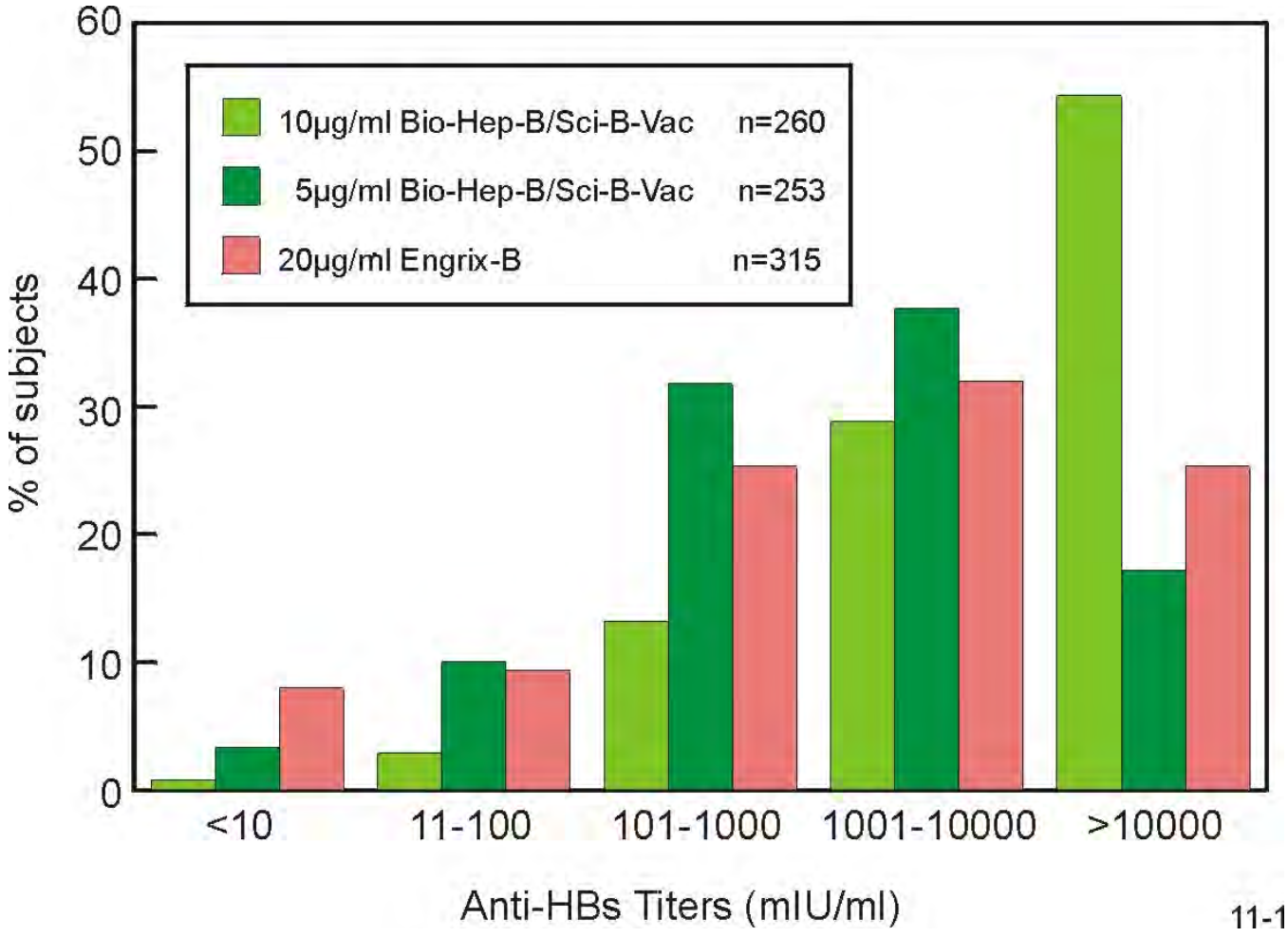
- Sci B Vac^{R} (Bio-Hep B^{TM} ,Hepimmune^{TM})

Shouval D, Ilan Y, Adler R, Deepen R, Panet A, Gorecki M, Even-Chen Z, Gerlich WH.
Improved immunogenicity in mice of a mammalian cell derived recombinant hepatitis B vaccine containing pre S1 and pre S2 antigens as compared to conventional yeast
derived vaccines. Vaccine 12:1453–1459, 1994

