Evidence of protection against clinical and chronic hepatitis B infection 20 year after infant vaccination in Thailand

## Burden of disease in Thailand

### Liver diseases (2004)

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Death per 100,000 X 1000 population</td>
<td>Death per 100,000 X1000</td>
</tr>
<tr>
<td>Liver cancer (HCC + cholangiocarcinoma)</td>
<td>18.8 61</td>
<td>8.7 27</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>8.2 26</td>
<td>3.5 11</td>
</tr>
</tbody>
</table>

BMC public Health 2011;11:53
1986-1989
HBV carrier in pregnant women 6%
Neonates were vaccinated within 12 hrs.
# HB Vaccination Clinical Trial in Newborn

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mother</th>
<th>Schedule</th>
<th>HBIG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986-87</td>
<td>222</td>
<td>S+/e+, S+/e-, S-/e-</td>
<td>0, 1, 2, 12</td>
<td>No</td>
</tr>
<tr>
<td>1987-88</td>
<td>65</td>
<td>S+/e+</td>
<td>0, 1, 2, 12</td>
<td>Yes</td>
</tr>
<tr>
<td>1988-89</td>
<td>119</td>
<td>S+/e+</td>
<td>0, 1, 6</td>
<td>Yes/No</td>
</tr>
</tbody>
</table>
Protective efficacy against chronic carriage of infants born to HBeAg +ve mother

Poovorawan et al. Arch Dis Child 1997

<table>
<thead>
<tr>
<th>Group</th>
<th>Vaccine Schedule</th>
<th>HBIg</th>
<th>chronic carrier</th>
<th>Protective efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0, 1, 2, 12</td>
<td>No</td>
<td>2/59</td>
<td>94.8</td>
</tr>
<tr>
<td>2</td>
<td>0, 1, 2, 12</td>
<td>Yes</td>
<td>1/65</td>
<td>97.6</td>
</tr>
<tr>
<td>3</td>
<td>0, 1, 6</td>
<td>No</td>
<td>3/59</td>
<td>92.2</td>
</tr>
<tr>
<td>4</td>
<td>0, 1, 6</td>
<td>Yes</td>
<td>0/60</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>6/243</td>
<td>96.2</td>
</tr>
</tbody>
</table>
High Protective Efficacy in Neonates with or without HBIg

Long Term Follow-up of high risk neonates vaccinated against hepatitis B

20 years follow up
GMT evolution 0, 1, 6 months schedule

- **Cohort 4**: booster + HBlg
- **Cohort 5**: no booster + HBlg
- **Cohort 6**: booster no HBlg
- **Cohort 7**: no booster no HBlg
Long-Term Benefit of Hepatitis B Vaccination among Children in Thailand with Transient Hepatitis B Virus Infection Who Were Born to Hepatitis B Surface Antigen–Positive Mothers

Yong Poovorawan,¹ Voranush Chongsrisawat,¹ Apiradee Theamboonlers,¹ Karthik Srinivasa,³ Yanee Hutagalung,² Hans L. Bock,⁴ and Bernard Hoet⁴

¹Center of Excellence in Clinical Virology, Faculty of Medicine, Chulalongkorn University, and ²GlaxoSmithKline Biologicals, Bangkok, Thailand; ³GlaxoSmithKline Biologicals, Bangalore, India; ⁴GlaxoSmithKline Biologicals, Rixensart, Belgium

Background. Transmission of hepatitis B virus (HBV) from carrier mothers to their babies appears to be one of the most important factors influencing the prevalence of chronic HBV infection in areas of high hepatitis B endemicity.

Methods. Infants born to HBV surface antigen (HBsAg)–positive mothers who were or were not positive for HBV e antigen (HBeAg) or to mothers who were negative for both HBsAg and HBeAg have been followed for 17 years for serological evidence of HBV infection. These infants were divided into 2 groups on the basis of their hepatitis B vaccination protocols: group 1 received vaccine at birth and 1, 2, and 12 months later, and group 2 received vaccine at birth and 1 and 6 months later. Follow-up involved annual clinic visits, during which a blood sample was taken and analyzed for the presence of HBsAg, antibody to HBsAg, and antibody to HBV core antigen (HbcAg). Selected blood samples that tested positive for HBV markers during ≥2 consecutive visits separated by a long interval were further investigated by polymerase chain reaction to detect HBV DNA.

Results. Transient presence of HBsAg or transient and/or long-term presence of antibody to HbcAg suggested that this population was heavily exposed to HBV during the follow-up period. Despite these findings, no new cases of chronic HBV infection were observed. None of the subjects with transient presence of HBsAg had any clinical symptoms of liver disease.

