Effectiveness of newborn hepatitis B vaccination programmes

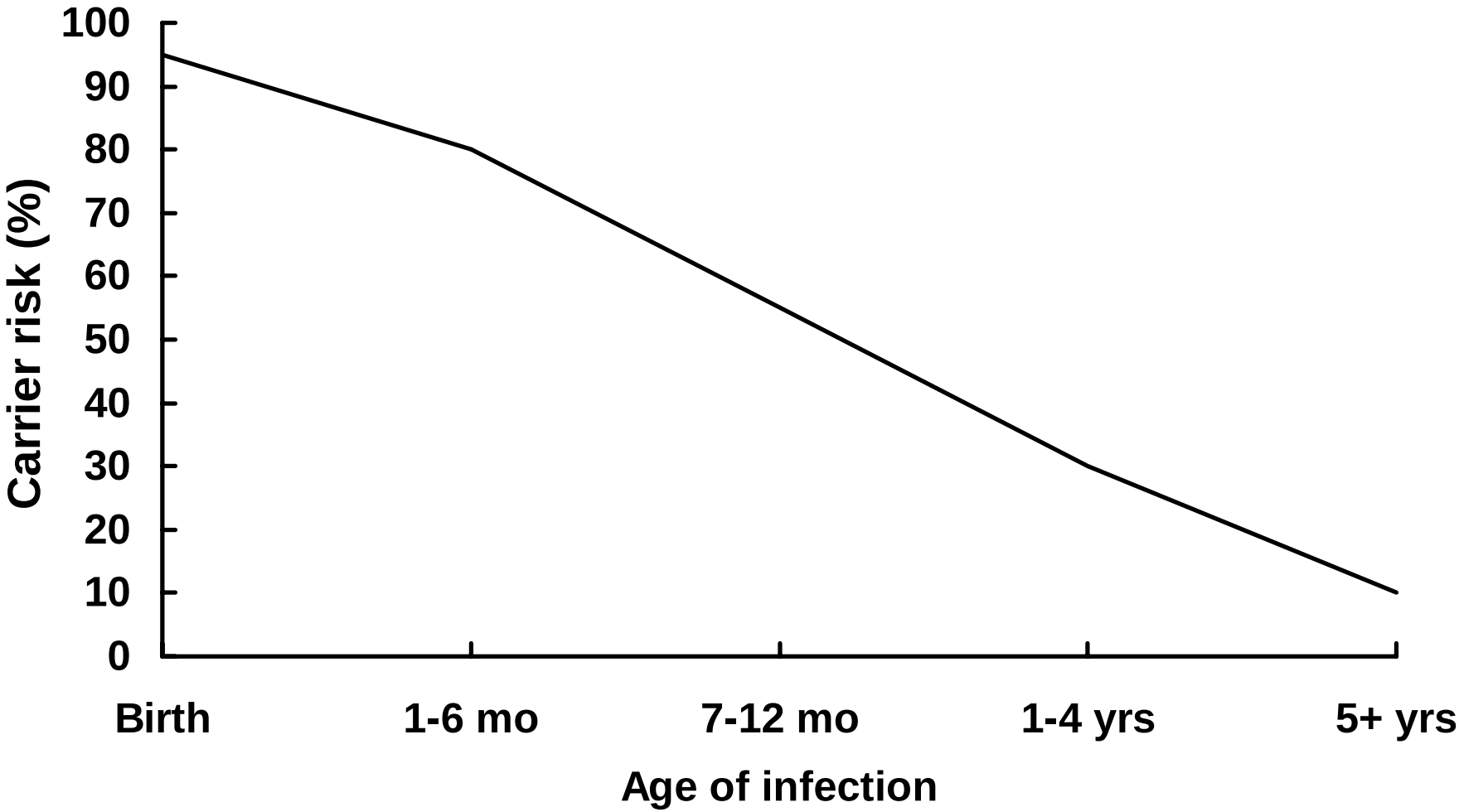
Francis E André
Consultant in Vaccinology
Belgium

Istanbul, March 15, 2006

Hepatitis B Perinatal Transmission

- If mother positive for HBsAg and HBeAg
  - 70%-90% of infants infected
  - 90% of infected infants become chronic carriers
- If positive for HBsAg only
  - 20% of infants infected
  - 90% of infected infants become chronic carriers

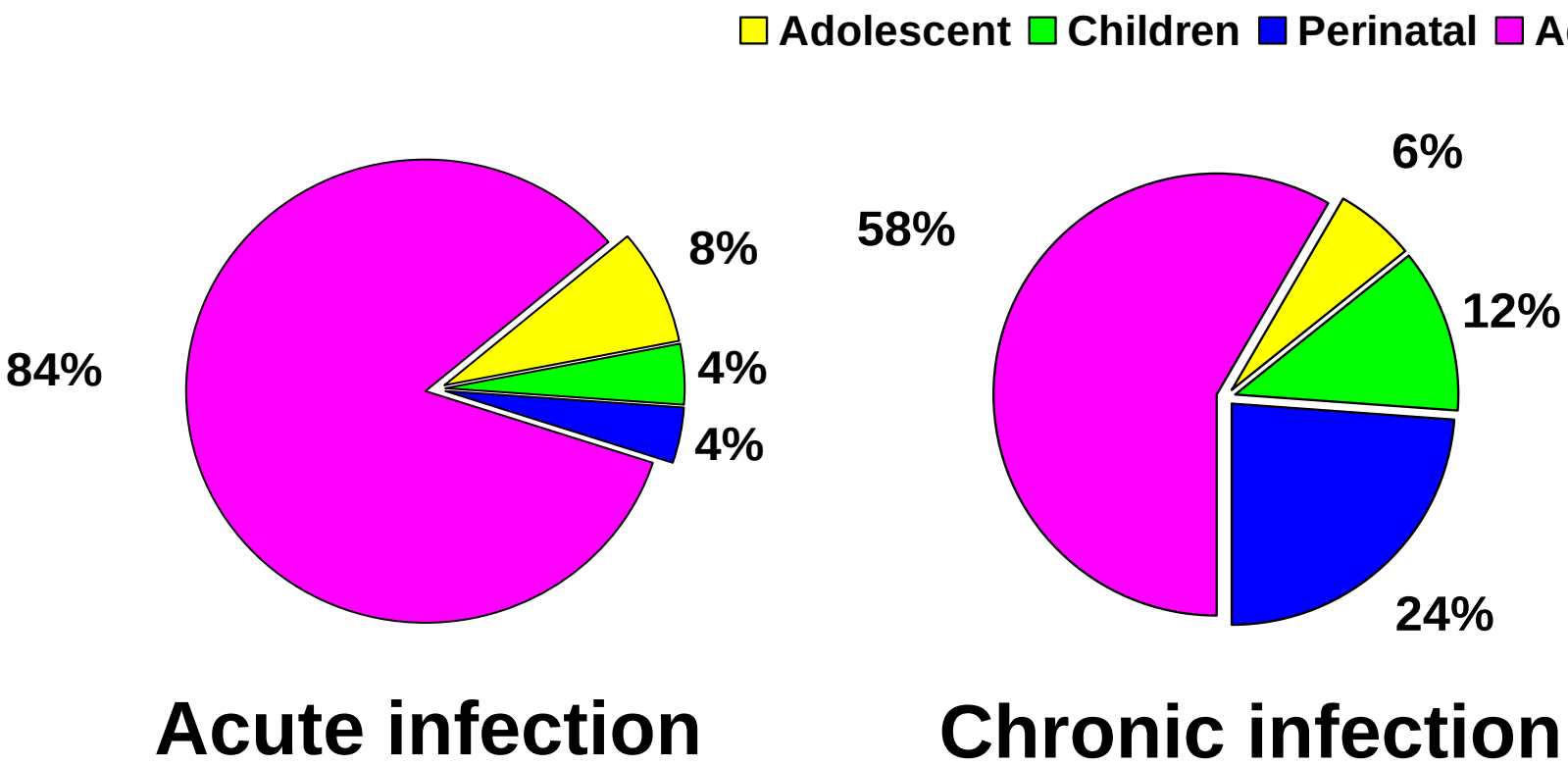
Risk of Chronic HBV Carriage by Age of Infection



Chronic Hepatitis B Virus Infection

- Chronic viremia
- Responsible for most mortality
- Overall risk 10%
- Higher risk with early infection

Age of Infection of Acute and Chronic Hepatitis B Virus Infection



CDC Sentinel Sites. 1989 data.