Enhancement of Immunogenicity of HBV Vaccines

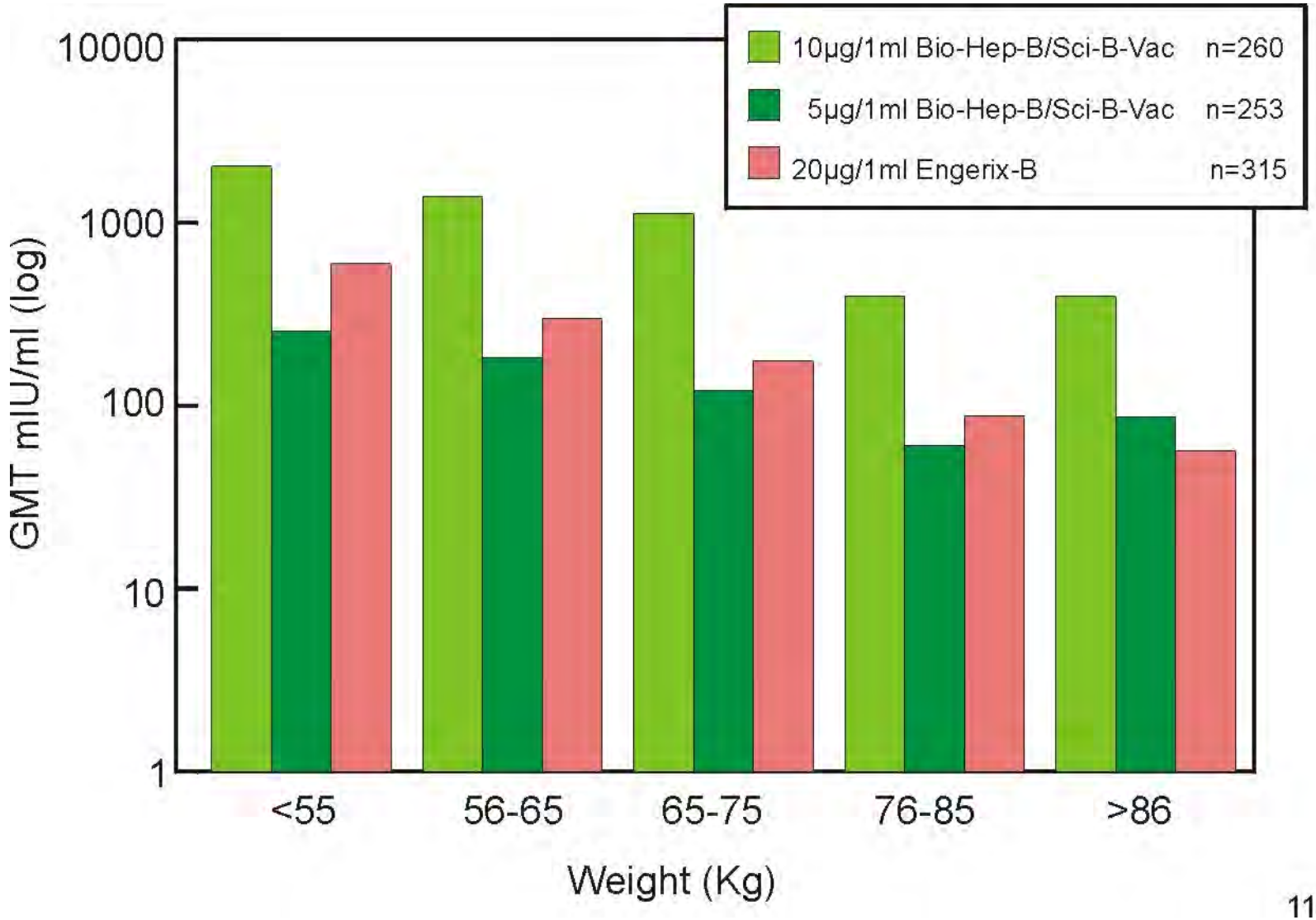
- Triple (or double) antigen vaccines (Pre-S_1/Pre-S_2/S**)
  - In non-responders to conventional HBV vaccines
  - In immune suppressed patients-i.e:.
    - HIV
    - CRF and Dialysis
    - Transplant patients
    - Celiac Disease
    - Chronic liver disease

Comparative quantitative anti-HBs response and distribution of titers following 3 doses of BioHep B or Engerix B in adults



