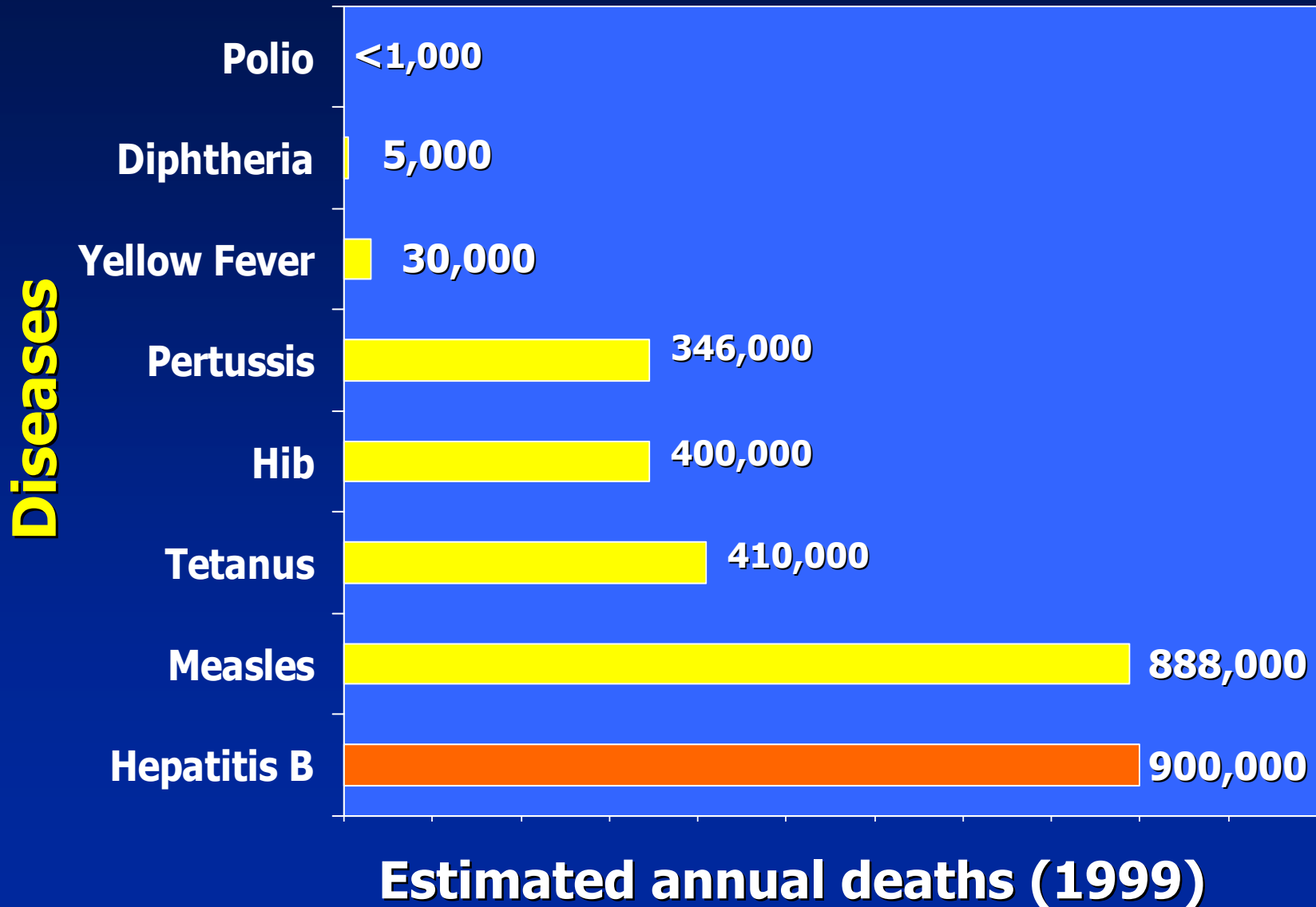


Hepatitis B: Impeding Liver Cancer through Prevention and Management

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Global Mortality from Vaccine Preventable Diseases

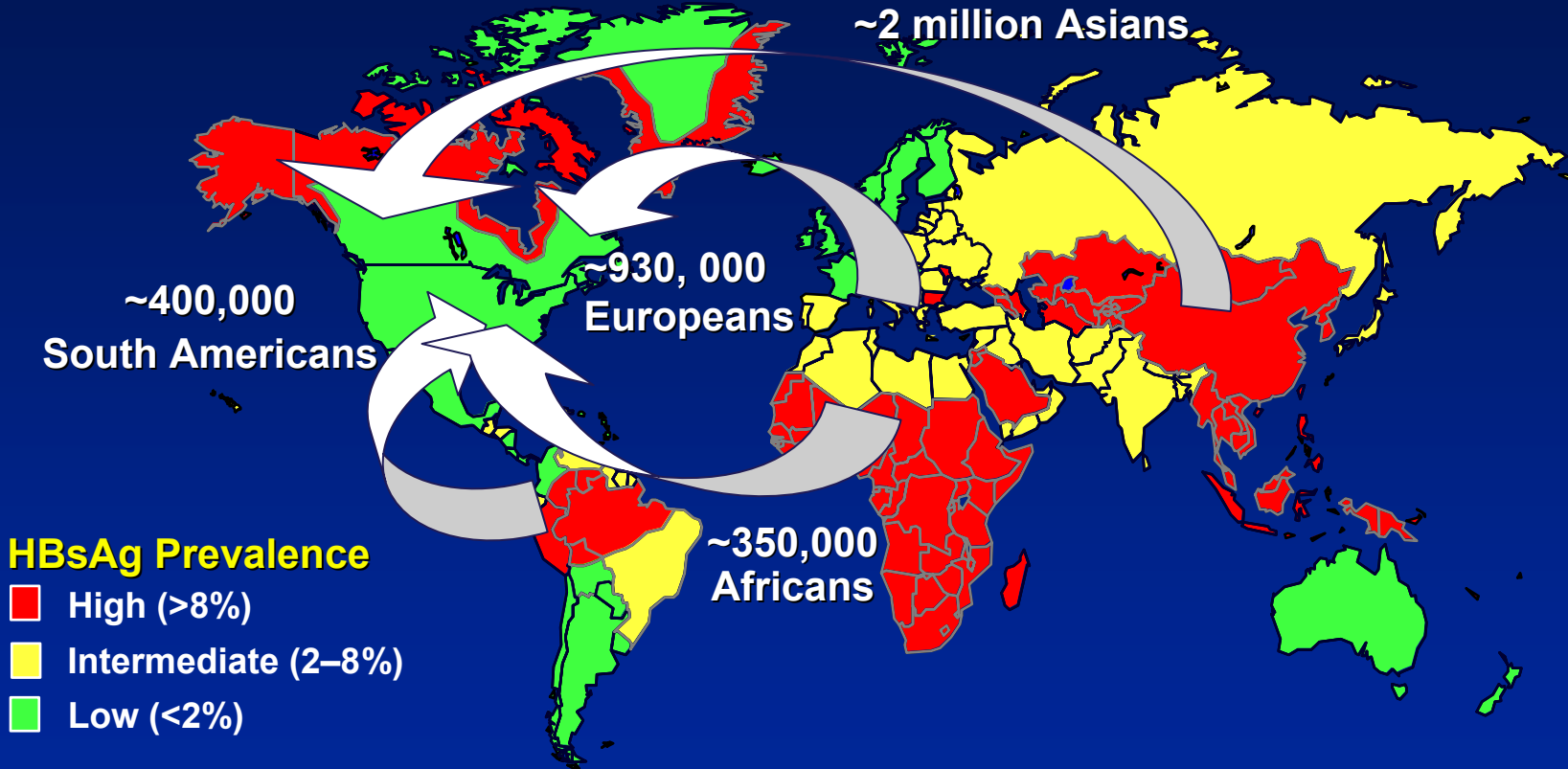


Hepatocellular Carcinoma

- Among solid tumors, 5th highest incidence worldwide and 3rd most common cause of cancer deaths
- In the U.S. in 2007, 13th most common cancer and **increasing faster** than all others from 1995 to 2004; 8th most common cause of cancer deaths
- Despite advancing technology and available treatments, 5-year survival rates are generally less than 5%

