Hepatitis B Infection: Primary Prevention

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Hepatitis B Infection in Taiwan

- 2.5 million people, 15%-20% of the adult population, are carriers
- Hepatoma is the leading cause of cancer death in male
- Cirrhosis and chronic liver disease rank the 6th of the 10 leading causes of death.
- 70-80% of hepatoma and liver cirrhosis are related to the chronic HBV infection in adults.
- Launch first HBV universal infant vaccination program in the world (1984-1986)
Flow Chart of Screening and Universal Immunization-TAIWAN, Singapore

Screening for Pregnant Women

- HBsAg(-)
  - Infant
    - Vaccine only (0,1,6 mo)

- HBsAg(+)
  - HBeAg(-)
    - Infant
      - Vaccine only (0,1,6 mo)
  - HBeAg(+)
    - Infant
      - HBIG & Vaccine (0,1,6 mo)

The first dose of vaccine and HBIG are given within 24 hours after birth.

Proven efficacy; save on the cost of HBIG for infants born to HBeAg-negative mothers. But, few HBeAg-negative mothers’ babies may be susceptible.
Flow Chart of Screening and Universal Immunization-Korea, USA, Argentina

Screening for Pregnant Women

HBsAg(-)
- Infant
  - Vaccine only
    - (0,1,6 mo)

HBsAg(+)
- Infant
  - HBIG & Vaccine
    - (0,1,6 mo)

One simple and inexpensive blood test for mothers; proven efficacy
Relatively expensive due HBIG use
Flow Chart of Screening and Universal Immunization - Vietnam, Thailand (partial), Pakistan

Screening for Pregnant Women

- HBsAg (+)
  - Infant HBIG & Vaccine
  - Infant Vaccine only (0, 2, 4, 6 mo)

- HBsAg (-)
  - Infant Vaccine only (0, 2, 4, 6 mo)
  - No HBIG use

No HBIG use
Very simple and inexpensive, cost-effective, but a certain failure rate can be expected
HBsAg Prevalence declined from 9.8% to 0.6% in Children and Young Adults in Taipei City: 1984-2014

The vaccination coverage rate for the infants is 97%.

Epidemiology of chronic hepatitis B in children before and after universal infant immunization programs.

Acute hepatitis B in Taiwan

Incidence /100,000

Data from CDC, Taiwan
Incidence rates of HCC among children born before or after the Taiwanese universal HBV vaccination program in July 1984

<table>
<thead>
<tr>
<th>Age at year</th>
<th>Birth year</th>
<th>No. of HCCs</th>
<th>Incidence rate (per 10^5 person-years)</th>
<th>Rate ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-9</td>
<td>1973-1979</td>
<td>36</td>
<td>0.51</td>
<td>1(referent)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1979-1984</td>
<td>38</td>
<td>0.47</td>
<td>0.93</td>
<td>.74</td>
</tr>
<tr>
<td></td>
<td>1984-1998</td>
<td>26</td>
<td>0.15</td>
<td>0.30</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>10-14</td>
<td>1968-1979</td>
<td>102</td>
<td>0.60</td>
<td>1(referent)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1979-1984</td>
<td>50</td>
<td>0.50</td>
<td>0.84</td>
<td>.29</td>
</tr>
<tr>
<td></td>
<td>1984-1994</td>
<td>28</td>
<td>0.19</td>
<td>0.32</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>15-19</td>
<td>1963-1979</td>
<td>138</td>
<td>0.52</td>
<td>1(referent)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1979-1984</td>
<td>80</td>
<td>0.80</td>
<td>1.55</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>1984-1989</td>
<td>10</td>
<td>0.16</td>
<td>0.30</td>
<td>&lt;.001</td>
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</tbody>
</table>

doi:10.1371/journal.pmed.1001774
http://127.0.0.1:8081/plosmedicine/article?id=info:doi/10.1371/journal.pmed.1001774
Vaccination rates in Taiwan

Data from Taiwan’s CDC, 2013
Hepatitis B vaccine Co-administered with DTPa-IPV/Hib

