Towards the Elimination of Hepatitis B : Challenges in implementing the WHO vision by 2030

CWN Spearman

Division of Hepatology
Department of Medicine
Faculty of Health Sciences
University of Cape Town

Global Burden of Disease

Global Burden of Disease study: 1990-2013 (183 countries)

- **Viral hepatitis is responsible for approximately 1.45 million deaths/yr**
  - **Cirrhosis, liver failure and liver cancer**
- **HIV/AIDS**: 1.3 million deaths/year
- **Malaria:** 0.9 million deaths/year
- **Tuberculosis:** 1.4 million deaths/year

Viral hepatitis is now the 7th leading cause of mortality worldwide

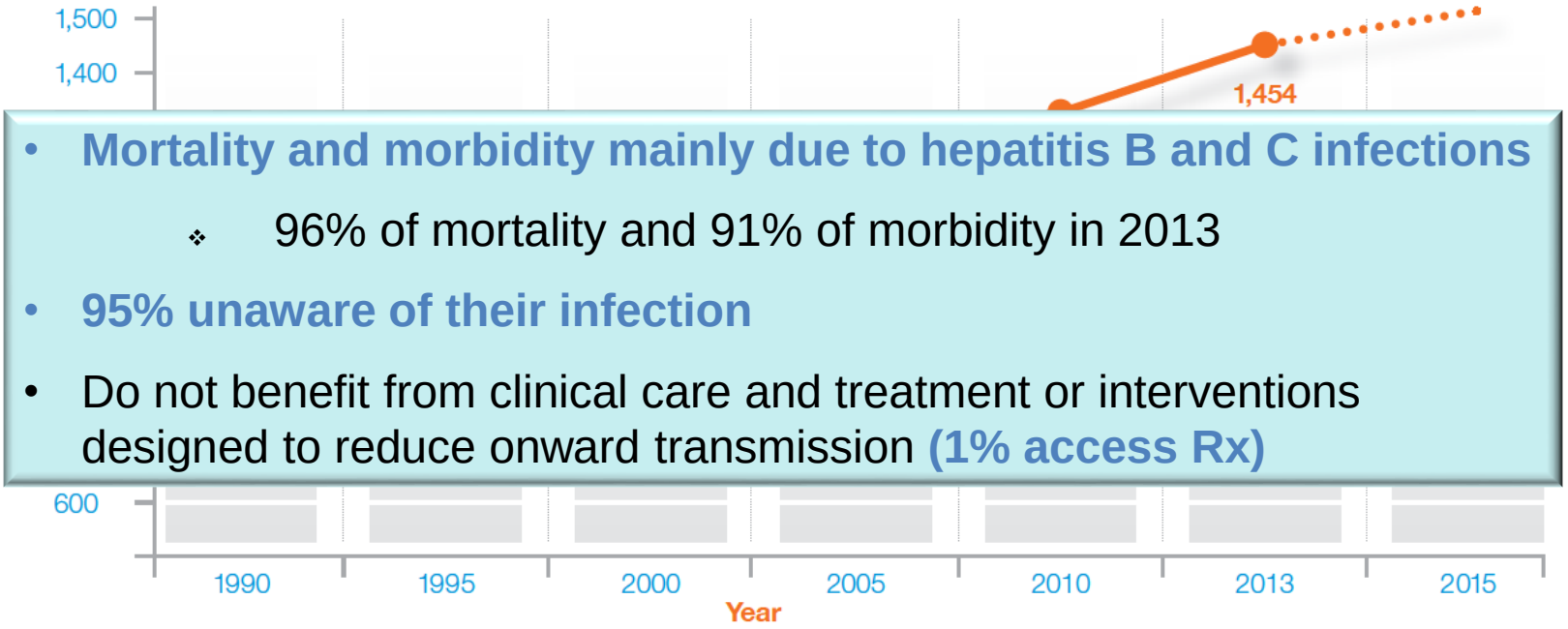
- ***Mortality*** due to viral hepatitis has ***increased by 63% since 1990***
- Persistent lack of global awareness of the severity of the problem
- Lack of commitment to combat and ultimately eliminate the disease

Lancet. 2012;380 (9859):2095; BMC Medicine 2014;12:159; WHO; 2014 [EB 134/36]; Lancet 6 July 2016

Viral Hepatitis Mortality

Global burden of Viral Hepatitis 1990-2013 (Lancet 6 July 2016)

Viral hepatitis kills more than 1.4 million people a year, yet there is a remarkable lack of global awareness and action to combat the disease.

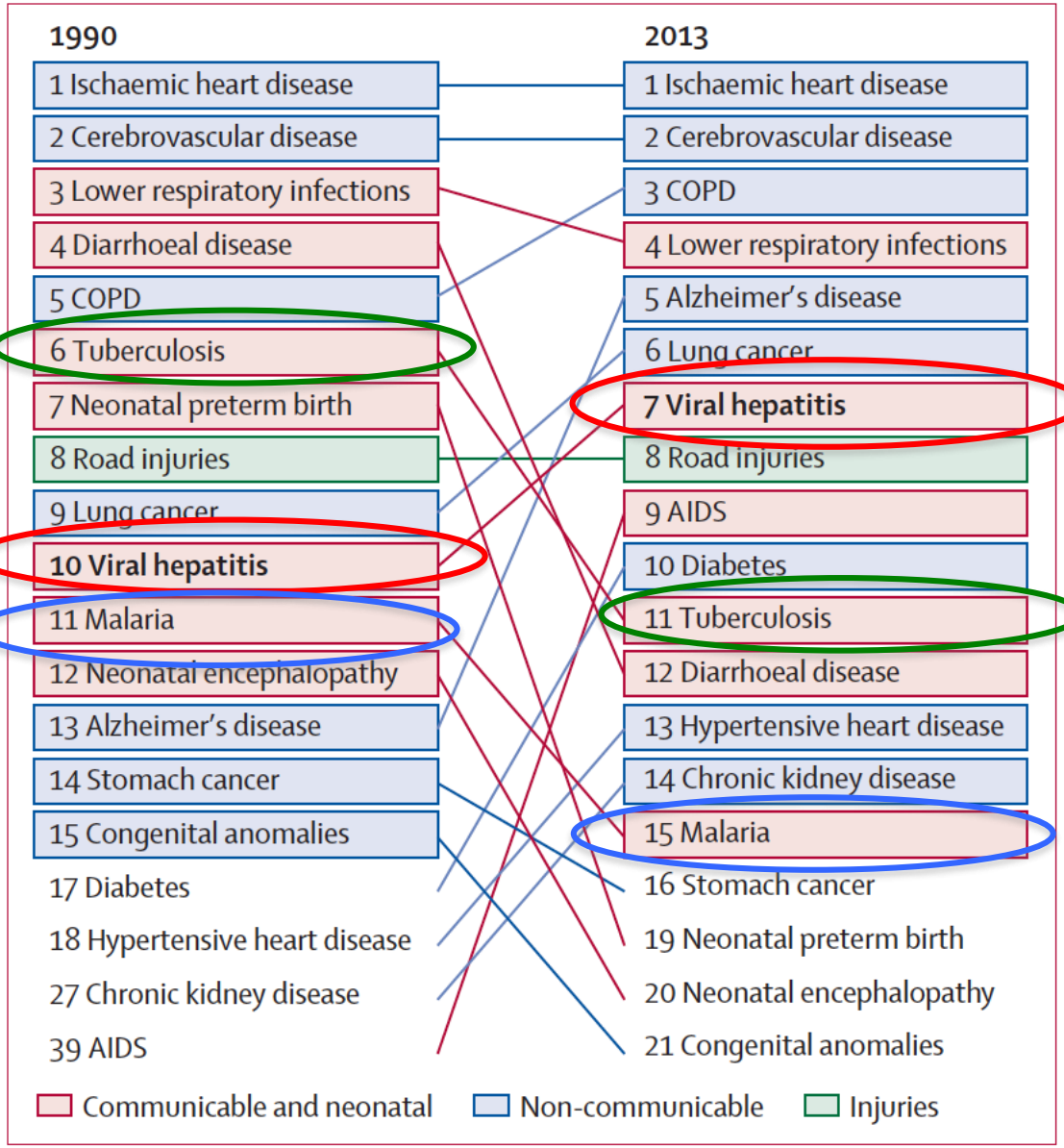


- **Mortality and morbidity mainly due to hepatitis B and C infections**
  - 96% of mortality and 91% of morbidity in 2013
- **95% unaware of their infection**
- Do not benefit from clinical care and treatment or interventions designed to reduce onward transmission **(1% access Rx)**

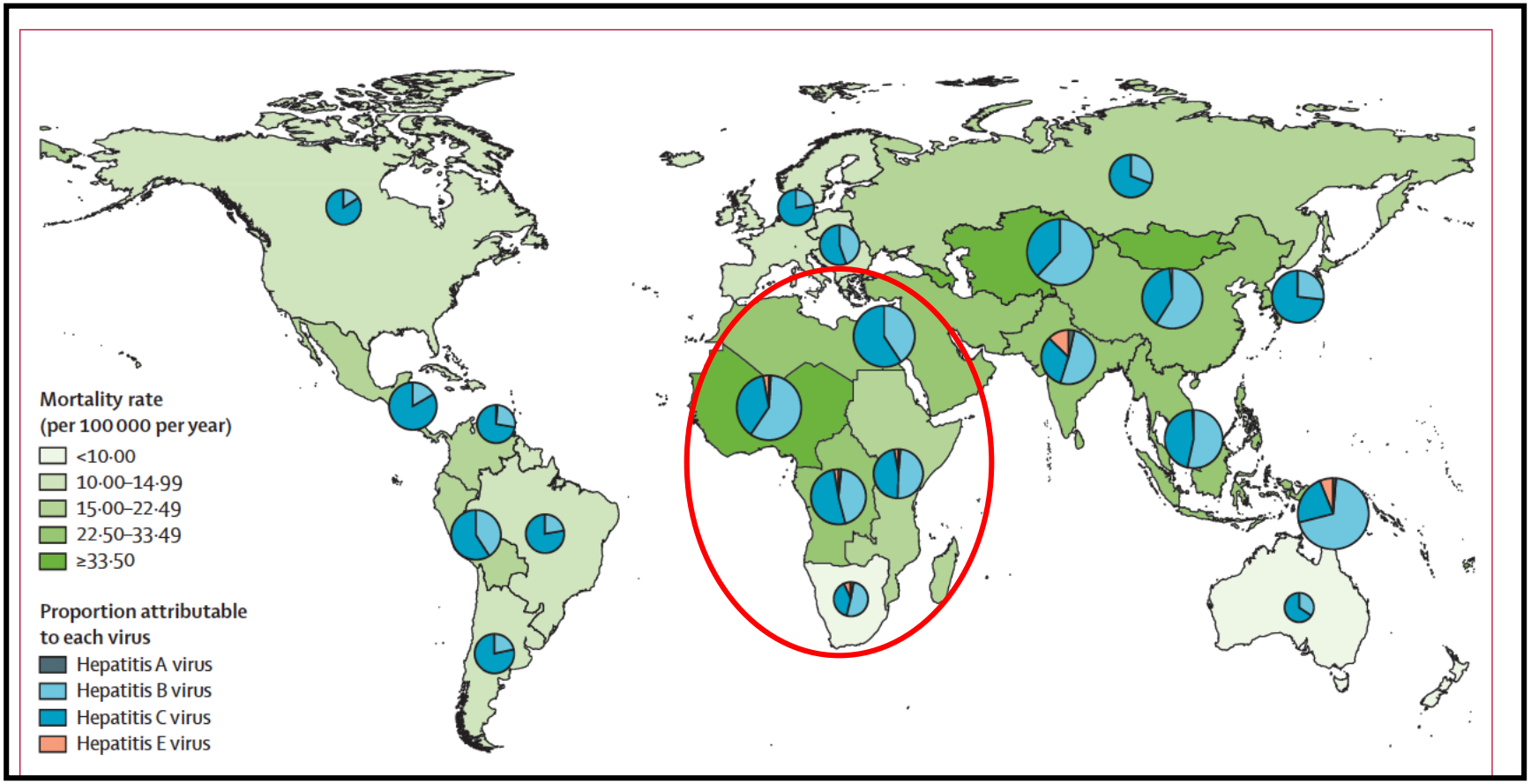
Data from 183 countries: Mortality increased from 890,000 deaths in 1990 to 1.45 million deaths in 2013

Leading causes of mortality and Trends 2013

Global burden of Viral Hepatitis 190-2013 (Lancet 6 July 2016)



