Hepatitis B Vaccine in Neonates

Anthony Fiore, MD, MPH

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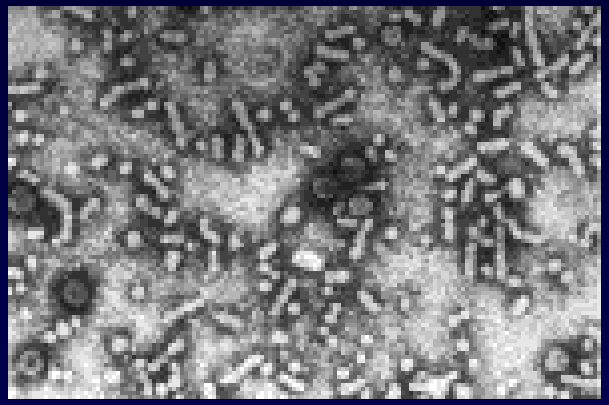
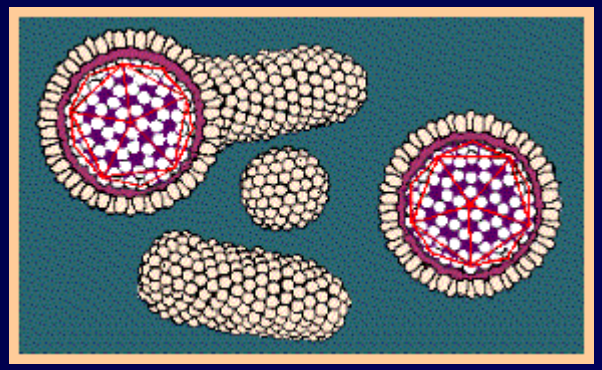
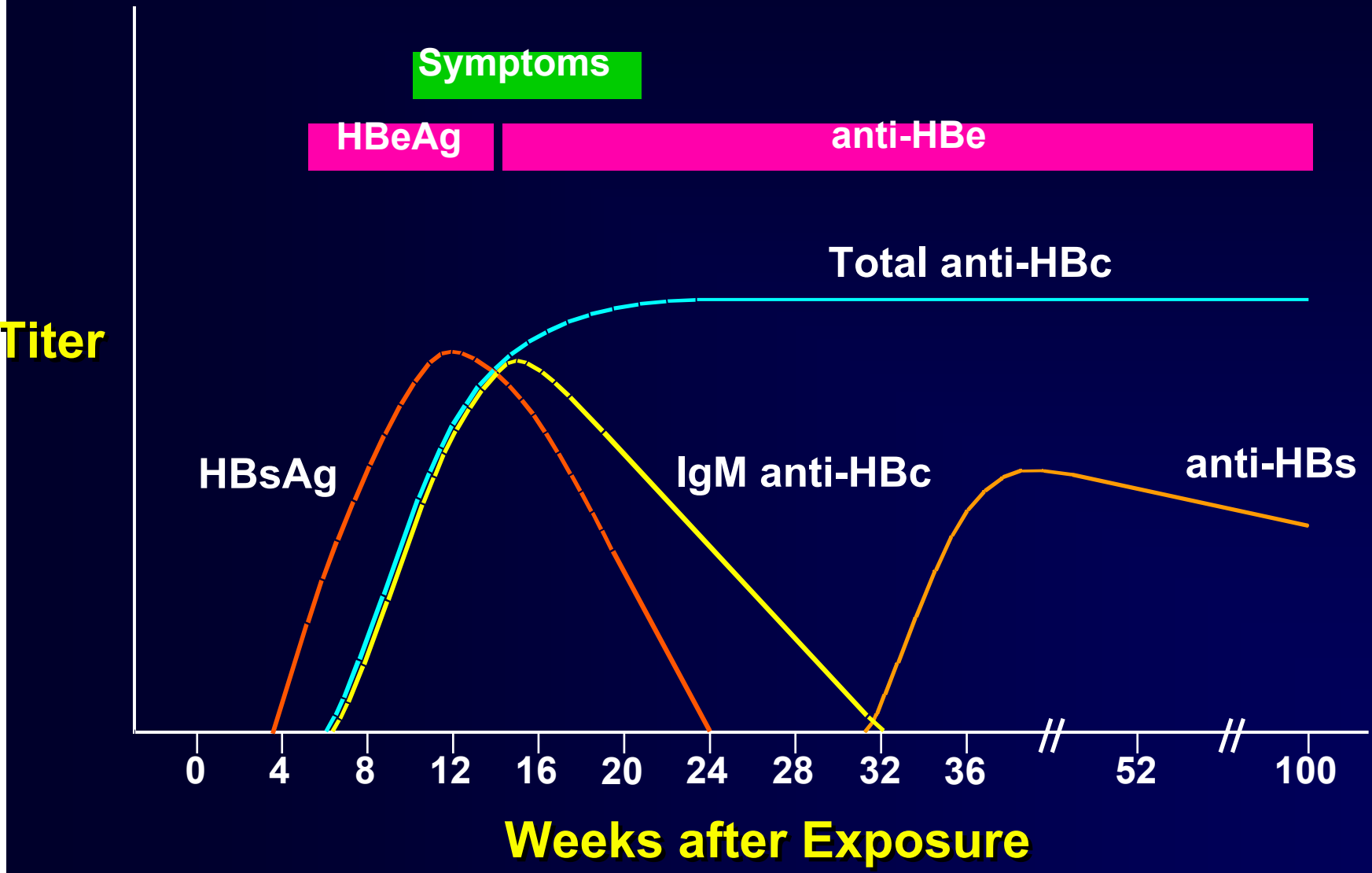
Hepatitis B Virus (HBV)

- 42 nm DNA virus
- HBV genome
  - ~3200 nucleotides
  - Circular, partially double stranded DNA
- HBV envelope (HBsAg)
  - Synthesized in 100-1000 fold excess
- Correlate of protection: antibody to hepatitis B surface antigen (anti-HBs) ≥ 10 milli-International Units/mL





