Methods to Evaluate Infant Hepatitis B Immunization Programs

Susan Goldstein, M.D.
Division of Viral Hepatitis
Centers for Disease Control and Prevention, USA
Why Do We Need to Evaluate Hepatitis B Immunization Programs

- Prove that what we are doing is working
  
  Immunization → Decreased mortality

- Increase public confidence in immunizations

- Advocate for sustainable immunization programs
Methods to Evaluate Hepatitis B Immunization Programs

- Immunization coverage surveys
- Serologic surveys
- Surveillance for acute hepatitis B
- Surveillance for HBV-related mortality
Evaluating Hepatitis B Immunization Programs

Immunization Coverage
Immunization Coverage

Include hepatitis B vaccine in:

- Routine (administrative) coverage
- Special coverage surveys
# Hepatitis B Vaccination Coverage Indicators

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>HepB1</td>
<td>Series initiation</td>
</tr>
<tr>
<td>HepB1 (birth dose)</td>
<td>Perinatal prevention</td>
</tr>
<tr>
<td>HepB3</td>
<td>Series completion</td>
</tr>
<tr>
<td>HepB3 vs. HepB1</td>
<td>Series drop-out</td>
</tr>
<tr>
<td>HepB3 vs. DTP3</td>
<td>Completion hep B series compared to an established vaccine</td>
</tr>
</tbody>
</table>
Limitations of Coverage Data

- Does not directly measure impact of vaccination on HBV-related morbidity and mortality
- Can have high vaccination coverage with low vaccine efficacy/effectiveness
  - frozen vaccine
  - improperly administered vaccine
- Administrative coverage data not always accurate
- Special coverage surveys may be necessary
Special Coverage Surveys

- WHO Immunization Coverage Survey - 30 cluster survey
- Multiple Indicator Cluster Survey (MICS)
- Demographic and Health Survey (DHS)
Discussion

1. Experience with routine coverage
2. Experience with special surveys
3. Indicators used
Evaluating Hepatitis B Immunization Programs

SeroLogic Surveillance
Serologic Surveillance

Objective: Compare seroprevalence of infection in target population before and after commencement of immunization program

Requirements:

1. Representative Population
2. Laboratory Capacity
3. Baseline Data
Population Criteria for Serologic Surveillance

- Prevalence within a country differs by:
  - age
  - sex
  - ethnicity
  - geographic area
  - socioeconomic status
  - risk group

- Want to draw conclusions about the larger population from the study population

- Need representative population
Example: Serologic Study Population

In a serologic survey among hospitalized children, the prevalence of HBsAg was 10%

• Is this population likely to be representative of the general population of children?
• What other populations might be used for serologic studies?
Representativeness of Hospitalized Children for Serologic Surveys

Hospitalized children may be more likely than the general population of children to have .....
Representativeness of Hospitalized Children for Serologic Surveys

Hospitalized children may be more likely than the general population of children to have.....

- Higher socioeconomic level
- Better access to medical care
- Received hepatitis B vaccine

Less likely to be infected with HBV
## Comparison of Various Populations for Serologic Surveys

<table>
<thead>
<tr>
<th>Population</th>
<th>Representative</th>
<th>Difficulty</th>
<th>Expense</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital-based</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Outpatient clinic</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>School-based</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Community/ Household</td>
<td>++++</td>
<td>+++++</td>
<td>+++++</td>
</tr>
<tr>
<td>Blood donors</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Sources for Baseline Serologic Data

**Historic data**
- Published papers: international, regional, medical school journals
- Unpublished papers: theses
- Blood bank
- Special studies: MOH, academic institutions

**Newly collected data**
- May be collected before/after immunization begins
- Collect data among various age groups
Laboratory Capacity

Requirements

- Infrastructure to draw, transport, and store blood specimens
- Lab with experience in hepatitis serology testing

Markers of infection

- **Anti-HBc**: chronic or resolved infection
- **HBsAg**: chronic infection
- Cannot use anti-HBs as marker of infection after vaccination
When Should Serologic Surveys be Conducted?

• 2-5 years after initiation of program
  – impact on perinatal and early childhood transmission
• Periodically thereafter as cohort ages
  – every 5-10 years?
• May be circumstances that require survey be done earlier or more frequently:
  – new vaccine formulation
  – new vaccination schedule
  – introduction of birth dose
Discussion

1. Country experience with serologic surveys
2. Examples of survey protocols
3. Possible convenience samples – will they work in all countries?
4. Timing of first survey
5. Need and frequency of follow-up surveys
6. Cost of survey
7. Lab testing
Evaluating Hepatitis B Immunization Programs

Surveillance for Acute Hepatitis B
Uses of Acute Viral Hepatitis Surveillance Data

