Development and utilization of the PreS/S hepatitis B vaccine in Israel

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The rational for development of a more immunogenic HBV vaccine

• Non–response to conventional HBV vaccines in special populations

• Fast induction of immunity to HBV in defined populations

• Low compliance with the 3 dose regimen of conventional HBV vaccines

• Emerging evidence on loss of post vaccination immune memory 20 years past primary immunization

• Possible protection against HBV envelope mutant(s)
<table>
<thead>
<tr>
<th>Generation</th>
<th>Type</th>
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</thead>
<tbody>
<tr>
<td>1st</td>
<td>Plasma-derived (HBsAg, Pre-(S_1) / Pre-(S_2))</td>
</tr>
<tr>
<td>2nd</td>
<td>DNA Recombinant, subunit vaccine (HBsAg, Pre-(S_2))</td>
</tr>
<tr>
<td></td>
<td>- E. Coli-derived</td>
</tr>
<tr>
<td></td>
<td>- Yeast-derived</td>
</tr>
<tr>
<td>3rd</td>
<td>Mammalian cell derived (HBsAg, Pre-(S))</td>
</tr>
<tr>
<td></td>
<td>- HBsAg, Pre-(S_2)</td>
</tr>
<tr>
<td></td>
<td>- HBsAg, Pre-(S_2), Pre-(S_1)</td>
</tr>
</tbody>
</table>
The Hepatitis B Virus

- 4 overlapping open reading frames
- Reverse transcriptase/DNA polymerase domain overlaps with surface gene
- 100 times more infective than HIV
- Found in blood and body fluids

Three Generations of Hepatitis B Vaccines

*Pre S/S HBV vaccine trade names: Bio Hep B, Hepimmune, Sci B Vac
Peptide composition
Recombinant HBV vaccines

D. Diminsky and Y. Barenholz, 1990.
BioHep B: Composition of HBsAg particles (%w)

D. Diminsky and Y. Barenholz, 1996.
Bypass of Non-responsiveness to Immunization in Mice

Antihbs, mIU/ml

Days after vaccination

N=10
Development of an PreS/S HBV Vaccine

- **Goals**
  - Evaluation of Safety & Immunogenicity
  - Registration

- **Approach**
  - GCP Standard Studies
  - Central Programs in Singapore & Israel
## Clinical Evaluation and Protocols

<table>
<thead>
<tr>
<th>Subject</th>
<th>Adults</th>
<th>Children</th>
<th>Neonates</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Studies</td>
<td>8</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Age</td>
<td>10-60 y</td>
<td>2m-10yrs</td>
<td>Newborn</td>
</tr>
<tr>
<td>Regime (month)</td>
<td>0,1,6</td>
<td>0,1,6</td>
<td>0,1,6</td>
</tr>
<tr>
<td>Doses used (mcg)</td>
<td>5,10 or 20</td>
<td>2.5 or 5</td>
<td>2.5 or 5</td>
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<tr>
<td>Blood drawn at month</td>
<td>0,1,2,6,7,12</td>
<td>0,2,6,7,12</td>
<td>0,1,6,9,12</td>
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<tr>
<td>HBV Marker Test</td>
<td>Abbott EIA</td>
<td>Abbott EIA</td>
<td>Abbott EIA</td>
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## CLINICAL STUDIES – Bio Hep B

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Dose (µg)</th>
<th>No. of Subjects Enrolled</th>
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<tbody>
<tr>
<td>Adults</td>
<td>5.0</td>
<td>474</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>579</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>21*</td>
</tr>
<tr>
<td></td>
<td><strong>Subtotal</strong></td>
<td><strong>1074</strong></td>
</tr>
<tr>
<td>Children</td>
<td>2.5</td>
<td>379</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>213</td>
</tr>
<tr>
<td></td>
<td><strong>Subtotal</strong></td>
<td><strong>592</strong></td>
</tr>
<tr>
<td>Neonates</td>
<td>2.5</td>
<td>883</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>476</td>
</tr>
<tr>
<td></td>
<td><strong>Subtotal</strong></td>
<td><strong>1359</strong></td>
</tr>
<tr>
<td><strong>Grand Total</strong></td>
<td><strong>3025</strong></td>
<td></td>
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</table>
Immunogenicity of Sci B Vac in Children