Strategy to Eliminate Hepatitis B Virus Transmission - United States

- Prevent perinatal HBV transmission
- Routine vaccination of all infants
- Vaccination of children in high-risk groups
- Vaccination of adolescents
- Vaccination of adults in high-risk groups

Prevention of Perinatal Hepatitis B Virus Infection

- Begin treatment within 12 hours of birth
- Hepatitis B vaccine (first dose) and HBIG at different sites
- Complete vaccination series at 6 months of age
- Test for response at 9-15 months of age

Protection* by Age Group and Dose

Dose	Infants**	Teens and Adults***
1	16%-40%	20%-30%
2	80%-95%	75%-80%
3	98%-100%	90%-95%

*** Anti-HBs antibody titer of 10 mIU/mL or higher**

**** Preterm infants less than 2 kg have been shown to respond to vaccination less often**

***** Factors that may lower vaccine response rates are age >40 years, male gender, smoking, obesity, and immune deficiency**

Hepatitis B Vaccine Long-term Efficacy

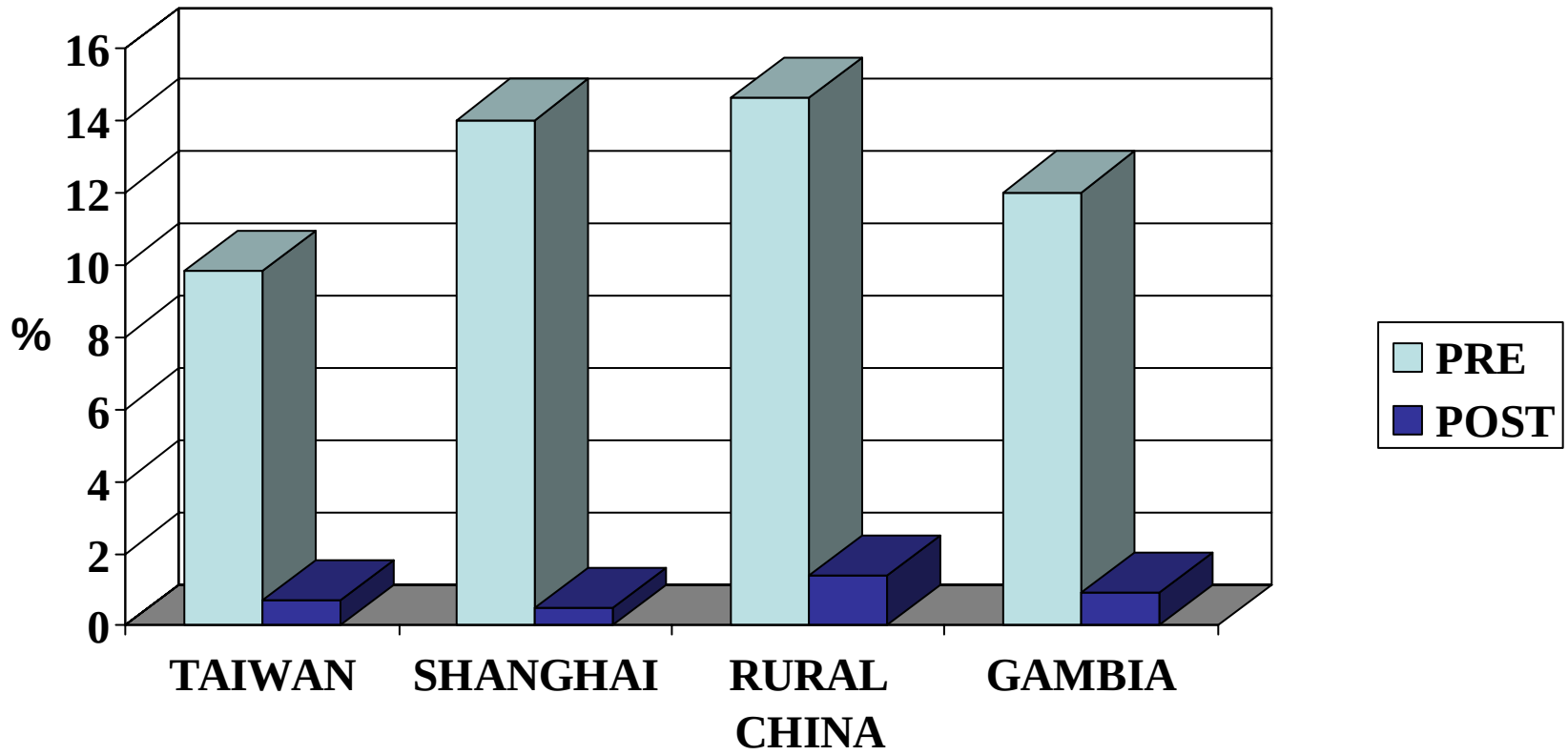
- Immunologic memory established following vaccination
- Exposure to HBV results in anamnestic anti-HBs response
- Chronic infection rarely documented among vaccine responders

