Follow-up of Hepatitis B Vaccination Programs in Taiwan and Singapore

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Taiwan Experience
The 1st Nationwide Hepatitis B Vaccination Program

July 1984
Taiwan Launched
A Mass HBV Vaccination Program for
Infants to **High-risk** Mothers
(HBsAg positive)

July 1986
HB Vaccination Was
Extended to **All Newborns**
After July 1986
UNIVERSAL HEPATITIS B VACCINATION IN TAIWAN

Infants of HBeAg & HBsAg Seropositive Mothers

HBV Vaccines

HBIG*

*< 24 Hrs. after Birth

Infants of HBeAg or HBsAg Seronegative Mothers

HBV Vaccines

3 doses of recombinant vaccine given in Month 0, 1, 6.
UNIVERSAL HEPATITIS B VACCINATION IN U.S.A.

Infants of HBsAg Seropositive Mothers

HBV Vaccines + HBIG*< 24 Hrs. after Birth

Infants of HBsAg Seronegative Mothers

HBV Vaccines
HBV VACCINATION PROGRAM IN SOUTHEAST ASIA

- No Maternal Screening for HBsAg, HBeAg
- No HBIG
- All Infants Received HBV Vaccine 3 Doses
Priorities and Timetable of Hepatitis B Vaccine Program in Taiwan

<table>
<thead>
<tr>
<th>Priority</th>
<th>Year performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns of HBsAg carrier mothers</td>
<td>1984, 91</td>
</tr>
<tr>
<td>All newborns</td>
<td>1985, 90</td>
</tr>
<tr>
<td>Preschool children</td>
<td>1987 - 1990</td>
</tr>
<tr>
<td>Elementary school**</td>
<td>1991 - 1993</td>
</tr>
<tr>
<td>Junior and high school</td>
<td></td>
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</tbody>
</table>
| Others                   | * July 1987 ~ Sep. 1990: Vaccinate preschool on voluntary base with payment. After Oct. 1990: Catch-up vaccination without charge for children up to 1st graders. ** After July 1991, all first graders were checked for their vaccination record. Non- or incompletely vaccinated pupils needed to be vaccinated. Department of Health, Taiwan

Department of Health, Taiwan
Immunization Coverage

(1997-1999 Birth Cohort)

(Primary School Entrants, 2000)

*Data of OPV, DPT, JE booster & MMR(99) is incomplete

Department of Health, Taiwan
Long-term immunogenicity and efficacy of universal HB vaccination in Taiwan

Seroprevalence of HBsAg

Positive rate of HBsAg, %

*: Average positive rates of HBsAg (age< 15 in 1999)

Seroprevalence of Anti-HBc

Positive rate of Anti-HBc, %

* : Average positive rate of anti-HBc (age<15 yrs)

Hepatitis B vaccination and control of hepatitis B-related liver disease

【Decrease pediatric fulminant hepatic failure】

【Decrease pediatric Hepatocellular carcinoma】

【Review】
Universal HBV Vaccination and Decreased Mortality from Fulminant Hepatitis in Infants in Taiwan

Annual mortality rate of fulminant hepatitis per 100,000 infants in Taiwan

1974-1984: 5.36*  
1985-1998: 1.71*

Universal HBV Vaccination July 1984

*The average mortality rate per 10^5 infants  
Mortality Ratio: 3.2 (p <0.001)

### Incidence Rates Ratios of HBV-Positive v.s. HBV-Negative FHF within 15 Years of the Universal Vaccination Program

<table>
<thead>
<tr>
<th></th>
<th>Year 1985~1999 Case no. (per 10^5)</th>
<th>IRR(&lt;1Y Vs 1~15 Yrs)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBV (+) FHF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 yr</td>
<td>33(0.74)</td>
<td>54.2 [26.1, 123.2]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>1-15 yr</td>
<td>10(0.014)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HBV (-) FHF</strong></td>
<td></td>
<td>15.2 [8.5, 27.2]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&lt;1 yr</td>
<td>25(0.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-15 yr</td>
<td>27(0.039)</td>
<td></td>
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</tr>
</tbody>
</table>

**IRR:** incidence rate ratio; [95% C.I.];

Infantile HBV-positive FHF related to HBsAg(+)/HBeAg(-) mothers

- Maternal HBsAg was found to be positive in 97% of the infants with HBV-positive FHF, and HBeAg was found to be negative in 84% of these infants.
- 74% of all HBV-positive FHF patients had been vaccinated.
- HBV-positive FHF was prone to develop in infants born to HBeAg-negative, HBsAg-carrier mothers; these infants had not received HBIG according to the vaccination program in place.

