Mathematical model of the antibody response to hepatitis B vaccines: implications for reduced schedules.

JN Wilson, DJ Nokes, GF Medley. Warwick University, UK
D Shouval. Hadassah University Hospital, Israel
Introduction:
different measures of vaccine effectiveness

- **Vaccine efficacy** (reduction in incidence of infection)

- **Vaccine immunogenicity** (antibody response to vaccine)
  - Often assumed to be directly related to efficacy
  - Used in support for vaccine licensure

- “Boostqbility” (immune memory)
Reduced number of HBV vaccine doses

- Limited data on vaccine efficacy with different schedules

- Interestingly no difference in incidence of HBsAg+ infection in 3 RCTs

<table>
<thead>
<tr>
<th>RCT</th>
<th>follow-up</th>
<th>doses</th>
<th>n</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hong Kong</td>
<td>22 yrs</td>
<td>2 v 3</td>
<td>318</td>
<td>Yuen 1999</td>
</tr>
<tr>
<td>Zambia</td>
<td>9 yrs</td>
<td>1 v 2 v 3</td>
<td>255</td>
<td>Van der Sande 2007</td>
</tr>
<tr>
<td>Italy</td>
<td>10 yrs</td>
<td>2 v 3</td>
<td>124</td>
<td>Da Villa 1997</td>
</tr>
</tbody>
</table>

- What is optimum vaccine schedule?
- Why use models to address this question?
A model of the antibody response to vaccination
Why use a mathematical model?

- Allows a quantitative (mathematical) description of a system
- Makes explicit assumptions about interactions and rates
- Allows comparison of model’s predictions to observed data
- Allows predictions of untested scenarios (vaccination schedules)
  - (eg 7 doses of vaccine?!)
Method: HBV vaccine model definitions

- **Immune Memory**
  - defined as the “ability to produce antiHBs”
  - clonal expansion memory B and T<sub>H</sub> cell
  - generation of cytokines

- **Immunity**
  - >10 mIU/ml (actual or potential)

- **Priming**
  - the generation of the “ability to produce antiHBs”

- **Boosting**
  - the actual production of antiHBs in the circulation (mIU/ml)
3 compartment mathematical model:

- **V** - Vaccine antigen (μg)
  - antigenaemia ~2 weeks

- **M** - Immune memory (mIU/ml)
  - potential to produce antibody

- **A** - Circulating antibody (mIU/ml)
  - non-exponential decay
Model structure

\[
\begin{array}{c}
V \\
\sigma \\
A
\end{array} 
\rightarrow_{\gamma} 
\begin{array}{c}
\text{M} \\
\beta
\end{array} 
\rightarrow_{\delta} 
\begin{array}{c}
A
\end{array} 
\rightarrow_{\mu}
\]
Engerix-B 20μg
V

A
HBV vaccine model (Excel spreadsheet)
Individual data requested:

- Dates and doses of vaccine, antiHBs levels
- Inclusion: RCTs and observational studies
- Exclusion: non-responders, children of HBsAg+ mothers
- 1,923 individuals
- 10,815 anti-HBs measurements
- 8 different HBV vaccines, 6 countries
Statistical analysis:

- Model simulated individual schedules
- 5 parameters optimised using Maximum likelihood methods
- fixed 2 parameters (Ag and Ab decay)
- Percentage error variation ($R^2$)
  - goodness of fit
# Results

