Global Status of Hepatitis B Virus

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Outline of Talk

- Epidemiology: Challenges in uncovering the Global Burden of Liver Disease due to HBV
- HBV in the USA
- Prevention of chronic HBV: Where are we succeeding and Where are We Falling Behind?
- Other considerations in Low (LIC) and Middle (MIC) Income Countries
  - Screening for HBV: How can it be done?
  - Management of Chronic HBV: What is needed?
- How did we reach the 2030 WHO and HHS goals for HBV in Alaska?

Global Burden of Liver Disease (GBD) Model*

BMC Medicine 2014;12:145-158 and 159-65

- GBD estimates 1 million all cause cirrhosis deaths in 2010:
  - For 39/187 (31%) countries there was no data
  - For another 39% estimated deaths were likely substantially underreported
- An additional 1 million deaths estimated due to hepatocellular carcinoma and acute hepatitis
- WHO estimates HCC is 3rd leading cause of cancer death in men in world: http://www.iarc.fr/en/media-centre/pr/2014/pdfs/pr224_E.pdf
- In the US, Cancer related deaths have risen for HCC in the past 2 decades but fallen for all other cancers

Collaboration coordinated by the Institute of Health Metrics and Evaluation, University of Washington, Seattle

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The Institute of Health Metrics and Evaluation Center is Preparing a 2019 Update on the Global Burden of HBV

- This is their first update since 2013;
- While I have reviewed this, I am not privy to sharing the findings with you until they have published it.
- Good news: Prevalence of HBV is falling in many countries due to universal childhood vaccine
- Bad news: HBV related deaths have increased and Linkage to care is poor

Sources of the Information I am Presenting are the GBD 2013 study and WHO data

- Prevalence
  - 248 million persons with chronic HBV
- Mortality:
  - 15% to 40% with chronic HBV will die of liver cancer or liver failure if not under management
    - 25%-40% of males
    - 10-15% females
    - Average decrease in life span for a person with chronic HBV is 6 years
- Cirrhosis
  - 10% to 20% of males and females with HBV
- ~686,000 deaths worldwide per year

Schweitzer et al. Lancet 2015; Global Burden of Disease, Lancet 2015; Lok & McMahon, Hepatology 2009

HBV Global Prevalence in 2013: Modified to include Ethnic Minorities with High Prevalence of HBV

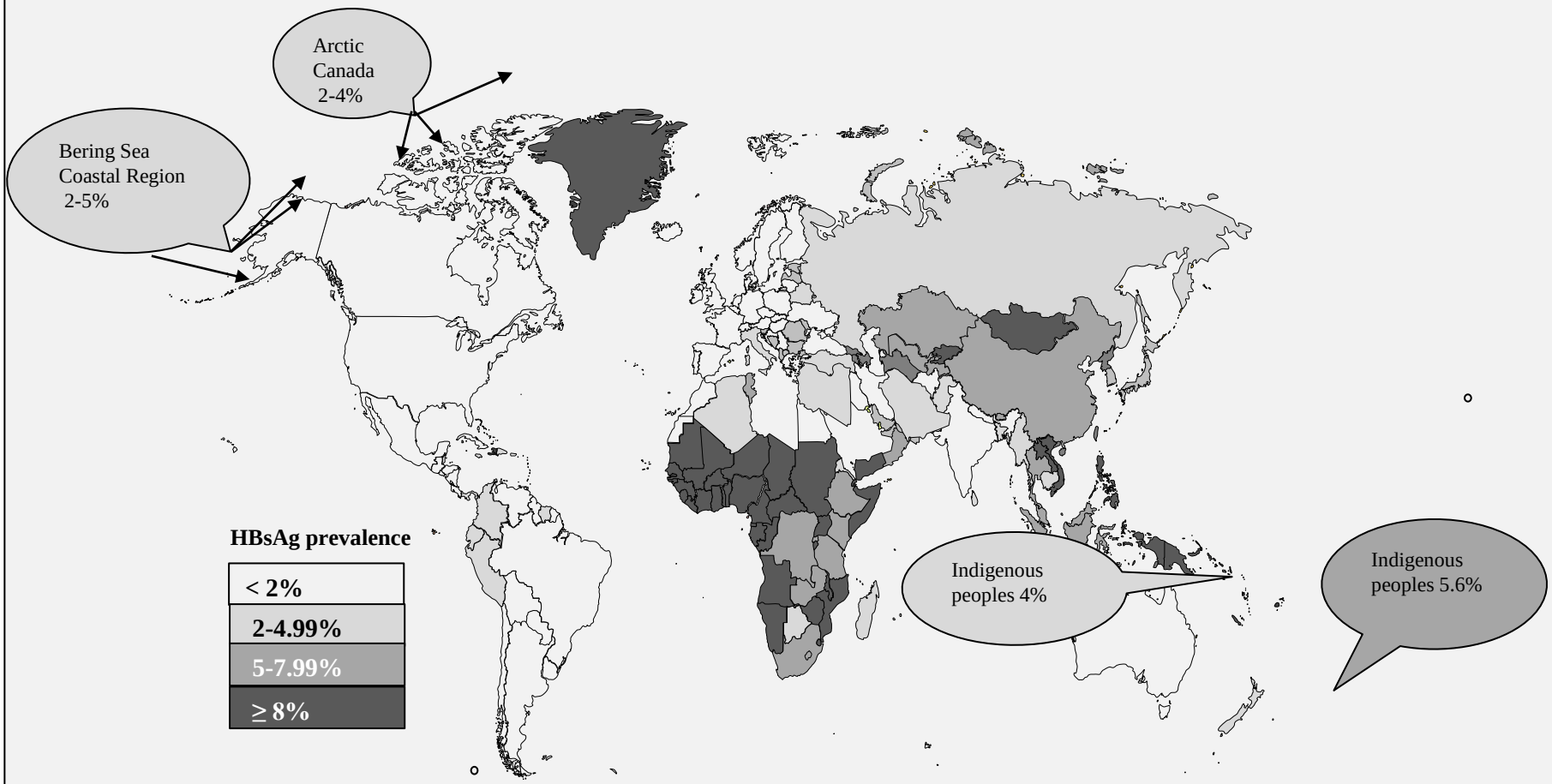
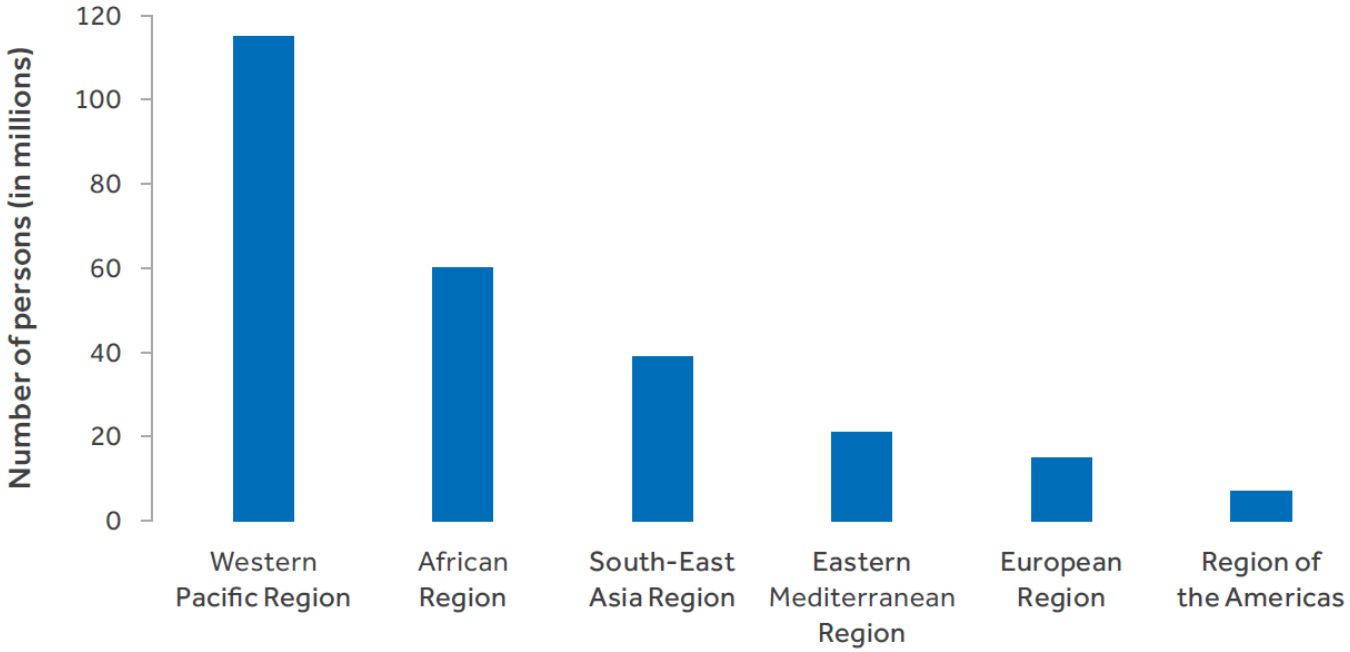