Age: 2m - 11y

*BiO Hep B
EFFICACY OF SCI-B-VAC IN NEONATES*
(COMPARATIVE STUDY)

Seroprotection (%)

1 7 12
Months

Sci-B-Vac (2.5ug)  Engerix-B (10ug)

*Three doses 0,1,6m
Distribution of anti-HBs titers following three doses of PreS/S vaccine

Immunogenicity of the Pre S/S vaccine according to weight
Comparative Immunogenicity of Hepatitis B Vaccines*

- **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**

* 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
Comparative Immunogenicity of Two Hepatitis B Vaccines*

*Shapira M et al. J Hepatology 2000
Area Under The Curve (AUC) of Anti-HBs during the First Month*

Immunogenicity of a Sci B Vac vaccine according to weight

![Bar chart showing GMT mIU/ml (log) for different weight groups and vaccine doses.](chart.png)
Immunogenicity of Sci B Vac in neonates born to HBsAg+ mothers (dose response)

Seroprotection (%)

Months

Sci-B-Vac (2.5 ug) Sci-B-Vac (5ug)

*Three doses 0,1,6m
Immunogenicity of Sci B Vac in neonates born to HBsAg+ mothers (by HBeAg status)

Sci-B-Vac = 5 µg

Seroprotection (%)

Months

HBsAg+/HBeAg+ mother

HBsAg+/HBeAg- mother
<table>
<thead>
<tr>
<th>Trial site</th>
<th>Dosage</th>
<th>No of subjects</th>
<th>Seroprotection (%)</th>
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<tbody>
<tr>
<td>Vietnam</td>
<td>2.5 mcg</td>
<td>17</td>
<td>83</td>
</tr>
<tr>
<td>Singapore +</td>
<td>5.0 mcg</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>Vietnam</td>
<td>5.0 mcg + HBIg</td>
<td>37</td>
<td>94</td>
</tr>
<tr>
<td><strong>Total No</strong></td>
<td></td>
<td><strong>64</strong></td>
<td></td>
</tr>
</tbody>
</table>

Data at month 12 (anti-HBs levels ≥10 mIU/ml)
Serial changes in anti-HBs antibodies in patients with chronic hepatitis B after liver transplantation*

*All patients received lamivudine (no HBIG)

Lo CM et al. HEPATOLOGY 2003;37:36-43
Mathematical model of the antibody response to hepatitis B vaccines: Implications for reduced schedules

- The model parameters are estimated from a data base of 10,815 post vaccination anti-HBs titer measurements obtained from 1923 adults participating in clinical vaccine trials.
- Model simulation suggests that a single vaccine dose could prime immune memory as shown by one booster dose at 6m; thus a two dose schedule will be sufficient for long-term protection against HBV (a concept not yet accepted by most immunologists).

Jamie N. Wilson, James Nokes, Graham F. Medley, Daniel Shouval. Vaccine 2007;25:3705
Figure: Optimized 95% confidence intervals for each study.

- (a) The rate of antigen-dependent memory generation ($\gamma$).
- (b) The rate of antigen-independent memory generation ($\beta$).
- (c) The peak antibody/memory level ($N$).
- (d) The predicted time taken for memory to reach 10 mIU/ml after a single vaccination.
Mathematical model of the antibody response to hepatitis B vaccines: Implications for reduced schedules

Vaccine Brandname

(a) Antigen-dependent memory generation
(b) Antigen-independent memory generation
(c) Peak antibody titre
(d) Predicted number of days taken to generate immunity (M>10 mIU/ml)

1.1 (Engerix 20)
1.2 (SL 20)
2 (Engerix 20)
3.1, 2 (Engerix 20)
3.3, 4 (BioHepB 10)
4.1, 2, 3 HBV/MF59 10)
4.4 (Recombivax 10)
4.5, 6 (Recombivax 20)
5.1 (Recombivax 10)
5.2 (Recombivax 20)
6.1 (Heberbiovac 10)
6.2 (Heberbiovac 20)
7.1 (HevacB 10)
7.2 (HBVax)
8.1, 2 (Engerix 20)
Average
Adoptive Transfer of Immunity in Mice: Comparison of Yeast and Mammalian cell Derived Vaccines

