The Epidemiology of Hepatitis B and A Infections

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Section A

Introduction to Hepatitis Virus
Hepatitis Viruses of Humans

- Hepatitis A virus (HAV)
- Hepatitis B virus (HBV)
- Hepatitis C virus (HCV), non-A, non-B hepatitis virus
- Hepatitis D virus (delta agent, HDV)
- Enteric non-A, non-B hepatitis virus (HEV)
- Hepatitis G virus
- Other hepatitis viruses?
  - For example, short-incubation-period HV?
### Characteristics of Hepatitis Viruses

<table>
<thead>
<tr>
<th>Virus</th>
<th>Nucleic Acid</th>
<th>Route Trans</th>
<th>Mortality</th>
<th>Risk Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAV</td>
<td>Unenveloped, single-stranded RNA</td>
<td>Fecal-oral</td>
<td>Low</td>
<td>None</td>
</tr>
<tr>
<td>HBV</td>
<td>Enveloped, double-stranded DNA</td>
<td>Parenteral, Sex</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>HCV</td>
<td>Enveloped, single-stranded RNA</td>
<td>Parenteral, Sex</td>
<td>Med</td>
<td>High</td>
</tr>
<tr>
<td>HDV</td>
<td>Enveloped, single-stranded RNA</td>
<td>With HBV</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>HEV</td>
<td>Unenveloped, single-stranded RNA</td>
<td>Fecal-oral</td>
<td>High</td>
<td>None</td>
</tr>
<tr>
<td>HGV</td>
<td>Enveloped, single-stranded RNA</td>
<td>Parenteral?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>
## Estimates of Acute and Chronic Disease Burden for Viral Hepatitis, United States

<table>
<thead>
<tr>
<th></th>
<th>HAV</th>
<th>HBV</th>
<th>HCV</th>
<th>HDV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute infections</td>
<td>&lt; 125-200</td>
<td>140-320</td>
<td>35-180</td>
<td>6-13</td>
</tr>
<tr>
<td>(x 1000)/year*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fulminant deaths/year</td>
<td>100</td>
<td>150</td>
<td>?</td>
<td>35</td>
</tr>
<tr>
<td>Chronic infections</td>
<td>0</td>
<td>1-1.25 million</td>
<td>3.5 million</td>
<td>70,000</td>
</tr>
<tr>
<td>Chronic liver disease deaths/year</td>
<td>0</td>
<td>5,000</td>
<td>8-10,000</td>
<td>1,000</td>
</tr>
</tbody>
</table>

Acute Viral Hepatitis by Type, United States, 1982-1993

Hepatitis A: 47%
Hepatitis B: 34%
Hepatitis C: 16%
Hepatitis Non-ABC: 3%

Adapted by CTLT from CDC.
Section B

Hepatitis B Virus: Epidemiology, Biology, and Virology
### Hospitalization and Death Rates Among Reported Cases of Acute Hepatitis B by Age Group, Sentinel Counties, United States, 1982-1998

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Total # cases</th>
<th>Hospitalizations&lt;sup&gt;a&lt;/sup&gt; n (%)</th>
<th>Deaths&lt;sup&gt;b&lt;/sup&gt; n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>15</td>
<td>3 (20.0%)</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>10-19</td>
<td>368</td>
<td>77 (20.9%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>20-29</td>
<td>1825</td>
<td>304 (16.7%)</td>
<td>3 (0.1%)</td>
</tr>
<tr>
<td>30-39</td>
<td>1019</td>
<td>170 (16.7%)</td>
<td>9 (0.9%)</td>
</tr>
<tr>
<td>40-49</td>
<td>398</td>
<td>103 (25.9%)</td>
<td>6 (1.5%)</td>
</tr>
<tr>
<td>≥50</td>
<td>313</td>
<td>137 (43.8%)</td>
<td>15 (4.8%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>3938</strong></td>
<td><strong>794 (20.2%)</strong></td>
<td><strong>35 (0.9%)</strong></td>
</tr>
</tbody>
</table>

<sup>a</sup> p<.001 for the proportion of patients ≥40 years old who were hospitalized compared to those<40 years old.