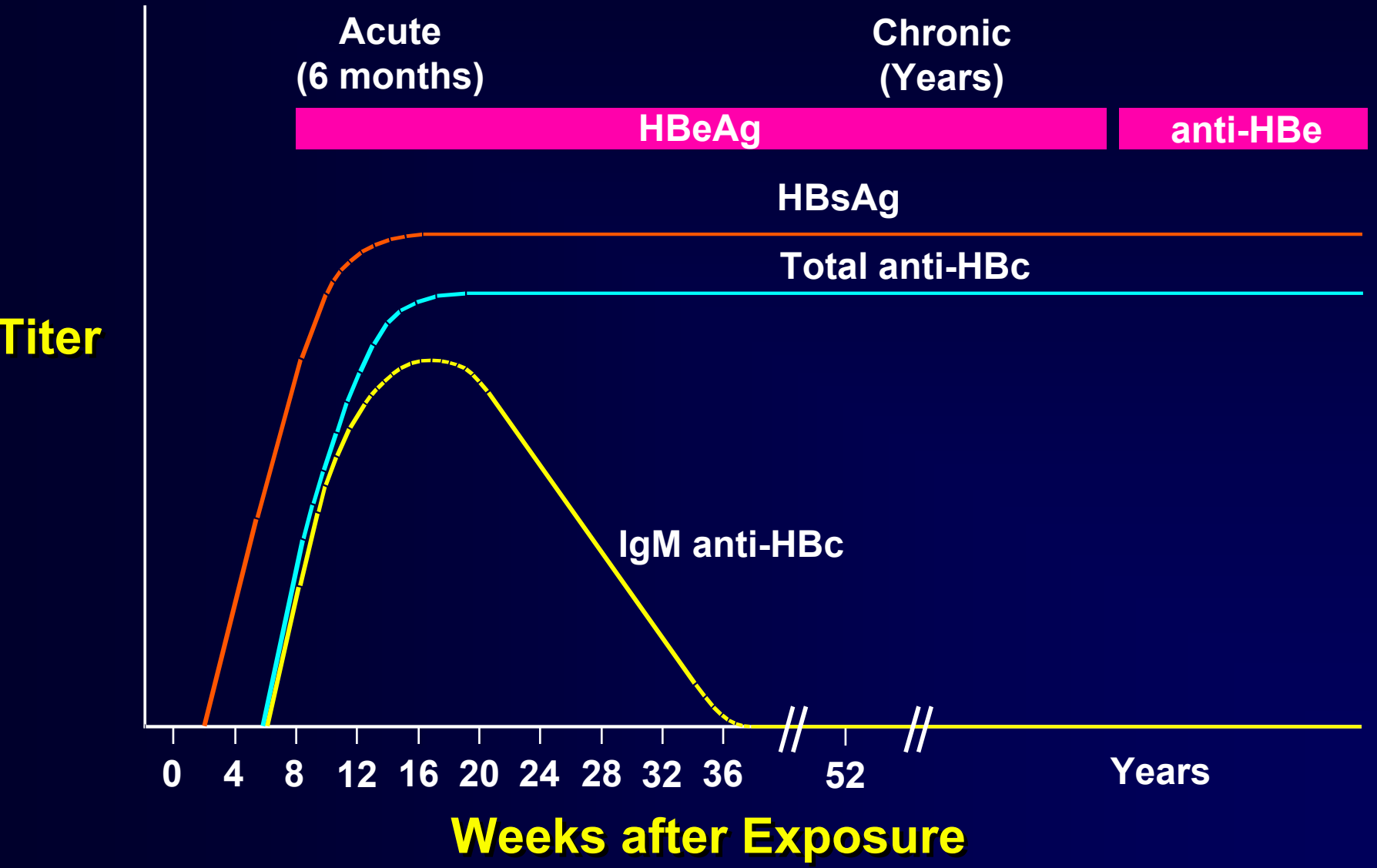
Acute Hepatitis B Virus Infection with Recovery



'a' Determinant of Hepatitis B surface antigen

- Amino acids 124-147 map to an external hydrophilic region of HBsAg
- Antibodies to 'a' determinant confer protection against HBV infection
- Tertiary structure important for antigenicity

Acute Hepatitis B Virus Infection with Progression to Chronic Infection



Morbidity and Mortality Caused by Chronic HBV Infection

- Chronic liver disease and cirrhosis
- Hepatocellular carcinoma (HCC)
  - HBV causes 60% of HCC in the world
- 15-25% of children with chronic HBV infection will die prematurely from HBV-related chronic liver disease

Leading Causes of Infectious Disease Deaths Worldwide (2000)

Disease	Deaths per Year
Lower respiratory tract infections	~3.5 million
HIV/AIDS	~3.0 million
Diarrheal diseases	~2.2 million
Tuberculosis	~2.0 million
Malaria	~1-3 million
Measles	~888,000
Hepatitis B	~630,000
Pertussis	~355,000
Neonatal tetanus	~300,000
Intestinal parasites	~135,000

ce: CDC, WHO, UNICEF, UNAIDS

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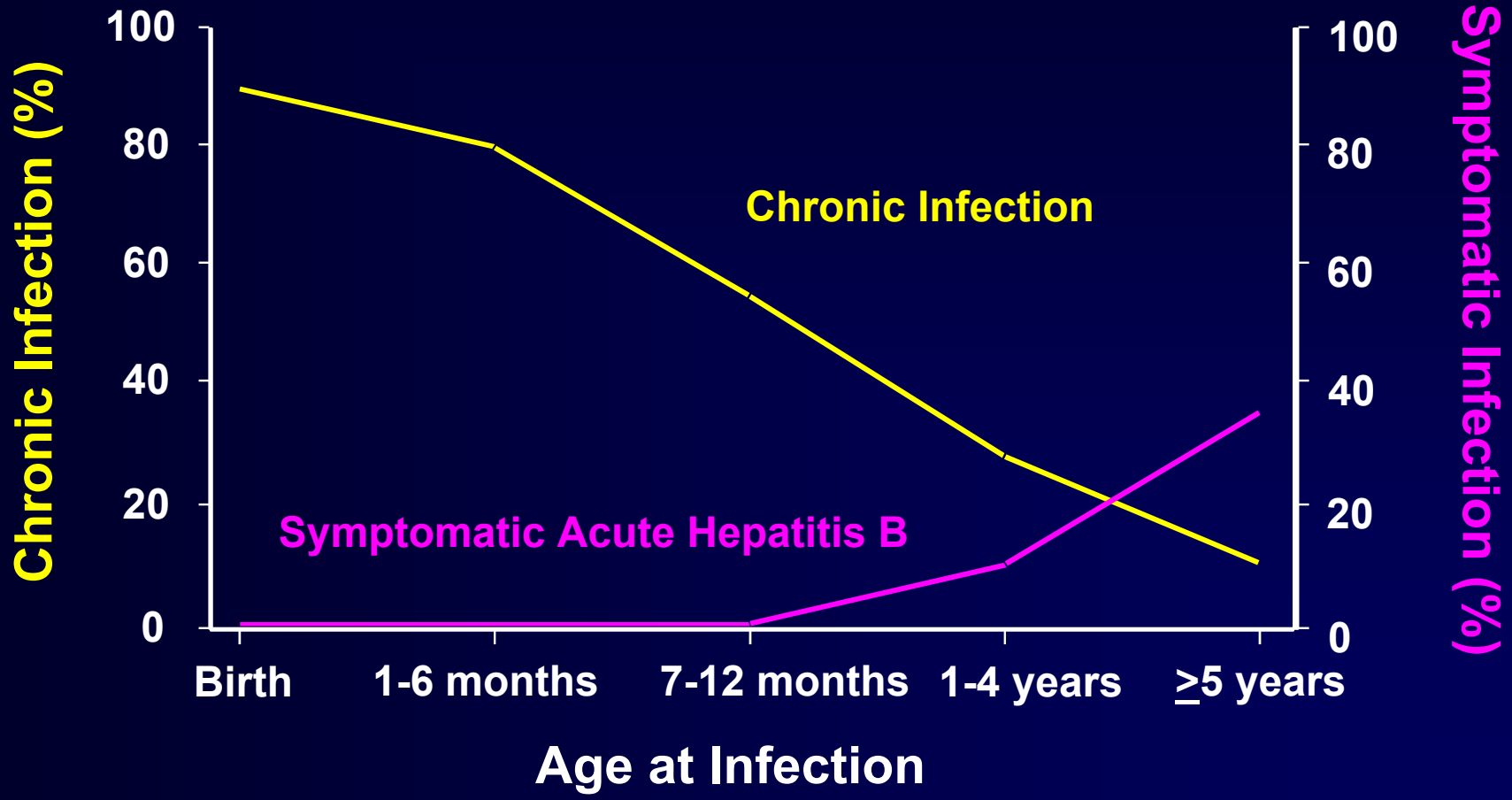
Outcome of HBV Infection by Age at Infection