Hepatitis B Vaccine

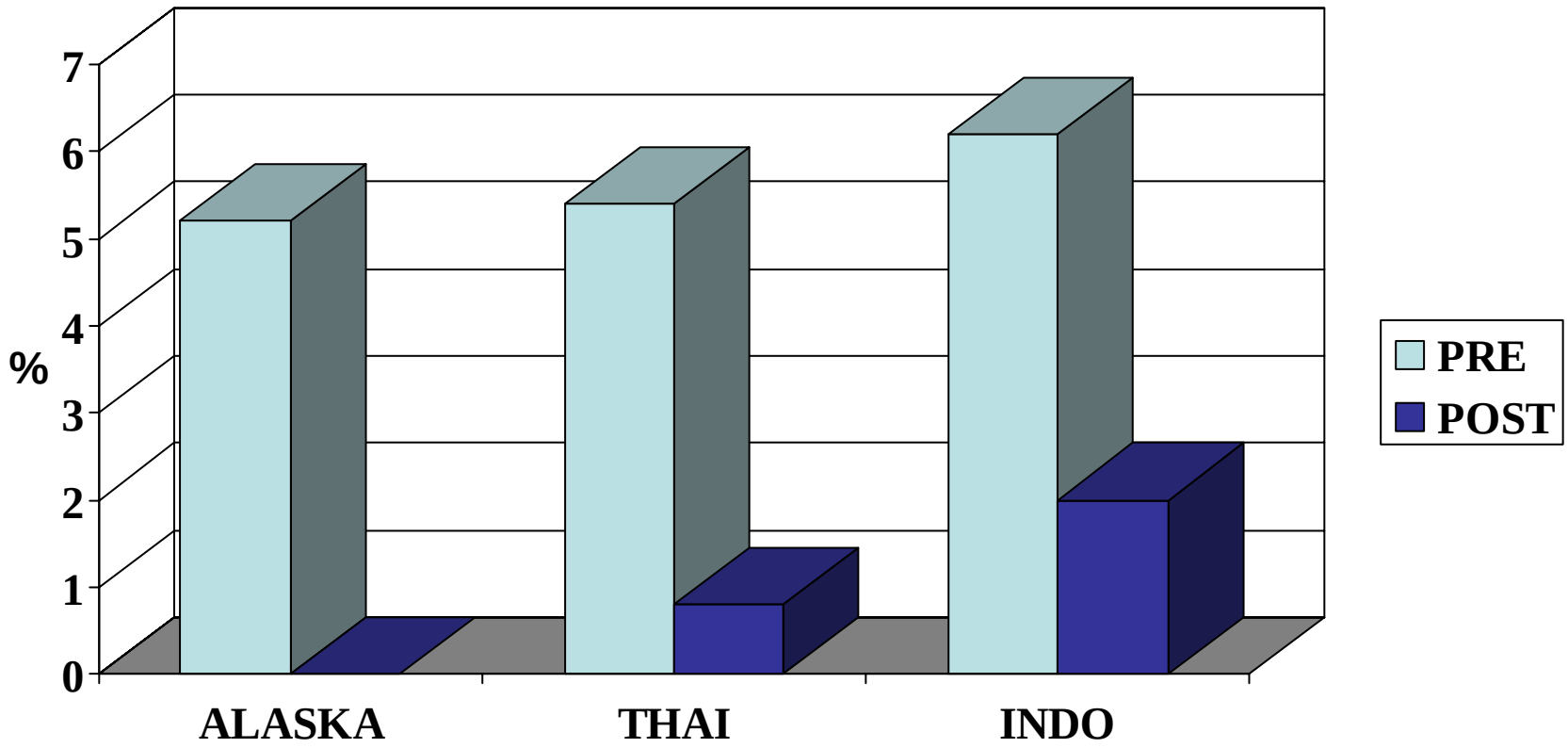
Routine booster doses are NOT routinely recommended for any group

EVIDENCE OF PROTECTIVE EFFICACY OF NEWBORN VACCINATION AGAINST HEPATITIS B

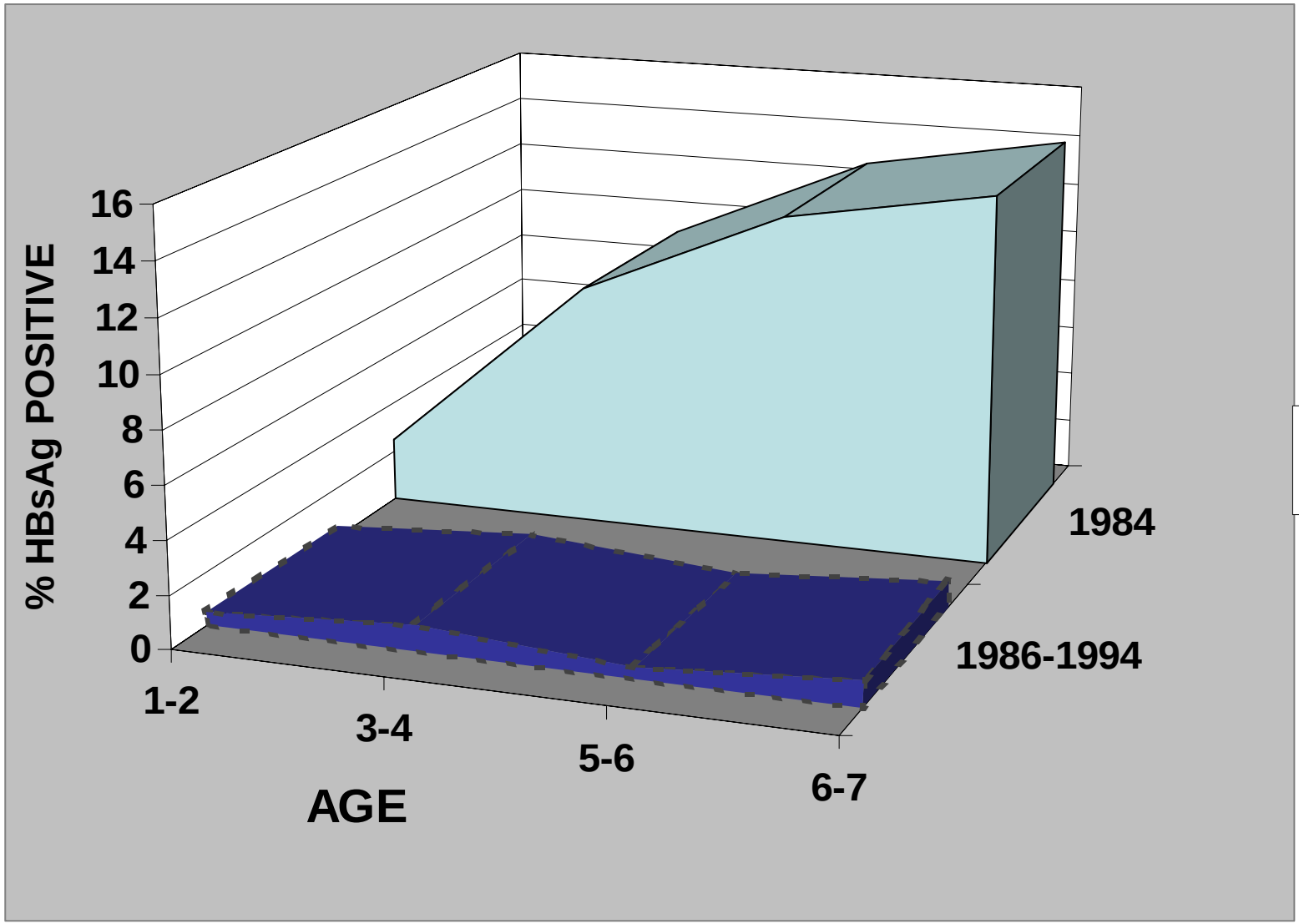
Hepatitis B carrier prevalence before and after immunization