- DTPa-IPV/Hib were given at 1.5m, 3.5m, 6m/o
- HBV vaccine were given for 1 dose at birth, and co-administered with DTPa-IPV/Hib at 3.5m and 6m/o

After 3 doses of HBV vaccines (at age of 7 months), 95% infants had seroprotective levels against HBV
## HBV vaccination programs in Asia

<table>
<thead>
<tr>
<th>Country</th>
<th>Coverage rate</th>
<th>HBig</th>
<th>Mother screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hong Kong, Korea, Singapore</td>
<td>&gt;97</td>
<td>Yes, free of charge</td>
<td>Yes, free of charge</td>
</tr>
<tr>
<td>Malaysia</td>
<td>85 (2010)</td>
<td>Not free of charge</td>
<td>Yes, free of charge</td>
</tr>
<tr>
<td>Pakistan</td>
<td>55 (2010)</td>
<td>Not free of charge</td>
<td>Not free of charge</td>
</tr>
<tr>
<td>Philippines</td>
<td>70 (2012)</td>
<td>Not free of charge</td>
<td>Not free of charge</td>
</tr>
<tr>
<td>Vietnam</td>
<td>92 (2012)</td>
<td>Not free of charge</td>
<td>Not free of charge</td>
</tr>
<tr>
<td>Thailand</td>
<td>95 (2010)</td>
<td>Yes, free of charge</td>
<td>Not free of charge</td>
</tr>
<tr>
<td>China</td>
<td>95 (2010)</td>
<td>Not free of charge</td>
<td>Not free of charge</td>
</tr>
</tbody>
</table>
WHO recommends that all infants receive HBV vaccine as soon as possible after birth, preferably within 24 hours. The birth dose should be followed by 2 or 3 doses of HBV vaccine to complete the primary prevention.

In 2013, 93 Member States have introduced the birth dose, 183 Member States vaccinate infants against hepatitis B as part of their EPI, and 81% of children received the hepatitis B vaccine.

Production: Immunization Vaccines and Biologicals, (IVB), World Health Organization.
WHO Member States. Date of slide: 26 July 2012.
Characteristics of evaluation for vaccine-preventable disease goals in WHO Western Pacific Region

- Year goal set • 2005
- Target year • 2017
- Definition of goal • <1% HBsAg prevalence in 5 yo children, immunization coverage >95% HB3 and >90% birth dose

Main source of data for evaluation: nationally representative seroprevalence surveys

_Vaccine_ 32 (2014) 4259–4266
**Vaccine efficacy**

active/passive immunization in children born to HBsAg (+) mothers

<table>
<thead>
<tr>
<th>Subject group</th>
<th>HBsAg (+) rate in vaccinated vs. unvaccinated children*</th>
<th>Vaccine efficacy (95th CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children born to HBeAg(+) mothers: HBIG + vaccines</td>
<td>9.3% vs. 88.1%</td>
<td>89.5% (86.3%, 91.9%)</td>
</tr>
<tr>
<td>Children born to HBeAg(-) mothers: HBIG + vaccines*</td>
<td>0.14% vs. 6.5%</td>
<td>97.9% (84.7%, 99.7%)</td>
</tr>
<tr>
<td>Children born to HBeAg(-) mothers: vaccines only*</td>
<td>0.29% vs. 6.5%</td>
<td>95.6% (86.1%, 98.6%)</td>
</tr>
</tbody>
</table>

*Comparison of data from current study with historical control:
Have we done a good job?