<table>
<thead>
<tr>
<th>No. of individuals</th>
<th>Vaccine</th>
<th>ω (µg)</th>
<th>Schedule (months)</th>
<th>β</th>
<th>γ</th>
<th>N</th>
<th>R²% (individual)</th>
<th>R²% (GMT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>Engerix-B®</td>
<td>20</td>
<td>0-1-2-12</td>
<td>0.013</td>
<td>0.018</td>
<td>14.0</td>
<td>84%</td>
<td>94%</td>
</tr>
<tr>
<td>50</td>
<td>SL*</td>
<td>20</td>
<td>0-1-2-12</td>
<td>0.010</td>
<td>0.016</td>
<td>14.0</td>
<td>79%</td>
<td>95%</td>
</tr>
<tr>
<td>35</td>
<td>Engerix-B®</td>
<td>20</td>
<td>0-1-6</td>
<td>0.094</td>
<td>0.005</td>
<td>11.0</td>
<td>85%</td>
<td>97%</td>
</tr>
<tr>
<td>9</td>
<td>Engerix-B®</td>
<td>20</td>
<td>0-1-6</td>
<td>0.070</td>
<td>0.019</td>
<td>11.2</td>
<td>79%</td>
<td>94%</td>
</tr>
<tr>
<td>8</td>
<td>Engerix-B®</td>
<td>20</td>
<td>0-6</td>
<td></td>
<td></td>
<td></td>
<td>92%</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>BioHepB®</td>
<td>10</td>
<td>0-1-6</td>
<td>0.023</td>
<td>0.117</td>
<td>12.7</td>
<td>78%</td>
<td>96%</td>
</tr>
<tr>
<td>10</td>
<td>BioHepB®</td>
<td>10</td>
<td>0-6</td>
<td></td>
<td></td>
<td></td>
<td>89%</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>HBV/MF59</td>
<td>10</td>
<td>0-1-6</td>
<td>0.016</td>
<td>0.366</td>
<td>14.0</td>
<td>67%</td>
<td>77%</td>
</tr>
<tr>
<td>36</td>
<td>HBV/MF59</td>
<td>10</td>
<td>0-2</td>
<td></td>
<td></td>
<td></td>
<td>99%</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>HBV/MF59</td>
<td>10</td>
<td>0-6</td>
<td></td>
<td></td>
<td></td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>Recombivax®</td>
<td>10</td>
<td>0-1-6</td>
<td>0.014</td>
<td>0.041</td>
<td>11.4</td>
<td>52%</td>
<td>88%</td>
</tr>
<tr>
<td>37</td>
<td>Recombivax®</td>
<td>20</td>
<td>0-2</td>
<td></td>
<td></td>
<td></td>
<td>92%</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>Recombivax®</td>
<td>20</td>
<td>0-6</td>
<td></td>
<td></td>
<td></td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td>88</td>
<td>Recombivax®</td>
<td>10</td>
<td>0-6-24</td>
<td>0.365</td>
<td>0.028</td>
<td>11.5</td>
<td>71%</td>
<td>88%</td>
</tr>
<tr>
<td>85</td>
<td>Recombivax®</td>
<td>20</td>
<td>0-6-24</td>
<td></td>
<td></td>
<td></td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>126</td>
<td>Heberbiovac®</td>
<td>10</td>
<td>0-1-2-12</td>
<td>0.033</td>
<td>0.023</td>
<td>10.1</td>
<td>36%</td>
<td>85%</td>
</tr>
<tr>
<td>140</td>
<td>Heberbiovac®</td>
<td>20</td>
<td>0-1-2-12</td>
<td></td>
<td></td>
<td></td>
<td>76%</td>
<td></td>
</tr>
<tr>
<td>676</td>
<td>HevacB®</td>
<td>10</td>
<td>0-1-2-14</td>
<td>0.006</td>
<td>0.038</td>
<td>14.0</td>
<td>73%</td>
<td>97%</td>
</tr>
<tr>
<td>331</td>
<td>HBVax I®</td>
<td>20</td>
<td>0-1-6</td>
<td>0.018</td>
<td>0.012</td>
<td>9.3</td>
<td>52%</td>
<td>60%</td>
</tr>
<tr>
<td>36</td>
<td>Engerix-B®</td>
<td>20</td>
<td>0-48</td>
<td>0.001</td>
<td>0.043</td>
<td>14.0</td>
<td>85%</td>
<td>94%</td>
</tr>
<tr>
<td>42</td>
<td>Engerix-B®</td>
<td>20</td>
<td>0-1-6</td>
<td></td>
<td></td>
<td></td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.056</td>
<td>0.050</td>
<td>12.3</td>
<td>65%</td>
<td>87%</td>
</tr>
</tbody>
</table>
Results

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
0-1-2-12 month schedule

Engerix-B  20µg
0-1-6 and 0-6 month schedules

Engerix-B 20µg
0-2 and 0-6 schedules

Recombivax HB 20µg
0-1-6 and 0-48 month schedules

• Some non-responders are primed
  • antiHBs levels remain low, but immune memory generated
  • respond to boosting (and infection?)