A Vaccination Program to Prevent A Virus Infection Can Prevent Its Related Cancer
EVALUATION OF THE EFFECT OF UNIVERSAL HEPATITIS B VACCINATION ON HEPATOMA

- Peak Age of Hepatoma: 40-60 Years of Age
- It May Take > 40 Years (Year 2024 or later) to See A Substantial Decrease of Hepatoma in Adults
Childhood Hepatoma in Taiwan

- Incidence ($/10^5$) & HB/HCC ratio
  - Taiwan: HB 0.37, HCC 0.70; HB/HCC: 1:2
  - U.S.: Total: 0.02-0.2; HB/HCC: 3.5:1
  (HB: hepatoblastoma; HCC: hepatocellular carcinoma)

- Childhood HCC
  - Nearly 100% HBsAg positive; 86% HBeAg negative

- Histology:
  - Tumor Portion: Similar to Adult Hepatoma
  - Non-tumorous Portion: Liver Cirrhosis 81% (21/26)
  - HBV genome integration into host genome

Is HCC in Children Closely Related to HBV and Similar to HCC in Adults? (Yes)

Can the Incidence of HCC in Children Reflect the Effect of HBV Vaccination on HCC?
HB Vaccination Reduces the Incidence of Hepatocellular Carcinoma in 6-14 Yrs Old

Incidence per 100,000


HCC Brain tumours

vaccination

6 yrs

EFFECT OF UNIVERSAL HEPATITIS B VACCINATION ON HCC IN TAIWAN

<table>
<thead>
<tr>
<th>Birth Year</th>
<th>HCC Incidence in Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>1974-84</td>
<td>0.52/10^5</td>
</tr>
<tr>
<td>1984-86</td>
<td>0.13/10^5</td>
</tr>
</tbody>
</table>

Figure. Incidence of Hepatocellular Carcinoma (HCC) in Boys and Girls Aged 6 to 14 Years

A Boys

B Girls

- Birth Cohort 1966-1977
- Birth Cohort 1978-1989

Chang MH et al. JAMA 2000; 284: 3040-42
Problems in Hepatoma Prevention by Vaccination

- **NO VACCINATION PROGRAM**
  - HBV:
    - Inadequate Resources: Asia, Africa
    - Anxiety to the Safety of Vaccine: Low Prevalence Areas
    - Ignorance
  - HCV: No Available Vaccine

- **POOR COMPLIANCE TO THE VACCINATION PROGRAM**
  - Cost Not Covered by the Government (Poor Compliance if Self-paid)
  - Anxiety to the Safety of Vaccine: Low Prevalence Areas
  - Ignorance

- **VACCINE FAILURE**
  - Intrauterine Infection
  - High Viral Load
  - Vaccine Escape Mutant
  - Genetic Hyporesponsiveness
  - Immune Compromized Host
The importance of chronic HCV infection in Taiwan

- Even HBV infection controlled by vaccination, HBsAg-negative HCC should be another problem.
- Besides of HBV, HCV infection is the major etiology of HCC in Taiwan.
Prevention and control of HBV infection in Singapore

- The Hepatitis B Info-Page (http://www.geocities.com/hbvinfo)
- Health Promotion Board: The hepatitis B immunisation programme (http://www.hpb.gov.sg/hpb/pro/pro0902.asp#3doses)
Singapore Experience
Nationwide Hepatitis B Vaccination Program

Oct. 1985

A Mass HBV Vaccination Program for Infants to High-risk Mothers (HBsAg positive)

Sep 1987

HB Vaccination Was Extended to All Newborns
UNIVERSAL HEPATITIS B VACCINATION IN SINGAPORE

Infants of HBeAg & HBsAg Seropositive Mothers

HBV Vaccines

HBIG*< 24 Hrs. after Birth

Infants of HBeAg or HBsAg Seronegative Mothers

HBV Vaccines

3 doses of recombinant vaccine given in Month 0, 1, 6.

Infants born to HBsAg carrier mothers should receive another booster dose in month 12.
Hepatitis B carrier status after vaccination

- Coverage: 85% in 1993, 91% in 1994, 94% in 1995
- For vaccinated babies born to carrier mothers, perinatal transmission has been reduced by 80% - 100%, with no carriers detected among newborns of HBeAg-negative mothers.
- In primary school children, HBsAg prevalence has dropped from 4% in 1987 to 0% in 1996.
- In secondary school children, the prevalence rate was <1% in 2001.
- Serological surveys in 1993 and 1998 showed that none of the vaccinated persons were HBsAg positive, whereas the antigen was detected in 4-5% of unvaccinated persons.
Decrease of acute hepatitis B

Incidences report of total and imported acute hepatitis B, 1982~2001

Oct. 1985 HB Vaccination

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of cases</th>
<th>Mean annual rate per 100,000*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983-85</td>
<td>27</td>
<td>1.44</td>
</tr>
<tr>
<td>1986-88</td>
<td>13</td>
<td>0.71</td>
</tr>
<tr>
<td>1989-91</td>
<td>8</td>
<td>0.43</td>
</tr>
<tr>
<td>1992-94</td>
<td>7</td>
<td>0.35</td>
</tr>
<tr>
<td>1995-97</td>
<td>3</td>
<td>0.14</td>
</tr>
<tr>
<td>1998-2001</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Age < 15 yrs
Age-gender distribution and age-specific incidence rates of acute hepatitis B, 2001