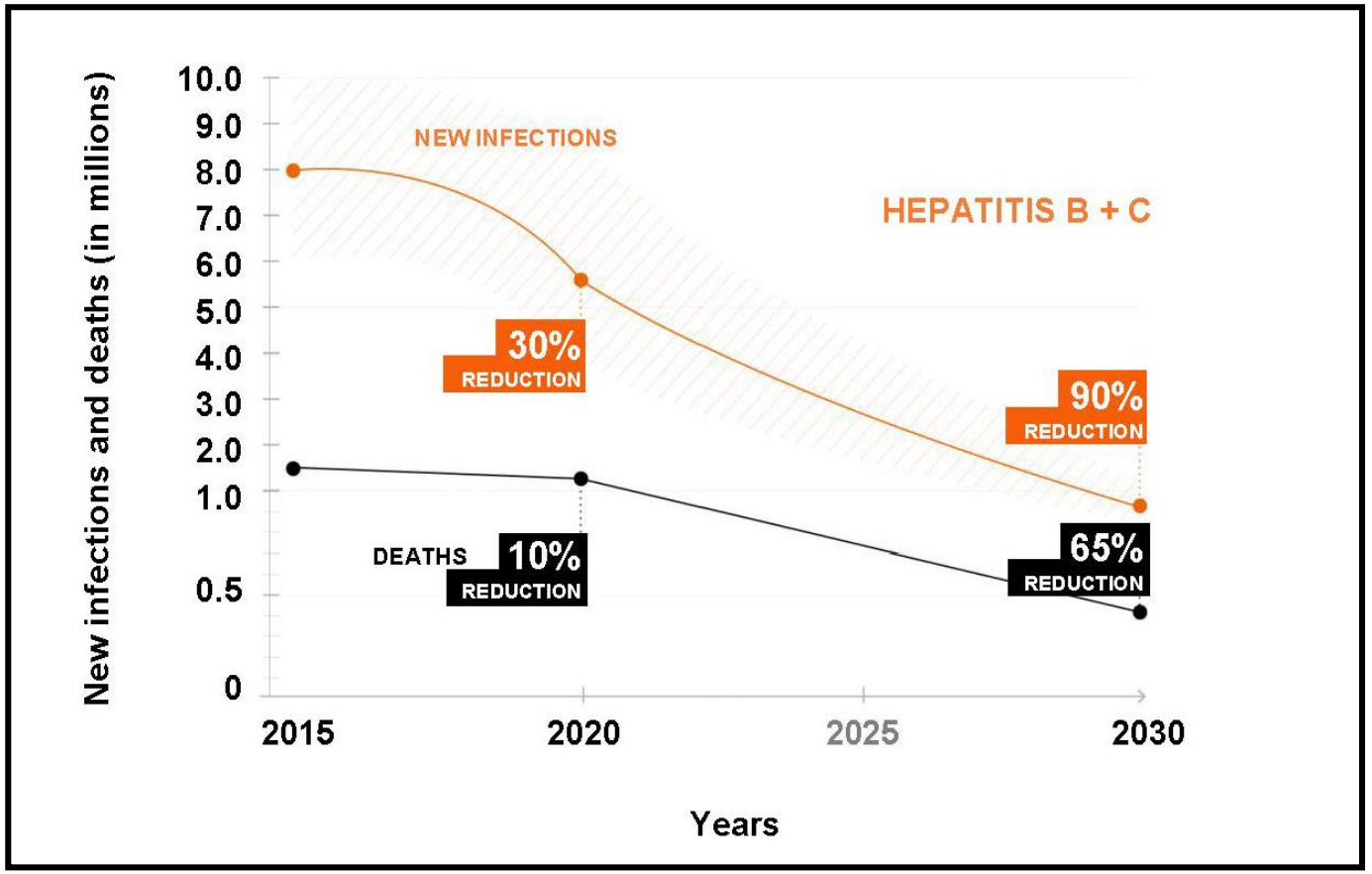
Global Viral Hepatitis Mortality



Africa Mortality rates ranging from:

- **< 10 000 per 100 000 per year (South Africa)**
- **10 - 33.49 per 100 000 per year (Central and Eastern Africa)**
- **≥ 33 - 50 per 100 000 per year (West Africa)**

Proposed WHO targets for reducing new infections and stopping deaths



Hepatitis B and C

- 80% people eligible for treatment being treated
- Requires identification and linkage to care

WHO: Elimination of Viral Hepatitis by 2030

WHO strategy : Key targets to eliminate Hepatitis B and C as a public health threat

- 90% infants receive a hepatitis B birth dose vaccination
- 100% blood donations screened
- 90% injections are safe
- 90% people aware of their illness
- 80% people treated

Saving 7.1 million lives

Elimination of Hepatitis B in sSA

Many sSA countries in the process of developing Viral Hepatitis Management Guidelines and Strategic plans to achieve these elimination goals

Major challenges to the elimination of Hepatitis B in sSA

- Effective prevention of mother to child transmission
- Access to affordable diagnostics: Identify HBV-infected individuals and link to care
- Addressing social stigmas associated with the diagnosis of HBV and screening of contacts

HBV and its associated complications of cirrhosis, liver failure & HCC

VACCINE PREVENTABLE

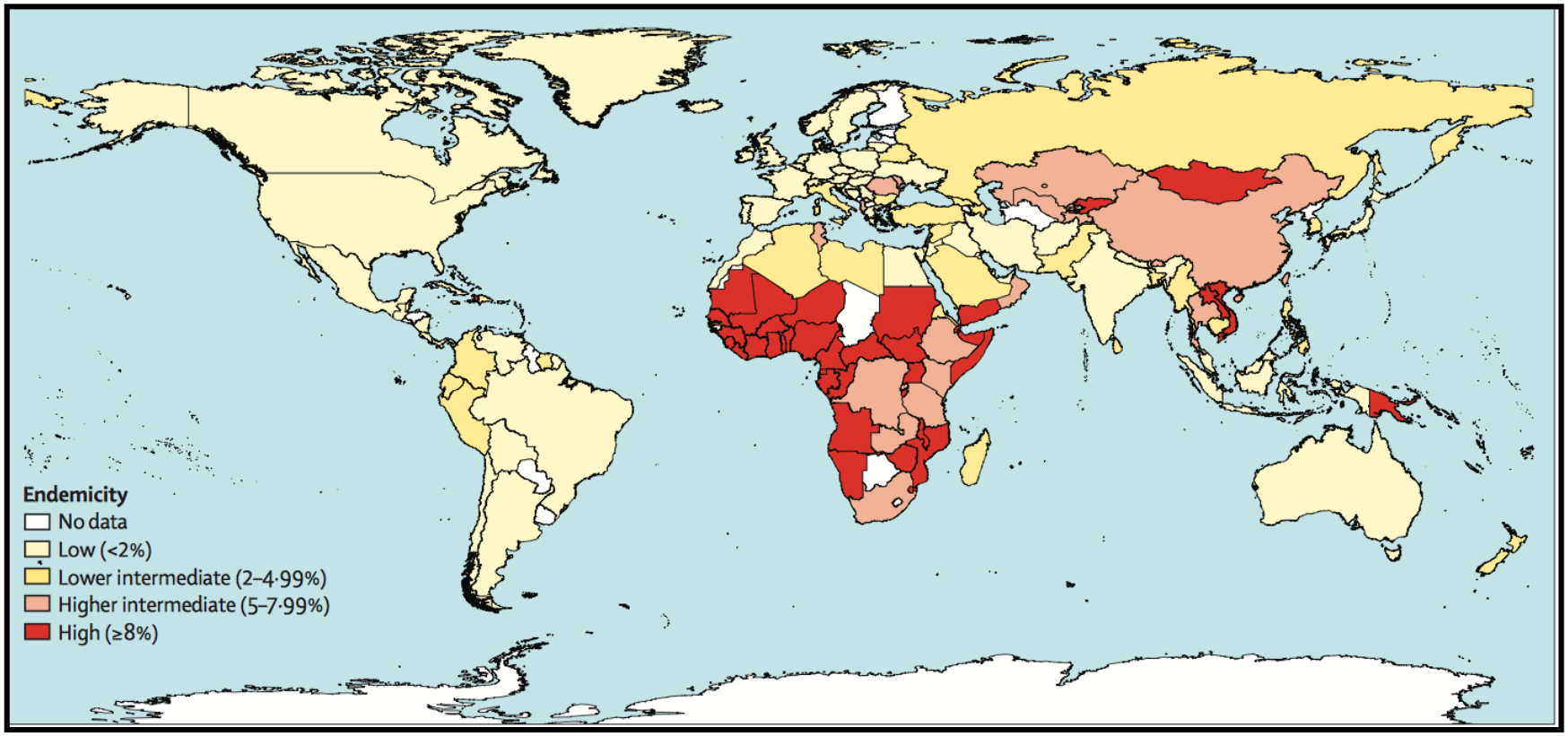
Hepatitis B

Effective vaccines since 1981 & effective antiviral therapy

- Hepatitis B remains a global health problem
- 2 billion people have serologic evidence of past or ongoing HBV infection
- 350-400 million people with chronic HBV infection
- 1 million people die annually from HBV & its associated complications
- **Life-time risk of cirrhosis, liver failure & HCC: 15-40%**
- Recent systematic review based on observational studies (1965-2013)
  - **Africa: 8.83% HBsAg seroprevalence (75.6 M) : high endemicity**
- **Chronicity determined by age of acquisition**
  - 90% after neonatal infection and 20-50% with childhood infection < 5years

Hepatology 2009;49 (5 Suppl):S45; Lancet 2015;386:1546; J Med Virol 2009;81(3):406; Vaccine 2012;30(12): 2212; S Afr Med J 2011;101(7):470; Int J STD AIDS 2007;18(3):152; Vaccine 2013;31(47):5579; J Hepatol 2006; 44(1 Suppl):S65 , Lancet Inf Dis 2002;2:395; Hepatology 2001;34:1225

Hepatitis B Epidemiology

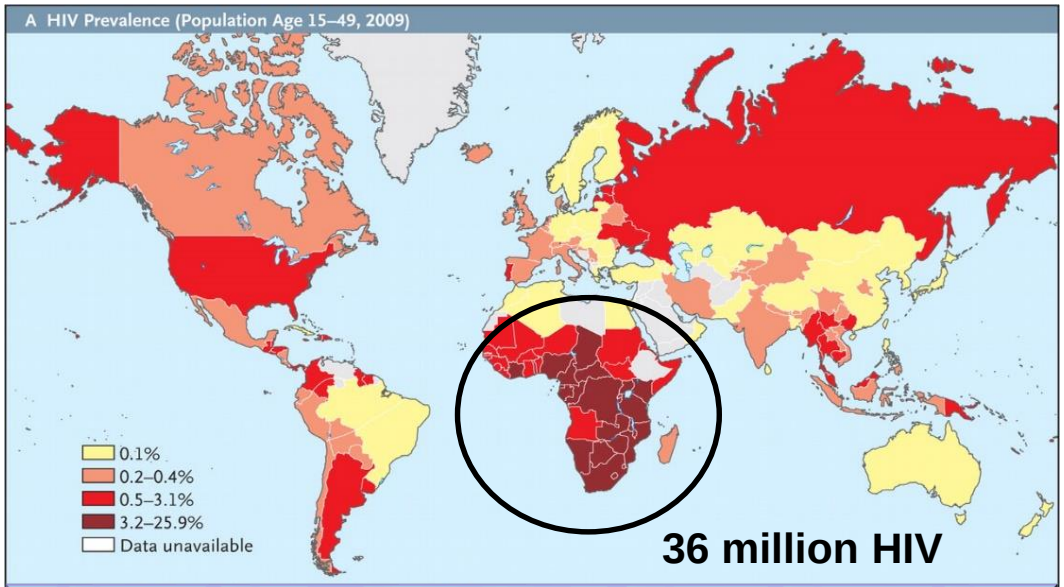


Global HBsAg endemicity (1957–2013)

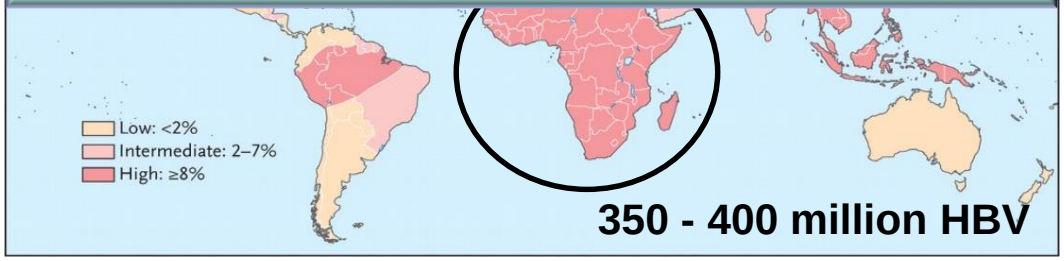
HBV endemicity is established in early childhood with HBsAg seroprevalence studies showing no difference between children aged 5-9 years and adults

Lancet 2015; 386: 1546-55

Impact of HIV/HBV Co-infection



- **Globally, up to 10% of HIV-infected individuals have HBV co-infection**
  - 4-6 M HIV/HBV co-infected individuals
- **HBV endemic countries up to 25% HIV/HBV co-infected**



70% of global 36 million people with HIV live in sSA

Increased mortality & morbidity

HIV co-infection promotes:

- Increased HBV replication & rates of HBV reactivation
- HBV MTCT 2.5 fold
- Increased rates of occult HBV
- Chronicity of newly acquired HBV infections
- *Progression to fibrosis and cirrhosis – 5x faster*
- *HCC - occurs at a younger age and is more aggressive*

N Engl J Med 2012;366:1749; Lancet Infect Dis 2007; 7:402; Hepatology 2009;49:Suppl:S138; AIDS 2005;19(6):593; J Acquir Immune Defic Syndr 2000;24(3):211; J Inf Dis 2013;208(9):1454; South Afr Med J 2012; 102:157–162; World J Hepatol 2010; 2: 65-73

