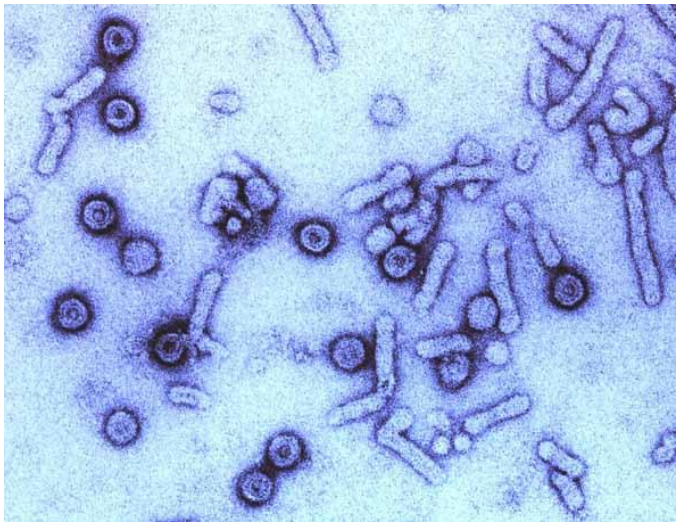
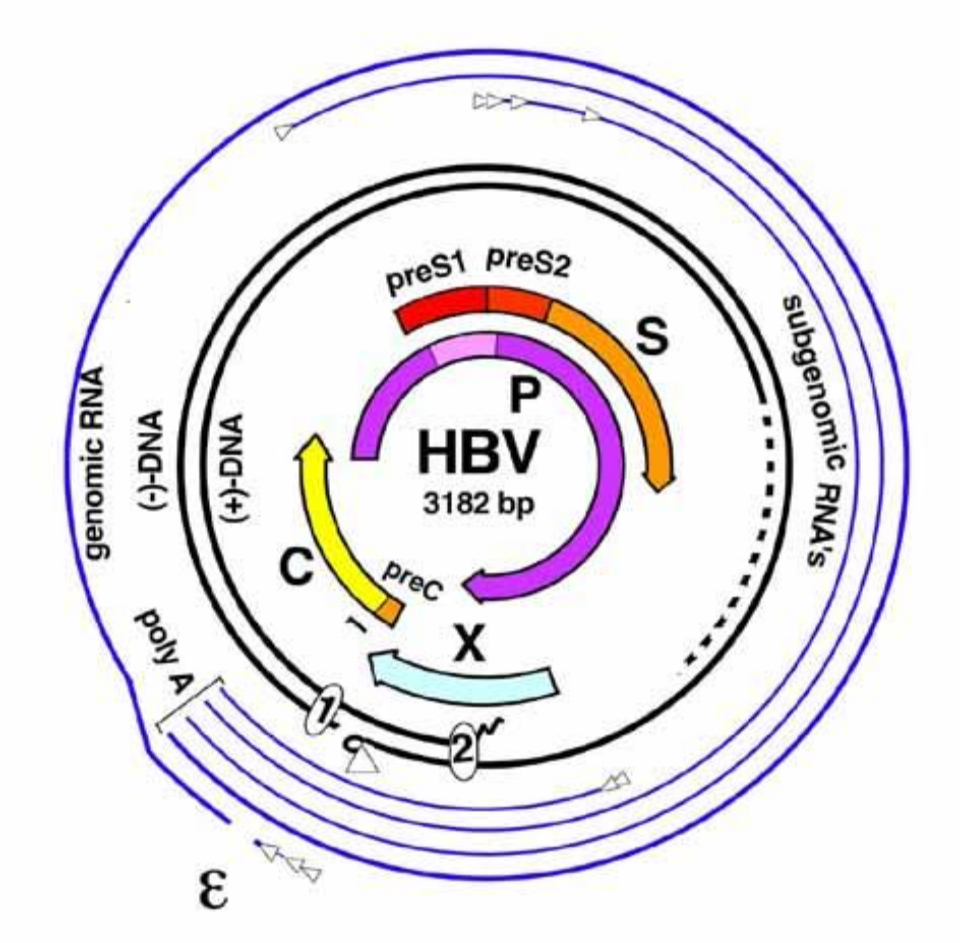
What do we need to do to prevent HBV related disease?

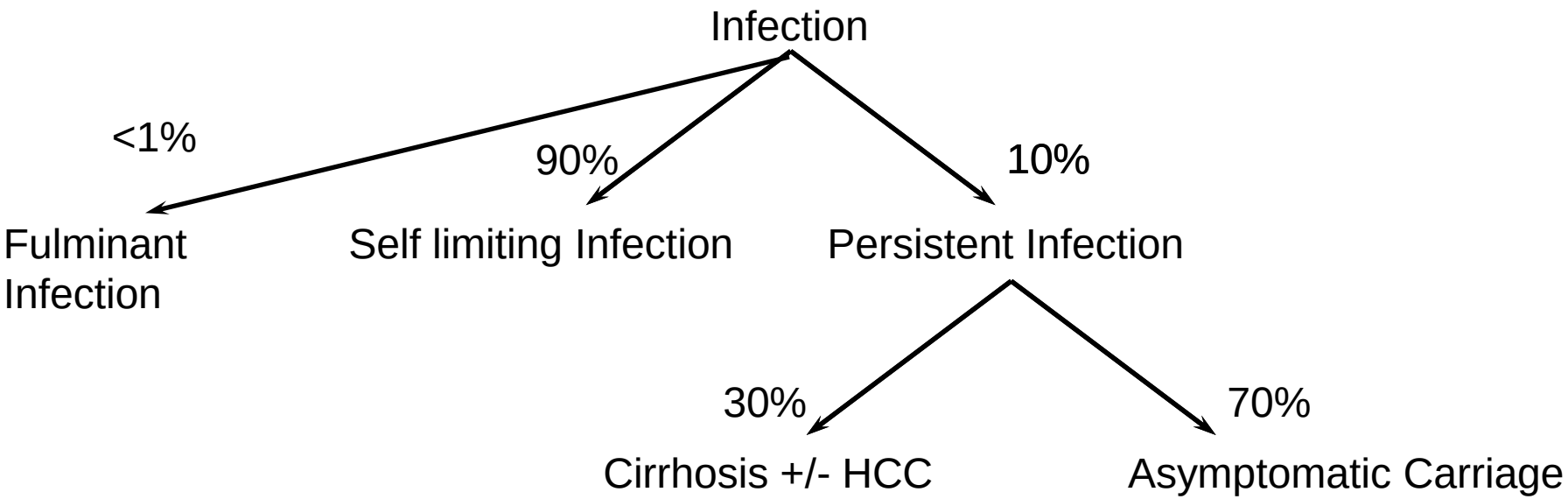
Mark Thursz
Professor of Hepatology
Imperial College

Genome structure of HBV



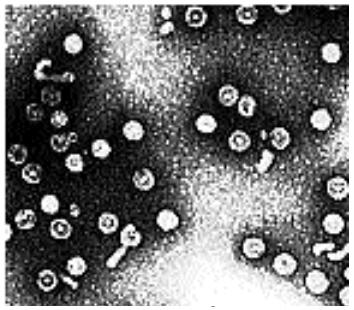


Outcome of HBV Infection

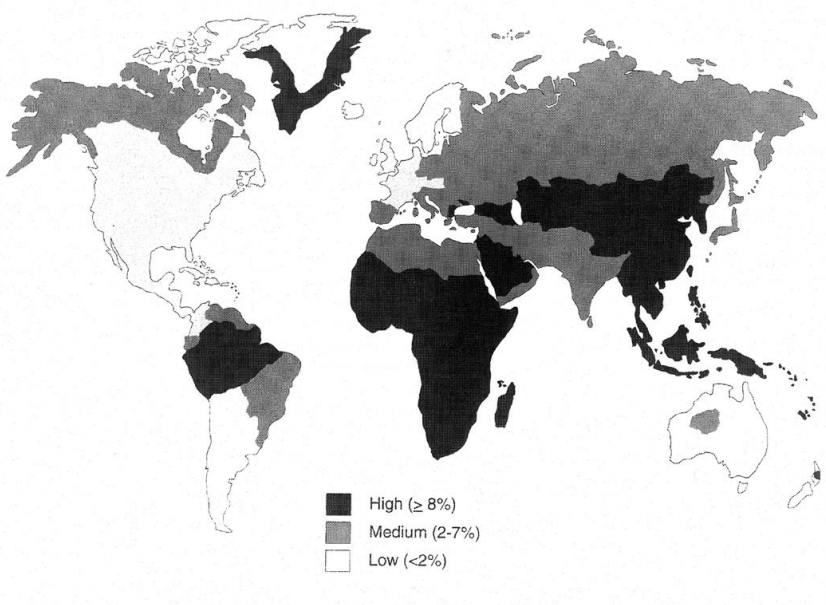


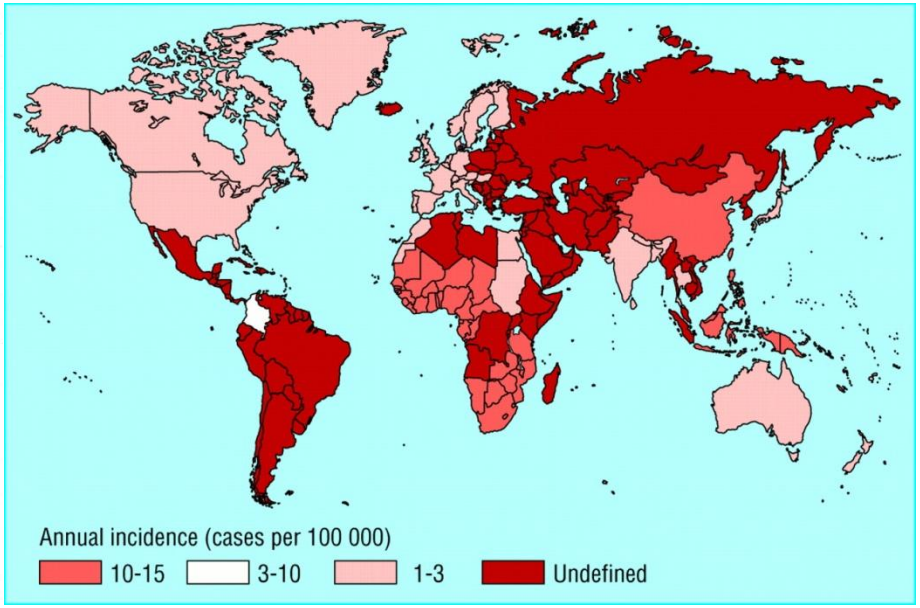
HBV Epidemiology

32 nM virus

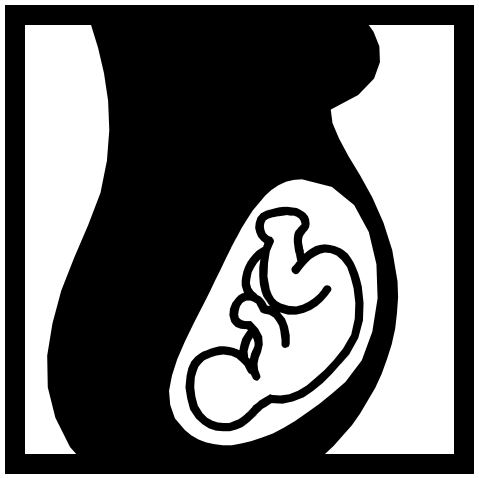


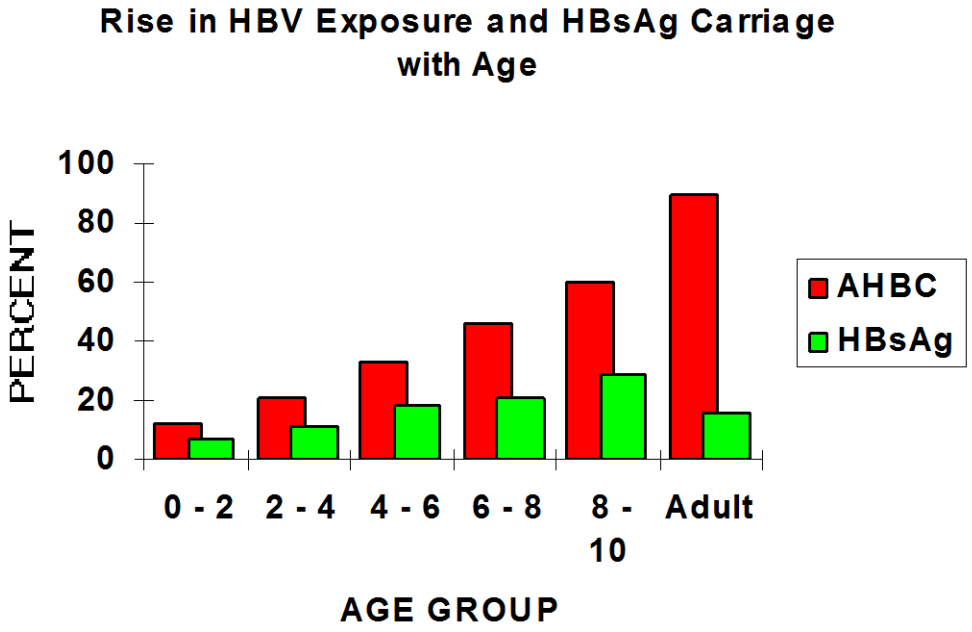
350 Million chronically infected
1 Million deaths per year