Engerix-B 20µg
Implications

1. A single vaccine dose causes priming of immune memory:
   - As evidenced by the similar absolute increase in antiHBs after 6 months in 0-6 and 0-1-6 schedules i.e. both schedules generate similar amounts of immune memory

2. Some individuals with antiHBs<10mIU/ml are immune
   - either primed but not boosted
   - or Ab decay post-booster

3. If immune memory is maintained in the absence of antiHBs then booster doses are not required to maintain immunity
Summary

- Constructed a mathematical model of antibody response:
  - Quantitative description; Explicit assumptions; Predictions

- Compared model predictions and data using 3 parameters (good explanatory power – high $R^2$)

- Generated hypothesis: do we need 3 doses of HBV vaccine?
  - Successful priming with a single dose
Acknowledgements

- Dr. G Leroux-Roels, Dept. Clinical Chemistry, University of Gent, Belgium.
- Dr. J Boslego and Dr. MA Abramson, Merck & Co., Pennsylvania, USA.
- Professor D Shouval and Dr. R Adler, Liver Unit / Division of Medicine, Hadassah Medical Organization, Jerusalem, Israel.
- Professor Trivello and Dr. B Vincenzo, Institute of Hygiene, University of Padua, Italy.
- Professor Mezzelani and Dr. Lugoboni, Institute of Clinica Medica, University of Verona, Italy.
- Dr. J Wiström, Dept. Infectious Diseases, University Hospital of Umea, Sweden.
- Dr. H Hsu, Chiron Corporation, USA.
- Dr. M Gonzalez Griego, CIGB, Cuba.
Do immunological results translate into protection from infection?

Vaccine efficacy (VE) = 1 - incidence in vaccinated population / incidence in unvaccinated population
Serological confusion:

Imprecise:
- non-responders (< 10 mIU/ml)
- seroconversion (>10 mIU/ml)

Prefer:
- failure to prime
- ability to produce antiHBs >10 mIU/ml
### Study details

Table 1
Study details and optimization results for 3-parameter model: (ω is vaccine dose, β, γ and N—see Table 2, MLE is maximum likelihood estimate; MLE/assays allows comparison between groups). Groups varying only in dose size or schedule within a study were analysed.

