

The background of the slide is a photograph of the Golden Gate Bridge in San Francisco, California. The bridge's iconic red-orange towers and suspension cables are visible against a clear blue sky. The bridge spans across the water, with the city of San Francisco visible in the distance. The text is overlaid on this image.

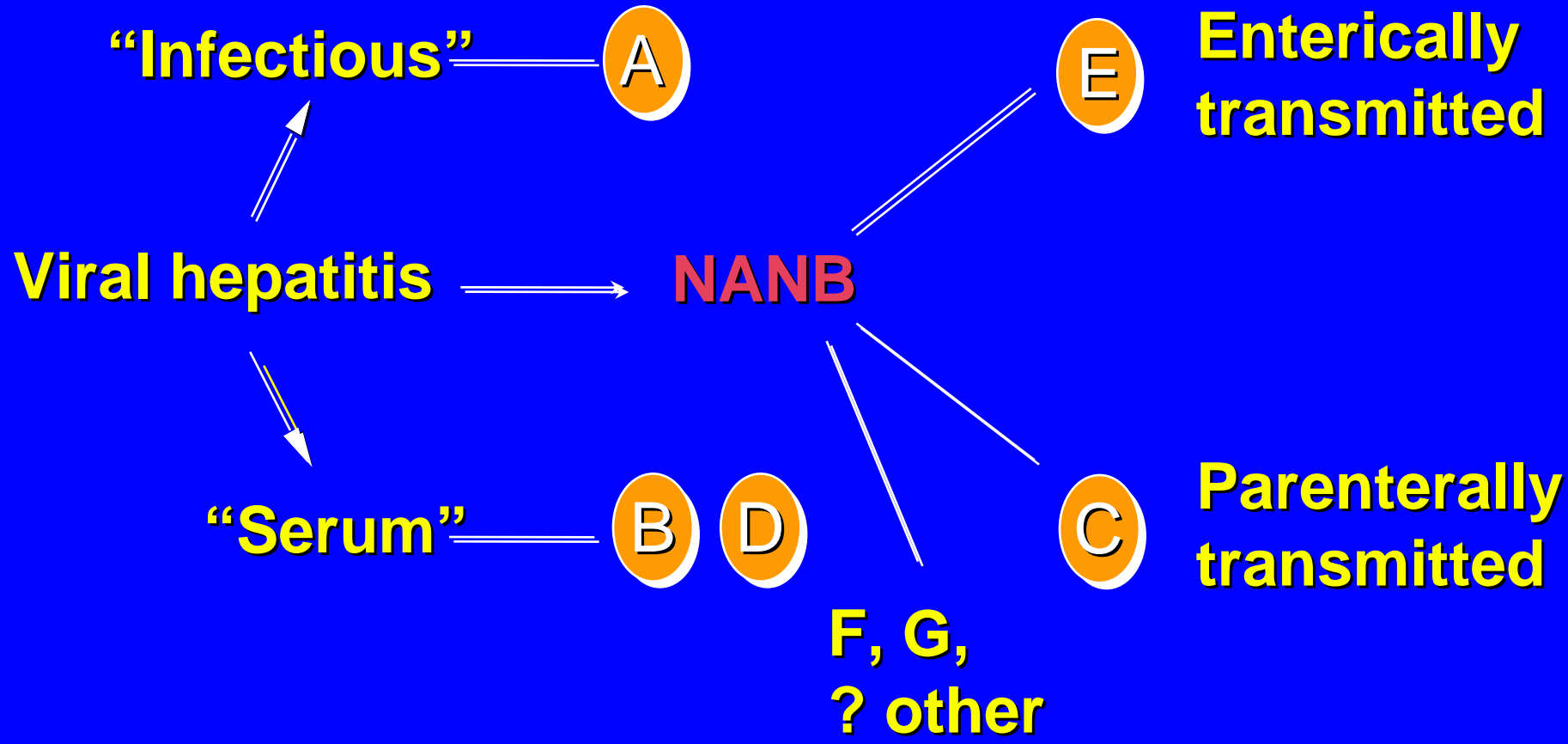
Viral Hepatitis B
**“To Treat or Not to Treat?”- And
are we making a difference by
vaccinating?**

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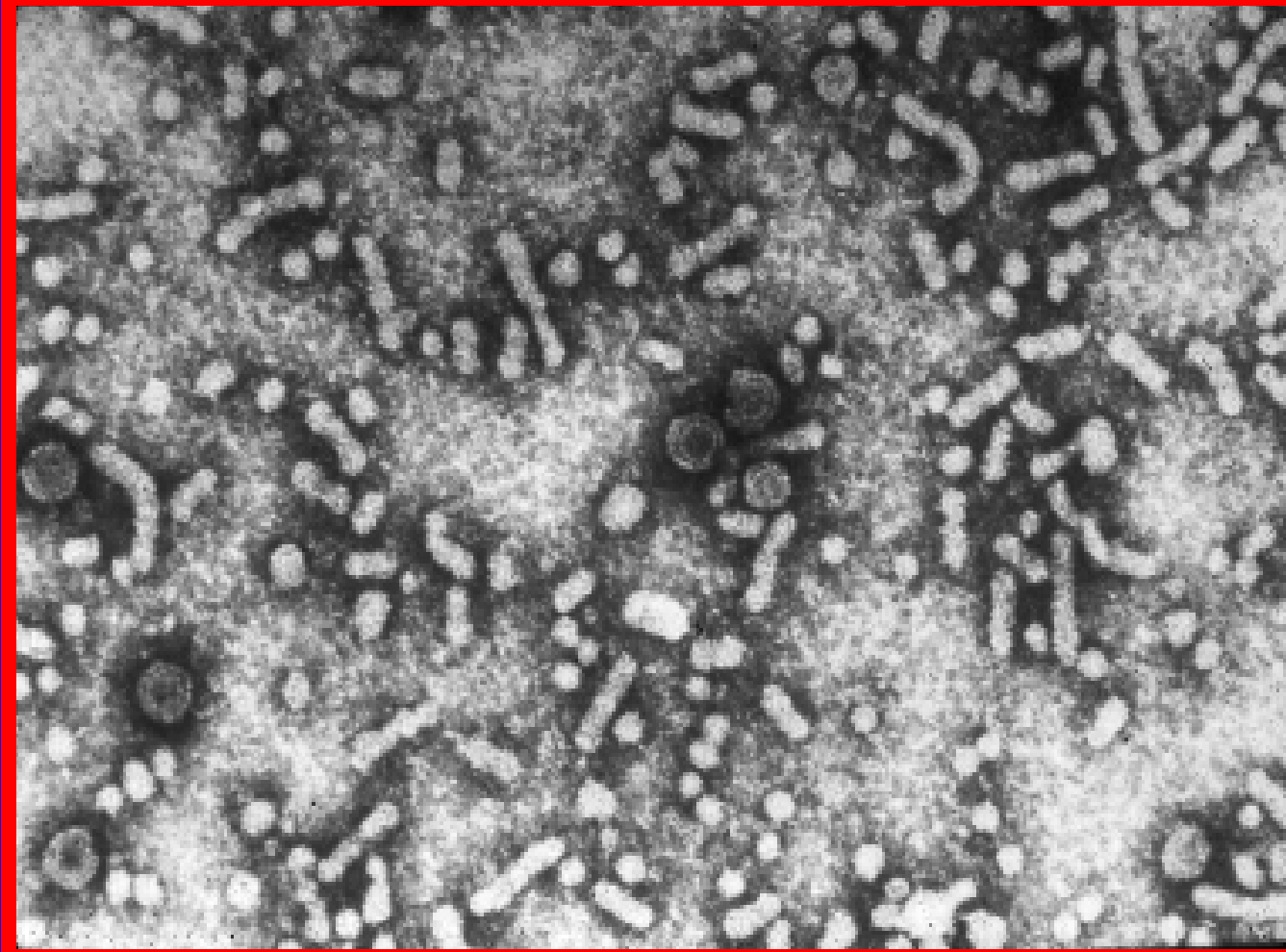
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 - Research Support from: Roche, Gilead, NIH
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- I do intend to discuss an unapproved/investigative use of a commercial product/device in my presentation