Hepatitis B carrier prevalence before and after immunization



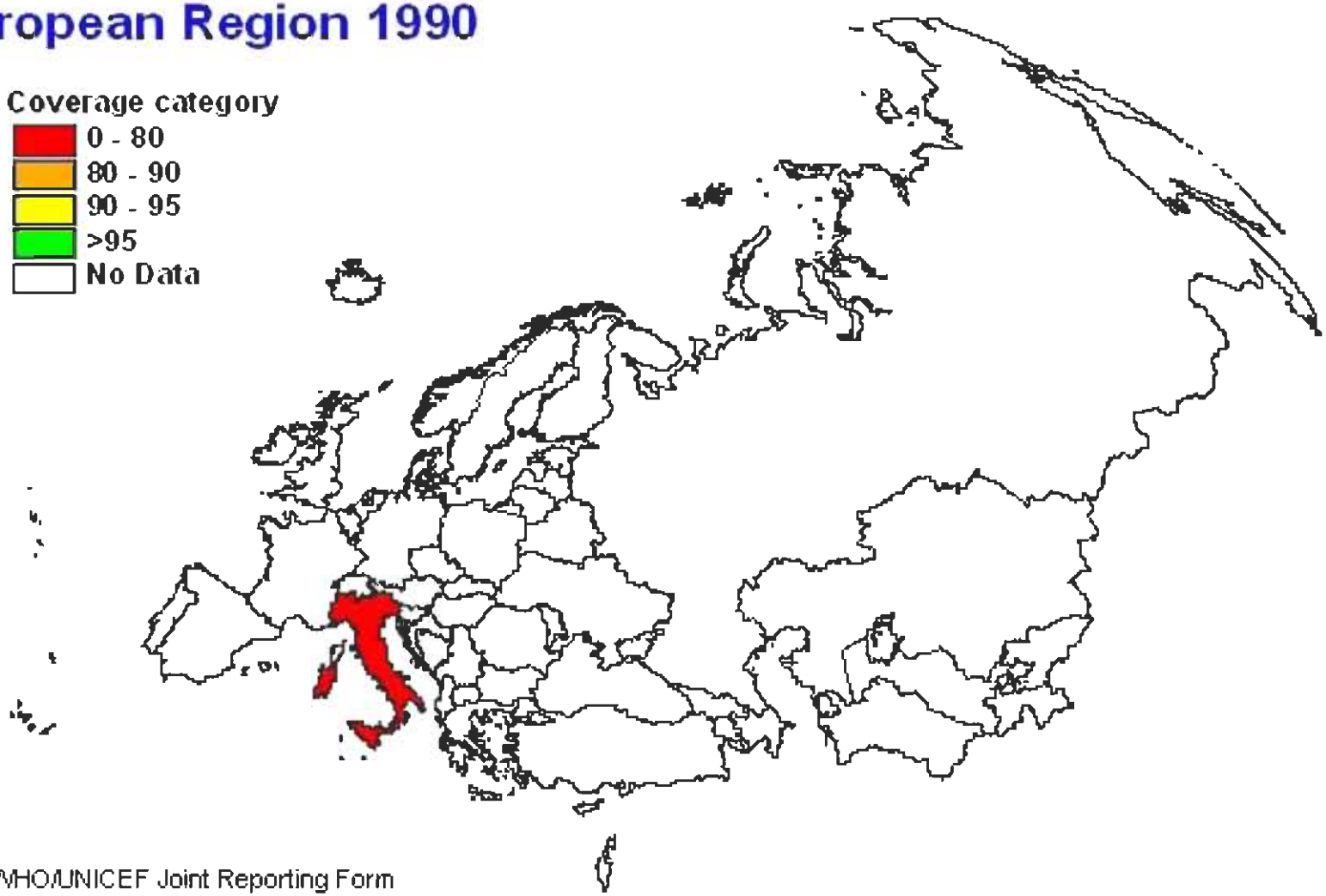
Hep B carriers before and after immunization, Shanghai



- **World Health Assembly, 1992: Hepatitis B vaccine should be integrated into national immunization programmes in all countries by 1997**

- **WHO 9th Programme of Work (1996-2001): Among children, new hepatitis B virus carrier incidence will be reduced at least 80% through integration of hepatitis B vaccine into national immunization programmes**

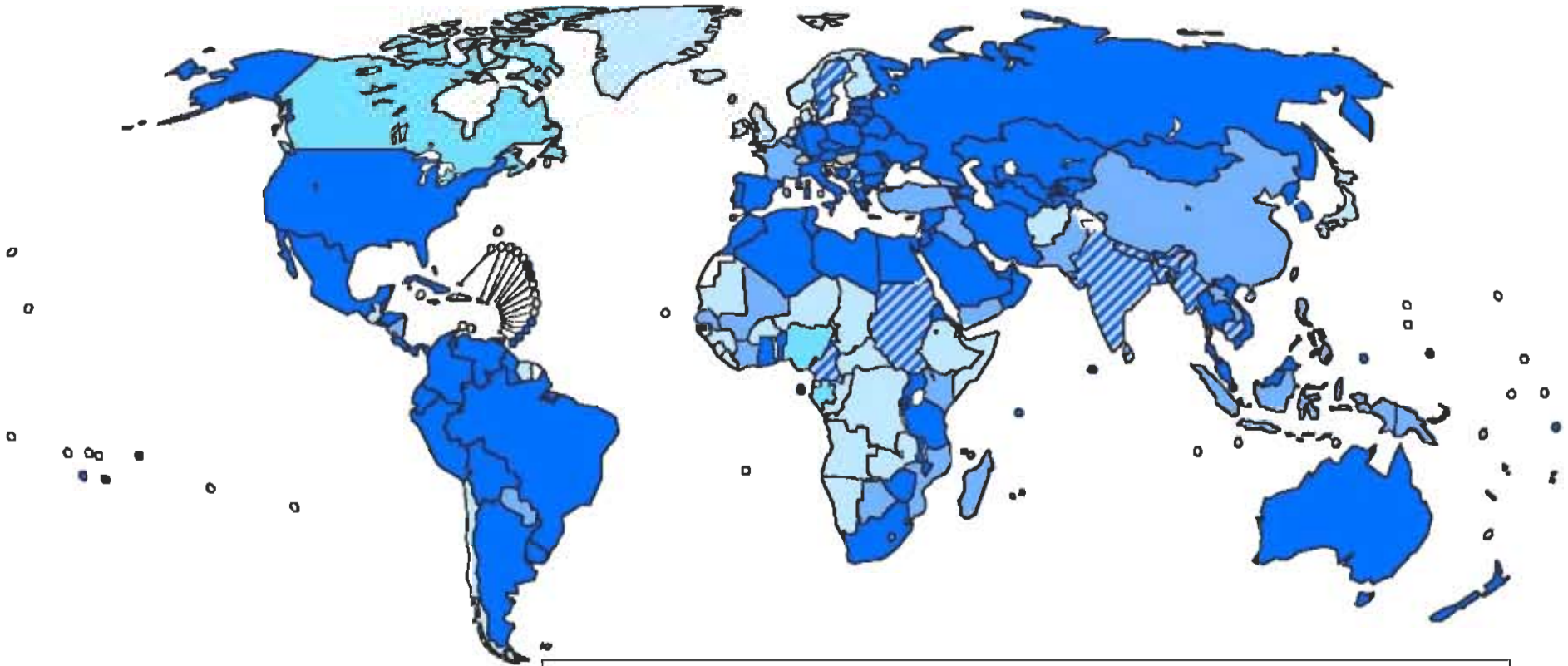
Hepatitis B vaccine (HepB3) coverage in the WHO European Region 1990



•Source; WHO/UNICEF Joint Reporting Form

Slide Date: September 05

Countries having introduced HepB vaccine and infant HepB3 coverage, 2004



(153 countries introduced in national infant immunization schedule)

- HepB3 ≥ 80% *(102 countries or 53%)*
- HepB3 < 80% *(36 countries or 19%)*
- HepB vaccine introduced but no coverage data reported *(5 countries or 3%)*
- HepB vaccine introduced in part of the country *(10 countries or 5%)*
- HepB vaccine administered for adolescence *(5 countries or 2%)*
- HepB vaccine not introduced *(34 countries or 18%)*