<table>
<thead>
<tr>
<th>Age group</th>
<th>Male</th>
<th>Female</th>
<th>Both (%)</th>
<th>Incidence rate per 100,000*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5 – 14</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15 – 24</td>
<td>7</td>
<td>7</td>
<td>14 (17.5)</td>
<td>2.8</td>
</tr>
<tr>
<td>25 – 34</td>
<td>36</td>
<td>6</td>
<td>42 (52.5)</td>
<td>7.6</td>
</tr>
<tr>
<td>35 – 44</td>
<td>4</td>
<td>2</td>
<td>6 (7.5)</td>
<td>0.9</td>
</tr>
<tr>
<td>45 – 54</td>
<td>11</td>
<td>2</td>
<td>13 (16.3)</td>
<td>2.6</td>
</tr>
<tr>
<td>55+</td>
<td>4</td>
<td>1</td>
<td>5 (6.3)</td>
<td>1.0</td>
</tr>
<tr>
<td>Total</td>
<td>62</td>
<td>18</td>
<td>80 (100.0)</td>
<td>2.4</td>
</tr>
</tbody>
</table>
Singapore integrated HBV vaccine administration into existing expanded childhood primary immunization program about 62% of 15 – 24 year olds will require immunisation

- Students (~14 yr-old, born after HB vaccination program): Secondary 3, Junior college 2 and centralised institute 3 in 2001, every year for 4 yrs.
- Polytechnic, university and Institute of Technical Education students (born before HB vaccination program) will be offered the program in 2001-2002.
- **free blood screening** and a **three-dose vaccination course for $25. (~12 EURO).**
- Students who have already received 3 doses of hepatitis B immunisation previously will not be given further immunisation or booster doses.
Decrease of HBsAg carrier rates and HCC incidence in non-vaccinated population

- Among national servicemen, the HBsAg-positive rate has also declined from 8.1% in 1984 to 4.4% in 1998.
- For antenatal women, the overall HBsAg prevalence was 4.4% in 1980-1981, 4.1% in 1983-1985, 2.9% in 1996, and 2.3% in 2000.
- The age-standardised incidence rate of HCC among males had also dropped from 27.8/10^5 per year during 1978 to 1982 to 19.0 /10^5 per year during 1988 to 1992.
4 Issues of this 24th VHPB meeting

- Long-term efficacy of hepatitis B vaccine and effectiveness of hepatitis B vaccination
- Immune memory induced by hepatitis B vaccine
- Current hepatitis B booster vaccination recommendations
- Potential impact of HBV mutants on hepatitis B vaccination programmes
Long term Immunogenicity and Efficacy of HBV Vaccination

- 1200 vaccinated school children, 7 years old, recruited one decade after the launch of universal HBV vaccination program.
- Determined HBsAg, anti-HBs, and anti-HBc.
- 200 of the 504 vaccinated non-carrier children with undetectable or low anti-HBs received booster vaccination at 7 years of age.
- They were observed annually until 14 years old.

Long-term immunogenicity and efficacy of universal hepatitis B virus vaccination in Taiwan

- HBsAg positive rate was 0.7%. No new HBsAg carrier was observed.
- The percentage of protective anti-HBs in 951 children without booster vaccination gradually decreased from 71.1% at age 7 years to 37.4% at age 12 years.
- Eleven children had new HBV infections with anti-HBc positivity as the only marker. (9/11 at least anti-HBc positive twice one year apart).
- None became positive for HBsAg or had detectable HBV DNA by polymerase chain reaction.
- Only 1 of the 200 children in the booster group and 2 of the 258 children in the nonbooster group developed new anti-HBc (+).

New Annual anti-HBc Seropositive Rate*

0.3% (N=3/1108) at Age 8,
0.1% (N=1/1020) at Age 9,
0.1% (N=1/958) at Age 10,
0% (N=0/925) at Age 11,
0.1% (N=1/914) at Age 12,
0.4% (N=3/769) at Age 13

* At least anti-HBc positive twice one year apart

The results suggest that routine booster vaccination may not be required to provide protection against chronic HBV infection before age 15 years.
Changes of hepatitis B surface antigen variants in carrier children before and after universal vaccination in Taiwan

- Rate of hepatitis B surface mutant at the “a” determinant site (target of HBV neutralization antibody) in children:
  - 7.8% (8/103) in those born before the vaccination program
  - 28.1% (9/32) in those born after the program

- Currently it is not a major problem in the HBV immunoprophylaxis.

Thank you for your attention!

謝謝您！