Hepatitis B Epidemiology

- HBV infection rates largely reflect a failure of maternal and child healthcare programmes to prevent HBV MTCT and early childhood transmission

sub-Saharan Africa

- Horizontal transmission - early childhood <5 years old
- Lower prevalence of HBeAg positive mothers
- Close household contacts, medical or traditional scarification procedures
- *30-50% risk of chronic infection*

Impact of HIV/HBV co-infection in pregnancy

- Pregnant women 3 x more likely to test positive for HBV DNA, higher HBV DNA
- Twice as likely to test positive for HBeAg
- **Increased risk of HBV MTCT**

Lancet Infect Dis 2007; 7:402

Elimination of Hepatitis B

Prevention of Mother-to-child-transmission (MTCT) of HBV

- **Identify:** Maternal HBsAg screening
  - Not routine in many sSA countries
- **Incorporate Birth dose HBV vaccine into EPI schedule**
  - Administration within 24 hours of delivery
- **Assess the need for Tenofovir in 3rd trimester of pregnancy**
  - Most women are immune tolerant or immune control phase - not candidates for treatment
  - Risk of MTCT if HBV DNA >200 000 IU/ml
  - HBIG and HepB-BD: 80-95 % effective in preventing MTCT
  - HBIG expensive and not routinely available
- **Ensure full HBV3 vaccine coverage**

Universal HBV Vaccination

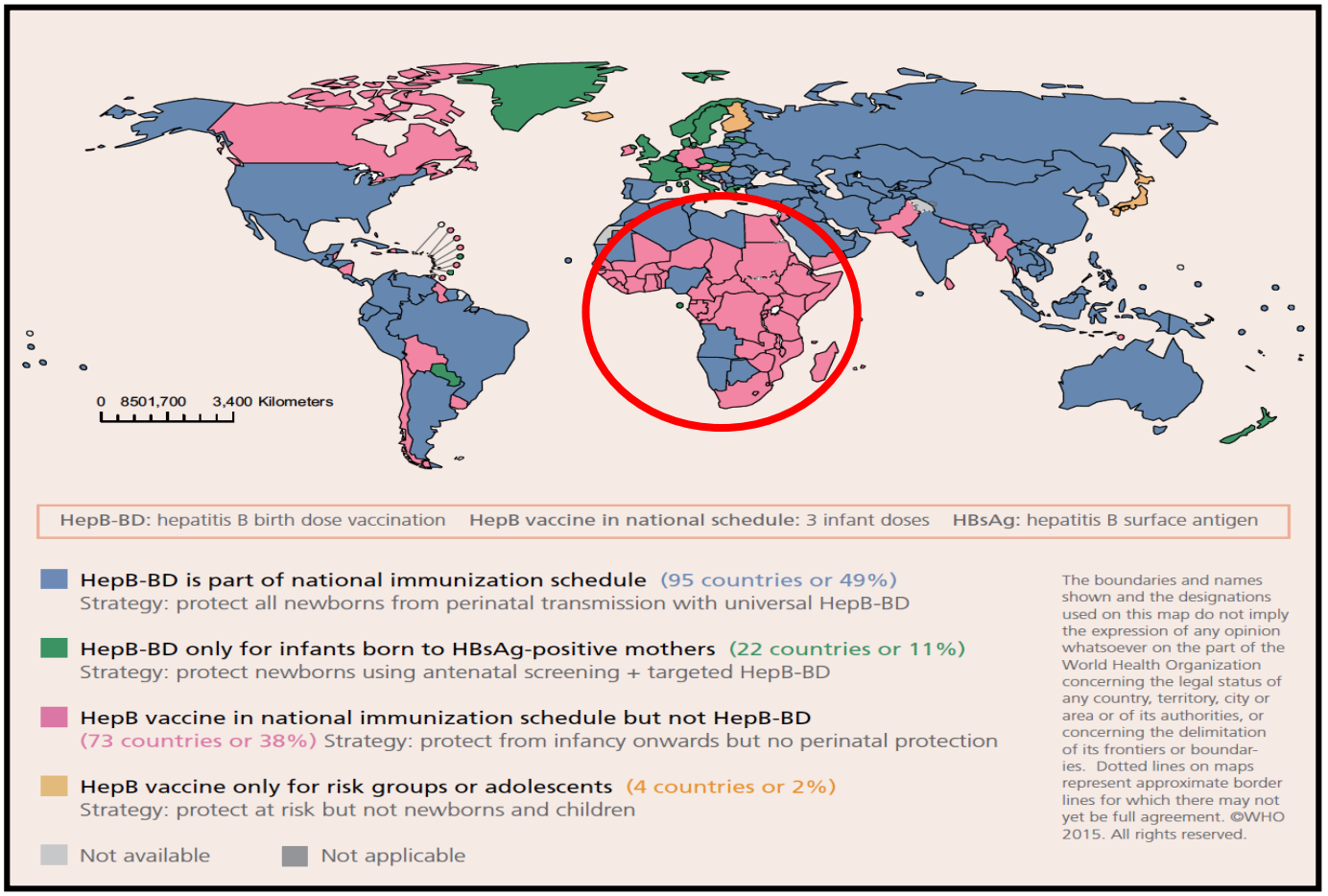
World Health Organization (WHO) recommended its incorporation into the Expanded Programme of Immunization (EPI) in 1991

- Most effective way to reduce global burden of HBV
- 194 countries worldwide and 45 in WHO Africa region have incorporated hepatitis B vaccination into EPI
- ***Systemic review (1990-2005)***: HBV seroprevalence has decreased in many regions of the world
- **Estimated to have prevented more than 1.3 million deaths**

In 2009, WHO recommended HBV Birth dose vaccine for all countries, even those with low HBV prevalence

Vaccine 2012;30:2212; Vaccine 2013;6:206; WHO position paper on hepatitis B vaccines. Geneva, World Health Organization, 2009 (http://www.who.int/wer/2009/ wer8440.pdf).http://apps.who.int/immunization_monitoring/globalsummary; Nature Gastro 2012; 9: 492

Global HepB-BD vaccine coverage



Data source: WHO/UNICEF Joint Reporting Form 2014, as at 05 November 2015 and ECDC published data at http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx

2014: only 96/194 countries (49%) reported offering HepB-BD as part of their national immunization programmes and **<38% of babies born worldwide received HepB-BD within 24 hours after birth**

HBV Vaccination :sSA

HBV Vaccine schedule 6,10 and 14 weeks

- Prevent childhood acquisition between 6 months and 5 years
- Based on acquisition being mainly horizontal
- **Concerns in HIV era of increased risk of perinatal MTCT of HBV**
- HBV monovalent vaccine is thermostabile and can be administered at same time as polio and BCG
  - Innovative approaches are required in settings of home deliveries

Chinese government in partnership with GAVI

(Vaccine 2013;31(Suppl 9):J29-J35)

- Free birth dose vaccine
- Upscaling of full vaccine schedule, improved maternal screening
- Utilising village lay healthcare workers
- **HBsAg seroprevalence now 0.96% in children < 5yrs (9.67% in 1992)**

Implementation: HBV Birth dose vaccine

- **Births take place in two main settings**
  - Formal healthcare facilities or in the 'home' delivery setting
- **Integrate birth dose vaccination with newborn care policies & practice**
- Assign responsibility for administering the birth dose
- Build capacity for vaccine storage, administration, reporting & recording
- **Formal healthcare facilities:** HBV Vaccine in or adjacent to delivery room
- **Home deliveries:** Educating mothers and other caregivers, during the antenatal period: Importance and timing of HepB-BD vaccine
- **Antenatal visits are a key opportunity for education**
  - 74% pregnant women in WHO African Region had at least one antenatal care contact
  - Community health workers and other antenatal care providers should be trained to include HepB-BD in counselling
- Auxiliary health workers or community health workers can be trained to administer vaccines at home
  - Single-dose vials or compact pre-filled auto-disposable devices (CPADs)

Implementation: HBV Birth dose vaccine

Pregnancy tracking to improve HepB-BD vaccine coverage

Vietnam *(Vaccine 2008;26(11):1411)*

Established strategy for tracking pregnant women in order to increase timely HepB-BD coverage

- In two districts where 20 - 36% of newborns were born at home
  - **Community health workers** tracked pregnancies by recording names, addresses and expected delivery dates of pregnant women
  - **Village health workers** informed community health workers of births to further ensure that HepB-BD was administered
- This system helped districts to achieve **90 - 97% coverage with HepB-BD vaccine**

HBV Birth dose vaccine

Indonesia *(Vaccine 2007;25(32):5985)*

- >90% of births occur at home
- **1990s:** Programme training village midwives in use of CPADs
  - **Allowed to store CPADs out of the cold chain in their homes**
- HepB-BD immediately available when midwife was called to a delivery
- Both village midwives and mothers preferred use of CPADs
- Successful use of CPADs was expanded nationwide
- Facility delivery rates still low: **HepB BD vaccine coverage is now 84%**

Compact pre-filled auto-disposable device (CPAD)

HBV Birth dose vaccine

MONOVALENT HEPATITIS B VACCINE MUST BE USED FOR THE BIRTH DOSE

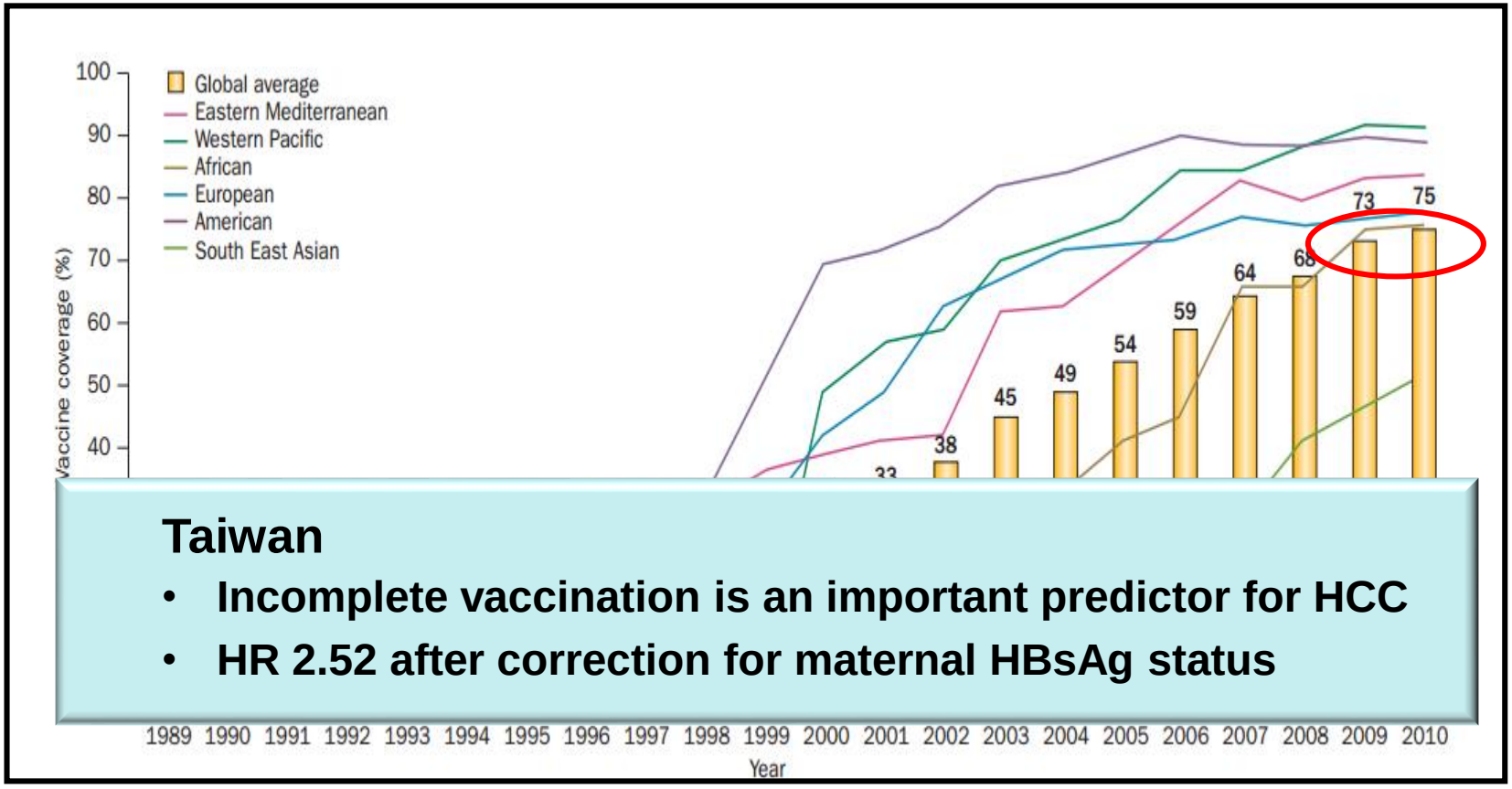
NAME OF DOSE	TIMING OF ADMINISTRATION OF DOSE	
	3-DOSE SCHEDULE	4-DOSE SCHEDULE**
HepB-BD	As soon as possible after birth (≤24 h)	As soon as possible after birth (≤24 h)
HepB1	HepB1 is not given (i.e. not counted*)	As per combination vaccine schedule
HepB2	4 weeks minimum after HepB-BD	As per combination vaccine schedule
HepB3	4 weeks minimum after HepB2	As per combination vaccine schedule

* Not counting HepB1 is recommended as a standard to allow for reporting coverage of HepB-BD and HepB3 when using a 3-dose schedule.
** In the 4-dose schedule, the second dose is still called HepB1 in order to avoid confusion with DTP1/Pentavalent1.