Viral Hepatitis - Historical Perspective



Hepatitis B Virus



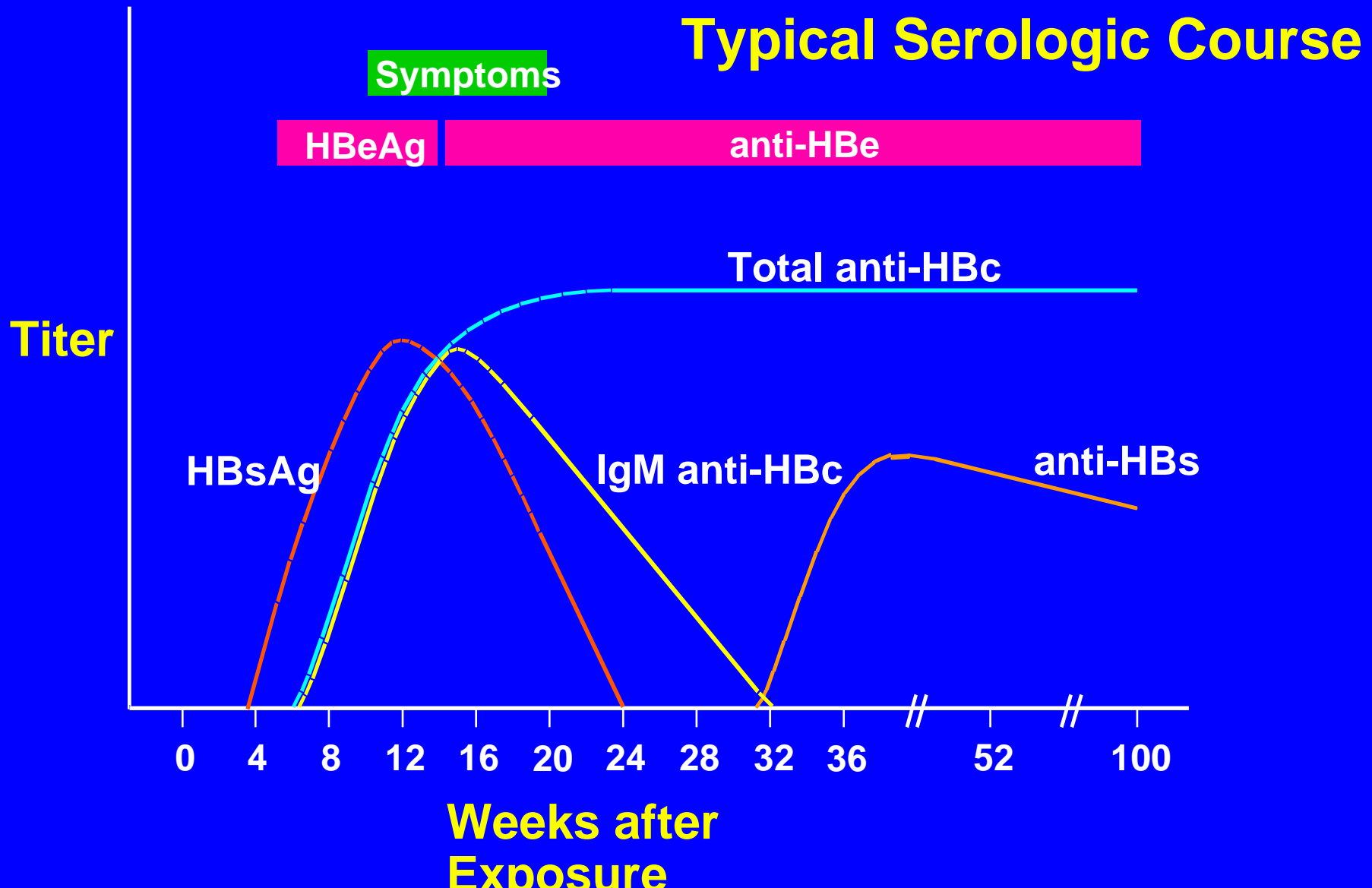
Hepatitis B Virus Terminology

- HBsAg- Hepatitis B surface antigen
- HBsAb- Hepatitis B surface antibody
- HBeAg- Hepatitis B “e” antigen
- HBeAb- Hepatitis B “e” antibody
- HBcAg- Hepatitis B core antigen
- HBcAb- Hepatitis B core antibody
- HBV DNA- Hepatitis B viral DNA

Hepatitis B - Clinical Features

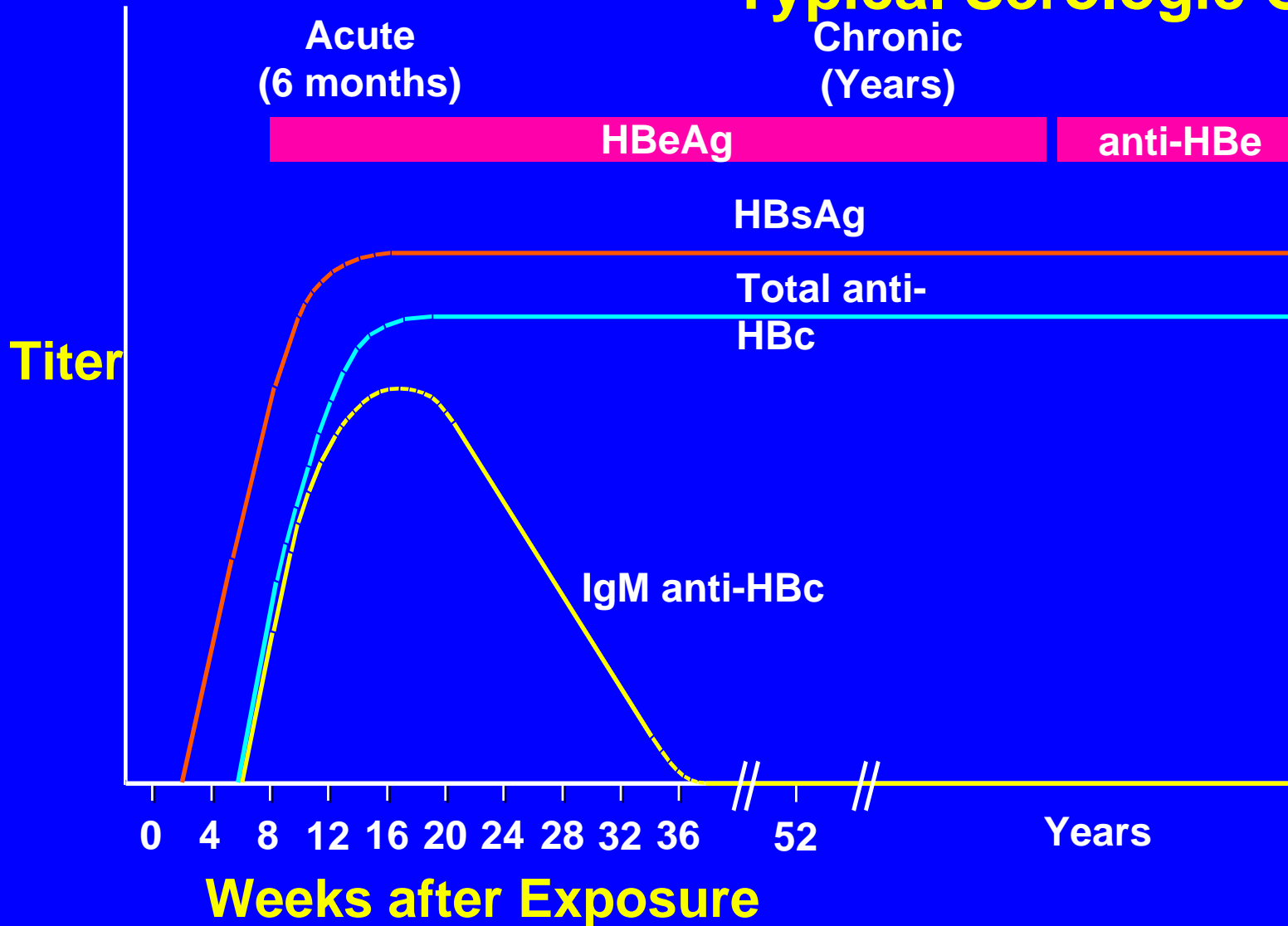
- Incubation period: Average 60-90 days
Range 45-180 days
- Clinical illness (jaundice): <5 yrs, <10%
≥5 yrs, 30%-50%
- Acute case-fatality rate: 0.5%-1%
- Chronic infection: <5 yrs, 30%-90%
≥5 yrs, 2%-10%
- Premature mortality from chronic liver disease: 15%-25%