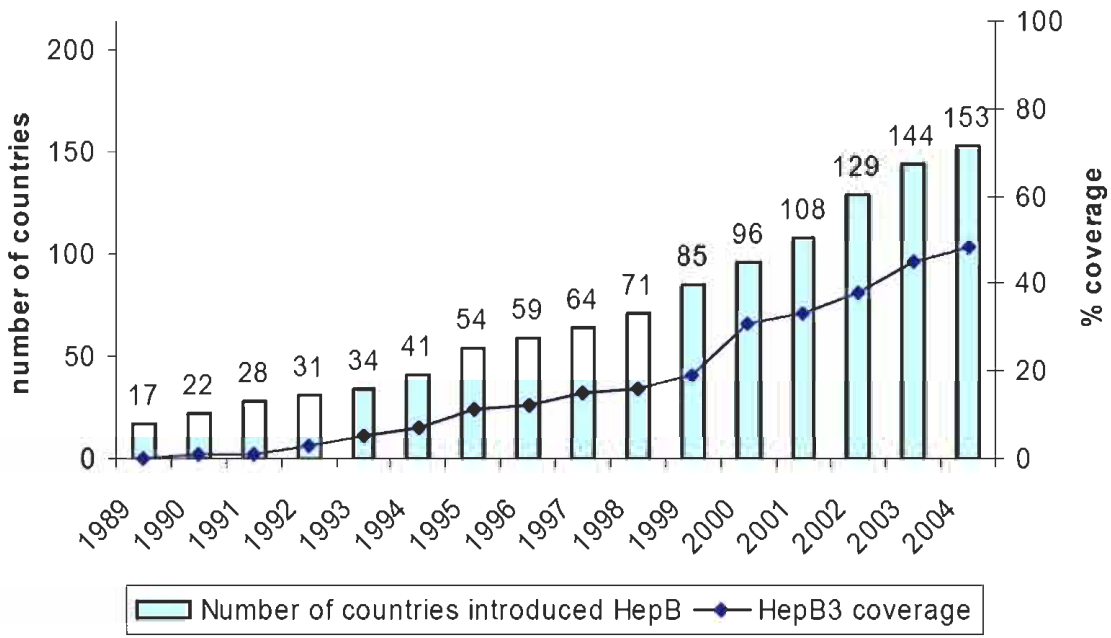
Source: WHO/UNICEF estimates, 2005

192 WHO Member States. Data as of September 2005

WHO

Slide Date: September 05

Number of countries introduced HepB vaccine and global infant HepB3 coverage, 1989-2004



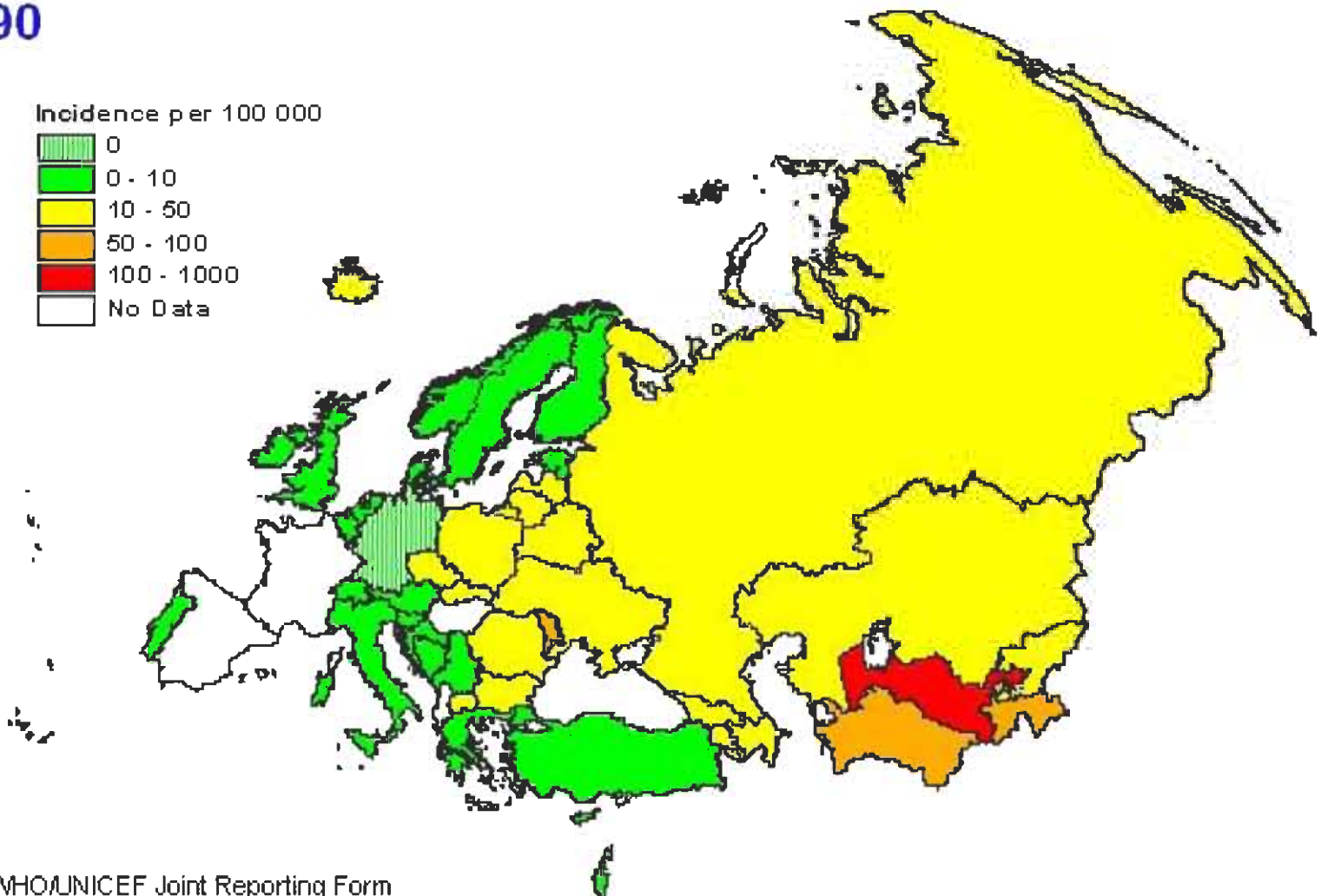
excluding 5 countries where HepB administered for adolescence

