

Global Hepatitis B Control Through Primary Prevention: Progress and Challenges

**Mark A. Kane MD, MPH
Mercer Island, WA**

Topics

- **Brief review of Hep B immunization history and progress**
- **GAVI and new alliances for health**
- **Birth Dose and remaining challenges**
- **Immunization of adolescents and adults**
- **Injection safety**
- **Role of CDC Hepatitis Division**
- **Recommendations and ways forward**

Take Home Messages

- Hepatitis B immunization has been a huge success globally, and a model for introduction of new and underutilized vaccines
- Development of cohesive Public Private Partnerships that provide new global financing mechanisms leading to large increases in funding
 - GAVI and IFFIM
- The price of monovalent Hep B vaccine has fallen to about \$0.21/pediatric dose but much is used in more expensive combination vaccines
 - The developing world now makes large quantities of Hep B vaccine and combo's
- The CDC Hepatitis Division has played a key role in supporting global Hep B control efforts and should be funded to continue this effort

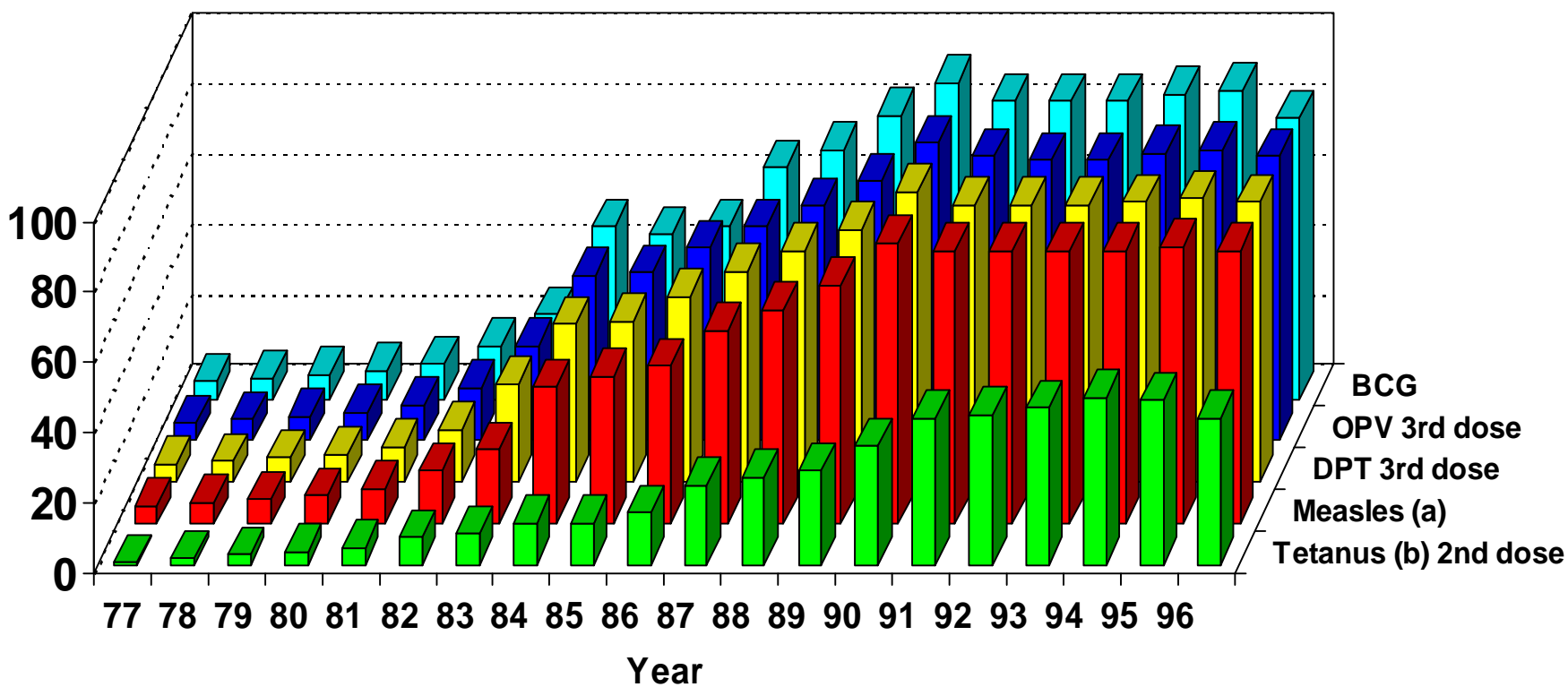
Take Home Messages

- Major challenges remain:
- Only 50% of countries deliver a birth dose of HepB vaccine and GAVI doesn't pay for this
- Programs to immunize home births next step
- Country financial sustainability not achieved
- Develop new infrastructure to reach adolescents and adults with new vaccines (HPV and future) and booster doses
- Extend the safety of injections and other medical procedures beyond immunization

Critical steps in Hep B control

- **Discovery of Australia Antigen and relationship with “serum hepatitis”**
- **Demonstration that serum from hep B patients could make a “plasma derived” vaccine**
- **Demonstration that hep B was the cause of most liver cancer**
- **Mechanism of perinatal transmission and prevention with HBIG and Hep B vaccine**
- **Hep B vaccine production in developing world**
- **Development of DNA recombinant vaccine**
- **Introduction of routine Hep B immunization into the EPI**

Expanded Programme on Immunization coverage



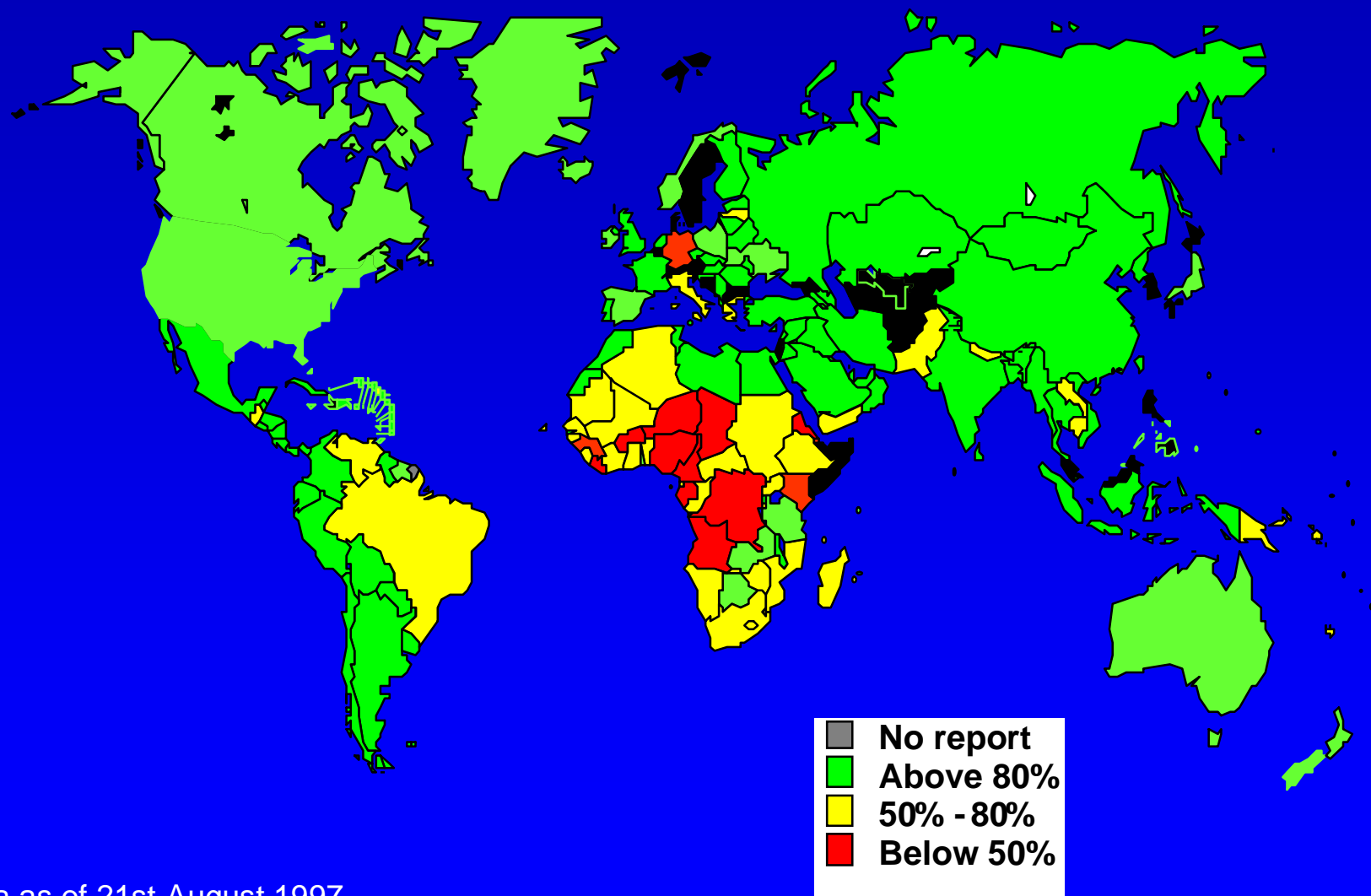
■ Tetanus (b) 2nd dose
 ■ Measles (a)
 ■ DPT 3rd dose
 ■ OPV 3rd dose
 ■ BCG



