Towards the Eradication of HBV

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Hepatitis B

- ☆ **Blumberg's discovery of Australia antigen (HBsAg)**
- ☆ **Test improvements led to**
  - Name change from Serum hepatitis to HBV
  - Epidemiologic studies
  - Clinical studies
  - Viral studies
  - Prevention
    - Immunization – HBIG and Vaccine
    - Blood screening
  - Treatment

Status of Viral Hepatitis - 1965

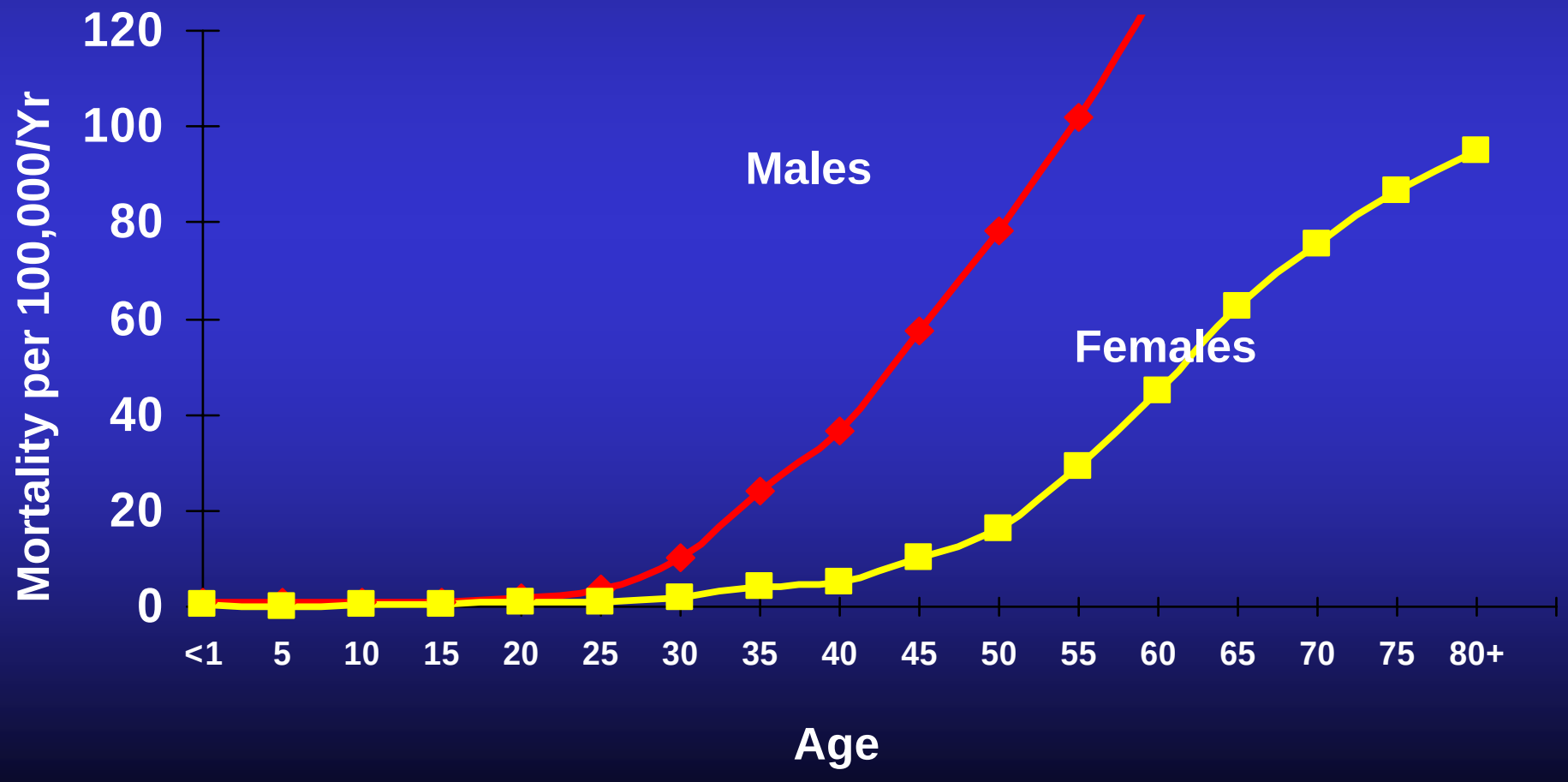
- **Classification**
  - HAV = Infectious Hepatitis = Short incubation hepatitis
  - HBV = Serum Hepatitis = Long incubation hepatitis
  - Other hepatitis viral agents not known
- **Agents not cultured nor characterized**
- **Epidemiology**
  - Transmission
    - HAV = fecal oral
    - HBV = inoculation
  - Carrier State following some HBV infections
- **Clinical**
  - HAV - Acute disease only
  - HBV – Acute and chronic hepatitis but association with cirrhosis and HCC not known

Global Burden of Disease - HBV

- ☆ 1 to 2 Billion Infected Persons
- ☆ 350 Million Chronic Carriers
- ☆ 5% Will Die From Chronic Liver Disease
  About 1 Million Deaths/Year
- ☆ 90% to 95% Preventable

From Mark Kane, WHO – December 1999

HCC Incubation Period from Infant Infections



Taiwan Prospective Study of Hepatitis B Carriers

- ☆ **Population Characteristics**
  - Male Chinese Civil Servants
  - 22,707 Study Participants
- ☆ **Recruiting**
  - Unselected for Health Status
- ☆ **Follow-up**
  - > 20 Years

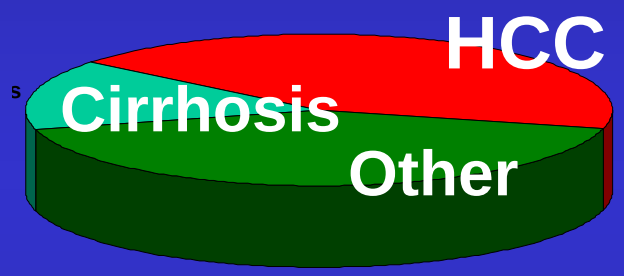
Taiwan Prospective Study

Relative Risk of HCC = 63

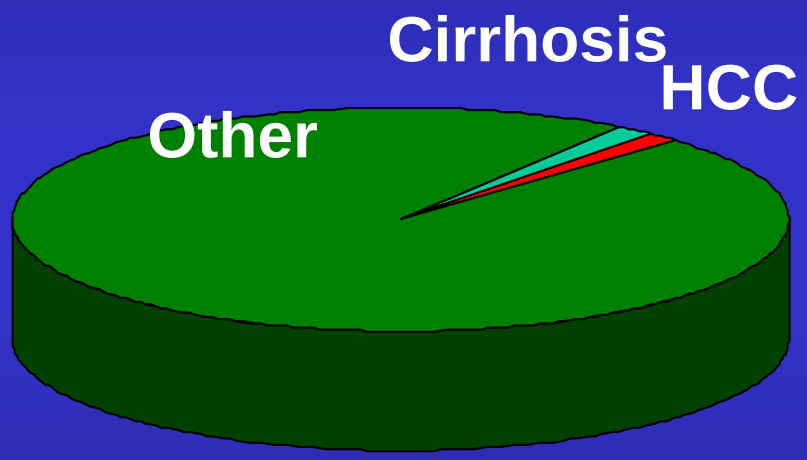
CI (95%) = 39 to 102

HBsAg+	3,454	204
HBsAg-	19,253	18
Total	22,707	222

Taiwan Prospective Study Proportion of Deaths



HBsAg+
(418)



HBsAg-
(960)

Hepatitis B Virus
Modes of Transmission

- ☆ **Perinatal**
- ☆ **Person to Person**
  - Sexual
  - Non-sexual via saliva
- ☆ **Parenteral**

Hepatitis B Virus
Modes of Transmission

- ☆ Vertical = Perinatal
- ☆ Horizonal
  - Intimate Person to Person
    - Saliva
    - Sexual
  - Parenteral

Hepatitis B Virus
Age and Modes of Transmission

- **Epidemiologically**
  - Perinatal transmission is the driving force that sustains the infection
  - Horizontal infections are epidemiologic dead ends
- **Clinically**
  - Acute manifestations are most common following infections in older children and adults
  - Chronic manifestations are usually the result of chronic infections established in infancy and early childhood

Hepatitis B Virus
Modes of Transmission - Vertical

- ☆ Perinatal transmission is the driving force that sustains HBV infections
- ☆ Most infections after early childhood are epidemiologic dead ends because few older persons become carriers