Shouval D, Roggendorf H, Roggendorf M.Med Microbiol Immunol. 2015 ;204:57-68

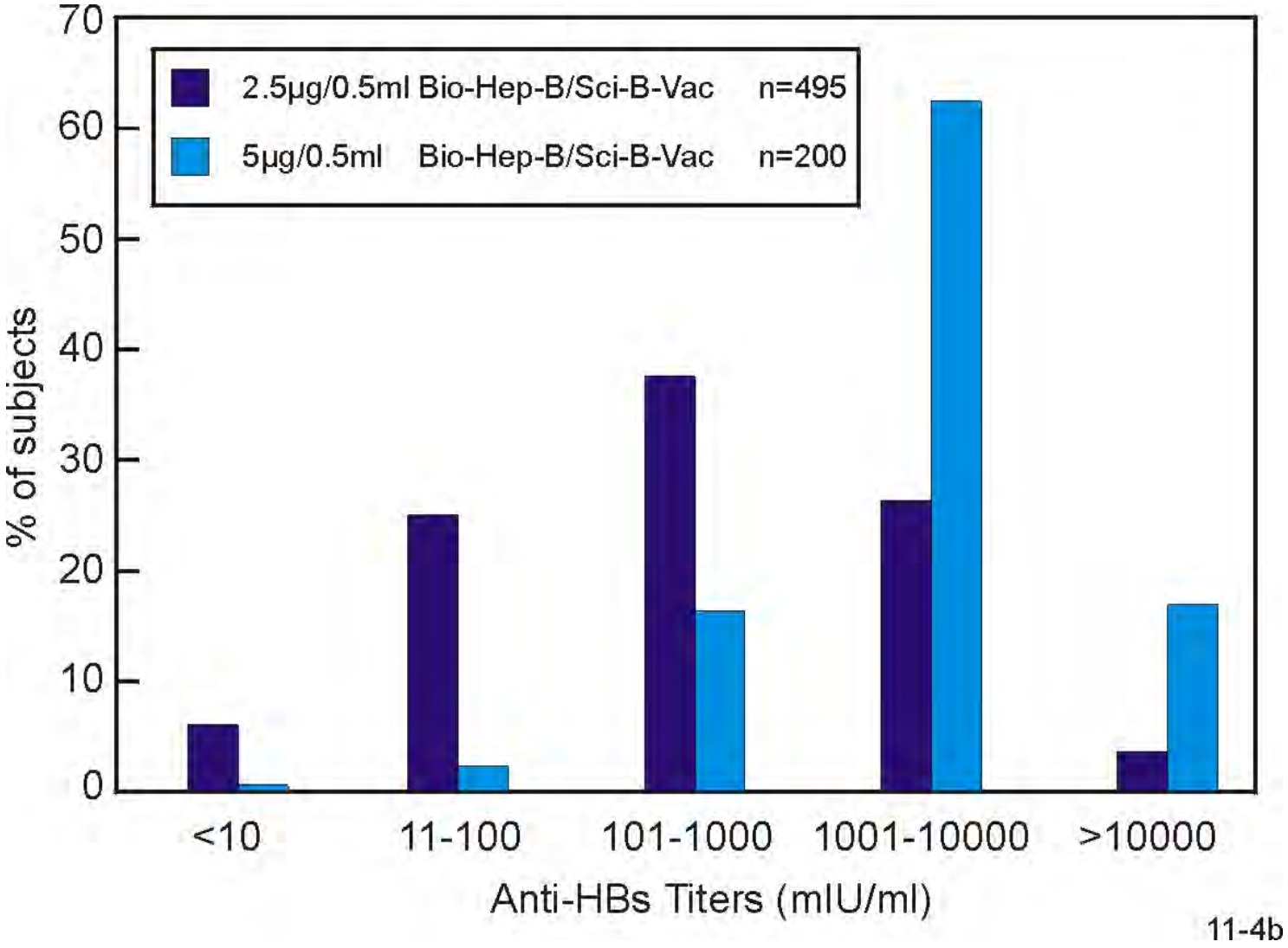
Immunogenicity of a Sci B Vac vaccine according to weight



11-2

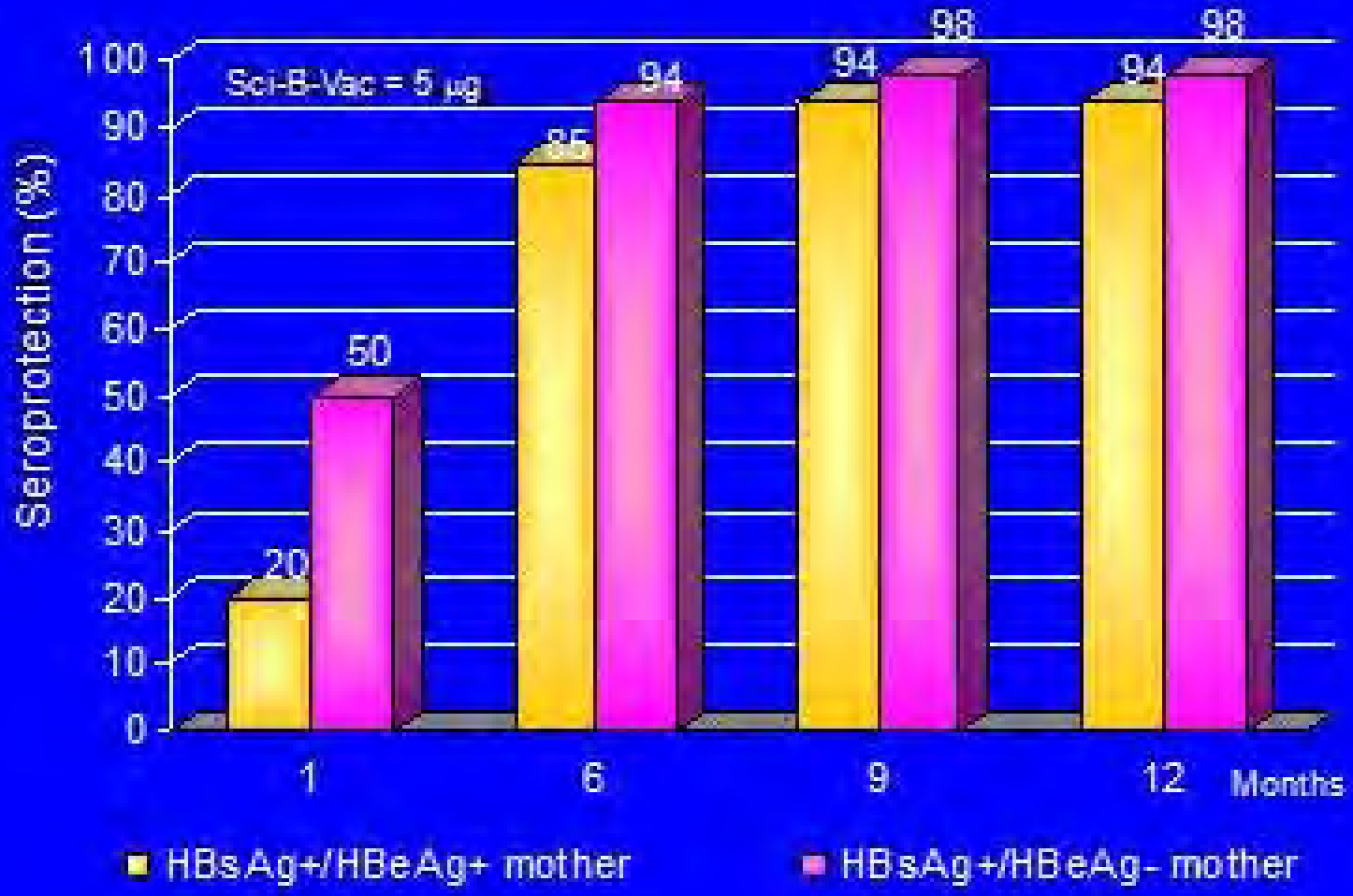
Shouval D, Roggendorf H, Roggendorf M.Med Microbiol Immunol. 2015 ;204:57-68