A brief history of the Expanded Programme on Immunization (EPI)

- **Until EPI, Vaccines primarily benefited children in industrial countries**
- **5% routine global coverage**
- **Smallpox eradication**
- **Since 1990 vaccines routinely reach ~ 75% of world's children and 90%+ in campaigns**
- **“Wedge” that expanded to primary health centers**
- **Greatest public health achievement in history?**
- **Need to extend this to new vaccines**

Global reported immunization coverage with three doses of DTP in infants, 1996



Data as of 21st August 1997

The designation employed and the presentation of material on this map do not imply the expression of any opinion whatsoever on the part of the secretariat of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

A long decade's journey into night (almost)

- **1980's UCI Common Agenda**
- **1990's Fragmented Agenda**
 - polio or routine or new vaccines or health reform: competitive zero sum game
- **System decay**
 - decreased donor support and interest; aging cold chain; little training and HR development; falling coverage; inability to integrate new vaccines
- **Paradigm shift**
 - child survival to health reform

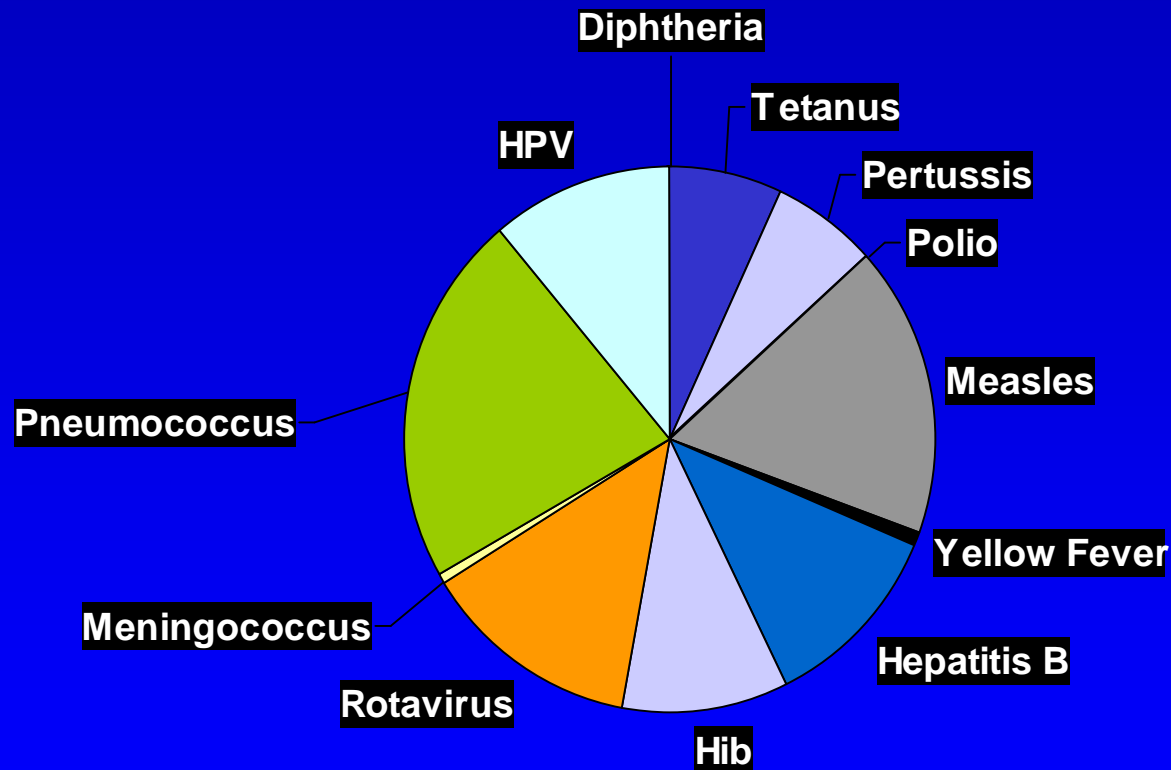
Cancer caused by infectious agents worldwide

AGENT	SITE	# CA	%CA
H Pylori	Stomach	592,000	5.5%
HPV	Cervix, other	561,200	5.2%
HBV, HCV	Liver	535,000	4.9%
HHV-8	Kaposi's sarcoma	54,000	0.9%
Schistosoma	Bladder	9,00	0.1%
HTLV-1	Leukemia	2,700	
Total		1,900,000	18%