Acute Hepatitis B Virus Infection with Recovery

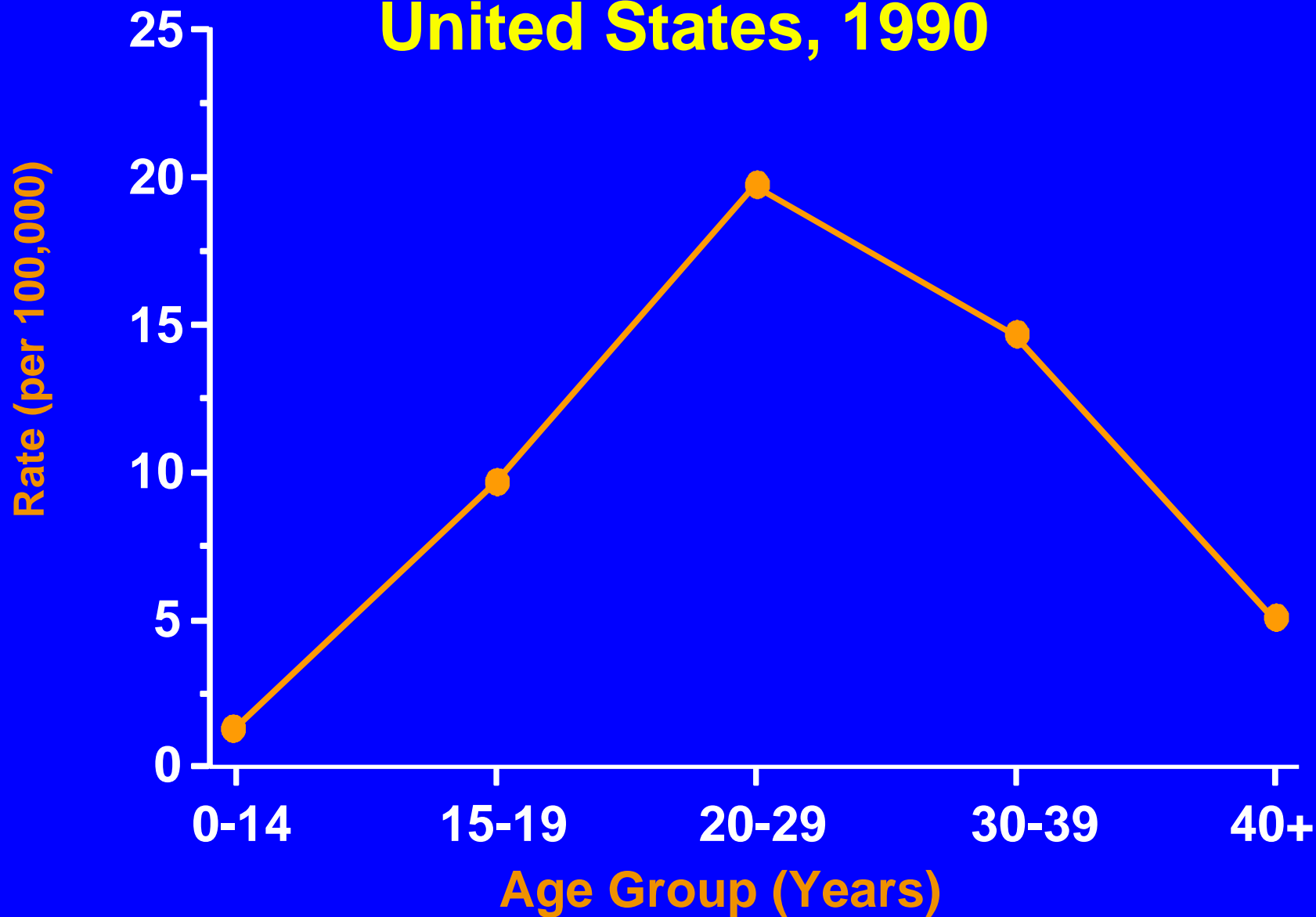


Progression to Chronic Hepatitis B Virus Infection

Typical Serologic Course



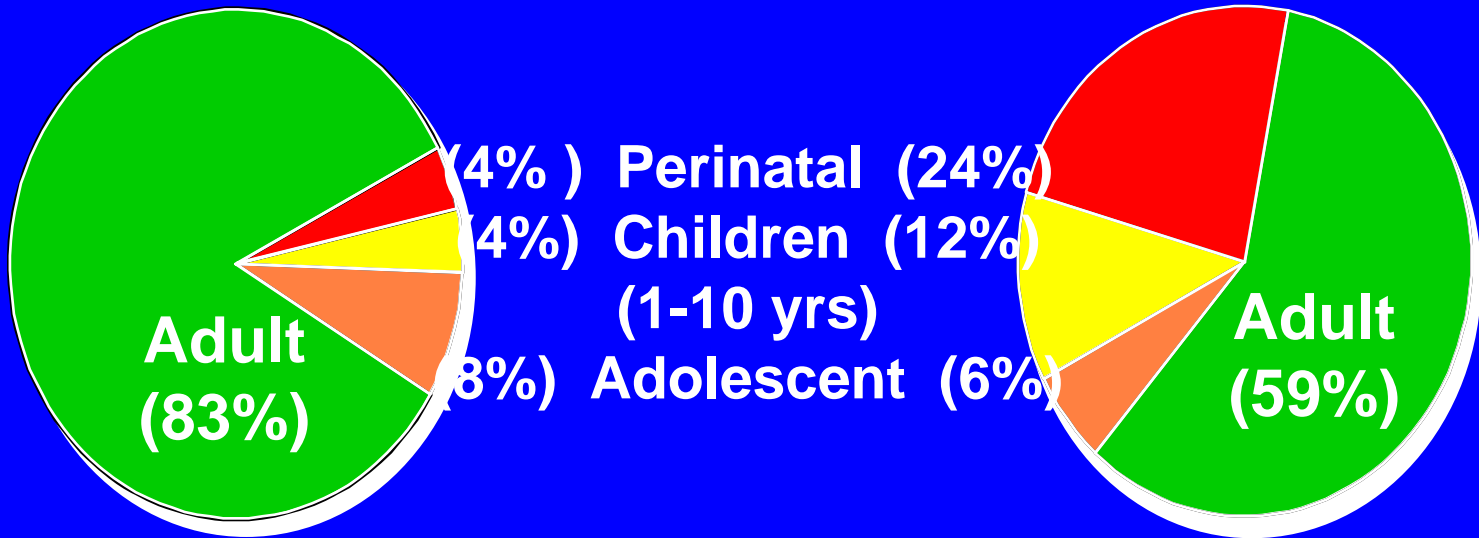
Rate of Reported Hepatitis B by Age Group United States, 1990



Source: CDC Viral Hepatitis Surveillance Program

Age at Acquisition of Acute and Chronic HBV Infection

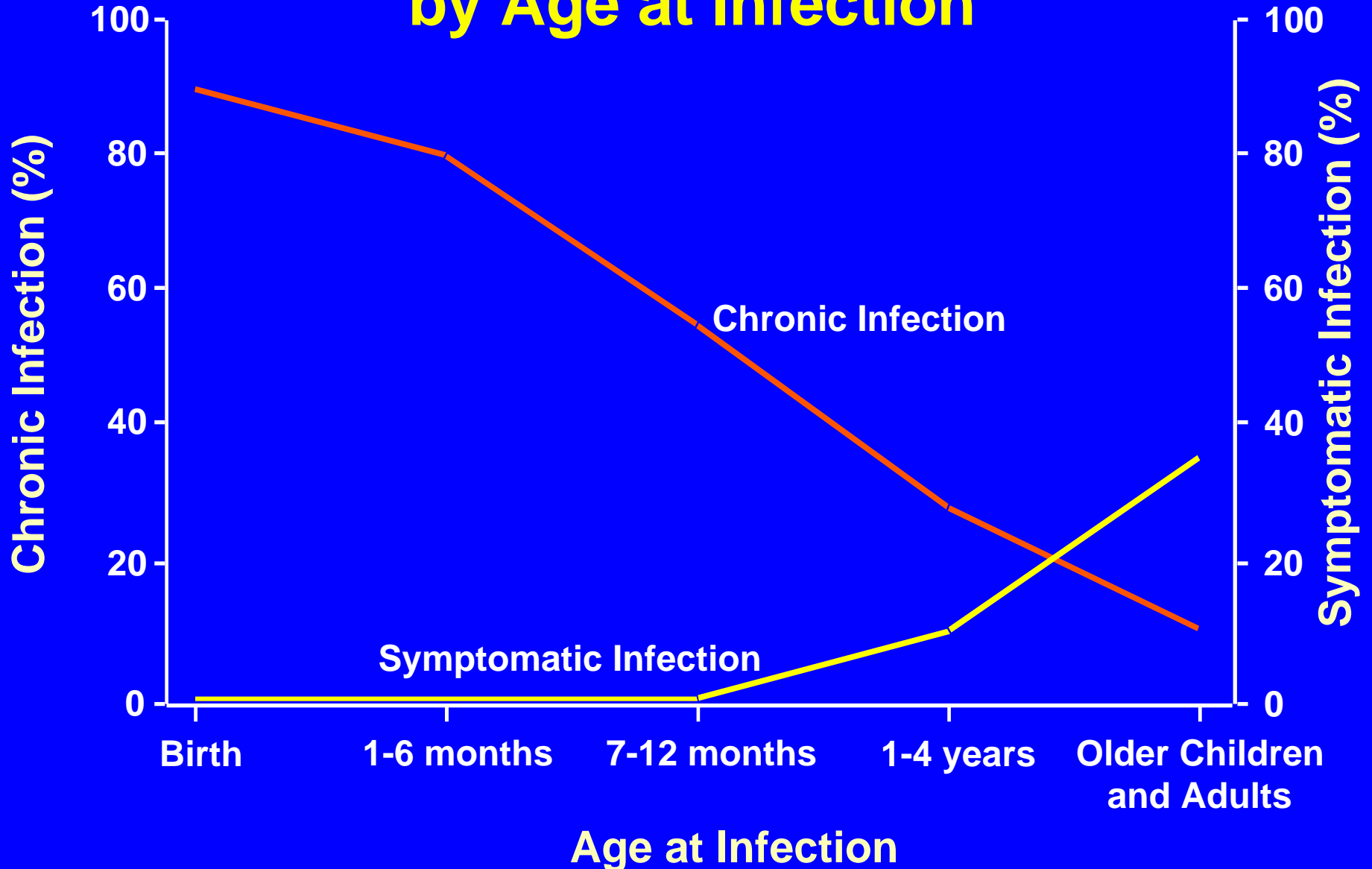
United States, 1989 Estimates



Acute HBV Infections

Chronic HBV Infections

Outcome of Hepatitis B Virus Infection by Age at Infection



Hepatitis B Virus Chronic Hepatitis

- 90% of infants infected during the first year of life become chronic carriers
- 80% of children are asymptomatic with almost normal LFTs despite an abnormal liver biopsy
- Chronically infected children carry a 25% lifetime risk of cirrhosis or hepatoma