- Immunization of Balb/C mice with a rHBV vaccine
- Transplantation of bone marrow from immunized mice to immune suppressed Balb/C mice
- Monitoring of cellular and humoral immune response to HBV
Adoptive transfer of immunity to HBV in mice: The humoral response
Comparison of yeast to CHO derived hepatitis B vaccines

Day of BMT

Anti-HBs, mIU/ml

Day after BMT

booster

S – yeast derived HBV vaccine
preS1/preS2, S – CHO derived HBV vaccine
Clearance of Serum HBV Markers in an HBsAg Carrier Following BMT*

*Ilan Y. et al., Gastroenterology 1993; 104:1818
Cellular and humoral immune response to a third generation hepatitis B vaccine (IFN Elispots)

Volunteers immunized with [●] Sci B Vac or [○] the control vaccine.

Journal of Viral Hepatitis
Volume 14, Issue 8, pages 592-598, 30 APR 2007 DOI: 10.1111/j.1365-2893.2007.00848.x
Cellular and humoral immune response to a third generation hepatitis B vaccine Proliferation assay
Cellular and humoral immune response to a third generation hepatitis B vaccine
Adoptive Immune Transfer of Hepatitis B Virus Specific Immunity From Immunized Living Liver Donors to Liver Recipients


FIGURE 1. Humoral and cellular immune responses of 46 potential living liver donors (LLDs). The x-axis indicates the number of vaccinations or booster-vaccinations. Thirty-two donors (*) were excluded from transplantation because of medical or psychological reasons. Fourteen donors ([white up pointing small triangle] SYMBOL) donated a part of their liver to the corresponding recipients. Values in donors one to three who transferred their hepatitis B virus (HBV)-specific immunity are depicted as hollow triangles with numbers 1-3. (A) Antibodies to hepatitis B virus surface antigen (anti-HBs)-titers in the LLDs before transplantation or after the last immunization, (B) cellular immune response in the proliferation-assay, and (C) in the IFN-[gamma]-ELISpot. The horizontal lines indicate the cut-off (stimulation index of 2.5 or 10 spots, respectively).
Adoptive Immune Transfer of Hepatitis B Virus Specific Immunity From Immunized Living Liver Donors to Liver Recipients

FIGURE 2. Donor/recipient pair 1: Hepatitis B virus (HBV)-specific immunity of the donor pretransplantation and the recipient pre- and posttransplantation. The x-axis indicates time points of analysis. (A) The y-axis shows anti-HBs titers in IU/L of the donor (SYMBOL) and the HBV negative recipient (SYMBOL). The curve indicates the half-life value time of antibodies to hepatitis B virus surface antigen (anti-HBs) derived from blood products during the transplantation. Negative (-) values for hepatitis B virus surface antigen (HBsAg) and antibodies to hepatitis B virus core antigen (anti-HBc) detection are indicated at the top. (B) The y-axis shows the ratio between stimulated and unstimulated proliferations (stimulation index) of the donor and the HBV negative recipient using l-HBsAg as stimulus. The horizontal line indicates the cut-off (stimulation index of 2.5). n.t.: not tested.

Summary

In 17 Clinical trials: Sci-B-Vac was shown to be safe & highly immunogenic:

- Low dose/inj.
- Rapid (early/higher) immune responses
- High sero-protection Rates
- Current data suggest that the regime of Sci-B-Vac equally protects neonates from e-antigen +ve or e-antigen –ve mothers.
- Induces sero-conversion in non-responders
Bypass of non-response to conventional using a Pre-S/S immunization against HBV vaccine
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
Study design

- Open
- Randomized
- Comparative
- Controlled
- Parallel-group
Study aims

Primary objective

To compare immunization with a PreS1/PreS2/S hepatitis B vaccine to conventional yeast derived HBV vaccine after one or two additional doses in healthy volunteers failing seroconversion after ≥4 prior vaccinations