DM Parkin (2006) Int J Cancer

D

Deaths from Vaccine-Preventable Diseases



**4.5 Million Deaths to Be Prevented (2000 estimates)
Almost half by vaccines introduced in the last few years!**

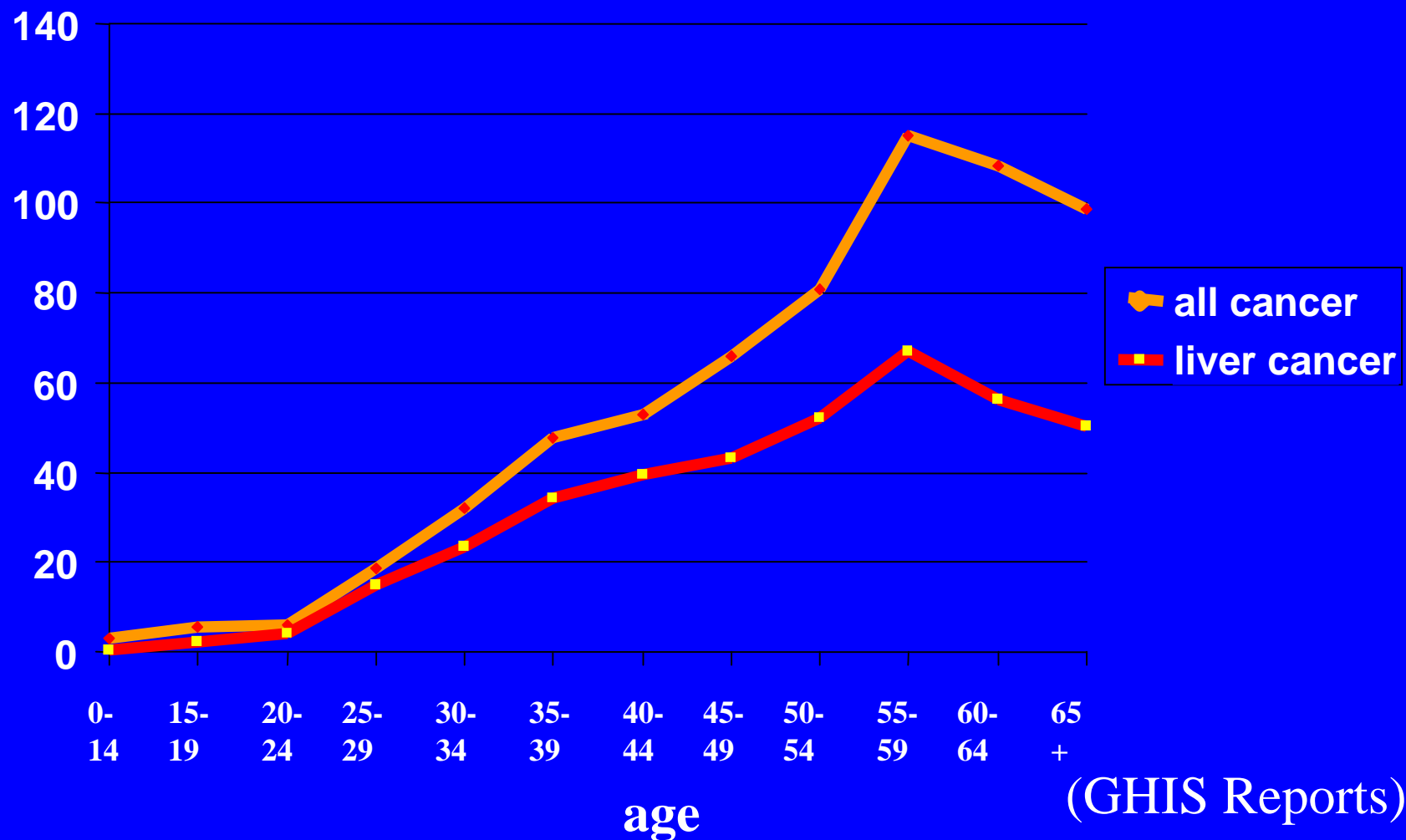
Un homme enceinte s'accouche dans son tombeau*



*A pregnant man delivers in his grave

Cancer rates, Gambian males 1986-96

incidence
per 100,000





Association Between HBV Infection and HCC and Cirrhosis

HBsAg status	Total deaths	HCC deaths	Cirrhosis deaths	Incidence HCC*
HBsAg-positive (n=3,454)	105 (3%)	40 (38%)	17 (16%)	1154
HBsAg-negative (n=19,253)	102 (5%)	1 (1%)	2 (2%)	5

Source: Beasley Lancet 1981

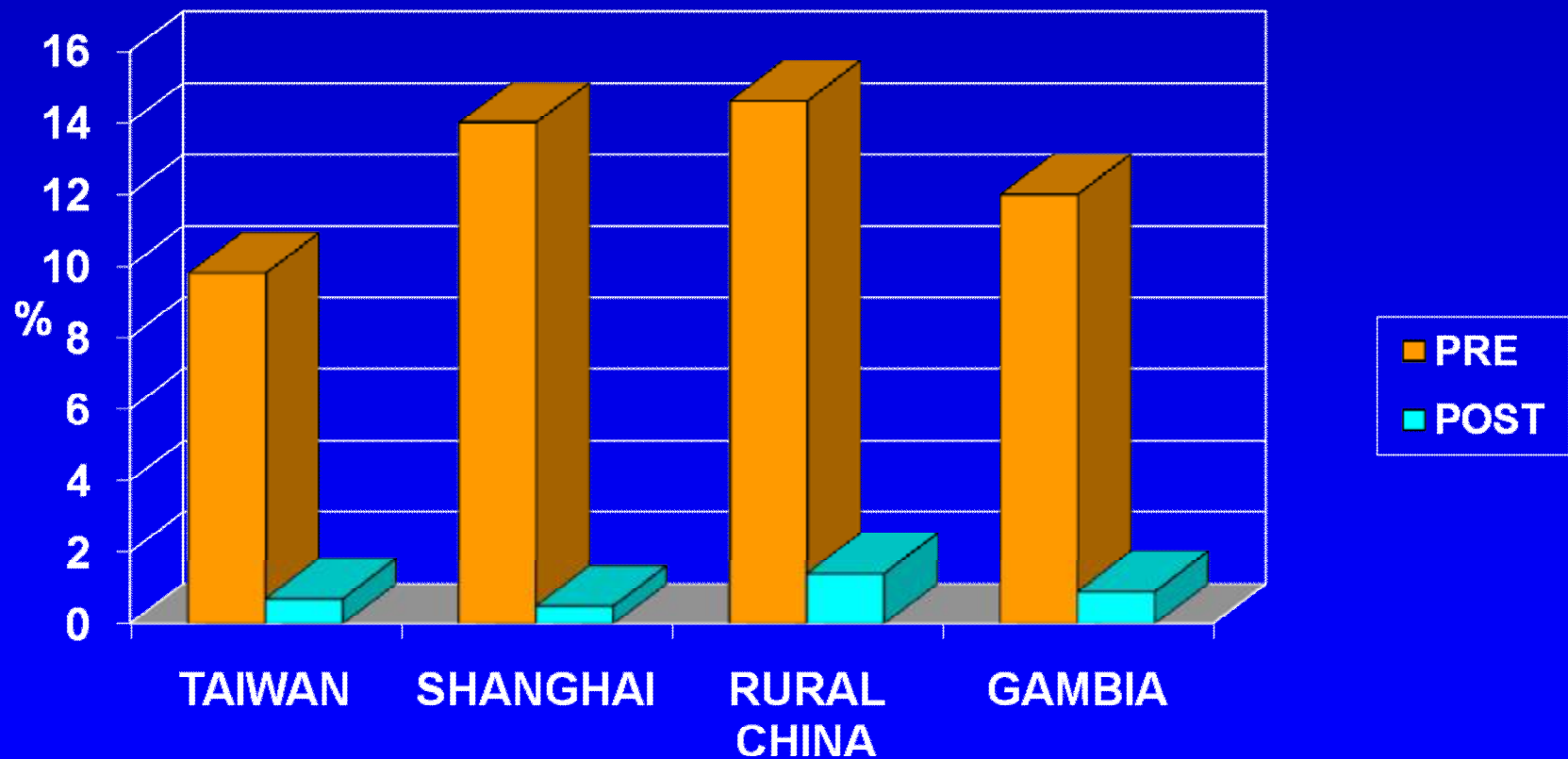
Introduction of Hep B vaccine

- Our initial strategy to immunize “high risk” groups failed (except for HCW’s)
- Depended on knowledge and action of 10’s of thousands of individuals
- No guaranteed funding
- Stigma of some risk groups
- In general “high risk” strategies are less effective (flu, adult pneumo)
- Realization that only “routine” funded immunization would have impact on HB disease
- Initial cost prohibited consideration of public health use in developing world