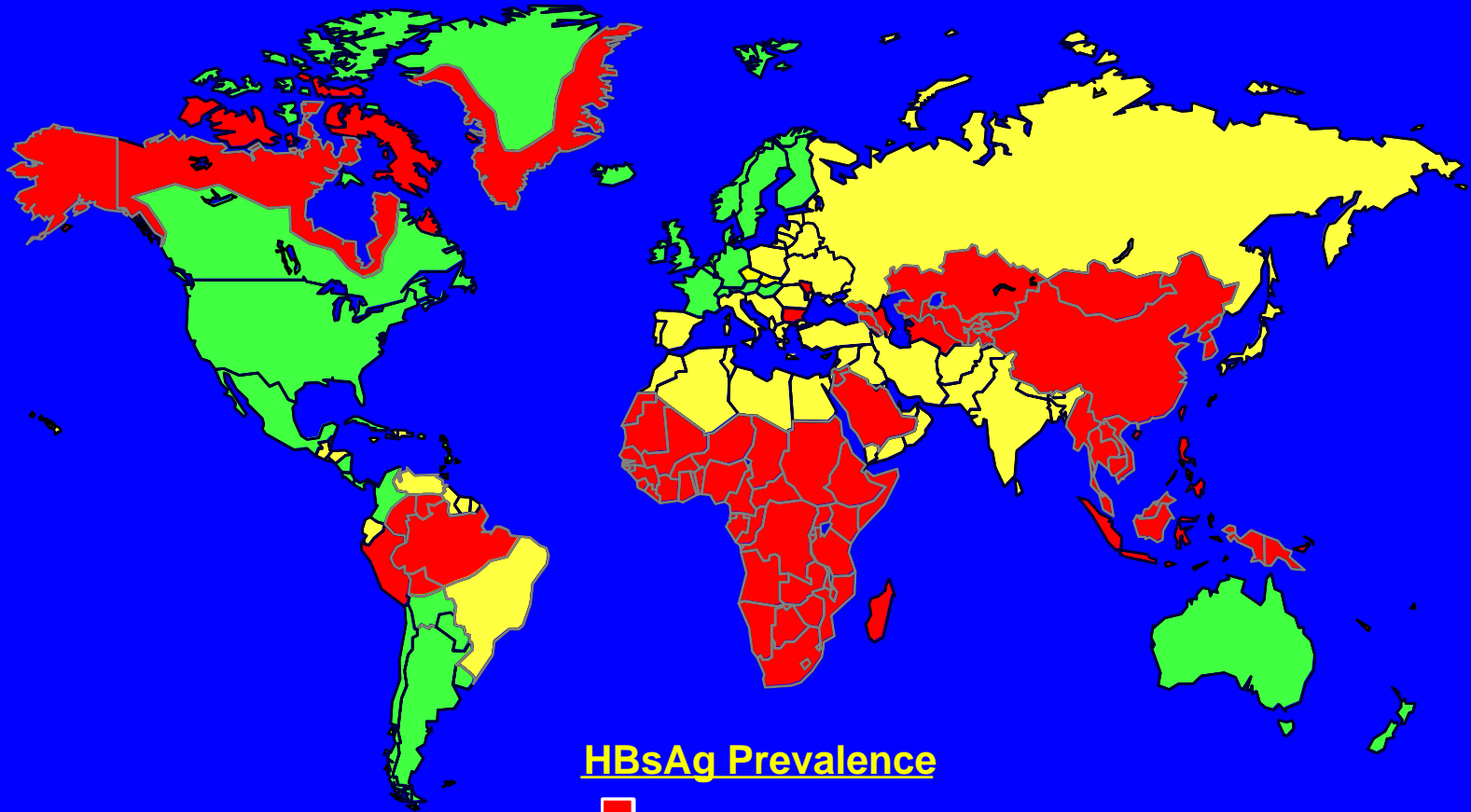
Chronic HBV Infection-HCC

- The risk of developing HCC is related to the time lapse between infection and anti-HBe seroconversion

Global Patterns of Chronic HBV Infection

- High ($\geq 8\%$): 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

Geographic Distribution of Chronic HBV Infection



HBsAg Prevalence

- $\geq 8\%$ - High
- 2-7% - Intermediate
- $< 2\%$ - Low

Concentration of Hepatitis B Virus in Various Body Fluids

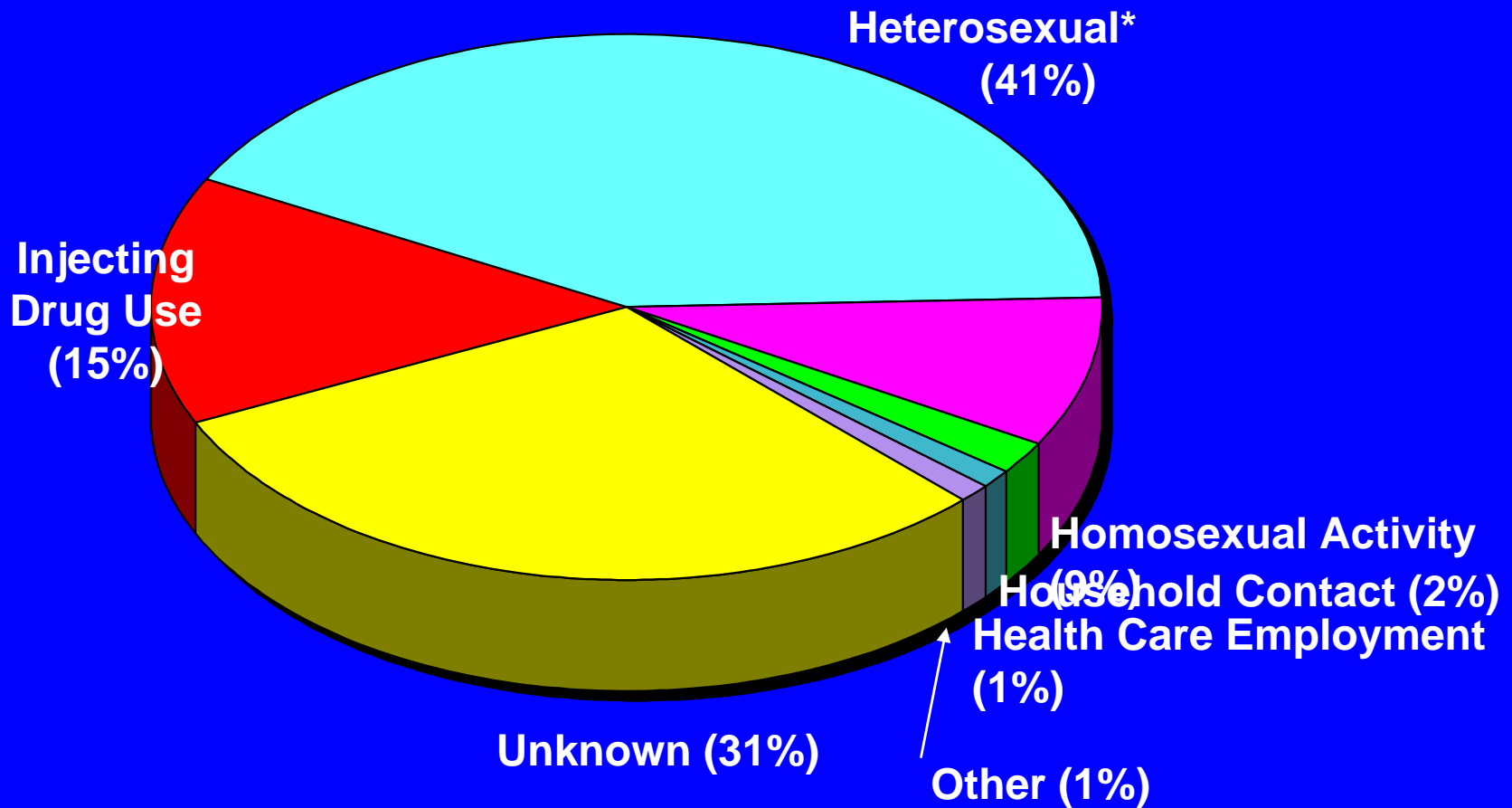
High	Moderate	Low/Not Detectable
blood	semen	urine
serum	vaginal fluid	feces
wound exudates	saliva	sweat
		tears
		breastmilk

Hepatitis B Virus

Modes of Transmission

- Sexual
- Parenteral
- Perinatal

Risk Factors for Acute Hepatitis B United States, 1992-1993



* Includes sexual contact with acute cases, carriers, and multiple partners.

Source: CDC Sentinel Counties Study of Viral Hepatitis

Elimination of Hepatitis B Virus Transmission United States

Objectives

- Prevent chronic HBV Infection
- Prevent chronic liver disease
- Prevent primary hepatocellular carcinoma
- Prevent acute symptomatic HBV infection

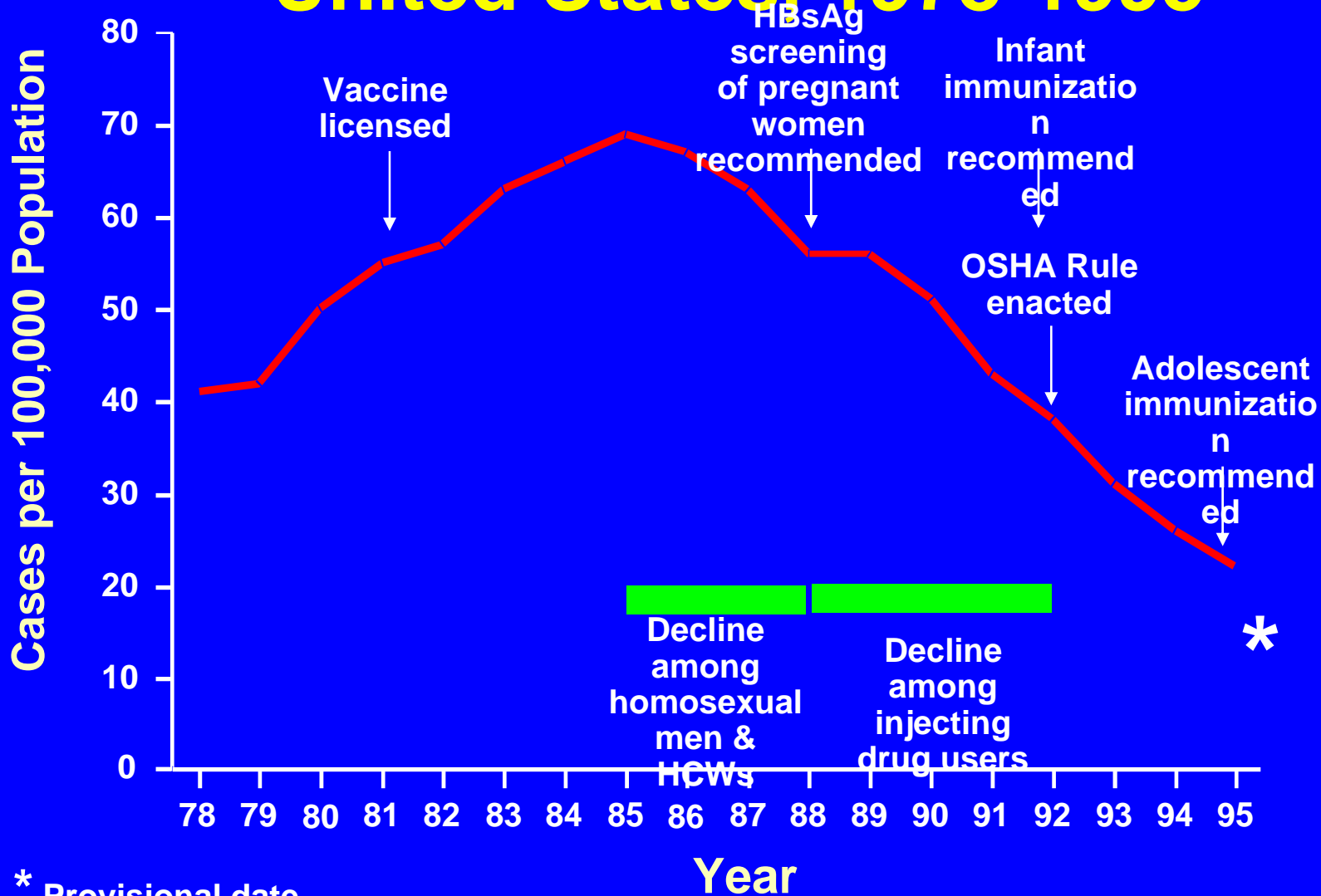
Elimination of Hepatitis B Virus Transmission United States