<sup>b</sup> p<0.001 for the proportion of patients ≥40 years old who died compared to those<40 years old.
Primary Etiology of Chronic Liver Disease, Mutually Exclusive Groups, Jefferson County, Alabama, 1989 (n=140)

- Hepatitis C Virus (26%)
- Alcohol (24%)
- Cryptogenic (17%)
- Hepatitis C Virus & Alcohol (14%)
- Hepatitis B Virus (11%) & Alcohol (3%) (14%)
- Other (5%)

Adapted by CTLT from CDC.
Outcome of Hepatitis B Infections, United States, 1987 Estimates

- **Hepatitis B Infections**: 300,000 per year
  - **Asymptomatic**: 150,000 (50%)
  - **Symptomatic**: 150,000 (50%)

- **Hepatitis B Chronic Carriers**: 18-30,000 (6-10%)
- **Death**: 322 (0.05%)

- **Chronic Liver Disease**
  - **Death from Cirrhosis**: 5100 (1.7%)
  - **Death-Primary Liver Cancer**: 1200 (0.4%)
Hepatitis B: Clinical Features

Hepatitis B - Clinical Features

- Incubation period: Average 60-90 days
  Range 45-180 days

- Clinical illness (jaundice):<5 yrs, <10%
  ≥5 yrs, 30%-50%

- Acute case-fatality rate: 0.5%-1%

- Chronic infection:<5 yrs, 30%-90%
  ≥5 yrs, 2%-10%

- Premature mortality from chronic liver disease: 15%-25%
Hepatitis B Virus

1. A double stranded (incomplete) circular DNA virus

2. 3200 nucleotides in length, 42nm (Dane particles)

3. Member of Hepadna Virus Group

   Group also contains:
   a. WHV (Woodchuck Hepatitis Virus)
   b. GSHV (Ground squirrel HV)
   c. DHBV (Pekin Duck HV)

4. Viral components
   a. Surface antigen (HBsAg), 22nm
   b. Core antigen (HBCag)
   c. e Antigen
   d. DNA polymerase

5. Several HBV subtypes (antibody specificities to HBsAg) ayw, ayr, adw, adr

6. Clinical

   Acute Hepatitis (Immune complex disease)
   Chronic Hepatitis
   Chronic Carrier State
   Hepatocellular Carcinoma
The viral genome is partially double-stranded (wavy black lines). The genome encodes four genes: the surface (S), core (C), polymerase (P), and X genes, shown as large arrows. The S and C genes give rise to various overlapping proteins (three for the S gene and two for the C gene). The longer core gene product is processed into the e antigen (red segment).
Hepatitis B Virus
The Replication Cycle of HBV

Course of Symptoms in Typical Acute Viral Hepatitis

- Fever, Rash, Arthritis (15%)
- Jaundice
- Dark Urine
- Malaise (95%)
- Anorexia (90%)
- Nausea (80%)
- RUQ Pain (60%)
- Itching (10%)

Incubation Period - Pre-icteric - Icteric - Convalescent Period
Acute Hepatitis B Virus Infection with Recovery

Typical Serologic Course

- **HBeAg**
- **Anti-HBe**

- **HBsAg**
- **IgM Anti-HBc**
- **Total Anti-HBc**
- **Anti-HBs**

**Titer**

**Weeks After Exposure**

Adapted by CTLT from CDC.
Progression to Chronic Hepatitis B Virus Infection

Progression to Chronic Hepatitis B Virus Infection
Typical Serologic Course

- Titer
- Acute (Six Months)
- Chronic (Years)
- Weeks After Exposure
- HBsAg
- Total Anti-HBc
- IgM Anti-HBc

Adapted by CTLT from CDC.
Natural History of Chronic HBV Infection

Occult Hepatitis B

Model of Occult Hepatitis B, Highlighting the Potential Role of the Immune System

- HBeAg
- HBsAg

- Chronic Hepatitis B
- Healthy Carrier
- Occult Hepatitis B
- Recovery

Lower Limit of Detection for Nested PCR
Lower Limit of Detection for Quantitative PCR

HBV DNA
(Weak) Immune Response (Strong)
### Typical Serological Profiles in Patients with Hepatitis B Infection