Perinatal HBV Transmission

- Risk of transmission for infants born to women with high HBV DNA concentrations (usually HBeAg-positive): ***>85%***
- Risk of transmission for infants born to women with lower HBV DNA concentrations (usually HBeAg-negative): ***5-10%***

Infants born to women with acute or chronic HBV infection are at high risk of acquiring a chronic HBV infection that is asymptomatic during childhood

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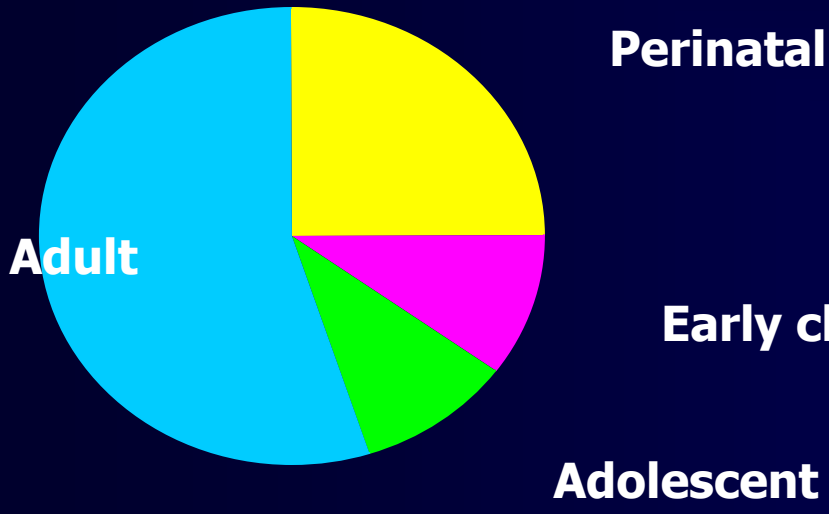
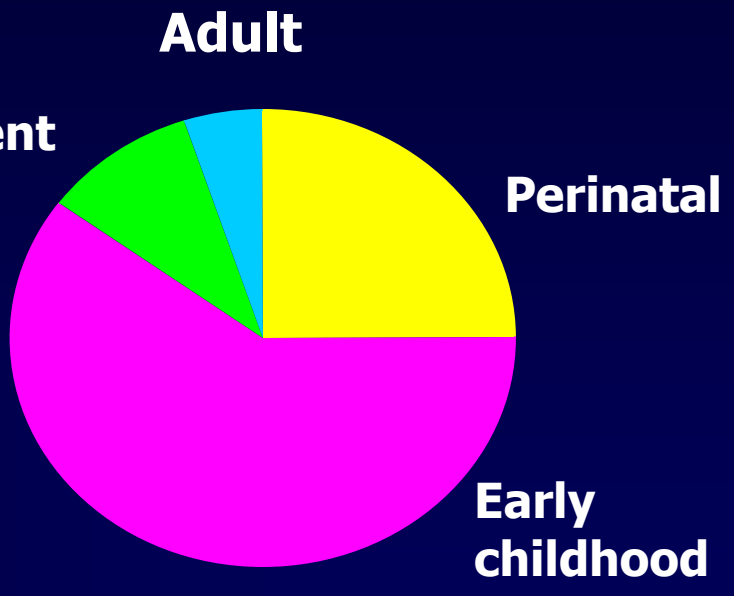
Differences in Age at Acquisition of Chronic HBV Infections by Endemicity

Low HBsAg Prevalence



Perinatal and early childhood infections: 30-40%

High HBsAg Prevalence



Perinatal and early childhood infections: 70-80%

Hepatitis B Vaccines

- Plasma-derived vaccines (1981)
  - Consist of 22-nm HBsAg particles derived from serum of persons with chronic HBV infection
  - Viral inactivation steps ⟶ non-infectious purified HBsAg
  - No reports of HBV transmission by vaccine
- Recombinant (yeast-derived) vaccines (1986)
  - 226 amino acid S gene translated by recombinant yeast cells
  - Protein self assembles into spherical particles
- Both vaccines elicit development of neutralizing antibodies to HBsAg (anti-HBs)
- Both vaccines contain adjuvant (aluminum hydroxide or phosphate)
- Since early 2000, no pediatric vaccine licensed for use in the U.S. contains thimerosal as a preservative
- Manufactured in many countries by pharmaceutical firms and state owned facilities
- Cost to developing countries: approximately $0.30 U.S.
- Common component of combination vaccines