Table 2 (with graph). Prevalence of HBV infection (HBsAg) in the general population by WHO region, 2015: the WHO African and Western Pacific regions have the highest prevalence and the largest number of persons living with HBV



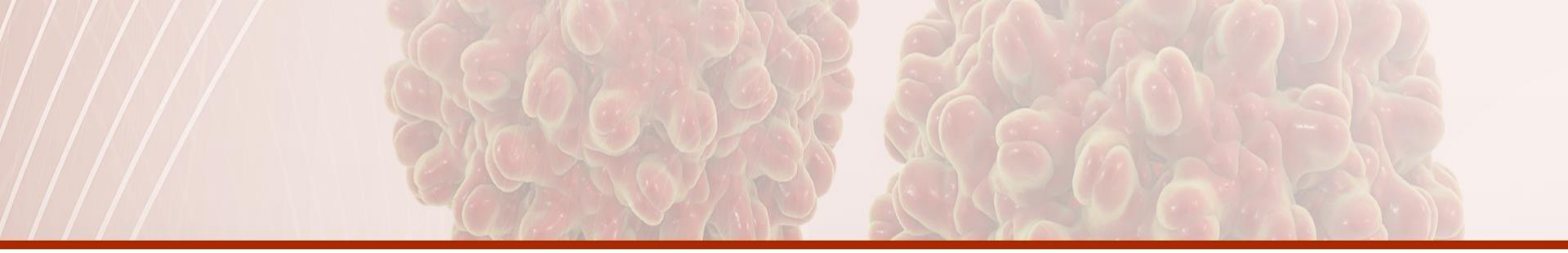
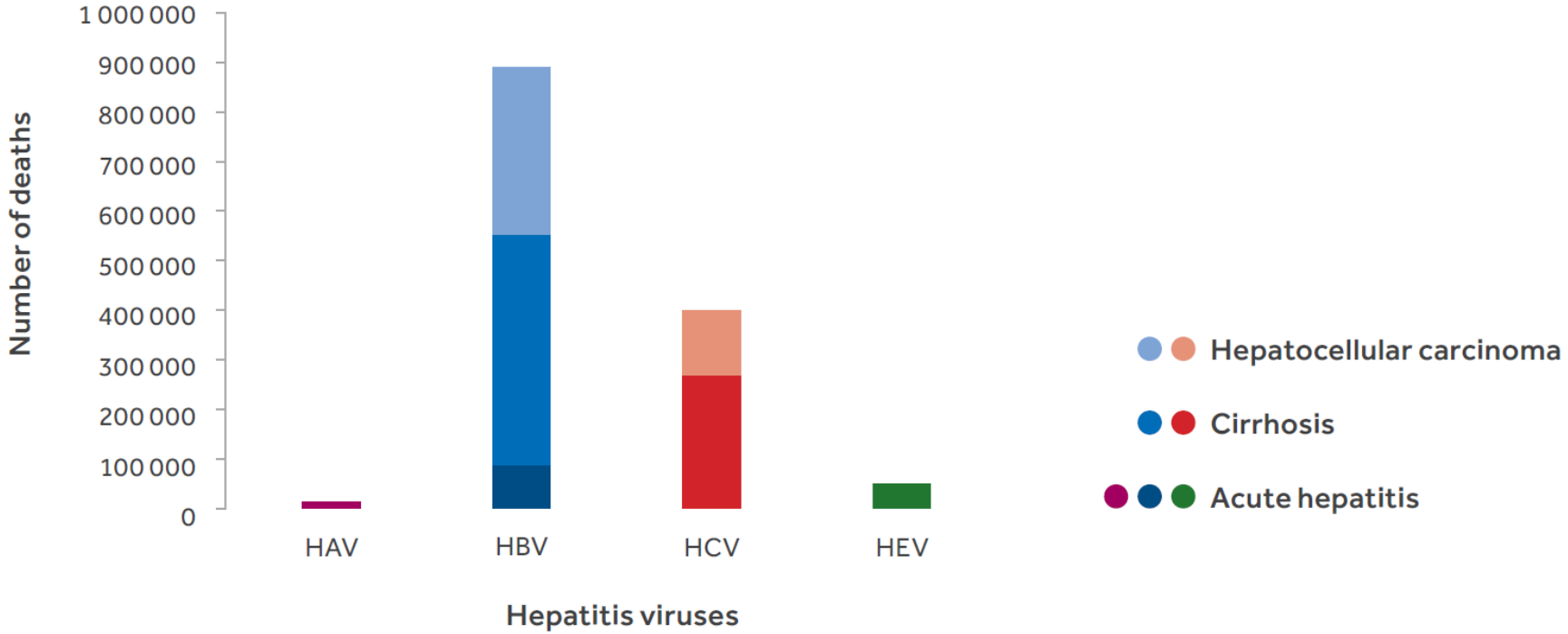
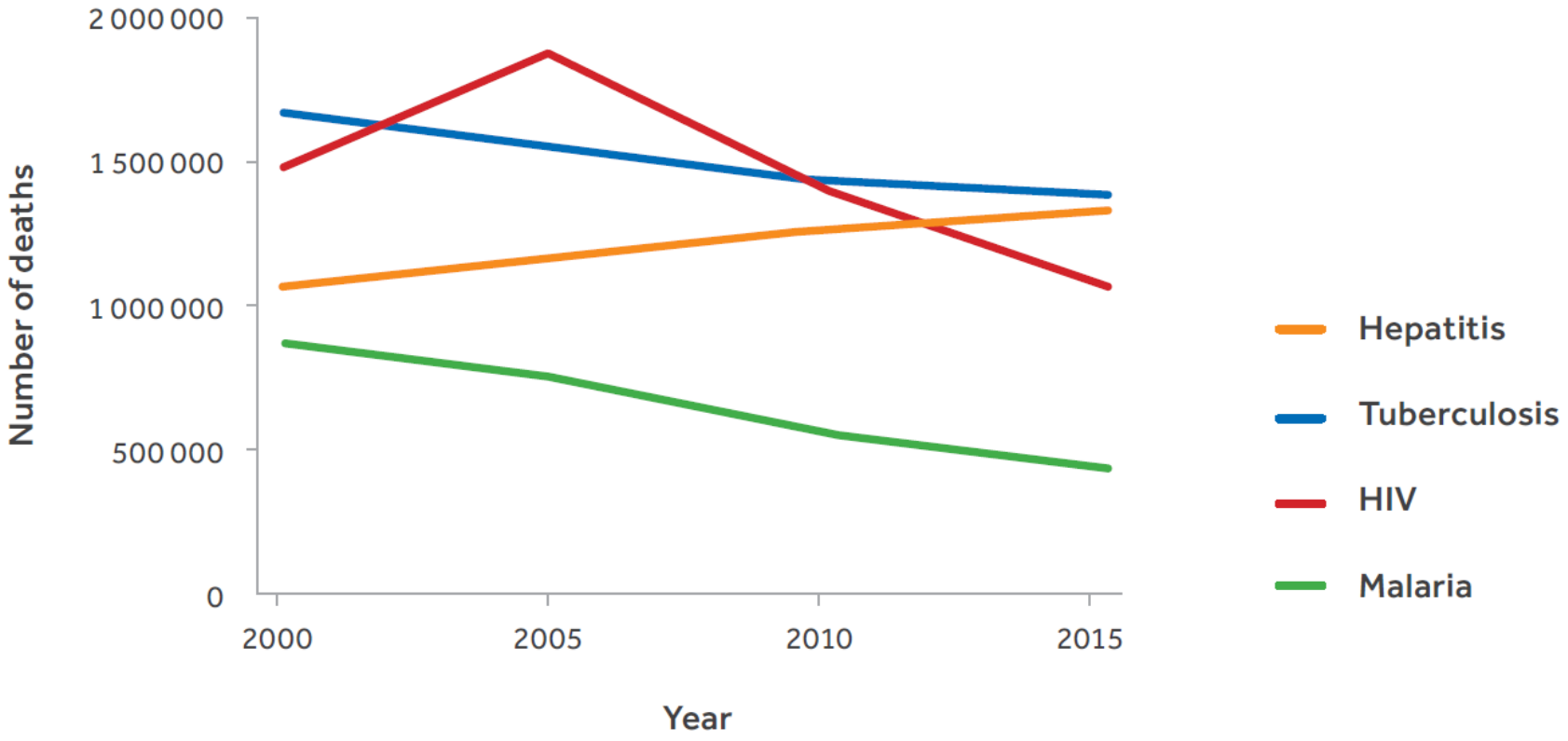


Fig. 1. Deaths from viral hepatitis, by virus and type of sequelae, 2015:
most viral hepatitis deaths are due to the late complications of HBV and HCV infection



HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; HEV: hepatitis E virus
Source: WHO global health estimates for 2015 published in 2016 (Global Health Estimates 2015: deaths by cause, age, sex, by country and by region, 2000–2015. Geneva: World Health Organization; 2016.)

Fig. 2. Global annual mortality from hepatitis, HIV, tuberculosis and malaria, 2000–2015: unlike HIV, tuberculosis and malaria, the trend in mortality from viral hepatitis is increasing



HBV in USA

- The number of chronic HBV infected persons in US is estimated to be 1.59 million persons (range 1.25–2.49 million)[1]
- In 2019, the age-adjusted death rate associated with hepatitis B in the US was 0.42 deaths per 100,000 population (n=1,662 deaths)[2]
- 3,192 acute hepatitis B cases were reported to CDC, resulting in 20,700 estimated infections (95% CI: 11,800–50,800) after adjusting for case under-ascertainment and under-reporting