Modes of Transmission HBV



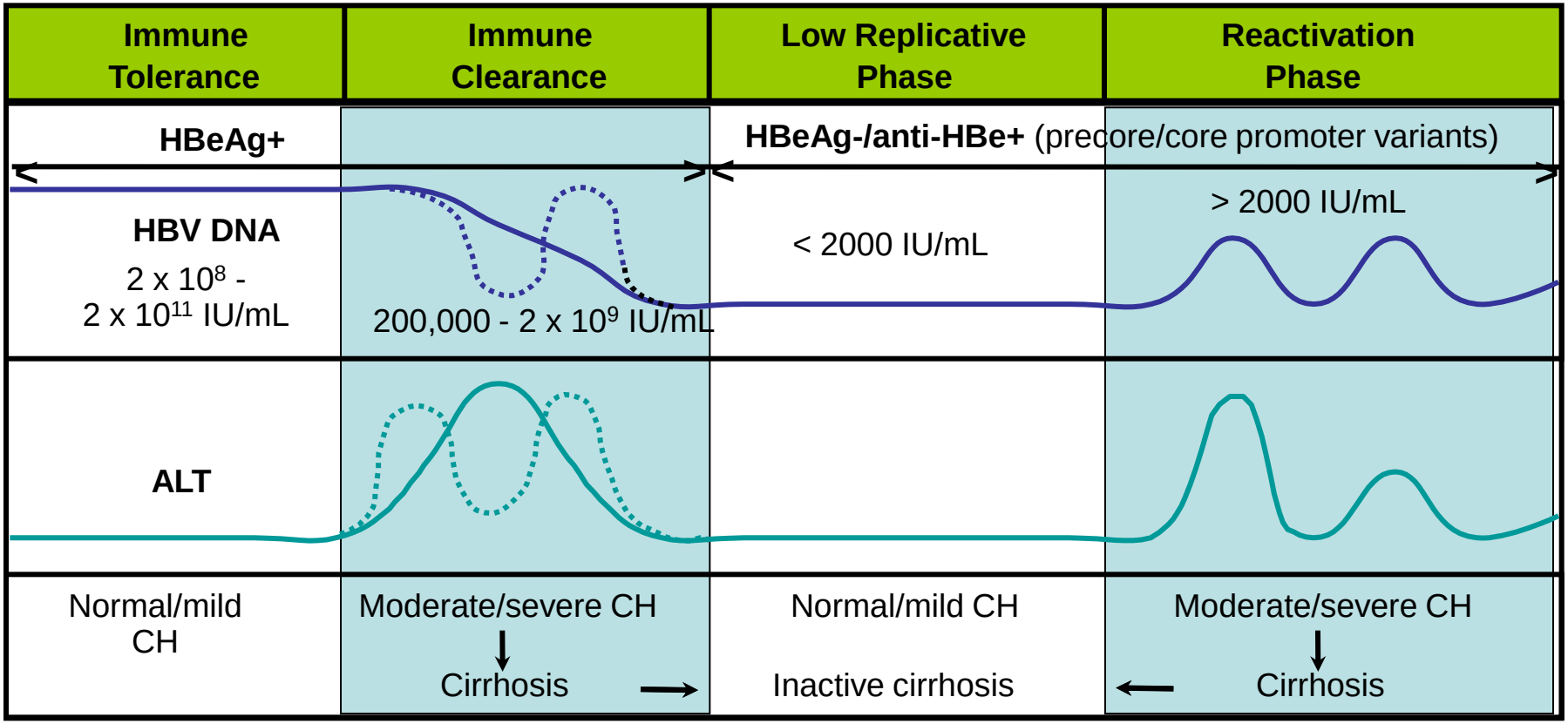


90% Chronicity

20% Chronicity

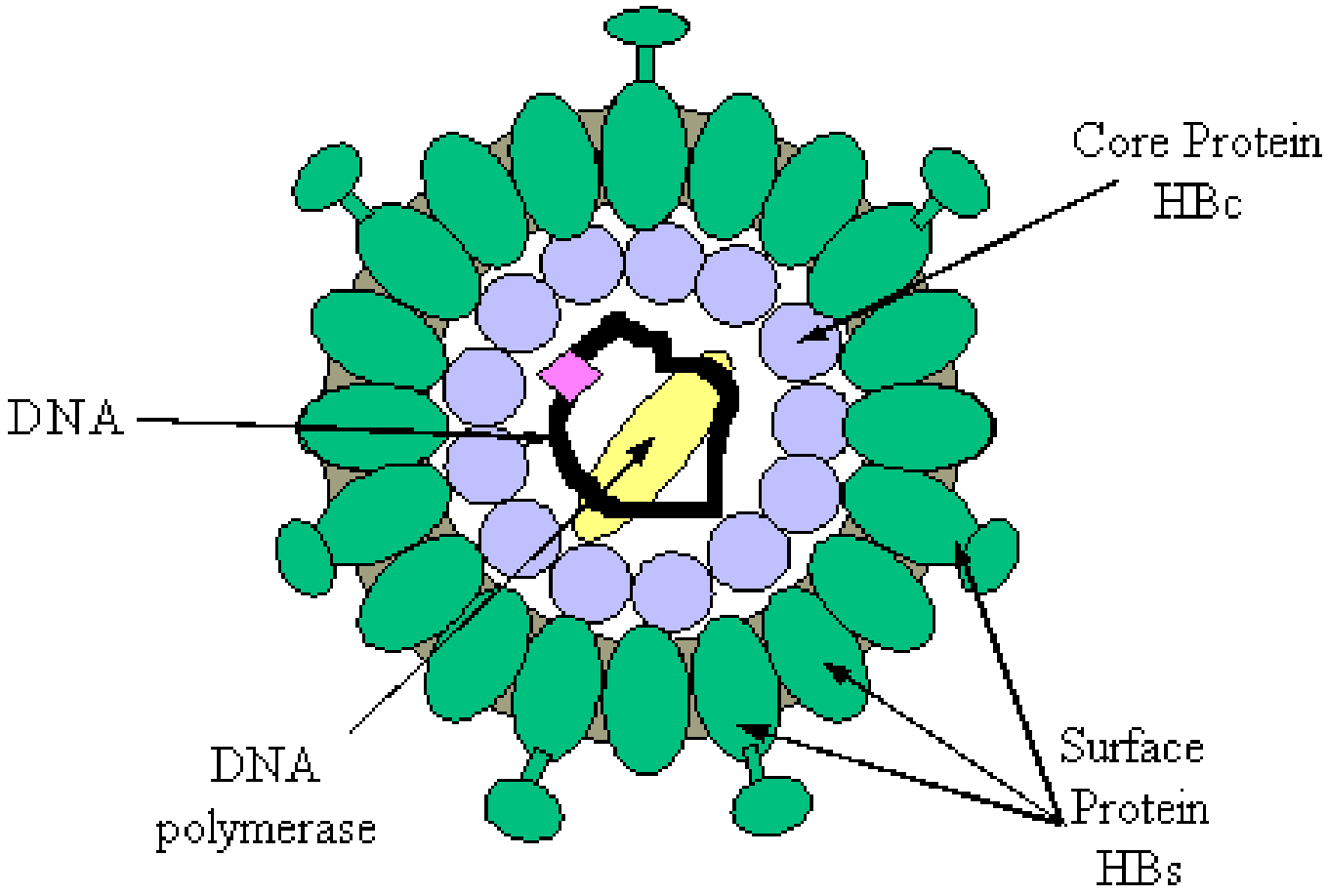
Sexual transmission - < 5% chronicity

Phases of Chronic HBV Infection

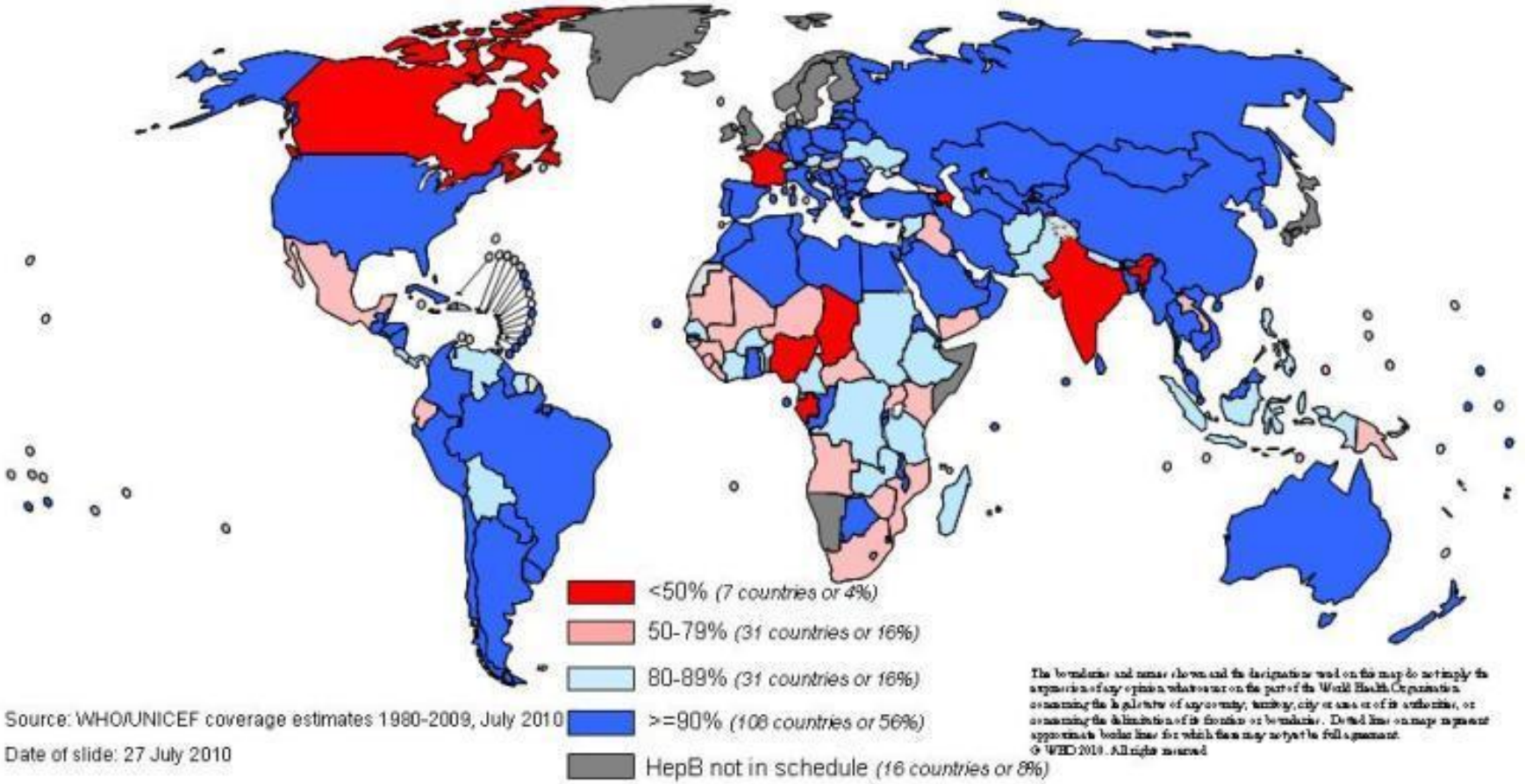


Slide courtesy of A. S. F. Lok, MD.

A Vaccine for Hepatitis B



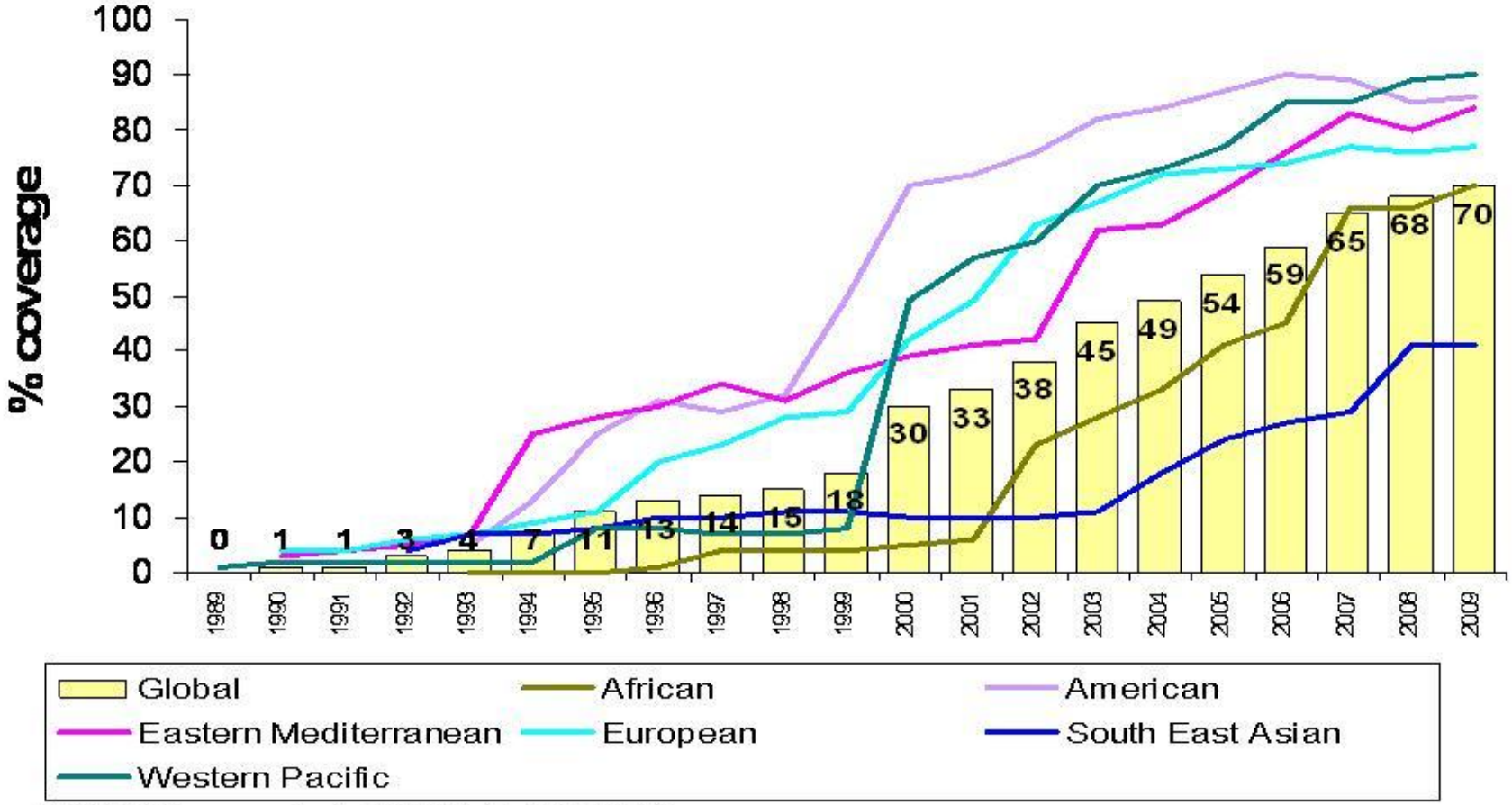
Immunization coverage with 3rd dose of HepB vaccines in infants, 2009



Source: WHO/UNICEF coverage estimates 1980-2009, July 2010

Date of slide: 27 July 2010

Global Immunization 1989-2009, 3rd dose of Hepatitis B coverage in infants global coverage at 70% in 2009



Source: WHO/UNICEF coverage estimates 1980-2009, July 2010, 193 WHO Member States. Date of slide: 26 July 2010

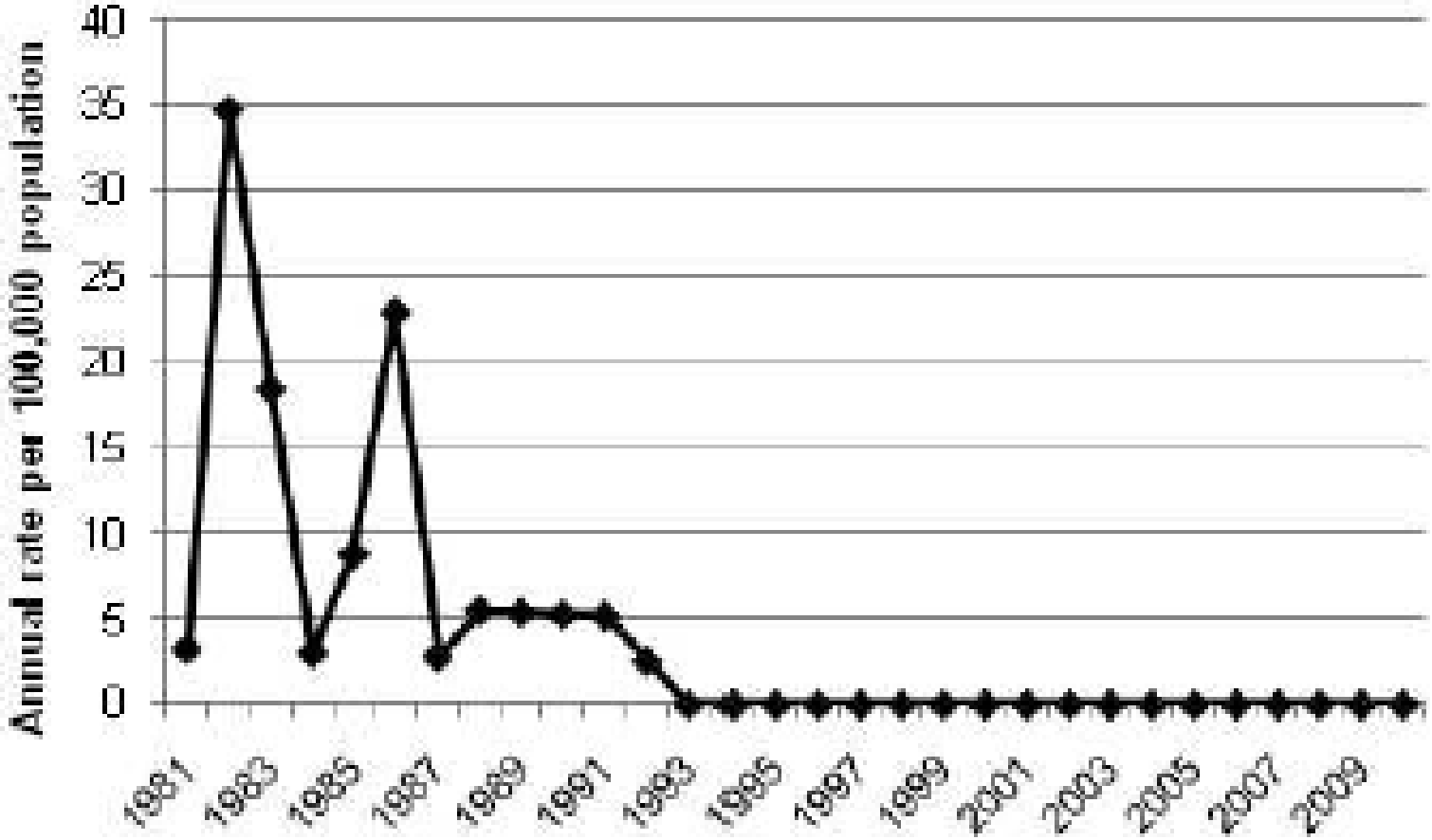
Vaccine Control of Chronic HBV in Gambia

	Fully vaccinated	Partially vaccinated	Unvaccinated
Infection (n/N, % 95% CI)	87/492 (17.7%, 14.4–21.3)	19/84 (22.6%, 14.2–33.0)	226/424 (53.3%, 48.4–58.1)
VE (95% CI)	67.0 (58.2–74.6)	57.7 (37.2–76.8)	Ref
Chronic carriage (n/N, % 95% CI)	2/492 (0.4%, 0.04–1.5)	1/84 (1.2%, 0.03–6.5)	51/420 * (13.2%, 10.1–16.8)
VE (95% CI)	96.6 (91.5–100)	90.1 (69.9–100)	ref

*four participants were HBsAg positive during the first screening, but could not be traced to confirm chronic carriage
VE: vaccine efficacy
CI: confidence interval
doi:10.1371/journal.pone.0000753.t002

