Methods to Evaluate Infant Hepatitis B Immunization Programs

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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

Indicator		Measure
HepB1	→	Series initiation
HepB1 (birth dose)	→	Perinatal prevention
HepB3	→	Series completion
HepB3 vs. HepB1	→	Series drop-out
HepB3 vs. DTP3	→	Completion hep B series compared to an established vaccine

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

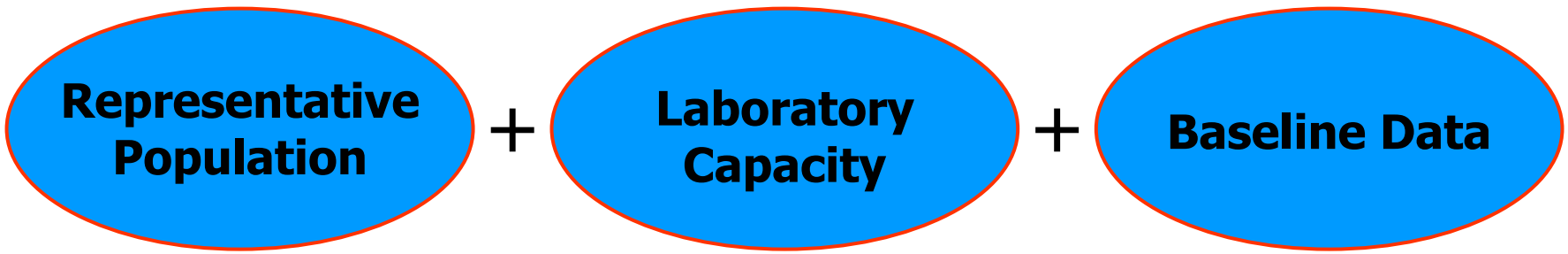
Evaluating Hepatitis B Immunization Programs

Serologic Surveillance

Serologic Surveillance

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

Requirements:



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 …..

History of past illnesses and hospitalizations

↓

Therapeutic injections, IV's, other invasive medical procedures

↓

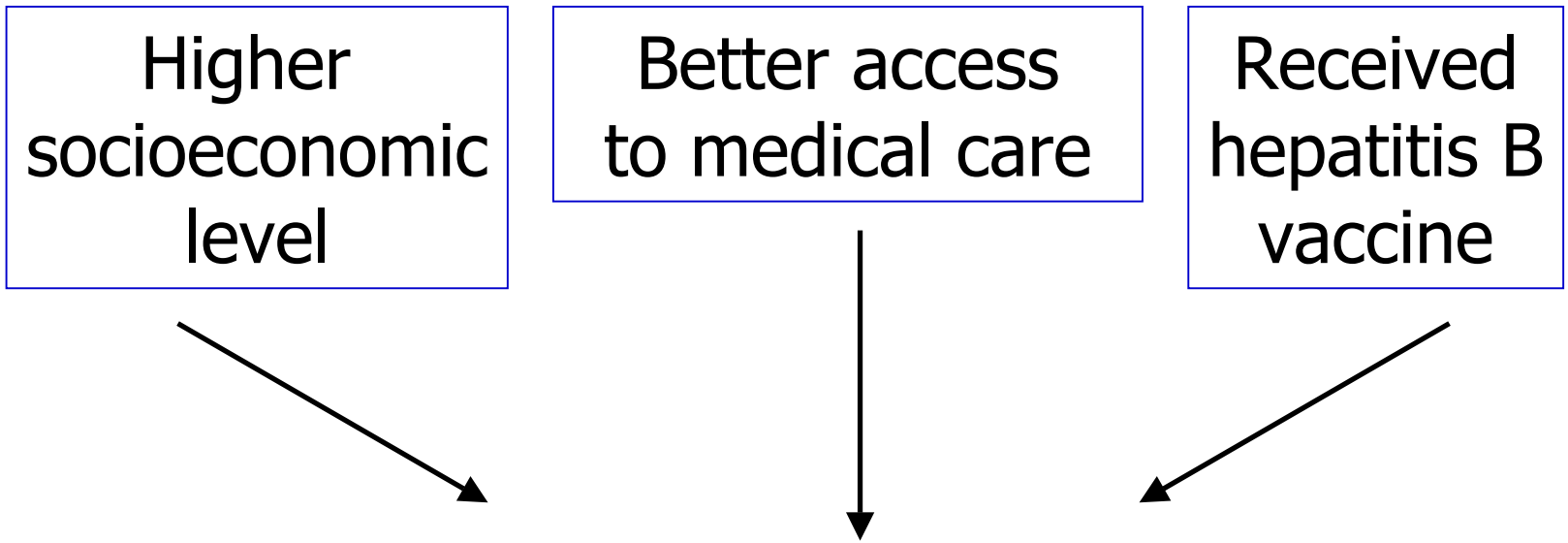
Exposure to nosocomial transmission of HBV