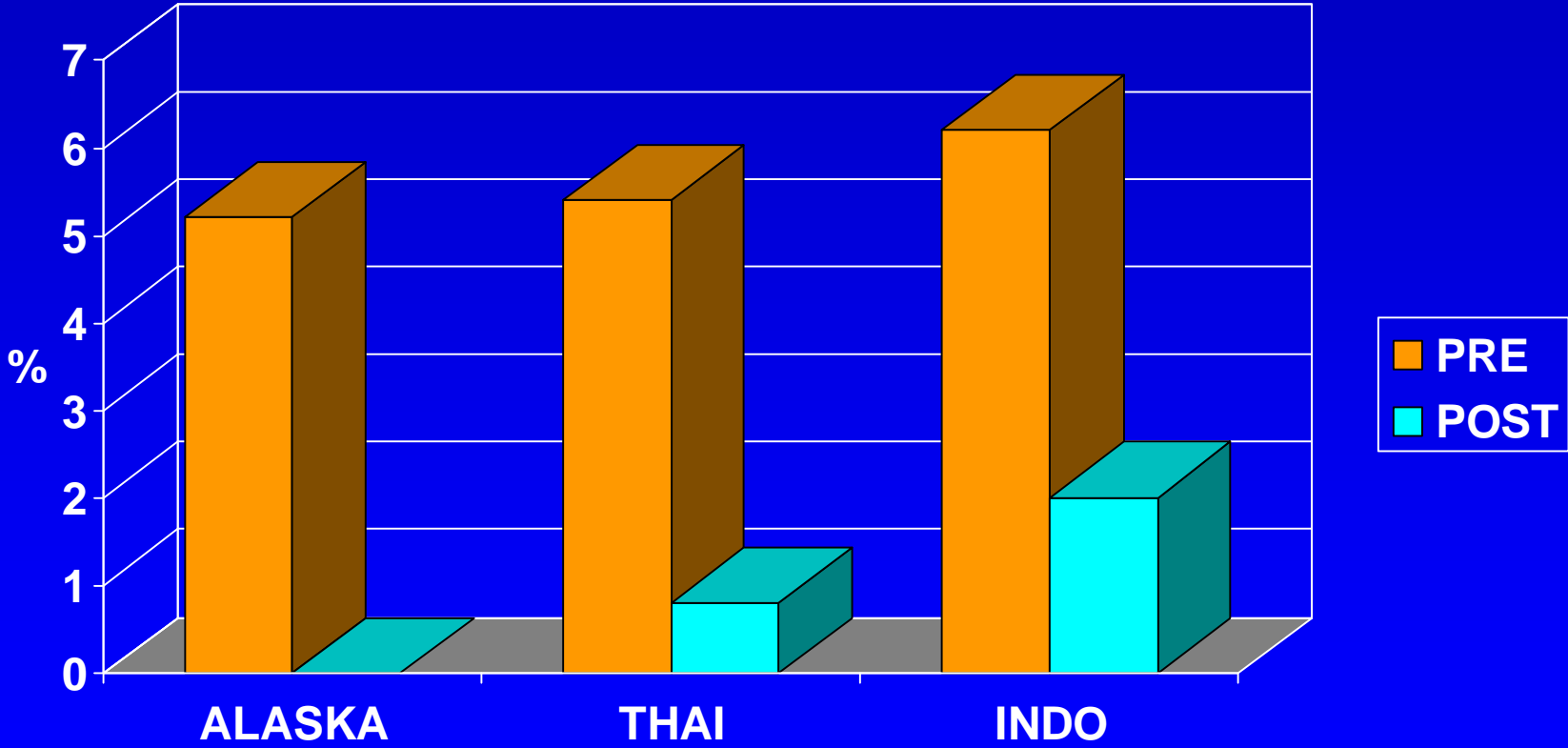
Hepatitis B Vaccine Timeline

- 1965: Hepatitis B virus discovered
- 1982: Hepatitis B vaccine first became available
- 1992: WHA resolution 45.17 called for member states, "...to integrate cost-effective new vaccines, such as hepatitis B vaccine, into national immunization programs in countries where it is feasible..."
- 1992: WHO recommended that all countries integrate hepatitis B (HepB) vaccine into national immunization programs by 1997
- Early 2000's: GAVI milestone, that by 2007, all countries with adequately performing immunization systems should have integrated hepatitis B vaccine into their national programmes.

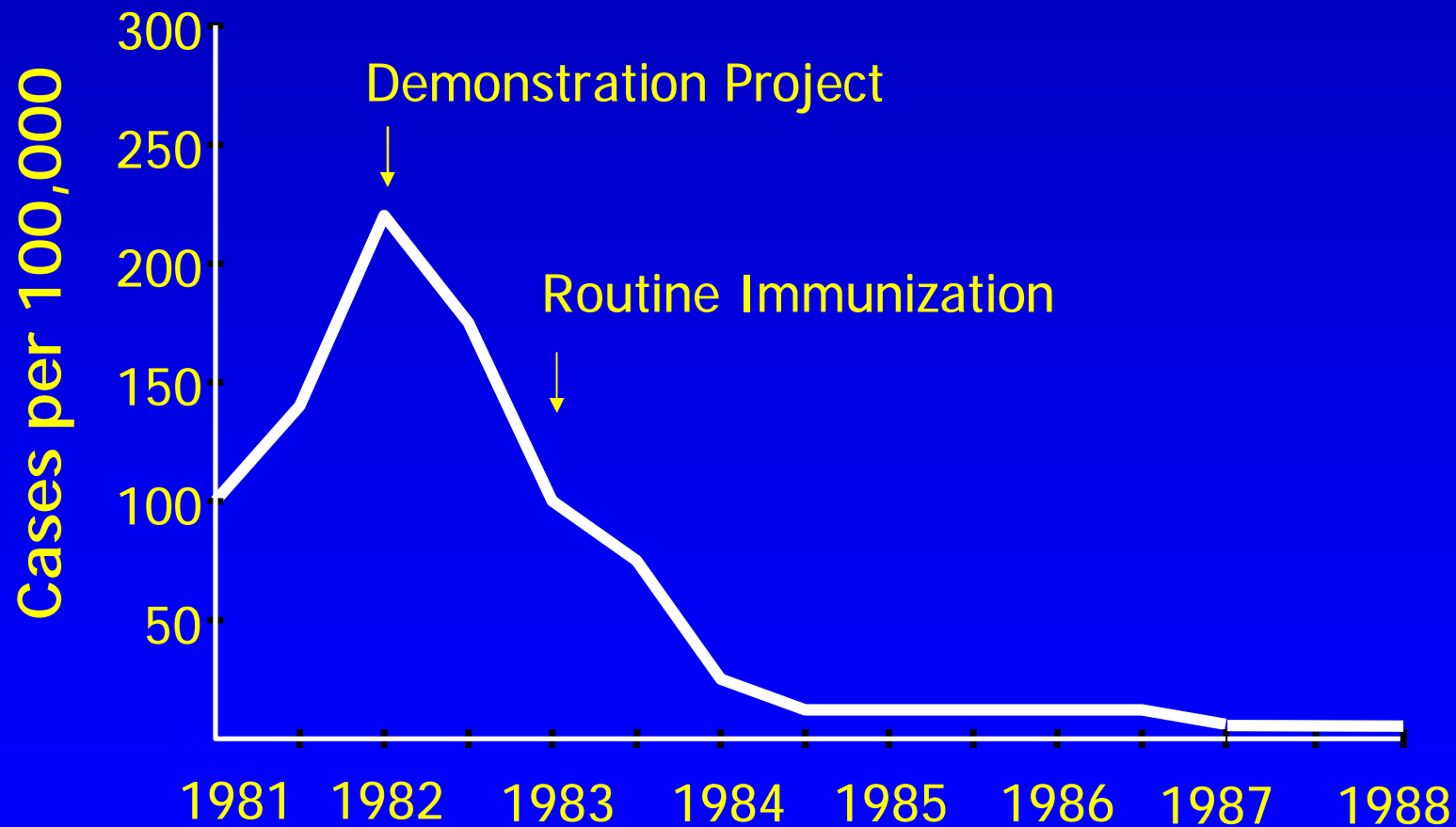
Hepatitis B carrier prevalence before and after immunization