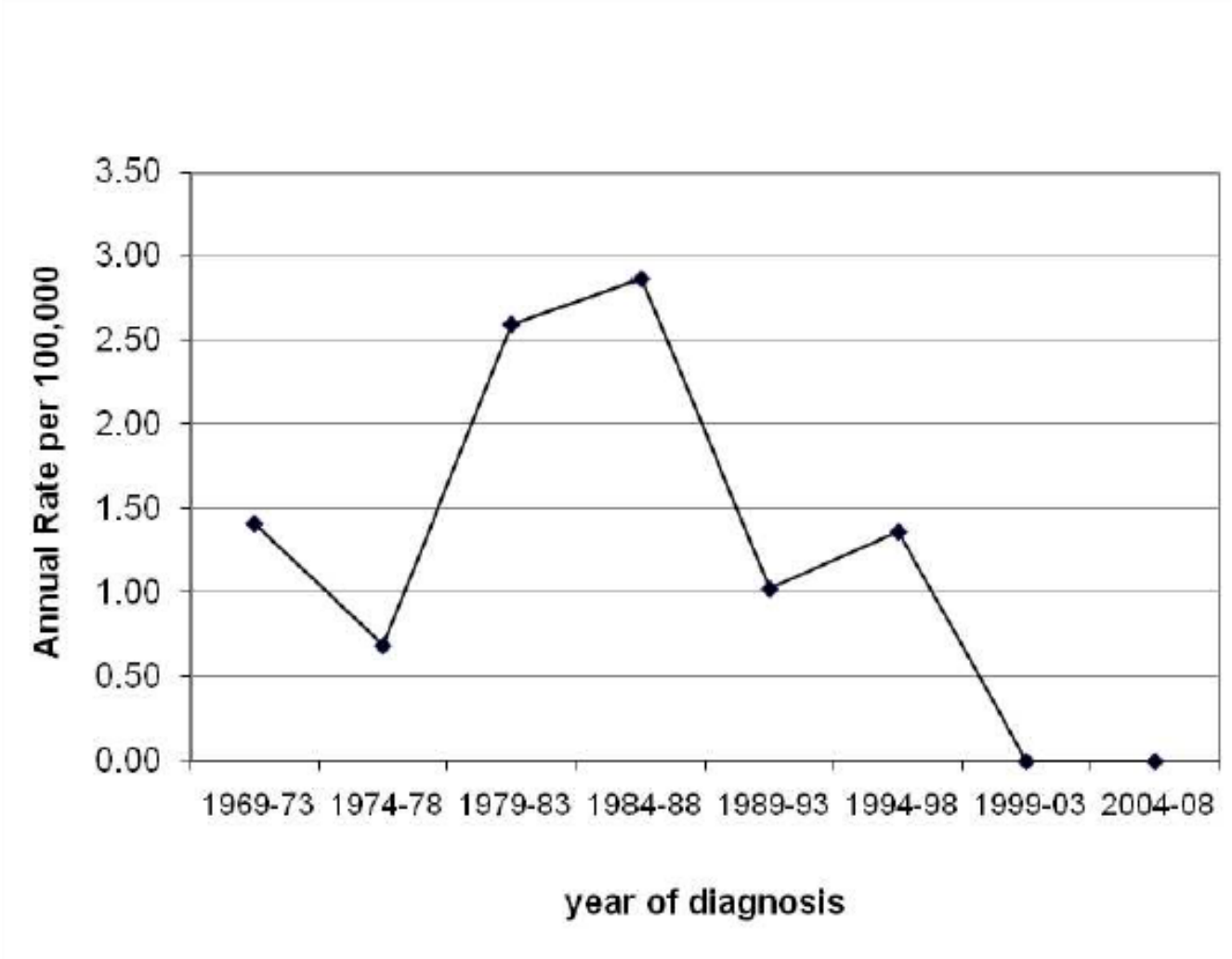
Van der Sande. Plos One 2007

Symptomatic Acute HBV In Alaska



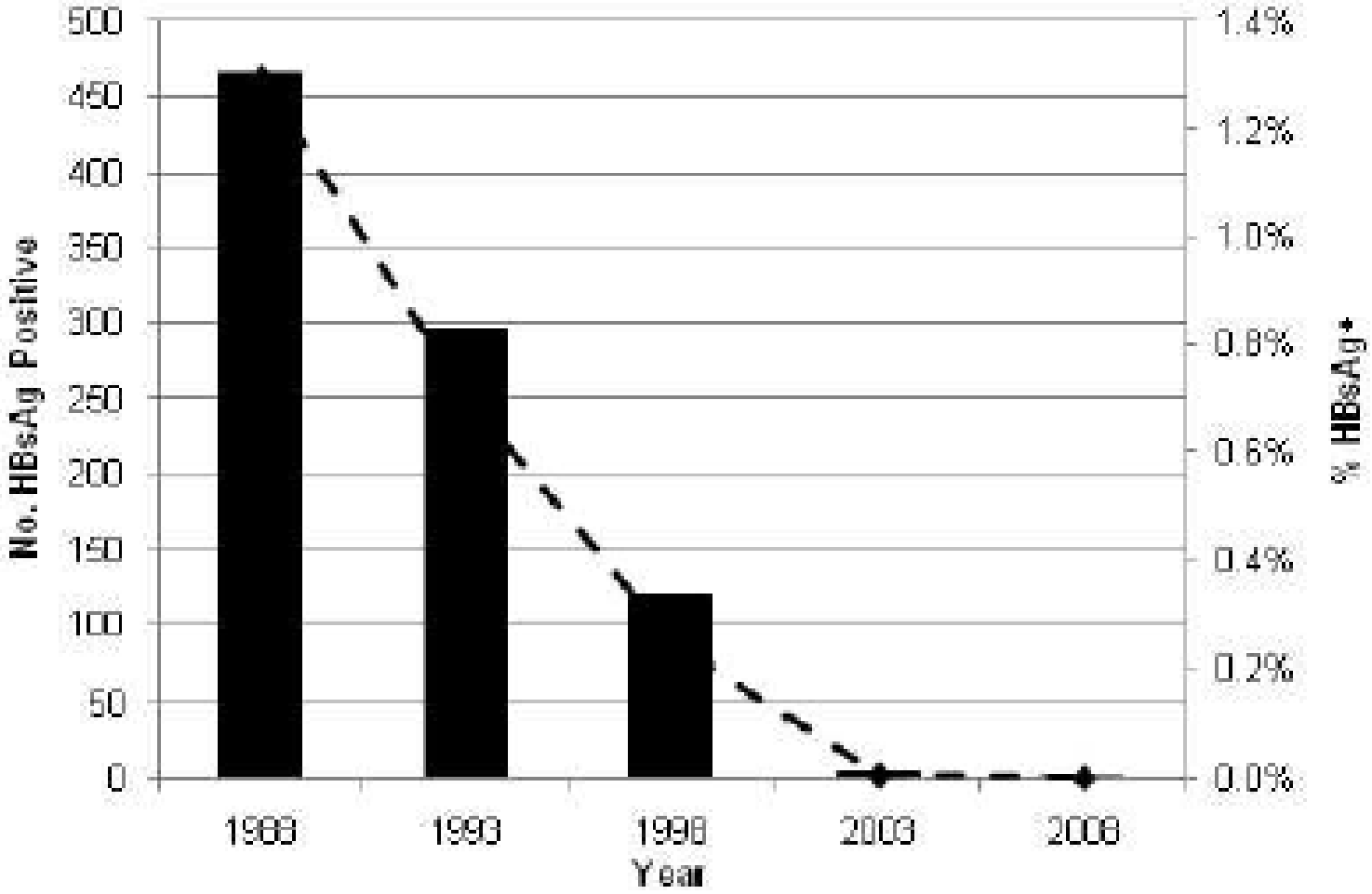
McMahon. Hepatology 2011

HBsAg Carriage Rate in Alaska (Under 21)



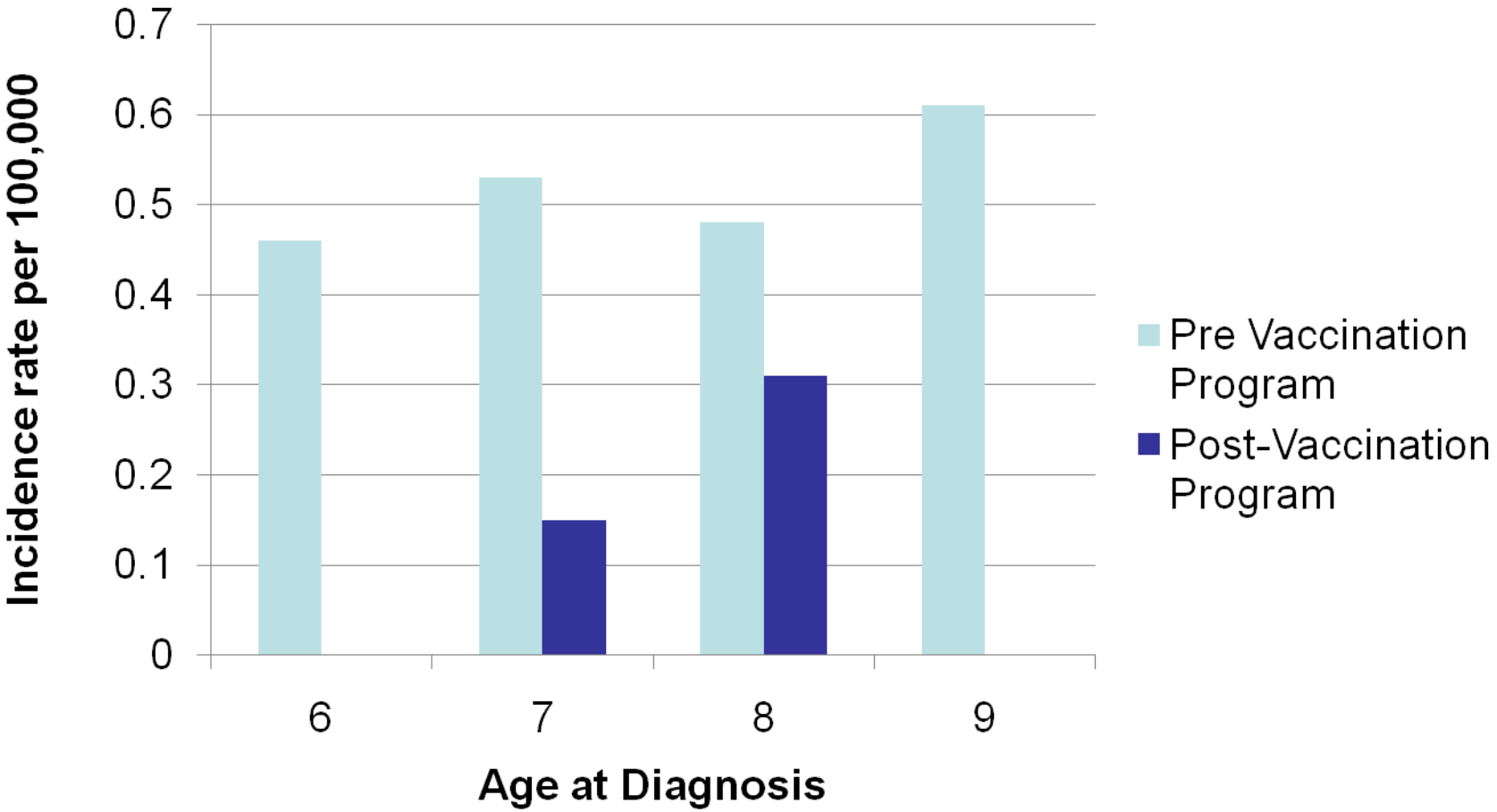
McMahon. Hepatology 2011

Annual Incidence of HCC in <21s



McMahon. Hepatology 2011

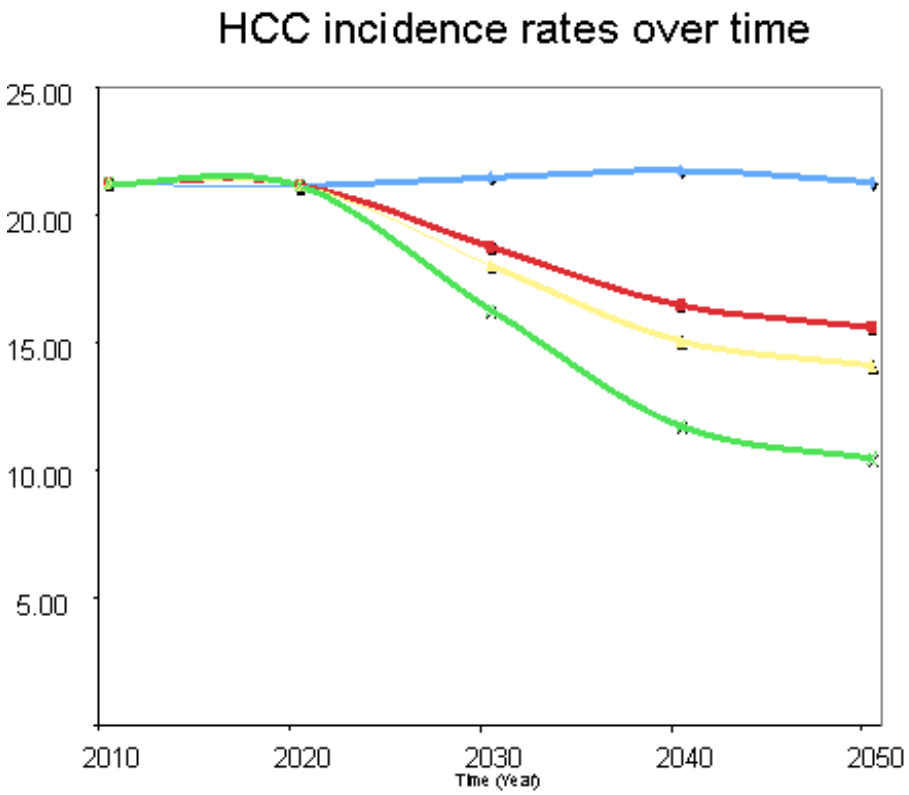
HCC Incidence in Taiwan Response to Vaccination

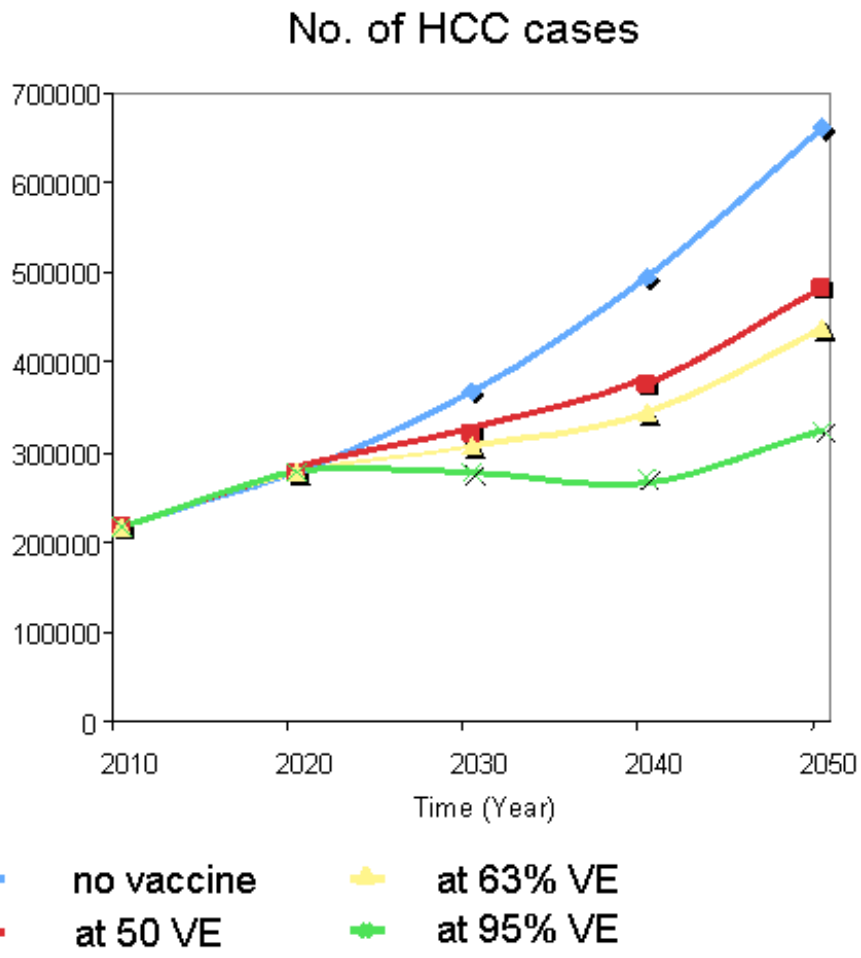


But..

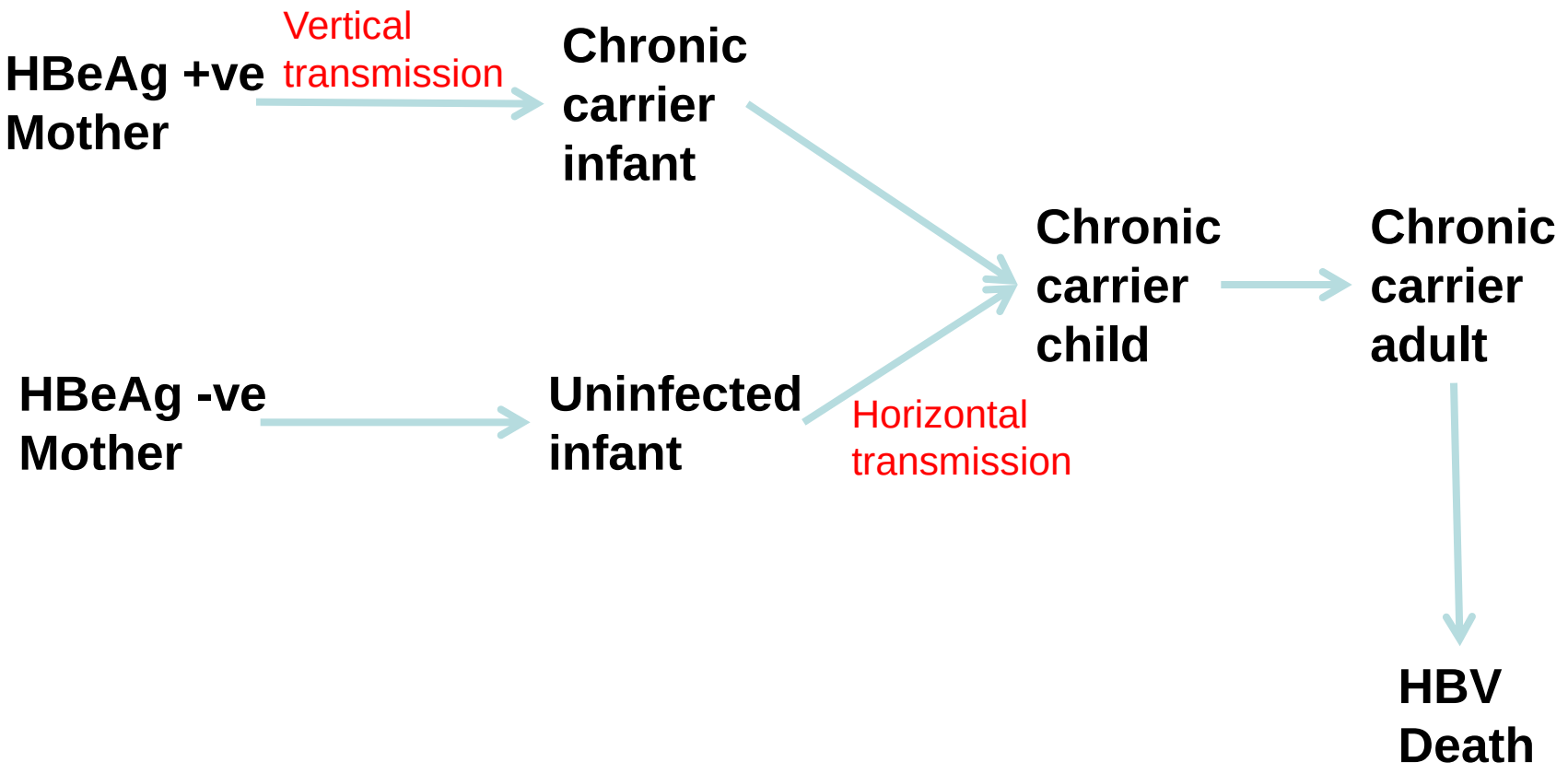
- HBV vaccination introduced in infants between 1990 – 2001
- Chronic HBV legacy in adults
- HBV coverage rates <= 70%