Source: WHO/UNICEF estimates and WHO IVB database, 2005

192 WHO Member States. Data as of September 2005

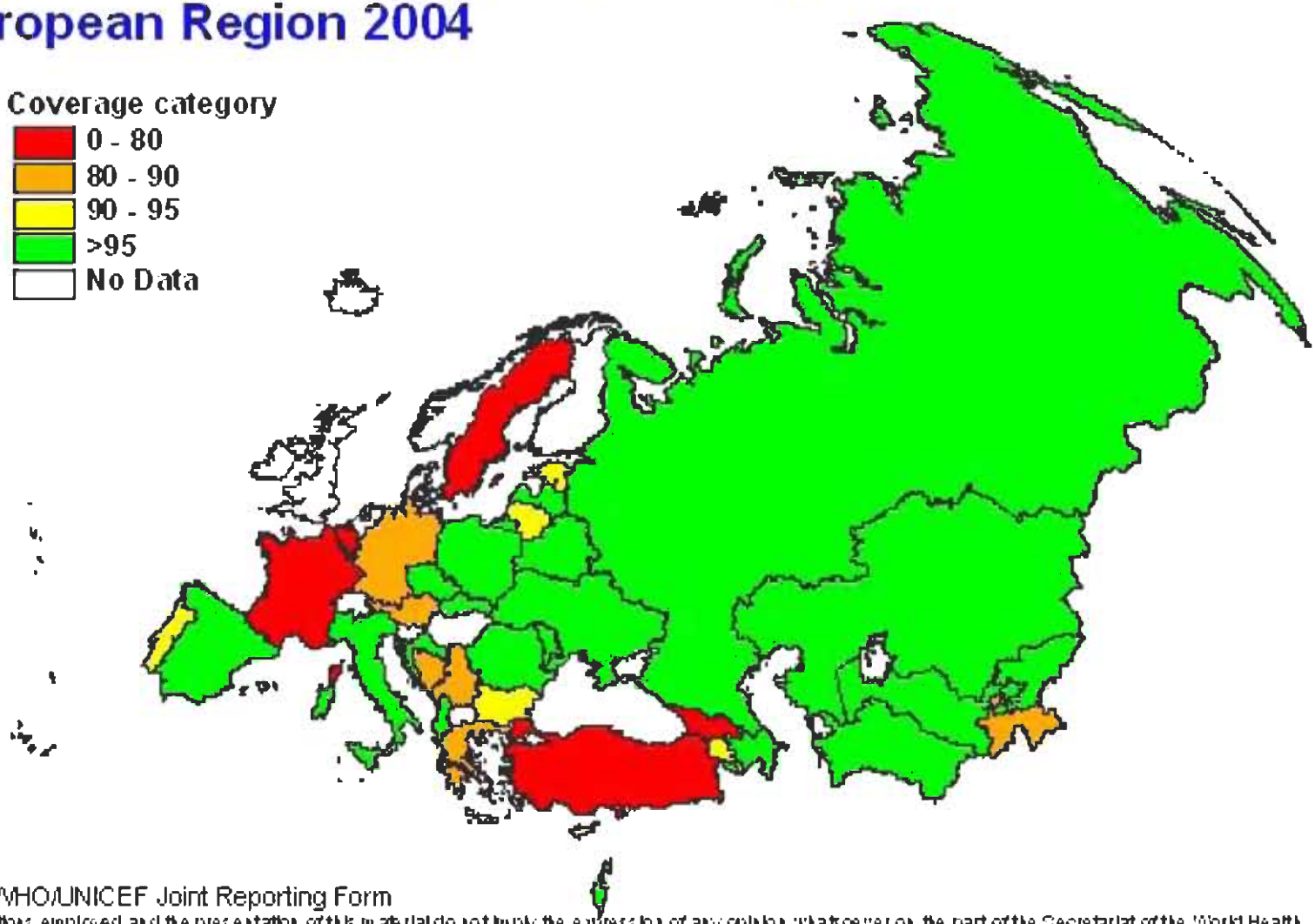
WHO

Hepatitis B Incidence in the WHO European Region 1990



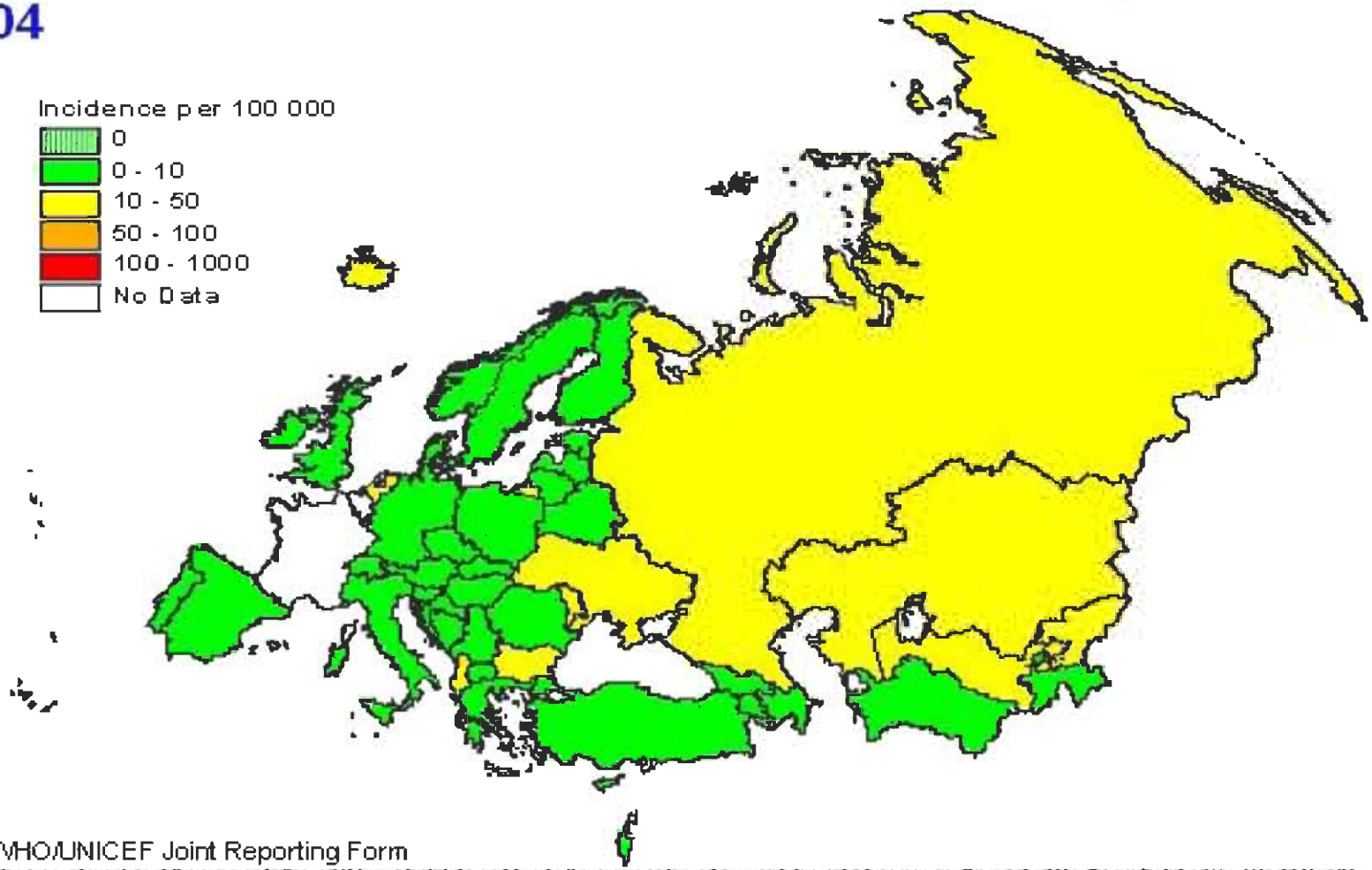
•Source; WHO/UNICEF Joint Reporting Form