Geographic Prevalence of Chronic Hepatitis B: Impact of Migration

Immigration Numbers Summed by Continent From 1996–2002



World Health Organization. Available at: <http://www.who.int/vaccines-surveillance/graphics/htmls/hepbprev.htm>. Accessed July 8, 2005.

2002 Yearbook of Immigration Statistics. Available at:

<http://uscis.gov/graphics/shared/aboutus/statistics/yearbook/2002.pdf>. Accessed July 8, 2005.

Mahoney FJ. *Clin Microbiol Rev.* 1999;12:351–366.

Chronic Hepatitis B

Morbidity and Mortality, U.S.

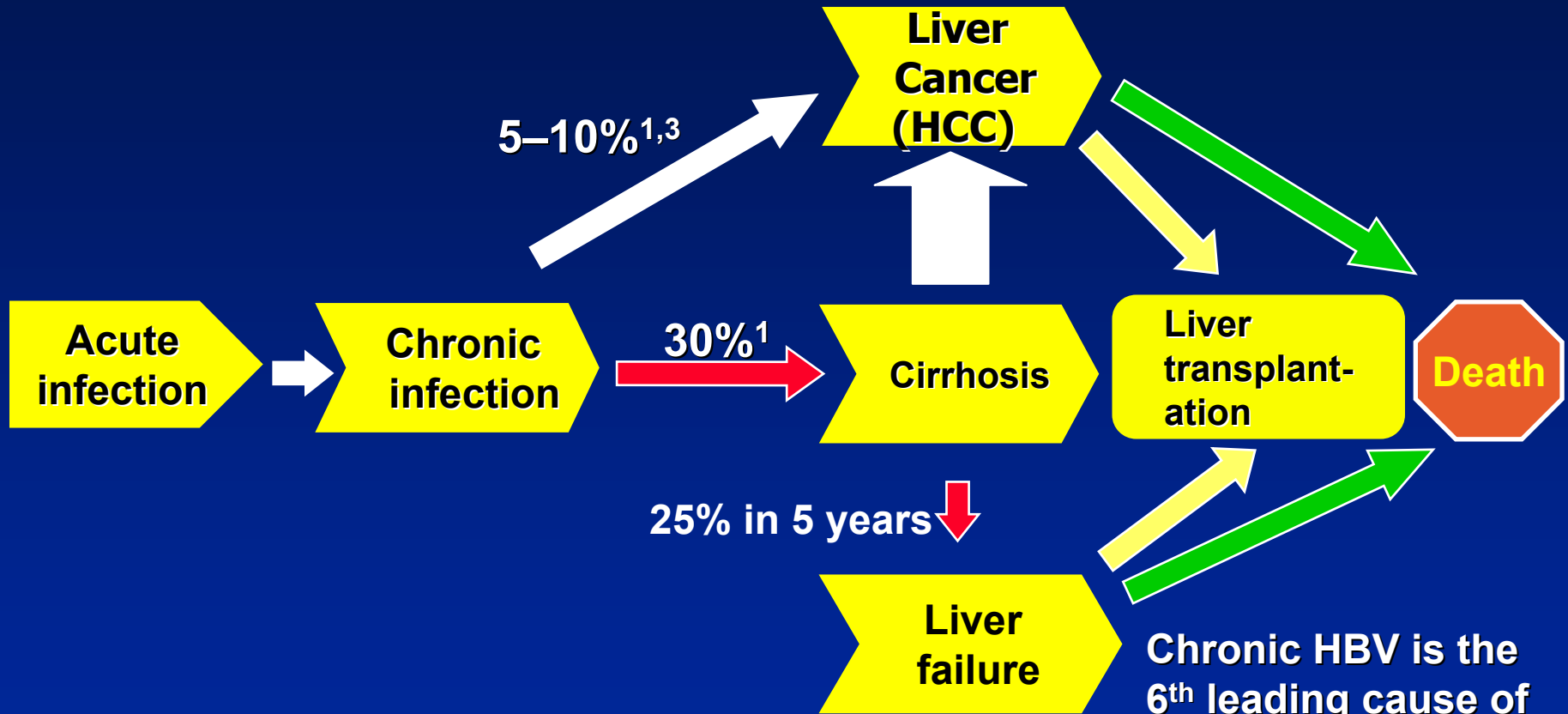
Previously infected individuals: ~10 million