Vaccination Alone is Not the Answer

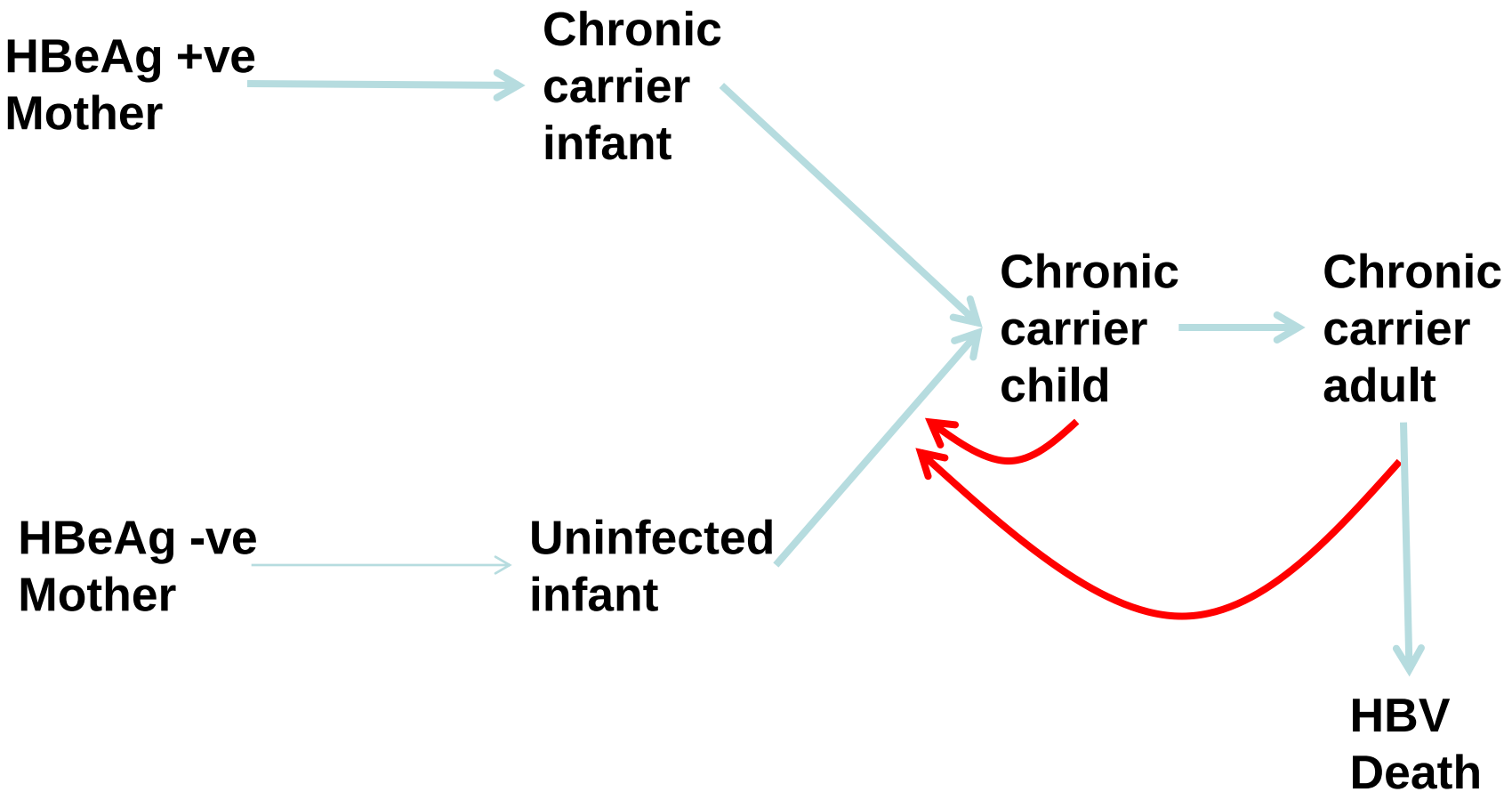




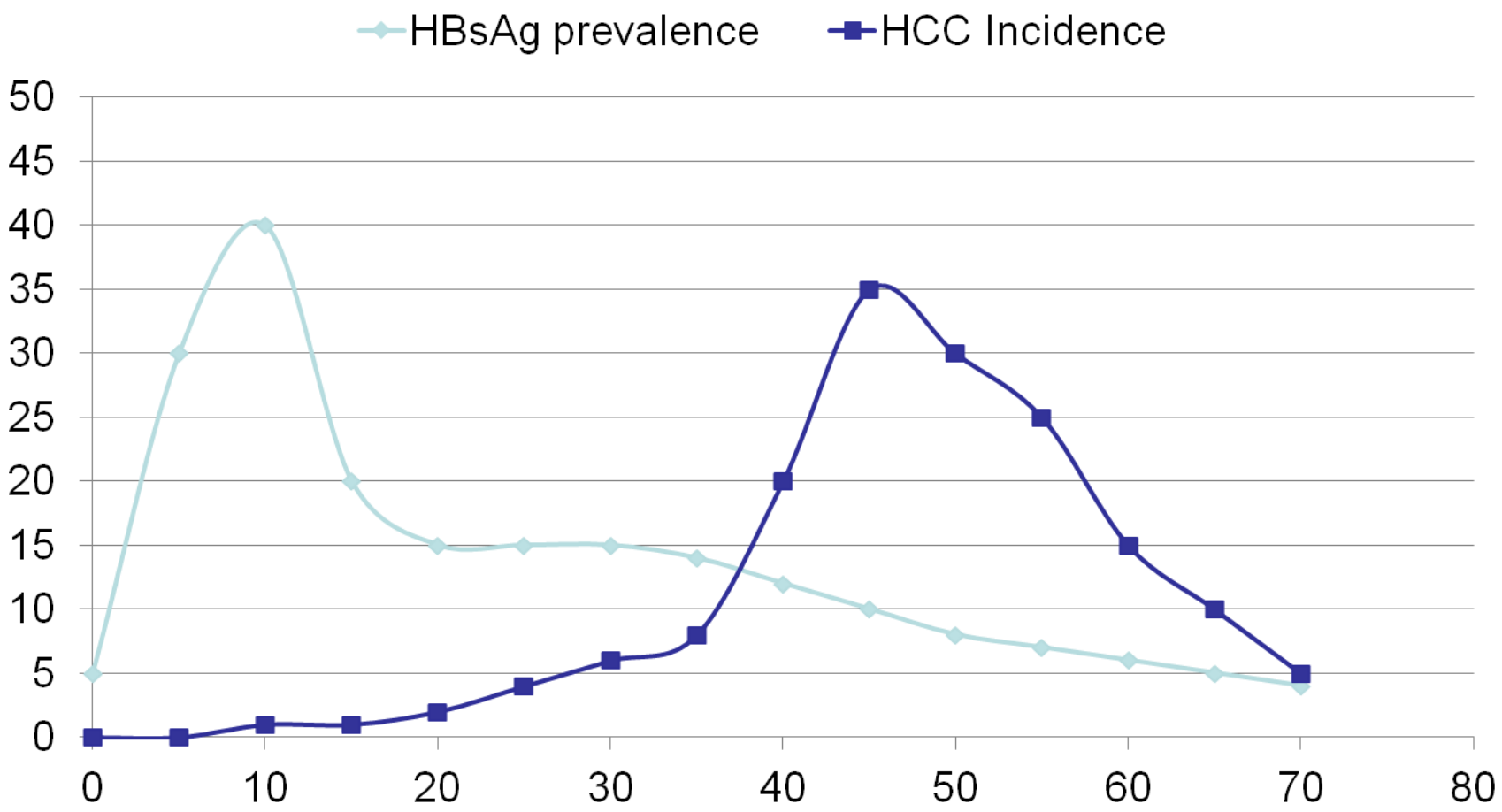
HBV Transmission



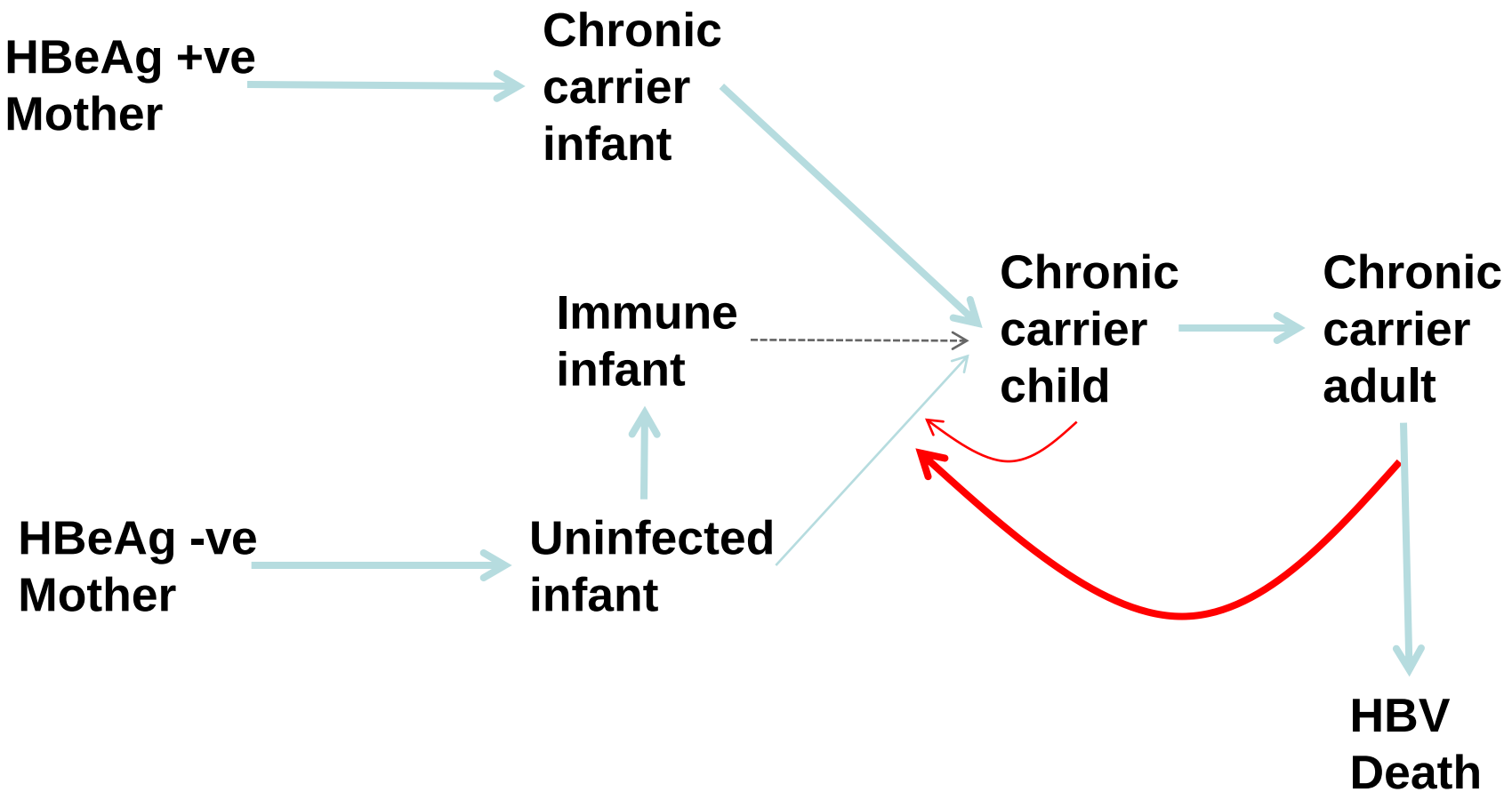
Infant Vaccination



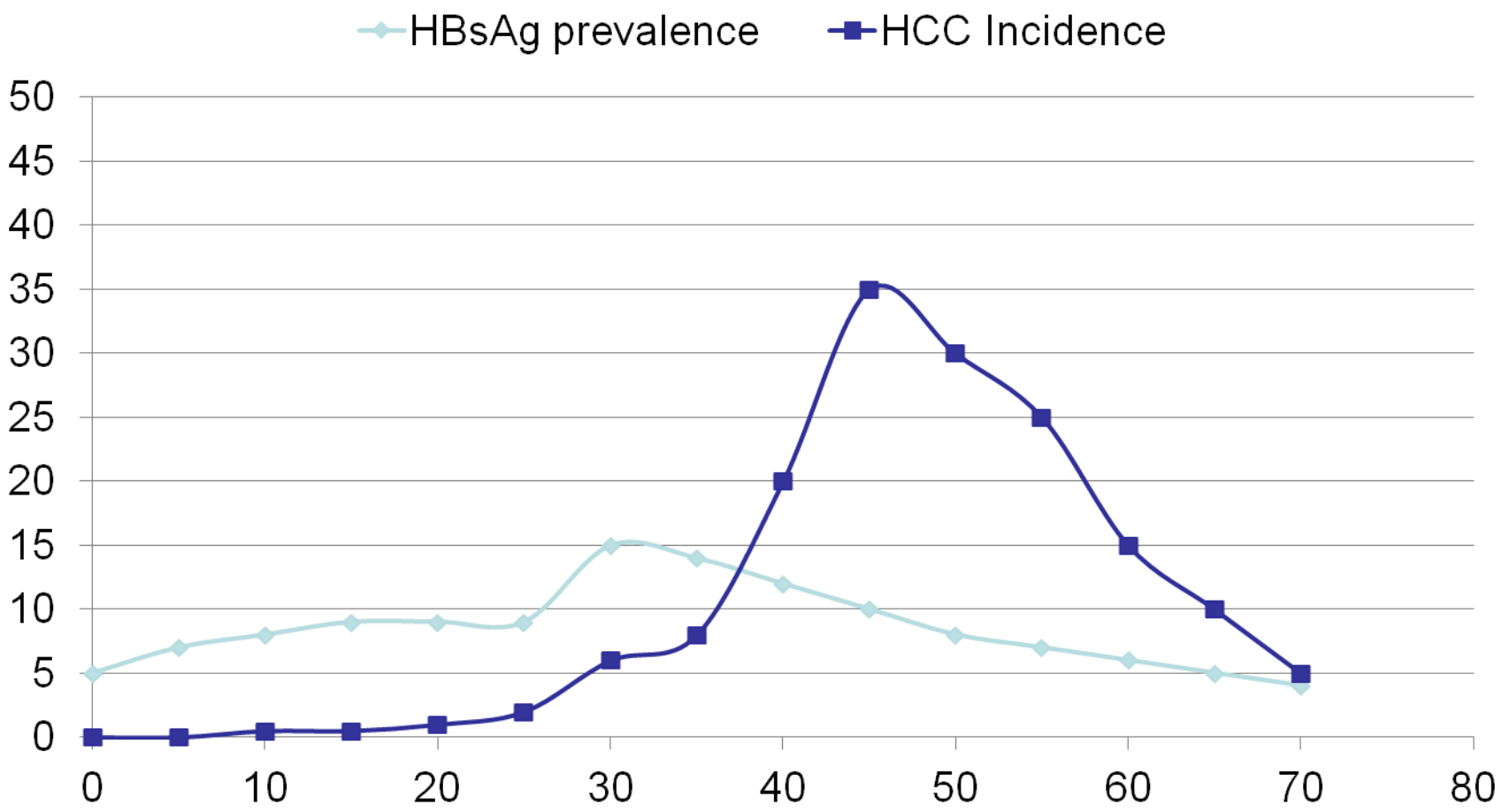
Control / Elimination of HBV Pre-Vaccination