Dose Range Study: Neonates Vietnam



Shouval D, Roggendorf H, Roggendorf M.Med Microbiol Immunol. 2015 ;204:57-68

Immunogenicity of Sci B Vac in neonates born to HBsAg+ mothers (by HBeAg status)



Comparative Immunogenicity of a Pwo dose Hepatitis B Vaccines protocol *

Protocol •

N - 36 (20M/16F) •

Mean age - 23y (19-28) •

Protocol - 2 doses of Sci B Vac 10 µg/dose •

or

- 2 doses of Engerix B 20 µg/dose

Time of i.m. injection: day 0; 6 months •

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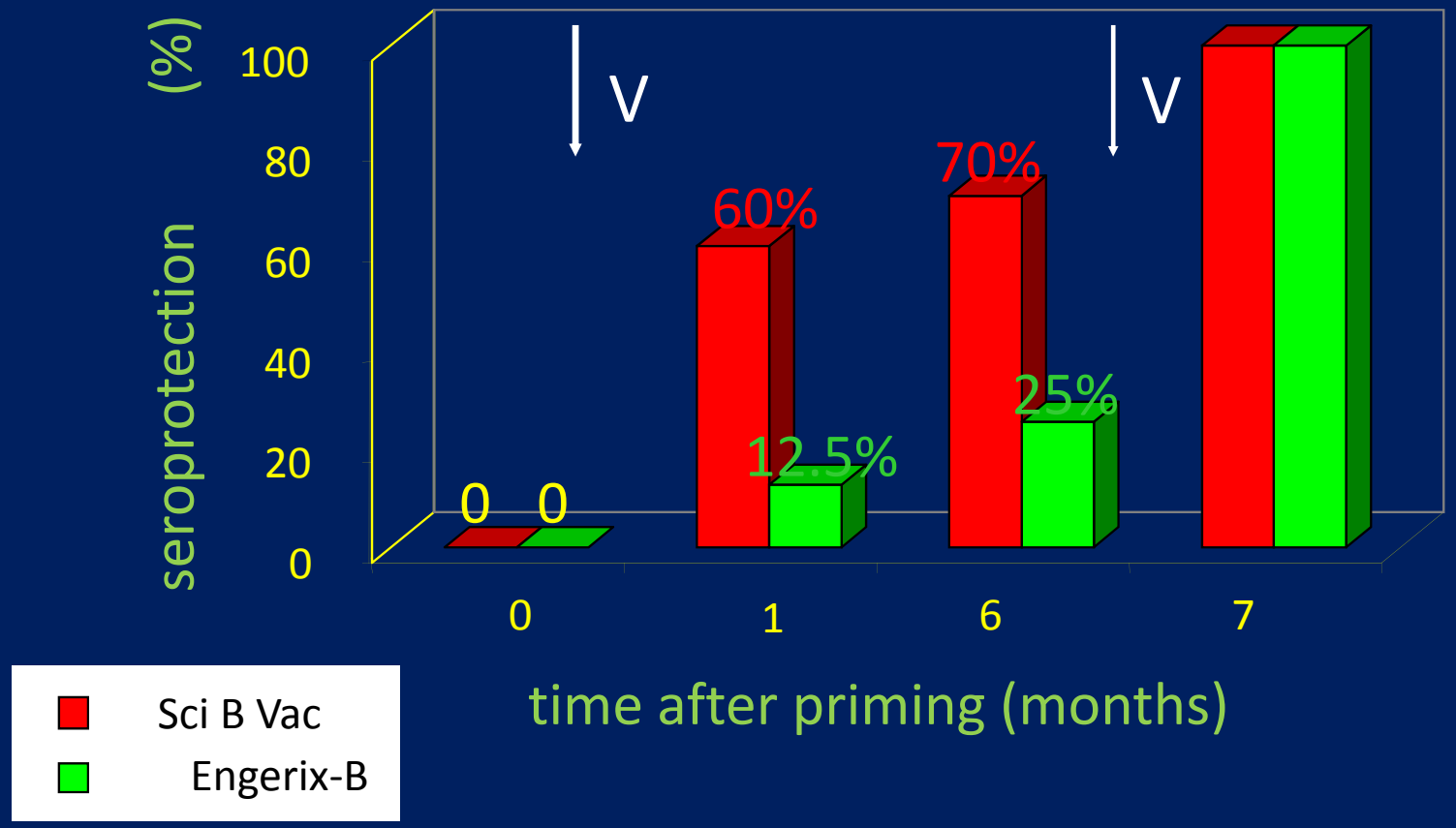
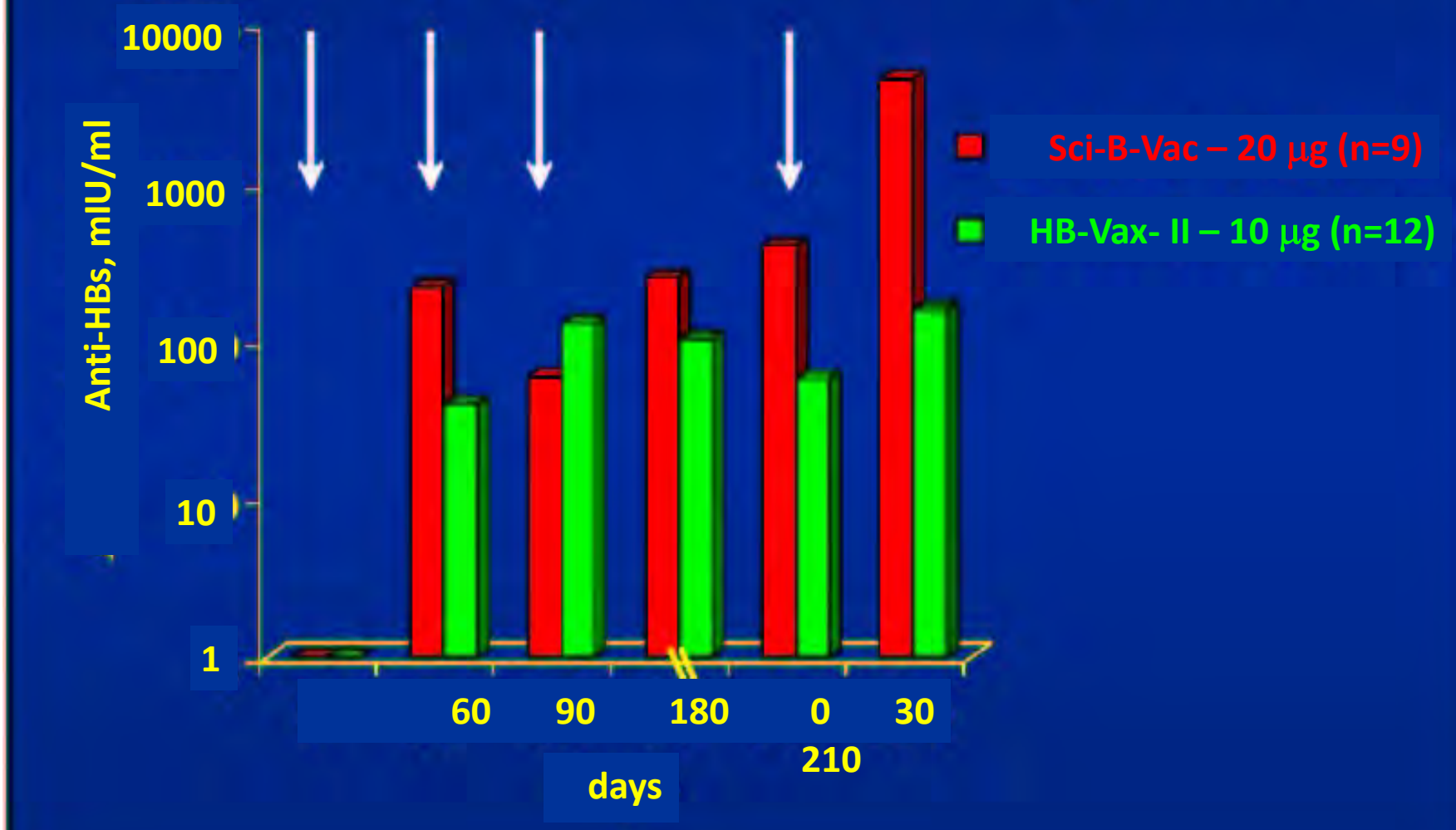
* *Shapira MY, Zeira E, Adler R, Shouval D. Rapid seroprotection against hepatitis B following the first dose of Pre-S1/Pre-S2/S vaccine. J. Hepatology 34(1):123-127, 2*

Immunogenicity of Two Hepatitis B Vaccines in Healthy <30y old Individuals*



*Shapira M et al. J Hepatology 2000

Enhanced immunogenicity of Sci-B-Vac in dialysis patients with kidney failure



Tel Aviv - 8 Jan, 2007

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Comparative immunogenicity of a PreS/S hepatitis B vaccine in non- and low responders to conventional vaccine

Pamela Rendi-Wagner[a,*], Daniel Shouval[b], Blaise Genton[c], Yoav Lurie[d], Hans Rümke[e], Greet Boland[f], Andreas Cerny[g], Markus Heim[h], Doris Bach[i], Manfred Schroeder[j], Herwig Kollaritsch[a]