Actively infected individuals: ~1-1.25 million

Annual cirrhosis deaths: ~4,000

Annual HCC deaths: ~1,000-1,500

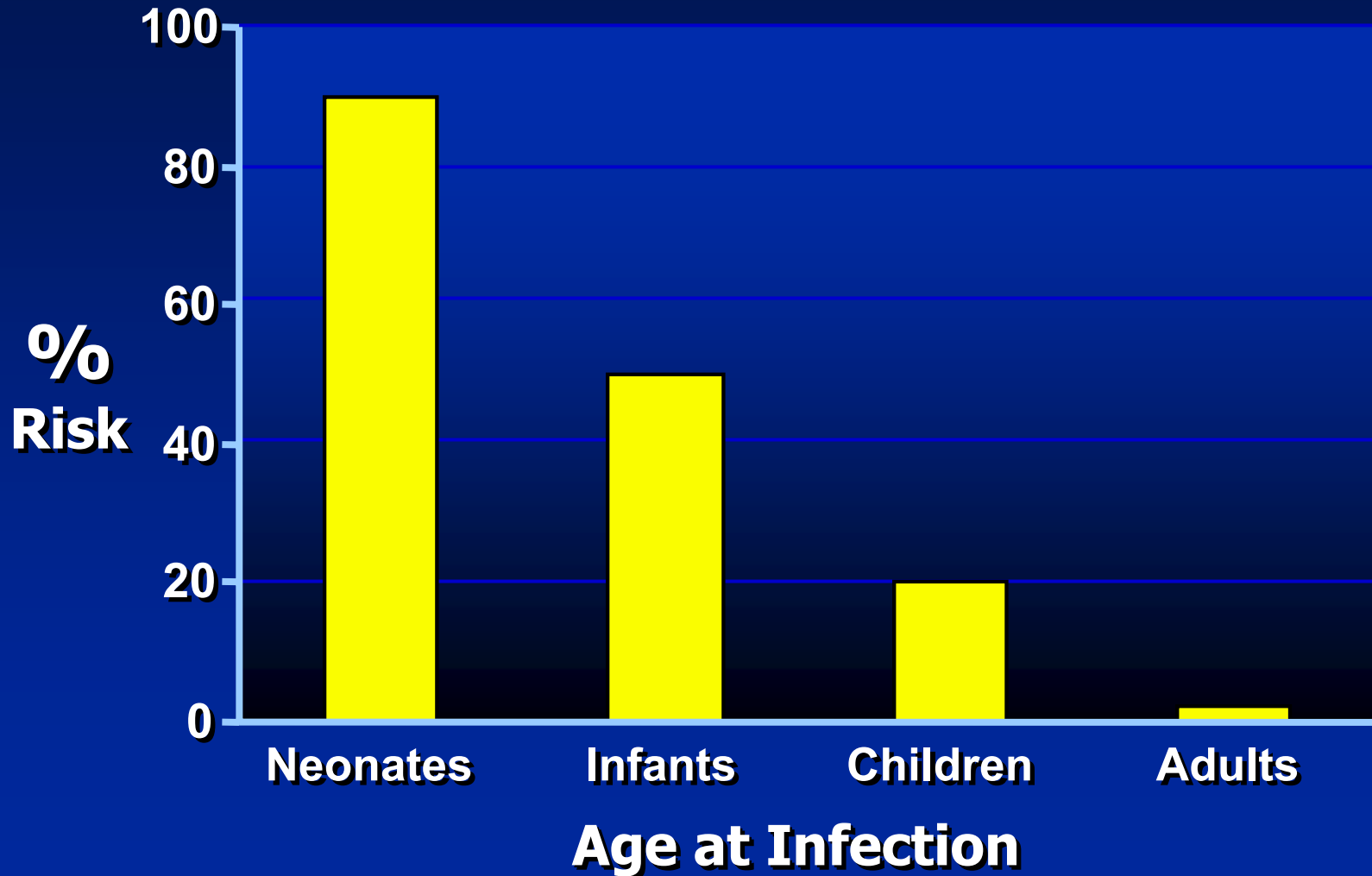
HBV Disease Progression



Chronic HBV is the 6th leading cause of liver transplantation in the US⁴

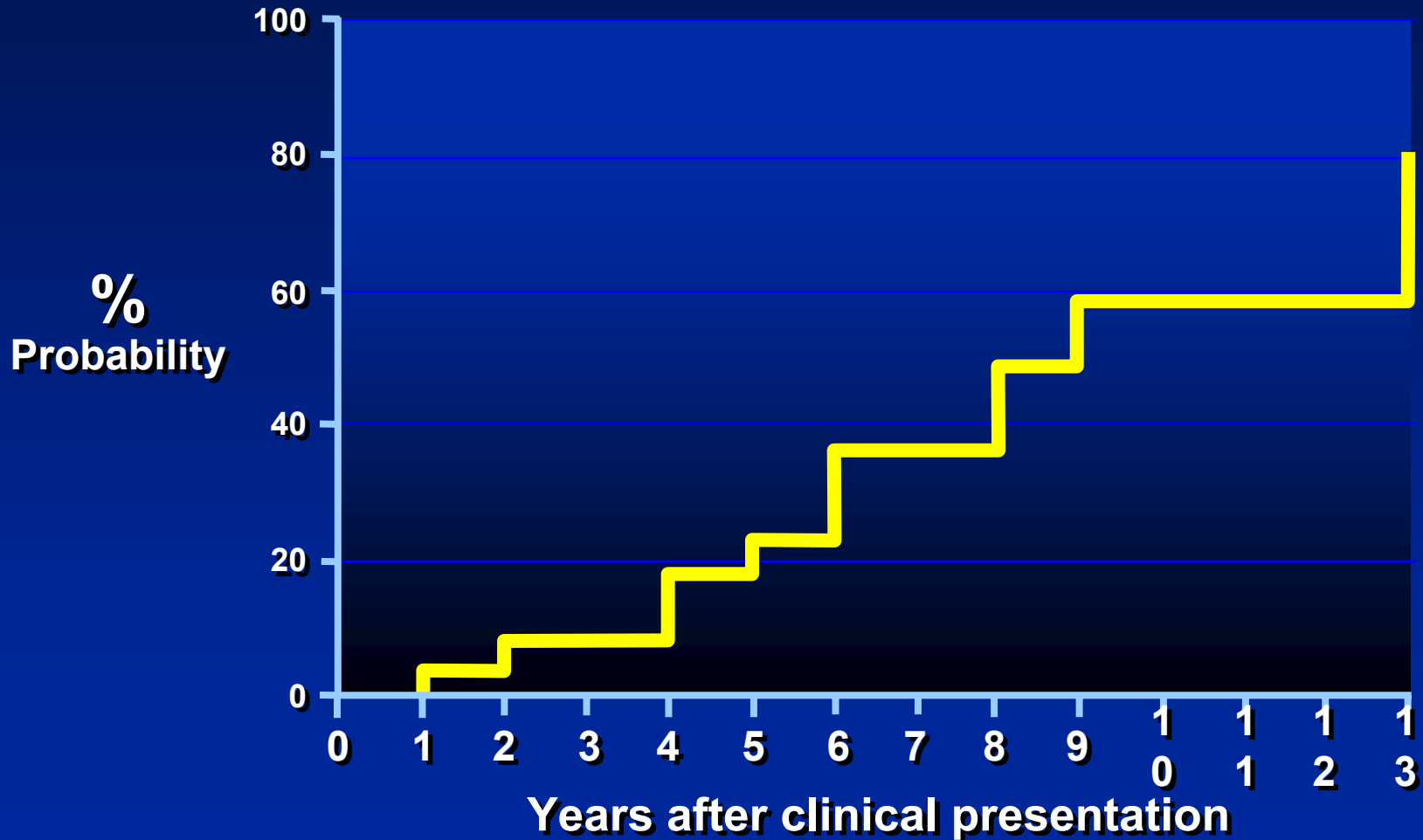
1. Torresi J. *Gastroenterology*. 2000;118(2 suppl 1):S83–S103.
2. Fattovich G. *Hepatology*. 1995;21:77–82.
3. Moyer LA. *Am J Prev Med*. 1994;10:45–55.
4. Perrillo R. *Hepatology*. 2001;33:424–432.