1. Lim et al, 2020

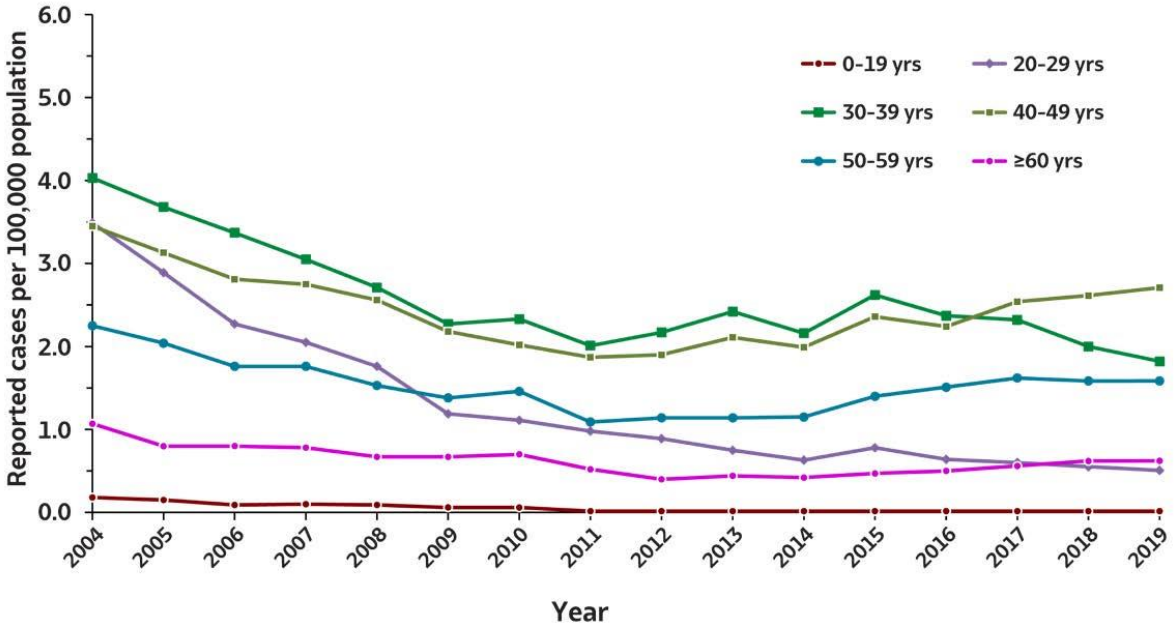
2. https://www.cdc.gov/hepatitis/statistics/2019surveillance/HepB.htm

National, State, and Selected Local Area Vaccination Coverage Among Children Aged 19–35 Months — United States, 2014 (cdc.gov)

3. https://www.cdc.gov/hepatitis/statistics/2019surveillance/HepB.htm

Rates of reported acute hepatitis B virus infection, by age group — United States, 2004–2019

2019 CDC Hepatitis Surveillance Report3:

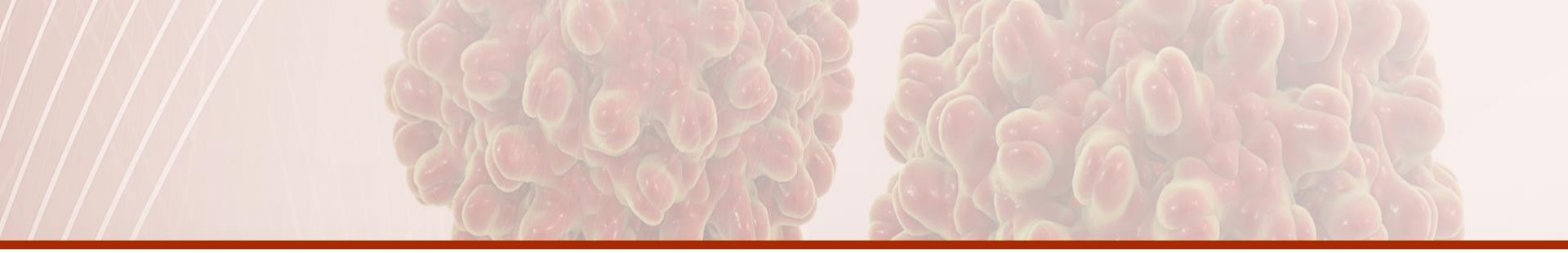


Transmission of HBV

- Perinatal: HBV infected mother with high viral load to infant at birth: 90% risk of chronic HBV (Beasley RP, Lancet 1983
- Horizontal:
  - Children ages birth to 5 years: 30% risk of chronic HBV
    - HBV survives on environmental surfaces at all temperatures for at least one week
    - Transmission occurs through open cuts or scratches
  - Children over 5 years and adults: 10% risk of chronic HBV
    - Transmission occurs via needle contamination, sexual contact or through open cuts or scratches (McMahon et al. JID 1985;151:599-603
- Adult HBV infection
  - 30% of adults with acute HBV infection will have symptomatic jaundice
  - <5% will develop chronic HBV
    - Exception is those infected with HIV who have higher risk of chronic HBV

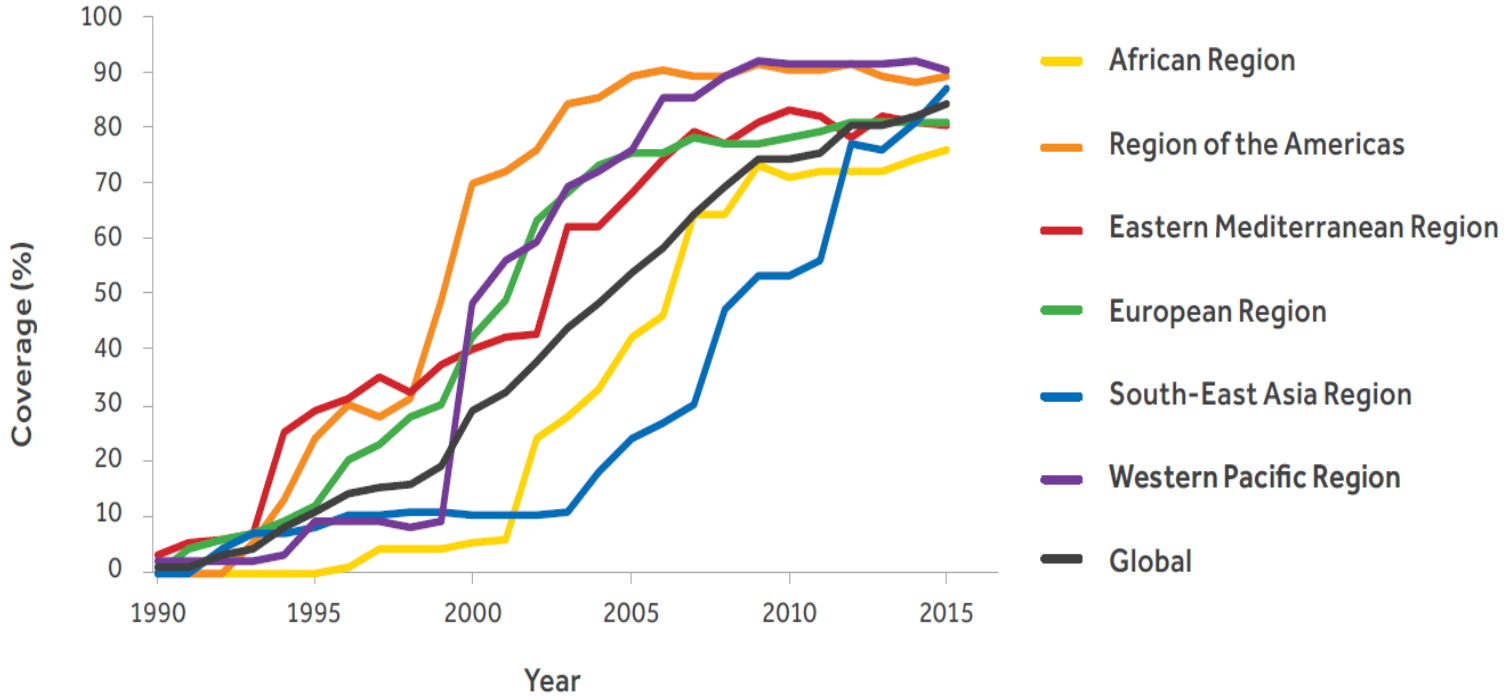
Crucial Actions in Reducing Morbidity and Mortality of HBV globally