- Monovalent HBV birth dose improves immunogenicity of penta/hexavalent vaccines
- 4 dose schedule does not immunologically compromise infants who do not access Hep-BD
- **Risk of chronic HBV infection, despite HepB-BD, is 3.74x higher if interval between 1st and 2nd vaccine dose >10 weeks**

Vaccine 2009;27:6110–6115

Global and regional infant vaccination rates



Taiwan

- **Incomplete vaccination is an important predictor for HCC**
- **HR 2.52 after correction for maternal HBsAg status**

WHO/UNICEF estimates of third dose of HBV vaccine coverage 1989-2010

Thurz et al Nature Gastro 2012 ; 9; 492-494

Efficacy: Universal HBV Vaccination

Taiwan *(JAMA 1687;257:2597; JAMA 1988;260:2231; JAMA 1996;276:906; Ann Int Med 2001;135:796)*

- **Universal vaccination in 1984, together with**
  - Catch-up vaccination programme
  - Improved maternal screening
- **HBsAg seroprevalence in children <15 years decreased**
  - **9.8% in 1984** to 0.7% in 1999 to **0.3% in 2009**
- **Infection rate (anti-HBc seropositive rate): children 15-20yrs after programme decreased from:**
  - **38% in 1984** to 16% in 1999 to **4.6% in 2009**

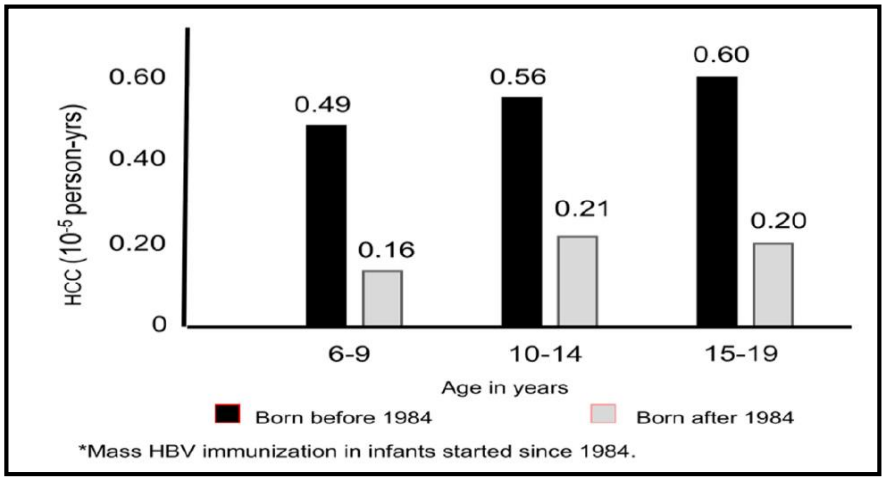
Efficacy: Universal HBV Vaccination

Taiwan *(N Engl J Med 1997;336:1855; J Natl Cancer inst 2009;101:1348)*

HCC incidence in children decreased, esp in boys

- Average annual incidence in children 6-14 years of age
  - 0.70 per 100,000 children in 1981-1986
  - 0.57 per 100,000 children in 1986 -1990
  - 0.36 per 100,000 children in 1990-1994

5.2 cases/million population (1984) to 1.3 cases/million in 1st vaccination cohort



Incomplete immunisation most important risk predictor for HCC

- **HR 2.52 after correction for maternal HBsAg status** *(Hepatology 2014;60:125)*

Efficacy : Universal HBV Vaccination

Singapore: Universal HBV vaccination 1987 *(Best Practice & Research Clinical Gastroenterology 2015;29:907)*

- Age-standardised HCC incidence rate among males decreased
  - 27.8 per 100,000 per year during 1978 -1982
  - 19.0 per 100,000 per year during 1988 -1992

Khon Kaen, Thailand *(Asian Pac J Cancer Prev 2008;9:507)*

- Age - standardized HCC incidence rates in children >10 years
  - Non-vaccinated: 0.88 per million
  - Vaccinated children: 0.07 per million

Alaska Natives *(Hepatology 2011;54:801)*

- 25 years after Universal HBV vaccination & mass screening
- HCC incidence in adolescents <20 years decreased
  - 3 per 100 000 in 1984 -1988
  - 0 per 100 000 in 1995 -1999
- **No cases of HCC documented since 1999**

Efficacy : Universal HBV Vaccination

Rural China: Qidong province: Neonatal HBV vaccination

(PLoS Med 2014;11:e1001774)

- Reduces infant fulminant hepatitis mortality rate: 69% efficacy (95% CI 34-85%)
- Reduces end stage liver disease mortality rates: 70% efficacy (95% CI 15-89%)
- Reduces HCC incidence rate: 84% efficacy (95% CI 23-97%)

Efficacy : Universal HBVvaccination

- **SA introduced universal HBV vaccination in April 1995**
  - Added to existing 6, 10 and 14 week EPI schedule, now 18 month booster
  - Hexavalent vaccine
- **Pre - HIV era epidemiological studies**
  - sSA: Mothers predominantly HBeAg negative
  - Lower risk of perinatal transmission: lower HBV replication
- **No birth dose, no catch-up programme & no formal policy of screening mothers for HBsAg**
- **Overall HBsAg seroprevalence declining from 12.8% to 3% in some studies**
- **Recent SA studies suggest that there is a potential problem**
  - Recent HBsAg seroprevalence rates vary between 3-25%
  - Highest rates in HIV infected individuals

Hepatology 2009;49 (5 Suppl):S45; Lancet 2015;386:1546; J Med Virol 2009;81(3):406; Vaccine 2012;30(12): 2212; S Afr Med J 2011;101(7):470; Int J STD AIDS 2007;18(3):152; Vaccine 2013;31(47):5579; J Hepatol 2006; 44(1 Suppl):S65

Efficacy : Universal HBV vaccination

- **SA introduced universal HBV vaccination in April 1995**
  - Added to existing 6, 10 and 14 week EPI schedule, now 18 month booster
  - Hexavalent vaccine
- **Pre - HIV era epidemiological studies**
  - sSA: Mothers predominantly HBeAg negative
  - Lower risk of perinatal transmission: lower HBV replication
- **No birth dose, no catch-up programme & no formal policy of screening mothers for HBsAg**
- **Overall HBsAg seroprevalence declining from 12.8% to 3% in some studies**
- **Recent SA studies suggest that there is a potential problem**
  - Recent HBsAg seroprevalence rates vary between 3-25%
  - Highest rates in HIV infected individuals

Hepatology 2009;49 (5 Suppl):S45; Lancet 2015;386:1546; J Med Virol 2009;81(3):406; Vaccine 2012;30(12): 2212; S Afr Med J 2011;101(7):470; Int J STD AIDS 2007;18(3):152; Vaccine 2013;31(47):5579; J Hepatol 2006; 44(1 Suppl):S65

SA : Impact of HIV : Maternal Transmission

Western Cape *(9 355 pregnant women from antenatal clinics comparing HIV-positive and negative women)* *Vaccine 2013;31(47):5579*

- Low HBsAg prevalence region in SA
  - HBsAg 3.4% (53/1 543 HIV pos) v. 2.9% (44/1 546 HIV neg)
- HBeAg 18.9% (10/53 HIV pos) v. 17.1% (7/41 HIV neg)
- HBV DNA levels were much higher in HIV positive women
  - **9.72×10^7 IU/ml v. 1.19×10^6 IU/ml**
- **One in six HBV-infected pregnant women, irrespective of HIV status is HBeAg seropositive**
- Neonates remain unprotected for first 6 weeks of life

SA : Impact of HIV : Maternal Transmission

KZN ***(****African Journal of Laboratory Medicine 2016; 5(1):1-5)*

- ***Retrospective cross-sectional study:*** July 2011 to December 2011
- 322 study samples from discarded residual dried blood spot samples following routine infant diagnosis of HIV

10% overall HBsAg seroprevalence

- HIV-positive infants: 21/161 infants HBV positive :13.0%; 95% CI 6.8-19.9
- HIV-negative infants: 12/161 HBV positive: 7.5%; 95% CI 2.5-13.7
- Not statistically significant

Concern

- High prevalence of HBV infection in children despite HBV vaccination
- Independent of HIV status

Prevention of Mother to Child Transmission

Prevention of HBV MTCT is critical step towards the eradication of HBV & reduction in the incidence of HCC

- Universal HBV vaccination including HepB-BD decreases HBsAg seroprevalence
- Immunoprophylaxis fails in 10 to 30% of infants born to mothers with HBV DNA level >6 $\log_{10}$ copies/ml
- HBIG expensive and not easily accessible

Third trimester prophylaxis

- AASLD now suggest Tenofovir 300mg daily at 28-32 weeks of pregnancy if HBV DNA >200 000 IU/ml to further reduce risk of perinatal transmission
- EASL suggests antiviral therapy in 3rd trimester if HBV DNA >10^{6-7} IU/ml
- WHO: no formal recommendation for routine use of antiviral therapy

J Hepatol 2012;57(1):167-85; J Hepatol 2012;57: 167

Prevention of Mother to Child Transmission

China: 5 geographic regions – *Pan et al, NEJM 2016;374:2324*

- HBeAg-positive mothers HBV DNA >200 000 IU/ml
- 300 mg TDF: 30 to 32 weeks of gestation until postpartum week 4
- ***Infants***: 200 IU HBIG & 10ug HBV vaccine within 12hrs, HBV vaccine & HBIG repeated at 1 month and HBV vaccine at 6 months
- ***All mother–infant dyads:*** evaluated at postpartum weeks 4, 12, 24 & 28
- *68% TDF-treated mothers (66/97) vs 2% (2/100) - target HBV DNA level < 200 000 IU/ml at delivery*
- Week 28, rate of MTCT (HBV DNA >20 IU/ml or HBsAg positive at 28 wks)
  - **ITT analysis: 5% infants (5/97) in TDF vs. 18% (18/100), p= 0.007**
  - Per-protocol analysis 0% infants in TDF vs. 7% (6/88), p= 0.01
  - No difference in maternal HBV serological outcomes
- No difference in birth defects - 2% (2/95) vs 1% (1/88)

Prevention of Mother to Child Transmission

Need to identify highly viraemic mothers

- HBeAg and HBV DNA quantification (expensive with limited access)
- Shared diagnostic platforms for viral loads: HIV and HBV

HBsAg quantification: Taiwan: *Wen et al, Hepatology epub*

- Maternal HBV DNA viral load > 6 -7 $\log_{10}$ IU/ml or
  HBsAg >4 to 4.5 $\log_{10}$ IU/ml : **substantial risk of perinatal transmission**

- Estimated perinatal infection rates at maternal HBsAg levels:
  - 4 $\log_{10}$ IU/ml (10,000 IU/ml): 2.4%
  - 4.5 $\log_{10}$ IU/ml (30,000 IU/ml): 8.6%
  - 5 $\log_{10}$ IU/ml (100 000 IU/ml): 26%

- **Optimal cut-off of maternal HBsAg level to predict perinatal infection:**

  4.1 $\log_{10}$ IU/ml (12,500 IU/ml): 100% sensitivity, 71% specificity

Prevention of adult acquisition and transmission

- Ideally all individuals should be vaccinated – no catch-up programmes

•Essential to identify and vaccinate high risk groups

- Health-care workers
- All laboratory staff working with clinical specimens
- Policemen, firemen and members of the armed forces
- Persons with endstage renal disease requiring dialysis
- Persons with chronic liver disease
- Residents and staff of facilities for the developmentally disabled
- Patients receiving frequent transfusions of blood or blood components
- Transplant candidates before transplantation

Dependent on ability to:

- Screen high risk individuals: HBsAg and anti-HBs
- Administer HBV Vaccine

At all levels of care

Diagnosis and Linkage to Care

It is essential to identify HBV- infected individuals in order to assess the need for treatment and appropriate frequency of follow-up

- Upscaling diagnosis and improving linkage to care
- **Accurate WHO accredited HBV point of care testing that can be easily administered at primary levels of care**
- Shared diagnostic platforms for viral quantification: HIV, HBV and HCV
- Establish clear pathways of referral for followup and treatment
- **Educate clinicians that HBV is a silent disease** : often only clinically presenting when life-threatening complications arise
- **Most HBV-infected individuals in sub-Saharan Africa** do not fit the clinical profile for Interferon-based therapy and will usually require **lifelong treatment with nucleos(t)ide analogues**
- Tenofovir is the preferred antiviral
- **Ensure access to antivirals for management of HBV mono-infection**

Elimination of Hepatitis B : Conclusions

- **Hepatitis B is endemic in sub-Saharan Africa**
  - Despite Universal HBV vaccination, estimated overall HBsAg seroprevalence remains high at 8.83 %

Achieve WHO vision to eliminate hepatitis B by 2030 in sSA

- Development and Implementation of National Guidelines for the Prevention and Treatment of Viral Hepatitis
- Actively implement a number of elimination strategies
  - Effective prevention of HBV MTCT
    - Tenofovir in 3rd trimester if HBV DNA >200 000 IU/ml
    - Birth dose vaccine
  - Ensure full HBV vaccine coverage
  - Upscale diagnosis and treatment of HBV- infected individuals
    - Accurate and affordable diagnostics
    - Ensure access to Tenofovir for mono-infected individuals
- Commitment from Governments and National Departments of Health

SA: HIV impacts HBV vaccination

Kwazulu-Natal, South Africa

- September to December 2014
- Screened for HBsAg, anti-HBs, anti HBc
- 183 HIV infected vs. 108 HIV uninfected children bet 5-15 years
- HBsAg positive in 2.1% vs. 0% in HIV + vs. HIV negative children
- **anti-HBs response to immunization: 15.8% (HIV+) vs 61.1% (HIV-) children**

TABLE I. Serologic Markers of Past and/or Ongoing Infection in the HIV-Infected and Uninfected Cohorts

	HIV-infected			HIV-uninfected		
	5–10 years	11–15 years	Total	5–10 years	11–15 years	Total
Ongoing infection	0/103 (0%)	1/80 (1.3%)	1/183 (0.5%)	0/74 (0%)	0/34 (0%)	0/108 (0%)
Past infection	2/103 (1.9%)	1/80 (1.3%)	3/183 (1.6%)	0/74 (0%)	0/34 (0%)	0/108 (0%)

HIV-infected children remain at risk of infection

TABLE II. Comparison of the Immunity Against HBV in the HIV-Infected and Uninfected Cohorts According to the Age Subgroup of the Patients

	HIV-infected			HIV-uninfected		
	5–10 years	11–15 years	Total	5–10 years	11–15 years	Total
Presence of anti-HBs	21/103 (20.4%)	8/80 (10%)	29/183 (15.8%)	49/74 (66.2%)	17/34 (50%)	66/108 (61.1%)

Beghin et al. *J Med Virology* 2016, epub.