Risk of Chronic HBV Infection



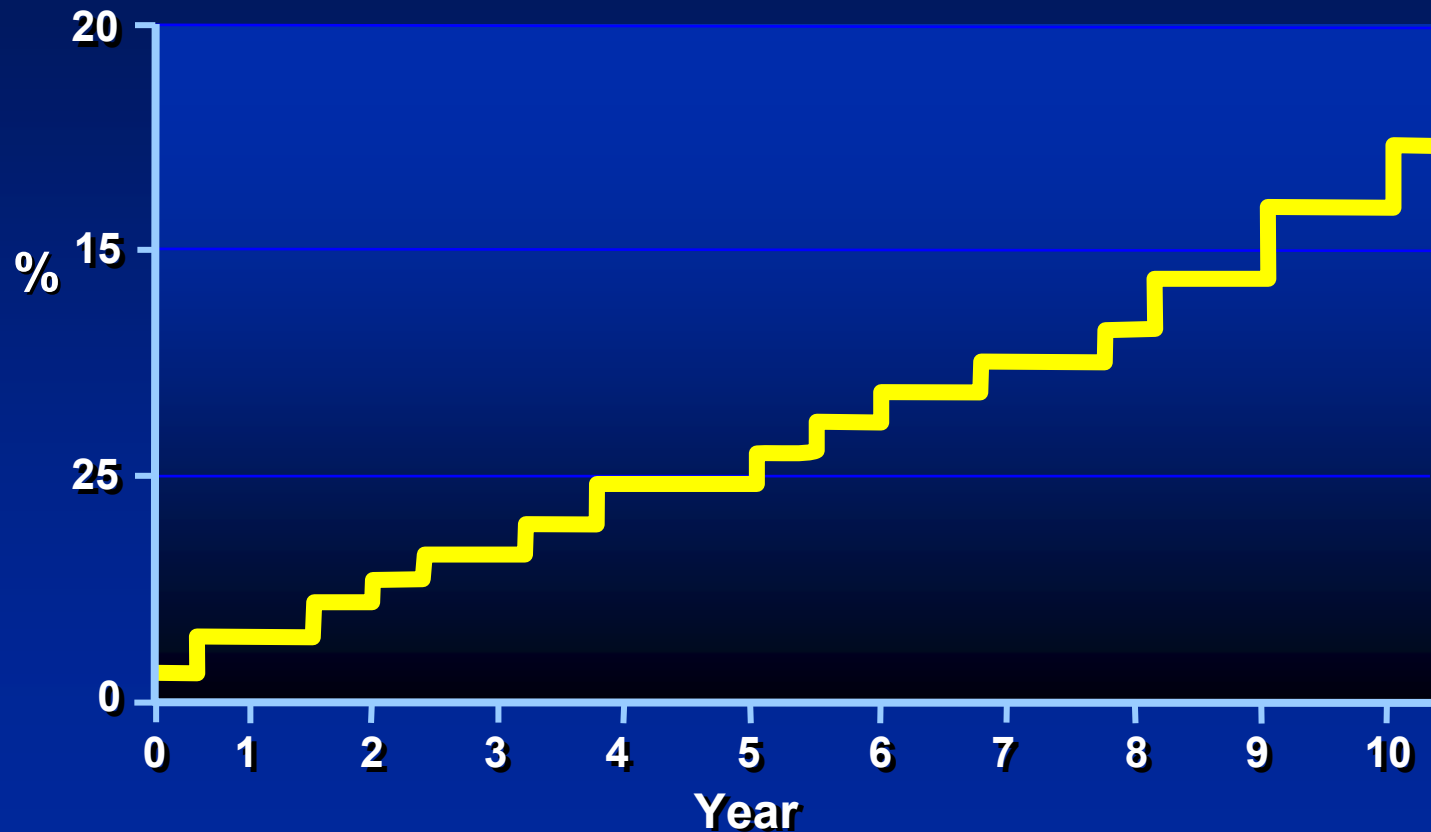
Chronic HBV Infection

Overall Risk of Progression to Cirrhosis



Chronic HBV Infection

Cumulative Probability of Developing HCC in Patients with HBV-Related Cirrhosis



Chronic Hepatitis B

Natural History of HBeAg-positive Disease in a 30-year old Asian

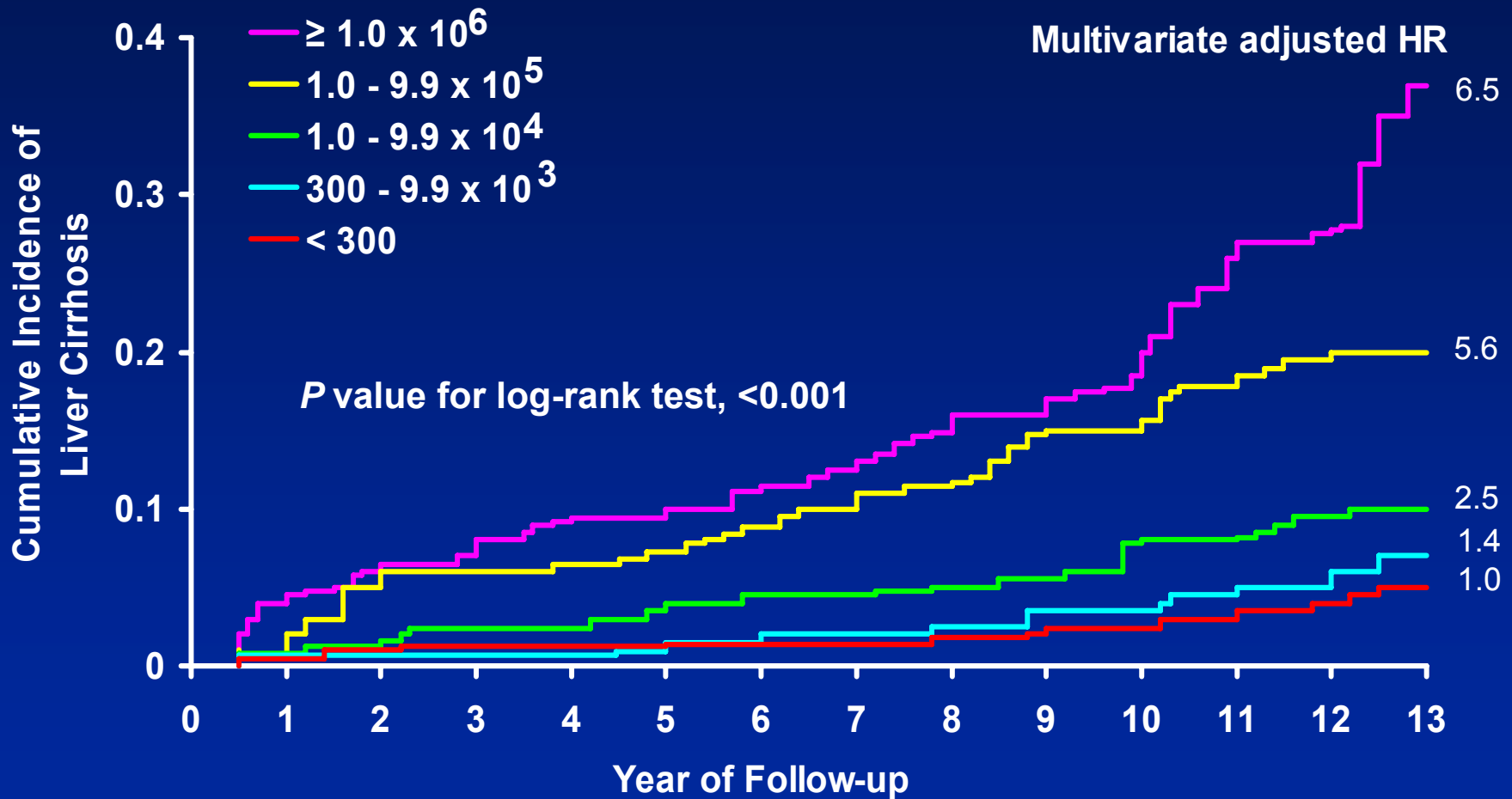
<i>Health state</i>	<i>Lifetime risk</i>
• Cirrhosis:	~42%
• Decompensation:	~14%
• Hepatocellular carcinoma:	~25%
• Liver-related death:	~37%