Hepatitis B Virus
Modes of Transmission - Horizontal

- ☆ **HBV is sustained by perinatal transmission**
- ☆ **Most horizontal infections are epidemiologic dead ends**
- ☆ **Only early childhood infections really matter**
  - Children infect children
  - Few adults infect children
  - Few adults become carriers

Hepatitis B Virus
Determination of Perinatal Transmission

Maternal Factors

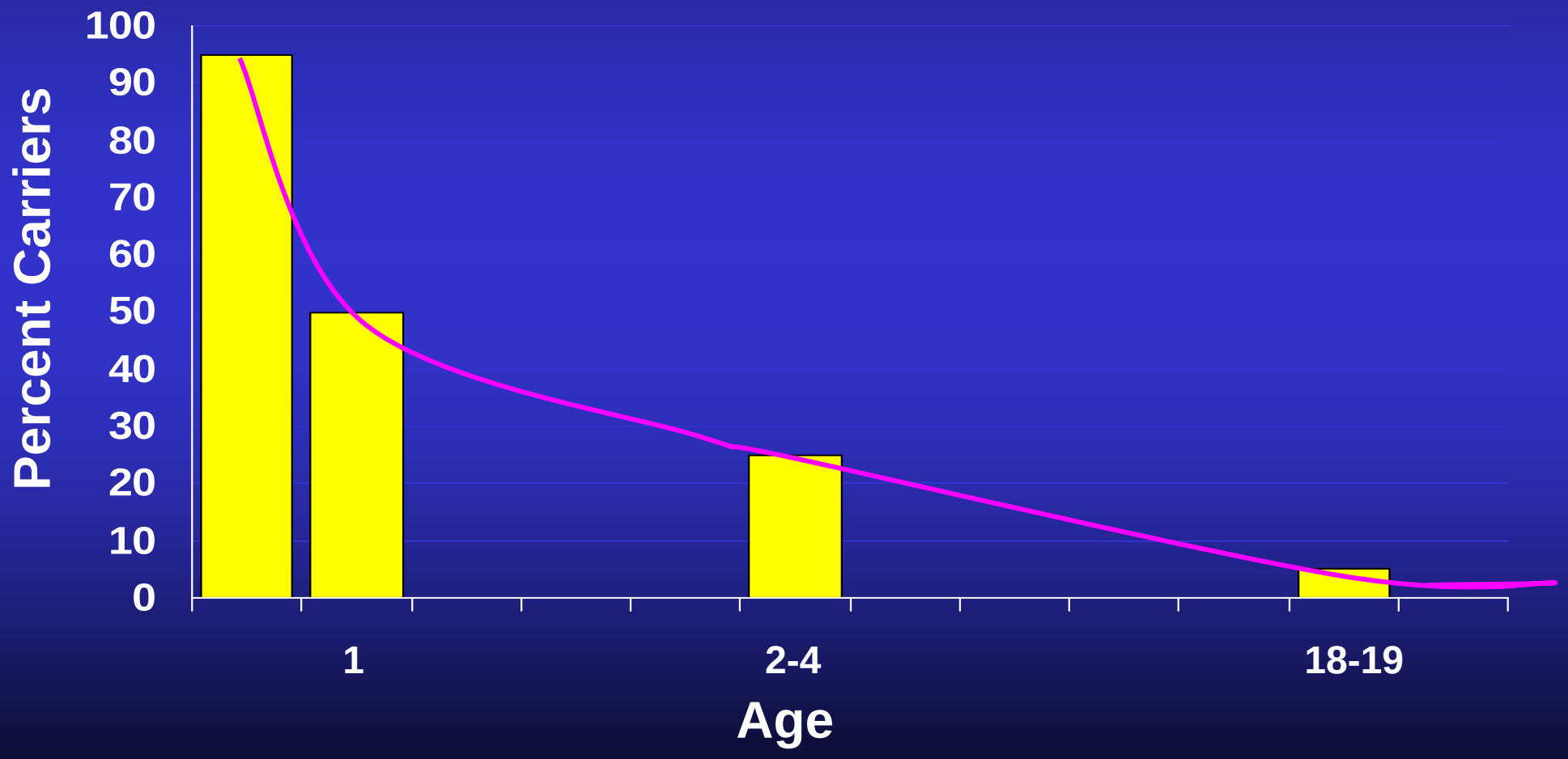
- ☆ **Circulating viral load**
  - **Reflected by**
    - HBV DNA
    - HBeAg
    - HBsAg titer
  - **Decline with Maternal age**
- ☆ **Leaky placentas**

Hepatitis B Virus
Modes of Transmission - Perinatal

Infants of e+ Carrier Mothers

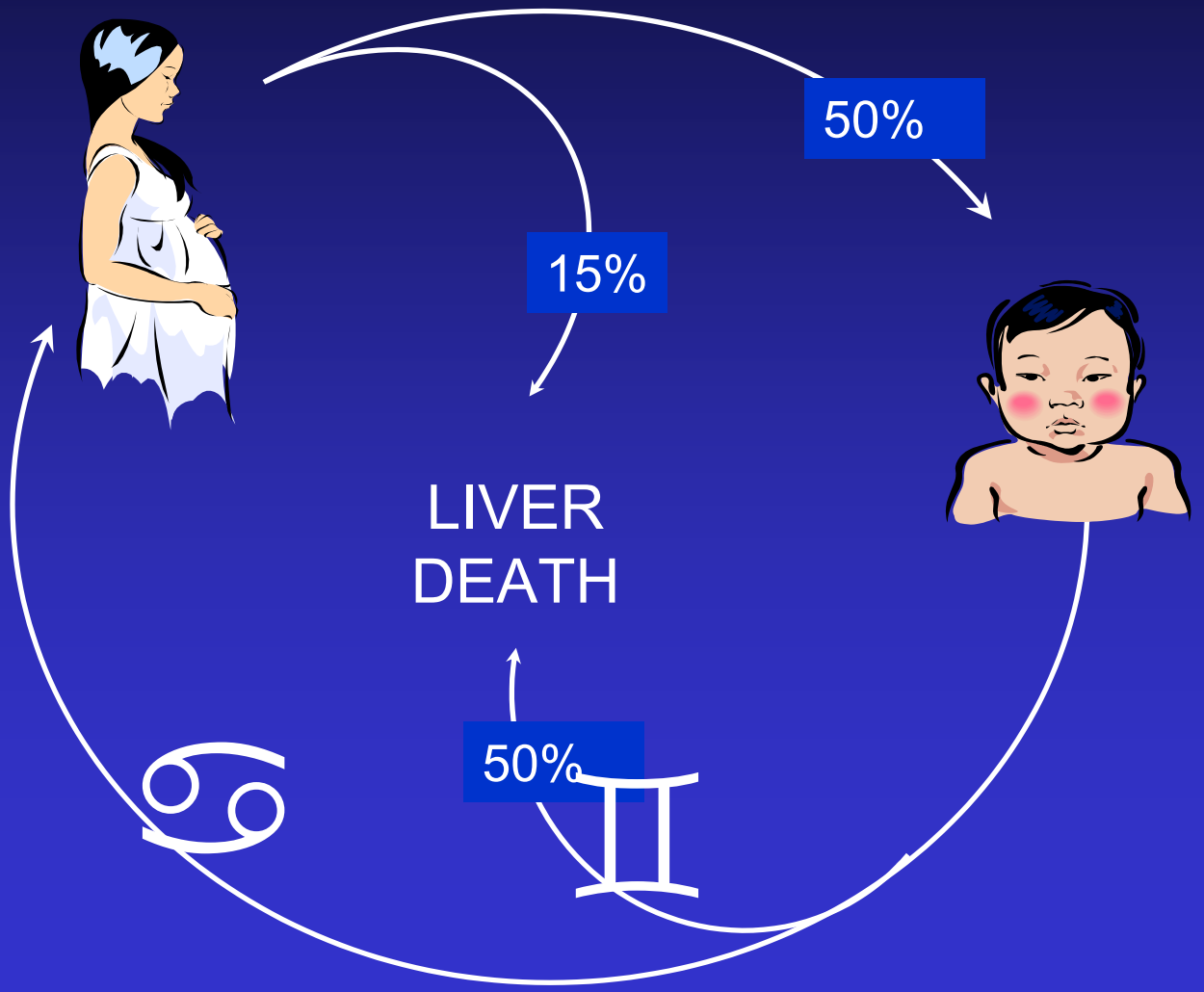
☆ In-Utero	2% to 5%
☆ Peripartum	95% to 98%
☆ Postpartum	0

