Hepatitis B Disease Burden:

A Model for Global Estimates and Impact of Vaccination

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Division of Viral Hepatitis

Barriers to Appreciating HBV Disease Burden and Vaccine Impact

- Chronic hepatitis B virus (HBV) infections - not easily identified or counted yet most morbidity and mortality associated with HBV occurs in persons with chronic infection
- Primary goal of hepatitis B immunization is to prevent chronic infections

Natural History of HBV Infection

- Very dependent on age of infection
- Among infected children acute (symptomatic) hepatitis B rare; likelihood of developing chronic infection high:

Age at infection	Acute HBV	Chronic HBV
<1 year	<1%	90%
1-5 years	5-15%	25-50%
>5 years	20-50%	6-10%

- Morbidity and mortality associated with chronic infection (cirrhosis, hepatocellular carcinoma or HCC) not apparent until adulthood

Modes of HBV Transmission in Infancy and Early Childhood

- Vertical transmission from infected mother to infant
- Horizontal transmission from infected household contact to child

➢ *Both modes of transmission can be prevented by vaccination of newborns!*

Vertical Transmission

- Transmission from infected mother to infant
- Percutaneous and permucosal exposure to mother's blood during birth
- *In utero* transmission rare: accounts for <2% of perinatal infections
- HBV **not** transmitted by breastfeeding

Risk of Vertical HBV Transmission by Serologic Status of Mother

Serostatus of Mother		Infants Infected
HBsAg	***HBeAg***	
Positive	Positive	70% - 90%
Positive	Negative	5% - 20%

- Immunoprophylaxis is highly effective in preventing vertical HBV transmission: hepatitis B vaccine alone prevents vertical transmission in up to 95% of infants when given soon after birth

Horizontal Transmission

- Transmission occurring during early childhood is a result of horizontal transmission of HBV within household
  - **to** young children **from** family members: usually infected parents, older siblings, and household members
- May be associated with breaks in skin barrier common in tropical areas – e.g., scabies, dermatitis

➢ Hepatitis B vaccination will prevent horizontal transmission in early childhood

Rationale for Hepatitis B Vaccine Birth Dose for All Infants

- Provides “safety net” for prevention of vertically transmitted HBV infections among children born to HBsAg-positive women
- Prevents early childhood HBV infections, including horizontally transmitted infections among children born to HBsAg-negative women

A Mathematical Model to Estimate Global Hepatitis B Disease Burden and Vaccination Impact