<table>
<thead>
<tr>
<th>Study no.</th>
<th>No. of individuals</th>
<th>No. of assays</th>
<th>Vaccine</th>
<th>ω (µg)</th>
<th>Schedule (months)</th>
<th>β</th>
<th>γ</th>
<th>N</th>
<th>MLE</th>
<th>MLE/assays</th>
<th>R² (%) (individual)</th>
<th>R² (%) (GMT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 [18]</td>
<td>50</td>
<td>300</td>
<td>Engerix-B*</td>
<td>20</td>
<td>0–1–2–12</td>
<td>0.013</td>
<td>0.018</td>
<td>14.0</td>
<td>538.7</td>
<td>1.8</td>
<td>84%</td>
<td>94%</td>
</tr>
<tr>
<td>1.2</td>
<td>50</td>
<td>300</td>
<td>SL*</td>
<td>20</td>
<td>0–1–2–12</td>
<td>0.10</td>
<td>0.16</td>
<td>14.0</td>
<td>566.0</td>
<td>1.9</td>
<td>79%</td>
<td>95%</td>
</tr>
<tr>
<td>2 [16]</td>
<td>35</td>
<td>135</td>
<td>Engerix-B*</td>
<td>20</td>
<td>0–1–6</td>
<td>0.094</td>
<td>0.005</td>
<td>11.0</td>
<td>219.3</td>
<td>1.6</td>
<td>85%</td>
<td>97%</td>
</tr>
<tr>
<td>3.1 [21]</td>
<td>9</td>
<td>88</td>
<td>Engerix-B*</td>
<td>20</td>
<td>0–1–6</td>
<td>0.070</td>
<td>0.019</td>
<td>11.2</td>
<td>275.5</td>
<td>1.8</td>
<td>79%</td>
<td>94%</td>
</tr>
<tr>
<td>3.2</td>
<td>8</td>
<td>63</td>
<td>Engerix-B*</td>
<td>20</td>
<td>0–6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>92%</td>
</tr>
<tr>
<td>3.3</td>
<td>10</td>
<td>92</td>
<td>BioHepB®</td>
<td>10</td>
<td>0–1–6</td>
<td>0.023</td>
<td>0.117</td>
<td>12.7</td>
<td>339.3</td>
<td>1.9</td>
<td>78%</td>
<td>96%</td>
</tr>
<tr>
<td>3.4</td>
<td>10</td>
<td>85</td>
<td>BioHepB®</td>
<td>10</td>
<td>0–6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>89%</td>
</tr>
<tr>
<td>4.1 [19]</td>
<td>47</td>
<td>219</td>
<td>HBV/MF59</td>
<td>10</td>
<td>0–1–6</td>
<td>0.016</td>
<td>0.366</td>
<td>14.0</td>
<td>1259.8</td>
<td>2.0</td>
<td>67%</td>
<td>77%</td>
</tr>
<tr>
<td>4.2</td>
<td>36</td>
<td>208</td>
<td>HBV/MF59</td>
<td>10</td>
<td>0–2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>99%</td>
</tr>
<tr>
<td>4.3</td>
<td>36</td>
<td>207</td>
<td>HBV/MF59</td>
<td>10</td>
<td>0–6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>88%</td>
</tr>
<tr>
<td>4.4</td>
<td>35</td>
<td>162</td>
<td>Recombivax®</td>
<td>10</td>
<td>0–1–6</td>
<td>0.014</td>
<td>0.041</td>
<td>11.4</td>
<td>1187.4</td>
<td>2.1</td>
<td>52%</td>
<td>88%</td>
</tr>
<tr>
<td>4.5</td>
<td>37</td>
<td>209</td>
<td>Recombivax®</td>
<td>20</td>
<td>0–2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>92%</td>
</tr>
<tr>
<td>4.6</td>
<td>36</td>
<td>200</td>
<td>Recombivax®</td>
<td>20</td>
<td>0–6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>88%</td>
</tr>
<tr>
<td>5.1 [20]</td>
<td>88</td>
<td>616</td>
<td>Recombivax®</td>
<td>10</td>
<td>0–6–24</td>
<td>0.365</td>
<td>0.028</td>
<td>11.5</td>
<td>2491.9</td>
<td>2.0</td>
<td>71%</td>
<td>88%</td>
</tr>
<tr>
<td>5.2</td>
<td>85</td>
<td>618</td>
<td>Recombivax®</td>
<td>20</td>
<td>0–6–24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>94%</td>
</tr>
<tr>
<td>6.1 [22]</td>
<td>125</td>
<td>624</td>
<td>Heberbiovac®</td>
<td>10</td>
<td>0–1–2–12</td>
<td>0.033</td>
<td>0.023</td>
<td>10.1</td>
<td>2415.0</td>
<td>1.9</td>
<td>36%</td>
<td>85%</td>
</tr>
<tr>
<td>6.2</td>
<td>140</td>
<td>673</td>
<td>Heberbiovac®</td>
<td>20</td>
<td>0–1–2–12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>76%</td>
</tr>
<tr>
<td>7.1 [17]</td>
<td>676</td>
<td>3952</td>
<td>HevacB®</td>
<td>10</td>
<td>0–1–2–14</td>
<td>0.006</td>
<td>0.038</td>
<td>14.0</td>
<td>7961.5</td>
<td>2.0</td>
<td>73%</td>
<td>97%</td>
</tr>
<tr>
<td>7.2</td>
<td>331</td>
<td>1648</td>
<td>HBVat 1st®</td>
<td>20</td>
<td>0–1–6</td>
<td>0.018</td>
<td>0.012</td>
<td>9.3</td>
<td>3587.5</td>
<td>2.2</td>
<td>52%</td>
<td>60%</td>
</tr>
<tr>
<td>8.1 [5]</td>
<td>36</td>
<td>219</td>
<td>Engerix-B*</td>
<td>20</td>
<td>0–48</td>
<td>0.001</td>
<td>0.043</td>
<td>14.0</td>
<td>600.2</td>
<td>1.5</td>
<td>85%</td>
<td>94%</td>
</tr>
<tr>
<td>8.2</td>
<td>42</td>
<td>197</td>
<td>Engerix-B*</td>
<td>20</td>
<td>0–1–6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>94%</td>
</tr>
</tbody>
</table>

Average<br>
|                   | 1923             | 10815          | 0.056    | 0.050  | 12.3   | 21472.2| 2.0    | 65%    | 87%          |

All data<br>
|                   | 21               | 152            | 0.031    | 0.025  | 11.3   | 24194.5| 2.2    | 56%    | 66%          |

All geometric mean titre (GMT) data analysed together.

---

*a Average weighted by number of anti-HBs measurements in each study.

*b All individual data analysed together.

*c All geometric mean titre (GMT) data analysed together.
Model v GMT data