- Newborn vaccination for HBV with selective catch-up vaccination
- Screening high risk persons and populations for HBV and linking those with chronic HBV to care.
  - CDC has determined the screening for HBV is cost effective in populations where the prevalence of HBsAg, the marker for active infection, is ≥2%
  - In US, this is all persons born in endemic countries and traditional high risk individuals
  - Globally, most countries have an HBsAg prevalence of ≥2% so this represents a challenge



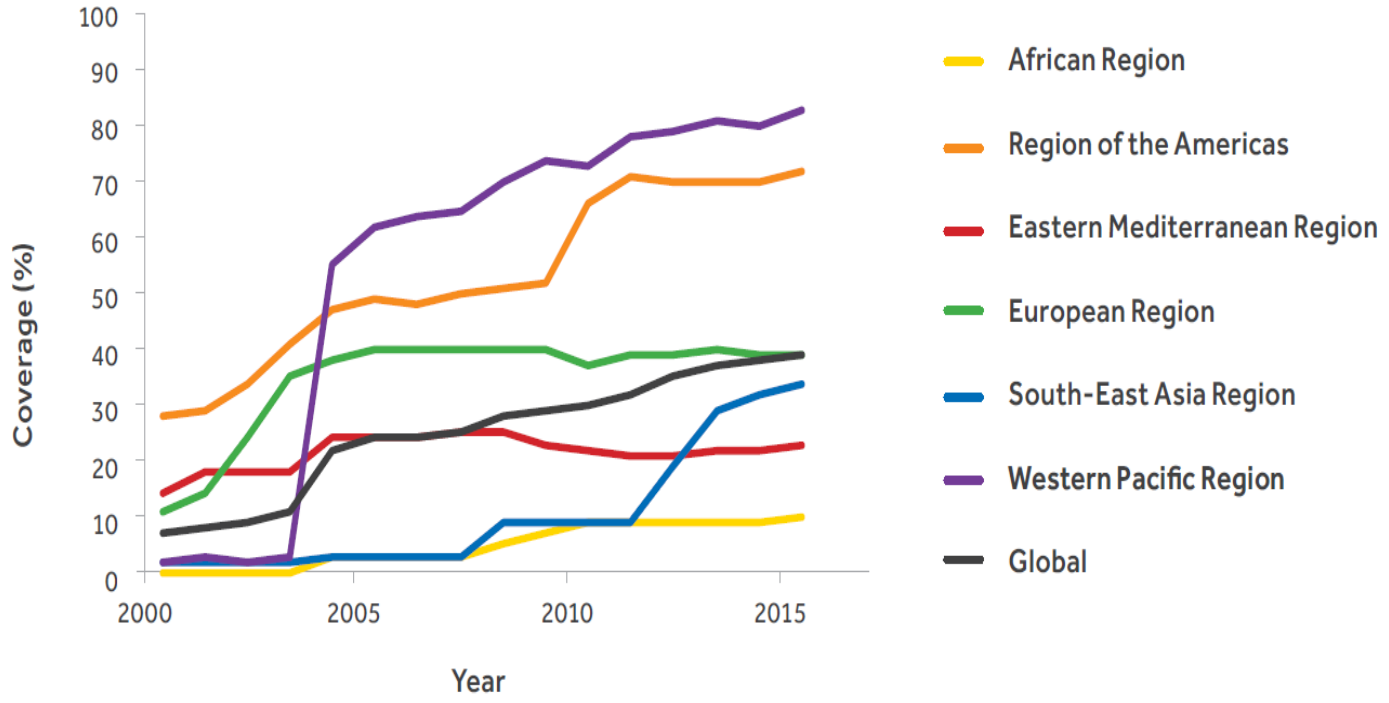
				Targets	
	Interventions	Indicator	2015 baseline	2020	2030
1	**Hepatitis B vaccination**	HEPB3 coverage	84%	90%	90%
2	**HBV PMTCT**[a]	HEP vaccine birth dose coverage	39%	50%	90%
3	**Blood safety**	Donations screened with quality assurance	97%	95%	100%
	Injection safety	Proportion of unsafe injections	5%	0%	0%
4	**Harm reduction**	Syringes & needles distributed/PWID/year	27	200	300
5	**Testing services**	% HBV-infected diagnosed	9%	30%	90%
		% HCV-infected diagnosed	20%	30%	90%
	Treatment	% diagnosed with HBV on treatment	8%[b]	–[c]	80%[d]