Treatment of CHB

Inhibition of HBV replication & Clinical Impact : Disease progression and HCC

Risk factors: Disease progression & HCC in patients with CHB

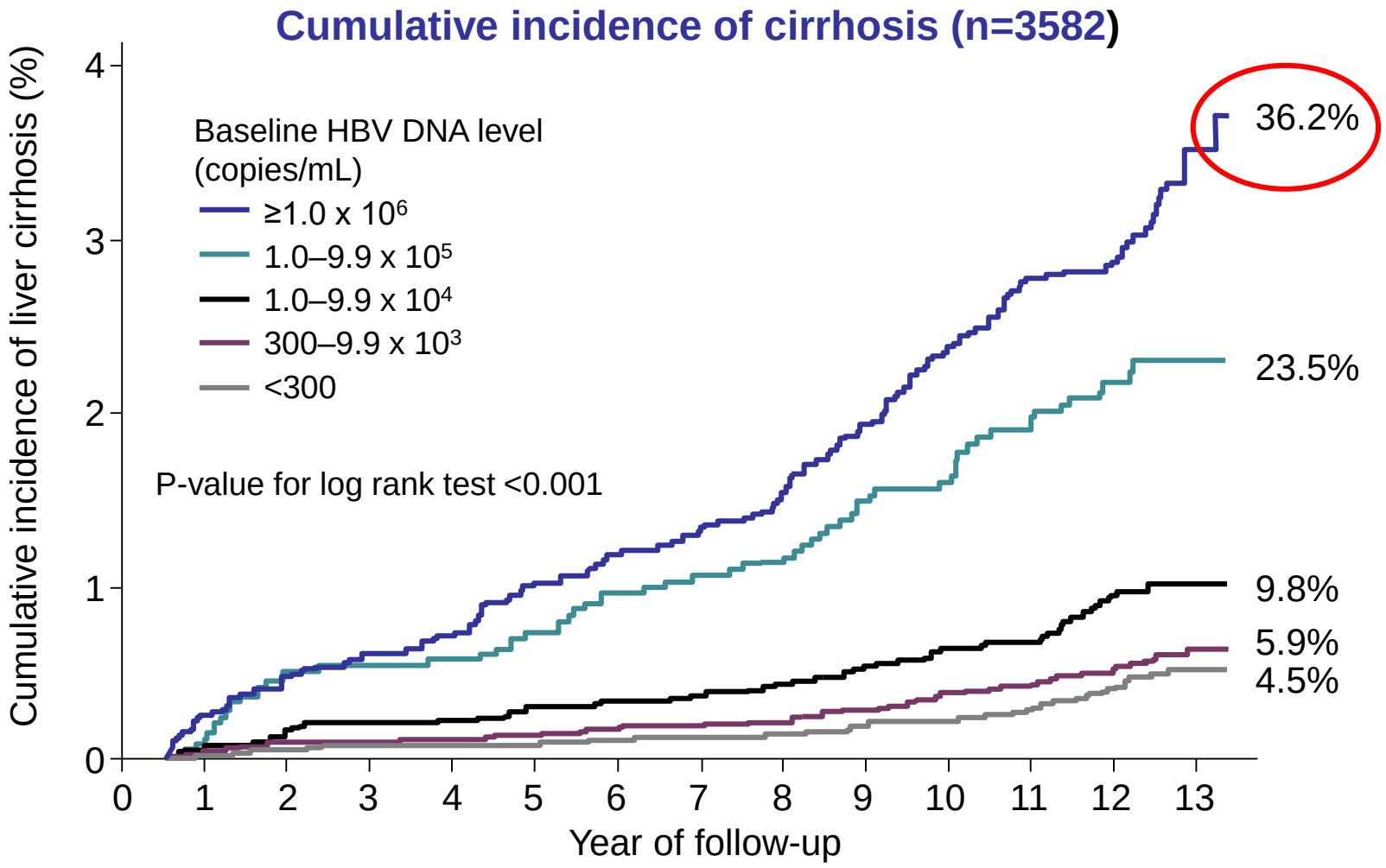
Host factors	Viral factors
Age (duration of infection?)	HBV DNA levels
Sex (males>females)	HBsAg levels
Genes (polymorphisms)	HBeAg status
Body mass index	HBV genotype (C/D>A/B)
Cofactors of liver disease (alcohol, NAFLD, Iron overload)	Basal core promotor mutations pre-core promoter mutations
Dietary factors (aflatoxin, coffee)	Pre-S deletions
Disease severity (decompensation>compensated cirrhosis>CHB>carrier state)	Protein X
Smoking?	

Non-modifiable factors - Modifiable factors

1. Chen CJ, et al. JAMA 2006;295:65
2. Sung J, et al. Aliment Pharmacol Ther 2008;28:1067
3. Vlachogiannakos J, Papatheodoridis G. World J Gastroenterol 2013; 19:8822

NAFLD: non-alcoholic fatty liver disease

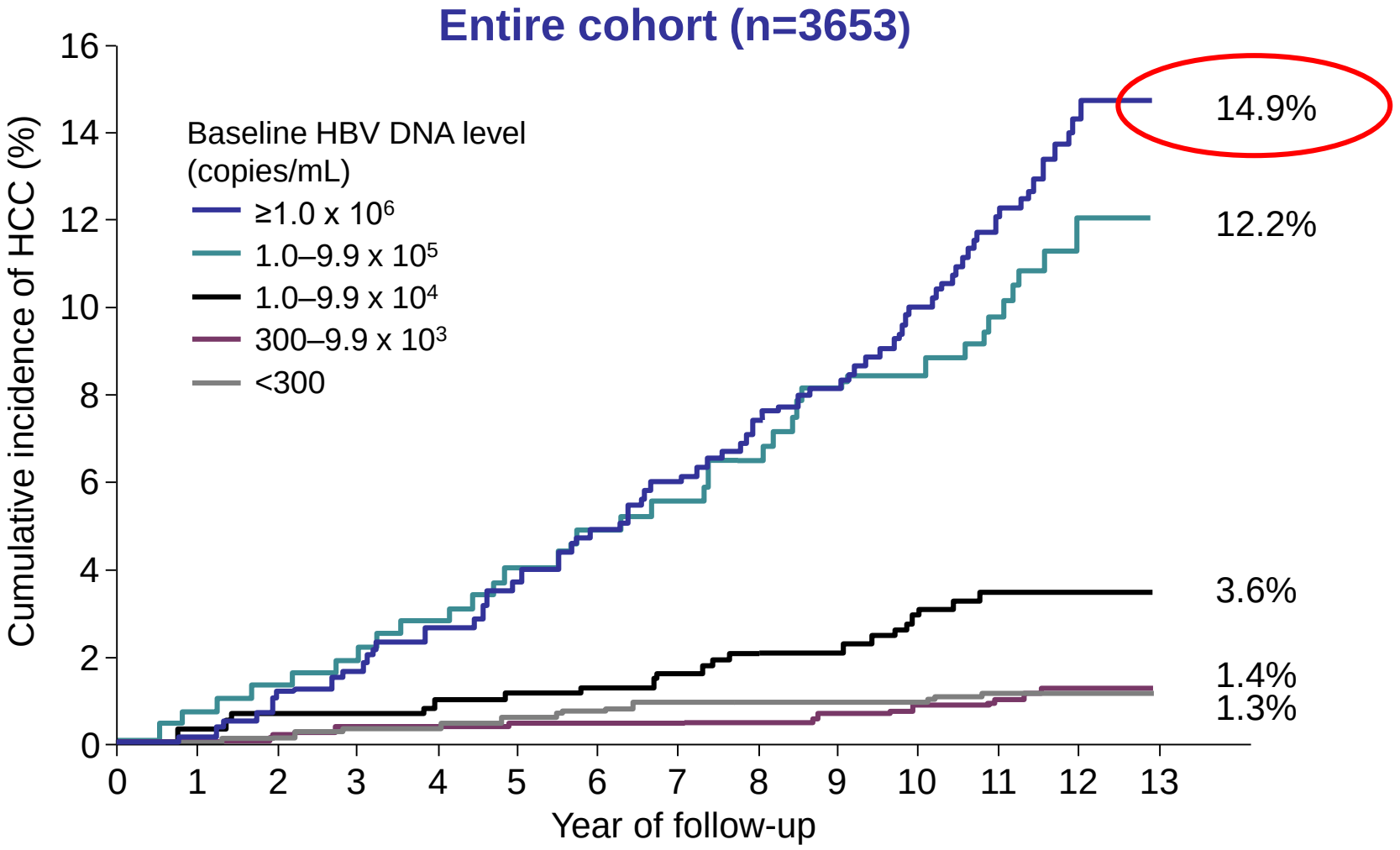
REVEAL demonstrated the association between HBV DNA levels and cirrhosis



Iloeje UE, et al. Gastroenterology 2006;130:678–86

No patient had cirrhosis at baseline

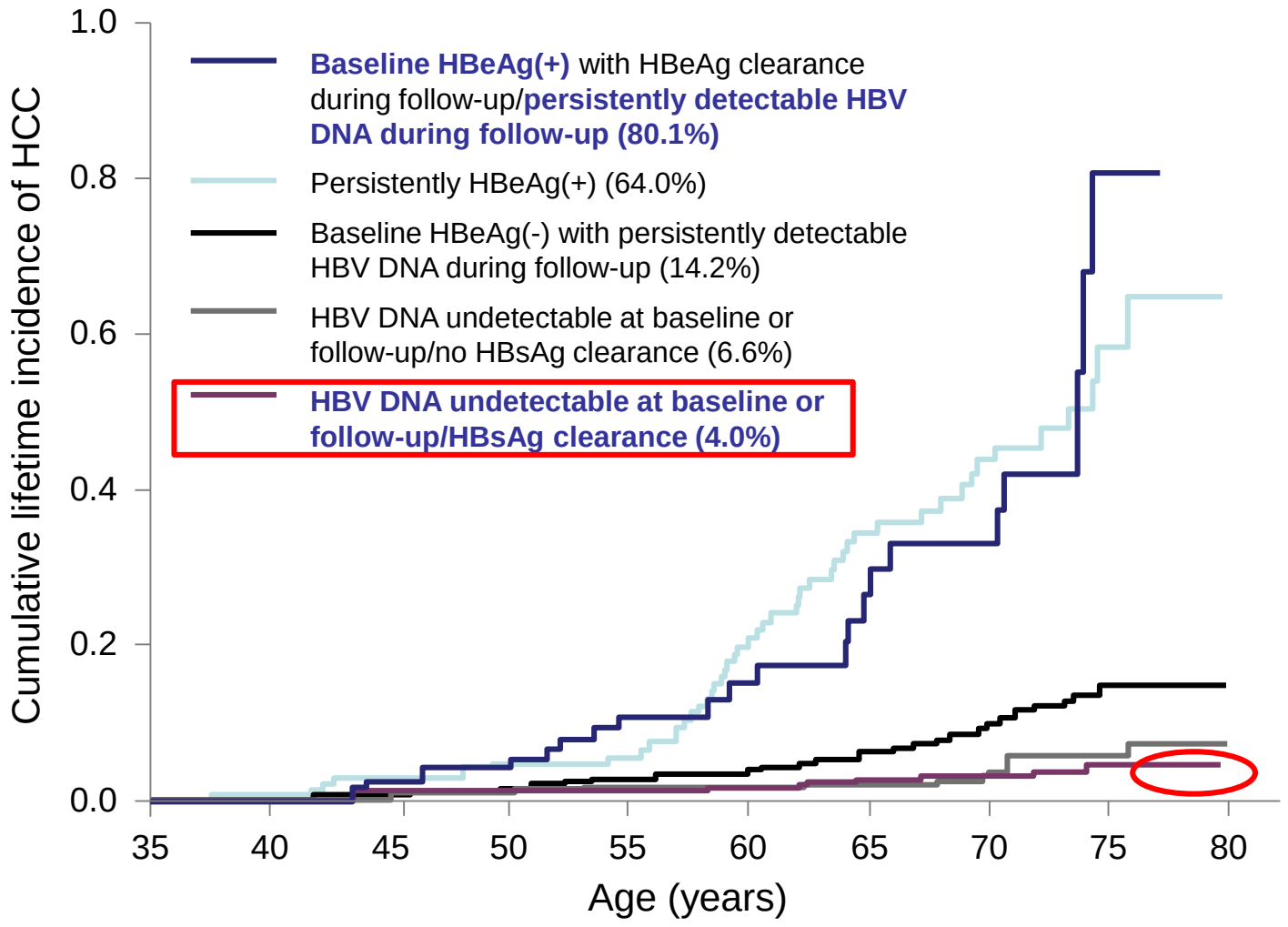
REVEAL demonstrated the association between HBV DNA levels and HCC