Chronic Hepatitis B

Factors Influencing Risk of Cirrhosis

- **Higher HBV DNA levels ($>10^4$ copies/mL)**
- **HBeAg-positivity**
- **Persistent ALT elevation**
- **HIV, alcohol, immunosuppression**

Cumulative Incidence of Cirrhosis for Five HBV DNA Categories (n=3,774)



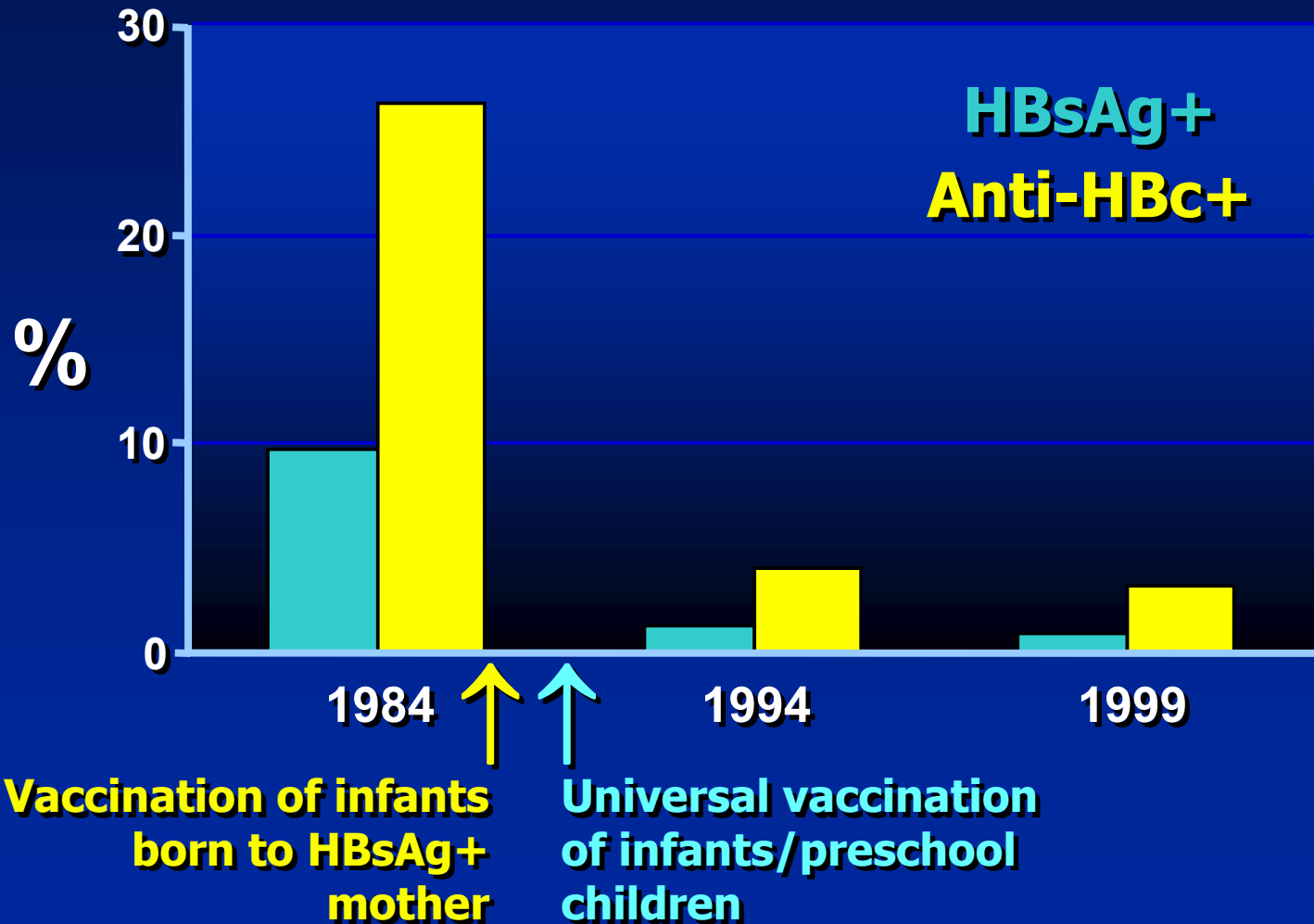
HBV DNA Levels and Risk of Hepatocellular Carcinoma: The Taiwan Natural History Study*

Serum HBV DNA (copies/mL)	Incidence (per 100,000)	Adj. Rel Risk	<i>p</i>
$\geq 1.0 \times 10^6$	1150	11.6	<.001
$\geq 1.0 \times 10^5 - < 1.0 \times 10^6$	952	7.2	<.001
$\geq 1.0 \times 10^4 - < 1.0 \times 10^5$	315	2.4	<.008
$> 300 - < 1.0 \times 10^4$	112	0.9	NS
< 300	145	1.0	---