<table>
<thead>
<tr>
<th>Serological tests</th>
<th>Hep B Immunization</th>
<th>Acute HBV</th>
<th>Recovered from HBV</th>
<th>Chronic Hep B</th>
<th>Healthy or inactive carrier</th>
<th>Occult hep B</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAb</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-/-</td>
</tr>
<tr>
<td>HBeAb</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-/-</td>
</tr>
<tr>
<td>HBsAg</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>HBeAg</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-/-</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+, &gt;10^5 copies</td>
<td>+, &lt;10^5 copies</td>
<td>+, &lt;10^3 copies</td>
</tr>
</tbody>
</table>

HbsAB, hep B surface antibody; HBcAb, hep B core antibody; HBeAb, hep B e antibody; HBsAg, hep B surface antigen; HbeAg, hep B e antigen
<table>
<thead>
<tr>
<th>Age</th>
<th>Infections resulting in persistent HBV carriage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 yr</td>
<td>70-90%</td>
</tr>
<tr>
<td>2-3 yr</td>
<td>40-70%</td>
</tr>
<tr>
<td>4-6 yr</td>
<td>10-40%</td>
</tr>
<tr>
<td>&gt;6 yr</td>
<td>6-10%</td>
</tr>
</tbody>
</table>
Outcome by Age at Infection

Outcome of Hepatitis B Virus Infection by Age at Infection

Chronic Infection (%)

Symptomatic Infection (%)

Age at Infection

Birth, 1-6 Months, 7-12 Months, 1-4 Years, Older Children and Adults

Adapted by CTLT from CDC.
Prevalence of HBV Infection, U.S., by Race and Age

Age and Race Specific Prevalence of Hepatitis B Virus Infection, United States, 1976-1980 (NHANES II)

Adapted by CTLT from McQuillon et al., NCHS.
### Prevalence of Hepatitis B Serologic Markers in Various Population Groups in the United States

<table>
<thead>
<tr>
<th>Population group</th>
<th>Prevalence of serologic markers of HBV infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBsAg(%)</td>
</tr>
<tr>
<td>Immigrants/refugees from areas of high HBV endemicity</td>
<td>13</td>
</tr>
<tr>
<td>Alaskan natives/Pacific islanders</td>
<td>5-15</td>
</tr>
<tr>
<td>Clients in institutions for the mentally retarded</td>
<td>10-20</td>
</tr>
<tr>
<td>Users of illicit parenteral drugs</td>
<td>7</td>
</tr>
<tr>
<td>Homosexually active men</td>
<td>6</td>
</tr>
<tr>
<td>Household contacts of HBV carriers</td>
<td>3-6</td>
</tr>
<tr>
<td>Patients of hemodialysis units</td>
<td>3-10</td>
</tr>
<tr>
<td>Health-care workers - frequent blood contact</td>
<td>1-2</td>
</tr>
<tr>
<td>Prisoners (male)</td>
<td>1-8</td>
</tr>
<tr>
<td>Staff of institutions for the mentally retarded</td>
<td>1</td>
</tr>
<tr>
<td>Heterosexuals with multiple partners</td>
<td>0.5</td>
</tr>
<tr>
<td>General population (NHANES II)</td>
<td></td>
</tr>
<tr>
<td>Blacks</td>
<td>0.9</td>
</tr>
<tr>
<td>Whites</td>
<td>0.2</td>
</tr>
</tbody>
</table>
Estimated Annual HBV Infections by Risk Group

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Estimated Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Infections - U.S. (1986)</td>
<td>300,000</td>
</tr>
<tr>
<td>IV Drug Users</td>
<td>81,000</td>
</tr>
<tr>
<td>Heterosexuals (Sexual/Household)</td>
<td>63,000</td>
</tr>
<tr>
<td>Homosexual Men</td>
<td>27,000</td>
</tr>
<tr>
<td>High-Risk HCWs</td>
<td>12,000</td>
</tr>
<tr>
<td>Transfusions, Dialysis</td>
<td>9,000</td>
</tr>
<tr>
<td>Unknown</td>
<td>108,000</td>
</tr>
</tbody>
</table>
Risk Factors for Patients Reported with Hepatitis B