Three-dose hepatitis B vaccine coverage, by WHO region, 2000–2015



Source: Joint UNICEF–WHO reporting form

Hepatitis B birth dose coverage, by WHO region, 2000–2015

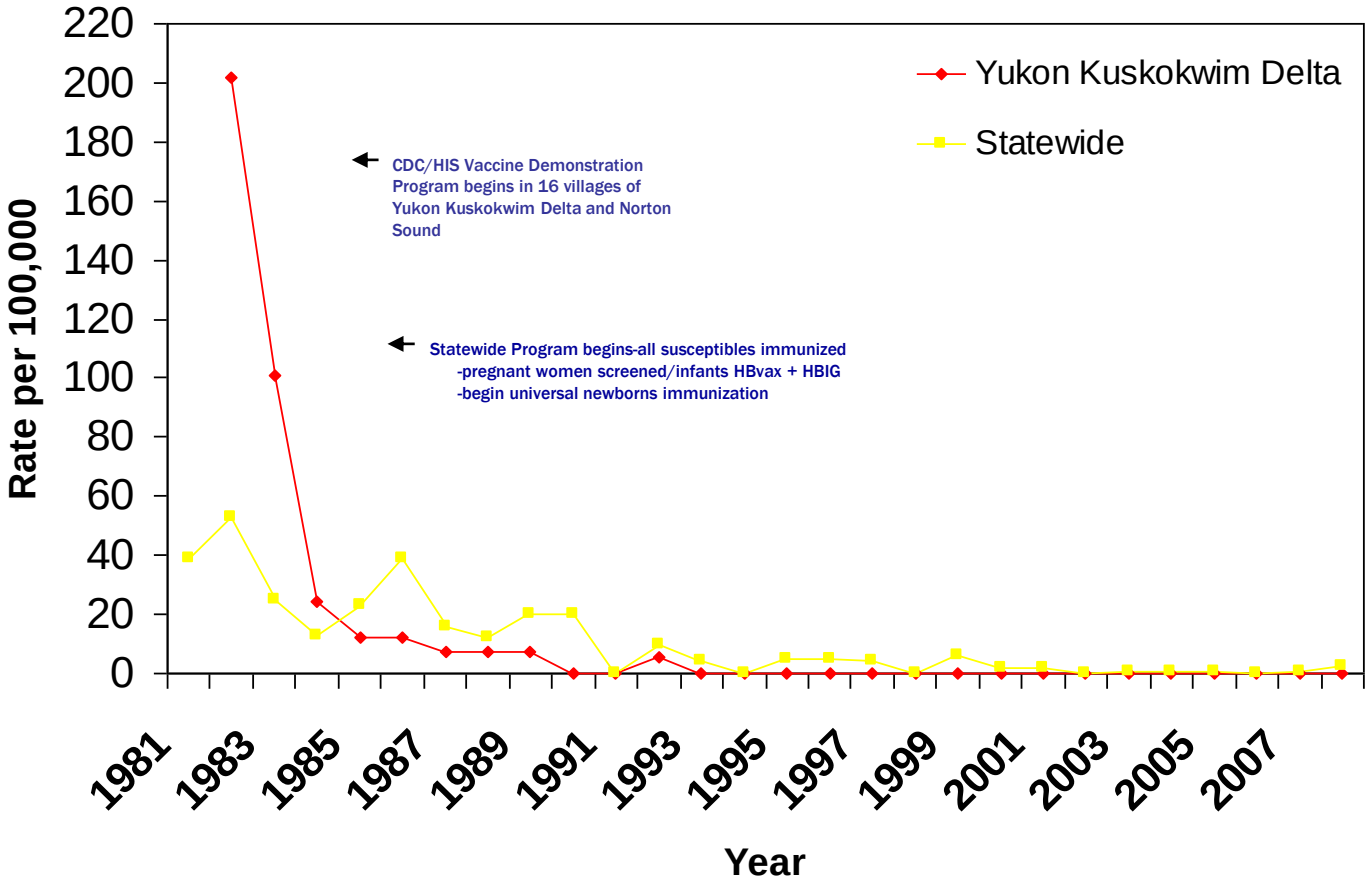


Source: Joint UNICEF–WHO reporting form

Alaska Native Hepatitis B Program

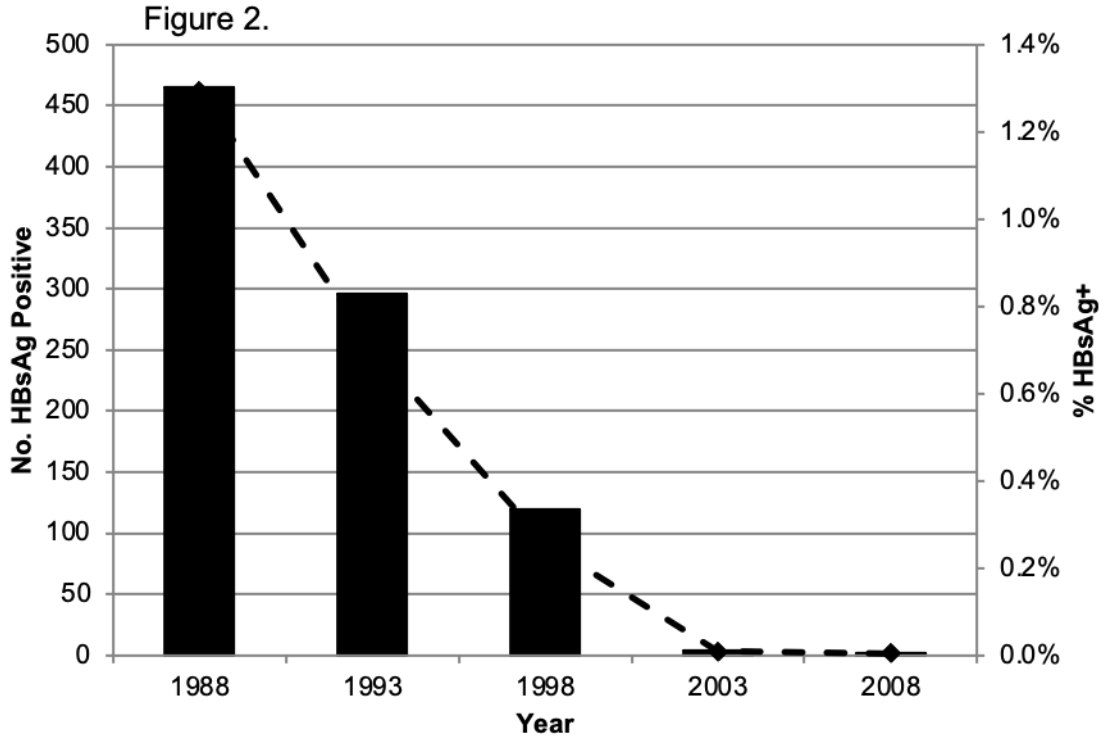
- Universal HBV Newborn vaccination introduced in 1983
- Screening and Catch-up vaccination of children and adults: 1983-1988
  - 53,000 persons screened; ¾ of population, 90% in endemic areas of western Alaska
- No new cases of acute HBV in AN children since mid 1990's
- No more AN children <20 have chronic HBV infection
- Rates of liver cancer in children which were highest reported in world have fallen to zero since mid 1990's