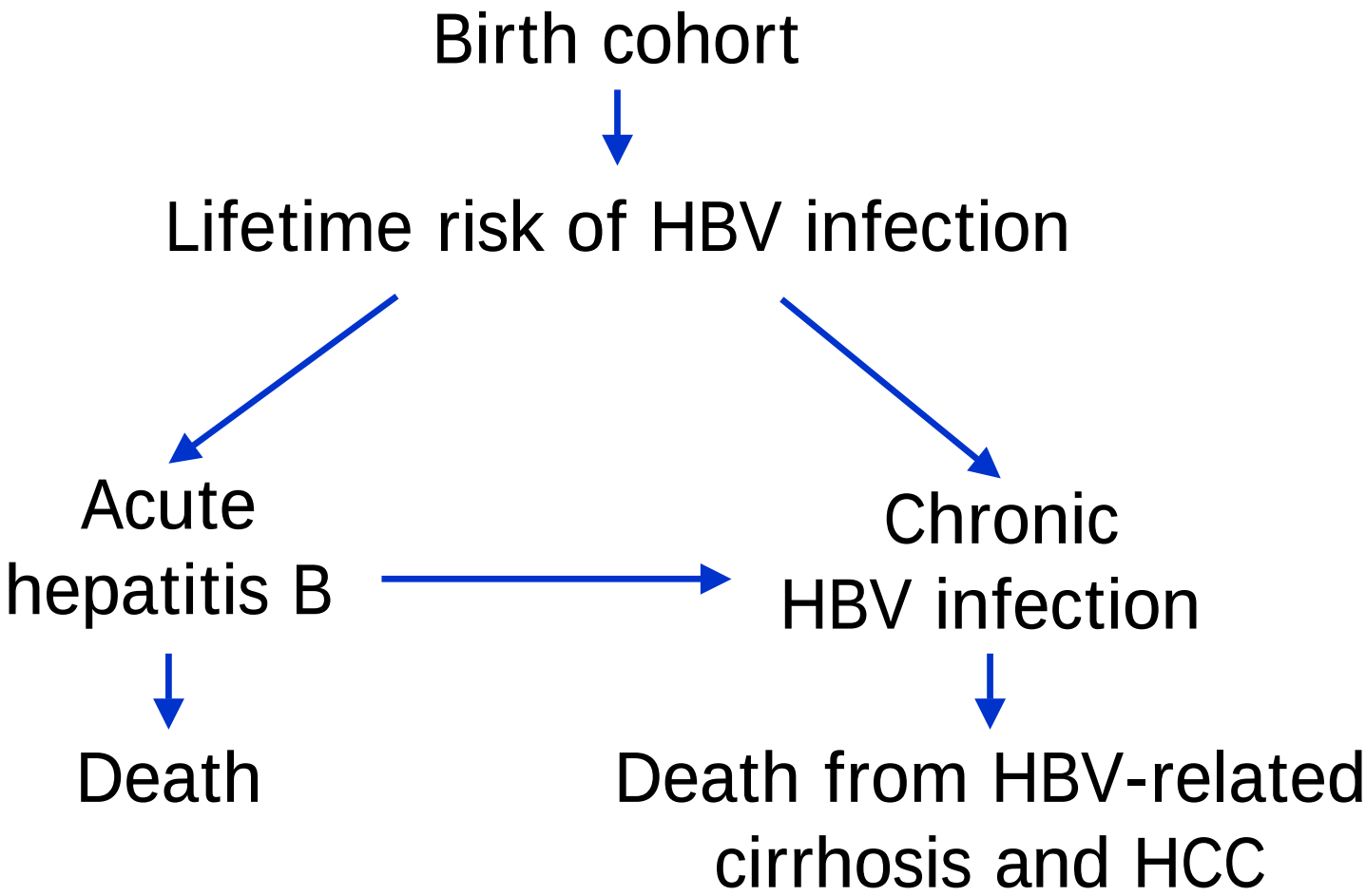
Susan T. Goldstein, Fangjun Zhou, Stephen C. Hadler, Beth P. Bell, Eric E. Mast, and Harold S. Margolis

International Journal of Epidemiology
2005;34:1329-1339.

The Disease Burden Model: Objectives

- Estimate HBV-related morbidity and mortality at the country, regional, and global levels
- Estimate reduction in HBV-related morbidity and mortality with different vaccination strategies
- Use as field tool at country level to facilitate introduction of hepatitis B vaccination

Model Overview



Risk of Acquiring HBV Infection

- Calculated from age-specific prevalence of HBV in population
- Accounted for country-specific infant mortality
- Infection assumed to occur in one of three age periods

Period	Age
Perinatal	Birth
Early childhood	After birth - 5 years old
Late	>5 years old

Infection Outcome: Acute HBV and Chronic HBV Infection

- Decision tree analysis
- Estimate age-specific risk
  - acute HBV infection
  - death from acute HBV infection
  - chronic HBV infection

Infection Outcome: Deaths From Chronic Infection

- Constructed age-specific HBV-related cirrhosis and HCC mortality curves from multiple data sources
  - cirrhosis: US, Taiwan
  - HCC: Alaska, China, Gambia, Taiwan
- Included difference in risk of developing HCC
  - males and females
  - HBeAg-positive and HBeAg-negative persons[1]
- Adjusted for country-specific background mortality

[1] Yang NEJM 2002

Hepatitis B Vaccine Efficacy & Effectiveness

Efficacy

- 3-dose vaccination series - 95% efficacious
- Birth dose – 95% efficacious in preventing perinatal infection
- Assumed lifelong protection from 3 doses

Effectiveness

- Vaccine efficacy
- Coverage with 3-dose vaccination series
- Receipt of birth dose of vaccine

Seroprevalence Data For Global and Regional Disease Burden Estimates

World

↓

6 WHO Regions — AFRO, AMRO, EMRO, EURO, SEARO, WPRO

↓

15 Sub-Regions — Similar background mortality and HBV prevalence

↓

Country — For each country in sub-region, used same estimate for each of the four seroprevalence inputs to run model