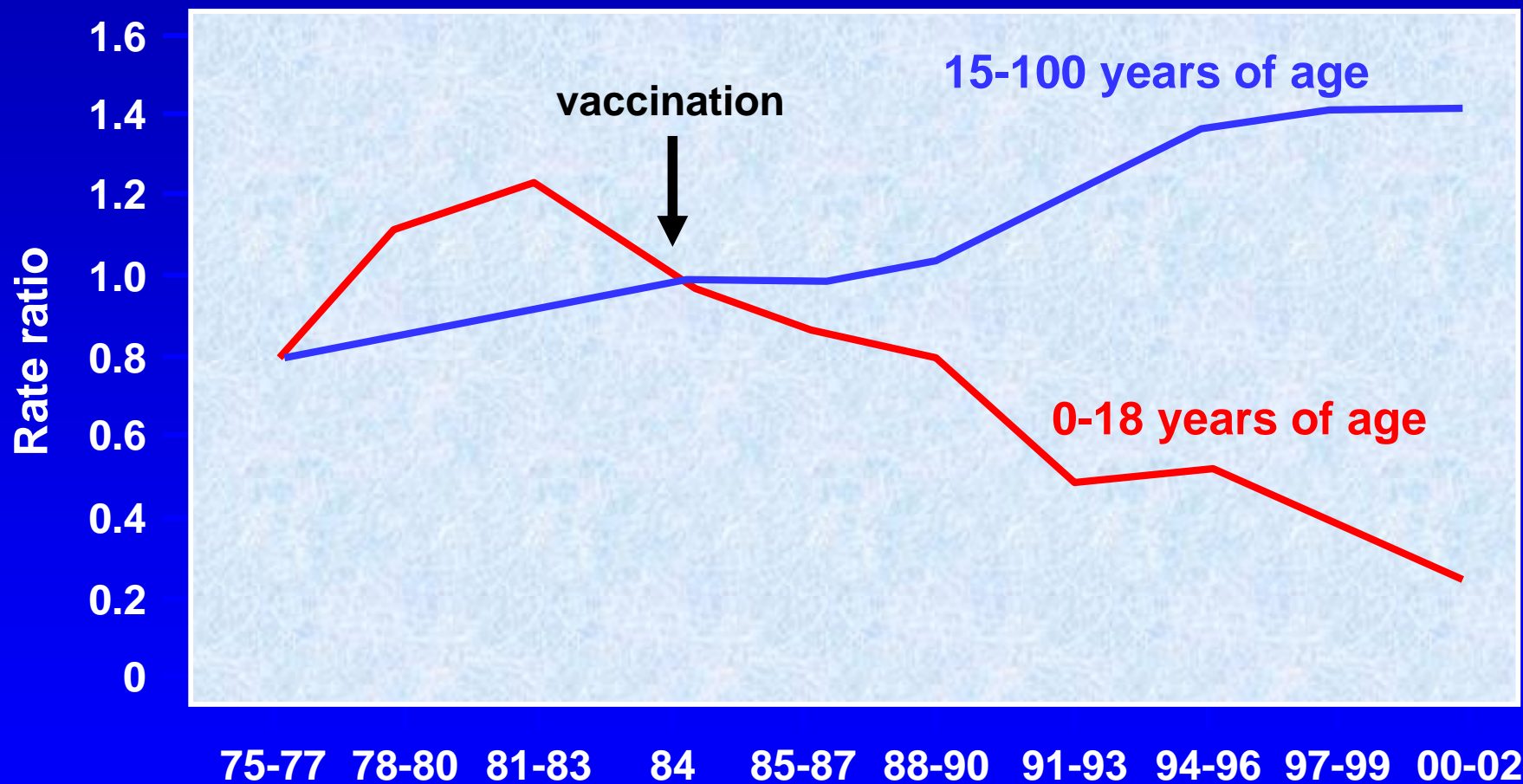
Hepatitis B carrier prevalence before and after immunization



Effect of Hepatitis B Vaccination on the Incidence of Acute Hepatitis B Alaska, United States



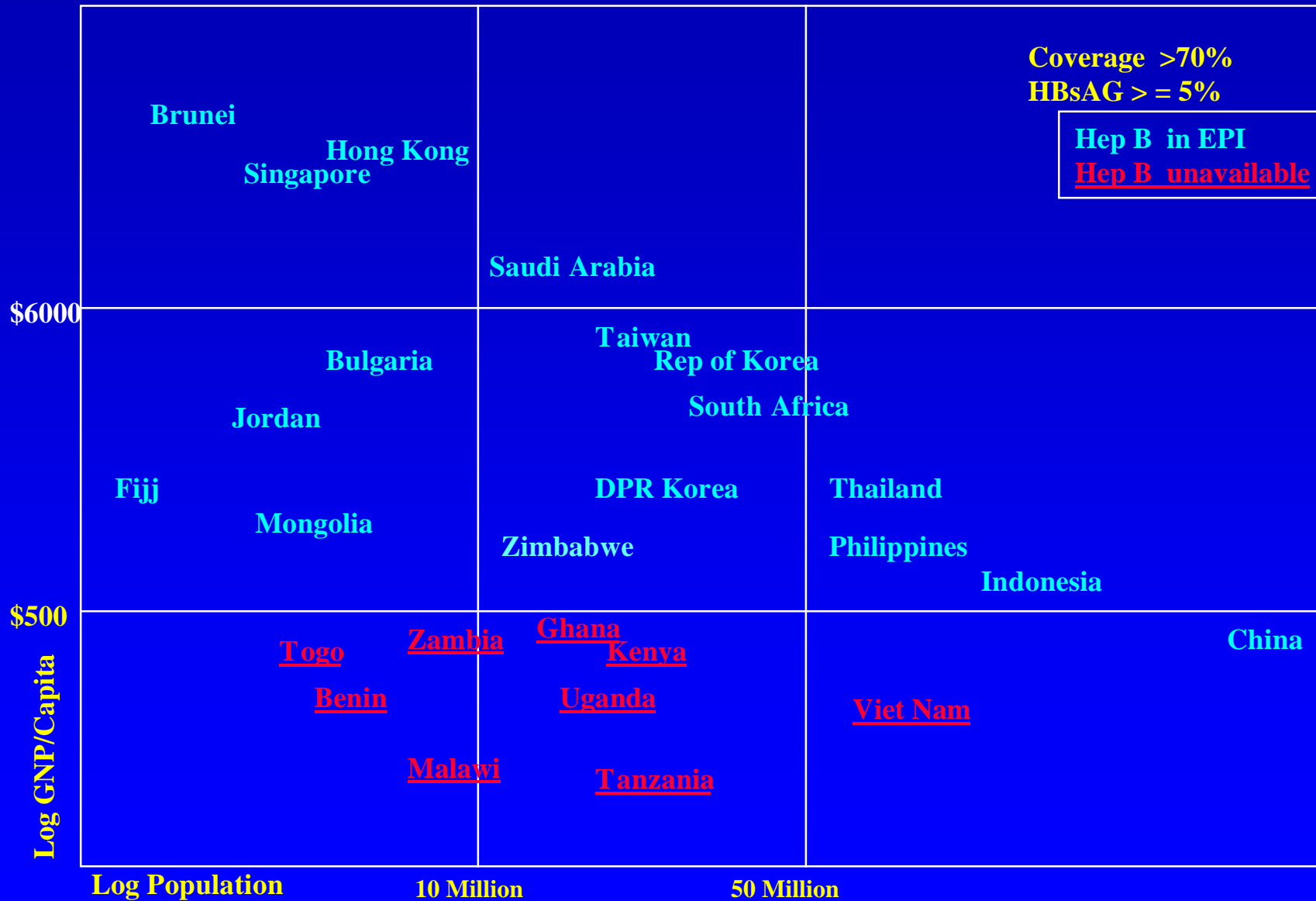
Hepatocellular Carcinoma Mortality Rate in Vaccinated and Unvaccinated Cohorts