↓

More likely to be infected with HBV

Representativeness of Hospitalized Children for Serologic Surveys

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



Comparison of Various Populations for Serologic Surveys

Population	Representative	Difficulty	Expense
Hospital-based	+/-	+	+
Outpatient clinic	++	++	++
School-based	+++	+++	+++
Community/ Household	++++	++++	++++
Blood donors	+/-	+	+
Pregnant women	+++	+	+

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

CDC

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

Age at infection	Acute hep B	Chronic infection
<1 year	**<1%**	**90%**
1-5 years	**5-15%**	**25-50%**
>5 years	**20-50%**	**6-10%**

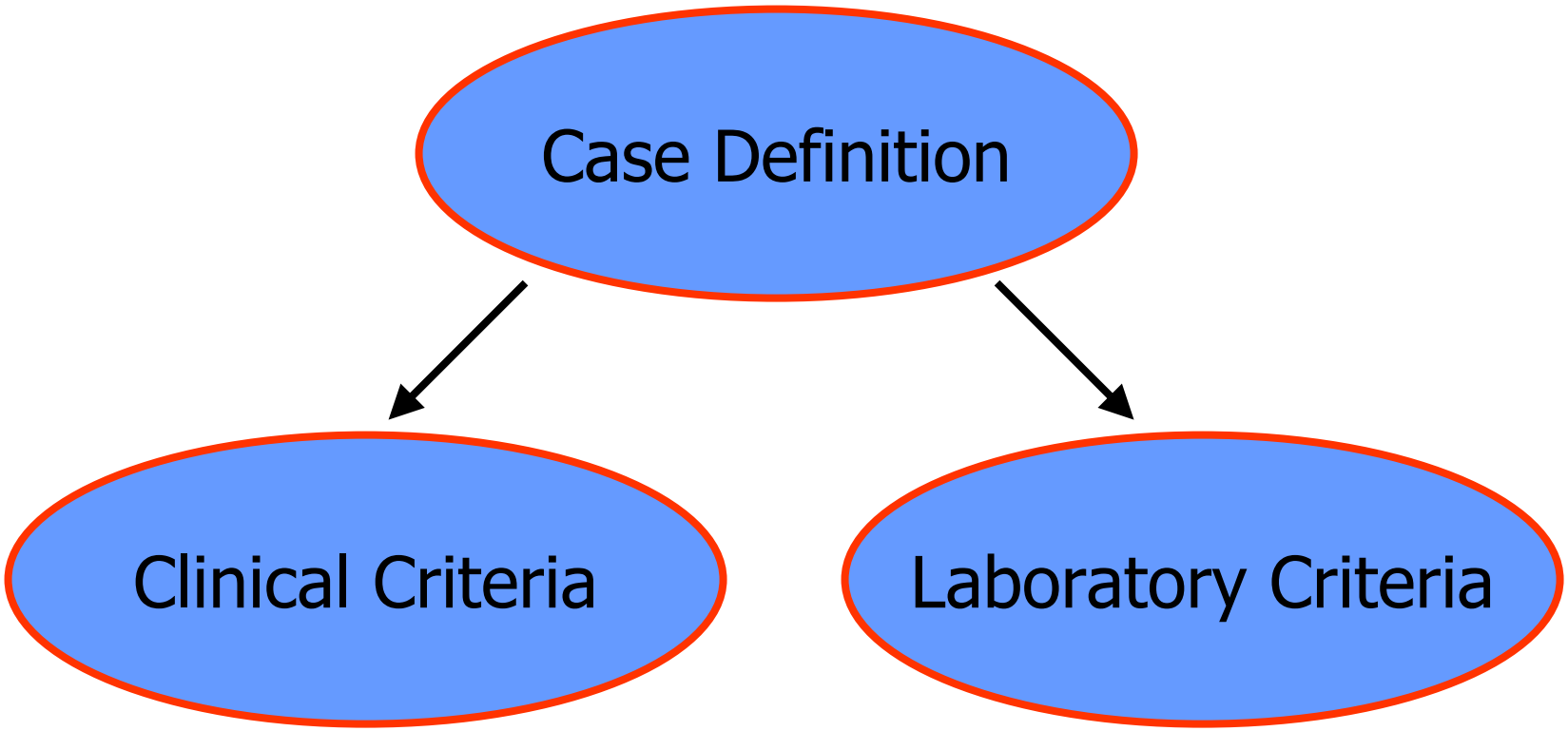
Feasibility of Conducting Surveillance for Acute Viral Hepatitis