Risk Factors for Patients Reported with Hepatitis B by Mutually Exclusive Groups, Females, United States, 1983-1989

- Contact with Hepatitis B
- Drug Use
- Medical/Dental Employment
- Blood Transfusion
- Dialysis

Percentage of Cases (%)

Year

Adapted by CTLT from VHSP, CDC.
Incidence per 100,000, 1982–1998

- Sentinel Counties Surveillance System
- National Notifiable Diseases Surveillance
Number of Cases, 1982–1998, by Risk Factor

- Male Homosexual Activity
- Injection Drug Use
- High-risk Heterosexual Activity
- Occupational Exposure
HBV, HCV, and HIV Transmission by Needlestick

![Graph showing transmission rates of HBV, HCV, and HIV by needlestick.](image)
Section C

Hepatitis B: Prevention Efforts and Global Distribution
Global Burden (350 Million Chronic HBV Carriers)\textsuperscript{1}

- 20–25% of carriers died of liver-related disease\textsuperscript{2}
- Worldwide—primary cause of cancer of the liver\textsuperscript{3}
  - For males—third leading cause of cancer mortality
  - For females—sixth leading cause of cancer mortality

\textsuperscript{1}\textit{WHO.} (2000)
Geographic Distribution of Chronic HBV Infection

Adapted by CTLT from CDC.
Births to HBsAg Positive Mothers Resulting in HBV Carrier Infants (U.S. Estimates, 1983)

- Asian: 57%
- Black: 16%
- Hispanic: 8%
- White: 18%
- American Indian: 1%
## Hepatitis B Carriers in Regions of Increased Prevalence

### Hepatitis B Carriers in Regions of Intermediate and High HBV Prevalence (1985)

<table>
<thead>
<tr>
<th>Region</th>
<th>Population</th>
<th>HBV carriers</th>
<th>No. of HBV carriers (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>413M</td>
<td>12%</td>
<td>49.5M</td>
</tr>
<tr>
<td>Asia</td>
<td>2,757M</td>
<td>8%</td>
<td>220M</td>
</tr>
<tr>
<td>Middle East</td>
<td>191M</td>
<td>4%</td>
<td>7.6M</td>
</tr>
<tr>
<td>Latin America</td>
<td>410M</td>
<td>1.6%</td>
<td>6.6M</td>
</tr>
<tr>
<td>Oceana</td>
<td>6M</td>
<td>10%</td>
<td>0.6M</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>3,777M</strong></td>
<td></td>
<td><strong>284.3M</strong></td>
</tr>
</tbody>
</table>
### HBV Carriers in the World

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese</td>
<td>=</td>
<td>150,000,000</td>
</tr>
<tr>
<td>Others</td>
<td>=</td>
<td>50,000,000</td>
</tr>
<tr>
<td>Total</td>
<td>=</td>
<td>200,000,000</td>
</tr>
</tbody>
</table>
Global Patterns of Chronic HBV Infection

- **High (≥8%):** 45% of global population
  - lifetime risk of infection > 60%
  - early childhood infections common
- **Intermediate (2%-7%):** 43% of global population
  - lifetime risk of infection 20%-60%
  - infections occur in all age groups
- **Low (<2%):** 12% of global population
  - lifetime risk of infection < 20%
  - most infections occur in adult risk groups
## Age and Transmission According to Endemicity

<table>
<thead>
<tr>
<th></th>
<th>Low endemicity</th>
<th>High endemicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Adults</td>
<td>Infants and children</td>
</tr>
<tr>
<td><strong>Transmission</strong></td>
<td>Sexual contact</td>
<td>Mother-infant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Close childhood contact</td>
</tr>
</tbody>
</table>
Immunization against HBV

Passive

Hepatitis B Immune Globulin
(Anti-HBs Titer >1:100,000)

- Needle-stick
- Acute sexual contact
- Perinatal transmission

Active

Hepatitis B Vaccine
Types of Hepatitis B Vaccines

Hepatitis B Vaccine

Types:

- Plasma derived*
- Recombinant DNA*
- Synthetic polypeptide
- Vaccinia virus recombinant
- Anti-ideotype
Protective Efficacy of Hepatitis B Vaccine