Strategy

- Prevent perinatal HBV transmission
- Routine vaccination of all infants
- Vaccination of children in high-risk groups
- Vaccination of adolescents
 - all unvaccinated children at 11-12 years of age
 - “high-risk” adolescents at all ages
- Vaccination of adults in high-risk groups

Estimated Incidence of Acute Hepatitis B

United States, 1978-1995



Evaluation of Patients with Chronic HBV- Initial Evaluation

- History & physical examination
- Laboratory tests to assess liver disease- CBC with platelets, hepatic panel & PT
- Tests for HBV replication- HBeAg, anti-HBe, HBV DNA
- Tests to rule out other causes of liver disease- anti-HCV, anti-HDV
- Tests to screen for HCC- AFP, ultrasound
- Liver biopsy to grade and stage liver disease

Follow-up of Patients with Chronic HBV- Not for Treatment

- HBeAg + with HBV DNA $>10^5$ copies/ml and normal ALT
 - ALT q 3-6 months
- If ALT $>1-2X$ ULN recheck ALT q 1-3 months
- If ALT $>2X$ ULN for 3-6 months & HBeAg+, HBV DNA $>10^5$ copies/ml, consider liver biopsy & Rx
- Consider HCC screen (AFP/UTZ)
- Inactive HBsAg carrier state
- ALT q 6-12 months
- If ALT $>1-2X$ ULN, serum HBV DNA & exclude other causes of liver disease
- Consider HCC screen (AFP/UTZ)

Chronic Hepatitis B

Treatment Aims

- Eradicate the virus
- Ameliorate liver disease
- Prevent complications

Chronic Hepatitis B

Spontaneous Viral Clearance

	Yearly rate
• HBeAg → anti-HBe	7-16%
• DNA clearance → active histology	24%
↘ inactive histology	11%
• HBsAg → anti-HBs	0.6%

Chronic Hepatitis B

Who Should Be Treated?

- Those with active disease, who are more likely to clear the virus spontaneously?
- Those with inactive disease, who are less likely to clear the virus spontaneously?

Chronic Hepatitis B

IFN- α : Randomized Trials

- IFN- α with or without steroid priming
- Lai et al (*Q J Med* 1991) 90 pts.
- Gregorio et al (*Hepatology* 1996) 96 pts.

Chronic Hepatitis B

IFN- α ± steroids

	% loss in treated/untreated of	
	HBV DNA	HBeAg
• Lai et al IFN- α 5MU/m ² (4 m)	7/0	3/0
IFN- α after 1.5 mths pred (0.6 mg/kg)	17/0	13/0
• Gregorio et al IFN- α 5MU/m ² (3 m)	37/26	40/16
• IFN- α after 1 mnth pred (1 mg/kg)	41/26	38/16

Hepatitis B Virus- IFN- α + steroids

- Anti-HBe seroconversion 12-18 months post Rx
- Treated patients: 24/65 (37%)
- Controls: 4/31 (13%)

$p < 0.05$

Treatment of Hepatitis B- IFN- α

Factors Predicting Response

- Baseline transaminase levels
- Baseline HBV DNA \leq 1000 pg/ml
- Severity of inflammatory changes on biopsy

Hepatitis B Virus- IFN- α Treatment

- Anti-HBe seroconversion in patients with baseline AST \leq 100 IU/L
- Treated patients: 16/50 (32%)
- Controls: 2/29 (7%)

$$p < 0.01$$

Gregorio et al. Hepatology 1996

Hepatitis B Virus- IFN- α Treatment

- Anti-HBe seroconversion in patients with baseline AST \leq 50 IU/L

- Treated patients: 6/20 (30%)

- Controls: 1/18 (6%)

$$p = 0.06$$

Gregorio et al. Hepatology 1996

HBV –IFN- α For Active Disease Inclusion Criteria

- HBsAg + > 6 months
- HBeAg + and HBV DNA + > 1 month
- Elevated ALT (X 2 ULN) for 6 months
- Chronic hepatitis on liver biopsy

Sokal et al Gastroenterology 1998

HBV –IFN- α For Active Disease

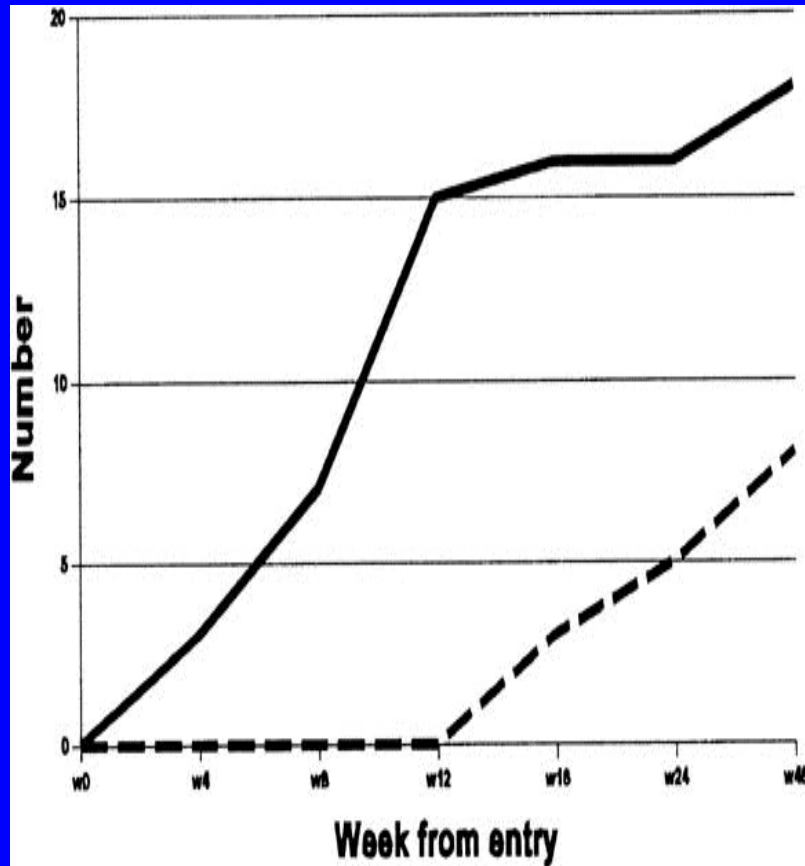
Results

	Treated	Untreated	P
	70	74	
• HBeAg/HBV DNA neg			
at 24 weeks	18 (26%)	8 (11%)	<0.05
at 48 weeks	23 (33%)	8 (11%)	<0.05
• HBsAg neg	7 (10%)	1 (1.2%)	<0.05

(no follow-up, no information on anti-HBe seroconversion)

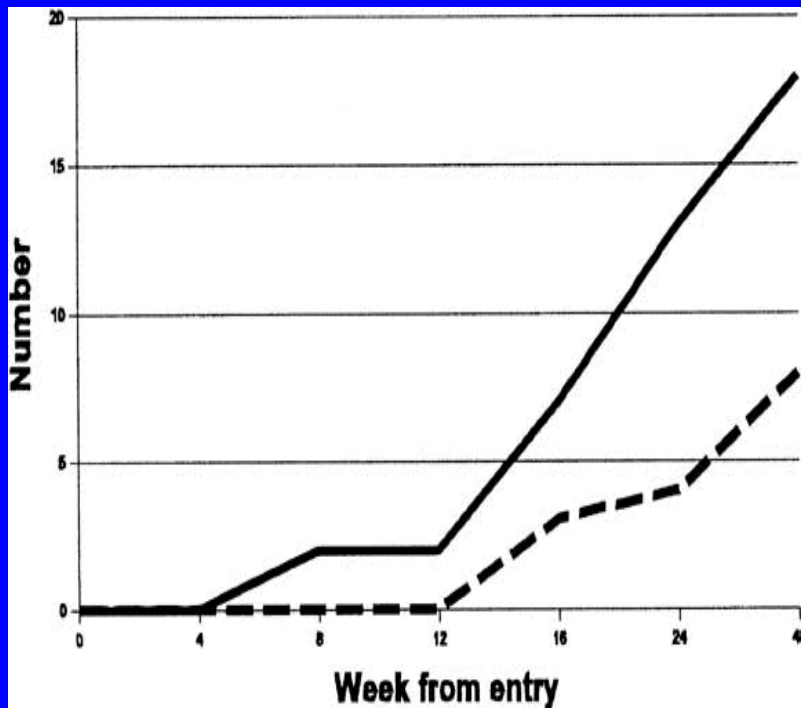
Sokal et al Gastroenterology 1998

RESULTS



- Cumulative number of children who became HBV DNA negative by time from entry in the 70 treated (*solid line*) and 74 control (*dotted line*) patients.