* Chen C-J et al. JAMA, 2006

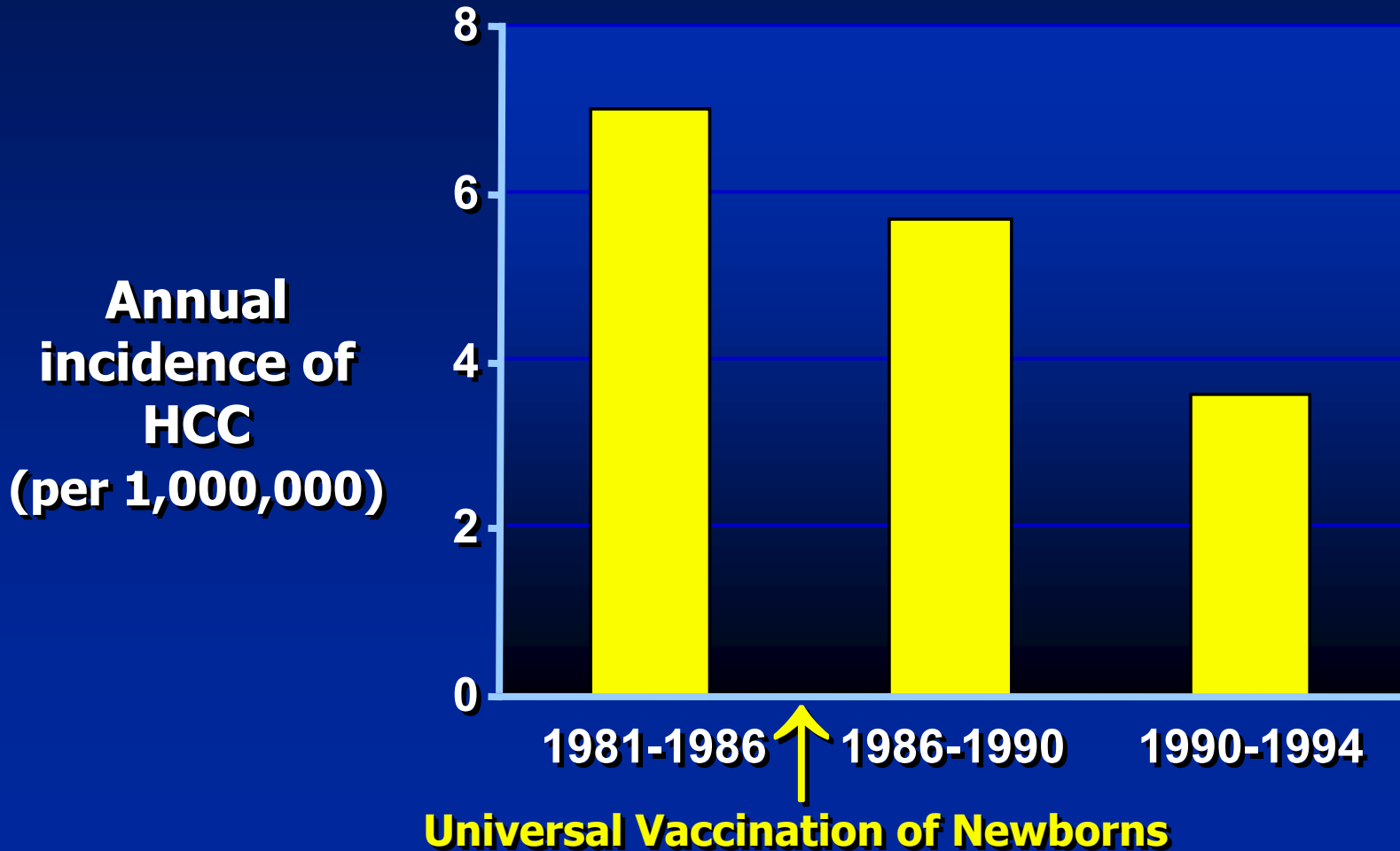
HBV Vaccination in Taiwan

Impact on HBV Infection in Children



HBV Vaccination in Taiwan

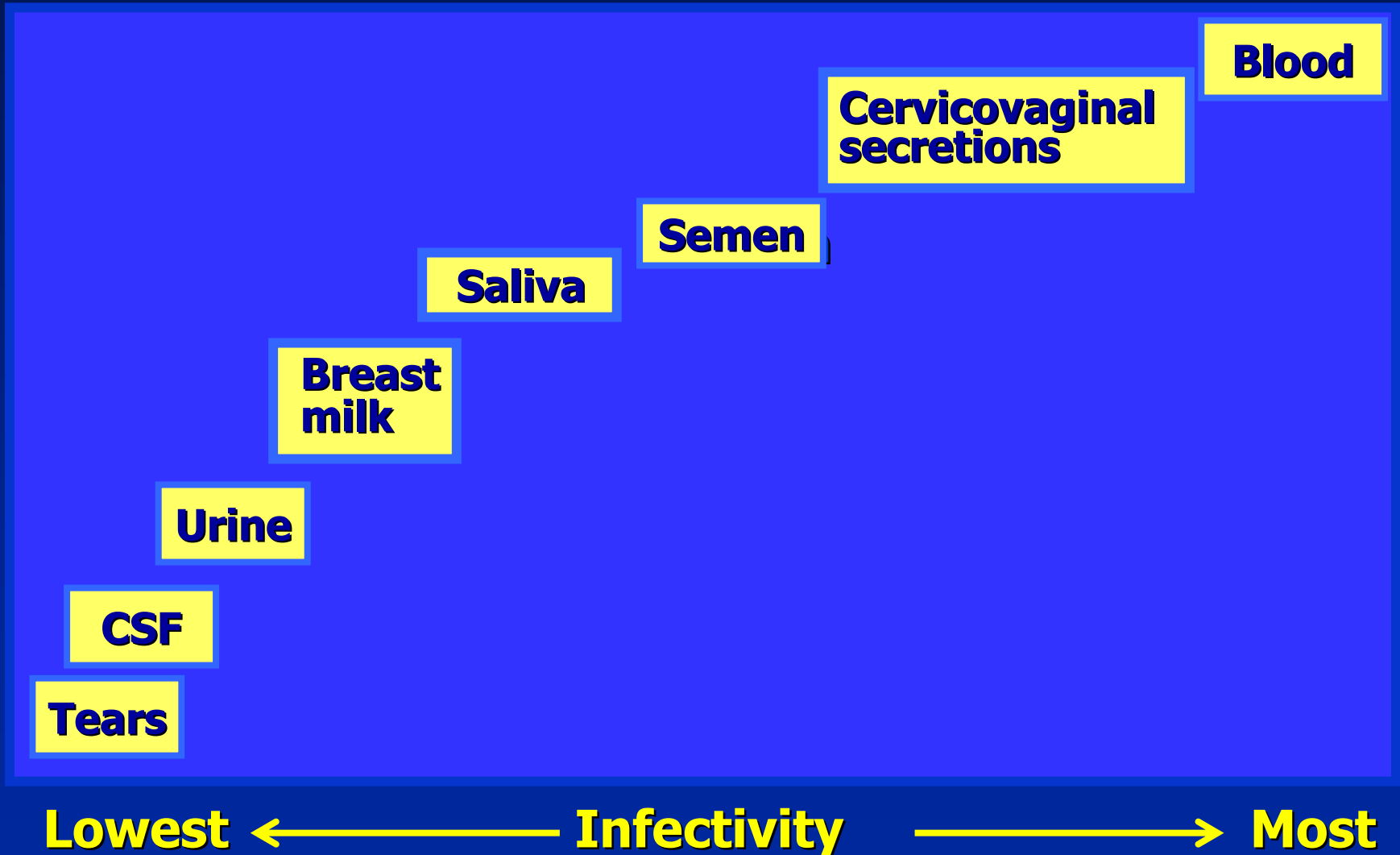
Impact on Incidence of HCC in Children



Epidemiology of HBV

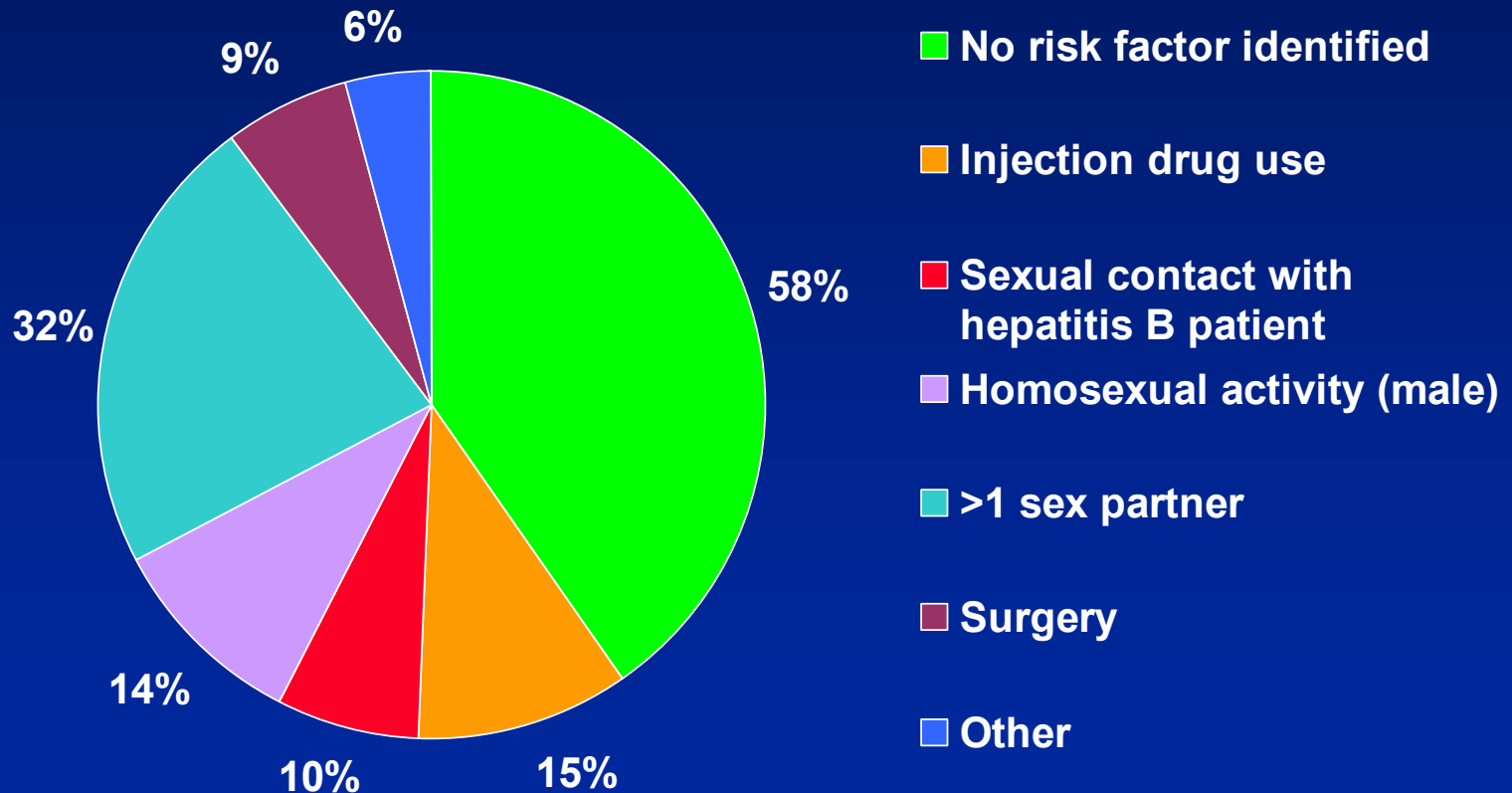
Hepatitis B Virus

Estimates of Infectivity in Body Fluids



Epidemiologic Characteristics of Patients With Hepatitis B — US, 2005*

More than 70% of newly acquired infections in 2005 were attributable to **high-risk sexual activity or injection drug use**



*Values total >100% because multiple risk factors could be reported for a single case.
CDC. *MMWR*. 2007;56(SS-3):1-25.

Hepatitis B

Factors Associated with Sexual Transmission

- **Multiple sexual partners, unprotected sex**
- **Injecting drug user as sexual partner**
- **Duration of sexual activity**