- 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?

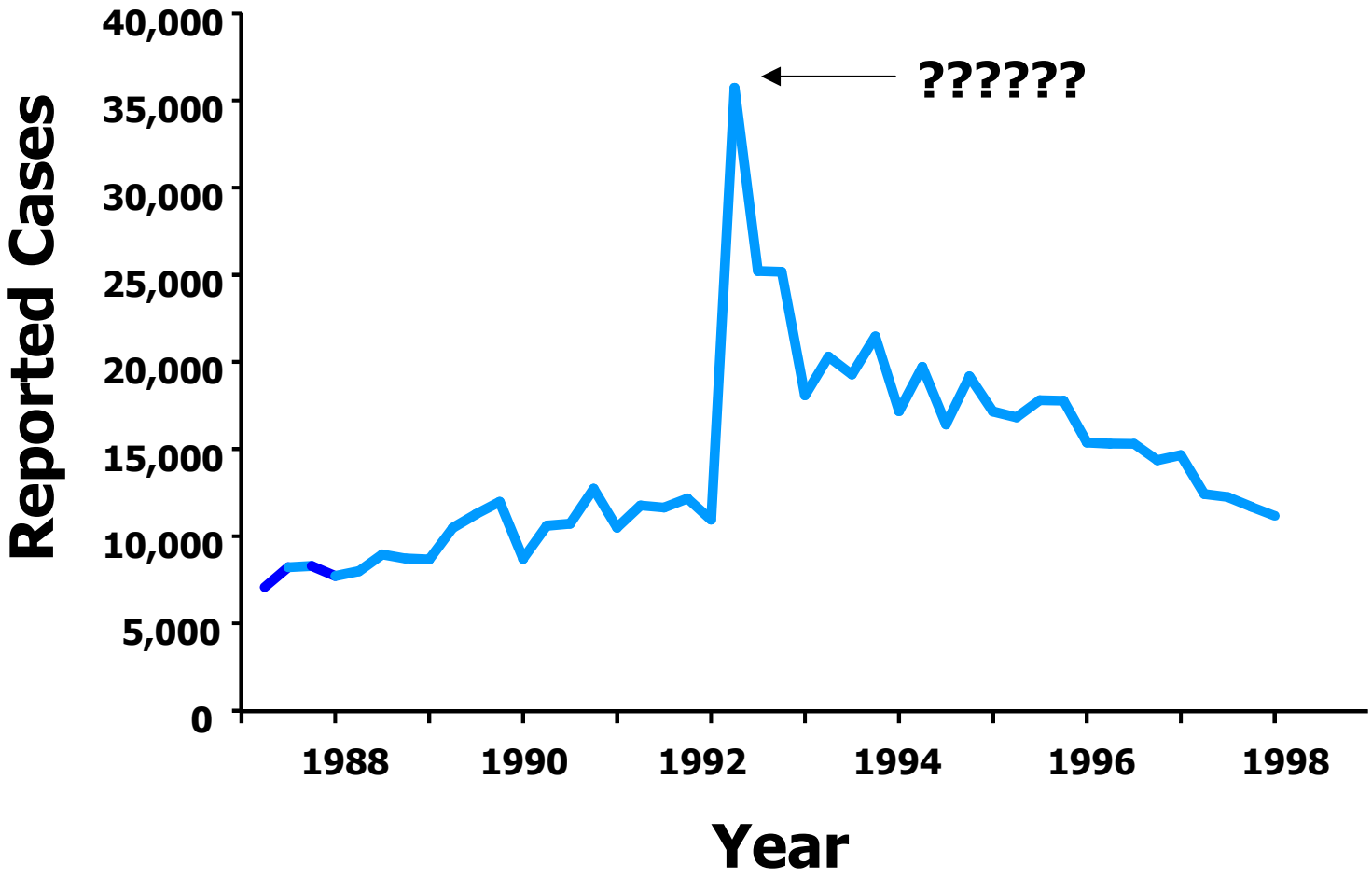
Case Definition for Acute Viral Hepatitis