Age Determines Outcome
Carrier/Infection Ratio vs Age

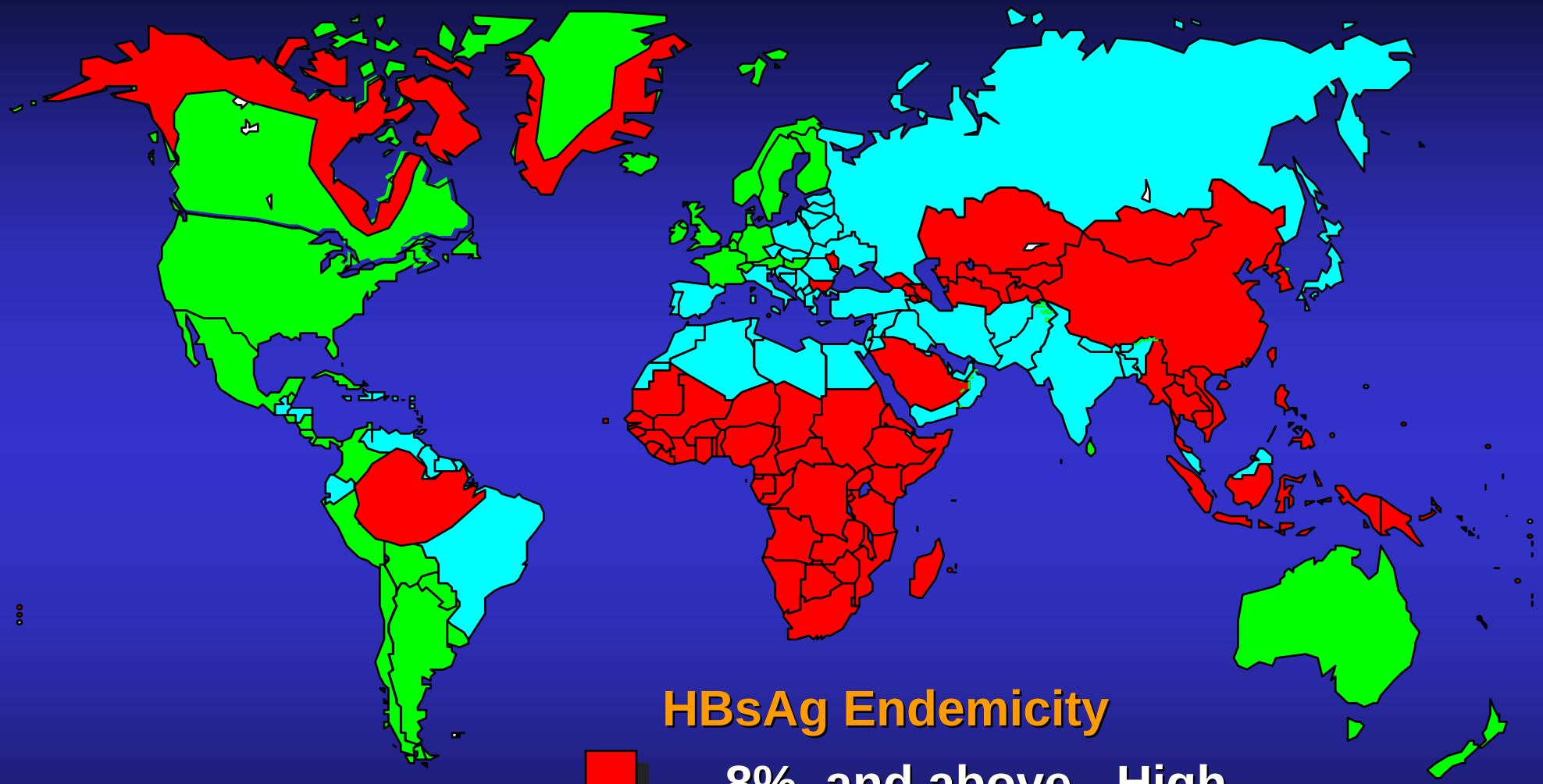


Taiwan Incidence Studies

HBV Cycles from Generation to Generation



Hepatitis B Carrier Prevalence



HBsAg Endemicity

- 8% and above - High
- 2% - 8% - Intermediate
- Below 2% - Low

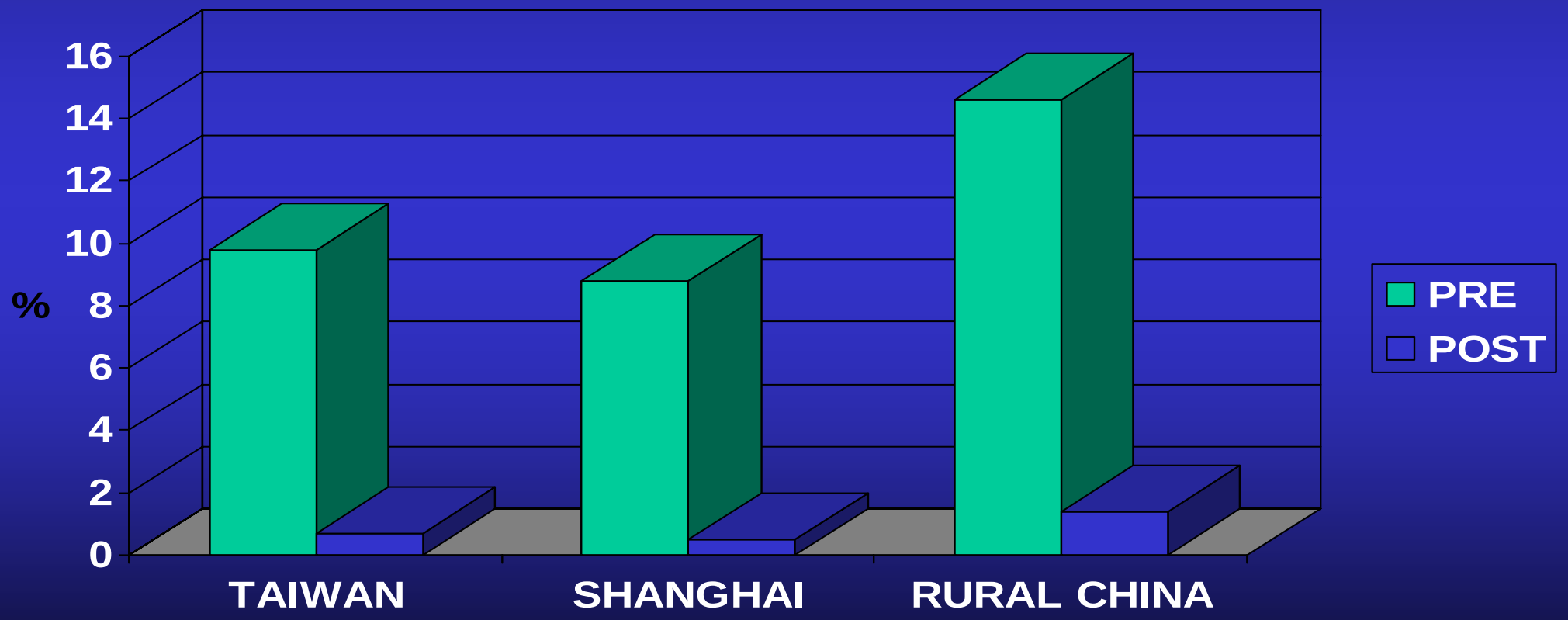
From Mark Kane / WHO

HBV Vaccine Programs Work

- ☆ **Reduces HBsAg Carrier State**
  Multiple countries, eg dramatic declines in Taiwan and Thailand
- ☆ **Reduces HCC**
  Taiwan