- Incidence of acute type B hepatitis reduced by 92%
- Incidence of HBs antigenemia reduced by 89%
- Almost 100% of persons in whom anti-HBs developed after 3 doses of vaccine were protected against acute type B hepatitis, asymptomatic hepatitis B infection, and chronic antigenemia
HBV Carrier Rate: Effect of Reduction Strategies

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>HBV Carrier Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>No Prophylaxis</td>
</tr>
<tr>
<td>A2</td>
<td>No Prophylaxis</td>
</tr>
<tr>
<td>B</td>
<td>HBIG x 1 - No Vaccine</td>
</tr>
<tr>
<td>C</td>
<td>HBIG x 3 - No Vaccine</td>
</tr>
<tr>
<td>D</td>
<td>HB Vaccine x 3 (1 mo.) - No HBIG</td>
</tr>
<tr>
<td>E1</td>
<td>HB Vaccine x 3 (1 wk.) - No HBIG</td>
</tr>
<tr>
<td>E2</td>
<td>HB Vaccine x 3 (Birth) - No HBIG</td>
</tr>
<tr>
<td>F</td>
<td>HBIG (Birth) + HB Vaccine x 3</td>
</tr>
</tbody>
</table>

CTLT
<table>
<thead>
<tr>
<th>Study Group</th>
<th>Follow-up</th>
<th>Anti-HBs loss (%)</th>
<th>HBV Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>(yr)</td>
<td>Anti-HBc(+)</td>
</tr>
<tr>
<td>Postexposure immunoprophylaxis: infants of HBeAg-positive mothers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Passive-active</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taiwan</td>
<td>199</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Taiwan</td>
<td>654</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>United States</td>
<td>315</td>
<td>4 to 11</td>
<td>12</td>
</tr>
<tr>
<td>Active</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>55</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Routine preexposure immunization of infants/children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Senegal</td>
<td>100</td>
<td>6</td>
<td>22</td>
</tr>
<tr>
<td>Alaska</td>
<td>600</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Venezuela</td>
<td>280</td>
<td>6</td>
<td>29</td>
</tr>
<tr>
<td>Preexposure immunization of adults</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homosexual men</td>
<td>634</td>
<td>9</td>
<td>54</td>
</tr>
<tr>
<td>Homosexual men</td>
<td>127</td>
<td>11</td>
<td>61</td>
</tr>
<tr>
<td>Alaskan Eskimos</td>
<td>272</td>
<td>10</td>
<td>38</td>
</tr>
</tbody>
</table>
**Response Rates in HIV+ and HIV- MSM**

Response rate to hepatitis B vaccine administered at 0, 1, and 6 months in HIV-positive and HIV-negative men who have sex with men

<table>
<thead>
<tr>
<th>Study</th>
<th>Response to hepatitis B vaccine (% [n/N])</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV+ men</td>
</tr>
<tr>
<td>Wong et al.</td>
<td>42.9 (6/14)</td>
</tr>
<tr>
<td>Loke et al.</td>
<td>33.3 (9/27)</td>
</tr>
<tr>
<td>Collier et al.</td>
<td>56.3 (9/16)</td>
</tr>
<tr>
<td>Carne et al.</td>
<td>52.9 (9/17)</td>
</tr>
</tbody>
</table>


**Carne et al.** Impaired responsiveness of homosexual men with HIV antibodies to plasma derived hepatitis B vaccine. BMJ 1987; 294:8668.
Prospective Study of HCC in Taiwan Civil Servants

- Prospective study of hepatocellular carcinoma (HCC) in Taiwanese Civil Servants (Beasley et al.)
  - Enrollment: March 15, 1976 to June 3, 1978
  - 22,707 civil servants
    - 12.8% of all 40-59 year old male government employees
    - 1.4% of all 50-59 men in Taiwan
    - 186,000 person-years of followup mean = 8.2 years/man
    - Passive surveillance and active surveillance
  - 151 cases of HCC by December 1985
Prospective Study of HCC in Taiwan Civil Servants

Incidence and Relative Risk of HCC by HBsAg Carrier Status among Taiwanese Civil Servants (Beasley et al.)