Incidence Symptomatic Hepatitis B in Alaska Native Peoples 1981- 2008

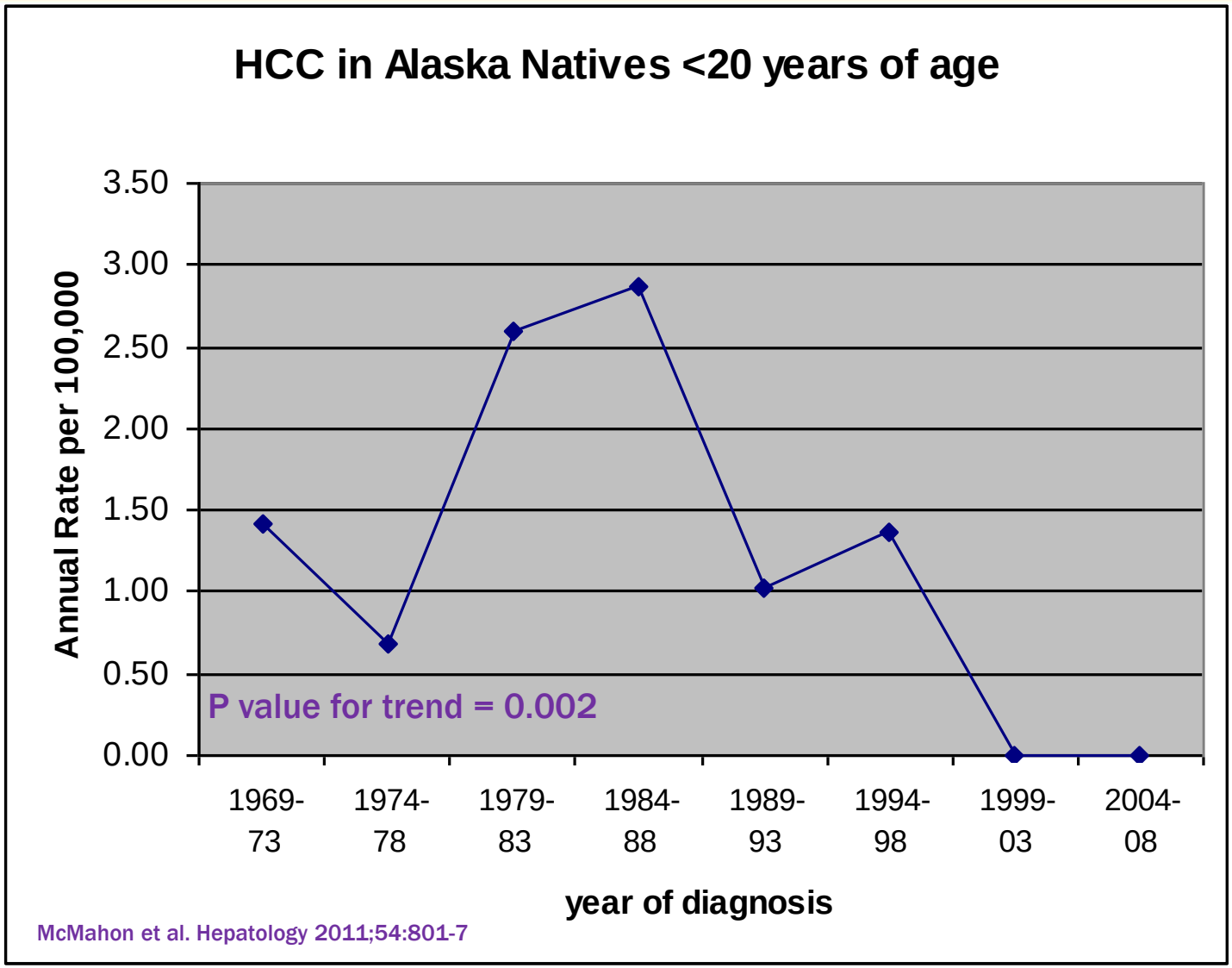


McMahon et al. Lancet, 1987; 330: 1134-1136

Number of HBsAg-positive Alaska Native Children Under 20 Years of Age: 1988-2008



As of 2013, there are no Alaska Native children known to be HBsAg-positive



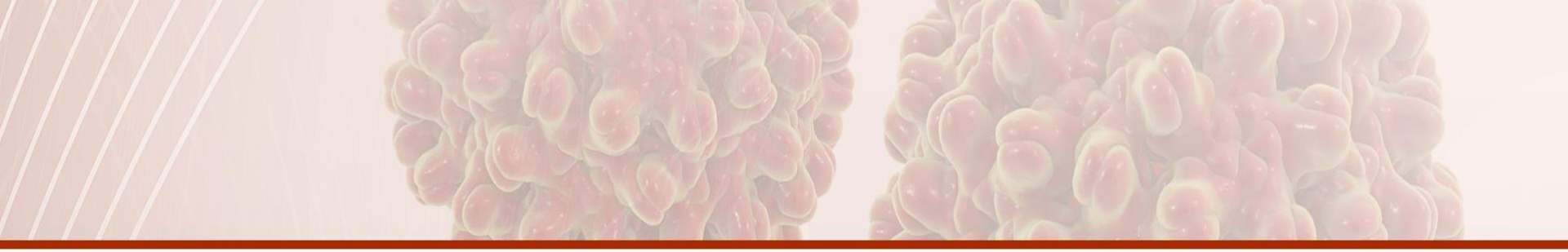
McMahon et al. Hepatology 2011;54:801-7

Barriers to Birth Dose

- In some countries a large proportion of births do not take place in a hospital
  - Infrastructure is not available in many countries to implement birth dose
- GAVI will not provide birth dose of HBV vaccine requiring country to pick this up
  - GAVI only supplies HBV vaccine in combination with other childhood vaccines
  - Some countries feel they can’t afford cost of birth dose but it is only 50 cents/dose
  - It may be that GAVI not supplying birth dose has negative impact on countries implementing it