RESULTS



- Cumulative number of children who became HBeAg negative by time from entry in the 70 treated (*solid line*) and 74 control (*dotted line*) patients.

HBV- IFN- α Treatment

Long-term Effect in 107 Treated Children Compared to 59 Controls

After 5 years of observation:

- HBeAg clearance: 60% of treated patients
65% of controls

But

- Loss of HBsAg: 25% of IFN responders
0% of controls

HBV- IFN- α Treatment

Long-term Effect in 107 Treated Children Compared to 59 Controls

Conclusions:

- IFN accelerates spontaneous seroconversion
- Improves the rate of HBsAg loss

HBV – IFN- α Treatment Problems

- Painful injections 3X/week
- Expensive
- Side effects
 - Loss of appetite
 - Growth arrest
 - Behavioral problems

Treatment of Chronic HBV Infection

Lamivudine

- Nucleoside analogue
- Inhibits viral DNA replication
- Oral drug

Treatment of Chronic HBV Infection

Lamivudine- Disadvantages

- YMDD mutation
- Sustained response?

Chronic HBV Infection in Children

Lamivudine vs. Placebo

Multinational Study

- 286 Children
- ALT > 1.3X ULN
- Active liver biopsies
- 3 mg/kg qd (maximum dose 100 mg qd) for 52 weeks
- Randomization 2:1
- 18% Asians

Chronic HBV Infection in Children

Lamivudine vs. Placebo

Multinational Study

- 191 Lamivudine
- 95 Placebo

Chronic HBV Infection in Children

Lamivudine vs. Placebo

Multinational Study

End of treatment (week 52) % response

	<i>lamivudine</i>	<i>placebo</i>	<i>P</i>
HBeAg neg/HBV DNA neg	23	13	0.04
Sustained normal ALT	55	12	<0.001
Anti-HBe +/- HBV DNA neg	22	13	0.06
Loss of HBeAg	26	15	0.03
Undetectable HBV DNA	61	16	<0.001
Loss of HBsAg	2	0	

Chronic HBV Infection in Children

Lamivudine vs. Placebo

Multinational Study

HBeAg neg/HBV DNA neg 6 months post
lamivudine

- 17% lamivudine
- 13% placebo

Chronic HBV Infection in Children

Lamivudine vs. Placebo

Multinational Study

- YMDD mutation 19%

Chronic HBV Infection in Children

Lamivudine Multinational Study

Follow-up in 276 Children

- 24-month open label extension of lamivudine treatment
- Stratification according to HBeAg status at week 48 of previous study

Chronic HBV Infection in Children

Lamivudine Multinational Study

Follow-up in 276 Children

- Treatment arm:
- 213 HBeAg+
 - 134 previous lamivudine, 79 placebo
- Observation arm:
- 63 HBeAg-
 - 49 previous lamivudine, 14 placebo

Chronic HBV Infection in Children Lamivudine Multinational Study Follow-up in 276 Children Results at month 24- Observation Arm

Previous Rx with

lamivudine

placebo

- HBeAg-/ HBV DNA - 87% 92%
- HBeAg-/ anti-HBe + 84% 100%

Chronic HBV Infection in Children

Lamivudine Multinational Study

Follow-up in 276 Children

Results at month 24- Treatment Arm

Previous Rx with

lamivudine

placebo

- HBeAg-/ HBV DNA - 21% 30%
- HBeAg-/ anti-HBe + 26% 34%
- HBsAg loss 2% 1%
- YMDD mutants 64% 49%

Chronic HBV Infection in Children Lamivudine Multinational Study Follow-up in 276 Children Results at month 24- Impact of YMDD

	YMDD+	YMDD-
	#100	#72
• HBeAg-/ HBV DNA -	5%	54%

Chronic HBV Infection in Children 2008

The majority have:

- Infancy acquired infection (adoptees, vaccine failure)
- Normal transaminases
- High HBV DNA
- Minimal histologic changes
- “Immunotolerance” to HBV

FDA Approved Hepatitis B Treatment in Children in USA

- Interferon α 2b
- Subcutaneous
- HBeAg+ 3X /week for 4-6 months
- HBeAg- 3X/week for 1 year
- Side effects-many
- Drug resistance - none
- Lamivudine
- Oral
- HBeAg+ Daily for ≥ 1 year
- HBeAg- Daily for >1 year
- Side effects-negligible
- Drug resistance - $\sim 20\%$, year 1, $\sim 70\%$ year 5

Adefovir

- Approved for use in adults and children >12 y.o.
- Benefit for lamivudine resistant patients, YMDD mutants and liver transplant patients

Chronic HBV Infection in Children

Who should be treated?

- Large studies in tolerant children are needed

Other Therapies

Not approved for use in children

- Entecavir
 - Oral
 - Once daily
 - Considered most potent
- Famciclovir
- Tenofovir

Pegylated Interferon

- IFN therapy limited by its limited half-life (4-6 hr.)
- PEG-IFN has a serum half-life of >90 hr. allowing once weekly dosing
- Not currently approved for use in children

Hepatitis B

Rare Indication for Liver Transplantation

- Fulminant liver failure
 - Infants of anti-HBe positive mothers
 - Childhood horizontal infection
- Decompensated chronic liver disease
- Suspicion of malignant transformation

Hepatitis B

Risk of Re-infection Post Liver Transplantation

- Chronic liver disease + high viral replication: High
- Chronic liver disease + no/low viral replication: Lower
- Fulminant liver failure: Low

Hepatitis B

Pre- Liver Transplantation

Management

- Lamivudine or adefovir in patients with high viral replication to lower viral load at time of transplant

Hepatitis B

Post Liver Transplantation

Management

- HBIG : Duration?
- Lamivudine or adefovir: Indefinitely or until mutants
- A combination of both HBIG + lamivudine/adefovair: duration?
- HBV vaccination

Are we making a difference by vaccinating?

- YES WE ARE!
- The decline in hepatitis B incidence began in the mid-1980s and has coincided with the stepwise implementation of the national vaccination strategy to eliminate HBV transmission. The 2006 rate of 1.6 cases per 100,000 population was the lowest recorded since surveillance began in 1966 and represents an estimated decline of >80% since the national strategy was implemented in 1991.
- The greatest declines have occurred among the cohort of children to whom the recommendations for routine infant and adolescent vaccination have applied. During 1990--2006, incidence among children aged <15 years declined 98%, from 1.2 cases per 100,000 population to 0.02 cases per 100,000 population. This decline correlates with high vaccine coverage rates among young children, with the most recent data indicating that coverage among children aged 19--35 months is >93%

Incidence of Acute HBV in US

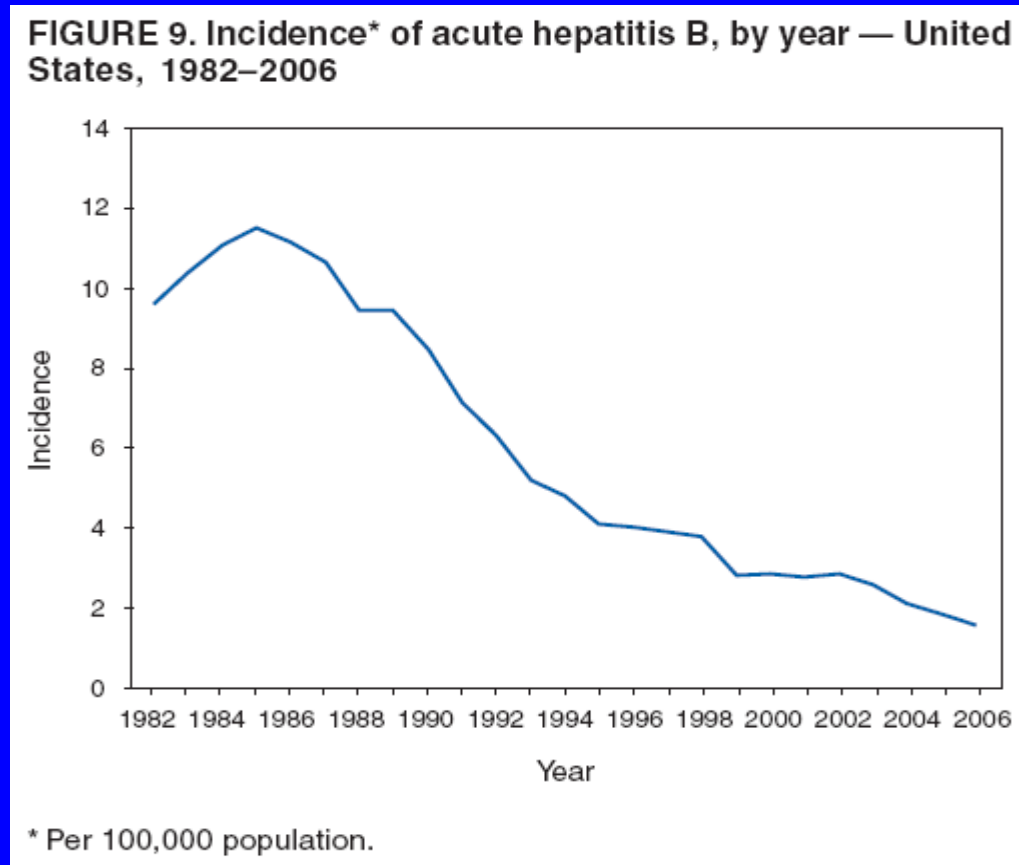
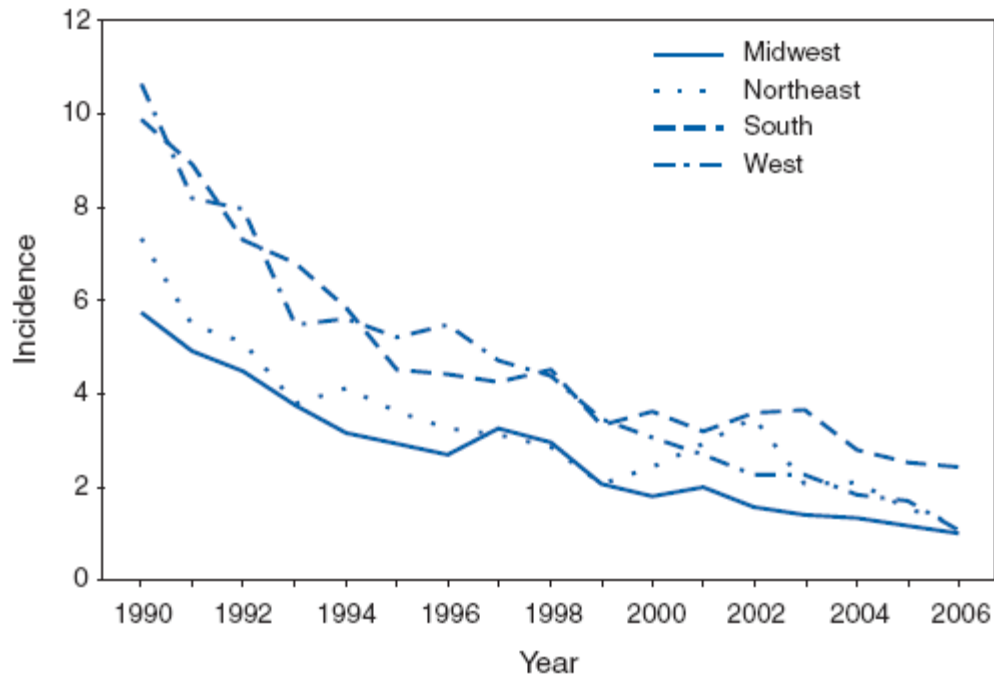