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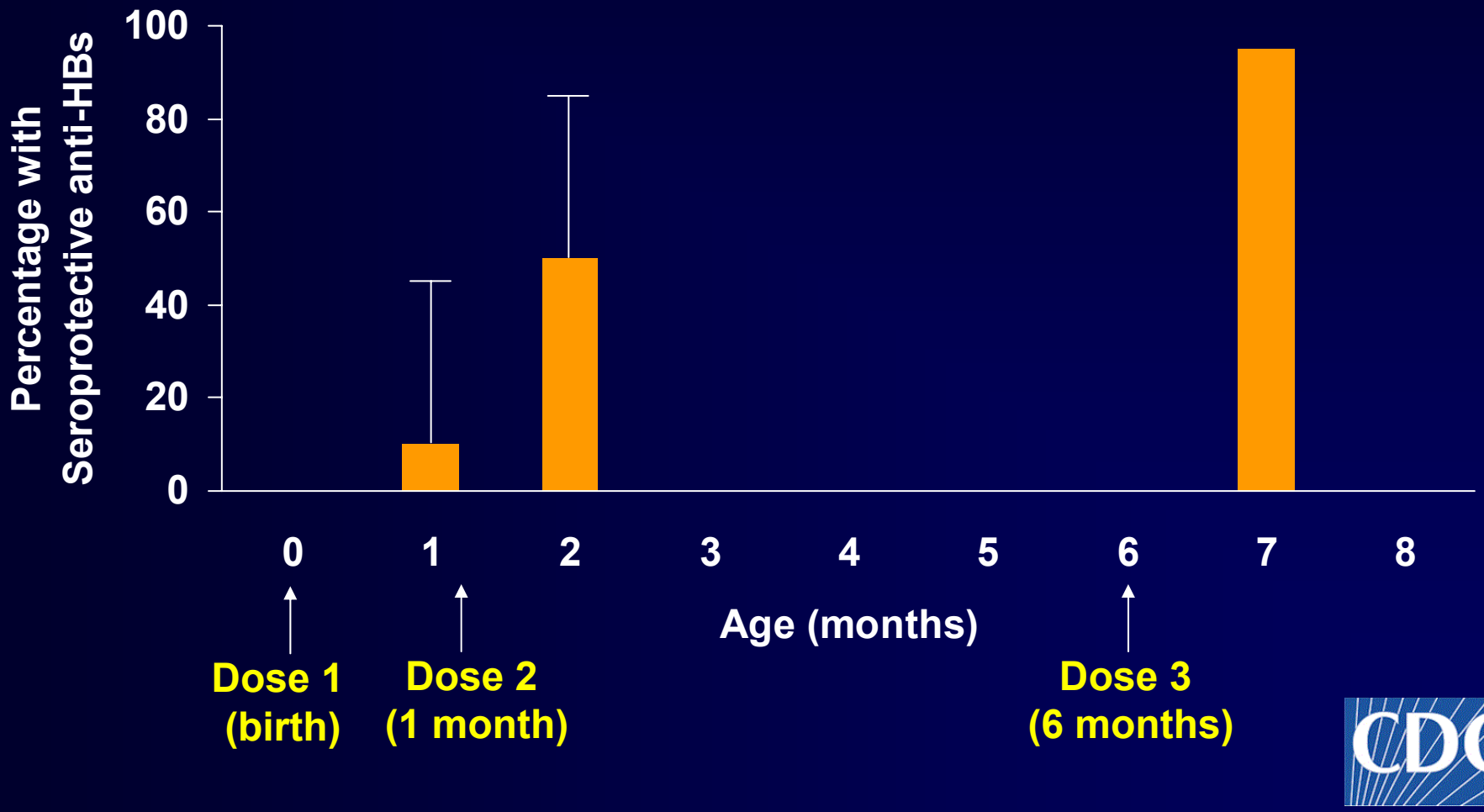
Hepatitis B Vaccine: Immunogenicity among Neonates

- >95% of vaccinated infants develop seroprotective concentrations of anti-HBs (≥10 mIU/mL) after completing any of the following tested schedules:
  - Birth, 1 month, 6 months
  - Birth, 2 months, 4 months
  - 2 months, 4 months, 6 months
  - 6 weeks, 10 weeks, 14 weeks
- Similar seroconversion rates with plasma-derived and recombinant vaccines

Proportion of vaccinated infants with seroprotective concentrations of anti-HBs (≥10 mIU/mL) after vaccination, by age



Hepatitis B Vaccine: Immunogenicity among Neonates

- Primary antibody response (post vaccination anti-HBs concentration) is similar to adults, but lower than that of older children
  - Reported range of geometric mean concentrations of anti-HBs range from 90-900 mIU/mL
  - Higher post-vaccination anti-HBs concentration predicts longer duration of detectable anti-HBs
- Infants with low birth weights (<2000 g) have somewhat lower seroconversion rates
  - By 1 month of age, premature infants show normal responses
- Presence of maternally-acquired anti-HBs does not reduce the proportion who develop seroprotective anti-HBs concentrations (≥10mIU/mL)
- Post-vaccination testing not recommended for most infants

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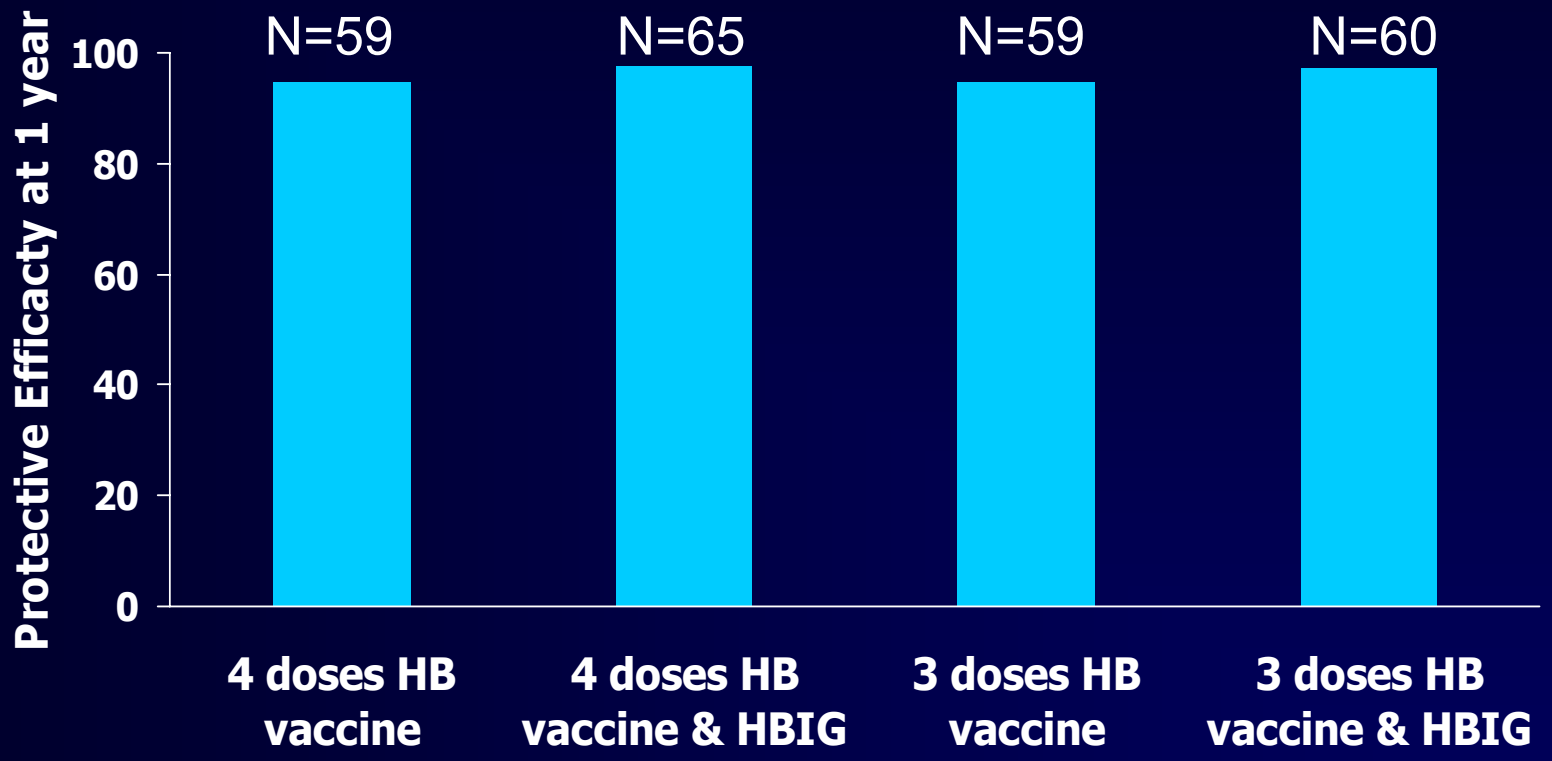
fficacy of hepatitis B vaccine with and without hepatitis immune globulin (HBIG) in preventing perinatal HBV infection