Same for all types of acute viral hepatitis

Differs for each type of acute viral hepatitis

Reported Cases of AIDS in the United States (1987-1998)



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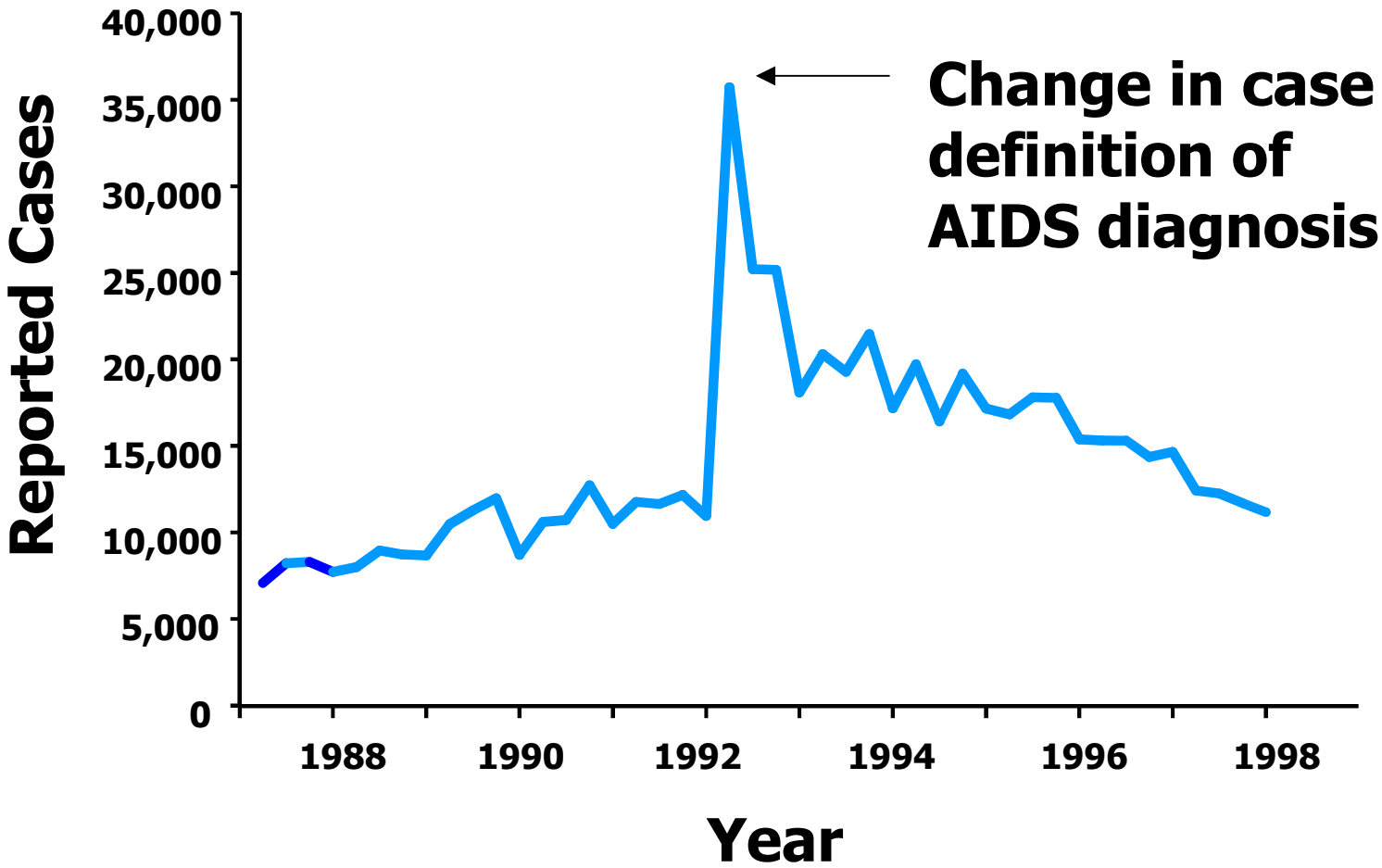