Secondary objective

To evaluate immunogenicity of the two vaccines in low responders after ≥4 and non responders after 3 prior vaccinations
Multy-center (8 centers)

- Switzerland:
  - Lausanne (n=42)
  - Lugano (n=8)
  - Basel (n=8)

- Israel:
  - Tel Aviv (n=60)
  - Jerusalem (n=29)

- The Netherlands:
  - Rotterdam (n=29)
  - Utrecht (n=30)

- Austria:
  - Vienna (n=505)
Vaccines

- VACCINE I (group A- Sci B Vac):
  0.5 ml Al(OH)3 HBV vaccine: 10µg HB S/preS1/preS2 antigen

- VACCINE II (group B, Engerix B)
  0.5 ml Al(OH)3 HBV vaccine: 20 µg HBsAg small antigen

Ratio: 2:1
Inclusion criteria

- Age: ≥18 years
- Non responders (HBs ≤ 9 IU/l) after ≥3 injections of conventional vaccine, or
- Low responders (HBs ≥ 10 to ≤99 IU/l) after ≥4 injections of conventional vaccine
Exclusion criteria

- HBs antigenemia
- Anti-HBc seropositivity
- Severe atopy
- Liver disease
- Drug-induced immunosuppression
- Investigational drug within 30 days
- Immunoglobulins or blood transfusion in last 3 months
- General contraindications against vaccination
- Pregnancy or lactation
Study population

Randomized
(n=719)

Pre-S/S vaccine
(n=479)
- NR after ≥4 vacc.
  (n=226)
- LR after ≥4 vacc.
  NR after 3 vacc.
  (n=253)

Conventional
(n=237)
- NR after ≥4 vacc.
  (n=107)
- LR after ≥4 vacc.
  NR after 3 vacc.
  (n=130)
### Studypopulation II

<table>
<thead>
<tr>
<th></th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; generation</th>
<th>Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study population</strong></td>
<td>474 (ITT)</td>
<td>235 (ITT)</td>
</tr>
<tr>
<td><strong>Nonresponder after ≥4 vaccinations (1°)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>224 (m/f: 126/98)</td>
<td>107 (m/f: 62/42)</td>
</tr>
<tr>
<td>Age (a)</td>
<td>50,2 (20,2-76,3)</td>
<td>49,6 (19,7-78,5)</td>
</tr>
<tr>
<td><strong>Lowresponder after≥4/Nonresponder after ≥3 vaccinations (2°)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>250 (m/f: 146/104)</td>
<td>129 (m/f: 76/53)</td>
</tr>
<tr>
<td>Age (a)</td>
<td>49,7 (18,3-80,1)</td>
<td>52,2 (21,4-78,6)</td>
</tr>
<tr>
<td><strong>No. pre-vaccinations ≥5 (all vaccinees)</strong></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>236 (49,2%)</td>
<td>118 (49,8%)</td>
</tr>
</tbody>
</table>
Time schedule

- **Blood draw**
  - day 1
  - day 36±7
  - day 85±7
  - day 120±7

- **Vaccination**

(*) if anti-HBs <100 IU/l

(Subset: HLA)

Follow-up
Immunogenicity
**1° study population:**

**Sero-protection** (after 1\textsuperscript{st} or 2\textsuperscript{nd} additional injection)

![Bar chart showing sero-protection rates for different vaccines.]

- **3rd generation vaccine:**
  - Response rate at 100 IU/l: 35.7% (p=0.006)
  - Response rate at 10 IU/l: 81.7% (p<0.001)

- **Conventional vaccine:**
  - Response rate at 100 IU/l: 20.8%
  - Response rate at 10 IU/l: 49.1%
2° study population:

Seroprotection (after 1^{st} or 2^{nd} additional injection)

![Bar chart showing seroprotection % at 100 IU/l for 3rd generation vaccine and conventional vaccine. The 3rd generation vaccine has a seroprotection of 64.0%, while the conventional vaccine has a seroprotection of 40.3%. The p-value is p<0.001.](image-url)
Geometric Mean Titres - GMT

- Primary population: GMT 61.4, p=0.054
- Secondary population: GMT 153.7, p<0.001