Hepatitis B vaccine (HepB3) coverage in the WHO European Region 2004



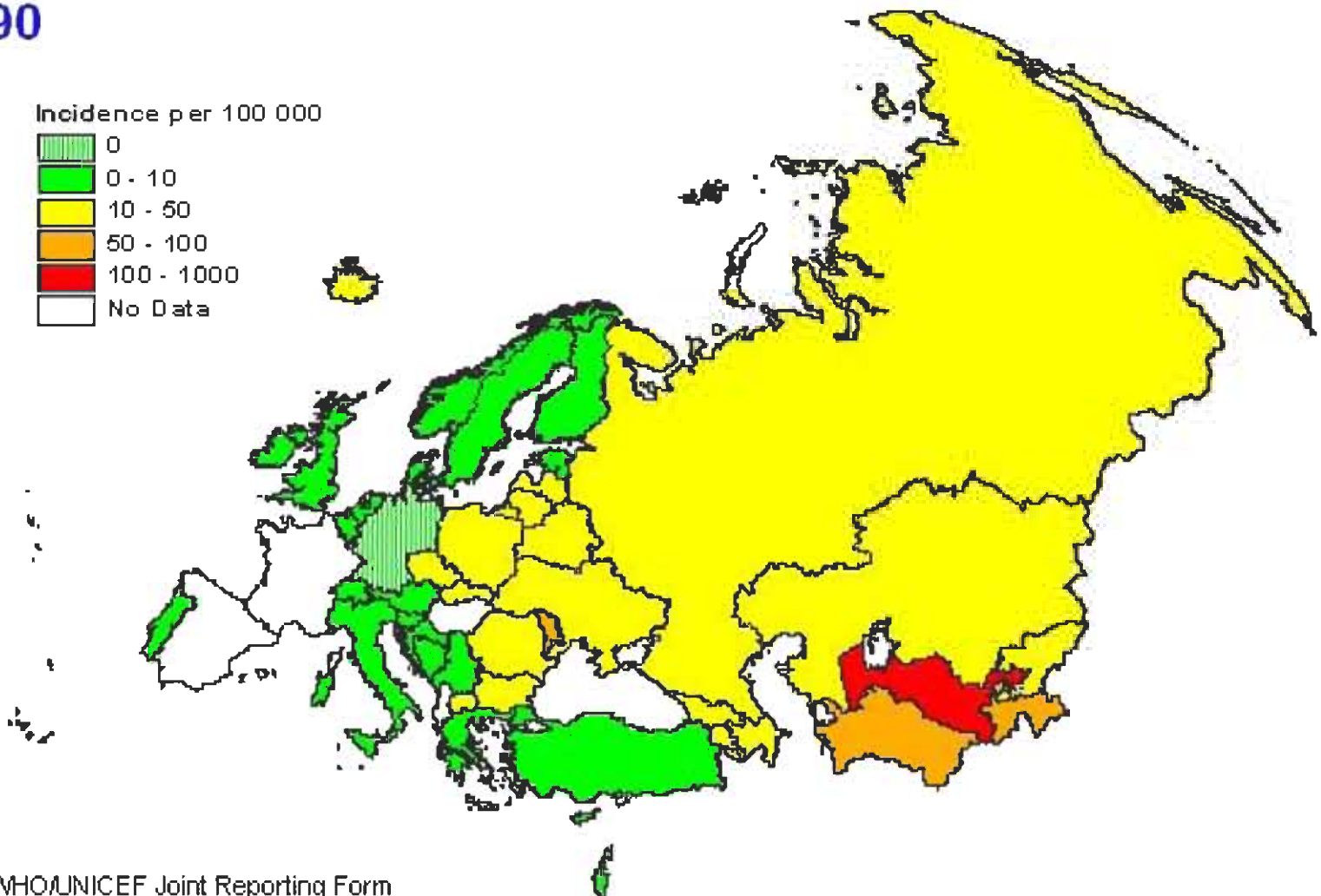
•Source; WHO/UNICEF Joint Reporting Form

Hepatitis B Incidence in the WHO European Region 2004



•Source; WHO/UNICEF Joint Reporting Form

Hepatitis B Incidence in the WHO European Region 1990



•Source; WHO/UNICEF Joint Reporting Form

HOW IMPORTANT IS ADMINISTRATION OF HBIg?

Cite this article as: BMJ, doi:10.1136/bmj.38719.435833.7C (published 27 January 2006)

Research

Effect of hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen: systematic review and meta-analysis

Chuanfang Lee, Yan Gong, Jesper Brok, Elizabeth H Boxall, Christian Gluud

Abstract

Objective To evaluate the effects of hepatitis B vaccine and immunoglobulin in newborn infants of mothers positive for hepatitis B surface antigen.

Design Systematic review and meta-analysis of randomised clinical trials.

Data sources Electronic databases and hand searches.

Review methods Randomised clinical trials were assessed for methodological quality. Meta-analysis was undertaken on three

gen, 70% to 90% of her children become chronically infected.[3 4] If a mother is positive for the surface antigen but negative for the e antigen, the risk of transmission is significantly lower.[5–9]

Two types of vaccines for hepatitis B have been licensed. One is derived from plasma (plasma derived vaccine) and the other is derived from yeast or mammalian cells (recombinant vaccine).[10] Repeated injections over months are required to mount an effective antibody response with vaccination. Hepatitis B immunoglobulin has high levels of antibody to hepatitis B surface anti-

with placebo or no intervention, hepatitis B immunoglobulin or the combination of plasma derived vaccine and hepatitis B immunoglobulin reduced hepatitis B occurrence (immunoglobulin 0.50, 0.41 to 0.60, one trial; vaccine and immunoglobulin 0.08, 0.03 to 0.17, three trials). Compared with vaccine alone, vaccine plus hepatitis B immunoglobulin reduced hepatitis B occurrence (0.54, 0.41 to 0.73; 10 trials). Hepatitis B vaccine and hepatitis B immunoglobulin seem safe, but few trials reported adverse events.

Conclusion Hepatitis B vaccine, hepatitis B immunoglobulin, and vaccine plus immunoglobulin prevent hepatitis B occurrence in newborn infants of mothers positive for hepatitis B surface antigen.

Introduction

Hepatitis B is a global communicable disease, associated with an estimated 350 million chronically infected patients.[1] Mother to child transmission occurs often, either in utero or through exposure to blood or blood contaminated fluids at or around birth.

month of life. We identified randomised trials from the register of the Cochrane Neonatal Group, the Cochrane Hepato-Biliar Group, the Cochrane central register of controlled trial Medline, PubMed, and Embase. The last search was carried ou n February 2004. We scanned references lists and contacte manufacturers of hepatitis B vaccine to ask for unpublished ran domised trials. We wrote to the authors of trials when data wer not provided in the report. Our primary outcome measure wa he occurrence of hepatitis B, defined as a blood specimen pos ive for hepatitis B surface antigen, hepatitis B e antigen, or ant body to hepatitis B core antigen.[15] The secondary outcom measures were antibody levels to hepatitis B surface antige < 10 IU/l (considered insufficient to prevent hepatitis B viru nfection[16, 17]) and adverse events.

IMMUNIZATION PROGRAMME AGAINST HEPATITIS B

What is the important question?

ANSWER: Will the proposed intervention prevent

CHRONIC INFECTION ?

J Med Virol 1994; 44(2): 144-151

Journal of Medical Virology 44:144–151 (1994)

Review: Protective Efficacy of Hepatitis B Vaccines in Neonates

Francis E. André and Arie J. Zuckerman

SmithKline Beecham Biologicals, Rixensart, Belgium (F.E.A.); Royal Free Hospital School of Medicine, London, United Kingdom (A.J.Z.)