Chen CJ, et al. JAMA 2006;295:65–73

No patient had cirrhosis at baseline;
HCC: hepatocellular carcinoma

Undetectable HBV DNA is a key goal as it is associated with the lowest risk of HCC

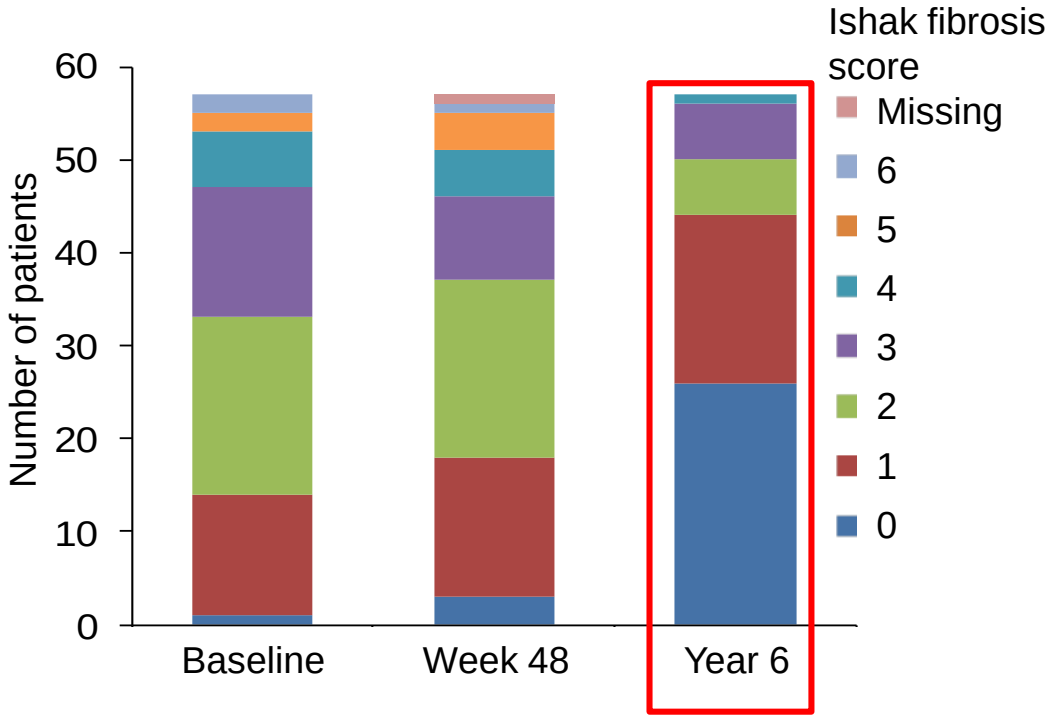


Liu J, et al. Gut 2013;62:440–51

Histological outcomes with ETV in patients with undetectable on-treatment HBV DNA levels

- NA naïve, HBeAg+ or HBeAg- patients with HBV DNA <300 copies/mL on ETV
  - N=57 had paired biopsies available
  - 86% had normal ALT
  - N=4 with cirrhosis
- Median interval 6 years
  - Range 3-7 years
  - 96% had histological improvement
  - 88% had improvement in fibrosis score

Ishak fibrosis score at baseline and treatment at Week 48 and Year 6

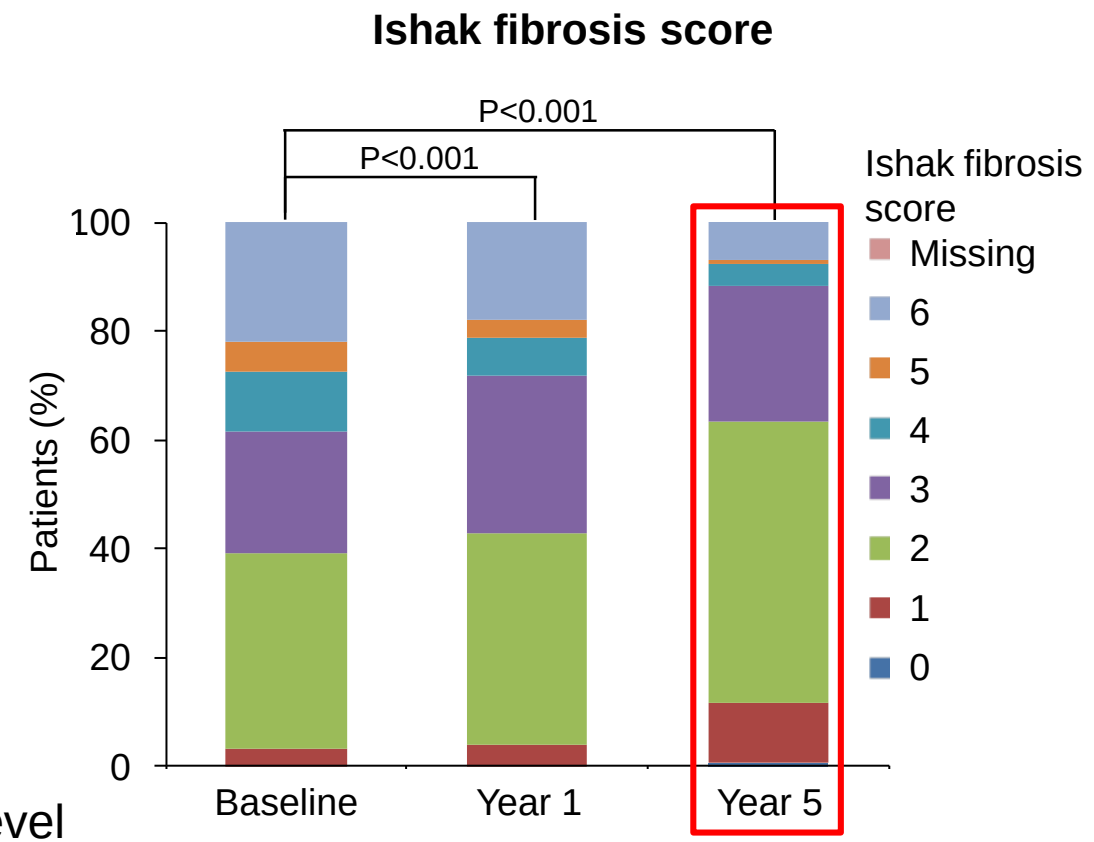


3 yr cumulative ETV therapy in Phase 3 studies & long term rollover studies

Chang TT, et al. Hepatology 2010;52:886

Histological outcomes with TDF treatment: liver fibrosis regression and cirrhosis reversal

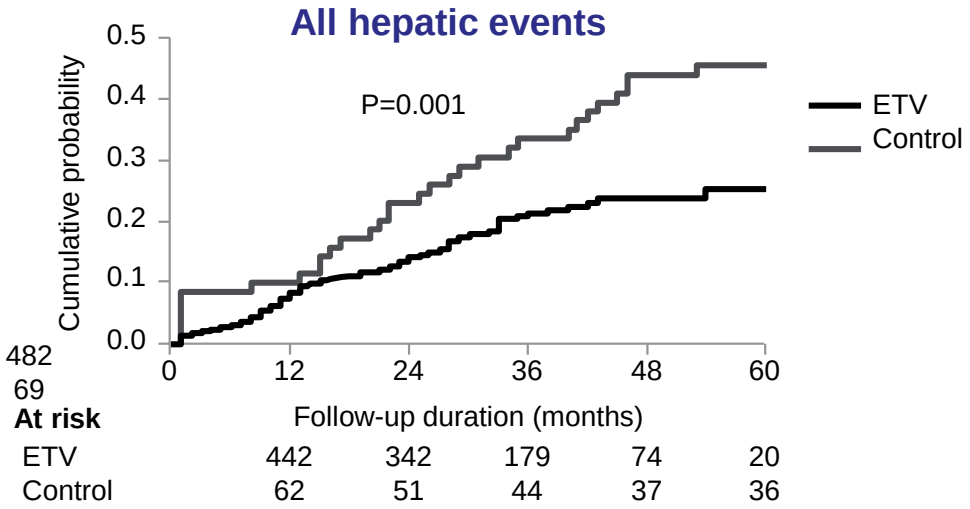
- TDF vs ADV for 48 weeks then open-label TDF in HBeAg- and HBeAg+ patients (Studies 102 and 103)
  - N=348 had biopsies at baseline and Year 5
  - N=96 with cirrhosis
- 87% (304/348) - histological improvement
- 74% (71/96) had reversal of cirrhosis
- Only low BMI was associated with fibrosis regression at Year 5
- Baseline BMI, diabetes at baseline & on-treatment ALT level associated with cirrhosis reversal

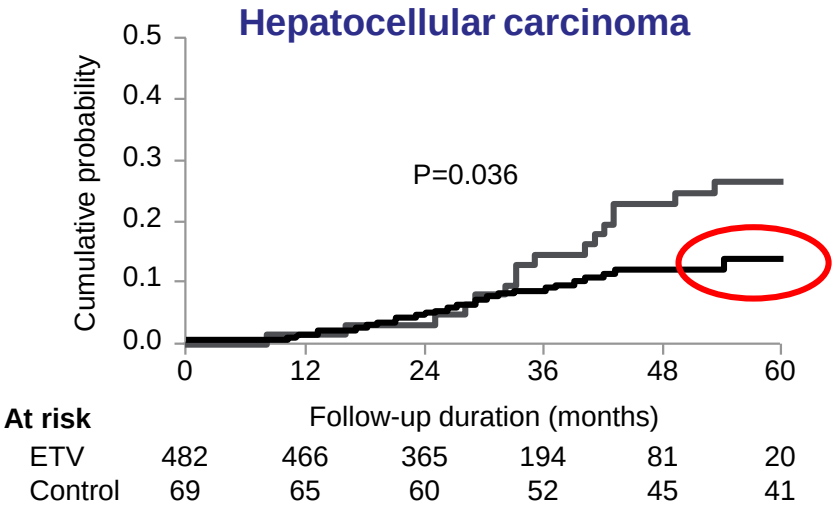


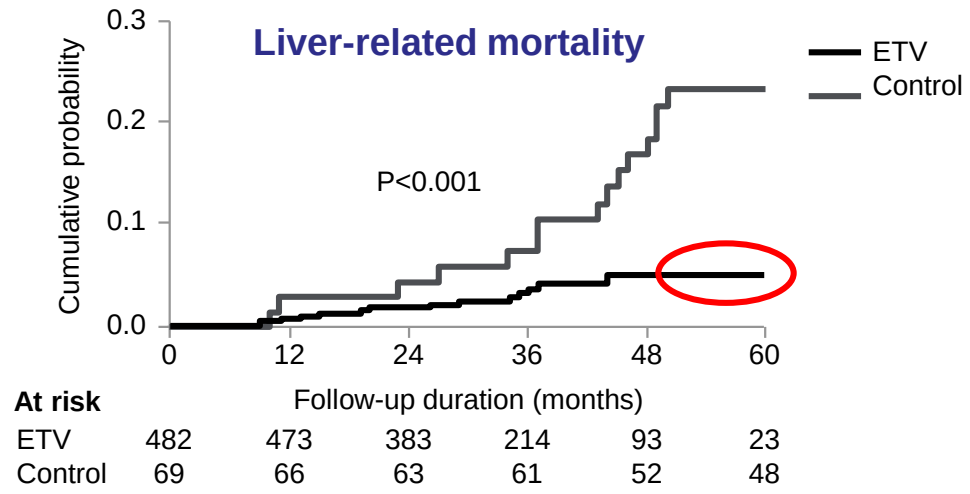
Histologically evaluable patients in the long-term histology cohort
344 patients had biopsies at baseline, year 1 and year 5