Case Definition for Acute Viral Hepatitis, United States

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

Hepatitis B Immunization in Taiwan

Year	Group included in Program
1984	Infants born to HBsAg-positive mothers
1986	All infants (routine infant immunization)
1987	Preschool children
1988	Primary school children
1989	Middle school children
1990	Adults

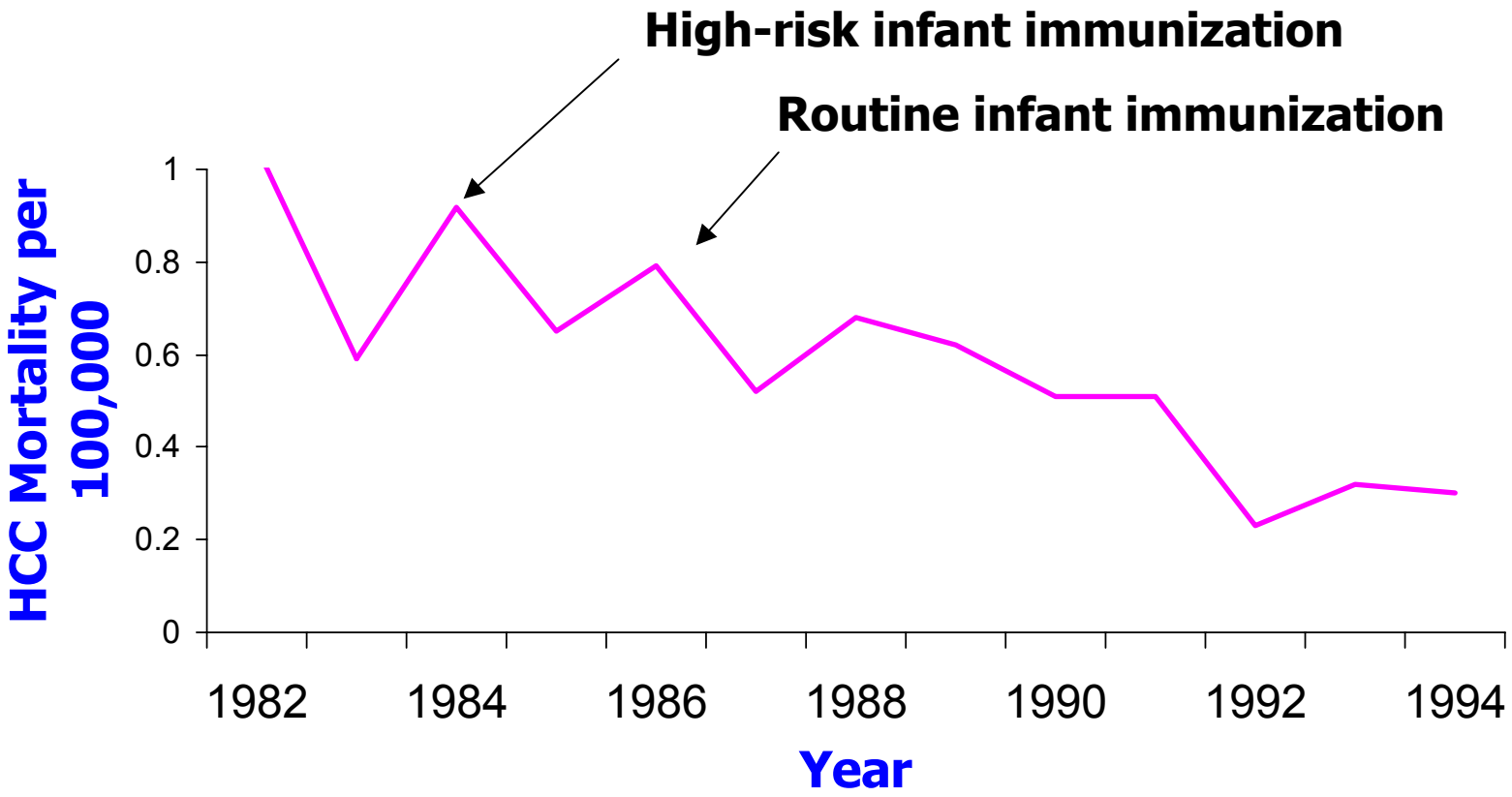
Source: Chang NEJM 1997.