Model Input and Output

Model Input

- HBsAg
- HBeAg

] women of child bearing age

- Anti-HBc at 5 years old
- Anti-HBc at ≥30 years old (lifetime risk of infection)

Model Output

- ***Current burden:*** HBV-related deaths in 2000
- ***Future burden:*** HBV infections (total and chronic) and HBV-related deaths in 2000 birth cohort

Current Hepatitis B Disease Burden[1]

Region	Total Deaths	Deaths From Chronic Infection
AFRO	69,000	90%
AMRO	12,000	92%
EMRO	21,000	90%
EURO	51,000	94%
SEARO	143,000	92%
WPRO	325,000	95%
Global	**620,000**	**94%**

[1] Year 2000

Future Hepatitis B Disease Burden[1]

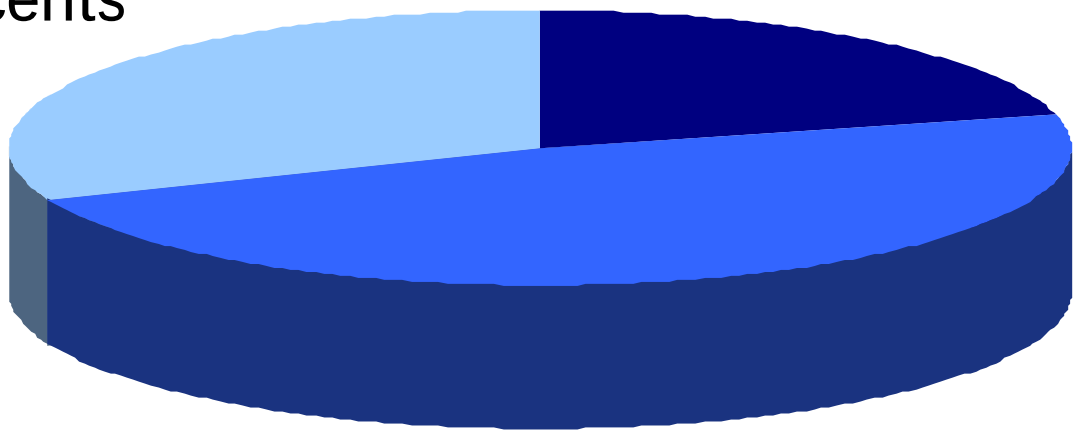
Region	Total Infections (millions)	Chronic Infections	Total Deaths[2]
AFRO	18.5	2,915,000	276,000
AMRO	1.3	174,000	28,000
EMRO	5.3	663,000	96,000
EURO	2.9	365,000	56,000
SEARO	17.4	2,386,000	368,000
WPRO	19.3	3,230,000	581,000
Global	**64.8**	**9,733,000**	**1,405,000[3]**

[1] 2000 birth cohort over course of lifetime without vaccination
[2] Acute hepatitis B and chronic HBV infection
[3] 95% from chronic infection and 5% from acute hepatitis B

Global HBV-Related Deaths By Age at Acquisition of Infection[1]

