Hepatitis B Disease Burden: A Model for Global Estimates and Impact of Vaccination

Susan A. Wang, MD, MPH
Division of Viral Hepatitis
Barriers to Appreciating HBV Disease Burden and Vaccine Impact

- Chronic hepatitis B virus (HBV) infections - not easily identified or counted yet most morbidity and mortality associated with HBV occurs in persons with chronic infection
- Primary goal of hepatitis B immunization is to prevent chronic infections
**Natural History of HBV Infection**

- Very dependent on age of infection
- Among infected children acute (symptomatic) hepatitis B rare; likelihood of developing chronic infection high:

<table>
<thead>
<tr>
<th>Age at infection</th>
<th>Acute HBV</th>
<th>Chronic HBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>&lt;1%</td>
<td>90%</td>
</tr>
<tr>
<td>1-5 years</td>
<td>5-15%</td>
<td>25-50%</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>20-50%</td>
<td>6-10%</td>
</tr>
</tbody>
</table>

- Morbidity and mortality associated with chronic infection (cirrhosis, hepatocellular carcinoma or HCC) not apparent until adulthood
Modes of HBV Transmission in Infancy and Early Childhood

• **Vertical** transmission from infected mother to infant

• **Horizontal** transmission from infected household contact to child

➢ *Both modes of transmission can be prevented by vaccination of newborns!*
Vertical Transmission

• Transmission from infected mother to infant
• Percutaneous and permucosal exposure to mother’s blood during birth
• *In utero* transmission rare: accounts for <2% of perinatal infections
• HBV **not** transmitted by breastfeeding
Risk of Vertical HBV Transmission by Serologic Status of Mother

<table>
<thead>
<tr>
<th>Serostatus of Mother</th>
<th>Infants Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg Positive</td>
<td>70% - 90%</td>
</tr>
<tr>
<td>HBeAg Positive</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>5% - 20%</td>
</tr>
<tr>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>

Immunoprophylaxis is highly effective in preventing vertical HBV transmission: hepatitis B vaccine alone prevents vertical transmission in up to 95% of infants when given soon after birth.
Horizontal Transmission

- Transmission occurring during early childhood is a result of horizontal transmission of HBV within household
  - to young children from family members: usually infected parents, older siblings, and household members
- May be associated with breaks in skin barrier common in tropical areas – e.g., scabies, dermatitis

- Hepatitis B vaccination will prevent horizontal transmission in early childhood
Rationale for Hepatitis B Vaccine
Birth Dose for All Infants

- Provides “safety net” for prevention of vertically transmitted HBV infections among children born to HBsAg-positive women.
- Prevents early childhood HBV infections, including horizontally transmitted infections among children born to HBsAg-negative women.
A Mathematical Model to Estimate Global Hepatitis B Disease Burden and Vaccination Impact

Susan T. Goldstein, Fangjun Zhou, Stephen C. Hadler, Beth P. Bell, Eric E. Mast, and Harold S. Margolis

The Disease Burden Model: Objectives

- Estimate HBV-related morbidity and mortality at the country, regional, and global levels
- Estimate reduction in HBV-related morbidity and mortality with different vaccination strategies
- Use as field tool at country level to facilitate introduction of hepatitis B vaccination
Model Overview

Birth cohort

Lifetime risk of HBV infection

Acute hepatitis B

Death

Chronic HBV infection

Death from HBV-related cirrhosis and HCC
Risk of Acquiring HBV Infection

- Calculated from age-specific prevalence of HBV in population
- Accounted for country-specific infant mortality
- Infection assumed to occur in one of three age periods

<table>
<thead>
<tr>
<th>Period</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal</td>
<td>Birth</td>
</tr>
<tr>
<td>Early childhood</td>
<td>After birth - 5 years old</td>
</tr>
<tr>
<td>Late</td>
<td>&gt;5 years old</td>
</tr>
</tbody>
</table>
Infection Outcome: Acute HBV and Chronic HBV Infection

- Decision tree analysis
- Estimate age-specific risk
  - acute HBV infection
  - death from acute HBV infection
  - chronic HBV infection
Infection Outcome: Deaths From Chronic Infection

- Constructed age-specific HBV-related cirrhosis and HCC mortality curves from multiple data sources
  - cirrhosis: US, Taiwan
  - HCC: Alaska, China, Gambia, Taiwan
- Included difference in risk of developing HCC
  - males and females
  - HBeAg-positive and HBeAg-negative persons
- Adjusted for country-specific background mortality

1 Yang NEJM 2002
Hepatitis B Vaccine Efficacy & Effectiveness

**Efficacy**
- 3-dose vaccination series - 95% efficacious
- Birth dose – 95% efficacious in preventing perinatal infection
- Assumed lifelong protection from 3 doses

**Effectiveness**
- Vaccine efficacy
- Coverage with 3-dose vaccination series
- Receipt of birth dose of vaccine
Seroprevalence Data For Global and Regional Disease Burden Estimates