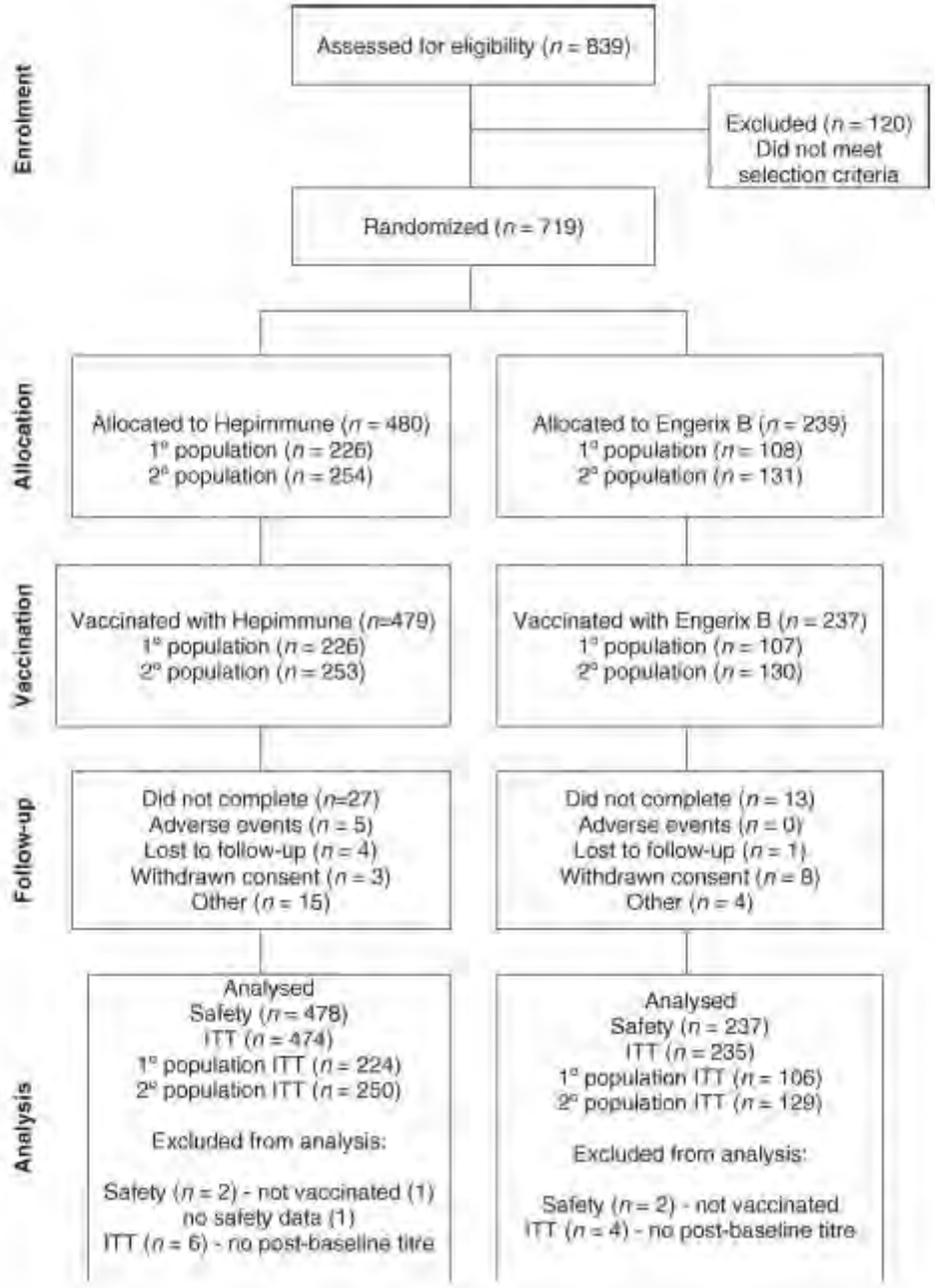
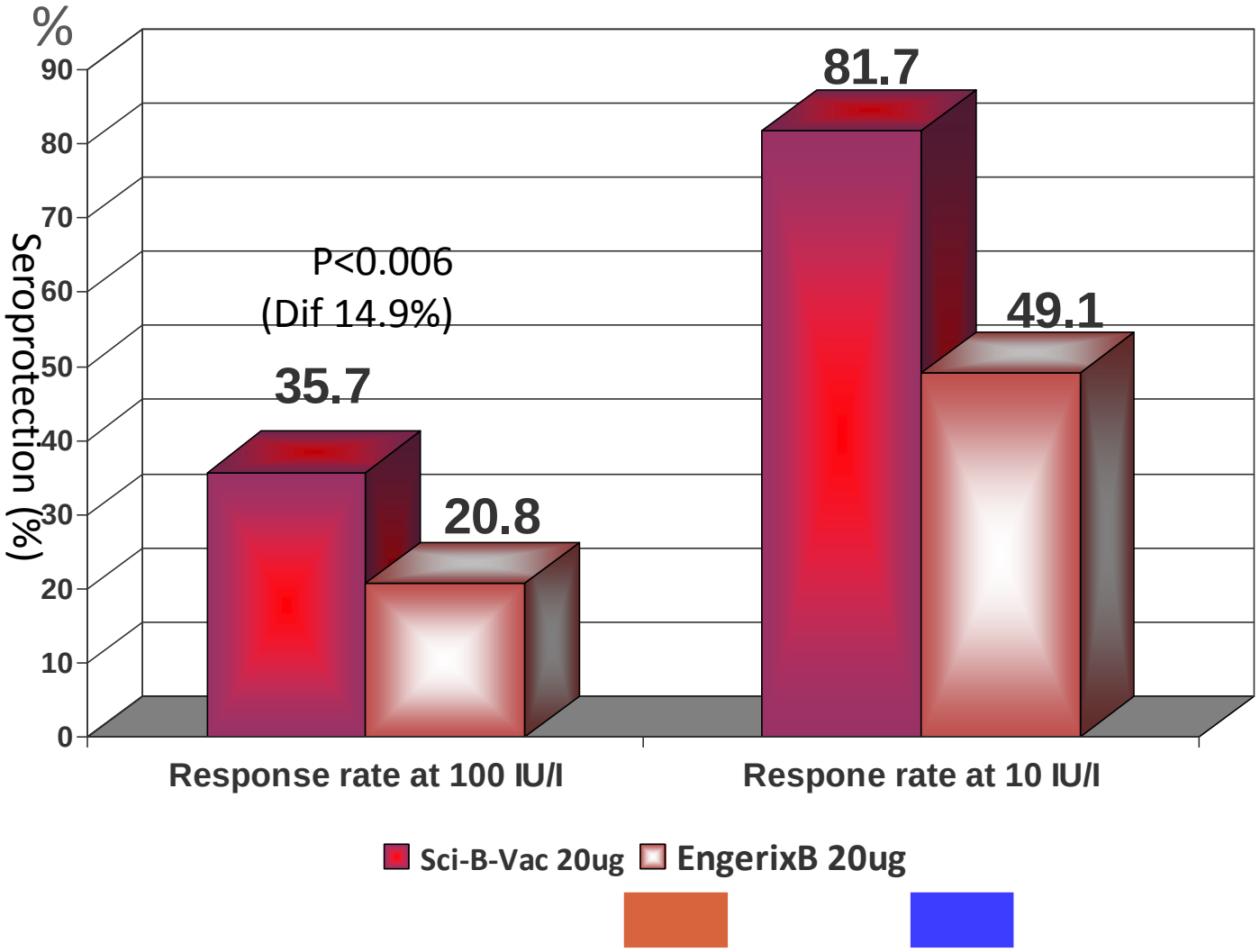