FIGURE 10. Incidence* of acute hepatitis B, by region† and year — United States, 1990–2006

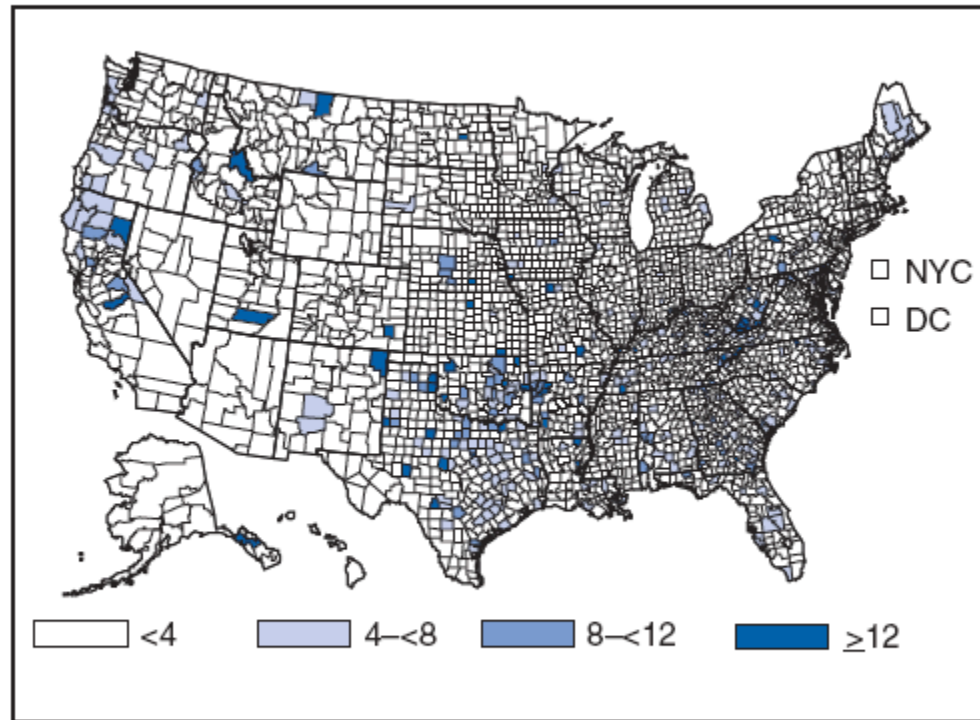


* Per 100,000 population.

† *Midwest*: Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin; *Northeast*: Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont; *South*: Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia; and *West*: Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, and Wyoming.

"Surveillance for Acute Viral Hepatitis--United States, 2006"

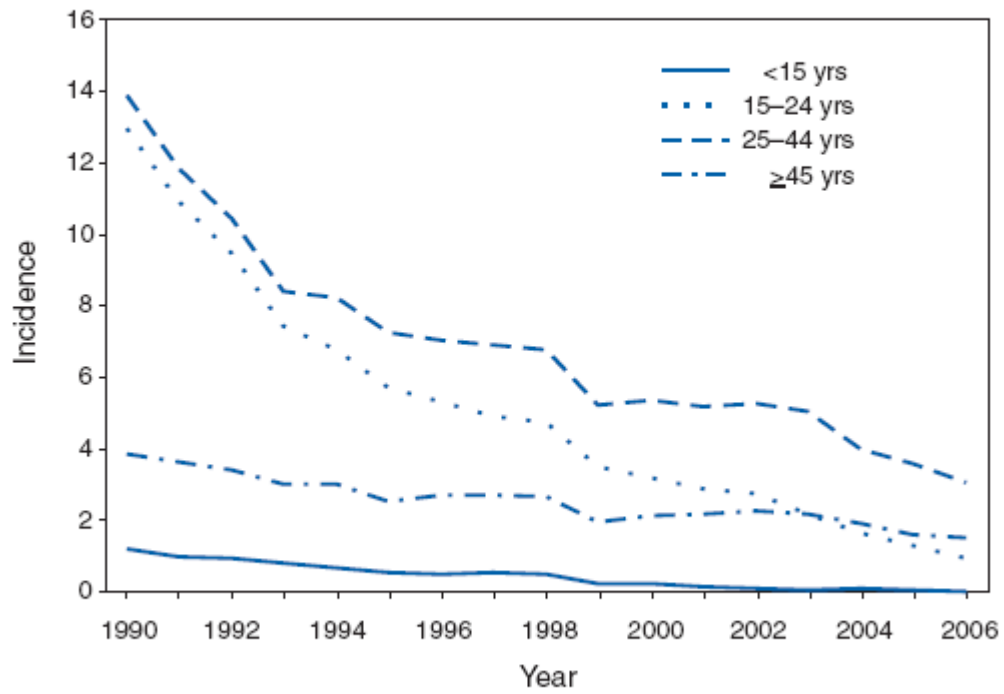
FIGURE 11. Incidence* of acute hepatitis B, by county — United States, 2006



Source: National Notifiable Diseases Surveillance System, 2006.
* Per 100,000 population.

"Surveillance for Acute Viral Hepatitis--United States, 2006"

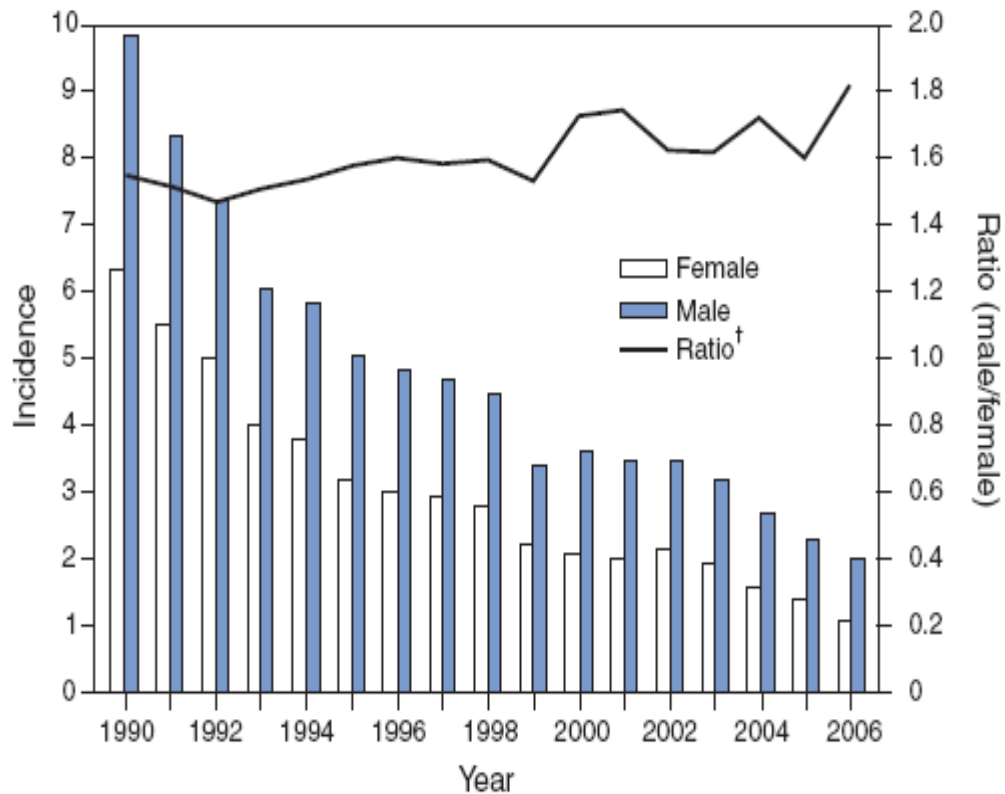
FIGURE 12. Incidence* of acute hepatitis B, by age group and year — United States, 1990–2006



* Per 100,000 population.