ovorawan, Pediatr Infect Dis J, 1992;11:816-21

Hepatitis B vaccination without HBIG is highly effective in prevention of perinatal HBV infection

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Vaccine Reactogenicity among Vaccinated Neonates

- Minor reactions reported in < 7%
  - Mild, transient rash or local injection site reactions
  - Irritability or poor feeding
  - Fever > 37.7 degrees C in <1%
  - Typically <24 hours duration
- Anaphylaxis risk estimated to be 1 in 600,000 doses among adults
  - No increase in allergic events among infants has been reported

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Rationale for Beginning Routine Hepatitis B Immunization at Birth

- Approximately 25% of chronic infections result from perinatal transmission of HBV
- Risk of infection for infants born to HBsAg+ women is high
- Vaccine has excellent post-exposure efficacy (if started within 12-24 hours of birth) for infants born to HBsAg+ women
- Safe and effective vaccine elicits protective concentrations of anti-HBs in neonates as in older children and adults
- Health care infrastructure exists
- Screening pregnant women not feasible or not universally performed

United States, 1991: Vaccination of all infants, preferably beginning at birth

WHO, 1992: Integrate hepatitis B vaccination into all childhood vaccination programs by 1997

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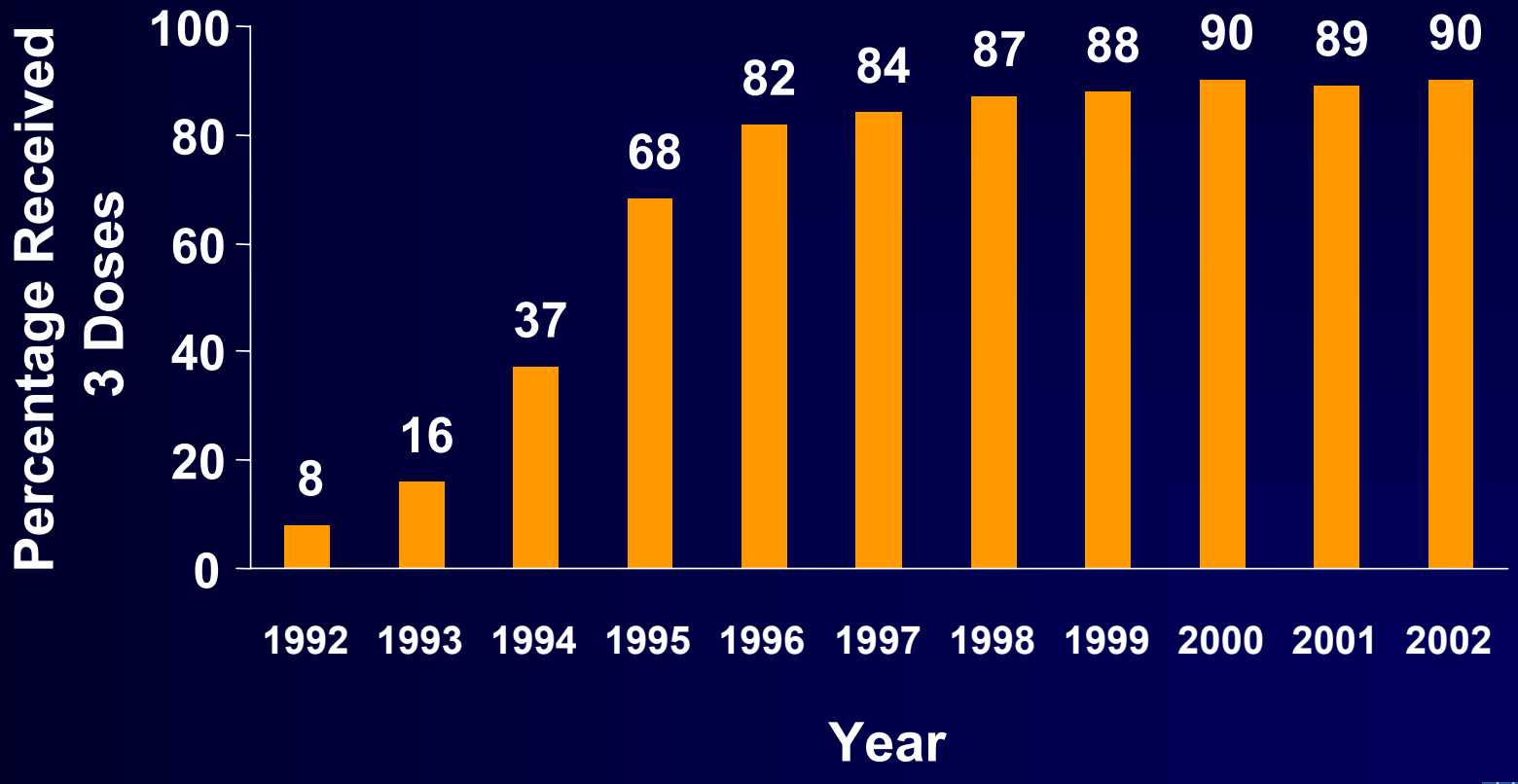
Key Elements of Perinatal Hepatitis B Prevention Programs, United States

- Perinatal hepatitis B prevention programs funded immunization grant programs
  - Testing all pregnant women for HBsAg
    - 2nd test in 3rd trimester for high risk women
  - Reporting of HBsAg-positive women
  - Providing case-management and tracking
  - Supporting routine birth dose as part of standing orders for all newborns
- Integration with other newborn disease prevention programs ("one-stop shopping")