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>No.</th>
<th>HCC</th>
<th>AR/100,000/yr</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pos</td>
<td>3,456</td>
<td>143</td>
<td>505</td>
<td>104*</td>
</tr>
<tr>
<td>Neg</td>
<td>19,253</td>
<td>8</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22,707</td>
<td>151</td>
<td>81/1</td>
<td></td>
</tr>
</tbody>
</table>

*95% CI: 50.9-212.0
Mortality from Primary Hepatocellular Carcinoma, Taiwan

Age-Sex Specific Mortality from Primary Hepatocellular Carcinoma in Taiwan 1970-1979

Mortality per 100,000

Age

Males

Females
Cumulative Incidence of Hepatocellular Carcinoma, 11,893 Men in Taiwan

- HBsAg+, HBeAg+
- HBsAg+, HBeAg-
- HBsAg-, HBeAg-

Cumulative Incidence (%) vs Year
Cumulative Incidence of Hepatocellular Carcinoma

Cumulative Incidence of Hepatocellular Carcinoma by Serum HBV DNA Level at Study Entry

Entire Cohort (n=3653)

Subcohort (n=2925)
### HCC Risk Factors

<table>
<thead>
<tr>
<th>Viral factors</th>
<th>Host factors</th>
<th>Environmental factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• HBV</td>
<td>• Age</td>
<td>• Dietary aflatoxins</td>
</tr>
<tr>
<td>• HCV</td>
<td>• Male gender</td>
<td>• Alcohol consumption</td>
</tr>
<tr>
<td></td>
<td>• Family history</td>
<td>• Cigarette smoking</td>
</tr>
<tr>
<td></td>
<td>• Diabetes/obesity</td>
<td>• Oral contraceptives</td>
</tr>
</tbody>
</table>
Pathogenesis of HCC

1. Exposure to Dietary Carcinogens and Tumor Promoters (Such as Aflatoxins and Alcohol)
2. Normal Hepatic Epithelium
3. Chronic Hepatitis and/or Cirrhosis
4. Phenotypically Altered Hepatocytes
5. Dysplastic Hepatocytes
6. Exposure to Inflammatory Oxidants (Such as HBV or HCV)
7. HCC

## Incidence of Liver Cancer per 100,000 Children in Birth Cohorts Determined According to the Date of Implementation of the Hepatitis B Vaccination Program

<table>
<thead>
<tr>
<th>Age at Diagnosis</th>
<th>Before-Program Cohort (July 1974-June 1984)</th>
<th>After-Program Cohort (July 1984-June 1986)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Population</td>
<td>Incidence</td>
</tr>
<tr>
<td>6</td>
<td>3,940,747</td>
<td>18 (0.46)</td>
</tr>
<tr>
<td>7</td>
<td>3,938,119</td>
<td>21 (0.53)</td>
</tr>
<tr>
<td>8</td>
<td>3,931,983</td>
<td>19 (0.48)</td>
</tr>
<tr>
<td>9</td>
<td>3,928,721</td>
<td>24 (0.61)</td>
</tr>
<tr>
<td>Total</td>
<td>15,739,570</td>
<td>82 (0.52)</td>
</tr>
</tbody>
</table>
The hepatitis B vaccine coverage rate and HBsAg sero-prevalence in infancy and at the age of six were estimated on the basis of data from previous field studies.

The immunization was given only to infants born between 1984 and 1986 to high-risk mothers.

The coverage from 1986 to 1992 was partially attributable to vaccination in the preschool period.
1. There are eight genotypes of HBV (A–H) which are geographically distributed
2. Genotypes B and C predominate in Asia
   – Genotype B is more likely to resolve, less risk of cirrhosis and liver cancer than genotype C
3. In U.S.A., genotypes A–G
   – Genotype B—less severe liver disease than A
4. In Africa, genotype E (Central Africa) has lower viral load and less perinatal transmission than A or D
Geographic Distribution of Hepatitis B Virus Genotypes
### Factors Associated with Increased Risk of Progression to Cirrhosis