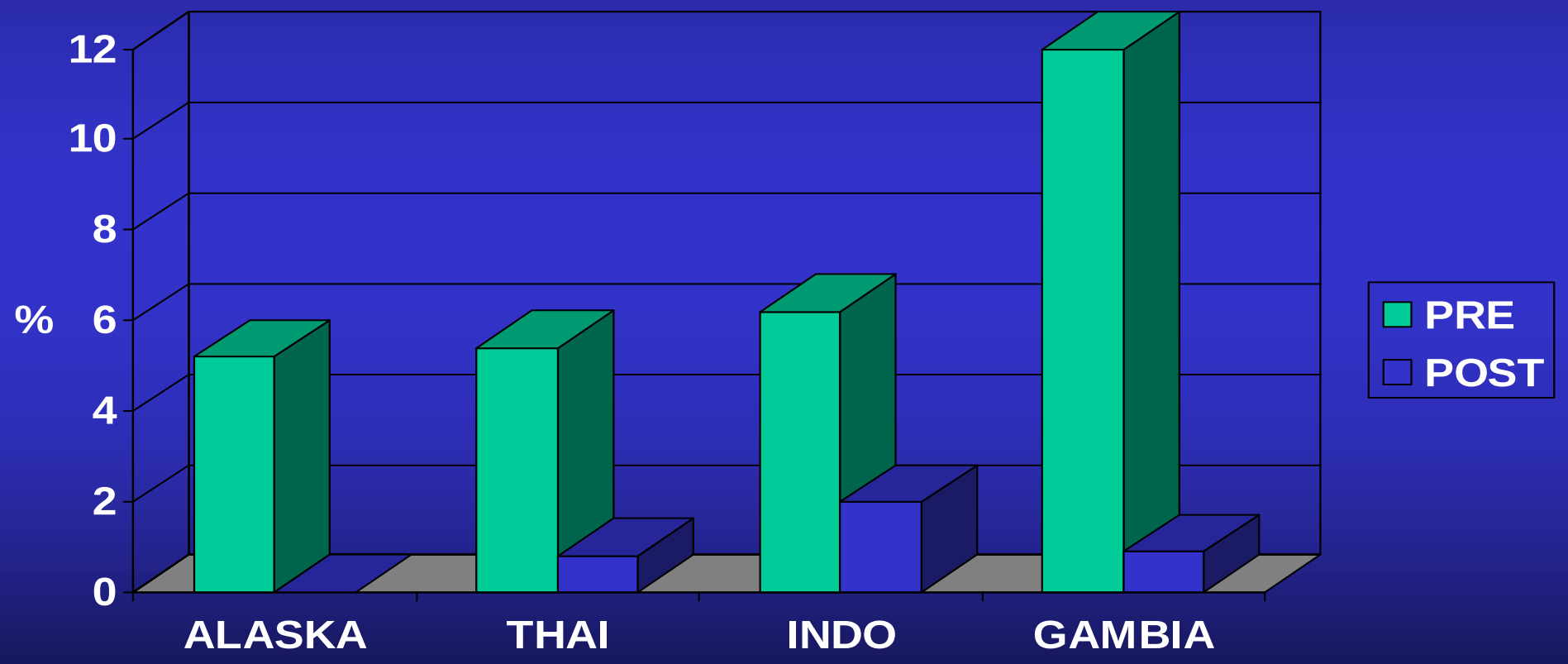
Chang, MH et al, NEJM 336:185-9, 1997

HBsAg Prevalence Pre and Post HBV Immunization - 1



From M. Kane, 1999

HBsAg Prevalence Pre and Post HB Immunization - 2



From M. Kane, 1999

Newborn HBV Immunization Program - Taiwan

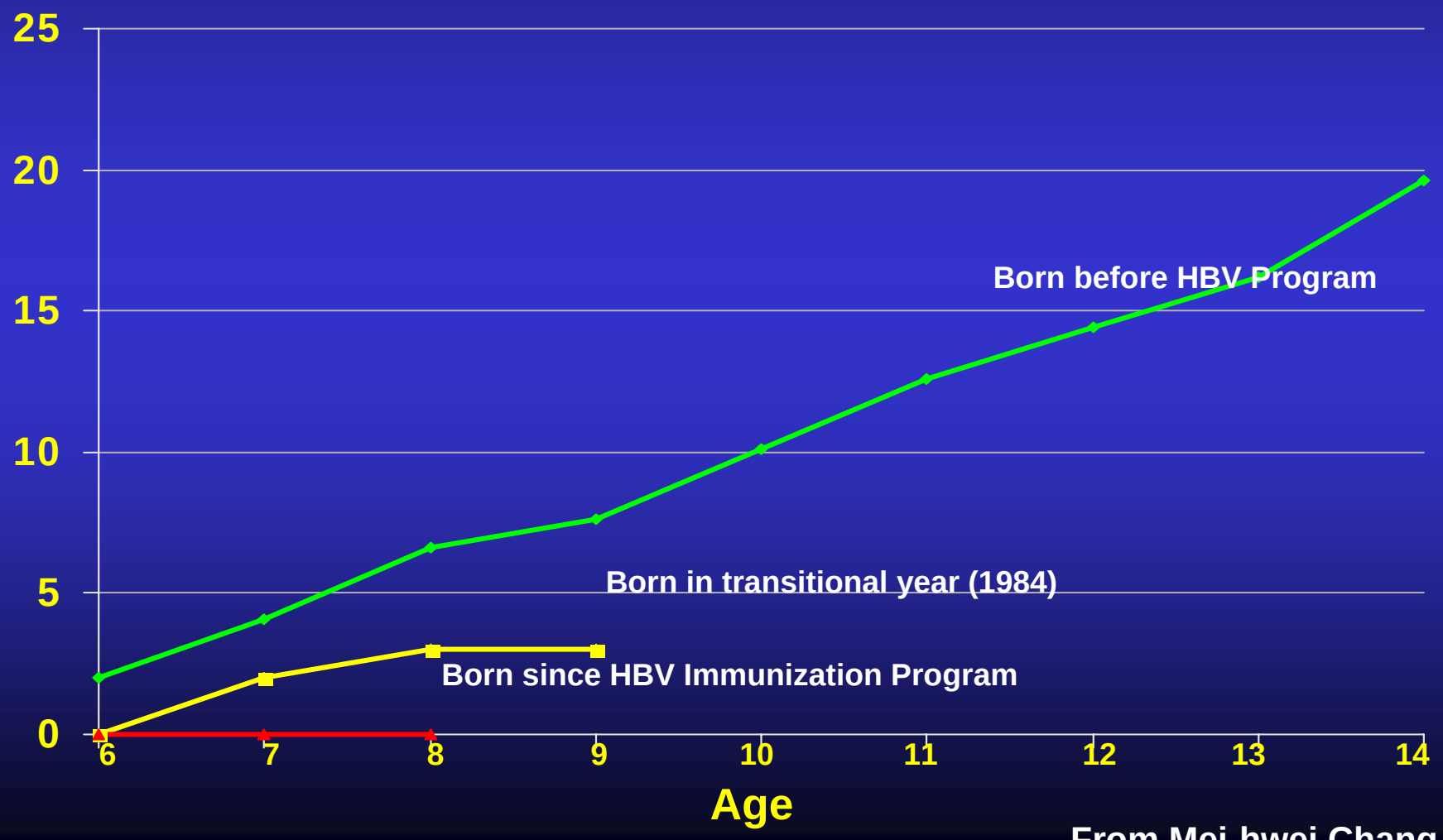
Outcome - HBsAg+ Six Year Olds

Year	Birth Year	HBsAg+ (%)
1989	1983	10.5
1991	1985	6.3
1993	1987	1.7
1995	1989	1.1
1997	1991	0.6

New Cancer Cases In Taiwan Children 1981-1993

Year	Liver	Brain
1981	19	35
1982	14	40
1983	10	33
1984	17	39
1985	14	38
1986	21	36
1987	23	50
1988	16	55
1989	23	57
1990	16	44
1991	16	60
1992	6	57
1993	8	48