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.

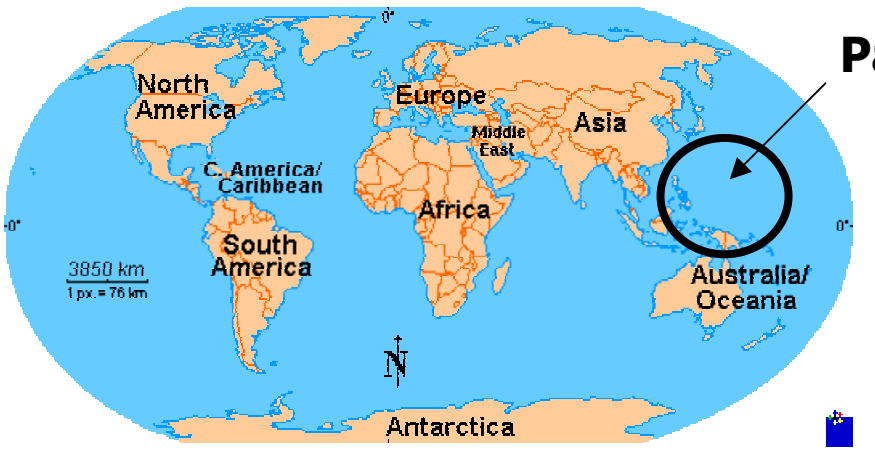
Mortality from Hepatocellular Carcinoma Among 6 to 14 Year Old Children: Taiwan (1982-1994)