A literature search was carried out to investigate the factors that influence the protective efficacy (PE) of hepatitis B vaccines when given to neonates of hepatitis B surface antigen and *e* antigen positive mothers. Hepatitis B vaccines with either high or low antigen doses are very effective in preventing chronic hepatitis B infection in neonates at risk, but there is evidence that with lower dosages simultaneous use of hepatitis B immune globulin (HBIG) administration is more important than with higher dosages to elicit good protection (PE ≥ 90%). There is also a ten-

carriers. Of all HBV carriers with a life expectancy greater than 30 years, 25–30% will die from cirrhosis, chronic liver disease, and hepatocellular carcinoma as a result of this infection [Szmuness et al., 1978; Maupas and Melnick, 1981]. The ensuing high premature death rate in socioeconomically productive adults has serious effects on the well-being of society. This is especially the case in developing areas with a high hepatitis B endemicity, such as in tropical Africa or Asia [Margolis et al., 1991].

The spread of hepatitis B disease from the pool of chronic carriers is most effective via blood but also

TABLE II. Hepatitis B Recombinant DNA Vaccines in Neonates of HBsAg and HBeAg-Positive Mothers

Reference	Dose (μg)	HBIG at birth	No. of recipients	Vaccination schedule (months)	PE (%)	Control group[a]
Pongpipat et al. [1989]	5	+	20	0,1,6	89	Historical
Assateerawatt et al. [1991]	2.5	−	29	0,1,2,12	66	Study
Lee et al. [1991a]	10	+	56	0,1,2,(12)	98	Historical
Lee et al. [1991a]	20	+	54	0,1,2,(12)	92	Historical
Lee et al. [1991a]	20	+	60	0,1,6	96	Historical
Liu et al. [1991]	5	−	15	NS	100	Assumed
Liu et al. [1991]	10	−	18	NS	100	Assumed
Liu et al. [1991]	20	−	28	NS	94	Assumed
Anonymous [1992b]	2.5	+	76	0,1,5	NS	NS
Anonymous [1992b]	5	+	for both	0,1,5	100	NS
Assateerawatt et al. [1992]	5	+	19	0,1,6	89	Study
Poovorawan et al. [1992]	10	−	57	0,1,2,(12)	95	Assumed
Poovorawan et al. [1992]	10	+	64	0,1,2,(12)	98	Assumed
Poovorawan et al. [1992]	10	−	54	0,1,6	95	Assumed
Poovorawan et al. [1992]	10	+	59	0,1,6	100	Assumed
Stevens et al. [1992]	5	+	351	0,1,6 or 0,1,9	92	Assumed
Assateerawatt et al. [1993]	20	+	26	0,1,2,(12)	95	Historical
Assateerawatt et al. [1993]	20	−	23	0,1,2,(12)	90	Historical

[a]NS = not specified; historical = use of historical control group by the authors; study = placebo control group within study; assumed = attack rate assumed to be 65%.

vorawan et al., 1992]. Among studies with plasma-derived vaccines, one study shows at 24 months a 100% PE with or without concomitant HBIG administration

Although 3 and 5 μg dosages can also give similarly high PEs when administered with HBIG [Lee, 1989; Ip et al., 1989; Theppisai et al., 1988], such lower dosages

Francis E. André and Arie J. Zuckerman

SmithKline Beecham Biologicals, Rixensart, Belgium (F.E.A.); Royal Free Hospital School of Medicine, London, United Kingdom (A.J.Z.)

A literature search was carried out to investigate the factors that influence the protective efficacy (PE) of hepatitis B vaccines when given to neonates of hepatitis B surface antigen and *e* antigen positive mothers. Hepatitis B vaccines with either high or low antigen doses are very effective in preventing chronic hepatitis B infection in neonates at risk, but there is evidence that with lower dosages simultaneous use of hepatitis B immune globulin (HBIG) administration is more important than with higher dosages to elicit good protection (PE ≥ 90%). There is also a tendency for lower dosages to confer high PE less consistently, with noticeably greater numbers of chronic surface antigen carriers in neonates who received a complete vaccination course. Furthermore vaccination courses with higher vaccine dosages give high PEs, without concomitant HBIG administration at birth, provided that the first vaccine dose is given at birth and that the second dose follows within 2 months.

carriers. Of all HBV carriers with a life expectan greater than 30 years, 25–30% will die from cirrhos chronic liver disease, and hepatocellular carcinoma a result of this infection [Szmuness et al., 1978; Maup and Melnick, 1981]. The ensuing high premature dea rate in socioeconomically productive adults has serio effects on the well-being of society. This is especial the case in developing areas with a high hepatitis endemicity, such as in tropical Africa or Asia [Margo et al., 1991].

The spread of hepatitis B disease from the pool chronic carriers is most effective via blood but al through other body fluids contaminated with blood, a though sexual transmission by semen and vaginal s cretions that are apparently free from blood undoub edly occur [Dienstag and Ryan, 1982; Margolis et a 1991]. There are two main modes of disease transmi sion; horizontally from close contact and perinatall Perinatal transmission is responsible for 35–40% of a new hepatitis B infections world-wide [Maynard, 198 Ghendon, 1987]. This perinatal mode of transmission particularly common in regions such as Southeast As

Strategies to Prevent Perinatal HBV Transmission

Selective Immunoprophylaxis

- Screen pregnant women for HBsAg
- Give prophylaxis to neonates of HBsAg+ mothers

Pros

– prophylaxis targeted to neonates that need it

– can administer both HBIG/HepB vaccine

Issues

– Requires extensive resources to screen pregnant women/track infants of HBsAg+ mothers

– Programmes not always succesful

Strategies to Prevent Perinatal HBV Transmission

Integrate as Component of Universal Infant Vaccination

- Vaccinate all neonates beginning at birth

Pros

- No need to screen pregnant women
- Very feasible to implement if a high proportion of neonates are born in health care facilities or accessible

Issues

- Need to assure effective HepB vaccine delivery for all neonates

WHO point of view

- Universal vaccination of all infants as an integral part of the national immunization program is the highest priority in all countries

- whenever feasible and according to the local epidemiology, countries should incorporate prevention of perinatal HBV transmission
  - by beginning vaccination of all infants at birth
  - screening pregnant women and provide PEP to exposed infants

WHO point of view

- Prevent perinatal HBV transmission:
  - relative contribution of perinatal transmission to the overall disease burden of HBV (HBeAg prevalence)
  - the feasibility of delivering the first dose of hepatitis B vaccine at birth (<12h.)
    - monovalent HB vaccine must be used at birth
    - HB combination vaccines cannot be used at birth (waste of combination vaccine)
      - Non-hepatitis B components have reduced immunogenicity in children less than 6 weeks of age

Options for adding hepatitis B vaccine to immunization schedules

Age	*visit*	*HBV1*	*HBV2*	*HBV3*
birth	0		HepB0	HepB0
6 weeks	1	HepB1	HepB1	HepB1
10 weeks	2	HepB2	HepB2	
14 weeks	3	HepB3	HepB3	HepB2

Prevention of perinatal transmission

- Offer hepB vaccine as soon as possible after birth, within 12-24h
- As a monovalent vaccine
- Efficacy of hepB vaccine offered later than 24h declines over time
  (ref: Marion et al. Am J Epidemiol, 1994)
- If specific hepBIg available, simultaneous administration, at an other injection site
  - Adds 2-3% protective efficacy (97% vs. 95%)
- Birth dose hepB can be combined with birth dose BCG (even increases the hepB antibody response)
  (ref. Ota et al.)

Thank you !