**World**

**6 WHO Regions**
AFRO, AMRO, EMRO, EURO, SEARO, WPRO

**15 Sub-Regions**
Similar background mortality and HBV prevalence

**Country**
For each country in sub-region, used same estimate for each of the four seroprevalence inputs to run model
Model Input and Output

Model Input

- HBsAg
- HBeAg
- Anti-HBc at 5 years old
- Anti-HBc at ≥30 years old (lifetime risk of infection)

Model Output

- **Current burden:** HBV-related deaths in 2000
- **Future burden:** HBV infections (total and chronic) and HBV-related deaths in 2000 birth cohort
## Current Hepatitis B Disease Burden\(^1\)

<table>
<thead>
<tr>
<th>Region</th>
<th>Total Deaths</th>
<th>Deaths From Chronic Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFRO</td>
<td>69,000</td>
<td>90%</td>
</tr>
<tr>
<td>AMRO</td>
<td>12,000</td>
<td>92%</td>
</tr>
<tr>
<td>EMRO</td>
<td>21,000</td>
<td>90%</td>
</tr>
<tr>
<td>EURO</td>
<td>51,000</td>
<td>94%</td>
</tr>
<tr>
<td>SEARO</td>
<td>143,000</td>
<td>92%</td>
</tr>
<tr>
<td>WPRO</td>
<td>325,000</td>
<td>95%</td>
</tr>
<tr>
<td><strong>Global</strong></td>
<td><strong>620,000</strong></td>
<td><strong>94%</strong></td>
</tr>
</tbody>
</table>

1 Year 2000
# Future Hepatitis B Disease Burden

<table>
<thead>
<tr>
<th>Region</th>
<th>Total Infections (millions)</th>
<th>Chronic Infections</th>
<th>Total Deaths$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFRO</td>
<td>18.5</td>
<td>2,915,000</td>
<td>276,000</td>
</tr>
<tr>
<td>AMRO</td>
<td>1.3</td>
<td>174,000</td>
<td>28,000</td>
</tr>
<tr>
<td>EMRO</td>
<td>5.3</td>
<td>663,000</td>
<td>96,000</td>
</tr>
<tr>
<td>EURO</td>
<td>2.9</td>
<td>365,000</td>
<td>56,000</td>
</tr>
<tr>
<td>SEARO</td>
<td>17.4</td>
<td>2,386,000</td>
<td>368,000</td>
</tr>
<tr>
<td>WPRO</td>
<td>19.3</td>
<td>3,230,000</td>
<td>581,000</td>
</tr>
<tr>
<td>Global</td>
<td><strong>64.8</strong></td>
<td><strong>9,733,000</strong></td>
<td><strong>1,405,000$^3$</strong></td>
</tr>
</tbody>
</table>

$^1$ 2000 birth cohort over course of lifetime without vaccination

$^2$ Acute hepatitis B and chronic HBV infection

$^3$ 95% from chronic infection and 5% from acute hepatitis B
Global HBV-Related Deaths By Age at Acquisition of Infection

- Perinatal Period (21%)
  - children >5
  - adolescents
  - adults

- Early Childhood Period (48%)
  - children ≤5

- Late Period (31%)
  - children >5

1 Future deaths, without vaccination
Proportion of Total Deaths in the 2000 Birth Cohort from Hepatitis B

1\(^{\text{Future deaths in 2000 birth cohort, without vaccination}}\)
Proportion of Total Deaths in the 2000 Birth Cohort from Hepatitis B, By Age at Infection

Future deaths in 2000 birth cohort, without vaccination
Reduction in HBV-Related Deaths in the 2000 Birth Cohort with Vaccination

Without administration of a birth dose of vaccine
Reduction in HBV-Related Deaths with Vaccination: Impact of Birth Dose

1 Administration of birth dose to 50% and 90% of the vaccinated cohort
Reduction in HBV-Related Deaths with Increasing Birth Dose Coverage

**United States**
- 0 birth dose: 70%
- 50% birth dose: 78%
- 90% birth dose: 84%

**Taiwan**
- 0 birth dose: 50%
- 50% birth dose: 68%
- 90% birth dose: 82%

1 Administration of birth dose to 50% and 90% of the vaccinated cohort
Updated United States Strategy to Eliminate HBV Transmission

- Universal infant vaccination (1991)
- New December 2005 recommendations address gaps in eliminating perinatal and childhood transmission and focus on immunizing all newborns before hospital discharge
Conclusions

• Globally, HBV infection causes substantial morbidity and mortality

• Most HBV-related deaths result from chronic sequelae of infection acquired in the perinatal and early childhood periods

• Inclusion of hepatitis B vaccine birth dose into national immunization programs could prevent >80% of HBV-related deaths
Field Use for Hepatitis B Disease Burden Model

- Run on desktop computer
- EXCEL software
- User-friendly interface
- User’s manual