3rd generation vaccine vs Conventional vaccine
Safety
<table>
<thead>
<tr>
<th>MedDRA system organ class/preferred term</th>
<th>Third-generation vaccine</th>
<th>Conventional vaccine</th>
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</thead>
<tbody>
<tr>
<td>Any vaccine-related adverse event</td>
<td>284 (59.4%)</td>
<td>101 (42.6%)</td>
</tr>
<tr>
<td>General disorders &amp; administrative site conditions</td>
<td>266 (55.6%)</td>
<td>93 (39.2%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>76 (15.9%)</td>
<td>28 (11.8%)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>46 (9.6%)</td>
<td>14 (5.9%)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>215 (45.0%)</td>
<td>66 (27.8%)</td>
</tr>
<tr>
<td>Injection site pruritus</td>
<td>32 (6.7%)</td>
<td>12 (5.1%)</td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>32 (6.7%)</td>
<td>8 (3.4%)</td>
</tr>
<tr>
<td>Malaise</td>
<td>32 (6.7%)</td>
<td>18 (7.6%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>8 (1.7%)</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>Musculoskeletal &amp; connective tissue disorders</td>
<td>86 (18.0%)</td>
<td>29 (12.2%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>27 (5.6%)</td>
<td>14 (5.9%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>75 (15.7%)</td>
<td>26 (11.0%)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>14 (2.9%)</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (2.9%)</td>
<td>1 (0.4%)</td>
</tr>
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</table>
Serious Adverse Events (SAEs)

- N=16
- 3% 3rd generation vaccine
- 0.8% conventional vaccine
- Only 1 SAE vaccine-related:
  One day after 3rd generation vaccine:
  Severe pain, hives, facial oedema, hot feeling
  → resolved without sequelae (responder)
Long-term follow-up
Long-term follow-up
Study population

<table>
<thead>
<tr>
<th></th>
<th>3rd Generation</th>
<th>Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. FU</td>
<td>437</td>
<td>216</td>
</tr>
<tr>
<td>ITT-FU analysis</td>
<td>209</td>
<td>63</td>
</tr>
</tbody>
</table>

ITT-FU population:

All subjects who successfully completed the core study (anti-HBs $\geq 100$ IU/l)
Follow-up
Schedule of assessments

*) if anti-HBs <100 IU/l after 2nd vaccination
Long-term follow-up

Sero protection rate at 100 IU/l

<table>
<thead>
<tr>
<th>Month</th>
<th>3rd generation</th>
<th>Conventional</th>
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</thead>
<tbody>
<tr>
<td>Month 6</td>
<td>59.5%</td>
<td>10%</td>
</tr>
<tr>
<td>Year 1</td>
<td>29.1%</td>
<td>13.6%</td>
</tr>
<tr>
<td>Year 2</td>
<td>23.4%</td>
<td>17.9%</td>
</tr>
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</table>

* p = 0.302
* p = 0.016
* p = 0.533
Pre S/S Vaccine in Non-responders

Summary –

• Significantly higher immunogenicity after 2 additional injections of 3rd generation PreS/S vaccine compared to conventional S vaccine at anti-HBs 10 and 100 IU/l level

• Influence of age, BMI and gender less pronounced in 3rd generation PreS/S vaccinees

• Higher reactogenicity after 3rd generation compared to conventional vaccine

• Confirms link between non response and DRB1*03 and *07, DQB1*02 HLA loci
Humoral immune response in 19 non responders immunized with Sci B Vac

Roggendorf M. et al
Cellular immune response in 19 non-responders immunized with Sci B Vac

Roggendorf M. et al.
Acknowledgements

Ruth Adler  
Yaffa Ashur  
Chezi Barenholz  
Ron Dagan  
Devorah Diminsky  
Marian Gorecki  
Yaron Ilan  
Ronit Koren  
Judy Lau  
George Lau  
Michael Roggendorf  
Arnon Nagler  
Amos Panet  
Michael Shapira  
Raul Raz  
Pamela Rendi-Wagner et al.  
Ivy Yap  
Shimon Slavin
The Hadassah-Hebrew University Medical Center
Jerusalem

Thank You