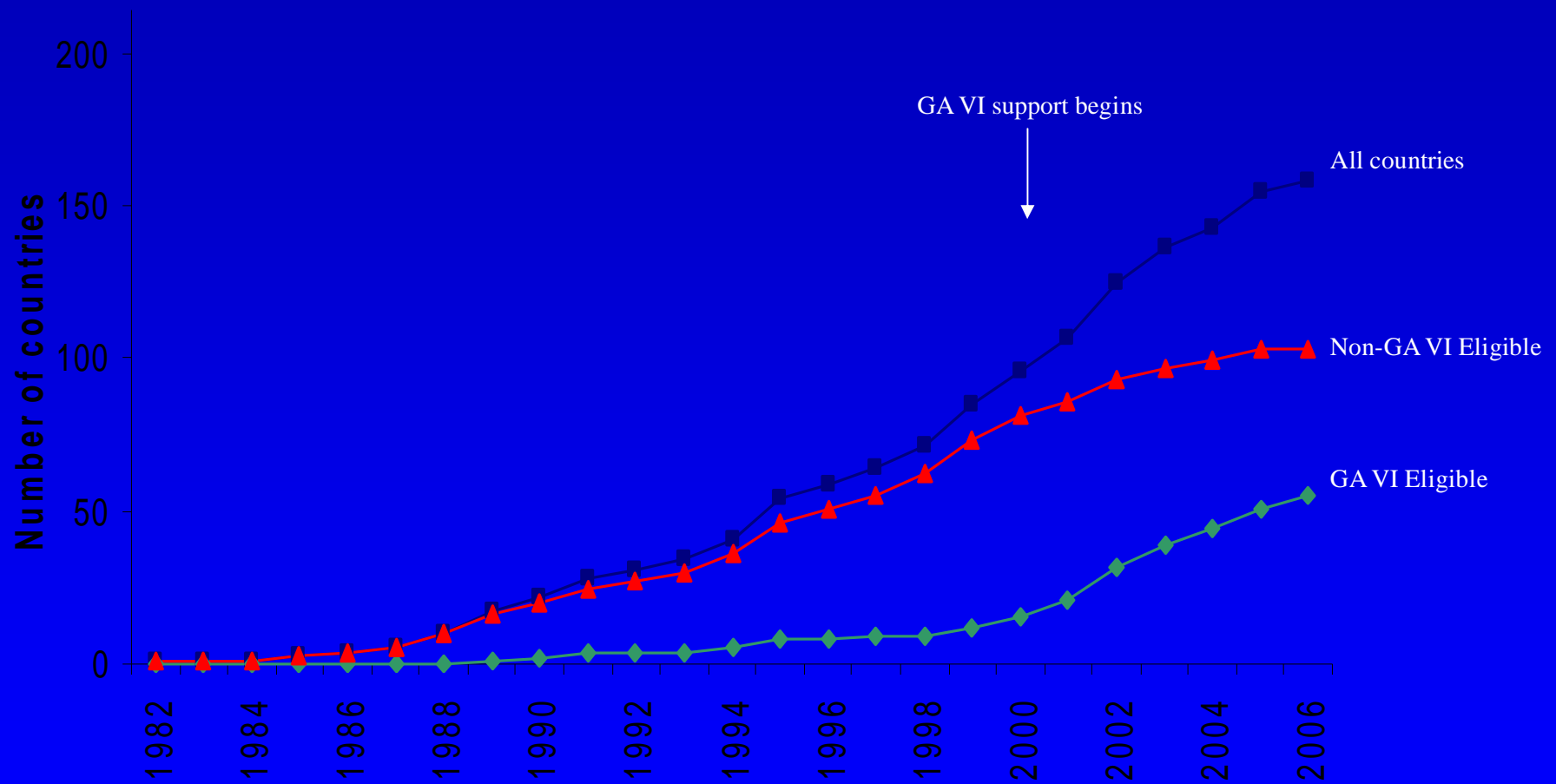
Courtesy of Chang, MH

Taiwan Province

Impact of income on programme implementation: Hepatitis B



Number of Countries Having Introduced HepB Vaccine Into Routine Infant Immunization System, 1982-2006



Source: IVB Data base, 2006 Provisional

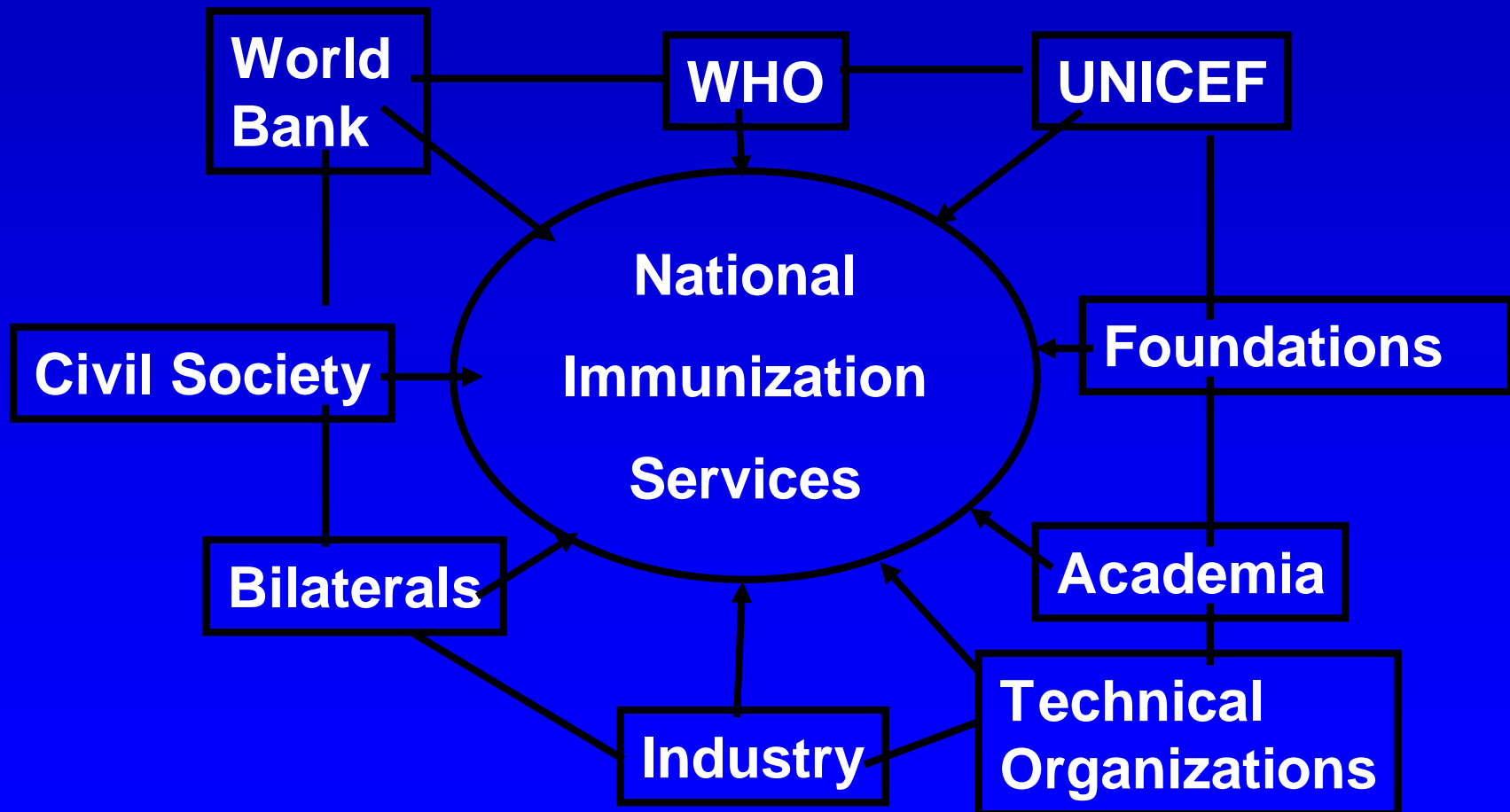
193 WHO Member States.