Hepatitis B Vaccine 3 Dose Coverage Among 19-35 Month Old Children, United States, by Year of Survey, 1990-2002*



*Source: National Immunization Surveys, MMWR

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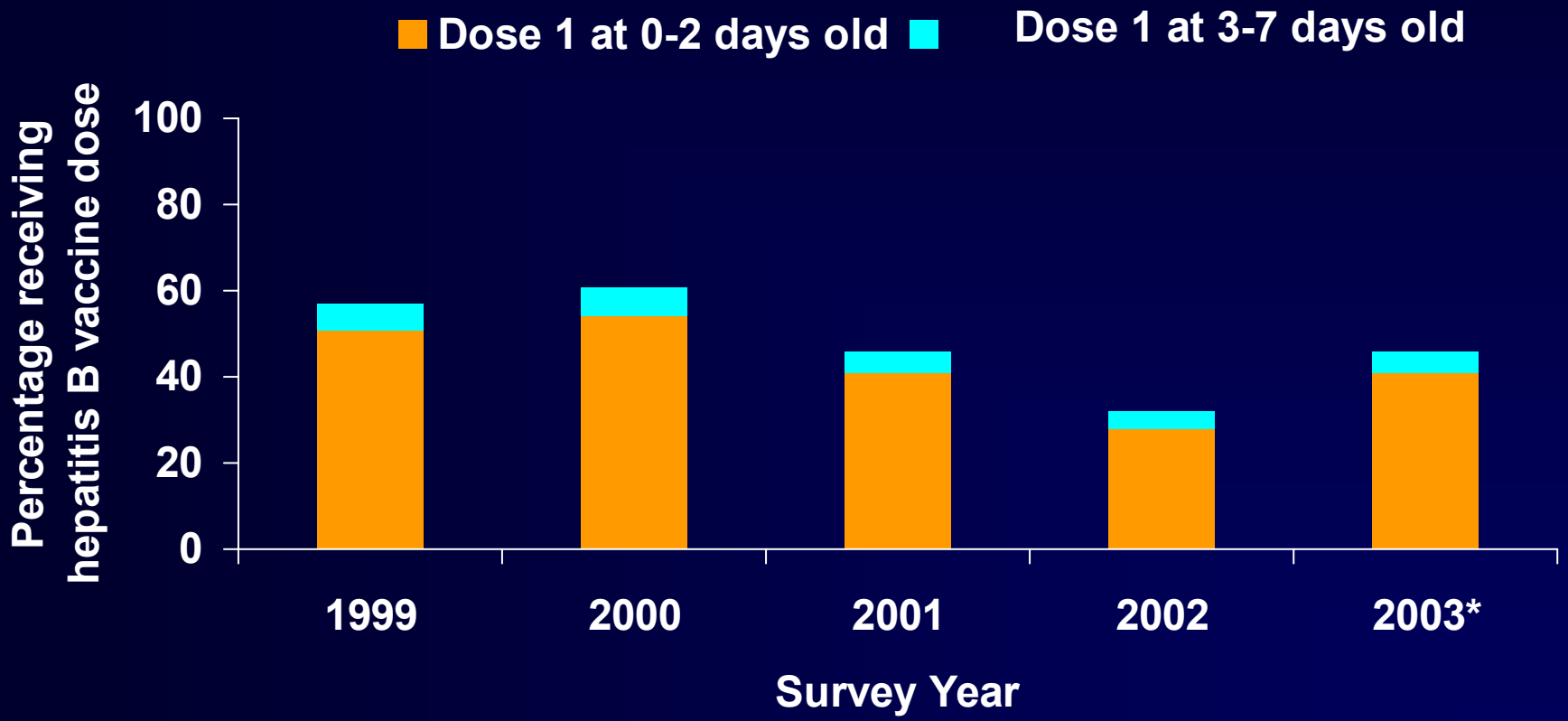
Percentage of U.S. infants receiving first dose of hepatitis B vaccine at ≤2 and ≤7 days old, by year of National Immunization Survey (NIS), 1999-2003



Note: NIS enrolls children 19-35 months old.
For example, children in the 2002 NIS were born in 1999-2001.
*L Barker, NIP. Preliminary data, includes only Jan-Jun 2003 NIS data

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Neonatal Hepatitis B Vaccination – Current Issues

- Improving birth dose coverage
- Ensuring actual and perceived vaccine safety
- Evaluating long term effectiveness
- Determining need for booster doses
- Evaluating the importance of antibody-resistant viral variants
- Demonstrating impact of programs that have focused on initiating vaccination at birth

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Likely Contributors to Decline in Birth Dose Coverage, United States

- Publicity about safety issues[1]
  - Thimerosal preservative (removed from U.S. pediatric hepatitis B vaccines in 1999-2000)
  - No evidence of harm
- Healthcare providers believe that tracking doses is more difficult[2]
- Healthcare providers have reimbursement concerns[2]
  - For some healthcare plans, vaccination in hospital costs more
  - Healthcare provider may receive less or no reimbursement for doses administered in the hospital
- Healthcare provider preference for combination vaccines given in later infancy[2]
  - Schedules consisting of single antigen birth dose / combination vaccine series completion endorsed by ACIP and AAP, but result is 4 dose series
- Parental preference

[1]CDC MMWR 2001; and others
[2]Cooper et al. Pediatrics

Hepatitis B Vaccine: Excellent Safety Profile for Neonates

- Numerous studies in the U.S. and elsewhere have shown NO association between infant hepatitis B vaccination and:
  - Sepsis workups
  - Febrile episodes
  - Sudden Infant Death Syndrome (SIDS)
  - Neonatal death
  - Asthma
  - Diabetes
- In the U.S., infant mortality rates and the incidence of SIDS have declined significantly during 1990's, while infant hepatitis B vaccine coverage has increased from <5% to 90%

Long-Term Protection with Hepatitis B Vaccine Among Vaccinated Infants

Country	Years f/u	n	Anti-HBs ≥10 mIU/ml at f/u	Anti-HBc Positive	HBsAg Positive
China	15	52	50%	6%	2%
Alaska	15	119	61%	1%	0
The Gambia	14	175	64%	31%	3%
Hong Kong	12	148	74%	1%	0
Taiwan	10	805	85%	14%	0.4%
Taiwan	10	118	67%	12%	0
Italy	10	53	68%	0	0
Italy	10	474	68%	1%	0

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Hepatitis B Vaccination of Neonates: Summary of Long-Term Protection Data

10-15 years after successful vaccination of cohorts of neonates in highly endemic areas:

- Few develop serologic evidence of HBV infection despite declines proportion with detectable anti-HBs
- No symptomatic infections
- No new chronic infections in most studies

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Immune memory after initiation of hepatitis B vaccination during neonatal period