Cumulative Average HCC in Children in Taiwan



From Mei-hwei Chang 1997

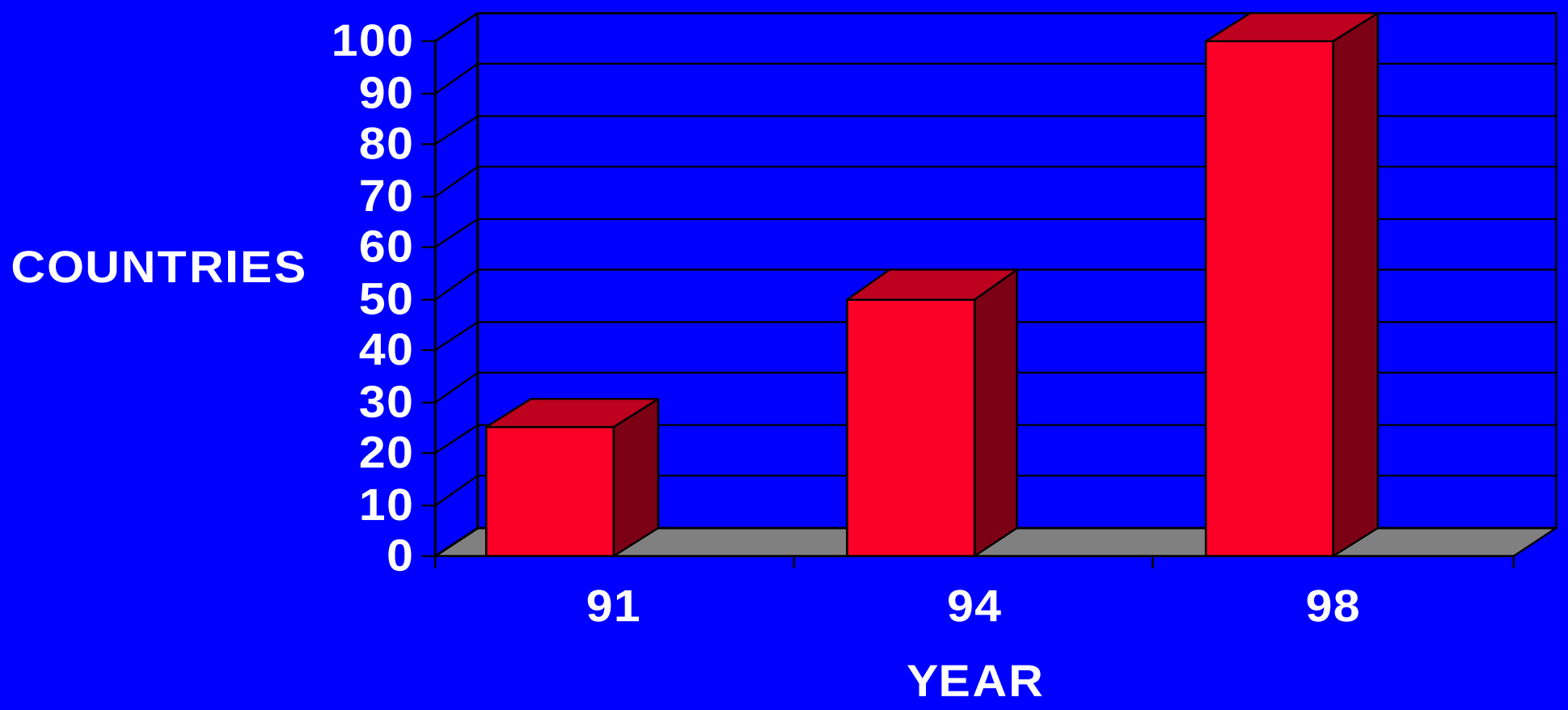
HBV Immunization Program History

- ✯ 1979 - 1st experimental vaccination of children
- ✯ 1991 - Adopted by World Health Assembly
- ✯ 1991 – 1999 Slow Implementation
  - Birth Immunization
  - Limited funds
  - Diversion of attention and resources by HIV/AIDS
  - But, excellent results from multiple countries
- ✯ 1997 Reduction of HCC documented in Taiwan
- ✯ 1999 > 100 countries with programs
- ✯ 2000 - Creation of GAVI – gives new hope

Countries with Universal HBV Immunization Policies - 1999

From M. Kane, 1999

HBV Vaccine
in National Immunization Programs



Global Eradication of HBV is Possible

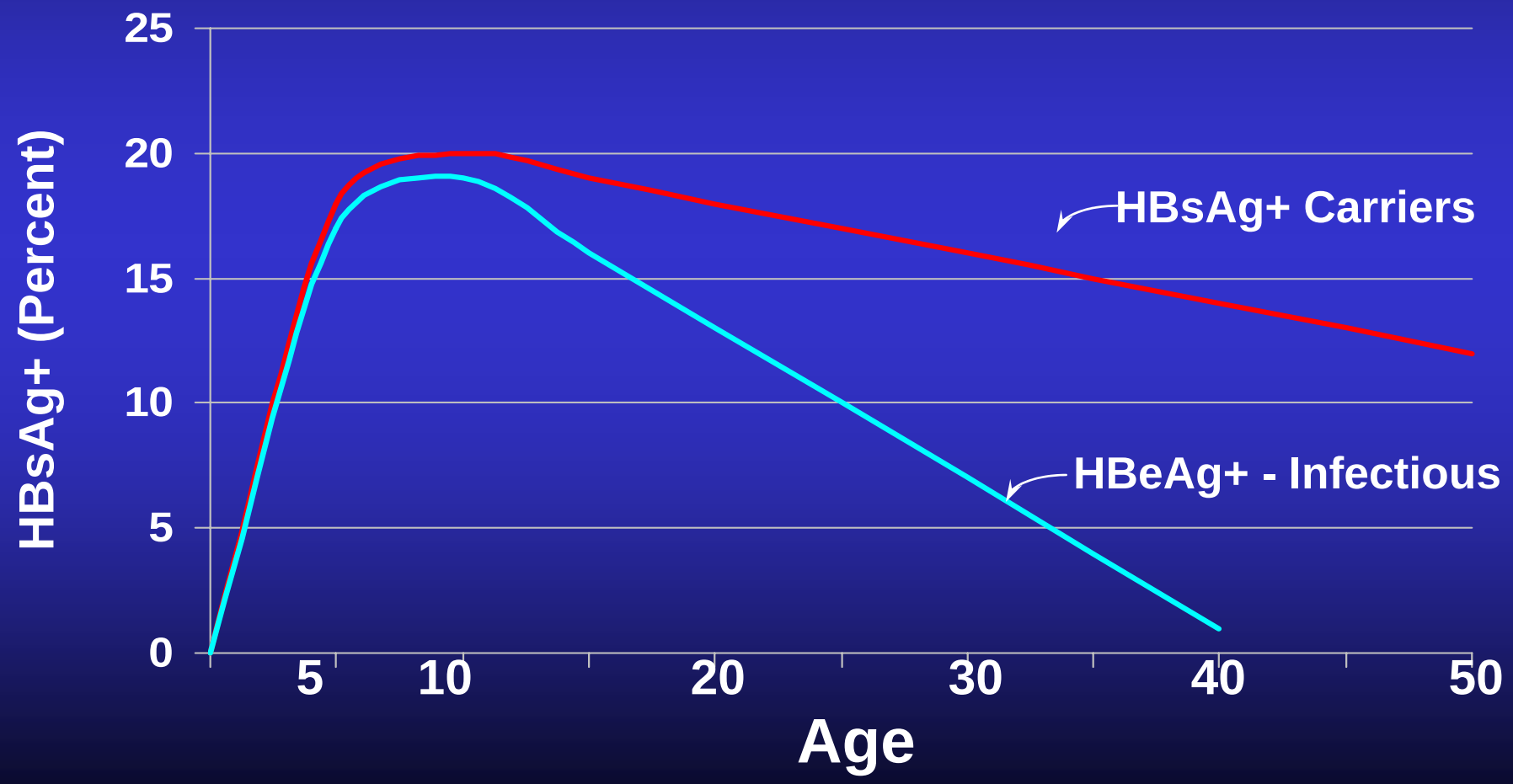
1. Feasible - not very difficult
2. All technical problems have been overcome
3. Cost Effective
4. Cost Beneficial
5. Enormous Booster for
   - Public health
   - Medicine
   - Medical sciences
   - Cancer research

Global Eradication of HBV
Biology Favors Eradication

- ☆ **HBV not very infectious,** **except:**
  - Perinatal transmission
  - Parenteral transmission
- ☆ **Carrier state declines with increasing age**
  - Infectivity declines even faster than carrier state
- ☆ **Carrier state rarely develops after early childhoo**
  - Infectivity lost more rapidly after adult infections
  - HCC may not occur following later infections

HBV Infectivity (HBeAg+)