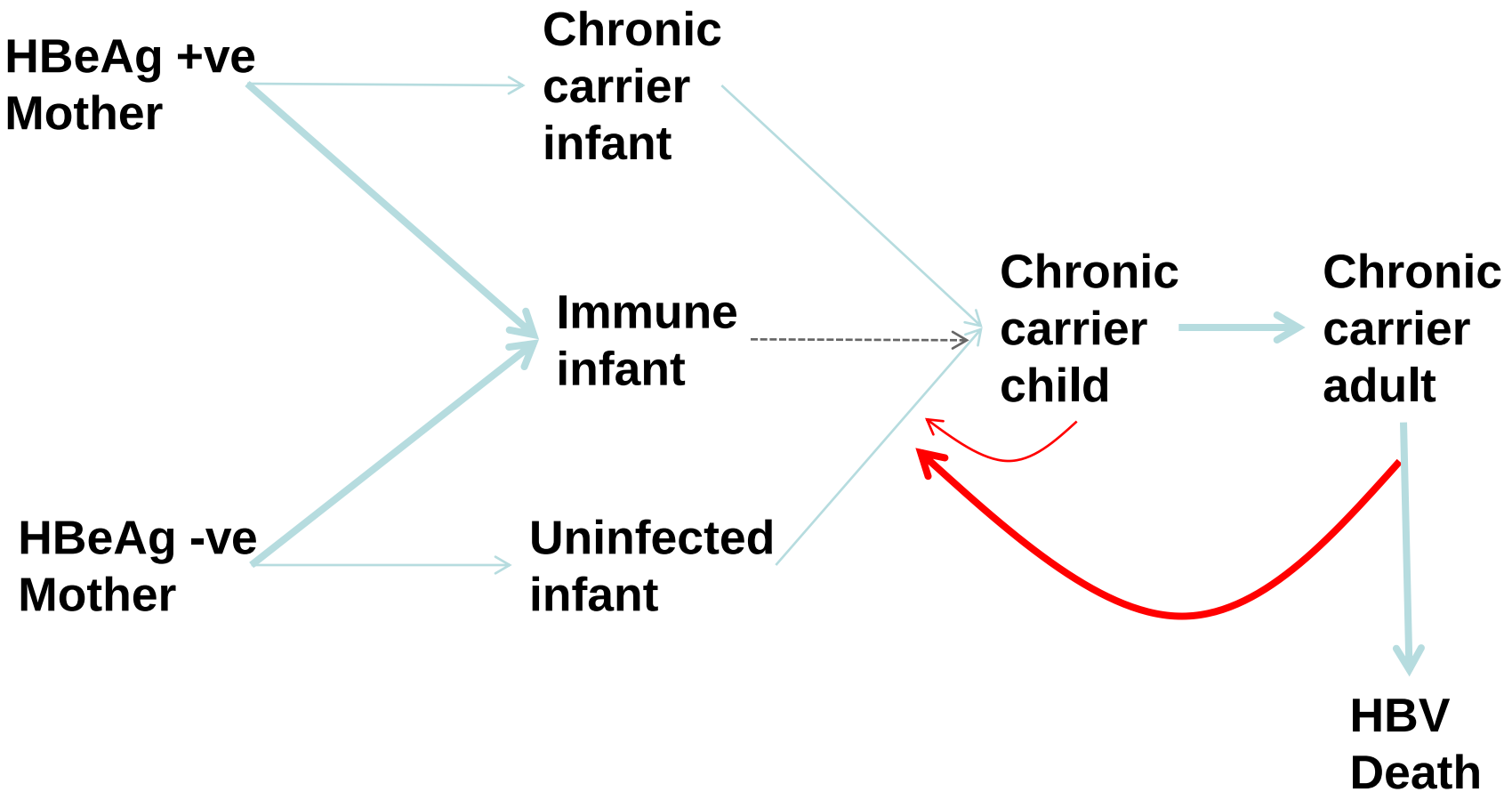
Infant Vaccination
EPI Regimen



Control / Elimination of HBV Based on Infant Vaccination



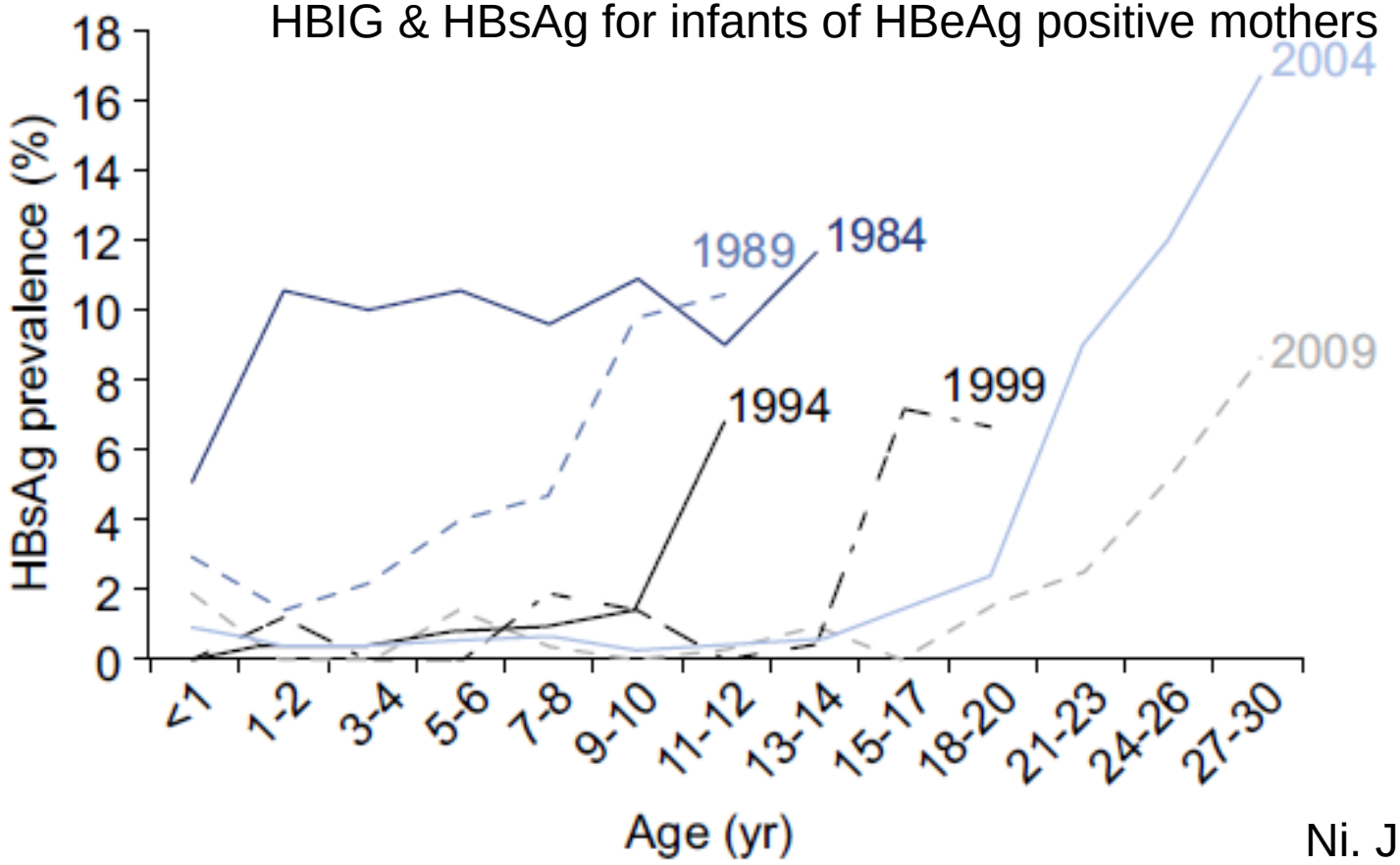
Neonatal Vaccination



Taiwanese Vaccine Program

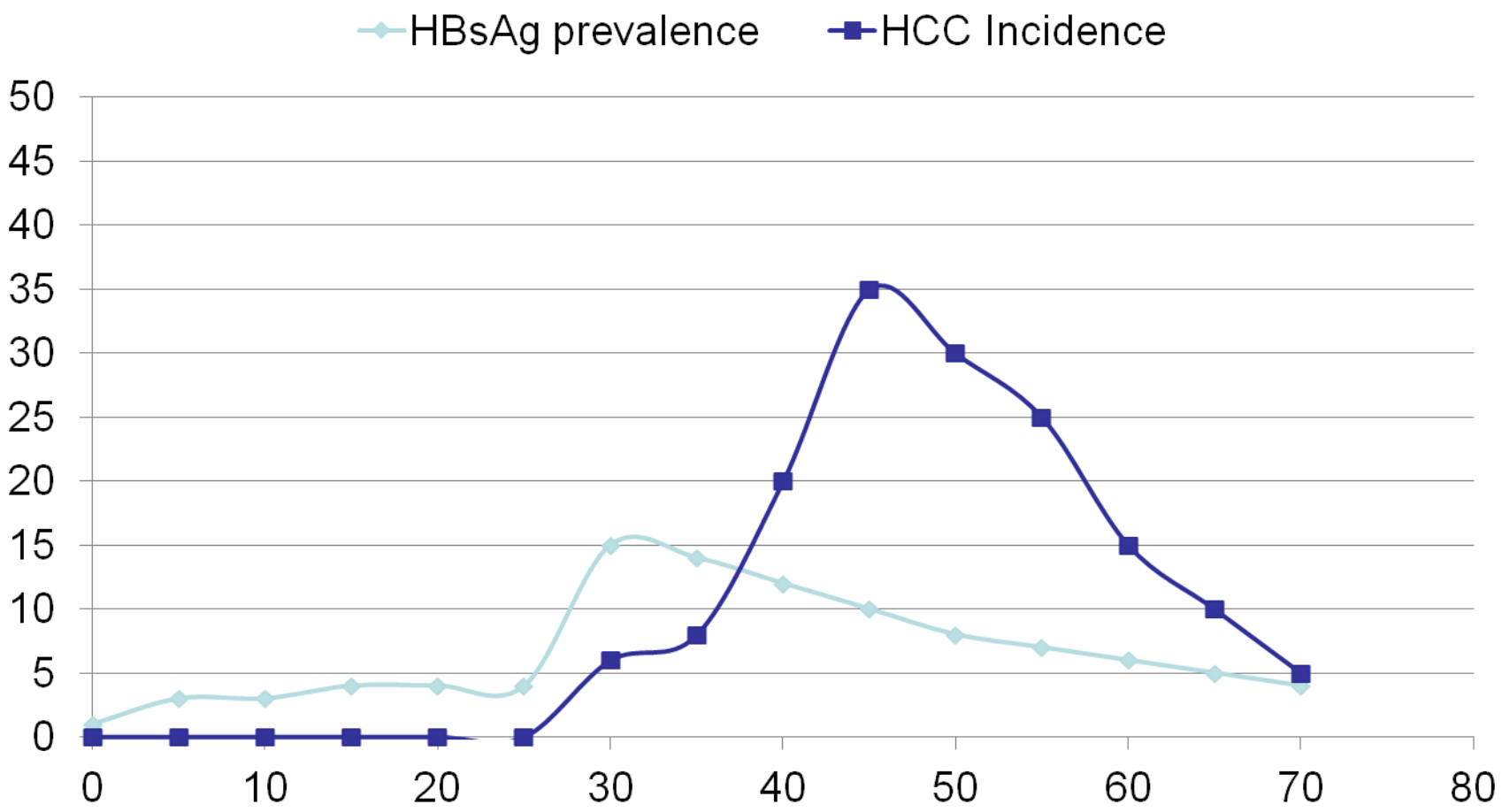
HBV vaccine program began 1984
- 1984-92 Plasma derived
- 1992 – present recombinant

Maternal screening
- HBIG & HBsAg for infants of HBeAg positive mothers

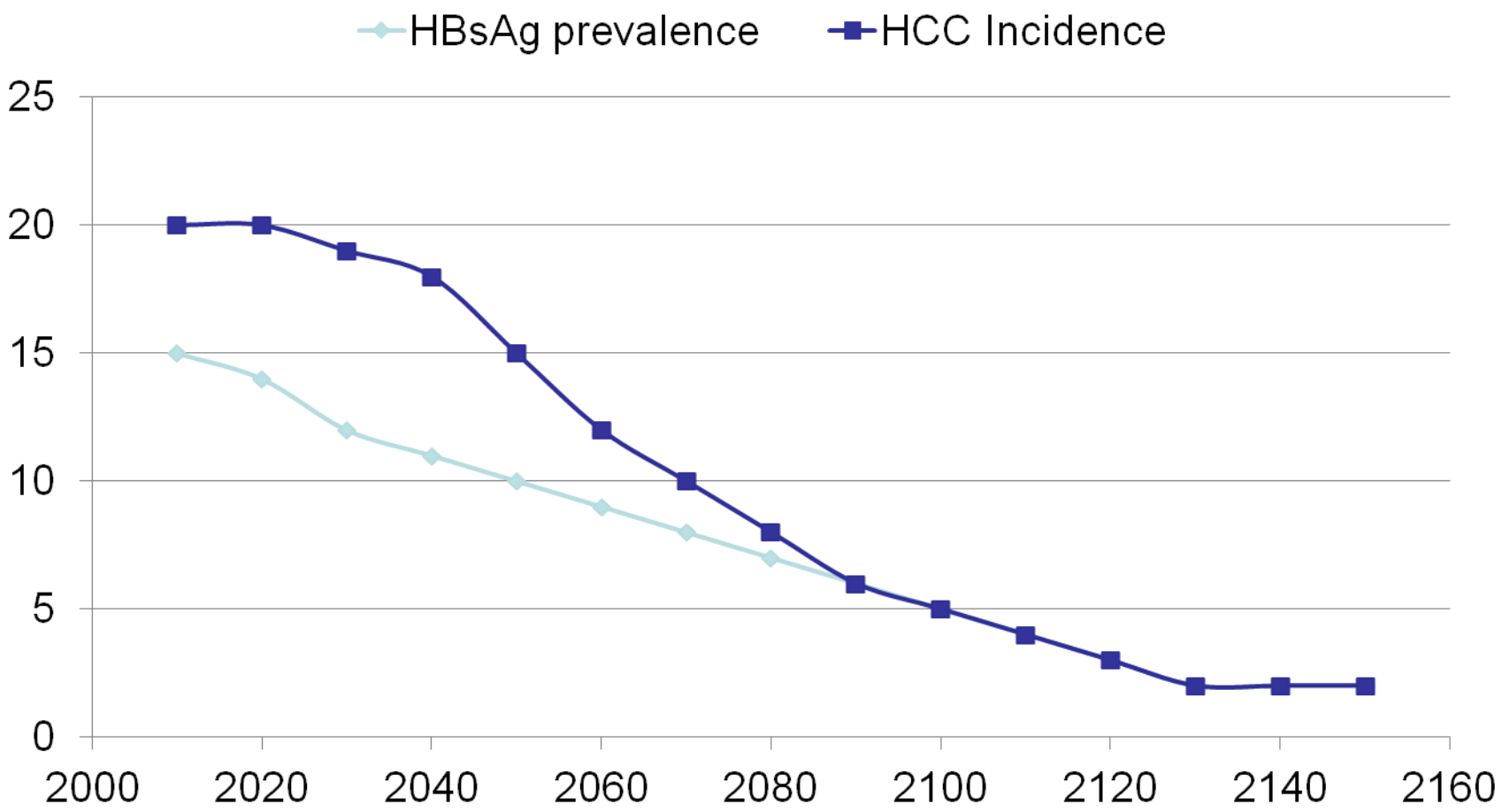


Ni. J.Hepatol 2012

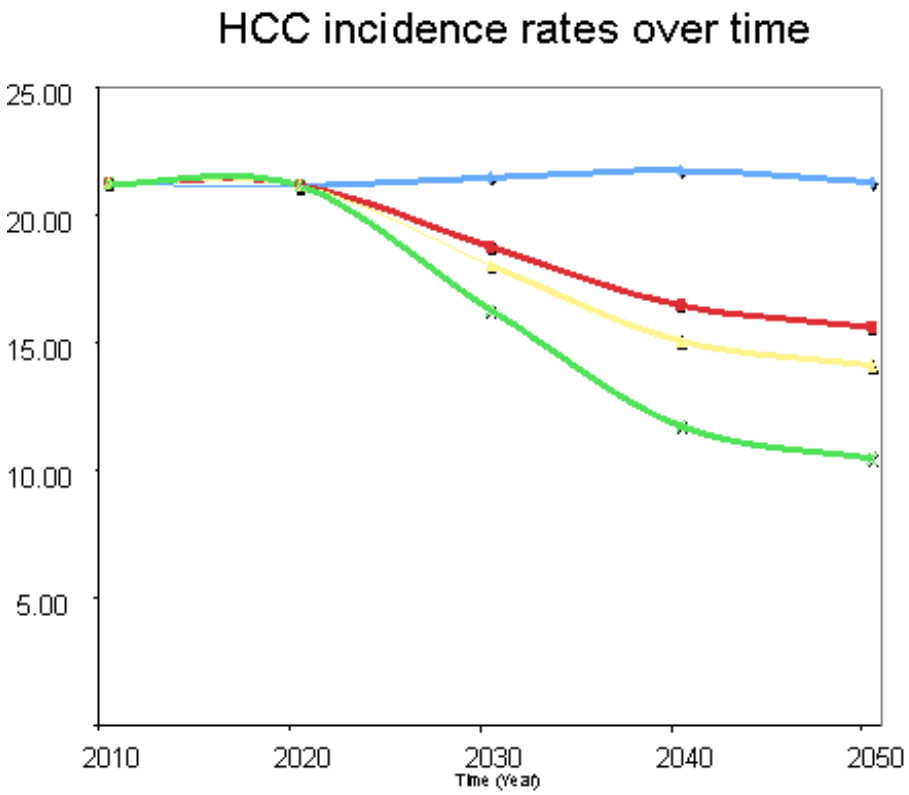
Control / Elimination of HBV Based on Neonatal Vaccination