Fig. 1. Trial profile.

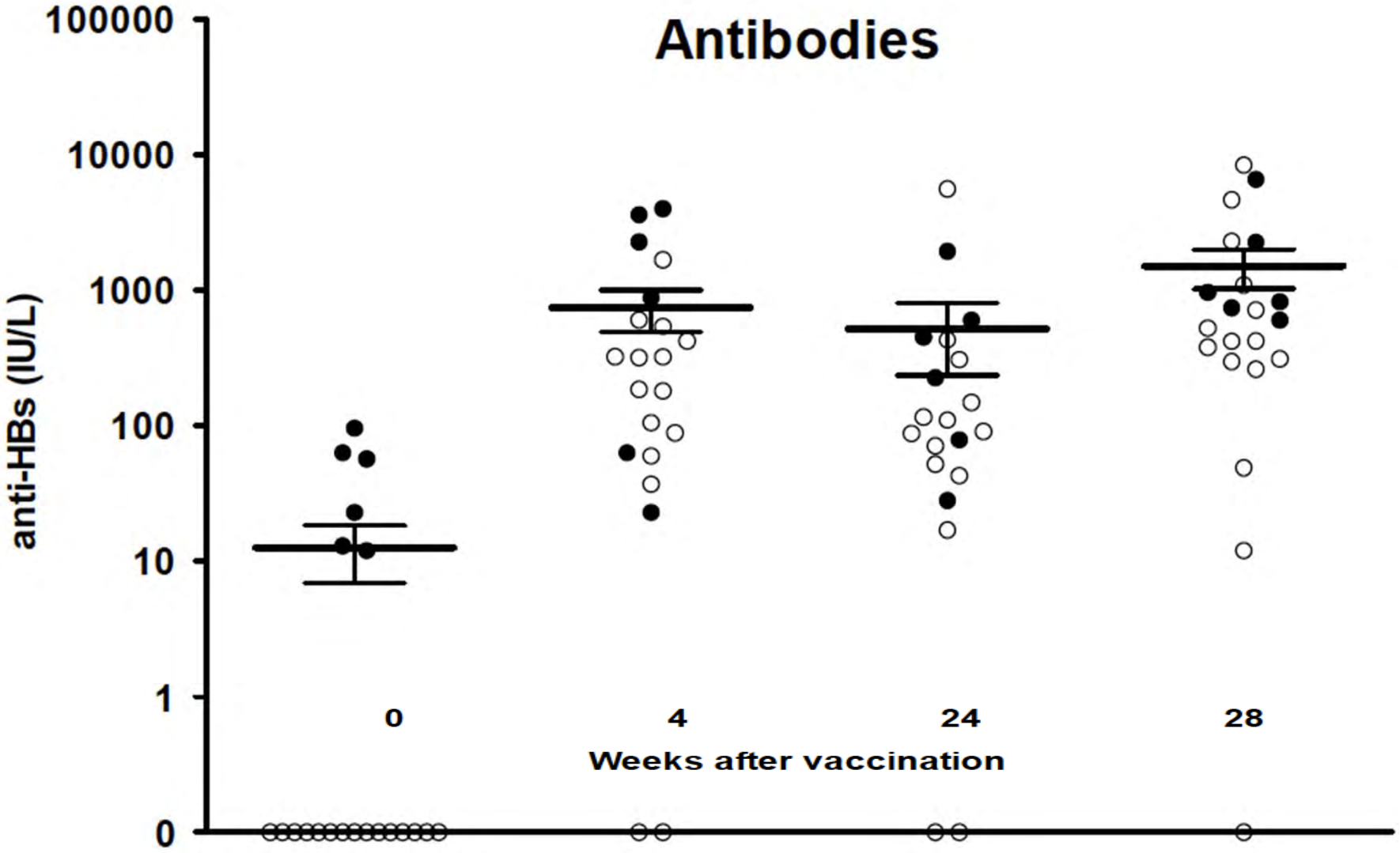
Immunization of Non-responders to HBV vaccines (post 4Xinj.) Comparative randomized trial