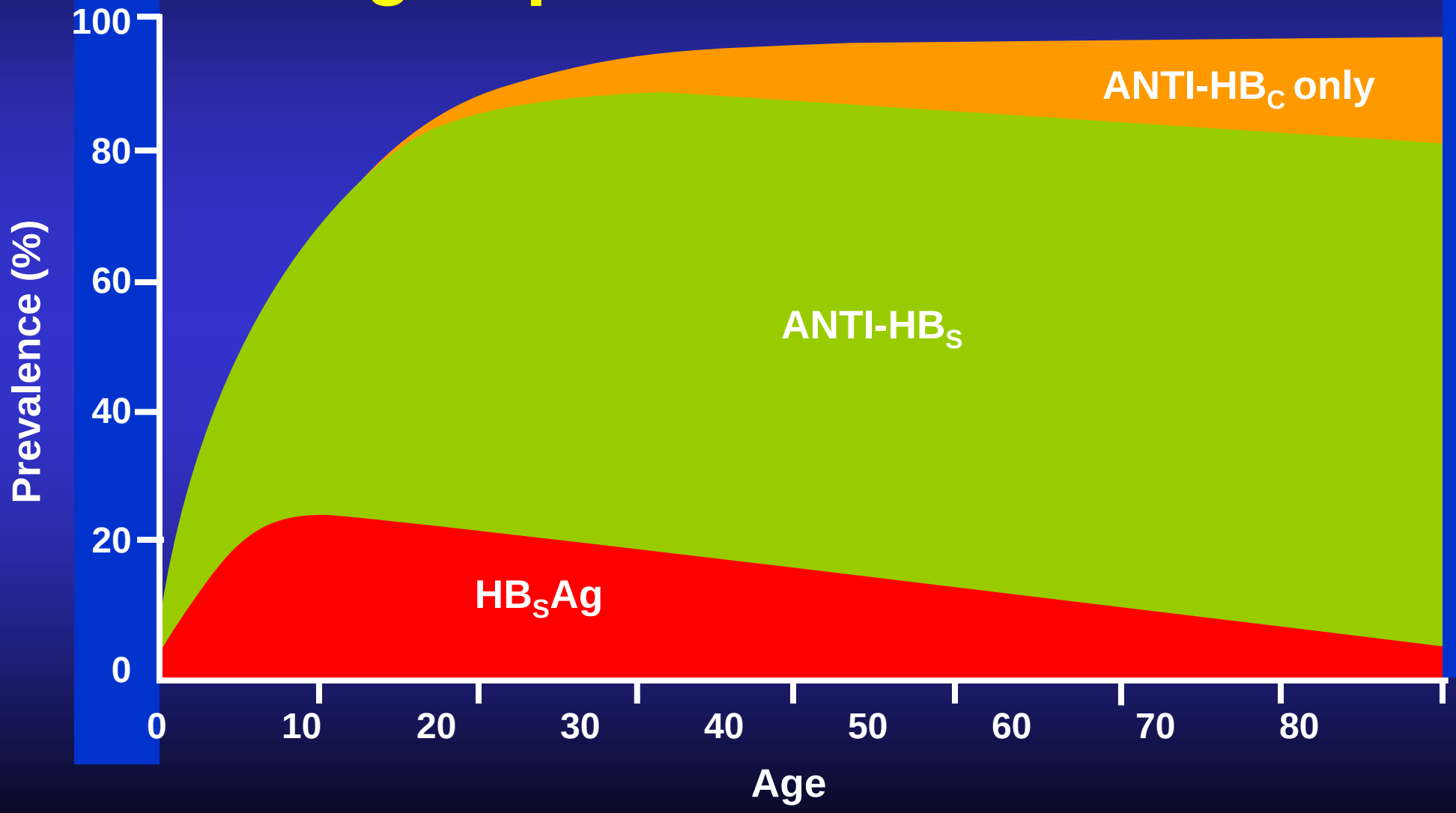
Declines with Age



Global Eradication of HBV Strategy is Simple

- ☆ Only requires immunization of newborns

HBV in East Asia
Age Specific Prevalence



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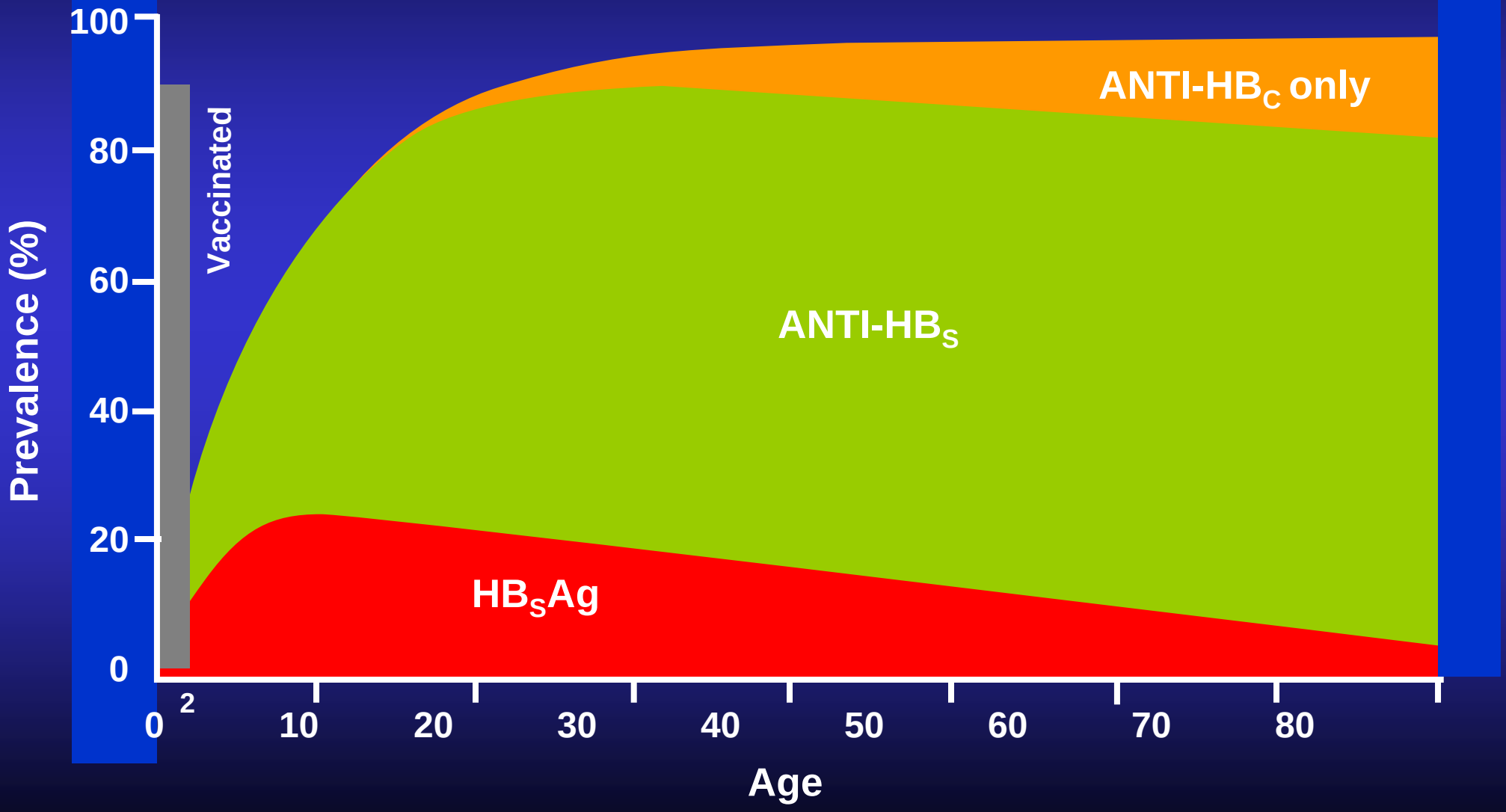