Excluding 4 countries where HepB administered for adolescence and 4 countries having introduced partially

The Three Gaps

- **ACCESS**
 - 30 million children un-immunized per year
 - stagnant or falling coverage in some regions
- **EQUITY**
 - many immunized children in developing countries lack important newer vaccines (hep B, Hib) and receive unsafe injections
- **INVESTMENT**
 - too little investment in vaccines which primarily impact developing countries

The Global Immunization Environment



The GAVI Alliance and Fund

- Major source of funding for 72 poorest countries
- Great improvement in immunization coverage
- Most countries introduced Hepatitis B vaccine and safe injections, some Hib and YF
- Developing country manufacturers now making DTP-HB and DTP-HB Hib and AD syringes
- China
- Now has \$4-5 billion committed over next 10 years (Gates Foundation, Governments, International Finance Facility for Immunization, Advanced Purchase Commitments)
- Unsure how many new vaccines it can introduce
- Needs to balance investment in new vaccines with infrastructure development and “health system strengthening”

DTP3 Coverage in GAVI countries in Sub Saharian Region

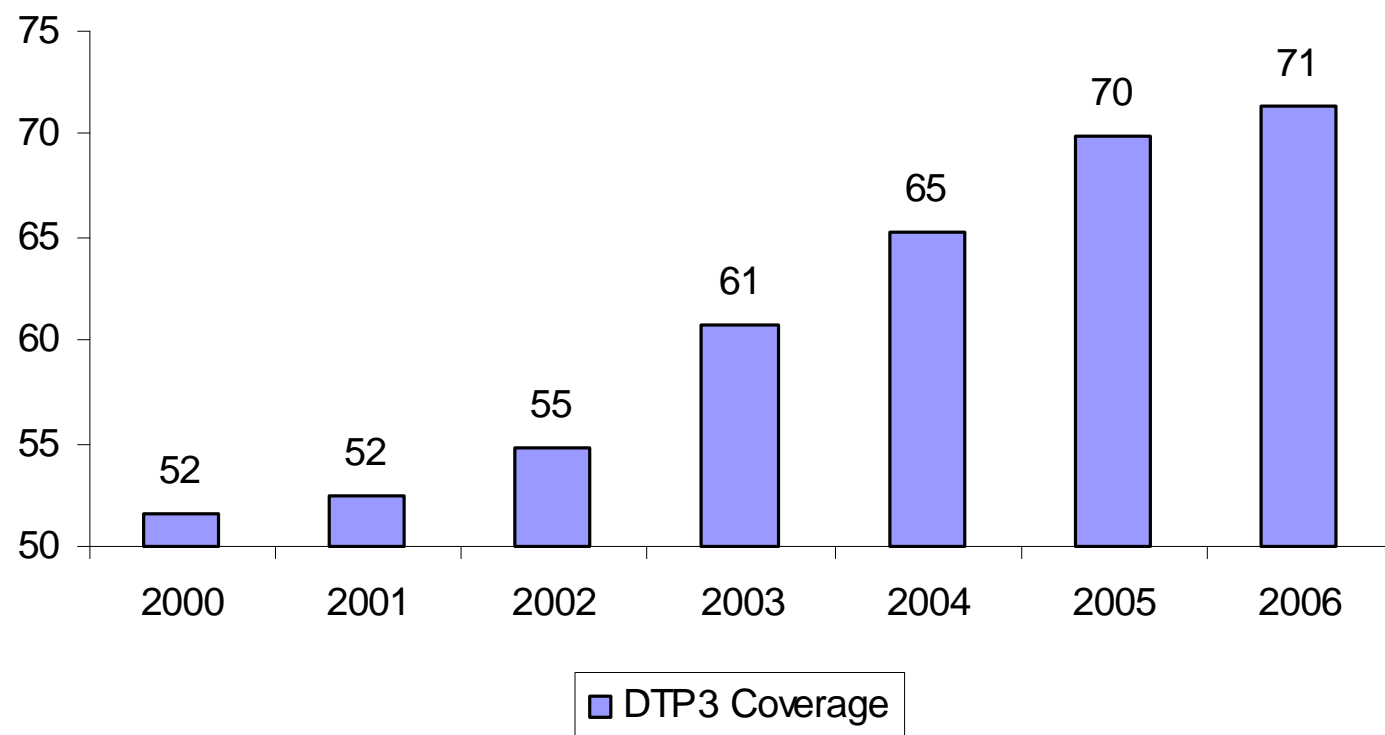


Fig DTP3 Coverage in GAVI Eligible SubSaharan African Countries 2000-2006

Immunization Coverage in GAVI Eligible countries

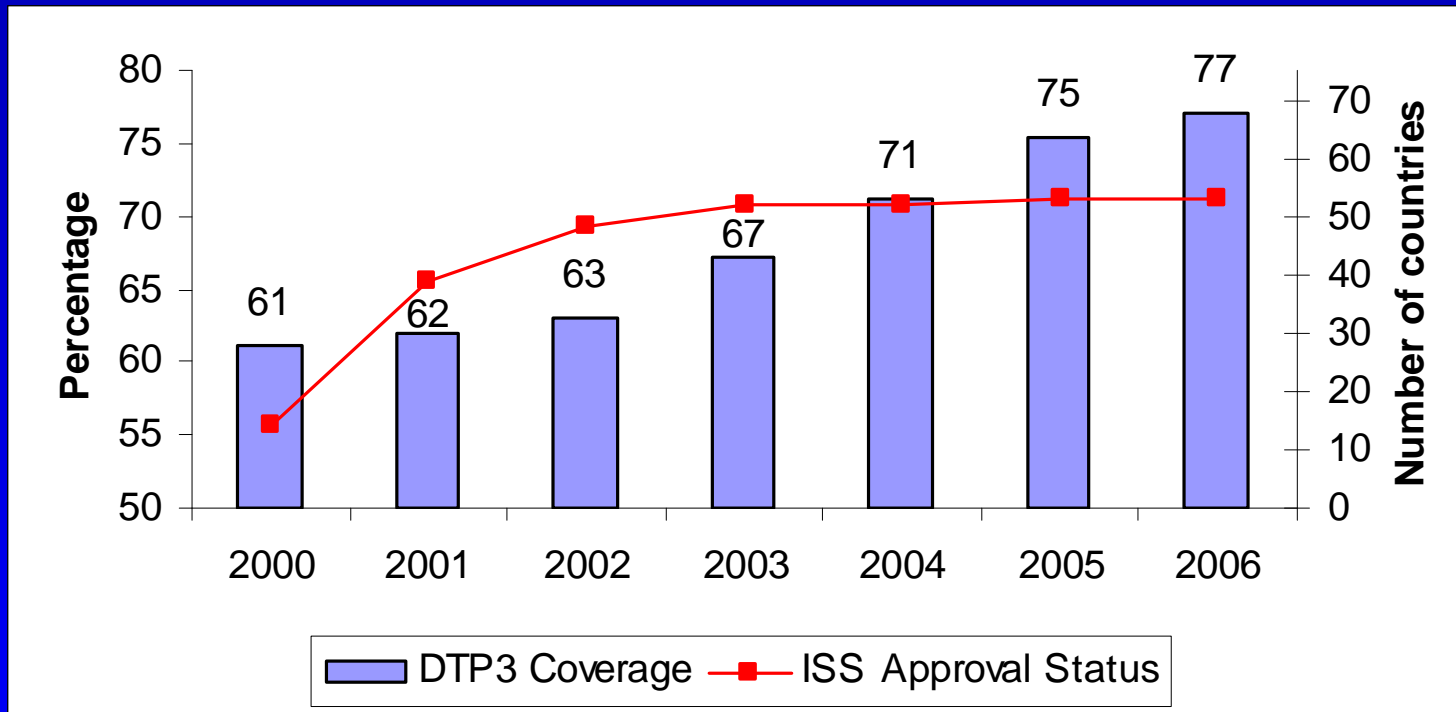
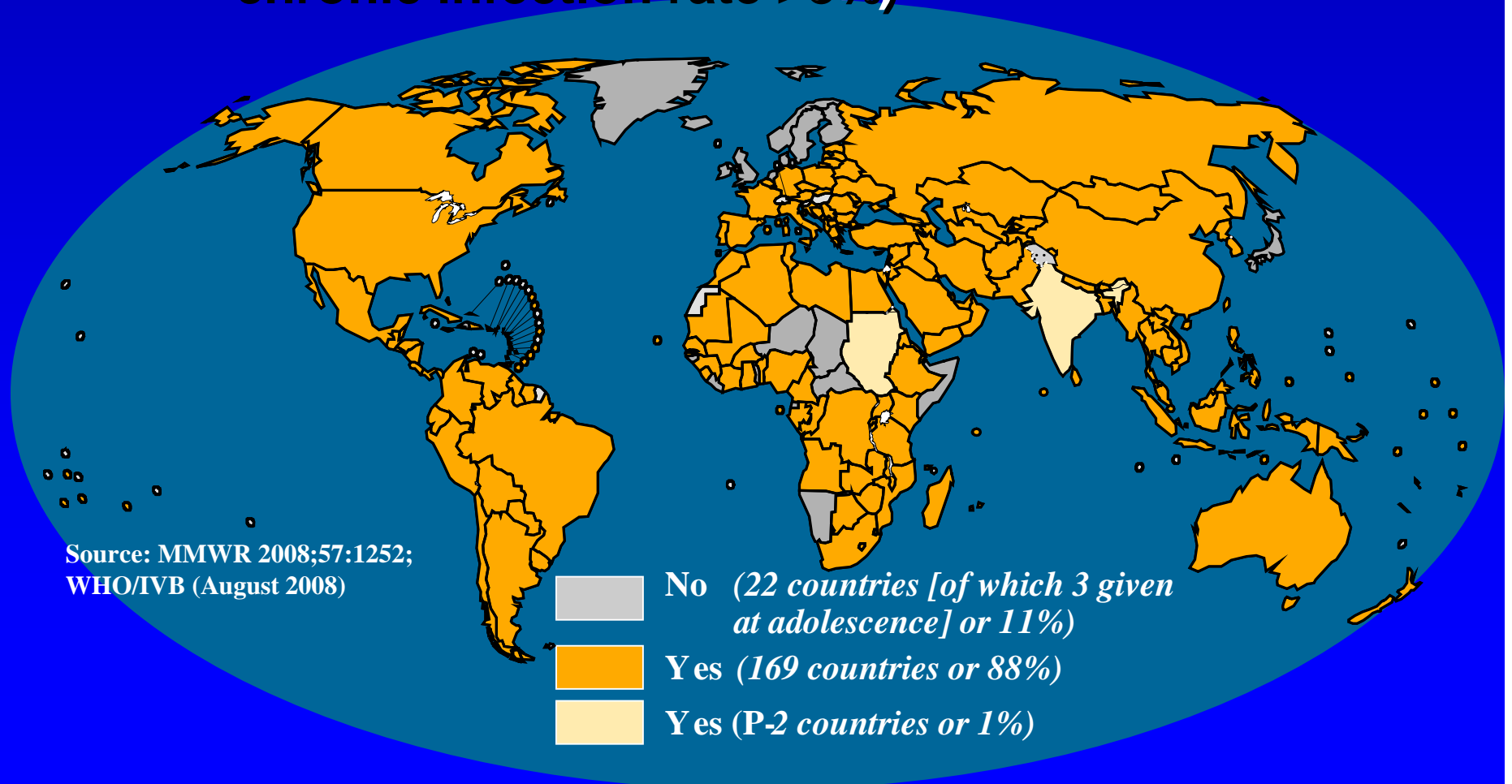


Fig DTP3 Coverage and Cumulative ISS Approvals in GAVI eligible countries excluding China, India, and Indonesia

Infant Hep B Immunization, 2006

- 84% of countries have hep B programs
- 65% of infants born in 2007 vaccinated
 - 27% got birth dose (36% in countries with chronic infection rate >8%)



Birth dose issues

- Only 50% of countries offer birth dose but coverage varies dramatically
- Perinatal transmission has different patterns in Asia and elsewhere
- Home vs institutional births
 - Delivery at institutional births not difficult but contraindications and administrative issues
 - Coverage of home births very low
 - Qualified vaccinators and cold chain issues
 - Extensive research on out of cold chain storage