Rendi-Wagner P[1] et alVaccine. 2006 ; 5;24(15):2781-

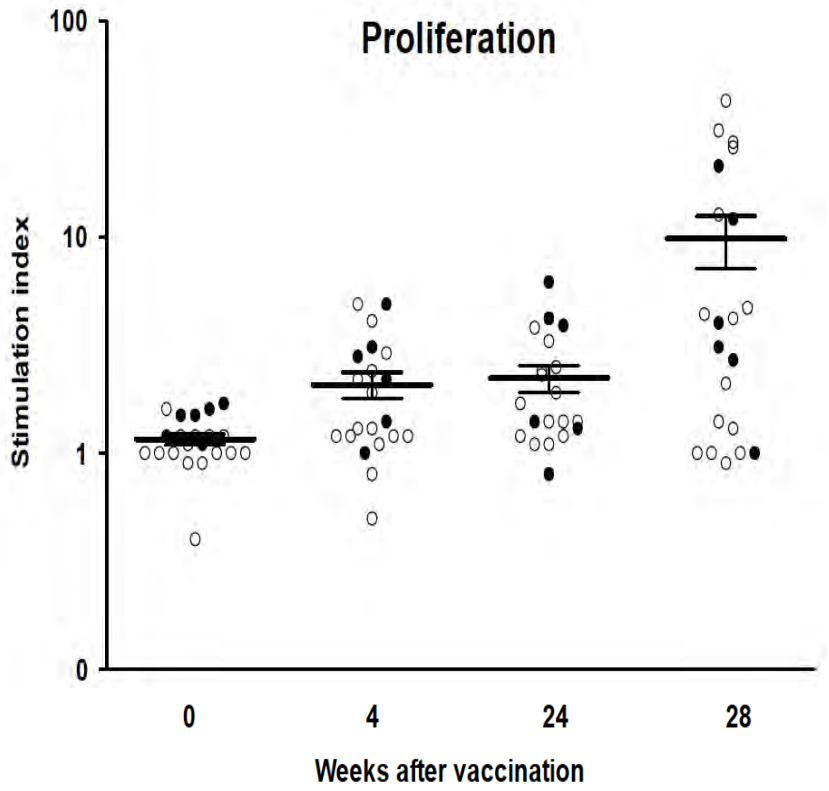
.

Humoral immune response in 19 non responders immunized with Sci B Vac



Roggendorf M. group et al. personal communicationl

Cellular immune response in 19 non-responders immunized with Sci B Vac



Roggendorf M group. Personal communication.

Evaluation of a new hepatitis B triple-antigen vaccine in inadequate responders to current vaccines

- In this double-blind, randomized, controlled study, healthcare professionals with a history of inadequate response to currently available single-antigen hepatitis B vaccines
- This study demonstrated that in healthcare workers who had responded inadequately to at least a full course of immunization (median, 5 doses), a single 20-microg dose of a new triple-antigen vaccine induced protective antibody level in more vaccinees (P =.002) and increased the average antibody titer (GMT) in those protected successfully to a greater degree (P <.001) than a further attempt with a current vaccine (Engerix B)

Zuckerman JN, Zuckerman AJ, and Study Group.Hepatology. 2001 ;34:798-802

Bypass of Non-Response to Hepatitis B Vaccines

ENHANCING

- Genetically determined resistance
- Advanced age
- Overweight
- Age
- Gender
- Smoking
- Immune suppression
- Chronic liver disease
- Miscellaneous (RF, systemic disease)

Pre-S1 , Pre-S2

ATTENUATING

Craven DE, et al. Ann Int Med1986;105:356, Alper CA et al. N Eng J Med 1989, 321:708-712, Milich DR Immunol Today 1988, 9:380-33
Hohler Tet al.Hum Immunol 1998, 59:212-218

Summary

- Several options (mainly experimental) for improving vaccine induced seroprotection against HBV in vaccine non-responders are available including:
  - New adjuvants
  - Inclusion of Pre-S/S epitopes in the vaccine formulation
  - Intradermal injection
  - Repeated immunization (double dose)
- The quality of evidence (controlled clinical trials phase III) supporting one of these methods is limited
- New guideline are needed

The Liver Unit at Hadassah

The Hadassah Medical Center in Jerusalem