HBeAg (+) pregnant mothers: ≈5%
Vaccine failure rate: 10%
Expected baby carrier rate after vaccine era: 5% x 10% = 0.5%
In 2009, the prevalence (<20 y/o) in Taipei city was 0.6%
Mother factor: High maternal viral load or intrauterine infection
Infant factor: immunity, microbiota?
Host factor: Immuno-compromized hosts (liver transplantation as an example)
Genetic Hypo-responsiveness
Vaccine failure - Chronic HBV carrier children born after the implementation of universal HBV vaccination program

Seroepidemiologic survey in Taipei, 2004

Failed in 40/7234 < 15 years of age born after the universal vaccination program

**Maternal HBsAg (+): 30**

Maternal HBsAg (-), but main caregivers HBsAg (+): 2

Maternal HBsAg Unknown: 5

Refuse query: 3

All 40 cases completed >3 doses of vaccination

Ni YH et al. Gastroenterology 2007; 132:1287-93
PREDICTED RATES OF HBV INFECTION

Predictive Rates with 95% CIs

HBsAg (+) rate in children (%) vs Maternal viral load (log10 copies/mL)

+ Lower/Upper limit of 95% CI
- Rate

Wen WH et al. J Hepatol 2013; 59:24-30
Efficacy of maternal TDF in interrupting mother-to-infant transmission of HBV

Maternal TDF from GA 30 wks --1 mo postpartum

Chen HL et al. Hepatology 2015
Faster HBV clearance in 12W than in ABX and 6W C3H/HeN

Delayed serum and liver HBV clearance in 6-week-old and ABX C3H/HeN mice

Overall 6-week-old and ABX mice showed tolerance phenotype to HBV

Chou HH et al. PNAS 2015; 112(7):2175-80.
Natural history of anti-HBs titer decline in children receiving primary vaccination in infancy

Preservation of immune memory 10 and 15 years after vaccination

- 118 vaccinated newborn born to HBeAg-positive carrier mothers and developed protective anti-HBs were checked 10 years later: 33% were seronegative for anti-HBs.
- A booster induced a protective level of anti-HBs (>10 mIU/mL) in almost all subjects (97.4%).
- On HBsAg stimulation to isolated lymphocytes, cellular immunity was augmented with a positive rate of 58%, 90%, and 100% for T-cell proliferation, IL-2 production, and IL-5 production, respectively.

Huang LM et al. Hepatology 1999;29:954
Seroprotective rates after booster doses in university students (18-23 y/o, n=127)

Jan CF et al. Hepatology 2010
Vaccine Boost Consideration

- No increase of acute hepatitis B in adolescents vaccinated 20 years ago in early infancy
- Preventing acute HBV infection in adolescents and adults will become a higher public health priority only after chronic HBV infections are successfully controlled.
- Universal booster is not an urgency, but it is necessary for immuno-compromised hosts.

Hepatitis B Vaccination Recommendations

- Routine for infants
- High risk groups
  - Immunocompromised hosts
  - Hemodialysis and frequent transfusion patients
  - Multiple sex partners or prior STD
  - Drug abusers
  - Others
Post-vaccination testing for infants born to HBsAg positive mothers

* should be performed after completion of the vaccine series, at age 9-18 months.
* HBsAg-negative infants with anti-HBs levels $>10$ mIU/mL need no further medical management.
* HBsAg-negative infants with anti-HBs levels $<10$ mIU/mL should be revaccinated with a booster and retested 1-2 months after the final dose of vaccine.
* Infants who are HBsAg positive should receive appropriate follow-up

Modified from CDC recommendation MMWR 2005; 54 (RR 16): 1-23
Three ways to eradicate HBV infection

1. Screening pregnant women and perinatal transmission prevention
2. Neonatal vaccination
3. General preventive measures*

- Screening high-risk population and register the carriers, then adequately management

- Wash your hands thoroughly after any potential exposure
- Practice safe sex with all partners
- Avoid direct contact with blood and bodily fluids
- Clean up blood spills with a fresh diluted bleach solution
- Cover all cuts carefully
- Avoid sharing sharp items such as razors, nail clippers, toothbrushes, and earrings or body rings
- Discard sanitary napkins and tampons into plastic bags
- Avoid illegal street drugs (injecting, inhaling, snorting, popping pills)
- Do not donate blood or body organs
- Make sure new, sterile needles are used for ear or body piercing, tattoos, and acupuncture

- Hepatitis B Foundation
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