- Define incidence of acute viral hepatitis
- Determine etiology (A, B, C, D, E, other)
- Determine risk factors for infection
- Evaluate effectiveness of prevention programs, including immunization
Acute Disease Surveillance to Evaluate Vaccination Program Effectiveness

• For most childhood vaccine-preventable diseases, infection results in immediate morbidity and mortality

  Polio → acute flaccid paralysis
  Measles → febrile rash illness
  Hib → meningitis

• Vaccination program effectiveness assessed using acute disease surveillance

• Acute disease surveillance more difficult for hepatitis B
Acute Hepatitis B

- Globally, most new HBV infections occur among infants and children
- Acute hepatitis B not common in these age groups, but does occur

<table>
<thead>
<tr>
<th>Age at infection</th>
<th>Acute hep B</th>
<th>Chronic infection</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>
Feasibility of Conducting Surveillance for Acute Viral Hepatitis

- Sufficient number of cases among children
  - likely in most countries CEE/NIS/Russia
- Mechanism to identify ill children
  - hospital-based vs. community-based
- Laboratory capabilities
  - clinical presentation of acute hepatitis of all etiologies similar
  - diagnosis requires laboratory confirmation
Countries Conducting Acute Viral Hepatitis Surveillance

- Romania
- Moldova
- Kyrgyzstan
- Kazakhstan
- Others?
Case Definition for Acute Viral Hepatitis

- Case Definition
  - Clinical Criteria: Same for all types of acute viral hepatitis
  - Laboratory Criteria: Differs for each type of acute viral hepatitis

Change in case definition of AIDS diagnosis
Case Definition for Acute Viral Hepatitis, United States

Clinical criteria

Acute illness with discrete date of onset

AND

Jaundice or elevated serum aminotransferase levels (ALT)
Case Definition for Acute Viral Hepatitis, United States

**Laboratory Criteria**

Hepatitis A  IgM anti-HAV positive

Hepatitis B  IgM anti-HBc positive **OR** HBsAg-positive  **AND** IgM anti-HAV negative (if done)

Hepatitis C  ALT>7X ULN  **AND**  IgM anti-HAV negative  **AND**  IgM anti-HBc or HBsAg negative  **AND**  Anti-HCV positive (RIBA, PCR, signal to cut off)
Considerations for Acute Disease Surveillance for Program Evaluation

National vs. sentinel surveillance

- Want representative population
- Consider regional/ethnic/economic differences

Continuous vs. intermittent surveillance

- Given expense and logistics, may be more feasible to conduct surveillance intermittently
Considerations for Acute Disease Surveillance for Program Evaluation

Age of population under surveillance

- Evaluate infant program - children
- Other uses of surveillance data that would require all age groups:
  - evaluate effectiveness of vaccination programs in older age groups - health care workers, injection drug users
  - determine etiology (A, B, C, D, E, other)
  - identify risk factors for infection
Discussion

1. National vs. sentinel surveillance
2. Continuous vs. intermittent surveillance – is intermittent surveillance feasible?
3. Practical aspects of surveillance
   a. Case definition
   b. How and by whom are cases identified?
   c. Who interviews cases?
   d. Lab testing algorithm
   e. Data collection forms
   f. Data analysis – frequency, software, summary reports, feedback to local level/hospital
Evaluating Hepatitis B Immunization Programs

HBV-Related Mortality
Liver Disease Mortality

**Determine Disease Burden**
- Deaths from acute viral hepatitis
- Deaths from chronic liver disease
  - cirrhosis
  - hepatocellular carcinoma (HCC)

**Determine Etiology**
- Proportion of chronic liver disease deaths attributable to HBV, HCV, delta, alcohol, other
HBV-Related Mortality

• To estimate disease burden: acute hepatitis B, cirrhosis, and HCC mortality
• For infant vaccination program evaluation
  – outcomes rare among children
  – cannot use to measure immediate impact
  – better suited for long-term evaluation
• Exceptions:
  – prevalence HBsAg and HBeAg very high
  – delta superinfection
<table>
<thead>
<tr>
<th>Year</th>
<th>Group included in Program</th>
</tr>
</thead>
<tbody>
<tr>
<td>1984</td>
<td>Infants born to HBsAg-positive mothers</td>
</tr>
<tr>
<td>1986</td>
<td>All infants (routine infant immunization)</td>
</tr>
<tr>
<td>1987</td>
<td>Preschool children</td>
</tr>
<tr>
<td>1988</td>
<td>Primary school children</td>
</tr>
<tr>
<td>1989</td>
<td>Middle school children</td>
</tr>
<tr>
<td>1990</td>
<td>Adults</td>
</tr>
</tbody>
</table>

Source: Chang  NEJM 1997.
Hepatocellular Carcinoma Mortality Study, Taiwan

- **Objective**: Determine incidence of HCC among 6 to 14 year old children before and after routine infant hepatitis B immunization