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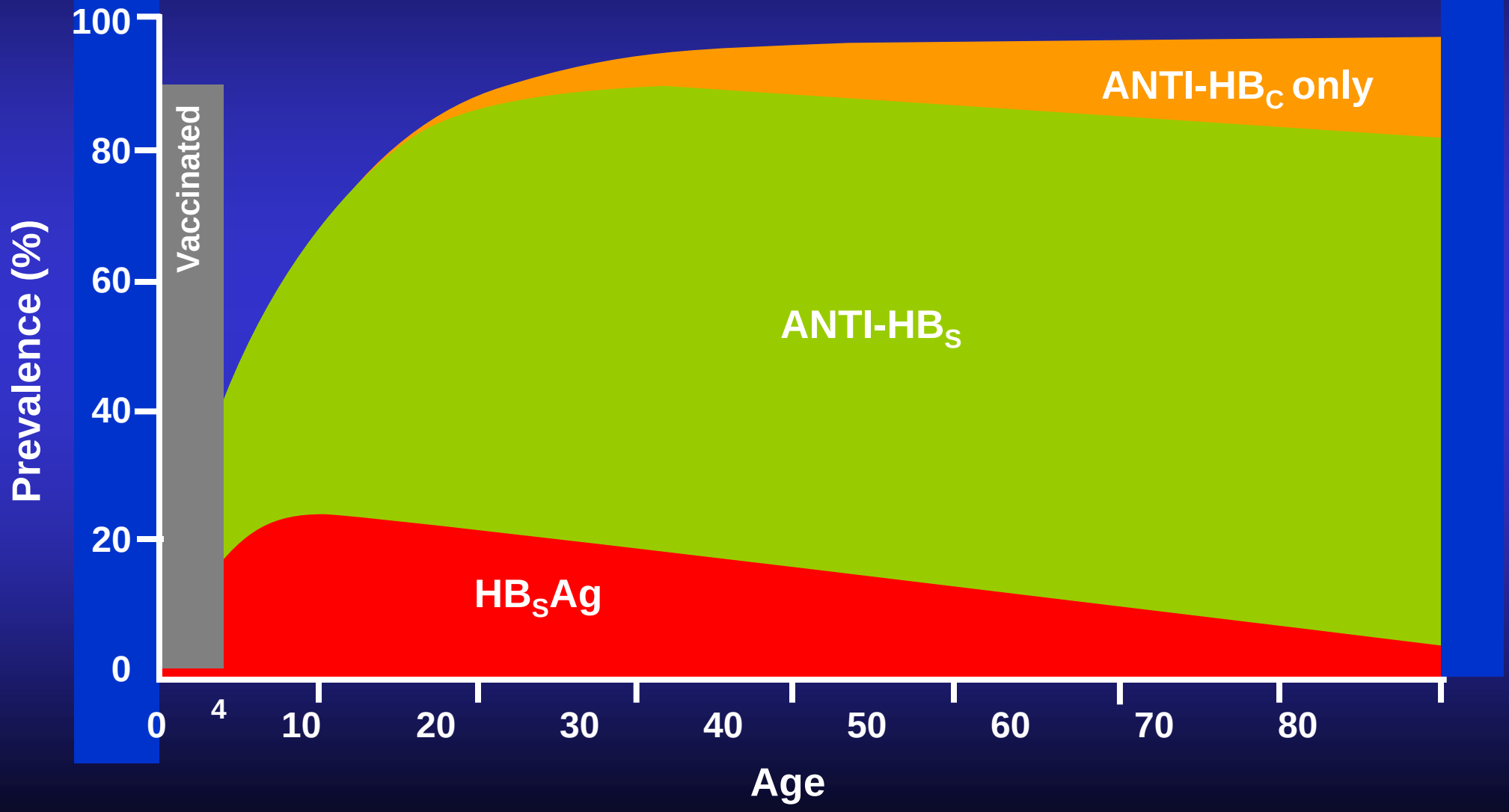

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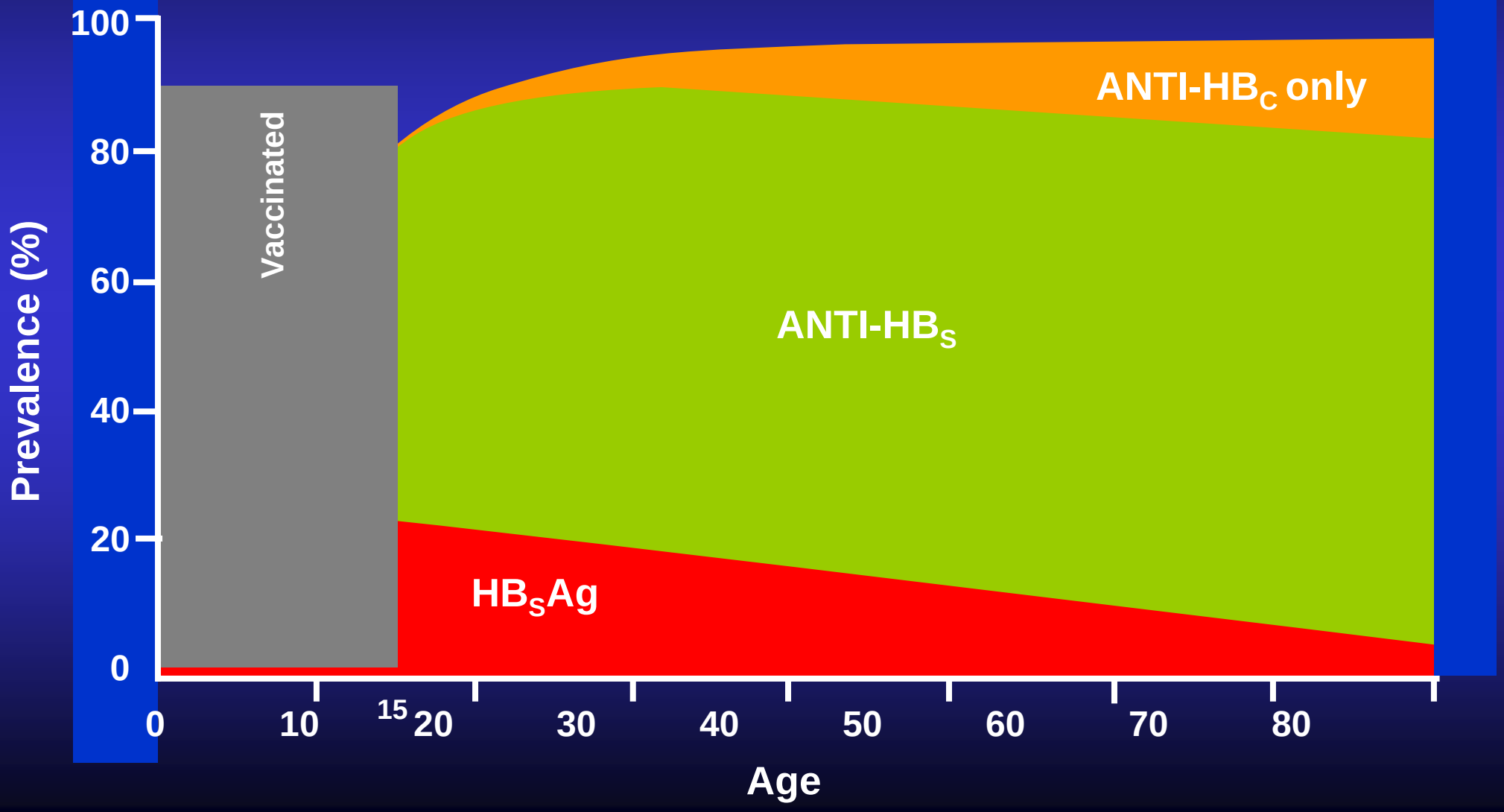


Global Eradication of HBV Strategy is Simple

☆ **What are the barriers ?**

HBV Eradication
Potential Inhibitors of Success

All can be overcome

1. Immunity
2. Genetic mutations of virus
3. In-Utero transmission is not preventable
4. Vaccine supply
5. Feasibility
6. Cost
7. Possible program interruptions
8. Lack of political will

HBV Eradication
Potential Inhibitors of Success

1. Immunity - Vaccine is Excellent

- ☆ High immunogenicity
- ☆ High efficacy
- ☆ Long duration of protection
- ☆ Two doses may be sufficient
- ☆ HBIG doesn’t interfere with vaccine

HBV Eradication
Potential Inhibitors of Success

1a. Immunogenicity and Efficacy

- ☆ **Infants and children**
  - Vaccine Immunogenecity – 100%
  - Protection - outstanding
  - Duration – Many Years