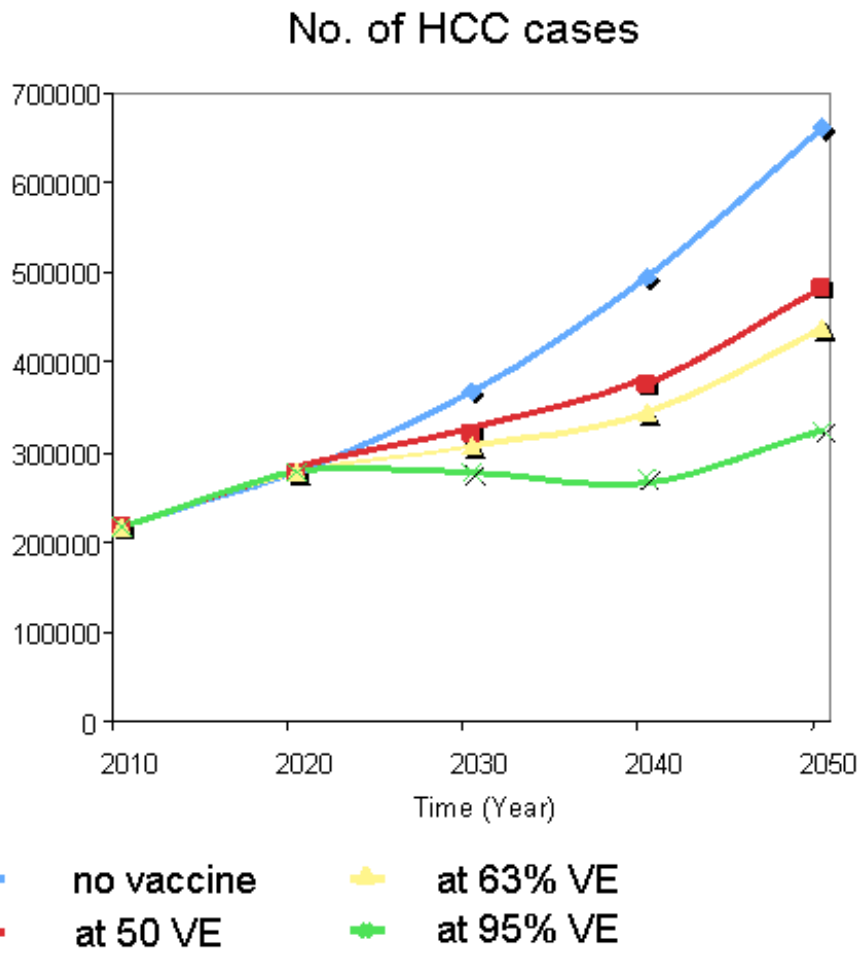


Control / Elimination of HBV

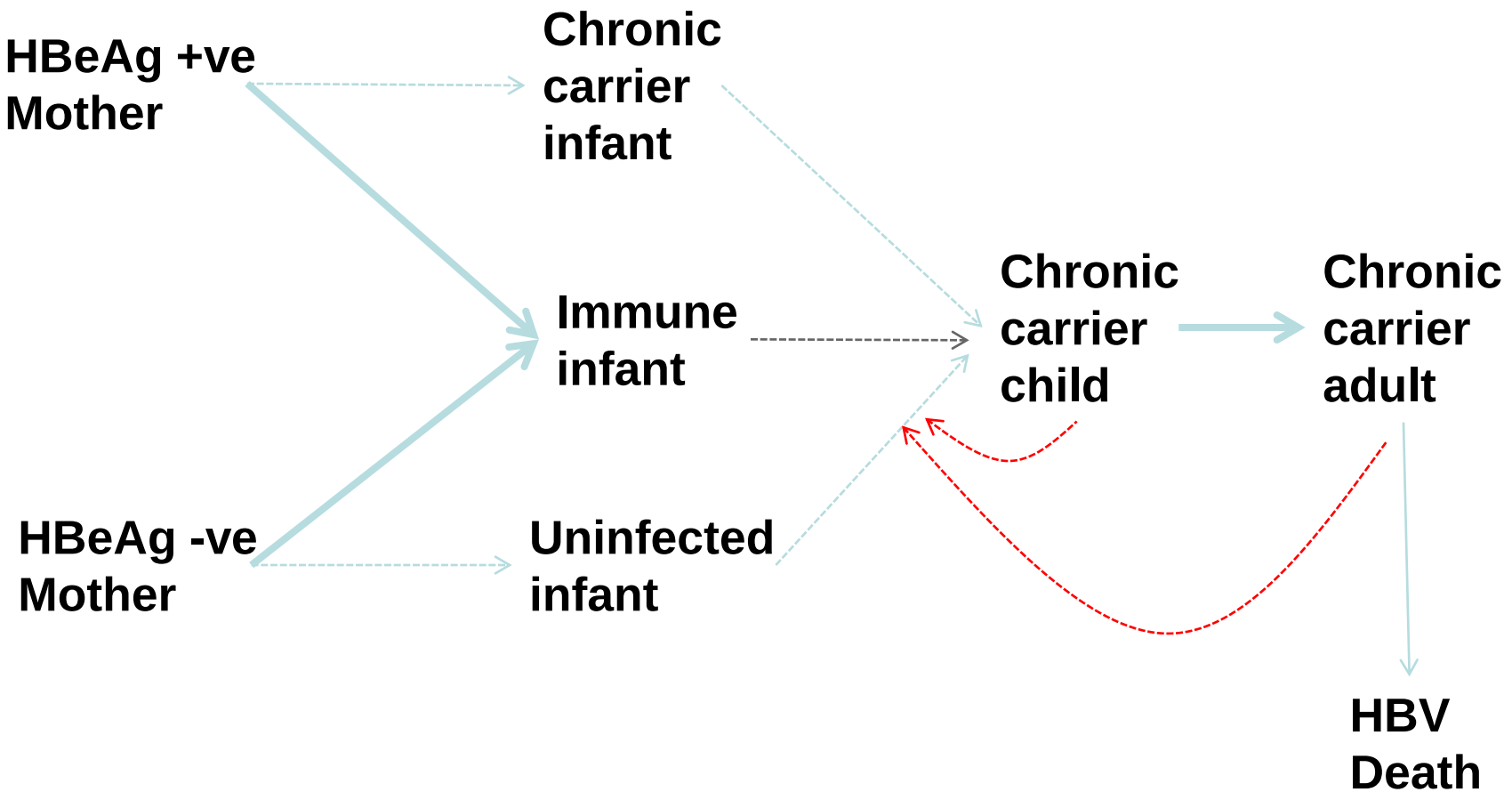


Vaccination Alone is Not the Answer

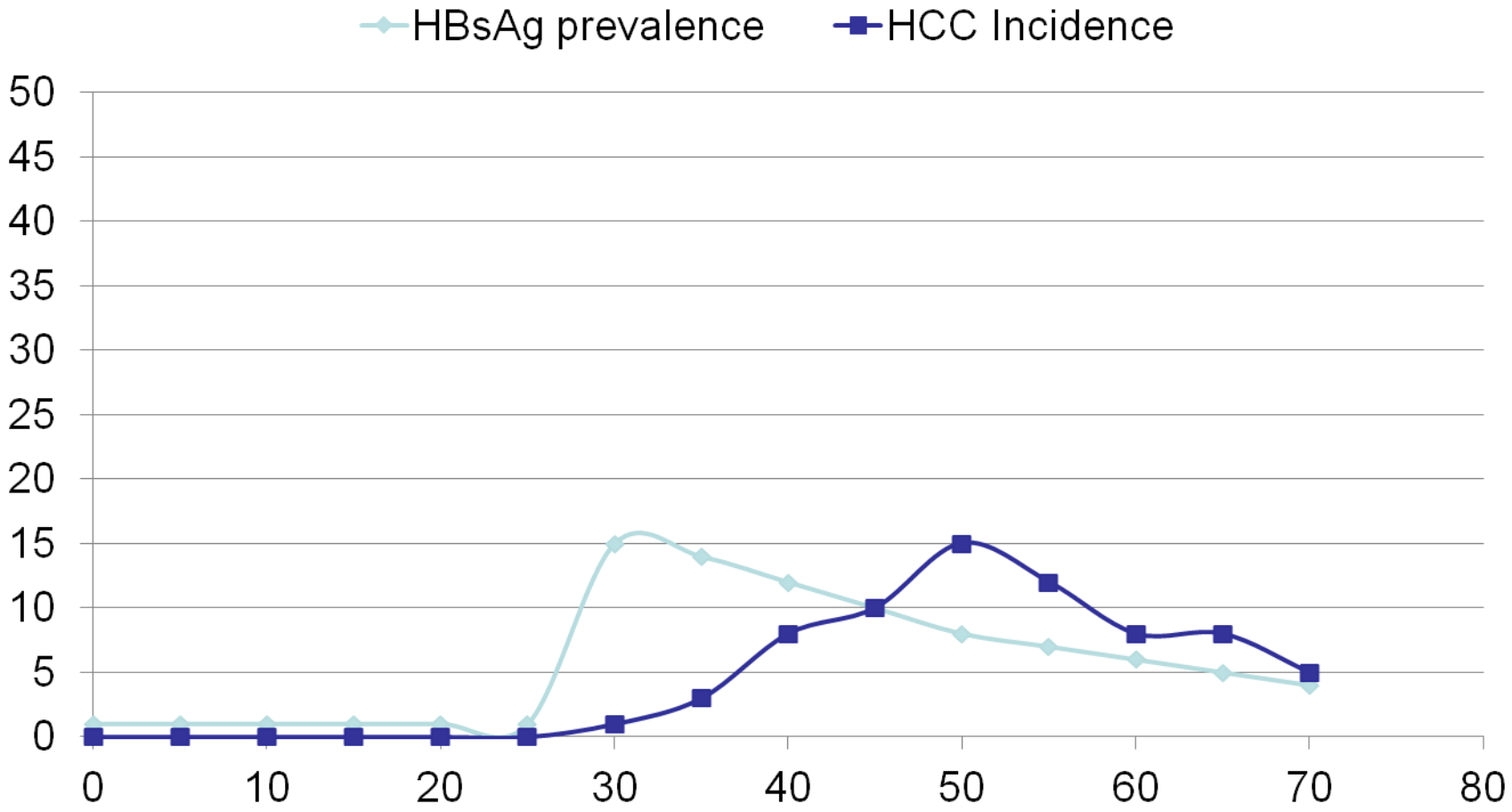




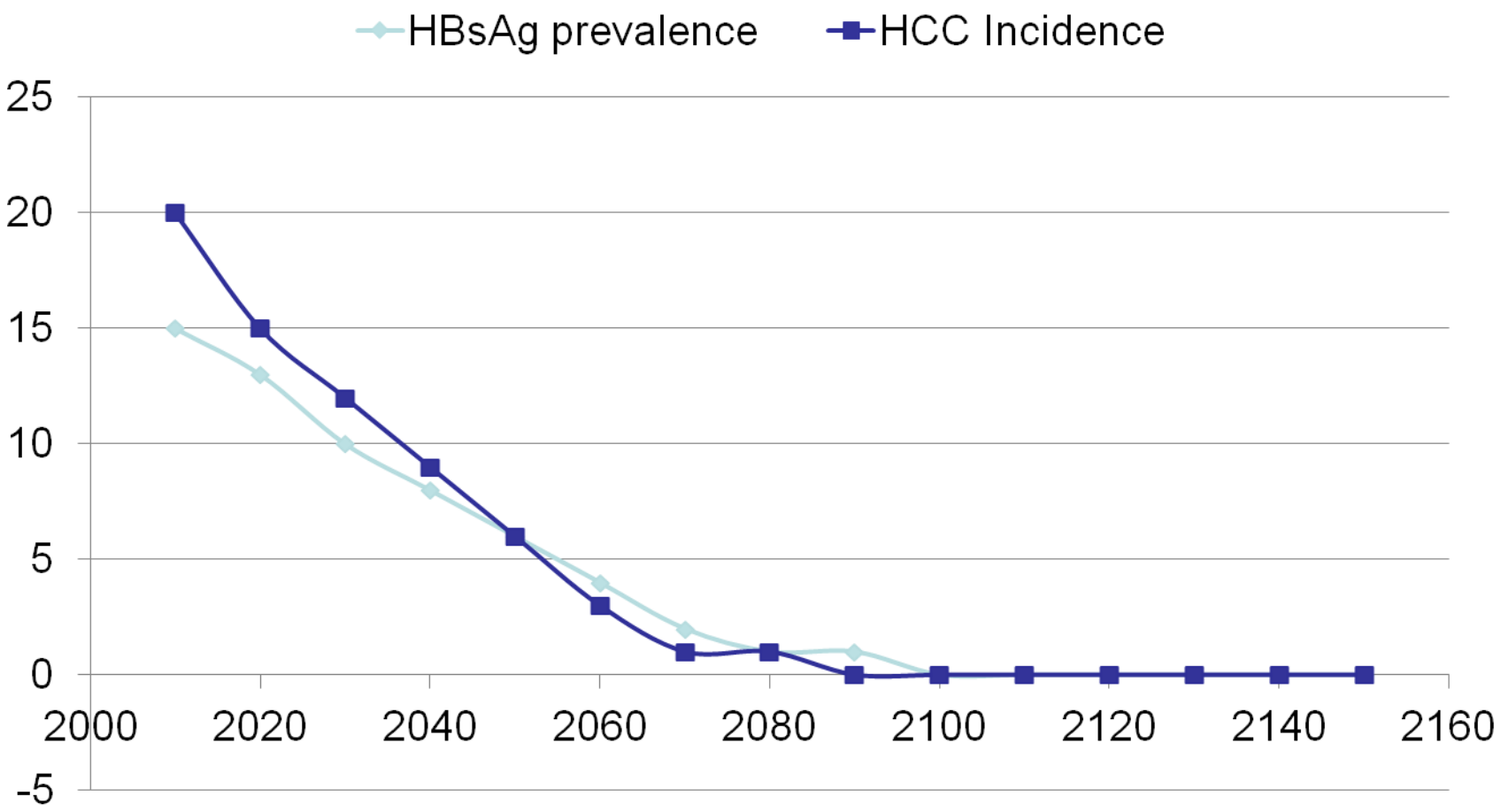
Neonatal Vaccination & Treatment



Control / Elimination of HBV Based on Vaccination and Treatment



Control / Elimination of HBV



Why No Treatment for HBV In Resource Poor Settings

- Global Health Agenda
- Requirement for complex diagnostics
- Drug cost and availability
- Skills and education

Driving the Global Health Agenda

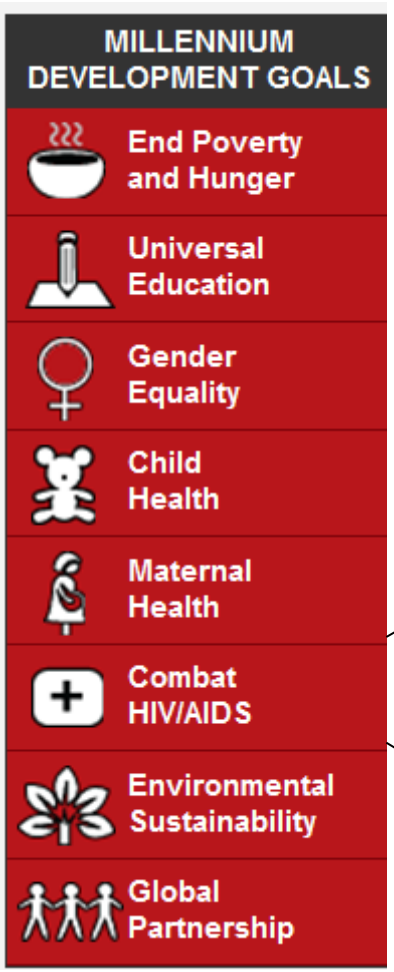
Willie Sutton

BILL & MELINDA GATES foundation

Priority Areas of Focus

Our work in infectious diseases focuses on developing ways to fight and prevent enteric and diarrheal diseases, HIV/AIDS, malaria, pneumonia, tuberculosis, and neglected and other infectious diseases.

- Visceral leishmaniasis is found in 62 countries.
- 80 percent of deaths from cervical cancer (caused by the human papillomavirus or HPV) are in poor countries.
- Flavivirus diseases, such as dengue and yellow fever, cause 19,000 deaths a year.
- 60 million Africans are at risk of infection from trypanosomiasis, also known as sleeping sickness.
- More than 2 billion people are infected with parasitic worms (helminths) that cause diseases such as hookworm, schistosomi-asis, and guinea worm.

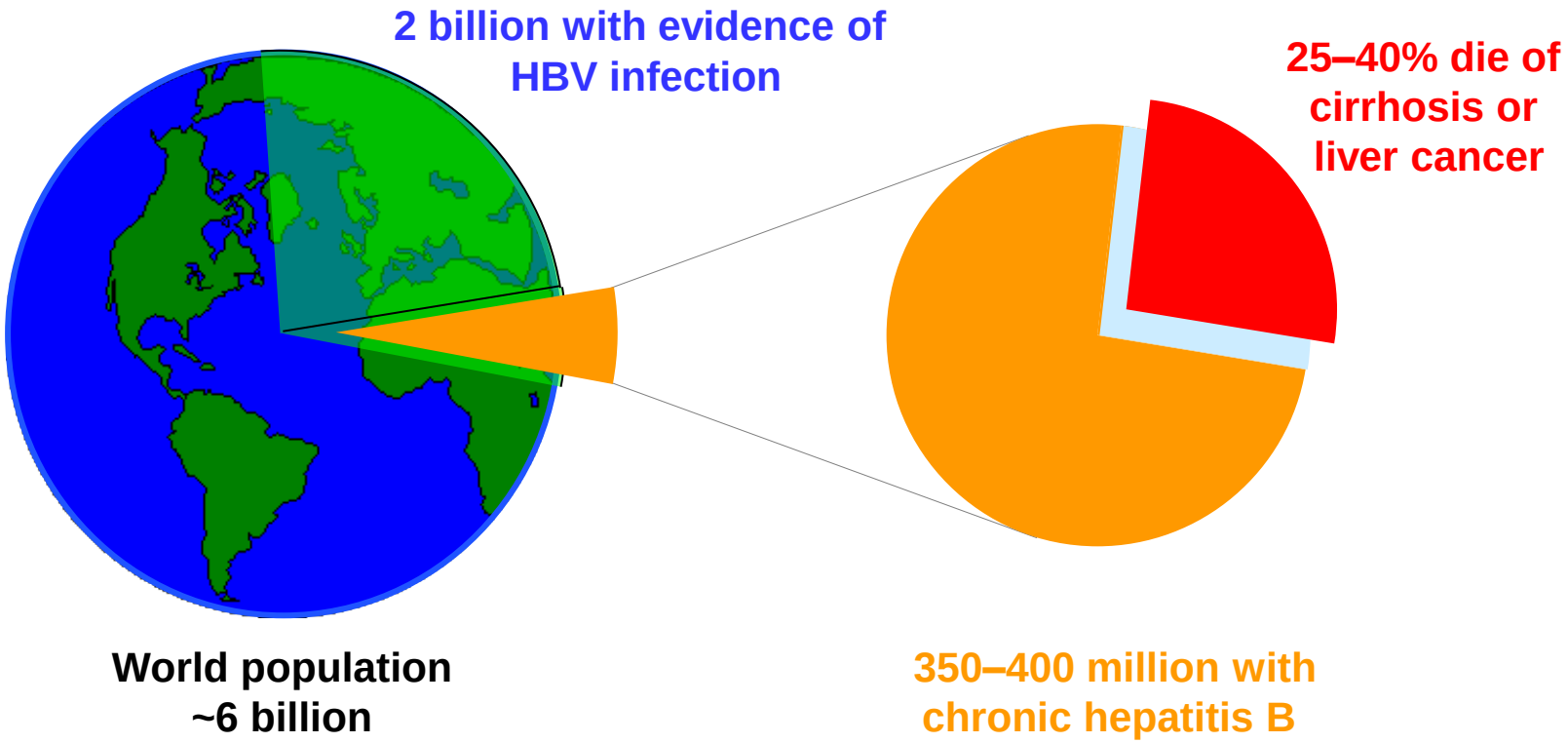


HIV
Malaria
TB

Neglected Diseases

Schistosomiasis
Filariasis
Hookworm
Leishmaniasis
Onchocerciasis
Cystercercosis
Trypanosomiasis
Leprosy
Dengue
etc

The global impact of HBV disease



The hepatitis B virus is 50 to 100 times more infectious than HIV.

WHO, Fact sheet No. 204; CDC, Viral hepatitis B fact sheet; Conjeevaram HS, Lok AS. J Hepatol. 2003;38:S90-103
Lee WM. N Engl J Med. 1997;337:1733-45. Lok AS. N Engl J Med. 2002;346:1682-3

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- Global Health Agenda
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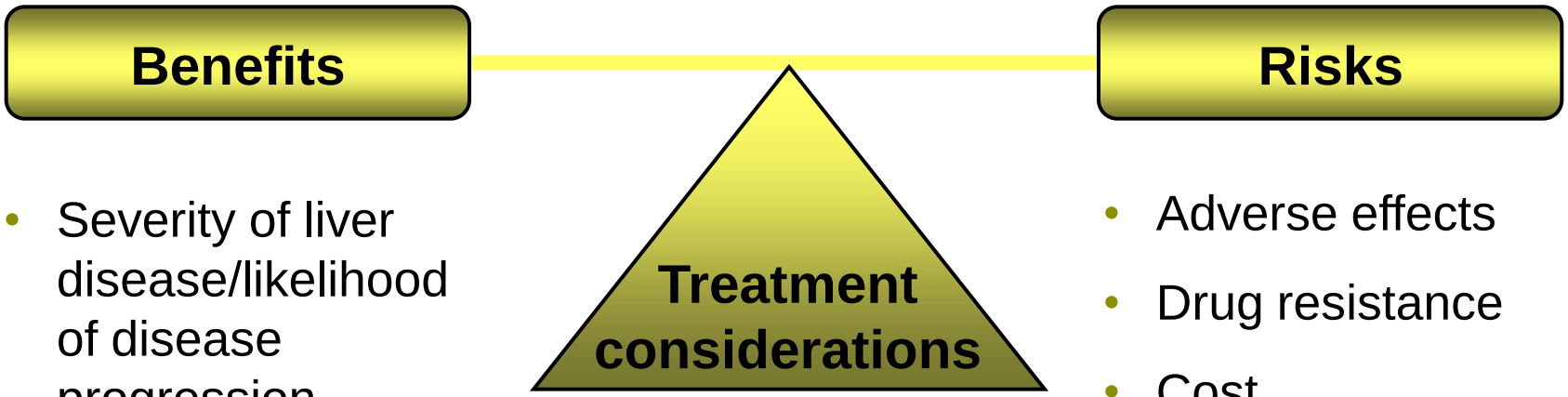
HBV Assessment

Different phases of chronic hepatitis B infection				
	Immuno-tolerant (Phase 1)	**Immunoactive (Phase 2)**	**Inactive HBsAg carrier (Phase 3)**	**HBeAg negative (Phase 4)**
HBsAg	+	+	+	+
HBeAg	+	+	-	-
Anti-HBe	-	-	+	+
ALT	Normal	High	Normal	High or fluctuating
HBV DNA (IU/ml)	$>2 \times 10^4$	$>2 \times 10^4$	$<2 \times 10^2$	$>2 \times 10^3$
Inflammation on histology	None or minimal	Active	None or minimal	Active