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

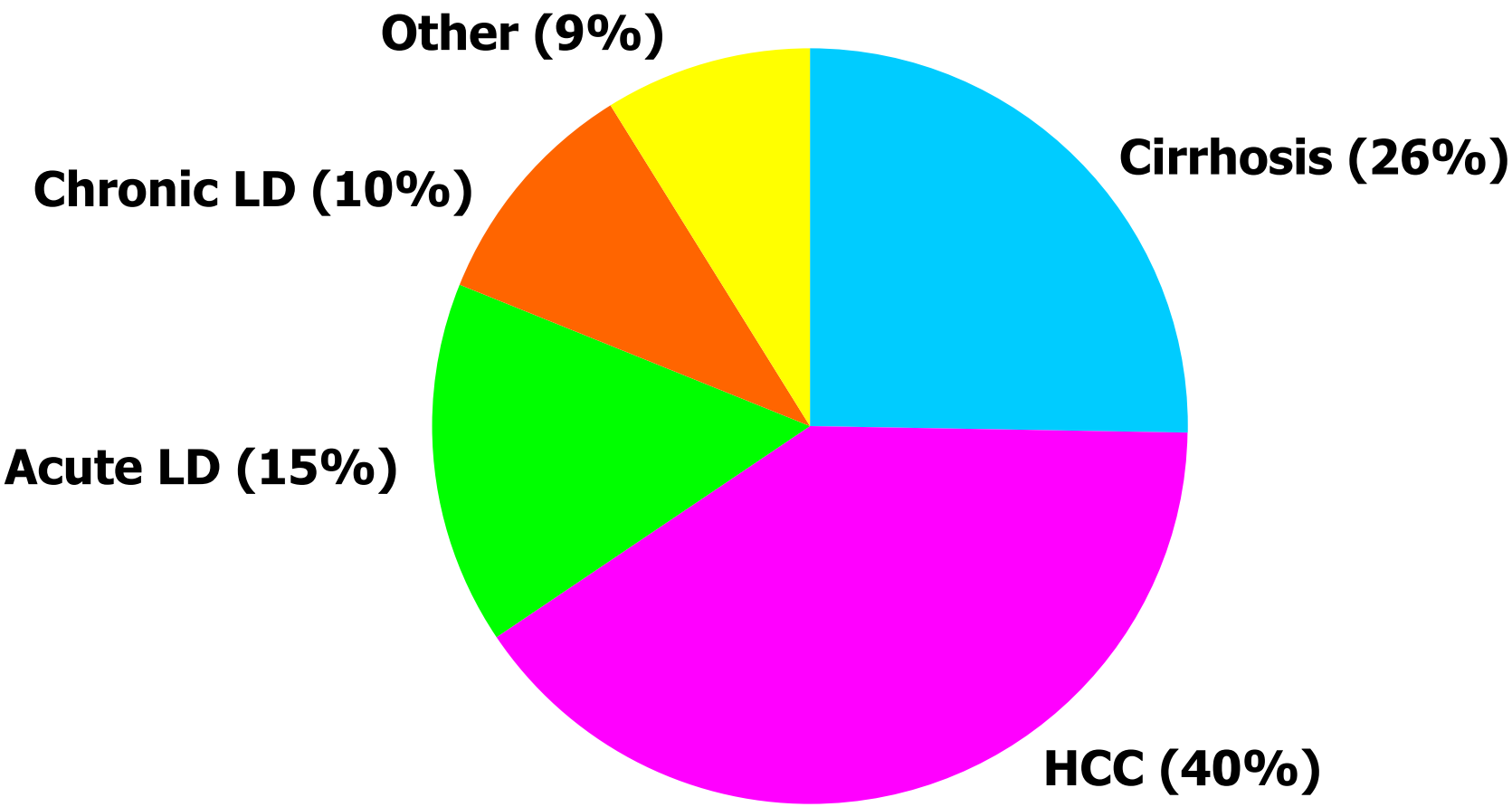
Adult Deaths, Palau, 1990-2002

	All Cause	Liver Disease
Total	1480	120
Median per year (range)	117 (97-133)	10 (3-13)

Overall, 8% of deaths due to liver disease

Source: T Vogt, DVH, CDC

Classification of Liver Disease Deaths, Palau, 1990-2002 (n=120)



Source: T Vogt, DVH, CDC

Death Rates from Cirrhosis and HCC, Palau and Worldwide

	Annual Death Rate per 100,000 Population	
	Palau	**Worldwide[2]**
Cirrhosis[1]	17.4	14.3
HCC	19.4	11.4

[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

Cause of death	HBV Serology Available	Percent HBsAg+
Cirrhosis (n=31)	26	73%
HCC (n=48)	37	84%
Acute liver disease (n=28)	11	73%
Chronic liver disease[1] (n=12)	9	89%
Other (n=11)	5	0%

[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

	Coverage Survey	Serosurvey	Acute Disease Surveillance	Morbidity & Mortality
Feasibility	+	+++	+++	+++
Expense	+	+++	+++	++
Frequency of evaluation	I*	I	I or C*	I or C
Program effectiveness				
short-term	-	+++	+	+
long-term	-	+++	+++	+++
Information collected	Coverage data	Prevalence of infection	Incidence new infection Risk factor information	Incidence chronic sequelea

* I=intermittent; C=continuous