Conclusions. This study demonstrates the efficacy of the HBV vaccine and its ability to protect against symptomatic disease.
Immunological patterns Observed in the study (204)

Chronic HBsAg and Anti-HBc seropositivity
Chronic HBV infection (n=6)

Anti-HBc seropositivity before Month 12 and all subsequent time points
Infection occurring during the first year (n=8)

Anti-HBc seropositivity before Month 12 and all subsequent time points
Infection occurring after the first year (n=15)

Intermittent Anti-HBc seropositivity
Transient infection (n = 15)

HBsAg seropositive at only ONE time point
Isolated event (n = 8)

Poovorawan JID 2009;200:33-38
Long-Term Humoral and Cellular Immune Response to Hepatitis B Vaccine in High-Risk Children 18–20 Years After Neonatal Immunization

Teeraporn Chinchai,1 Chintana Chirathaworn,2 Kesmanee Priaananthathavorn,3 Apiradee Theamboonlers,3 Yanee Hutagalung,4 Bock P. Hans L.,4 Pattarawat Thantiworasit,5 and Yong Poovorawan3

Abstract

Eighty-seven high-risk individuals in Thailand who had received a complete course of recombinant HBV vaccine 18–20 y ago were investigated with regard to their immunological memory. To evaluate humoral immunity, anti-HBs antibody titers were measured. Cellular immunity was determined by ELISPOT to detect HBV-specific IFN-γ-producing cells. Overall 83.9% of participants developed circulating anti-HBs (titer ≥1 mIU/mL) and 58.6% were seroprotected (titer ≥10 mIU/mL). As for cellular immunity, 50.6% were positive on ELISPOT. Moreover, there was no correlation between the level of anti-HBs and positive ELISPOT results. However, the proportion of subjects (26.5%) whose titer of HBsAg declined below 10 mIU/mL was significantly lower than those with positive ELISPOT results.
Anti-HBs status (A) and numbers of seropositive participants (B) who displayed HBsAg-specific IFN-γ-producing cells.

HBsAg-specific IFN-γ-producing cells or SFC (A) and numbers of SFC-positive participants (B) who were anti-HBs seropositive.
Evolution of anti-HBs geometric mean antibody concentrations in pooled boosted and unboosted groups until Year 20 (HB vaccine; 0, 1, 2 and 12 mos)
Evolution of anti-HBs geometric mean antibody concentrations in each group until Year 20 (ATP persistence cohort). Number in each group: (s+/e+) boosted N= 14, unboosted N=17; (s+/e-) boosted N=26, unboosted N=19; (s-/e-) boosted N= 16, unboosted N

A: Subject who seroconverted for antibodies against HBc during the follow-up period.

B: Subject (not boosted at year 5) with >1 serological marker indicative of hepatitis B infection, unaccompanied by anti-HBs booster response or seroconversion to HBc.

C: Subject who seroconverted for antibodies against anti-HBc during the follow-up period without an anti-HBs booster response.

D: Response to possible subclinical breakthrough HBV infection in a low responder after primary and booster vaccination

# Incidence of hepatitis B infectious events in the second decade

<table>
<thead>
<tr>
<th>HBV status</th>
<th>Mother</th>
<th>Mother</th>
<th>Mother</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBsAg+HBeAg+</td>
<td>HBsAg+HBeAg-</td>
<td>HBsAg=HBeAg-</td>
</tr>
<tr>
<td></td>
<td>N = 39 (%)</td>
<td>N = 80 (%)</td>
<td>N = 28 (%)</td>
</tr>
<tr>
<td>False positive</td>
<td>4 (10.3)</td>
<td>13 (16.3)</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td>Isolated natural</td>
<td>6 (15.4)</td>
<td>5 (6.3)</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>Booster response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occult HB infection</td>
<td>10 (25.6)</td>
<td>6 (7.5)</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>Clinical HBV infection</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>New chronic HBV infection</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Poovorawan JID 2009;200:33-38
Immune response to the HBV challenge dose at Year-20
n = 29 (anti-HBs < 100 mIU/ml)

anti-HBs antibody concentrations
\( \geq 3.3\text{mIU/ml} \): 100%
\( \geq 10\text{mIU/ml} \): 96.6% (95% CI: 82.2-99.9)
\( \geq 100\text{mIU/ml} \): 93.1% (95% CI: 77.2-99.2)

Poovorawan et al.
Abstract presented at ICTP 2011, Bangkok, Thailand
Submitted for publication to a peer-review journal
GMC evolution of anti-HBs antibodies from Month-1 to Year-20 post dose-1 (vaccine schedule: 0, 1, 2, 12 months)

Year-20
Seropositive (≥ 3.3 mIU/ml): 92.0% (74.0-99.0)
Seroprotective (≥ 10mIU/ml): 64.0%(42.5-82.0)

Poovorawan et al.
Abstract presented at ICTP 2011, Bangkok, Thailand
Submitted for publication to a peer-review journal
Immune response to the HBV challenge dose at Year-20
n = 43 (anti-HBs < 100 mIU/ml)

GMC pre-challenge yr.20 < 100mIU/ml

Booster effect
Boost yr.5: 100% (76.8-100)
Unboost yr.5: 93.1% (77.2-99.2)

Poovorawan et al.
Abstract presented at ICTP 2011, Bangkok, Thailand
Pending submission to a peer-review journal
Evolution of anti-HBs geometric mean concentrations in boosted and unboosted groups

Year-20
Seropositive: 94.7%
Seroprotective: 84.2%

Year-20
Seropositive: 76.0%
Seroprotective: 44.0%

Poovorawan et al.
Abstract presented at ICTP 2011, Bangkok, Thailand
Pending submission to a peer-review journal
We would like to express our gratitude towards the entire staff of the Center of Excellence in Clinical Virology, Faculty of Medicine, Chulalongkorn University and Hospital, for their tireless effort in collecting the multitude of data required. We also would like to thank the Commission on Higher Education, CU Centenary Academic envelopment Project, Chulalongkorn Hospital for supporting our group and GSK.