"Surveillance for Acute Viral Hepatitis--United States, 2006"

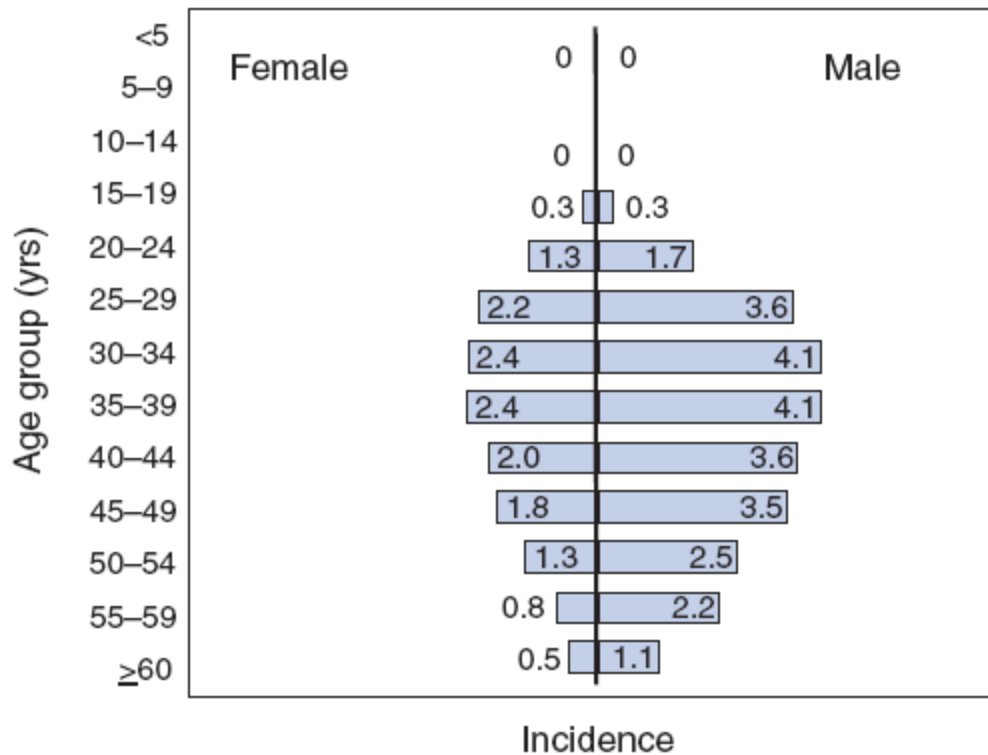
FIGURE 13. Incidence* of acute hepatitis B, by sex and year — United States, 1990–2006



* Per 100,000 population.

† The bars indicate the rate per 100,000 (the left y-axis) by sex; the line is the ratio (right y-axis) of the incidence among males to that among females.

FIGURE 14. Incidence* of acute hepatitis B, by age group and sex — United States, 2006†

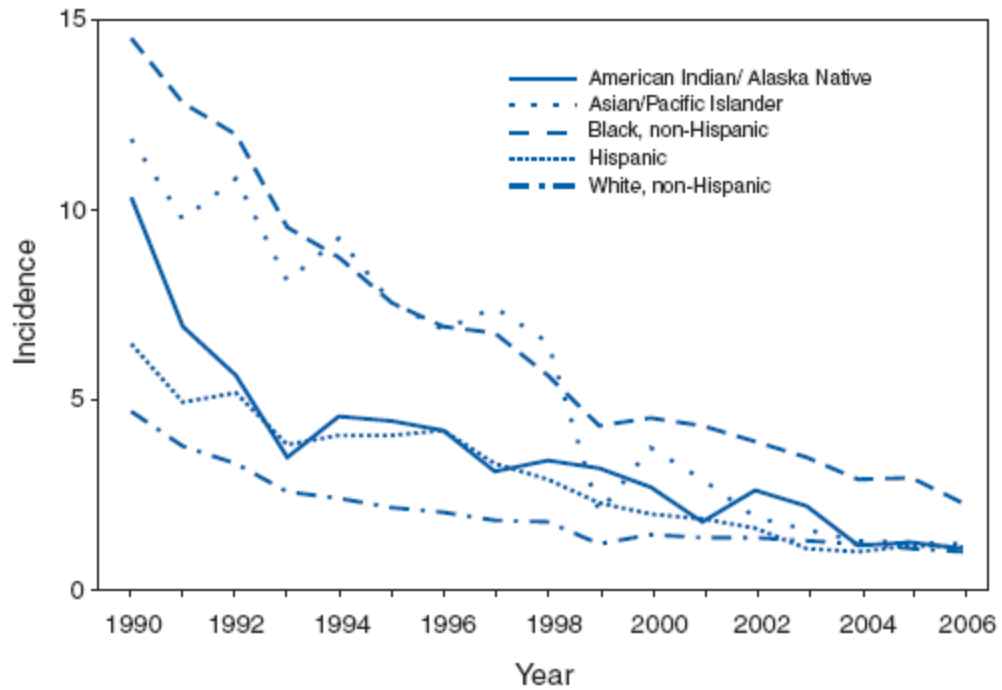


* Per 100,000 population.

† A total of 4,713 cases of hepatitis B were reported. Rates exclude patients for whom data on age or sex were missing.

"Surveillance for Acute Viral Hepatitis--United States, 2006"

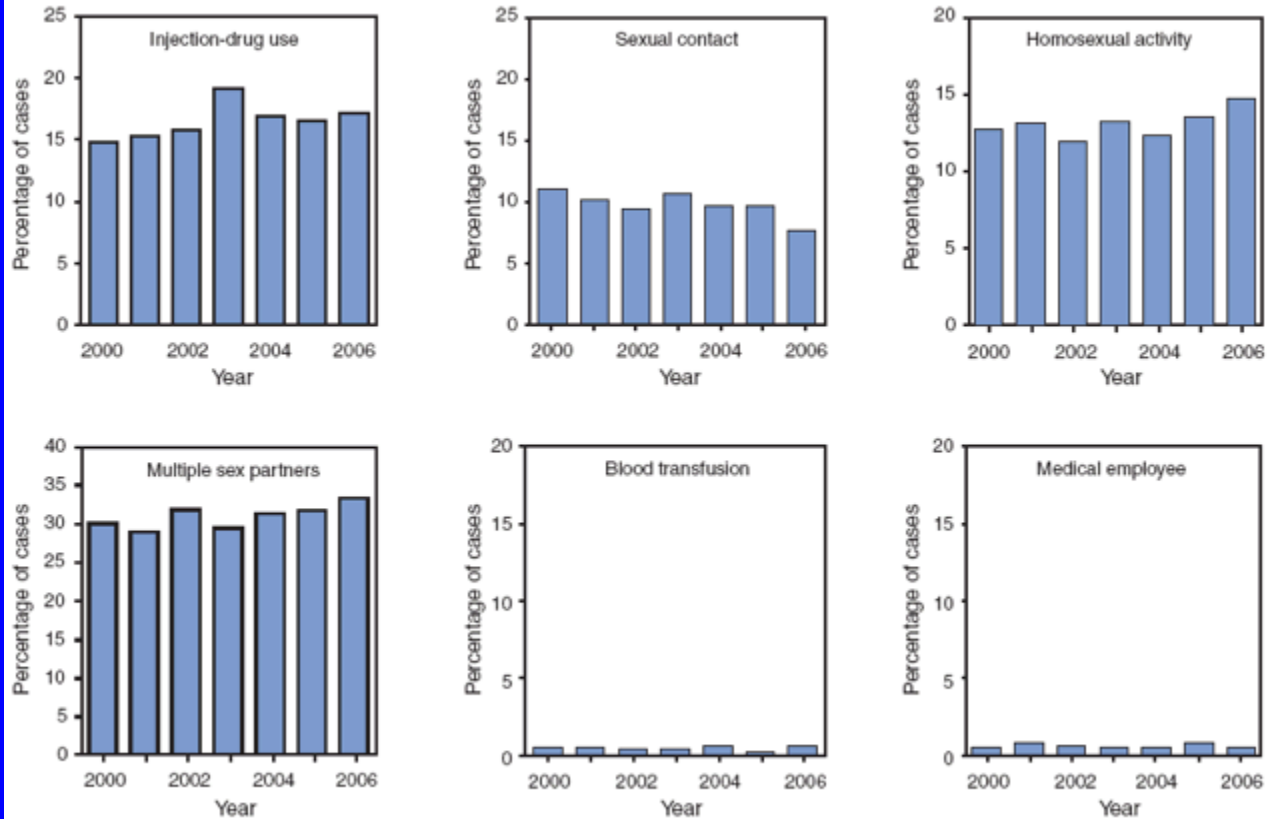
FIGURE 15. Incidence* of acute hepatitis B, by race/ethnicity and year — United States, 1990–2006



* Per 100,000 population.

"Surveillance for Acute Viral Hepatitis--United States, 2006"

FIGURE 16. Trends in selected epidemiologic characteristics among patients with acute hepatitis B, by year — United States, 2000–2006*



* The percentage of cases among persons for whom a specific risk factor was reported was calculated on the basis of the total number of persons for whom any information for that exposure was reported. Multiple risk factors may be reported for a single case.

"Surveillance for Acute Viral Hepatitis--United States, 2006"