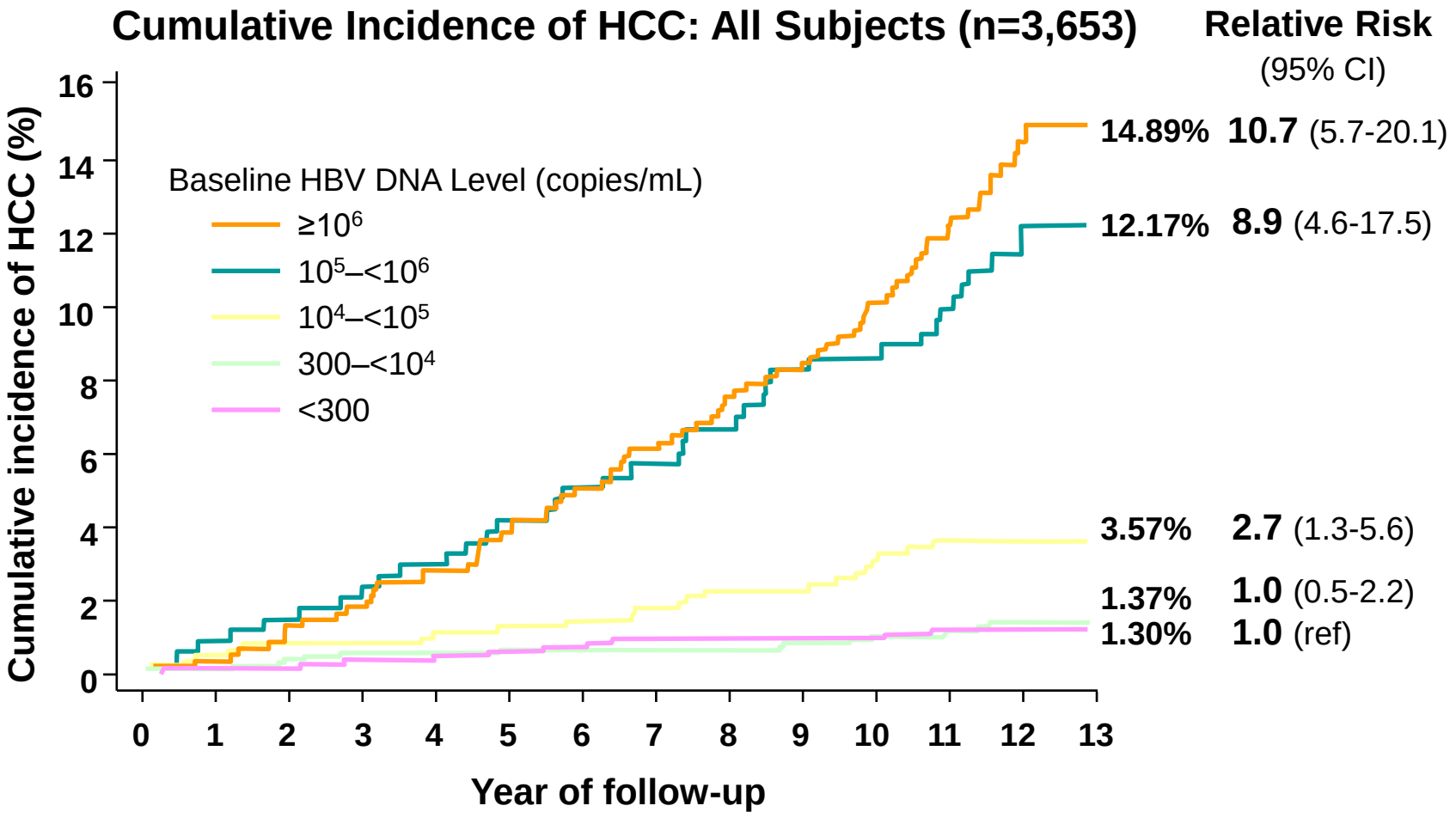
Who should be treated?



- Severity of liver disease/likelihood of disease progression to cirrhosis and liver cancer
- Probability of treatment response

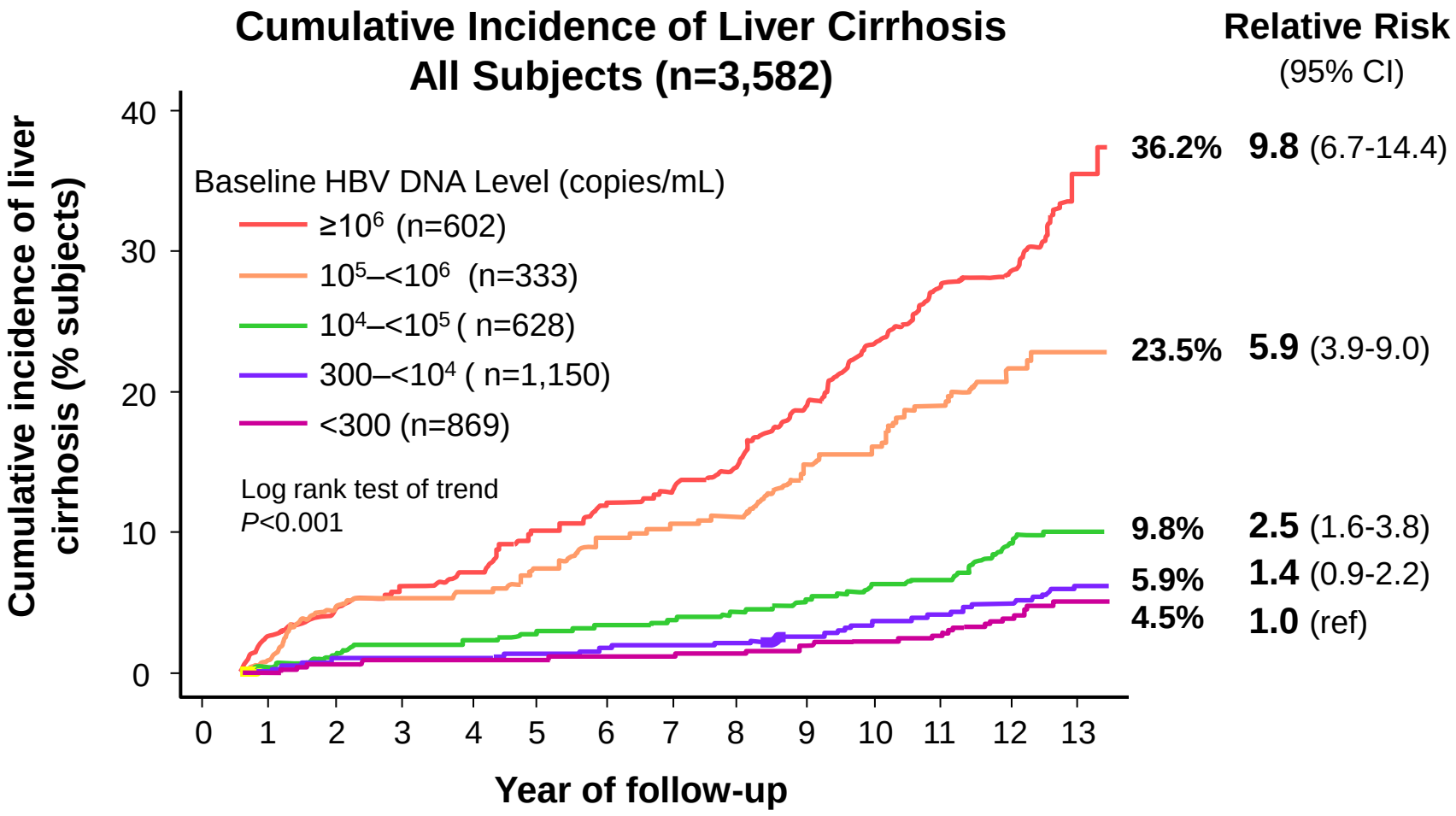
- Adverse effects
- Drug resistance
- Cost

R.E.V.E.A.L:
High Baseline HBV Viral Load is Associated with Increased Incidence of HCC



Chen CJ, et al. JAMA. 2006; 295:65–73.

R.E.V.E.A.L:
High Baseline HBV Viral Load is Associated with Increased Incidence of Cirrhosis



Iloeje UH, et al. Gastroenterology 2006; 130;678–686.

AASLD Guidelines

HBeAg Status	HBV DNA	ALT	Management
Positive	> 10^5copies/ml	<2 x ULN	No treatment
Positive	> 10^5copies/ml	> 2 x ULN	Treat
Negative	> 10^5copies/ml	> 2 x ULN	Treat
Negative	> 10^4copies/ml	1 – 2 xULN	Liver biopsy
Negative	< 10^4copies/ml	< 1 x ULN	Observe
Positive or Negative	Any detectable	Cirrhosis	Treat

EASL 2009

- HBV DNA > 2000 iu/l
- ALT > ULN
- Fibrosis > 2/4 (Metavir)
- Cirrhosis & any viraemia

No Treatment Required

- Immunotolerant
  - Age < 30
  - ALT < ULN
  - HBV DNA > 10^8
- No significant histological injury
  - Fibrosis < 2
  - Necroinflammatory < 2

Investigations Required for Treatment Decision

- Haematology
- Biochemistry
- Viral serology
- Molecular virology (viral load)
- Liver biopsy & histology

Investigations Available

- Haematology
- Biochemistry
- Viral serology
- Molecular virology (viral load)
- Liver biopsy & histology

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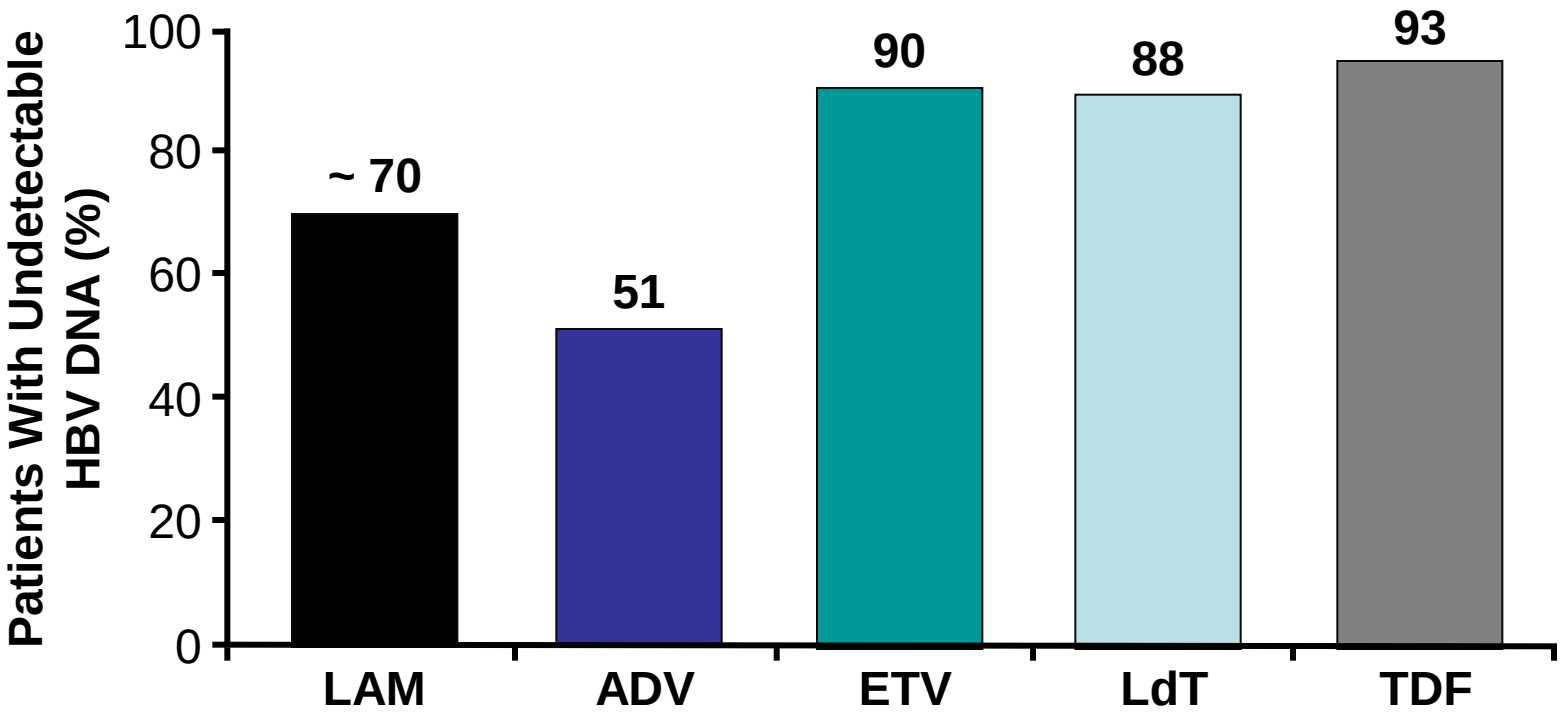
Interferon Treatment

Outcome Measure	Interferon Treated	Controls
Loss of HBV DNA	37%	17%
Loss of HBeAg	33%	12%
Loss of HBsAg	7.8%	1.8%

Interferon is NOT an Option

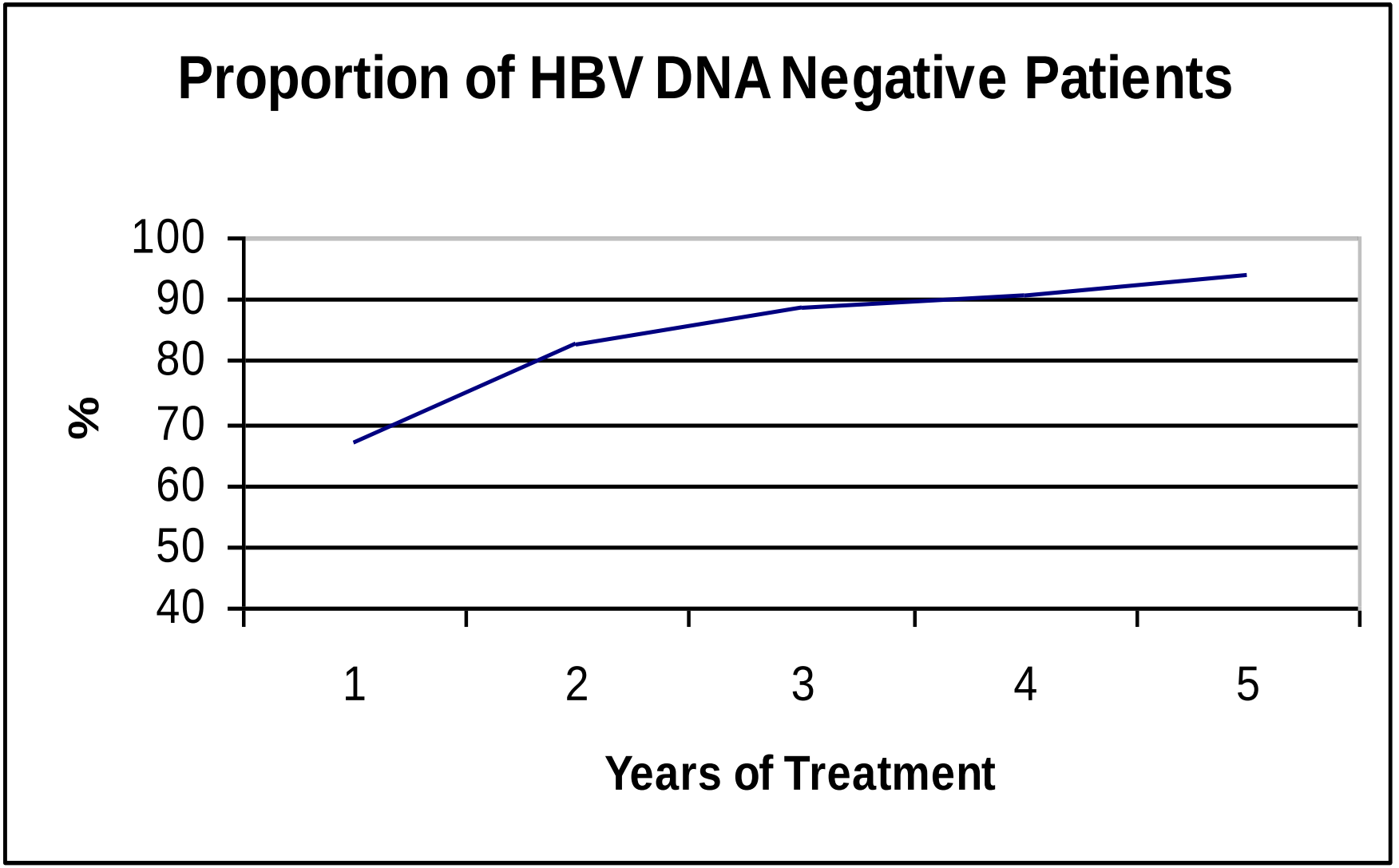
- High prevalence of side effects
- Requirement for intensive monitoring
- Not indicated in cirrhotics
- Expensive

Nucleoside Analogue Treatment

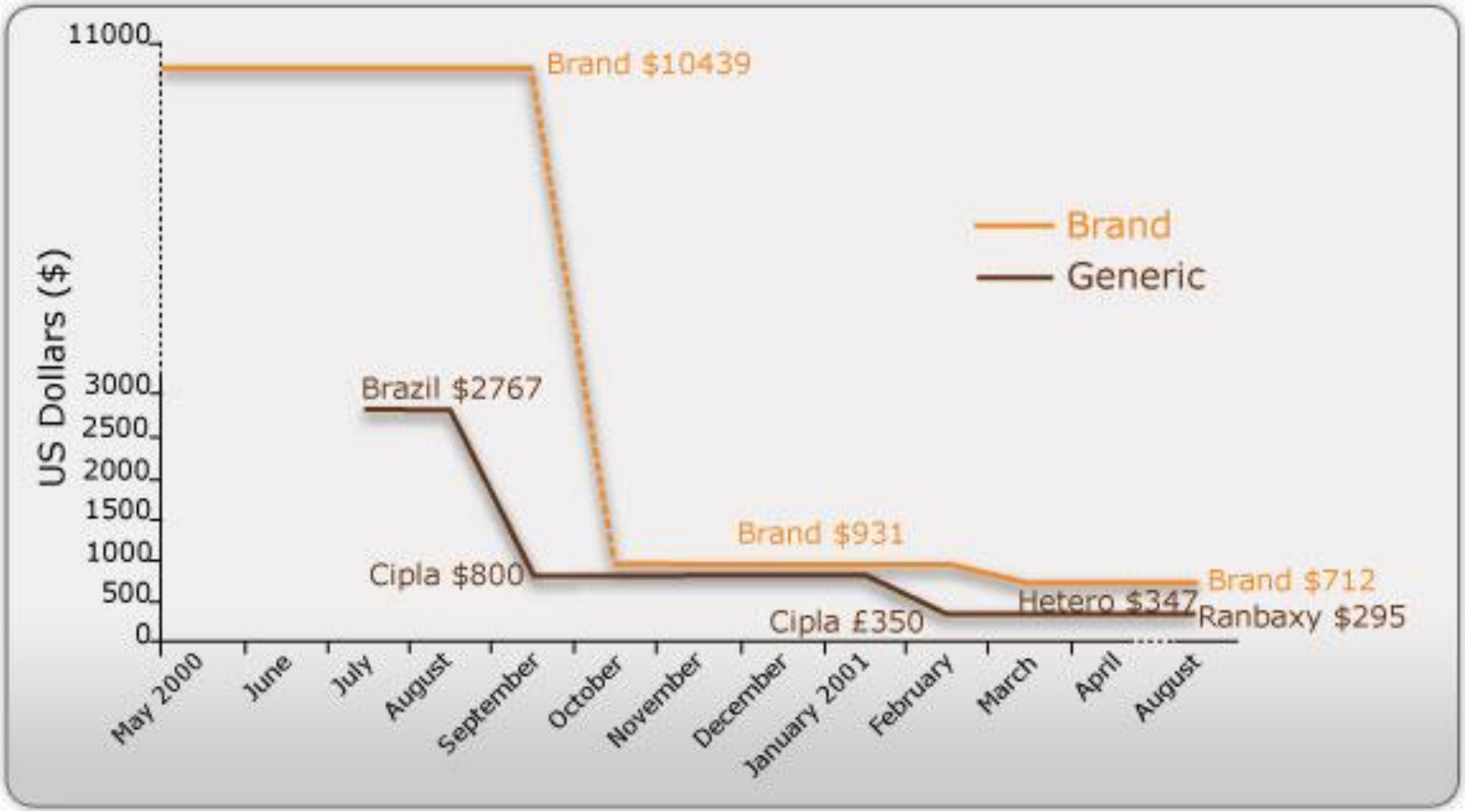


Adapted from Lok AS, et al. Hepatology 2007;45:507-539.
Marcellin P, et al. AASLD 2007. Abstract LB2.