Late Period (31%)
- children >5
- adolescents
- adults

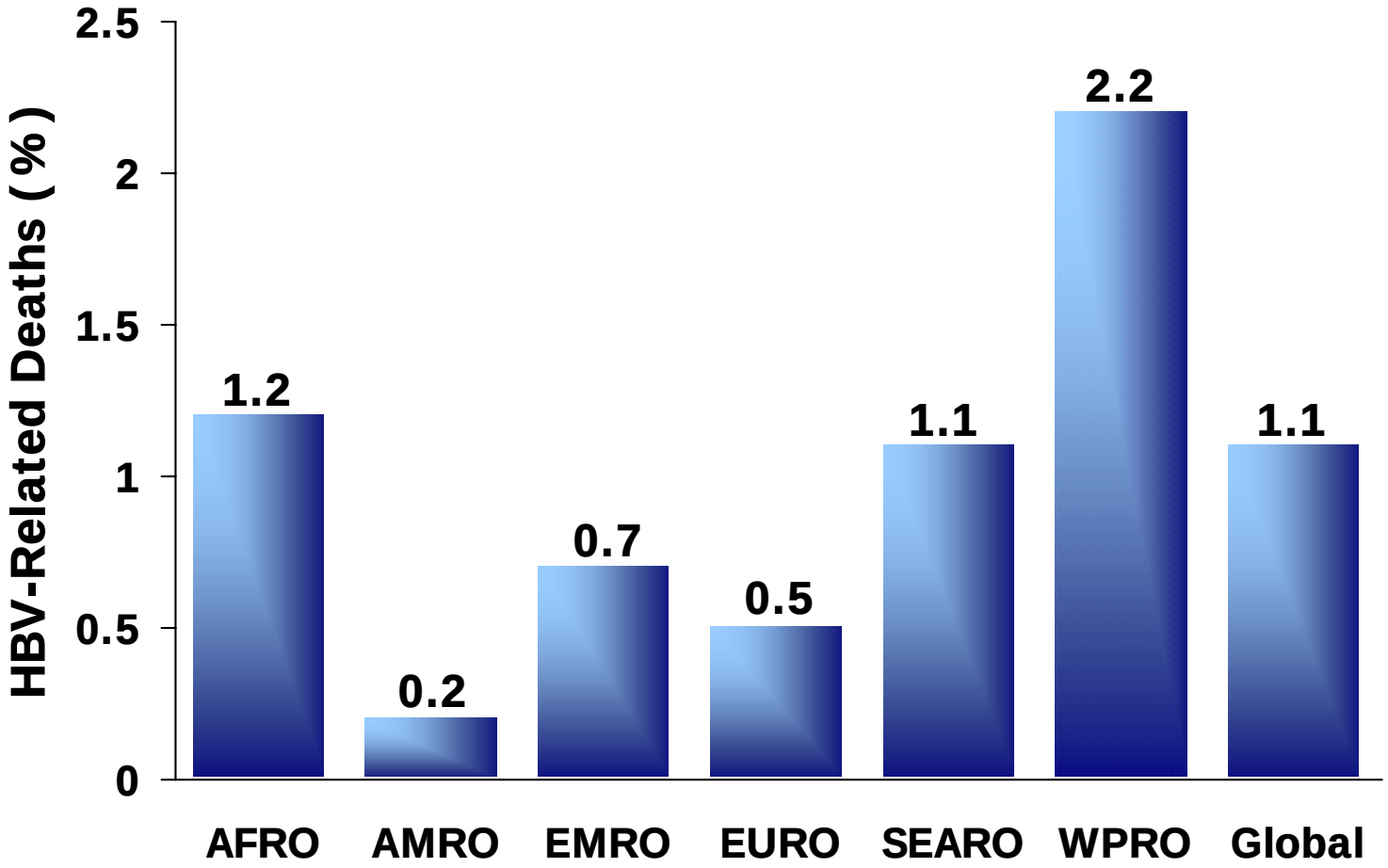
Perinatal Period (21%)