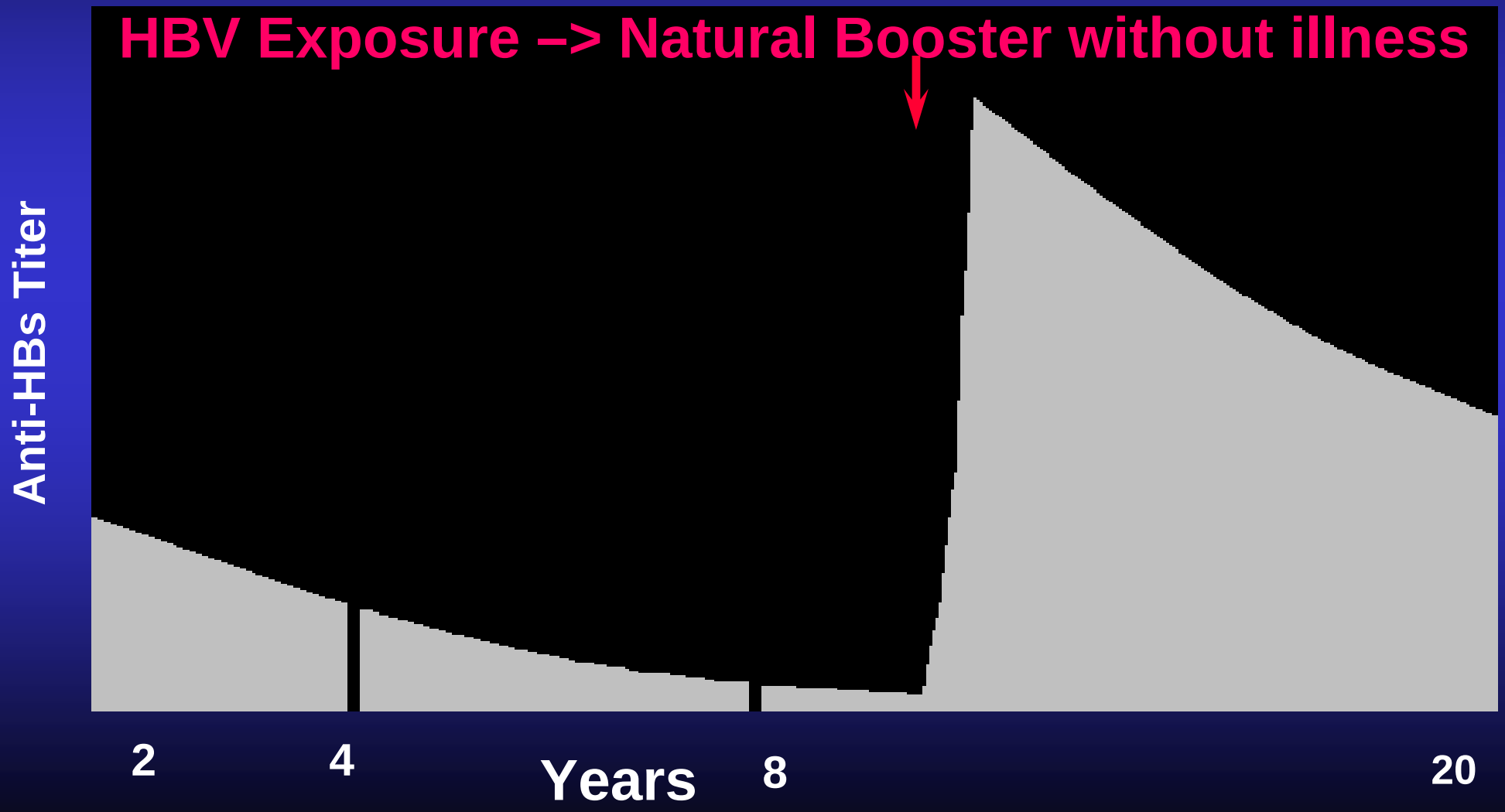
- ☆ **Adults**
  - Vaccine response diminishes with age, but
  - Not important
    - Adults rarely become carriers
    - Adults seldom infect others

HBV Eradication
Potential Inhibitors of Success

1b. Duration of Vaccine Induced Immunity

- ☆ Long lasting antibodies
- ☆ Antibody titers wane, but
  - Immune memory very prolonged
  - Sustained protection against
    - Acute clinical hepatitis
    - HBsAg carrier state
    - Chronic hepatitis
    - Cirrhosis
    - Hepatocellular Carcinoma

HBV Vaccination – Out Years



HBV Eradication
Potential Inhibitors of Success

2. Genetic Escape Mutants

- ☆ Escape Mutants are interesting, but
- ☆ Mutants are probably not important
  - No evidence they are limit vaccine programs
  - Research should continue

HBV Eradication
Potential Inhibitors of Success

2a. Genetic Escape Mutants – Chimp Challenge

- ☆ Virulent mutants don't infect immunized chimps
- ☆ Chimpanzee Challenge study
  - Controls infected
  - Vaccinated chimps protected

Ogata, N, et al, Hepatology 30:779-86, 1999

HBV Eradication
Potential Inhibitors of Success

3. In-Utero Transmission

- ☆ 2 to 5% of perinatal transmission
- ☆ Cause not known – not predictable
- ☆ Not preventable by immunization
- ☆ BUT – very limited carry forward to next generation

HBV Eradication
Potential Inhibitors of Success

4. Supply of Immunogens

- ☆ Vaccine
- ☆ HBIG

HBV Eradication
Potential Inhibitors of Success

4a. Vaccine Supply

- ☆ Ample Supply
- ☆ Many manufacturers
- ☆ Competition -> falling price

HBV Eradication
Potential Inhibitors of Success

5. Feasibility - Issues

☆ Problems

- At birth delivery – required

☆ Advantages

- Stable vaccine – cold chain not required
- Two doses might be adequate
- Boosters – not necessary

HBV Eradication
Potential Inhibitors of Success

4. Supply of Immunogens

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- ☆ HBIG

HBV Eradication
Potential Inhibitors of Success

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HBV Eradication
Potential Inhibitors of Success

5a. Feasibility – At birth immunization is best

- ☆ At birth initiation of vaccination
  - Hospital Deliveries – vaccination is easy
  - Home Deliveries are a challenge
    - Many of the poorest countries
    - Asia is doing well with at birth immunizations
    - Africa – postnatal infections predominate

HBV Eradication
Potential Inhibitors of Success

5b. Feasibility - Beyond the Cold Chain

☆ **Problems to Overcome**

- Babies born at home
- Rural areas - NO Electricty
- Illiterate midwifes
- Transportation by bicycle or foot

☆ **Study** - Rural Kwangxi Province of China

☆ **Results**

- Vaccine can be stored at room temperature
- No loss of immunogenicity

HBV Eradication
Potential Inhibitors of Success

6. Cost

- ☆ Vaccine costs are low
- ☆ Poorest countries can’t afford immunization
- ☆ GAVI is the BIG HOPE

HBV Eradication
Potential Inhibitors of Success

7. Potential Program Interruptions

- ☆ Not a serious problem
- ☆ HBV not highly infectious
- ☆ HBV will have difficulty reestablishing itself
- ☆ Still provides herd immunity
- ☆ Vaccinated individuals benefit anyway

HBV Eradication
Potential Inhibitors of Success

8. Lack of Political Will is the real problem

Political WILL!

POLITICAL WILL!!

POLITICAL WILL!!!

HBV Eradication
Potential Inhibitors of Success

8a. Lack of Political Will - Reasons

- ☆ AIDS Epidemic
- ☆ Lack of Funds
- ☆ Lack of knowledge
- ☆ Lack of publicity
- ☆ Lack of leadership

HBV Eradication
Potential Inhibitors of Success

8c. Lack of Political Will - Detractors

- ☆ Low Endemnicity Countries
- ☆ Poorest countries
- ☆ Misguided Anti-vaccine activists

HBV Eradication

Easier than Smallpox, Polio or Measles

- ☆ HBV less infectious
- ☆ Most infections won’t transmit
- ☆ Program doesn’t depend on disease surveillance
- ☆ Booster doses not required
- ☆ Not dependent on cold chain
- ☆ Program interruption less damaging

HBV Eradication
Easier than Smallpox, Polio or Measles - 2

But –

- ☆ May take longer
- ☆ Proof will be difficult

HBV Eradication Conclusion - 1

- ✯ Requires different strategies than other viruses and than the current EPI program now uses.
- ✯ Relatively easy where infants are accessible at birth – much of the world including Asia where perinatal transmission is highest.
- ✯ Highly beneficial even when initiation delayed til first EPI encounter.
- ✯ Adolescent and adult programs not needed for eradication.
- ✯ Low infectivity of HBV means virus will be slow to spread in the event of program lapses and failures.
- ✯ Schedule probably could be reduced to two doses

HBV Eradication Conclusion - 2

- ☆ **Will eliminate 75% to 80% of HCC plus a high proportion of all chronic liver disease for all time !**

HBV Eradication Conclusion - 3

- ☆ Doubters and detractors will never disappear
- ☆ Be positive!
- ☆ Think big
- ☆ Commit to the future
- ☆ If we won’t eliminate HBV does any cancer vaccine stand a chance?

A Special Message to Pediatricians

- ☆ The help of pediatricians is particularly needed
- ☆ Reassure public about vaccine safety
- ☆ Emphasize perinatal programs; vaccination of adolescents is secondary
- ☆ Support global immunization

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