- **Male to female, male to male, female to male**
- **History or serologic evidence of other sexually transmitted diseases**

Prevention of Hepatitis B

Hepatitis B Prevention Strategies

Reducing the Risk of Infection

- **Decreasing exposure opportunities**
- **Decreasing susceptibility**
 - ***immunization with hepatitis B vaccines***

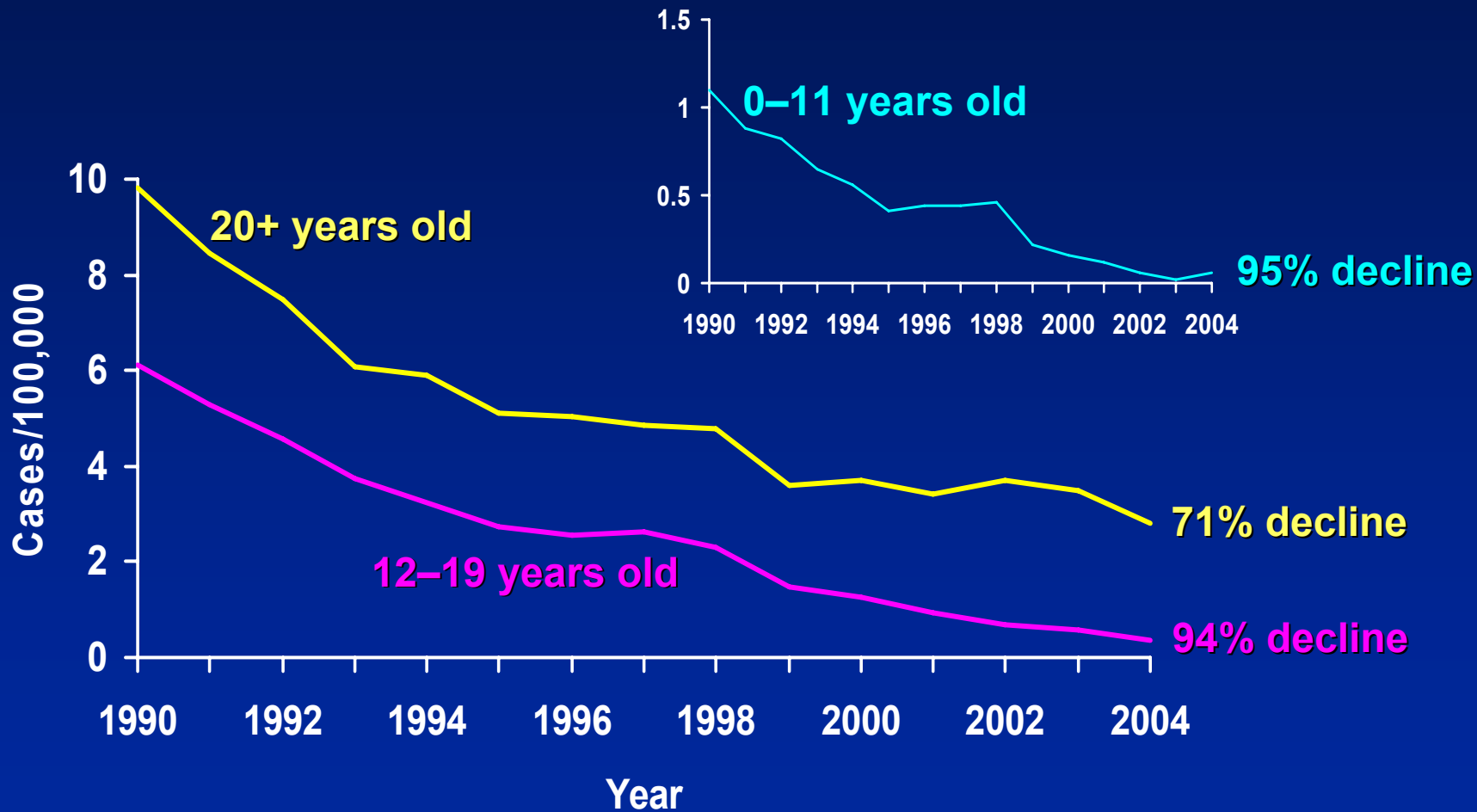
Non-vaccine Prevention of HBV

- Screening of blood donors for HBsAg, anti-HBc (future screening for HBV DNA)
- Screening of organ and tissue donors
- Safe-sex practices
- Reduction in sharing equipment for IV drug use
- Needle-exchange programs and education about cleaning equipment
- Avoidance of intranasal cocaine use
- Inspection of tattoo and body-piercing shops
- Sterilization of manicure/pedicure equipment
- Avoidance of multidose vial misuse

Vaccine-based Strategies for Eliminating HBV Transmission in the U.S.