- **Data Sources**
  - national cancer registry
  - multicenter childhood HCC registration study
  - national mortality registry

Source: Chang  NEJM 1997.
Mortality from Hepatocellular Carcinoma Among 6 to 14 Year Old Children: Taiwan (1982-1994)

Source: Chang  NEJM 1997.
Liver Disease Mortality Study, Palau

- Palau - island nation in Pacific Ocean
- Prevalence of HBsAg ~20%
- Liver disease thought to cause substantial morbidity and mortality
Liver Disease Mortality Study, Palau

Objective

• Characterize deaths from acute and chronic liver disease
• Determine proportion of liver deaths associated with HBV infection

Methods

• Death certificate review
• 1990-2002 (13 years)
• Determined cause of death by review of ICD-9 code and written description
• Obtained hepatitis B serology from public health and hospital records
## Adult Deaths, Palau, 1990-2002

<table>
<thead>
<tr>
<th></th>
<th>All Cause</th>
<th>Liver Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1480</td>
<td>120</td>
</tr>
<tr>
<td>Median per year (range)</td>
<td>117 (97-133)</td>
<td>10 (3-13)</td>
</tr>
</tbody>
</table>

Overall, 8% of deaths due to liver disease

Source: T Vogt, DVH, CDC
Classification of Liver Disease
Deaths, Palau, 1990-2002 (n=120)

- Cirrhosis (26%)
- HCC (40%)
- Acute LD (15%)
- Chronic LD (10%)
- Other (9%)

Source: T Vogt, DVH, CDC
## Death Rates from Cirrhosis and HCC, Palau and Worldwide

<table>
<thead>
<tr>
<th></th>
<th>Palau</th>
<th>Worldwide²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cirrhosis¹</strong></td>
<td>17.4</td>
<td>14.3</td>
</tr>
<tr>
<td><strong>HCC</strong></td>
<td>19.4</td>
<td>11.4</td>
</tr>
</tbody>
</table>

¹ For Palau, includes all deaths coded as cirrhosis, chronic hepatitis, and ESLD  
² Global Burden of Disease Project, WHO

Source: T Vogt, DVH, CDC
Etiology of Liver Disease Deaths, Palau, 1990-2002

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>HBV Serology Available</th>
<th>Percent HBsAg+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis (n=31)</td>
<td>26</td>
<td>73%</td>
</tr>
<tr>
<td>HCC (n=48)</td>
<td>37</td>
<td>84%</td>
</tr>
<tr>
<td>Acute liver disease (n=28)</td>
<td>11</td>
<td>73%</td>
</tr>
<tr>
<td>Chronic liver disease(^1) (n=12)</td>
<td>9</td>
<td>89%</td>
</tr>
<tr>
<td>Other (n=11)</td>
<td>5</td>
<td>0%</td>
</tr>
</tbody>
</table>

\(^1\) Not specified as cirrhosis

Source: T Vogt, DVH, CDC
Data Collection for HBV-Related Morality

Possible sources of data

- Municipal death records
- Hospital death records
- Cancer registry

Considerations

- Representativeness of data source(s)
- Method of diagnosis: clinical, radiographic, histologic
- Autopsy performed?
- Laboratory confirmation HBsAg positive?
Discussion

1. Country experience with mortality studies
2. Availability and completeness of death certificates
3. Availability and completeness of cancer registries
4. Methods to identify chronic liver disease patients
   a. outpatient
   b. inpatient
   c. differentiation of etiologies: hepatitis, alcohol
## Comparison of Methods to Evaluate Hepatitis B Immunization Programs

<table>
<thead>
<tr>
<th></th>
<th>Coverage Survey</th>
<th>Serosurvey</th>
<th>Acute Disease Surveillance</th>
<th>Morbidity &amp; Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Feasibility</strong></td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Expense</strong></td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Frequency of evaluation</strong></td>
<td>I*</td>
<td>I</td>
<td>I or C*</td>
<td>I or C</td>
</tr>
<tr>
<td><strong>Program effectiveness</strong></td>
<td>-</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>short-term</td>
<td>-</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>long-term</td>
<td>-</td>
<td>+++</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Information collected</strong></td>
<td>Coverage data</td>
<td>Prevalence of infection</td>
<td>Incidence new infection</td>
<td>Incidence chronic sequelea</td>
</tr>
<tr>
<td></td>
<td>Coverage</td>
<td>Prevalence</td>
<td>Incidence</td>
<td>Risk factor information</td>
</tr>
<tr>
<td></td>
<td>data</td>
<td>of infection</td>
<td>new infection</td>
<td>information</td>
</tr>
</tbody>
</table>

* I=intermittent; C=continuous