After 10-15 years, anti-HBs undetectable in 20-50% of children vaccinated as neonates, however:

- **Anamnestic response after booster indicates intact immune memory among 61%-100% of those vaccinated as infants**
  - **Comparison of studies difficult**
    - **Most booster studies involve small numbers of children**
    - **Variety of primary series vaccine dose, type, and schedules**
    - **Differences in local endemicity and serologic status of mother**
- **Marker of immune memory is needed**

Booster dose(s) not currently recommended by US or WHO immunization advisory panels

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HBsAg Variants ("Vaccine Escape Mutants")

- HBV with altered HBsAg detected in chronically infected persons despite the presence of seroprotective levels of anti-HBs
- Infection with HBsAg variants reported among:
  - Vaccinated infants born to HBeAg+ (high HBV DNA concentration) women
  - Vaccinated, post-liver transplant (chronic HBV infection) patients
- Infections due to variants with mutations in the 'a' determinant of surface antigen
  - Point mutation → conformational change in anti-HBs neutralization epitope

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Public Health Importance of HBsAg Variants

- Not a cause of late infections (10-15 years after primary series) among vaccinated children
- No clear evidence of horizontal transmission among vaccinated children
- Vaccinated chimps protected from challenge with most common mutant strain[1]
- Mothers of infants who were successfully immunoprophylaxed as likely to have HBsAg variants as mothers of infants who failed immunoprophylaxis[2]
- Most common mutant (G145R) may have diminished stability and ability to be secreted[3]

[1]Ogata, Hepatology 1999
[2]Nainan, J Med Virol 2002
[3]Kalinina, Hepatology 2003

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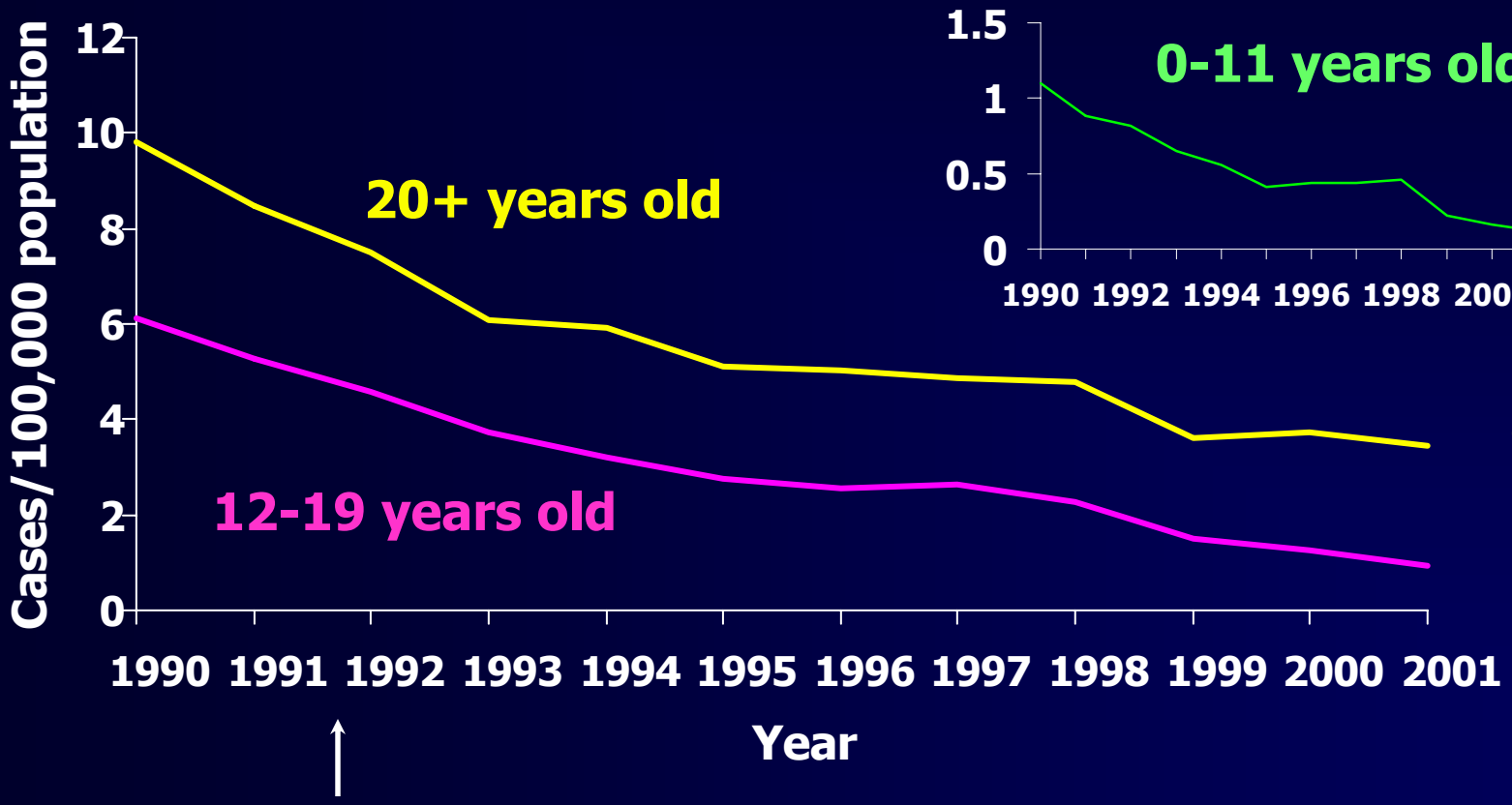
Incidence of Acute Hepatitis B by Age, U.S., 1990-2001



Measuring the Impact of Infant Vaccination on Perinatal and Childhood HBV Infections

- Is routine infant vaccination reducing HBV infections among children?
- Challenges:
  - Most perinatal and childhood infections are asymptomatic
  - Changes in the incidence of liver cancer or cirrhosis among adults will not be apparent until decades later
- Approaches:
  - Seroprevalence studies among children in high risk populations (Bristol Bay, Alaska)
  - Incidence of rare but reportable outcomes among children over time in highly endemic areas
    - Hepatocellular carcinoma (Taiwan)