<table>
<thead>
<tr>
<th>Host Factors</th>
<th>Virus Factors</th>
<th>Environmental Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age (longer duration)</td>
<td>High levels of HBV replication</td>
<td>Concurrent infection (HCV, HDV, HIV)</td>
</tr>
<tr>
<td>Male</td>
<td>Genotype (C&gt;B)*</td>
<td>Alcohol consumption</td>
</tr>
<tr>
<td>Immune status</td>
<td>HBV variant (core promoter)</td>
<td>Obesity</td>
</tr>
</tbody>
</table>
Maximum α-Fetoprotein Level and Associated Clinical Condition

(3,387 Tests Performed)

Clinical Condition

- Pregnancy (n=100)
- Acute Hepatitis B (n=8)
- Chronic Hepatitis (n=1)
- Undetermined (n=8)
- Asymptomatic PHC* (n=8)
- Symptomatic PHC* (n=3)

* Primary Hepatocellular Carcinoma
AFP Levels Before and After Resection of Primary HCC

α-Fetoprotein Levels Before and After Resection in Asymptomatic Persons with Primary Hepatocellular Carcinoma

Resection of PHC

Months Before and After Resection of Primary Hepatocellular Carcinoma
Section D

Hepatitis A
Hepatitis A Virus—Picornavirus

Hepatitis A Virus - Picornavirus

27 nm

Capsid

VPG

ss RNA
(2.5 x 10^0 daltons)

Viral Polypeptides

VP1

VP2

VP3

VP4
### Clinical Features of Hepatitis A

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Hepatitis A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incubation Period</td>
<td>15-45 Days</td>
</tr>
<tr>
<td>Symptoms</td>
<td>1/3 of all infected persons</td>
</tr>
<tr>
<td>Onset</td>
<td>Usually Abrupt</td>
</tr>
<tr>
<td>Mode of Transmission</td>
<td>Fecal/Oral (Enteric)</td>
</tr>
<tr>
<td>Carrier State</td>
<td>None</td>
</tr>
<tr>
<td>Chronicity</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.1% to 0.2%</td>
</tr>
</tbody>
</table>
Clinical Features of Hepatitis A

Hepatitis A - Clinical Features

- **Incubation period:**
  - Average 30 days
  - Range 15-50 days

- **Jaundice by age group:**
  - <6 yrs, <10%
  - 6-14 yrs, 40%-50%
  - >14 yrs, 70%-80%

- **Complications:**
  - Fulminant hepatitis
  - Cholestatic hepatitis
  - Relapsing hepatitis

- **Chronic sequelae:**
  - None
HAV Infection: Typical Serologic Course

Hepatitis A Virus Infection; Typical Serologic Course

- ALT
- Total Anti-HAV
- IgM Anti-HAV

Adapted by CTLT from CDC.
Hepatitis A Virus Transmission

- Close personal contact
  (e.g., household contact, sex contact, child day care centers)

- Contaminated food, water
  (e.g., infected food handlers, raw shellfish)

- Blood exposure (rare)
  (e.g., injecting drug use, transfusion)
Age-Specific Incidence of Hepatitis A, United States


- 0-4 yrs.
- 5-14 yrs.
- 15-24 yrs.
- 25-39 yrs.
- ≥40 yrs.

Reported Cases (per 100,000)

Year

‘83 ‘85 ‘87 ‘89 ‘91 ‘93

Adapted by CTLT from CDC, National Notifiable Diseases Surveillance System.
Sources of HAV Infection, 1983–1993

Sources of Hepatitis A Virus Infection by Mutually Exclusive Groups
United States, 1983 – 1993

Adapted by CTLT from CDC, Viral Hepatitis Surveillance Program.
Maricopa County, Arizona, 1974–1978

Cases of Hepatitis Type A or Hepatitis of an Unspecified Type Reported in Maricopa County, Arizona, 1974 – 1978

Number of Cases

- All Cases
- Day Care Related Cases

Month, Year

Relation of Age of Day-Care Child to Occurrence of Hepatitis in Family Contacts in Households with One Child and to Occurrence of Clinical Hepatitis in the Day-Care Child

Age of Day-Care Child (Year)