- **Maternal screening for HBsAg:** providing post-exposure prophylaxis to infants of HBsAg-positive women
 - HBIG within 12 hours of birth and first of 3 doses of HBV vaccine
 - **Routine vaccination of all newborn infants**
 - **Catch-up vaccination:** for children aged <19 yrs
 - **Targeting high risk:** children, adolescents, adults
- **Screening and vaccination:** household and family members of HBsAg-positive persons

Incidence of Acute Hepatitis B United States by Age (1990–2004)



Source: CDC, National Notifiable Diseases Surveillance System (NNDSS).

2007 Vaccine-based Strategies to Eliminate Hepatitis B Transmission in the Young

- Establish standing orders for first dose of HBV vaccine at birth
- Improve identification of and immunization of infants born to HBsAg-positive mothers and those in whom the maternal HBsAg status is unknown
- Develop HBV vaccination record reviews of all children aged 11 to 12 years and for individuals <19 years of age born in endemic regions
- Make hepatitis B vaccination a requirement for school entry
- Incorporate HBV vaccine delivery into adolescent care services

2007 Vaccine-based Strategies to Eliminate Hepatitis B Transmission in Adults

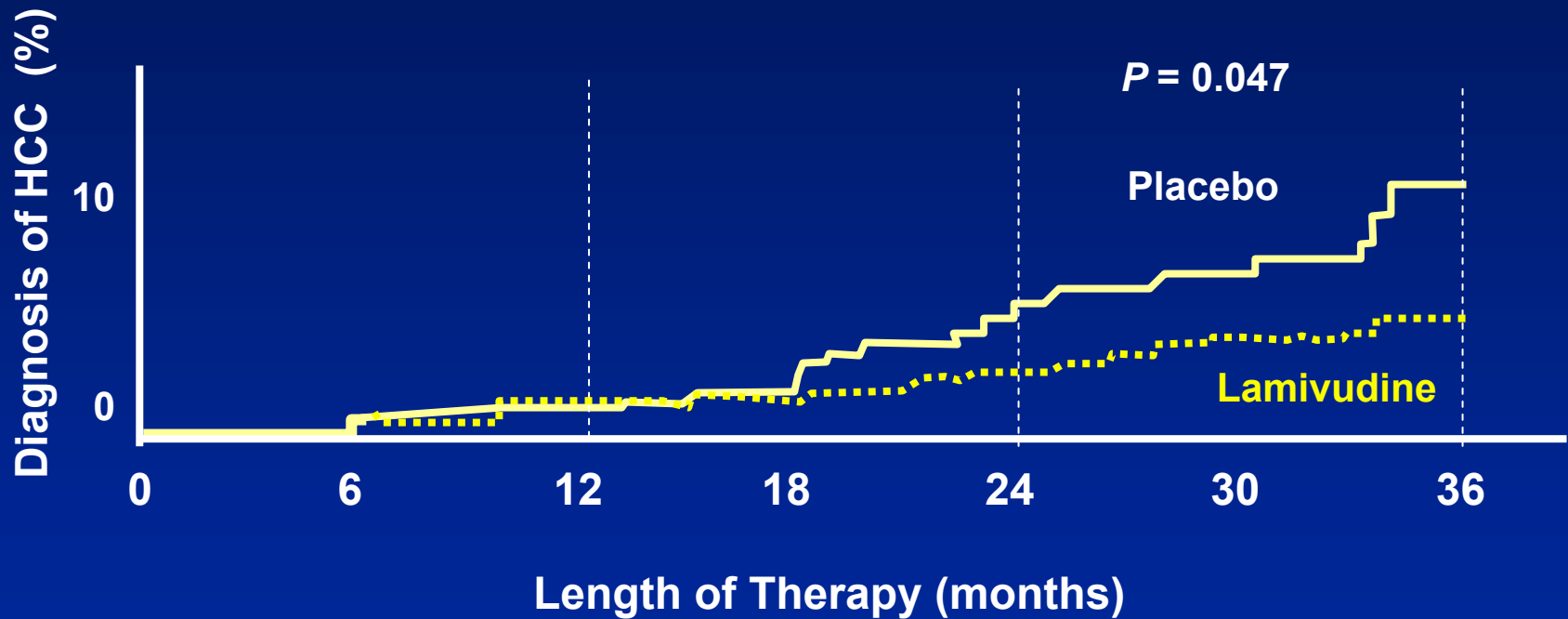
- Vaccinate high-risk adults attending facilities for individuals with high risks for sexual or parenteral exposure
- Educate adults in primary or specialty care settings about risks of infection, benefits of vaccination, and current recommendations; vaccinate those who report risks
- Vaccinate any individual requesting protection
- Establish standing orders by health-care workers to identify those recommended for vaccination and to vaccinate as part of routine care
- **Initiate vaccination in individuals who fail to acknowledge a risk factor**

Treatment of Chronic Hepatitis B

Chronic Hepatitis B Management Goals

- Suppression of viral replication
- Improvement in hepatic necroinflammatory disease
- Reduction in long-term sequelae: HBV-associated cirrhosis, hepatocellular carcinoma
- Reduction of infectivity

Effect of Lamivudine on Incidence of HCC in Chronic HBV with Advanced Fibrosis



Chronic Hepatitis B

Candidates for Treatment

Patients with:

Elevated or normal ALT levels and:

- HBeAg-positive and HBV DNA $\geq 10^{4-5}$ copies/mL by PCR**
- HBeAg-negative and HBV DNA $\geq 10^4$ copies/mL by PCR**
- +/- liver biopsy evidence of disease**

Cirrhosis with detectable HBV DNA

HBV Treatment Options in 2008

- **Pegylated interferon alfa-2a**
- **Interferon alfa-2b**
- **Nucleoside analogs**
 - **Entecavir**
 - **Lamivudine**
 - **Telbivudine**
- **Nucleotide analogs**
 - **Adefovir**
 - **Tenofovir (likely to be FDA-approved soon)**

Chronic Hepatitis B

Comparing Oral Antivirals and Interferon

	<i>Orals</i>	<i>IFN</i>
Oral administration:	Yes	No
Side effects:	Minimal	Frequent
Duration of treatment:	Prolonged	Finite
Flares during treatment:	Rare	Yes
Resistant mutant	Yes	No
Rate of HBsAg clearance:	Low	Higher
Improved outcomes:	Yes	Yes

Treatment of HBV Patients: Now and in the Future

- Focus on HBV DNA suppression
- Treatment decisions based on HBV DNA levels, disease severity, drug efficacy and resistance patterns (for oral agents)
- Combination oral therapy emerging
- New agents with prolonged activity after end-of-treatment, e.g. clevudine

Other Management Strategies

- Immunization against HAV, other infections
- Avoidance of alcohol, hepatotoxic herbals
- Screening for hepatocellular carcinoma
 - imaging studies, AFP, others
 - appropriate timing
- Case-finding (family, non-family contacts) for vaccination

Summary

- Hepatitis B is the major global cause of HCC
- Safe and effective vaccines: result in dramatic declines of HBV infection in children and HCC
- Many at-risk individuals remain unvaccinated; a large reservoir of infected persons exists
- Treatment should reduce HBV transmission and improves outcomes but is expensive and long-term for most patients
- Concomitantly with increasing vaccine coverage, education on reducing high-risk lifestyles must be a continuing focus