Early Childhood Period (48%)
- children ≤5

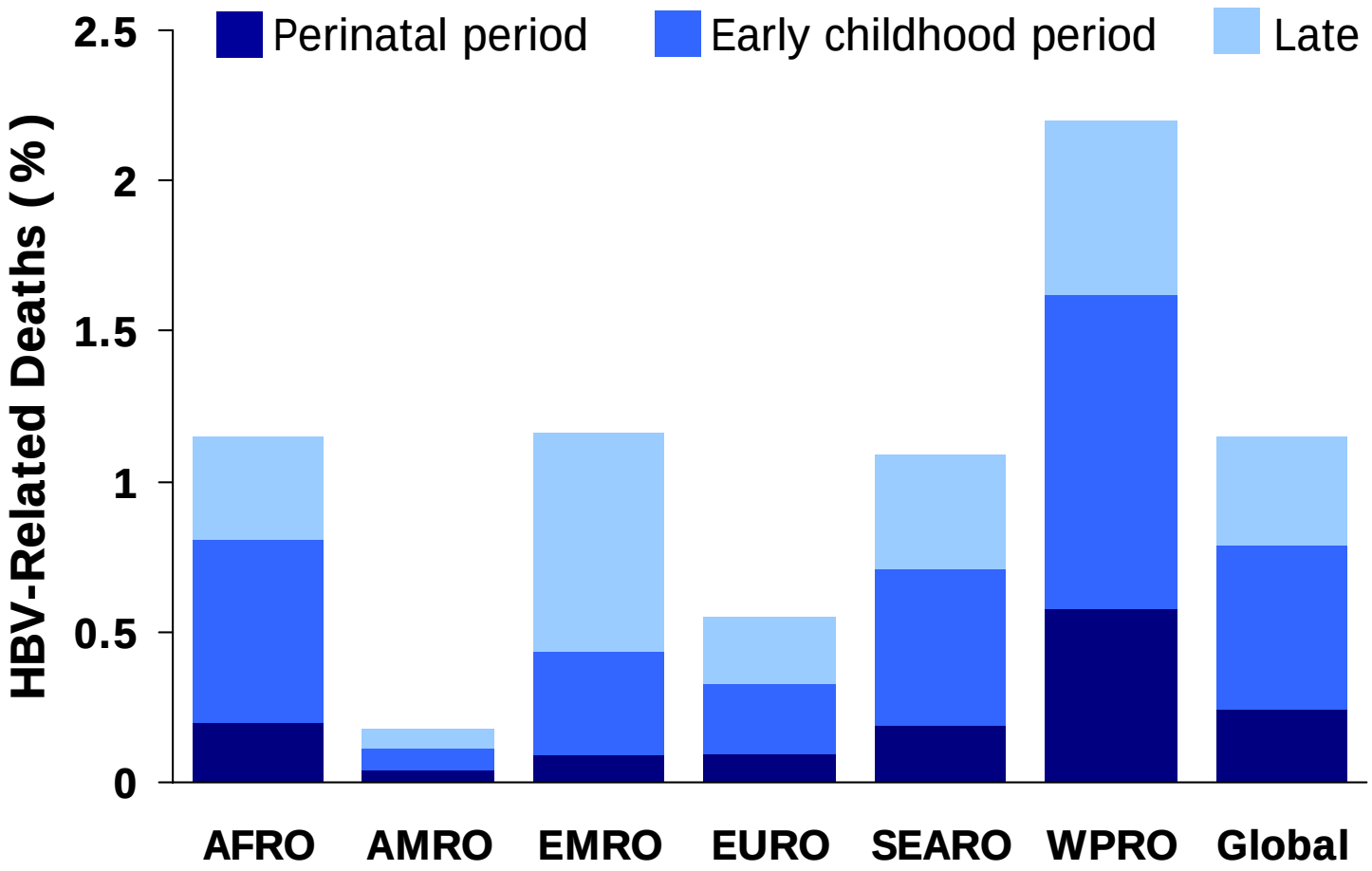
[1] Future deaths, without vaccination

Proportion of Total Deaths in the 2000 Birth Cohort from Hepatitis B[1]