Birth Dose of HBV Vaccine

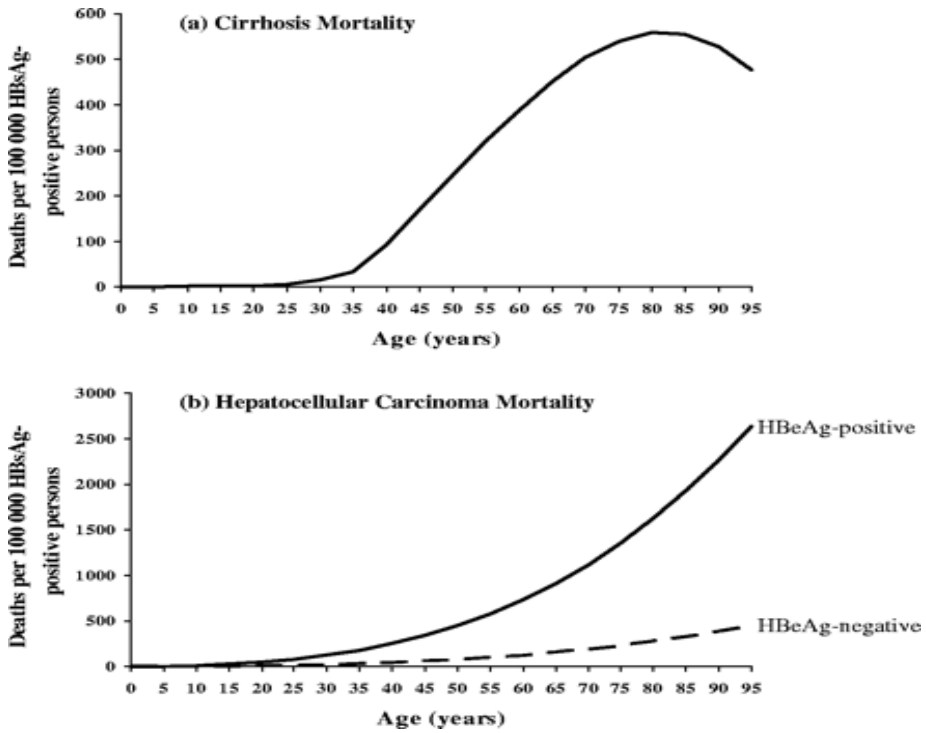
- Examples of countries doing well
  - US, Singapore, Taiwan (reduction in the prevalence of HBsAg in Children has been reduces to <1%.
- Examples of countries where birth dose is not routine
  - Most countries in sub-Saharan Africa, many regions of Asia
- Reduction of HBsAg in children not receiving birth dose
  - In countries where 50% of pregnant women are HBeAg-positive (e.g. Korea, Vietnam, China or wherever else genotype C predominates)
    - 50% reduction (e.g. 10% to 5%)
  - In countries where 15% to 30% of women are HBeAg-positive (e.g. Africa or where genotypes A and D predominate
    - 70%-90% (e.g. 10% to 1-3%)



Impact of Reduction of Prevalence of HBV in Children on the Incidence of HCC

- 3-4 decade lag time in overall reduction of HCC incidence in countries once successful vaccination programs in newborns have been introduced
- During this time, any reduction in incidence of HCC will take:
  - Identification of persons with chronic HBV
  - Linking those with chronic HBV to care
  - Identifying candidates meeting guidelines for care
  - Regular surveillance for HCC based on Guidelines recommendations

Mathematical Model: Age-specific hepatitis B-related cirrhosis and HCC mortality



Goldstein Int J Epidemiol 2005;34;1329-39

Long-term Protection from HBV Vaccination

- Evidence of long-term protection from vaccination
  - Studies from Alaska have found that evidence of humoral and cellular immunity in persons vaccinated >6 months of age last for at least 30 years
  - For those vaccinated as newborns, duration of protection lasts at least 18 years
    - Duration only needed 1st 5 years of life to have greatest impact on reduction of chronic HBV
  - Need for more serosurveys from MIC/LIC countries in children 5-years post infant vaccination

Bruce et al. J Infect Dis 2016;214:16-22
Simons-Petrusa et al. J Infect Dis 2016;214:273-80

Challenges for Identifying Persons with Chronic HBV in Low Middle Income Countries

- Screening strategies
- In HIC, screening is usually recommended in persons born in endemic areas with prevalence of HBsAg > 2%
  - How well are these recommendations working?
  - Almost all LMIC have HBsAg prevalence >2%: Screening the entire populations is a noble goal

– Which strategies for vaccination and screening are cost effective (The Alaska Model in 1980's)
  - This will depend on the cost of the screening test and the cost of the vaccine

1. Give first dose of HBV vaccine; at the same time screen for anti-HBc;
   – If anti-HBc negative, finish vaccine course
   – If anti-HBc is positive, test for HBsAg and if positive, link to care
2. Use HBsAg rapid screen test:
   1. If positive, link to care. If negative, give full course of vaccine (this scenario does not rely on a central laboratory)
3. Test for all three HBV markers and vaccinate only those negative for all.

Challenges for Identifying Persons with Chronic HBV in LMIC

- Where is screening currently being done?
  - Blood donors in blood banks and hospitals funded by Global HIV Program
- Where could screening be expanded
  - Household and sexual contacts of HBsAg+ persons identified by current screening
  - Piggybacked onto screening programs for HIV (including HCV)
  - Patients with liver disease or abnormal LFT
  - Healthcare workers (HCW) coupled with vaccination programs

- WHO Guidelines for Management of Chronic HBV have been developed using PICO methodology: http://www.who.int/hiv/events/hepB-guidelines-APASL/en/

What is Needed for Antiviral Therapy for HBV

- Cost of ETC and TDF need to be reasonable as treatment duration is long; TDF can be purchased for $6/month in some LIC
- Appropriate training of providers on following Guideline to know which patients meet criteria, when to start, when to stop and how to monitor
- Ultimately, better antiviral drugs are needed that target multiple sites in viral replication and have potential for short term duration of treatment and at least functional cure of HBV

WHO Implementation Considerations for National Programs

- Key Principals
  - Considering national response to HBV care within broader health contexts
    - Most countries are now developing National hepatitis B and C programs
  - Financial resources and political support
    - Cost: Who pays for all of this?
  - Human Resources: Training and teaching materials for HCW and specialists
  - Establishing clinics of excellence to manage patients with HBV infection
  - Laboratory and radiology capabilities
    - Developing the widespread capacity for HBV DNA testing as well as reliable serology tests
    - Needed inexpensive platforms and reagents
    - US, CT, MRI

Other Considerations in the Implementation of WHO Guidelines in LMIC

- Adequate Drug supply
- Instituting programs for HCC surveillance in areas where facilities able to treat early tumors with resection or local ablation are available.
- Monitoring and evaluation
- Implementation plan

- Unofficial Principal
  - WHO Hepatitis Program put under their HIV program
  - In US at CDC, Division of Viral Hepatitis is under Center responsible for HIV, TB and STI
    - Viral hepatitis program receives < $200,000 of one billion plus budget
    - Viral Hepatitis kills more persons in US than all other infectious diseases combined except influenza
  - Very successful HIV programs in US and abroad' s willingness to use their platform to incorporate HBV screening and treatment

Conclusions

- Better data on epidemiology of HBV related cirrhosis and HCC are needed to help plan programs for care
  - In much of Africa and many other countries
- Better Birth dose coverage of vaccine is needed
- WHO Practice Guidelines for HBV are now published and provide impetus to planning management of HBV in MIC and LIC
- Innovation strategies to develop programs to follow WHO Guidelines in LMIC are needed