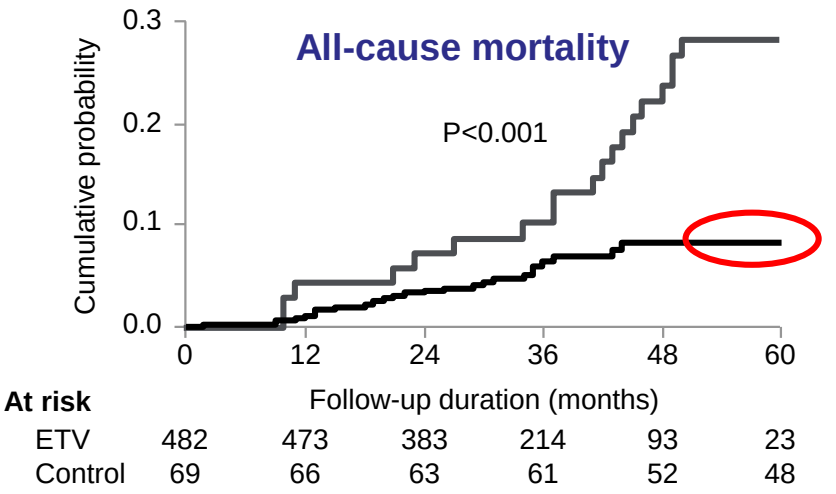
Marcellin P, et al. Lancet 2013;381:468

ETV treatment in cirrhotic patients



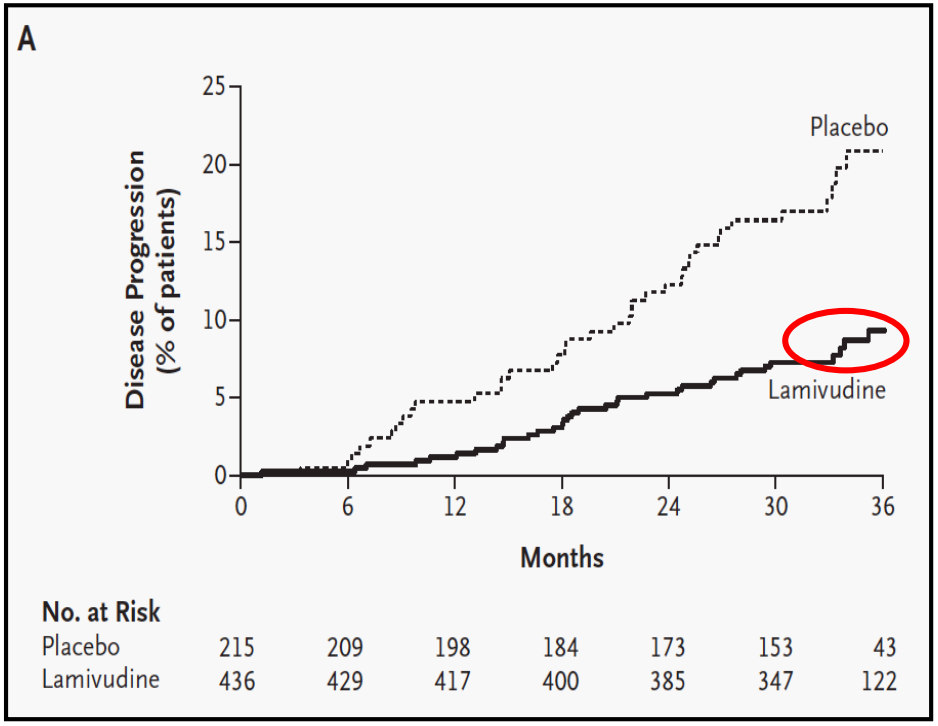


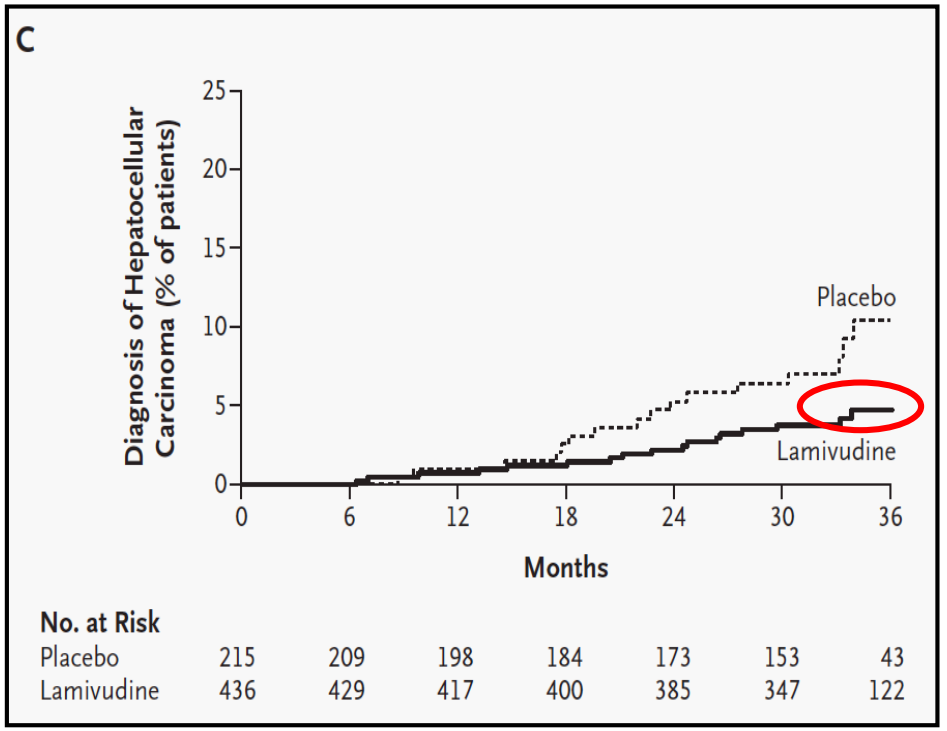




Wong GL et al. Hepatology 2013;58:1537

Lamivudine Efficacy: Disease Progression and HCC
Cirrhosis Asian Lamivudine Multicentre Study Group





651 patients (98 percent Asian and 85% male)

- Study was terminated after median duration of treatment of 32.4 months (range, 0 to 42)
  - clear benefit of lamivudine in preventing disease progression and liver related death

HCC: 3.9 % in lamivudine group & 7.4% in placebo group (Hazard Ratio, 0.49; P=0.047)

Liaw et al; N Engl J Med 2004;351:1521-31

Cumulative HCC risk scores: Asian CHB pts[1]

	Age	Sex	Alb (g/L)	TBil (μmol)	ALT (U/l)	HBeAg status	HBV DNA (cp/mL)	Cirrhosis	AUROC
GAG-HCC[2]	In years	M: 16 F: 0	NA	NA	NA	NA	3 × log	Yes: 33 No: 0	5yr: 0.87 10yr: 0.88
CU-HCC[3]	≤50: 0 >50: 3	NA	≤35: 20 >35: 0	≤18:1.5 >18:1.5	NA	NA	<4 log: 0 4–6 log: 1 >6 log: 4	Yes: 15 No: 0	5yr: 0.76 10yr: 0.78
REACH-B[4]	30–34: 0 35–39: 1 40–44: 2 45–49: 3 50–54: 4 55–59: 5 60–65: 6	M: 2 F: 0	NA	NA	<15: 0 15-44: 1 ≥45: 2	+: 2 -: 0	<4 log: 0 4–5 log: 3 5–6 log: 5 ≥6 log: 4*	NA	5yr: 0.8 10yr: 0.77 **Cirrhosis** 5yr: 0.7 10yr: 0.65

AUROC for HCC prediction: Caucasian pts with compensated CHB treated with ETV/TDF

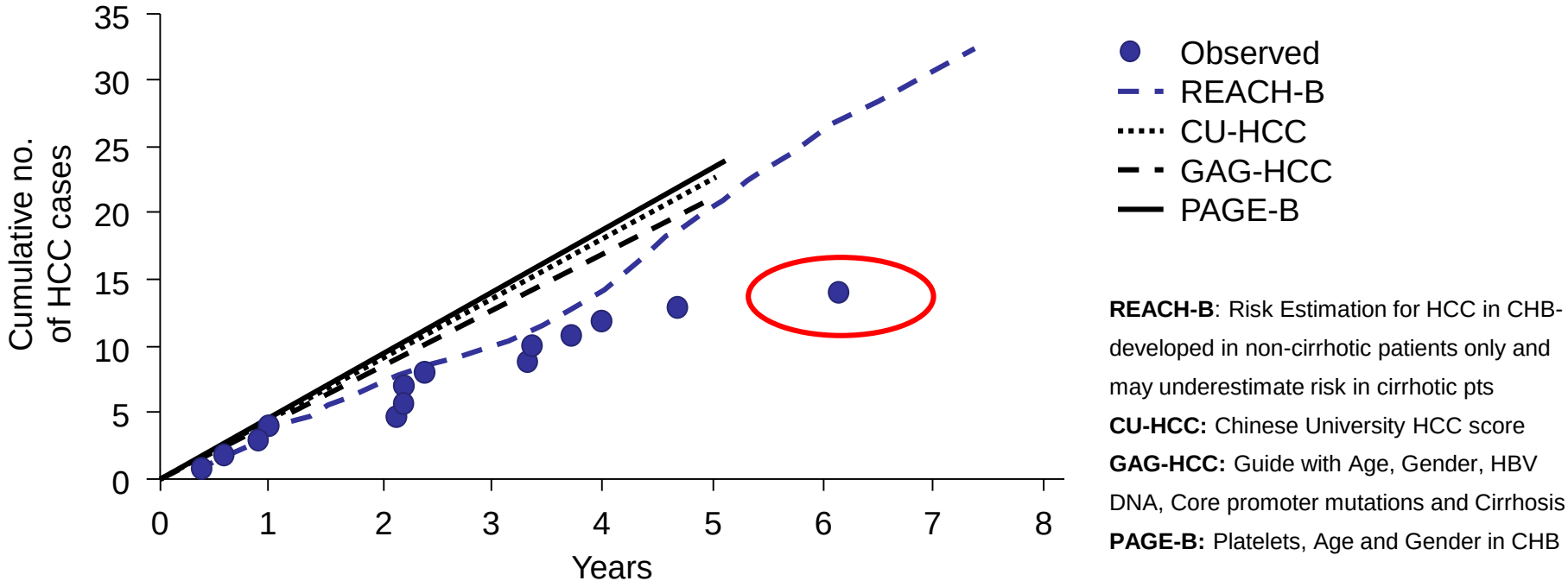
GAG-HCC: 0.76 CU-HCC: 0.62 REACH-B: 0.61

1. Papatheodoridis GV, et al. J Hepatol 2015;62:363
2. Yuen MF, et al. J Hepatol 2009;50:80
3. Wong VW, et al. J Clin Oncol 2010;28:1660
4. Yang HI, et al. Lancet Oncol 2011;12:568

*The risk score attributed to HBV DNA ≥10^6 copies/mL was less than that for HBV DNA of 10^5–<10^6 copies/mL because most patients with HBV DNA ≥10^6 copies/mL were also HBeAg-positive, thus sharing the associated higher score for this category.

Risk of HCC is predicted to be decreased with longterm TDF therapy

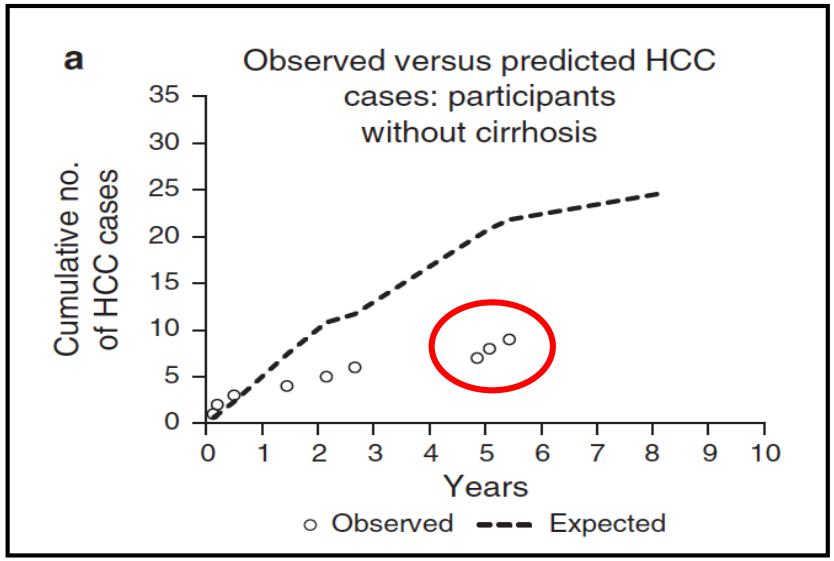
- 7.4 year longterm follow-up from pivotal TDF studies (N=641) compared with predicted rate of HCC from 3 new models
- **Risk models predicted similar scores that were consistently higher** than the 14 cases of HCC that occurred during follow-up (n=404)
- Despite viral suppression by TDF there is still risk of HCC
  - **Need for constant monitoring for HCC**