- Monovalent cheap but GAVI doesn't provide it
- Next major step in Global Hep B control

Percent of Countries with HepB Vaccine in Schedule that Provide Birth Dose

Region	No. Countries	No. countries with HepB in schedule	No. countries providing birth dose (%)
AFR	46	31	5 (16)
AMR	35	33	12 (36)
EMR	21	17	10 (59)
EUR	52	39	27 (69)
SEAR	11	9	2 (22)
WPR	27	25	22 (88)
Global	192	154	78 (51)

Excludes 4 countries with special schedule for birth dose

Differences in Infant and Adolescent/Adult Immunization

Characteristic	Infant Immunization	Adolescent/Adult Immunization
Delivery Infrastructure	Highly developed	Poorly developed
Funding	Usually Govt funded	Often poorly/not funded
Govt Policy and Recommendations	Strongly recommended	Often no recommendations
Access to care	Frequent	Often only for acute care
Public Knowledge	High	Low

Adolescent and adult immunization

- **Few developing countries immunize adolescents or adults except for some booster doses**
- **Health care worker Hep B immunization is recommended in many countries**
- **Data rarely collected on adolescent/adult immunization**
- **Cost effectiveness of adolescent/adult immunization with Hep B vaccine unclear in developing countries**

Prevention of nosocomial transmission

- ~50% of 12 Billion injections /yr unsafe
- Major source of Hep B and C, some HIV
- Injection safety a gift from Immunization to the rest of public health
- AD syringe program of GAVI
- SIGN
- Basic problem lack of understanding of germ theory of disease
- Lack of resources

Recommendations

- Birth dose is the next major challenge for global Hep B control. Research on how to provide it and out of cold chain studies should be supported
- Immunization of adolescents and adults needs to be a priority for the future. C/E of health care worker immunization needs to be studies in the developing world
- WHO regions should follow the lead of WPRO in establishing Certification Commissions to refocus country interest in control of Hep B

Recommendations

- **The CDC Hepatitis Division has played a key role in supporting the global effort in control of Hep B and injection safety and should continue to be funded in this effort**

Thank You