Cumulative Benefit of Entecavir Treatment in HBeAg Positive Patients



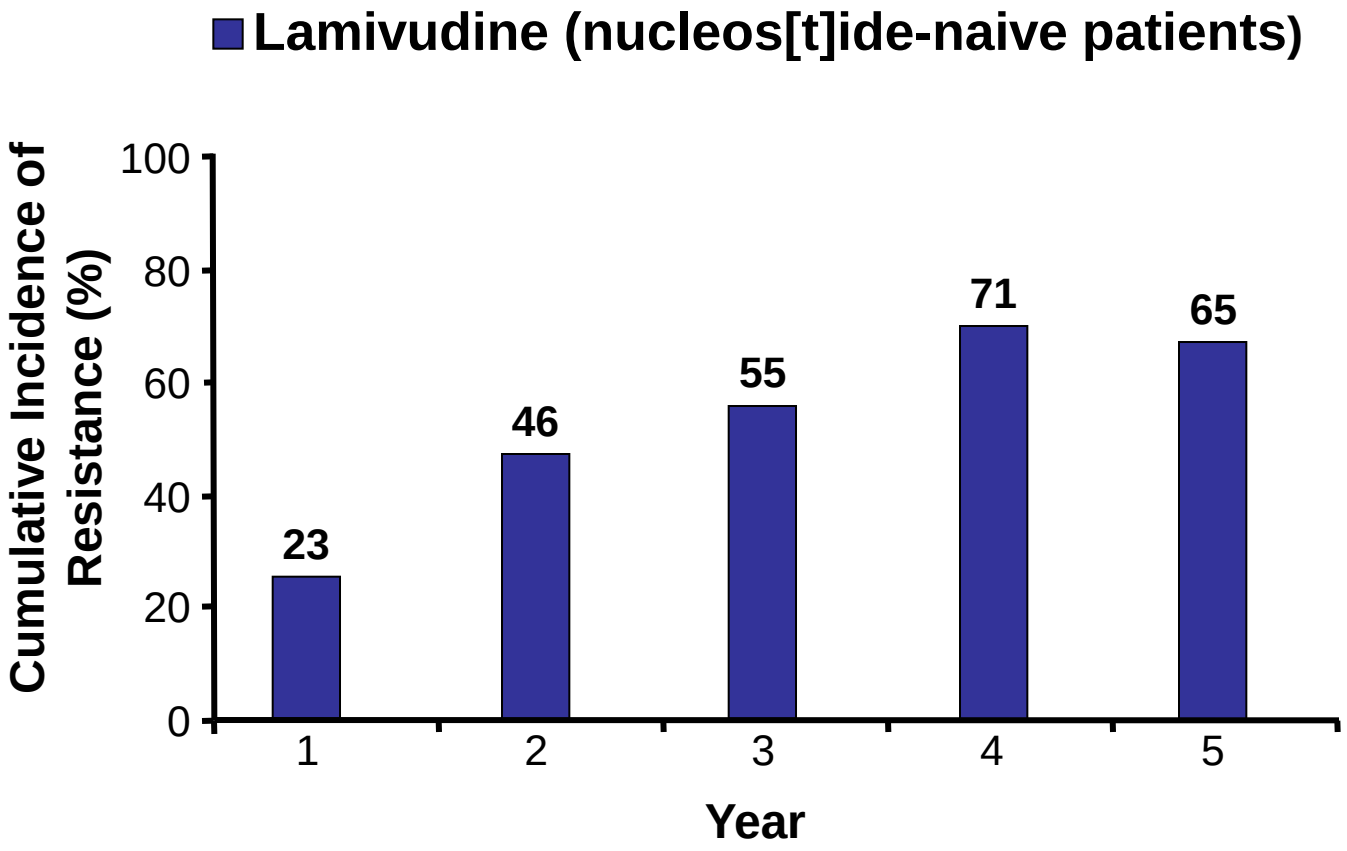
Generic Anti-Virals in Developing Countries



Generic Drug Prices

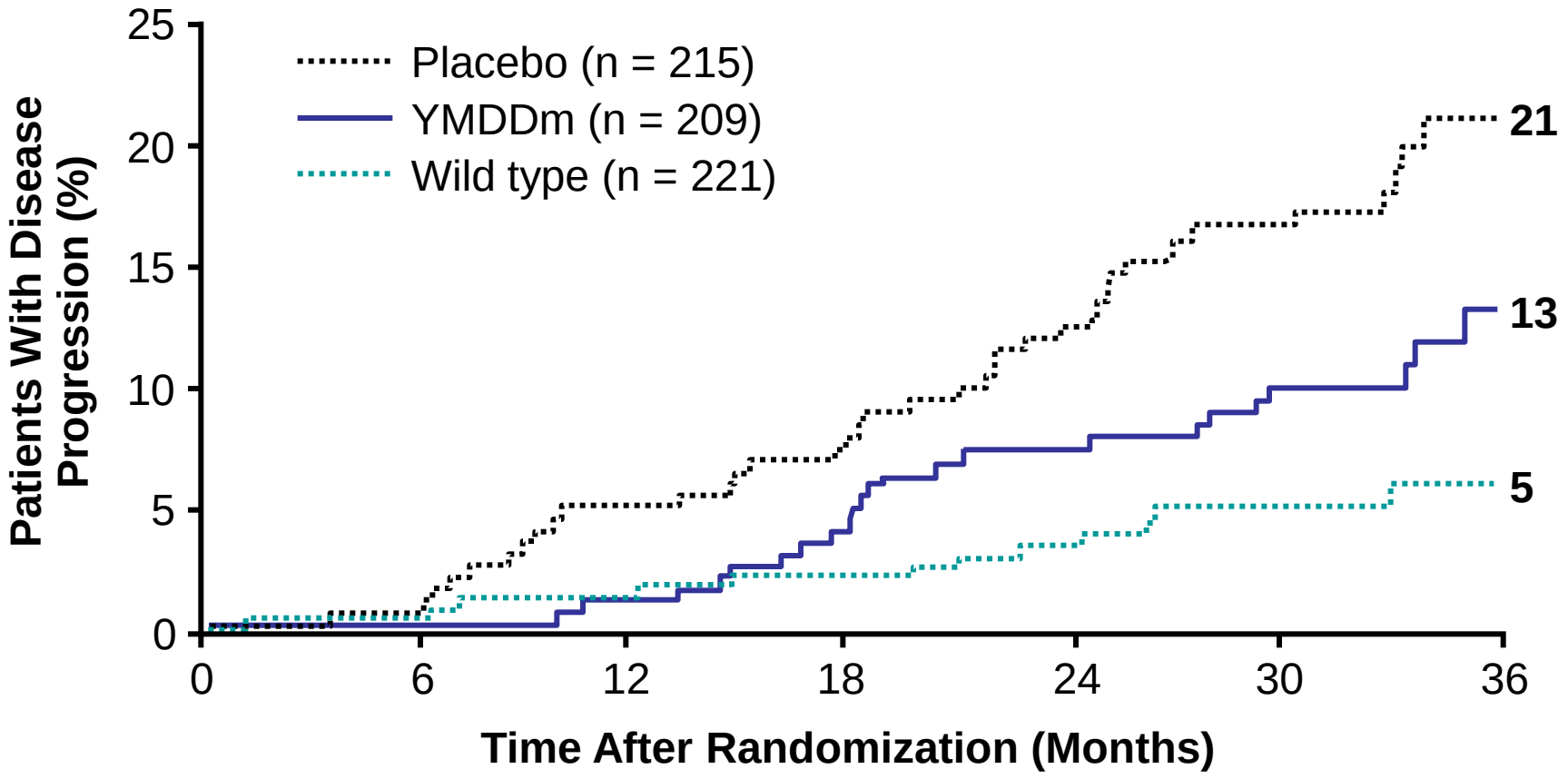
Drug	Lamivudine	Tenofovir	Tenofovir & Lamivudine	Tenofovir & Emtricitabine
Europe	£1,015	£3,094	£4109	£3,094
Global Fund Generic	£13.58	£58	£84	£127

Incidence of HBV Resistance



Lai CL, et al. Clin Infect Dis. 2003;36:687-696.
Lok AS, et al. Gastroenterology. 2003;125:1714-1722.

LAM Resistance Associated With Faster Progression of Liver Disease



Liaw YF, et al. N Engl J Med. 2004;351:1521-1531.

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Regional antiretroviral therapy coverage

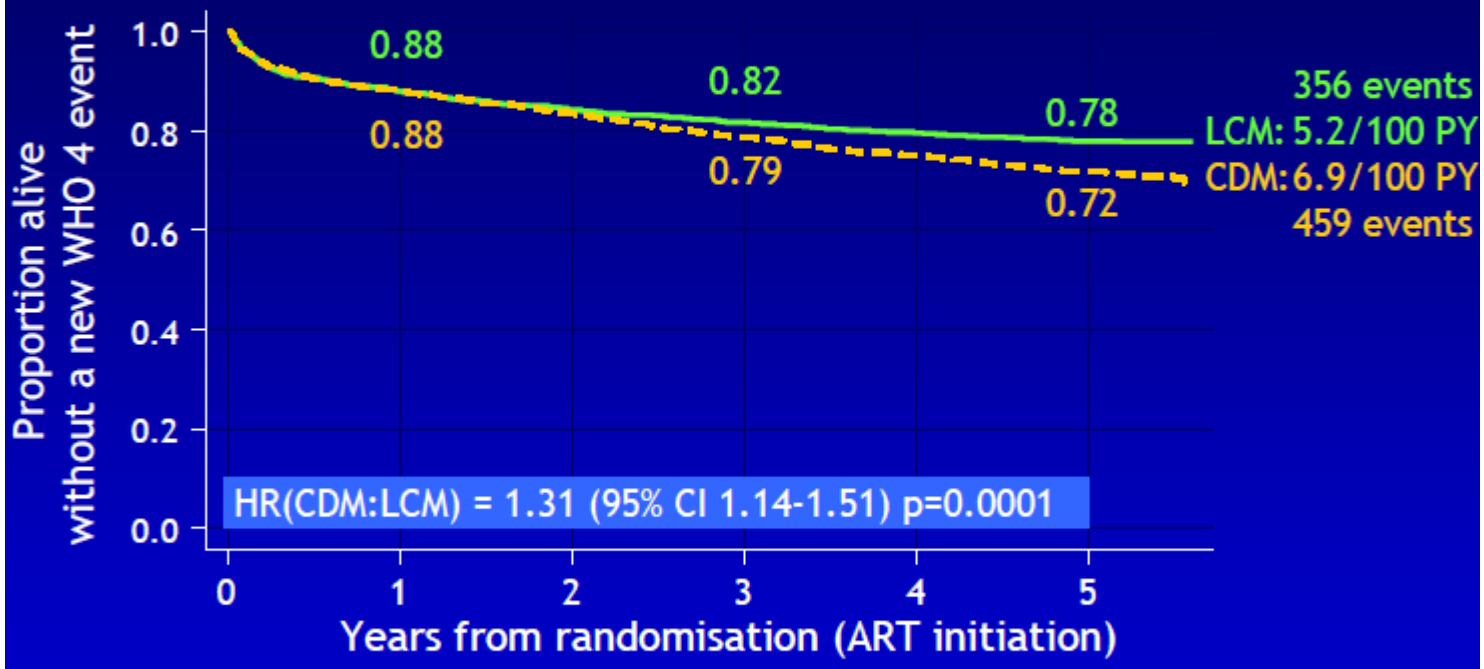
Region (lower-and middle-income countries)	Antiretroviral therapy coverage	Estimated number of people receiving antiretroviral therapy	Estimated number of people needing antiretroviral therapy
Sub-Saharan Africa	37%	3,911,000	10,600,000
Eastern and Southern Africa	41%	3,203,000	7,700,000
Western and Central Africa	25%	709,000	2,900,000
Latin America and the Caribbean	50%	478,000	950,000
Latin America	51%	425,000	840,000
The Caribbean	48%	52,400	110,000
East, South and South-East Asia	31%	739,000	2,400,000
Europe and Central Asia	19%	114,000	610,000
North Africa and the Middle East	11%	12,000	100,000
Total	36%	5,254,000	14,600,00

Source: WHO/UNAIDS/UNICEF (2010) 'Towards Universal Access: Scaling up priority HIV/AIDS Interventions in the Health Sector'

Monitoring Requirements

- Side effects of treatment
- Treatment failure
  - Alternative regimens
- ? Finite duration of therapy

Progression to new WHO 4 event or death (primary endpoint)



LCM: n=	1656	1438	1364	1306	1255	682
CDM: n=	1660	1443	1354	1262	1184	613

Adjusted and discounted costs and benefits

	LCM N = 1656	CDM N = 1660	Difference (LCM - CDM)
Overall mean total costs US$ 2008 - Adjusted for censoring and discounted at 3% [95% confidence interval]*	$3318	$2405	$913 [$783, $1095]
Overall survival days** - Discounted at 3% [95% confidence interval]*	1863	1827	37 [-10, +83]
Incremental Cost Effectiveness Ratio - Adjusted for censoring and discounted at 3% [95% confidence interval]*	$9016 [$3835, Dominated]		

* 95% CI estimated with bootstrapping percentile method

** Estimated through the area under the Kaplan-Meier survival curve, with censoring applied at the longest observed time of the arm whose maximum observed time occurs first

Integration with HIV Serivces

- Benefits
  - Trained staff
  - Lab facilities
  - Drug supply
  - Management of co-infection
- Problems
  - Stigmatisation
  - Lack of molecular virology

Why No Treatment for HBV In Resource Poor Settings

- Global Health Agenda
- Requirement for complex diagnostics
- Drug cost and availability
- Skills and education

- Lack of Political Will

Agenda item 11.12 21 May 2010

Viral hepatitis

The Sixty-third World Health Assembly,

Having considered the report on viral hepatitis;[1]

Taking into account the fact that some 2000 million people have been infected by hepatitis B virus and that about 350 million people live with a chronic form of the disease;

Considering that hepatitis C is still not preventable by vaccination and around 80% of hepatitis C virus infections become a chronic infection;

Considering the seriousness of viral hepatitis as a global public health problem and the need for advocacy to governments, all parties and populations for action on health promotion, disease prevention, diagnosis and treatment;

Expressing concern at the lack of progress in the prevention and control of viral hepatitis in developing countries, in particular in sub-Saharan Africa, due to the lack of access to affordable, appropriate treatment and care as well as an integrated approach to the prevention and control measures of the disease;

Considering the need for a global approach to all forms of viral hepatitis – with a special focus on viral hepatitis B and C, which have the higher rates of morbidity;

Recalling that one route of transmission of hepatitis B and C viruses is parenteral and that the Health Assembly in resolution WHA28.72 on utilization and supply of human blood and blood products recommended the development of national public services for blood donation and in resolution WHA58.13 agreed to the establishment of an annual World Blood Donor Day, and that in both resolutions the Health Assembly recognized the need for safe blood to be available to blood recipients;

- (1) to implement and/or improve **epidemiological surveillance** systems and to strengthen **laboratory capacity**, where necessary, in order to generate reliable information for guiding prevention and control measures;

- (2) to support or enable an integrated and cost-effective approach to the **prevention, control and management of viral hepatitis** considering the linkages with associated coinfection such as HIV through multisectoral collaboration among health and educational institutions, nongovernmental organizations and civil society, including measures that strengthen safety and quality and the **regulation of blood products**;

- (3) to incorporate in their specific contexts the policies, strategies and tools recommended by WHO in order to define and implement **preventive actions**, diagnostic measures and the provision of assistance to the population affected by viral hepatitis including migrant and vulnerable populations;

- (4) to strengthen national health systems in order to address prevention and control of viral hepatitis effectively through the provision of health promotion and national surveillance, including **tools for prevention, diagnosis and treatment of viral hepatitis**, vaccination, information, communication and injection safety;

- (5) to provide vaccination strategies, infection-control measures, and means for injection safety for health-care workers;

- (6) to use national and international resources, either human or financial, to provide **technical support** to strengthen health systems in order to provide local populations adequately with the most cost-effective and **affordable interventions** that suit the needs of local epidemiological situations;

- **REQUESTS the Director-General:**
- (1) to establish in collaboration with Member States the necessary guidelines, strategies, time-bound goals and tools for the surveillance, prevention and control of viral hepatitis;

- (2) to provide the necessary support to the development of scientific research related to the prevention, diagnosis and treatment of viral hepatitis;

- (3) to improve the assessment of global and regional economic impact and **estimate the burden of viral hepatitis**;

- (4) to support, as appropriate, resource-constrained Member States in conducting events to mark World Hepatitis Day;

- (5) to invite international organizations, financial institutions and other partners to give support and assign resources in strengthening of surveillance systems, prevention and control programme, **diagnostic and laboratory capacity**, and management of viral hepatitis to developing countries in an equitable, most efficient, and suitable manner;

Key Requirement to Initiate HBV Treatment in Resource Poor Settings

- Strengthen Laboratory capacity
- Research treatment initiation guidelines
- Build clinical expertise
- Integration with HIV services
- Invest in the drugs
- Educate Educate Educate
  - Governments
  - Doctors
  - Public