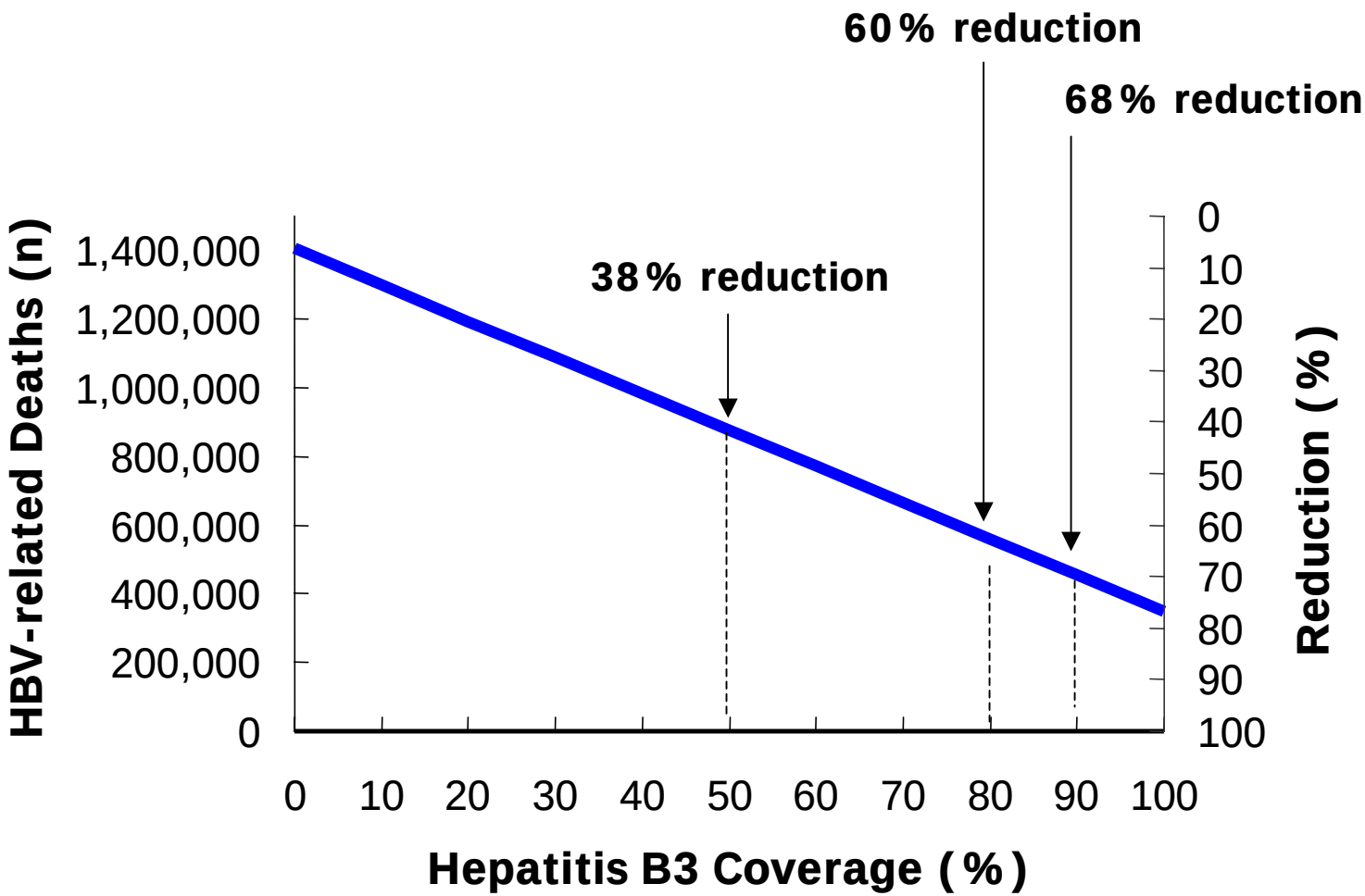
[1]Future deaths in 2000 birth cohort, without vaccination

Proportion of Total Deaths in the 2000 Birth Cohort from Hepatitis B, By Age at Infection[1]