Number of Cases

Hepatitis in Family Contacts

Hepatitis in Day-Care Child

Attack Rate per 1,000
Geographic Distribution of HAV Infection
Global Patterns of Hepatitis A Virus Transmission

<table>
<thead>
<tr>
<th>Endemicity</th>
<th>Disease Rate</th>
<th>Peak Age of Infection</th>
<th>Transmission Patterns</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Low to High</td>
<td>Early childhood</td>
<td>Person to person; outbreaks uncommon</td>
</tr>
<tr>
<td>Moderate</td>
<td>High</td>
<td>Late childhood/young adults</td>
<td>Person to person; food and waterborne outbreaks</td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
<td>Young adults</td>
<td>Person to person; food and waterborne outbreaks</td>
</tr>
<tr>
<td>Very low</td>
<td>Very low</td>
<td>Adults</td>
<td>Travelers; outbreaks uncommon</td>
</tr>
</tbody>
</table>
### Hepatitis A Vaccine Efficacy Studies

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Site/Age Group</th>
<th>N</th>
<th>Vaccine Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAVRIX® (SKB) 2 doses 360 EL.U.</td>
<td>Thailand 1-16 yrs</td>
<td>38,157</td>
<td>94% (79%-99%)</td>
</tr>
<tr>
<td>VAQTA™ (Merck) 1 dose 25 units</td>
<td>New York 2-16 yrs</td>
<td>1,037</td>
<td>100% (85%-100%)</td>
</tr>
</tbody>
</table>

*JAMA 1994;271:1363-4
Hepatitis A Vaccination Strategies: Epidemiologic Considerations

- Many cases occur in community-wide outbreaks
  - no risk factor identified for most cases
  - highest attack rates in 5-14 year-olds
  - children serve as reservoir of infection

- Persons at increased risk of infection
  - travelers
  - homosexual men
  - injecting drug users
# Age-Specific Mortality Due to Hepatitis A

## Age-specific Mortality Due to Hepatitis A

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Case-Fatality (per 1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>3.0</td>
</tr>
<tr>
<td>5-14</td>
<td>1.6</td>
</tr>
<tr>
<td>15-29</td>
<td>1.6</td>
</tr>
<tr>
<td>30-49</td>
<td>3.8</td>
</tr>
<tr>
<td>&gt;49</td>
<td>17.5</td>
</tr>
<tr>
<td>Total</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Source: Viral Hepatitis Surveillance Program, 1983-1989
Preexposure Vaccination Recommendations

ACIP Recommendations - Hepatitis A Vaccine
Preexposure Vaccination

- Persons at increased risk for infection
  - travelers to intermediate and high HAV-endemic countries
  - homosexual and bisexual men
  - drug users
  - persons with chronic liver disease

- Communities with high rates of hepatitis A (e.g., Alaska Natives, American Indians)
  - routine childhood vaccination
U.S. Hepatitis A Incidence by Year, 1966–2003

US Hepatitis A Incidence by Year, 1966–2003

Cases per 100,000 Population

Year

'66 '70 '74 '78 '82 '86 '90 '94 '98 '02

Vaccinating States
Overall
Nonvaccinating States
Incidence Rates in Israel

Annual Incidence Rates in Israel of Reported Infectious Hepatitis, 1993 – 2004

- Total Population
  - Total “Infectious Hepatitis”
  - Hepatitis A

- Jewish Population

- Non-Jewish Population
HAV Antibody Prevalence among Children in Bangkok

Age-Specific Hepatitis A Antibody Prevalence Among Schoolchildren in Bangkok

- Group A, 1987
- Group B, 1988
- School B, 1977

Prevalence of Anti-HAV Antibody (%) vs. Age Group (Years)
Incidence in the U.S. and Shanghai County, PRC

Incidence Patterns of Reported Cases of Hepatitis A, United States and Shanghai County

Hepatitis D (Delta) Virus
Hepatitis D—Clinical Features

- **Coinfection**
  - severe acute disease
  - low risk of chronic infection

- **Superinfection**
  - usually develop chronic HDV infection
  - high risk of severe chronic liver disease
HBV-HDV Superinfection: Typical Serologic Course

Adapted by CTLT from CDC.