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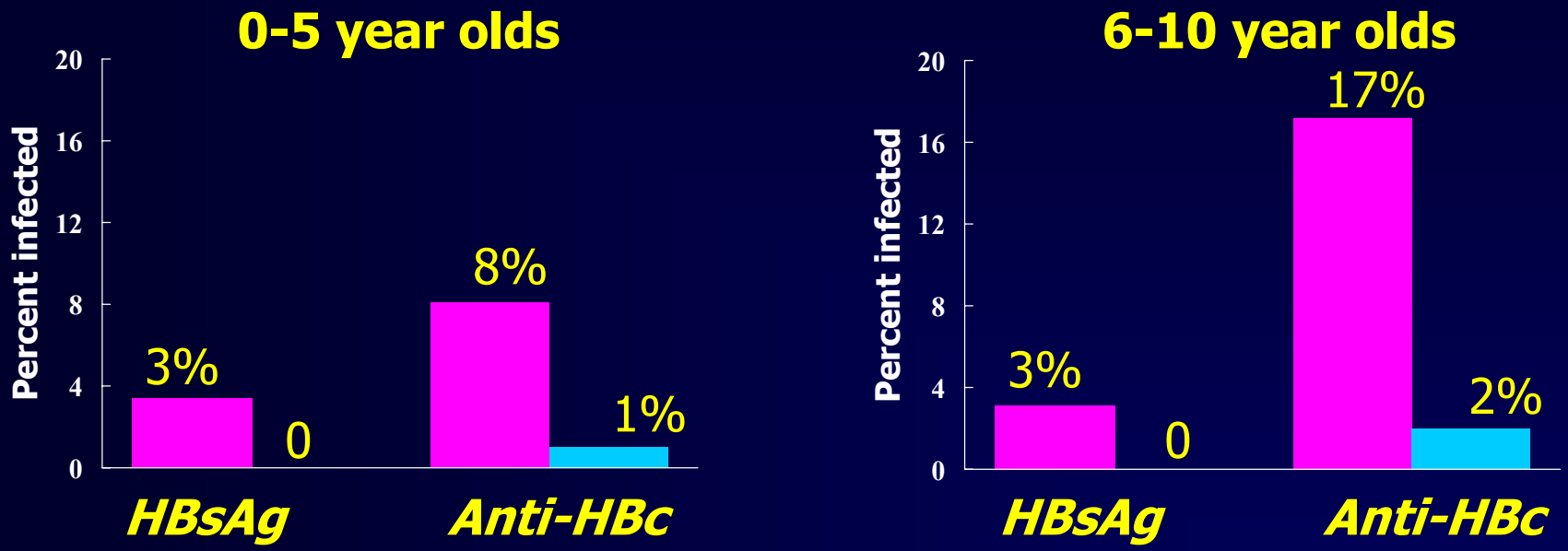
Prevalence of HBsAg and Anti-HBc Among Alaskan Native Children: Bristol B Alaska



1973 (pre-vaccination program)

1993 (post-vaccination program: HepB3 coverage=93%)

Sources: McMahon. Am J Med 1983; Harpaz. J Infect Dis 2000.

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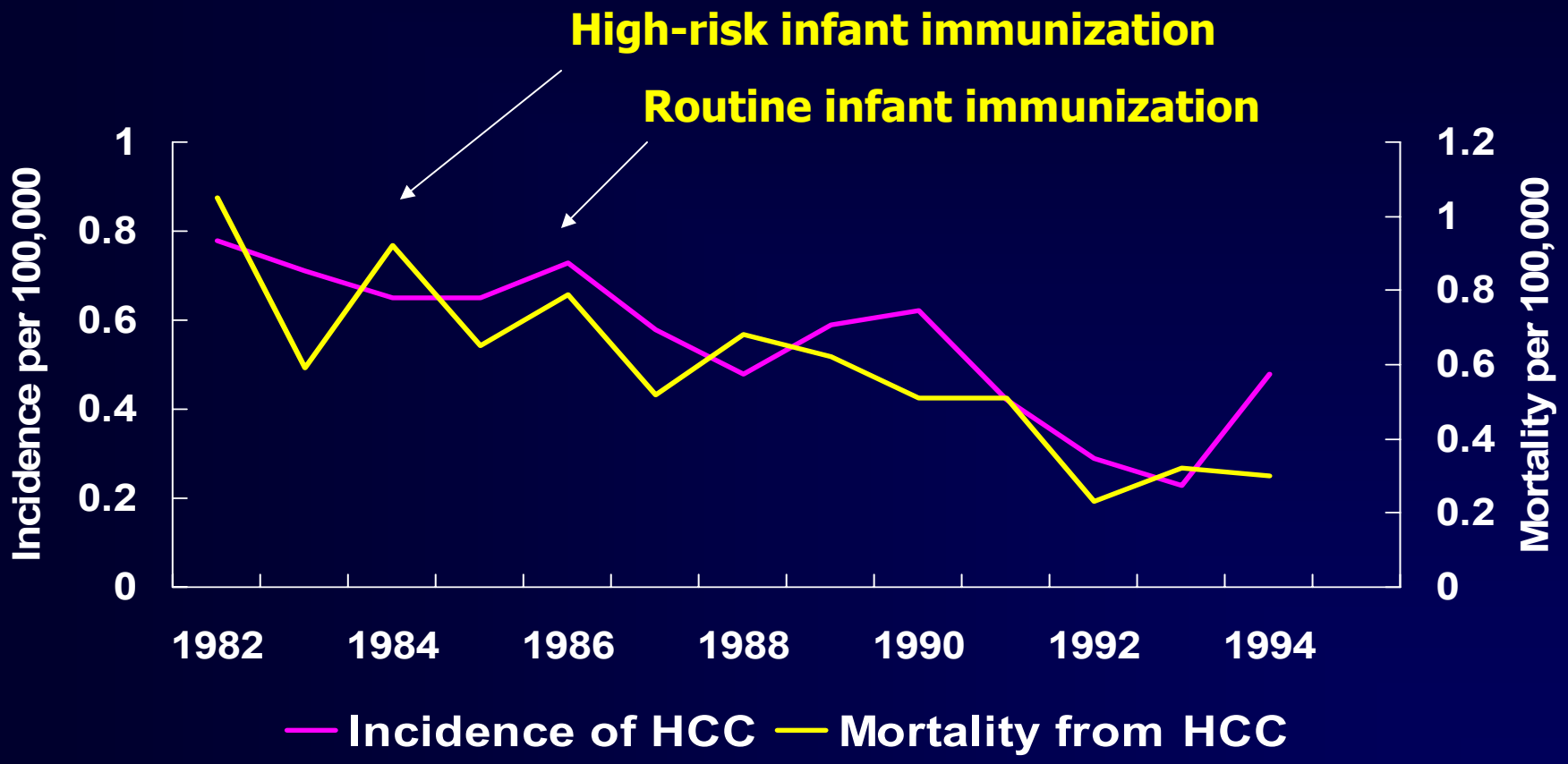
Incidence of and Mortality from Hepatocellular Carcinoma Among 7 to 14 Year Olds: Taiwan



Source: Chang, N Engl J Med 1997.

Conclusions: Effectiveness of Hepatitis B Vaccination Programs

Hepatitis B immunization programs decrease:

- Incidence of acute hepatitis B
- Prevalence of chronic HBV infection
- Incidence of and mortality from hepatocellular carcinoma