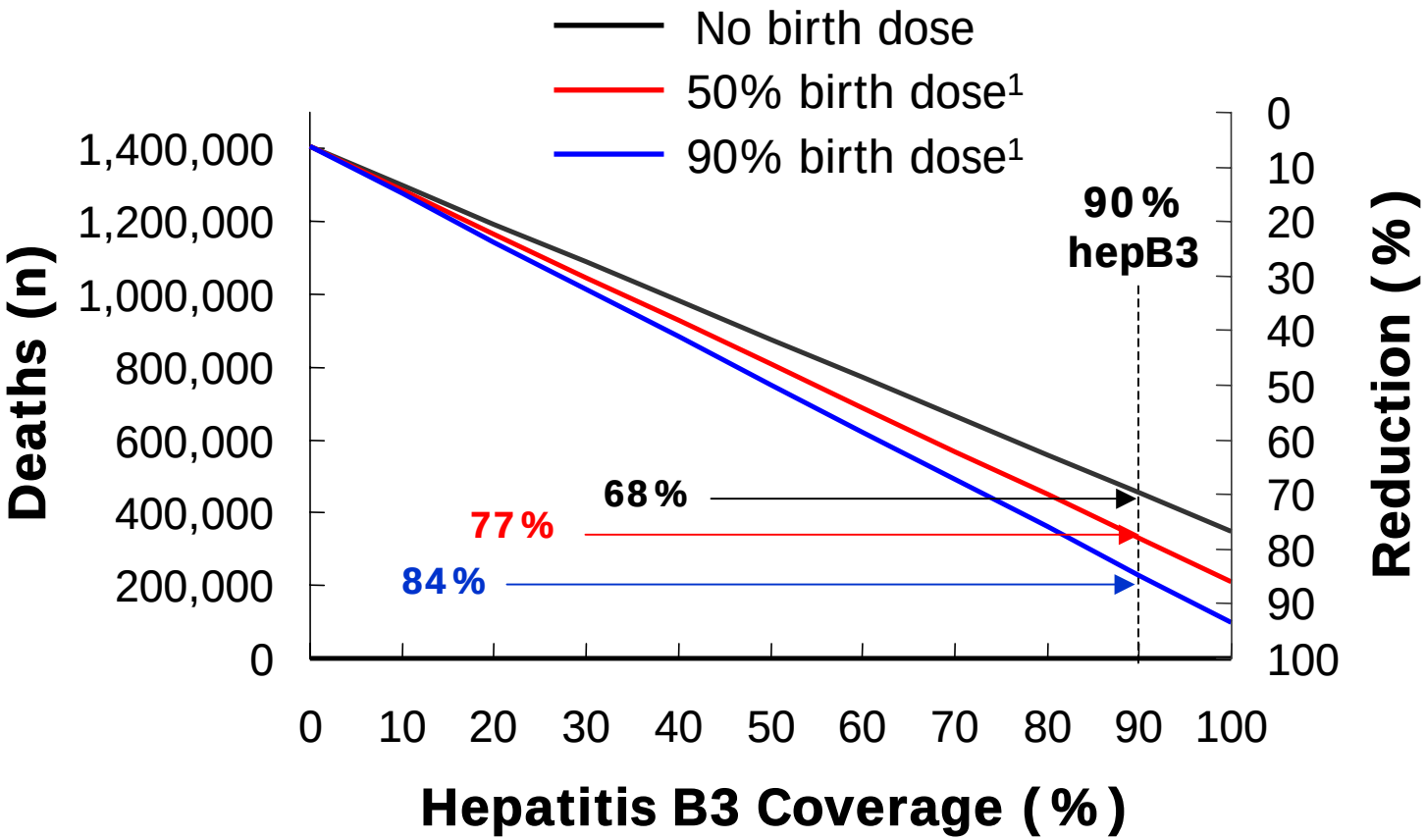
[1]Future deaths in 2000 birth cohort, without vaccination

Reduction in HBV-Related Deaths in the 2000 Birth Cohort with Vaccination[1]



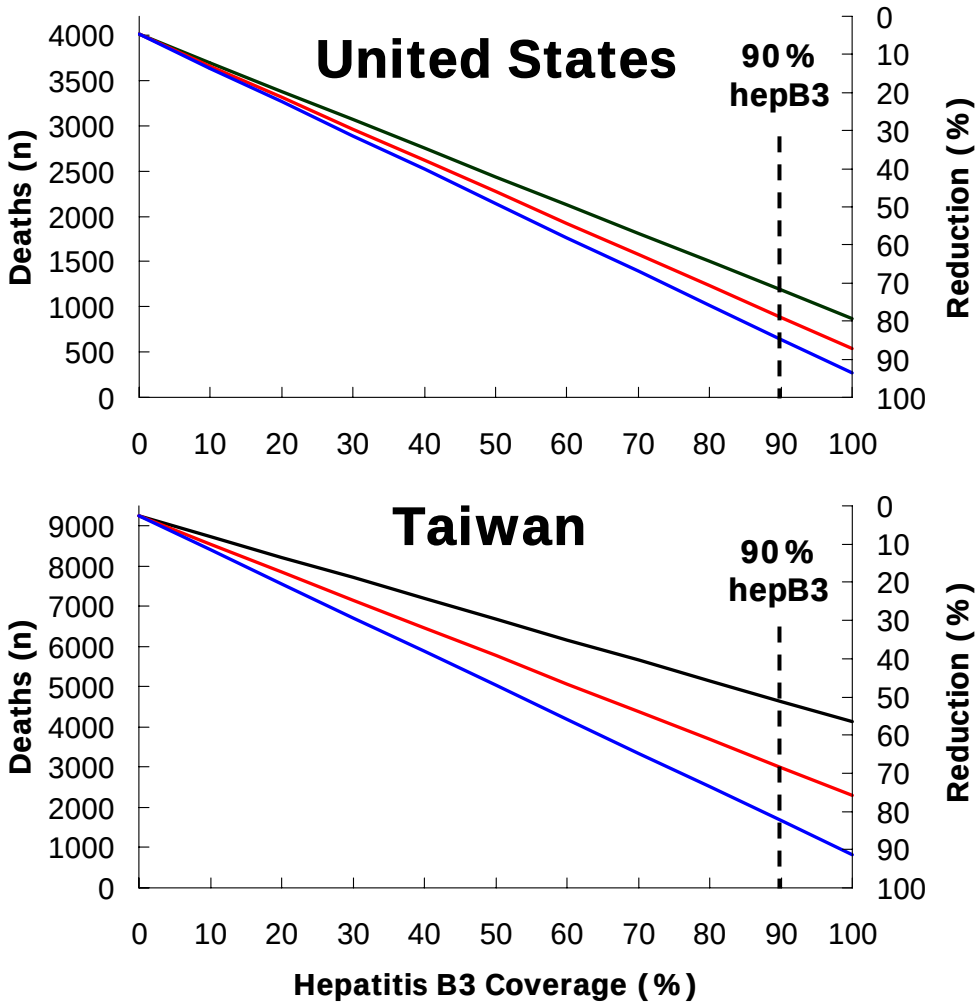
[1] Without administration of a birth dose of vaccine