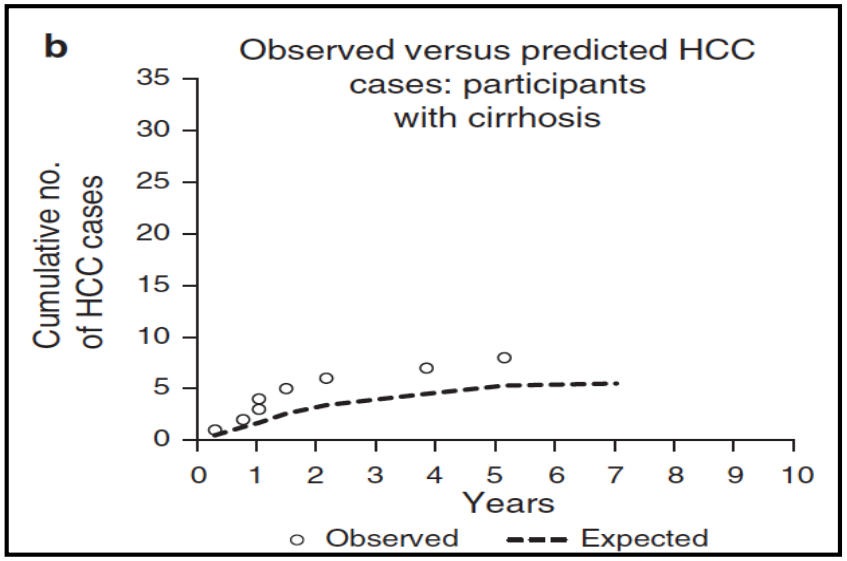


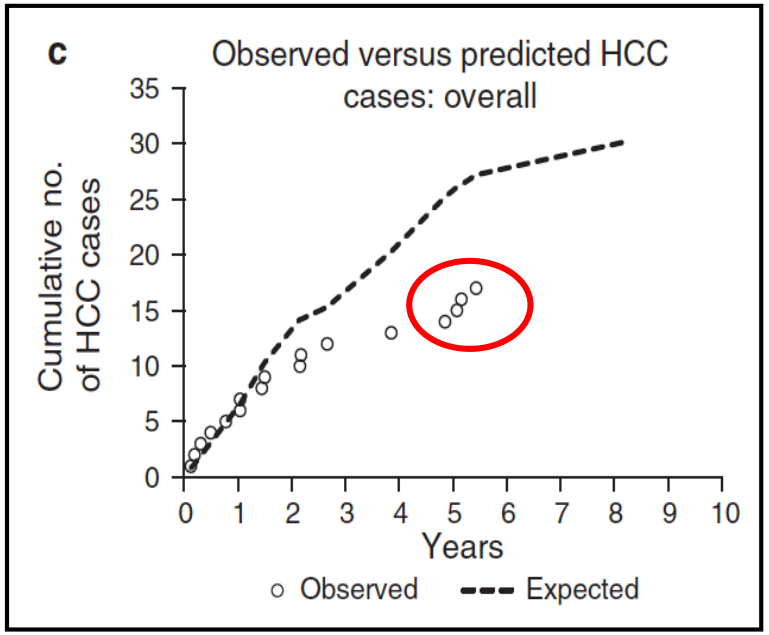
REACH-B: Risk Estimation for HCC in CHB-developed in non-cirrhotic patients only and may underestimate risk in cirrhotic pts
CU-HCC: Chinese University HCC score
GAG-HCC: Guide with Age, Gender, HBV DNA, Core promoter mutations and Cirrhosis
PAGE-B: Platelets, Age and Gender in CHB

Kim WR, et al. EASL 2015; Oral #RS-1690

ENUMERATE STUDY : ETV and the risk of HCC







Am J Gastroenterol 21 June 2016

USA STUDY: 841 patients - 646 male (65%) - multicentre

•84% Asian, median age 47 yrs, 36% HBeAg positive

•9.4% with cirrhosis

Median follow-up of 4 years

•17 (2.6%) HCC

•8/61 (13.1%) with cirrhosis

•9/585 (1.5%) without cirrhosis

17 HCC pts: 53 yrs vs 47 yrs and more likely to have cirrhosis at 47.1% vs. 8.4%

REACH-B prediction model

Max follow-up time of 8.2 years: Significantly lower than predicted HCC incidence was noted with an SIR of 0.56 (95% confidence interval: 0.35–0.905)

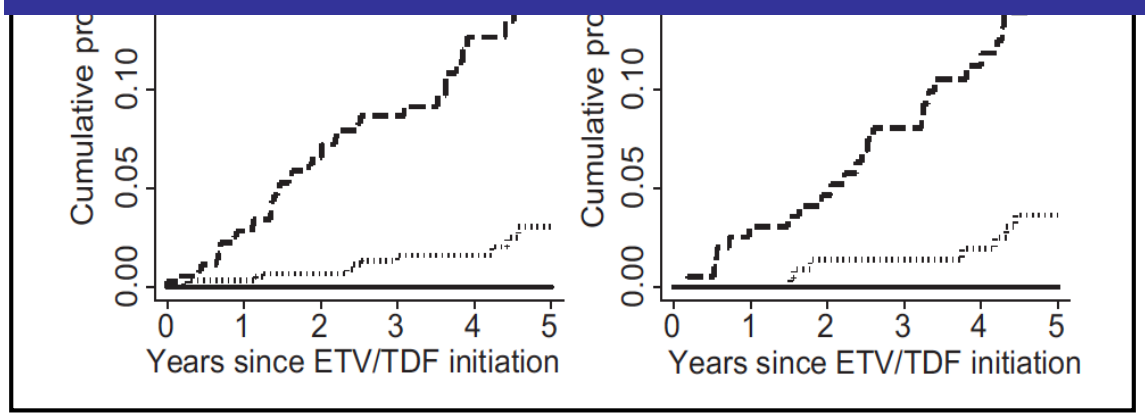
Risk of HCC predicted to be decreased antiviral therapy : ETV and Tenofovir

Validation of PAGE-B (age, gender and platelets)

- **1815 Caucasians with CHB & no HCC at baseline: ETV/TDF ≥ 12 mnths**
- Using data from eight centers (derivation dataset, n = 1325): HCC risk score

NONE OF THE HCC RISK SCORES VALIDATED IN AFRICA

40% HCC occur in young non-cirrhotic patients



J Hepatol 2016;64;800

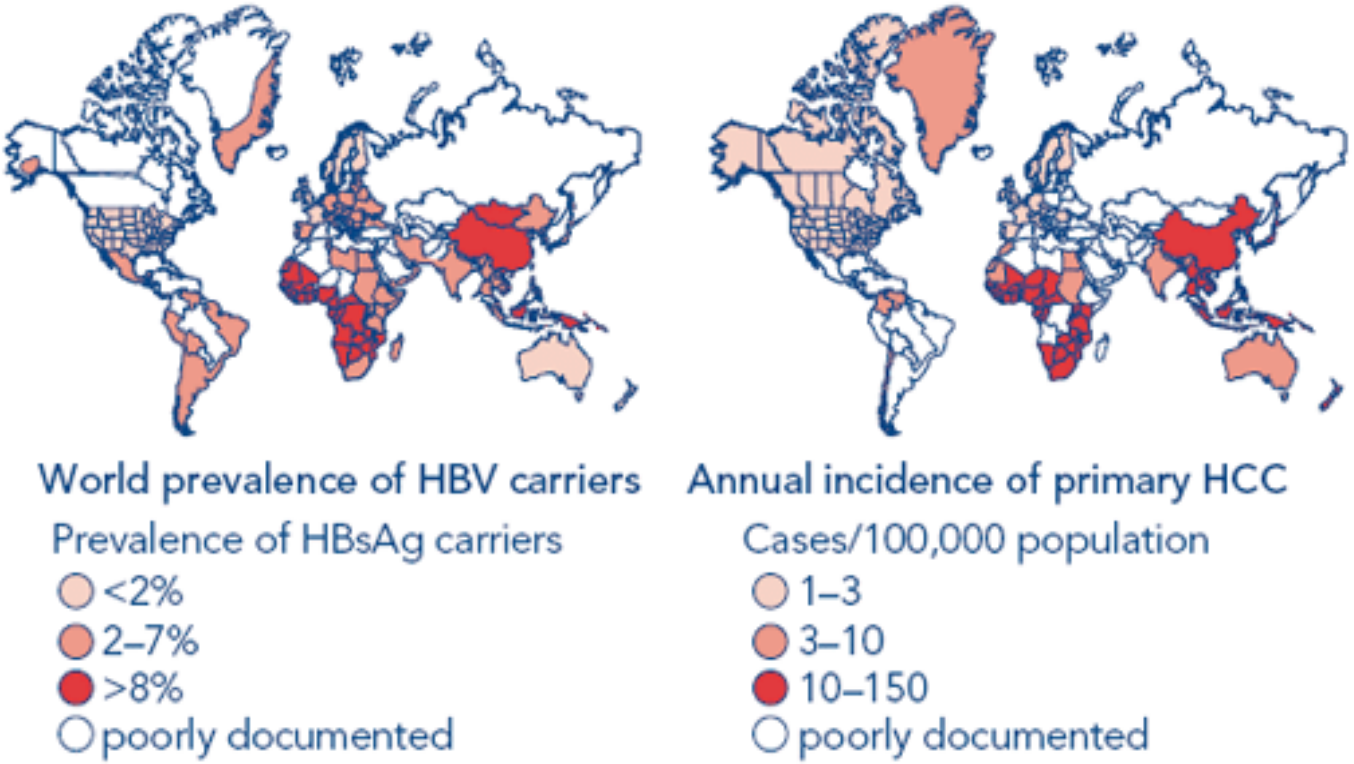
≥18: 17% in derivation & 16% invalidation dataset

PAGE-B: *Simple & reliable score for prediction of 5-yr HCC risk in Caucasian CHB patients under ETV/TDF*

Towards the Elimination of HBV and HCC

- **Hepatitis B and its associated complications are vaccine preventable**
- Implement WHO recommendations of HBV Birth dose vaccine
  - Full impact of birth vaccination will take 2-3 decades
- Ensure full coverage of HBV vaccination
- Maternal HBsAg screening and consider Tenofovir in 3rd trimester if HBV >200 000 IU/ml
- Vaccinate high risk groups
- Identify HBV-infected individuals and link to appropriate care & follow-up
- Antivirals have had an impact on development of cirrhosis & risk of HCC
  - Improving liver-related and all cause mortality
- Have not eliminated HCC risk: Antiviral Rx & monitoring usually lifelong
- **NEED A CURE AIMED AT ERADICATION OF cccDNA**

Worldwide Prevalence of Hepatitis B and Incidence of Hepatocellular Carcinoma



sSA : HBV causes 80% HCC and cirrhosis only present in 60% HCC

- Highest in Mozambique - 101.7 per 100 000 persons/yr

Can J Gastroenterol 2000;14:703; WHO HBV Vaccines 2003

Efficacy : Universal HBV Vaccination

South Korea *(Korean J Intern Med 2013;28:413)*

- Overall HBsAg seroprevalence
  - 4.61% in 1998 and 2.98% in 2010
- Adolescents (10 -19 years)
  - 2.2% in 1998 to 0.12% in 2010

American Samoa

- HBsAg seroprevalence decreased amongst children: 7.5% to 0%

Gambia

- HBsAg seroprevalence: 10.3% to 0.6%

Italy

- HBsAg seroprevalence: 3.4% to 0.9%

Saudi Arabia

- HBsAg seroprevalence: 6.7% to 0.3%

Lancet Infect Dis 2002;2:395

Efficacy: Universal HBV Vaccination

Taiwan *(JAMA 1687;257:2597; JAMA 1988;260:2231; JAMA 1996;276:906; Ann Int Med2001;135:796)*

- **Universal vaccination in 1984, together with**
  - Catch-up vaccination programme
  - Improved maternal screening
- **HBsAg seroprevalence in children <15 years decreased**
  - **9.8% in 1984 to 0.7% in 1999 to 0.3% in 2009**
- **Infection rate (anti-HBc seropositive rate): children 15-20yrs after programme decreased from:**
  - **38% in 1984 to 16% in 1999 to 4.6% in 2009**
- **Taiwanese Survey: Prevalence of Hyperglycemia/Hyperlipidemia/HT**

  (J Hepatol March 2015)
  - 2002: 6602 individuals and followup in 4088 individuals in 2007
  - HBsAg seroprevalence 13.7% & 68.46% anti-HBc positive
  - None of vaccinated cohort became HBsAg positive: durability of vaccination
  - Backlog of substantial HBV infection in Taiwan

Elimination of Hepatitis B

- Many sSA countries in the process of developing Viral hepatitis Management Guidelines and Strategic plans to achieve these elimination goals

Major challenges to the elimination of Hepatitis B in sSA

- Effective prevention of mother to child transmission
  - Maternal HBsAg screening
  - HBV Birth dose vaccine – implementation
  - Universal HBV vaccination with full coverage of vaccine
- Access to affordable diagnostics: Identify HBV-infected patients and link to care
- Addressing social stigmas associated with the diagnosis of HBV

Cost-effectiveness analysis: Additional birth dose of HBV vaccine

Mozambique (*Vaccine 2012,31(1):252)*

- Cost-effectiveness of an additional birth dose of Hepatitis B (HBV) vaccine administered by professional birth attendants in medical settings
- **Markov model:** analyse costs and effects associated with avoiding perinatal transmission of HBV through a birth dose vaccination in addition to existing vaccination schedule (2008 birth cohort of 2008)
- ***Comparator intervention*** - existing vaccination 6-10-14 week schedule
- Low-income setting - main outcome measure was disability-adjusted life years (DALYs) averted
- **Found incremental cost-effectiveness ratio (ICER) for the additional birth dose of 250.95 US$ per DALY averted**
- Assuming a willingness-to-pay threshold of 441 US$ (GDP per capita for Mozambique in 2008)

Additional birth dose was highly cost-effective