Reduction in HBV-Related Deaths with Vaccination: Impact of Birth Dose



[1] Administration of birth dose to 50% and 90% of the vaccinated cohort

Reduction in HBV-Related Deaths with Increasing Birth Dose Coverage



United States

0 birth dose	70%
50% birth dose	78%
90% birth dose	84%

14%

Taiwan

0 birth dose	50%
50% birth dose	68%
90% birth dose	82%

32%

[1] Administration of birth dose to 50% and 90% of the vaccinated cohort

Updated United States Strategy to Eliminate HBV Transmission

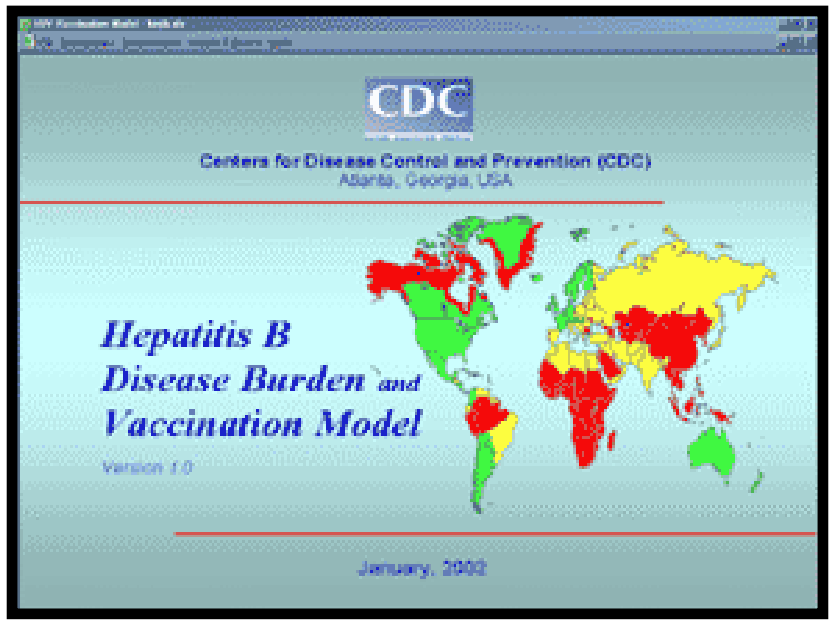
- Universal infant vaccination (1991)
- New December 2005 recommendations address gaps in eliminating perinatal and childhood transmission and focus on immunizing all newborns before hospital discharge

Conclusions

- Globally, HBV infection causes substantial morbidity and mortality
- Most HBV-related deaths result from chronic sequelae of infection acquired in the perinatal and early childhood periods
- Inclusion of hepatitis B vaccine birth dose into national immunization programs could prevent >80% of HBV-related deaths

Field Use for Hepatitis B Disease Burden Model

- Run on desktop computer
- EXCEL software
- User-friendly interface
- User's manual



- Available at http://aim-e-learning.stanford.edu/en/vaccines/hepb/assessBurden/model/index.html