BEST OF EASL

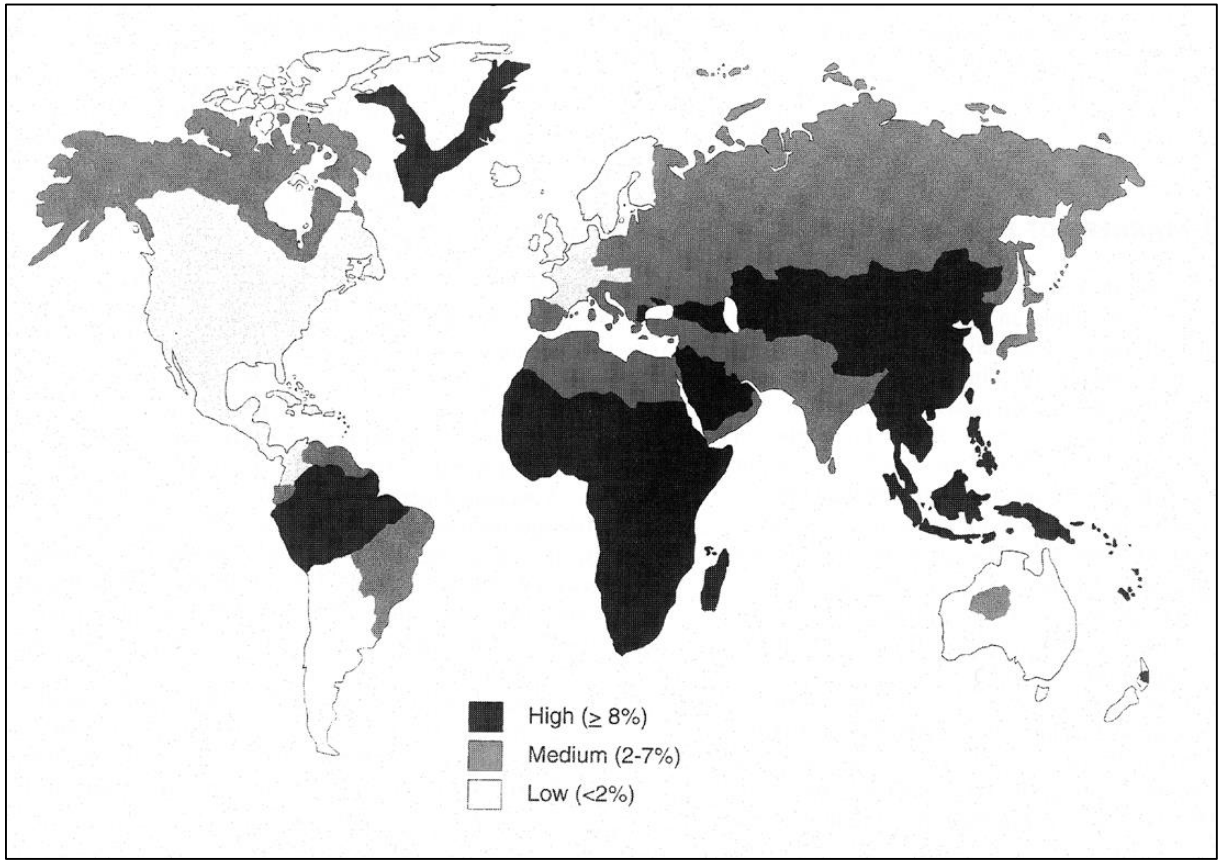
Screening, transmission, prevention, access to care

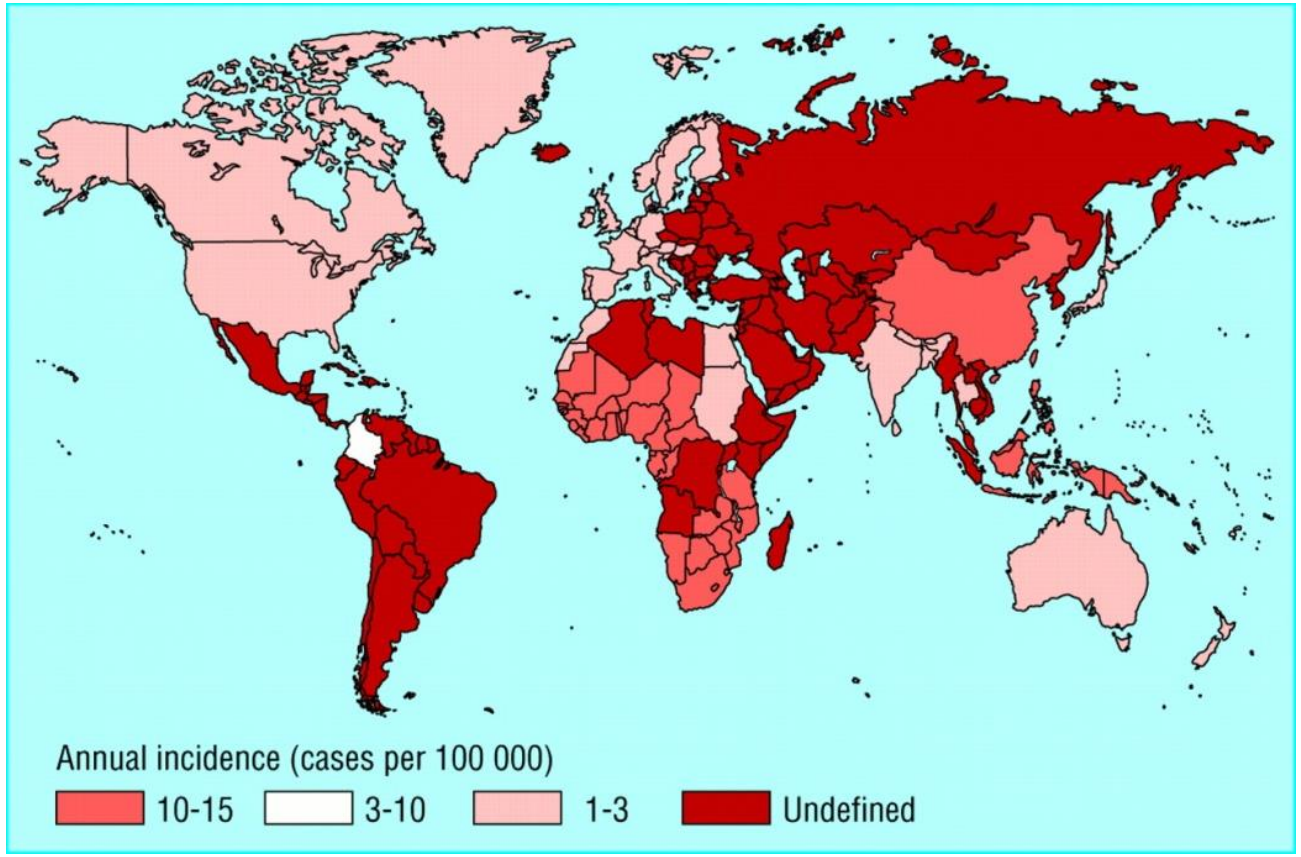
Strategies to combat liver diseases

Francesco Negro
University of Geneva - Switzerland

HBV epidemiology

250-350 million chronically infected – 700,000 deaths per year

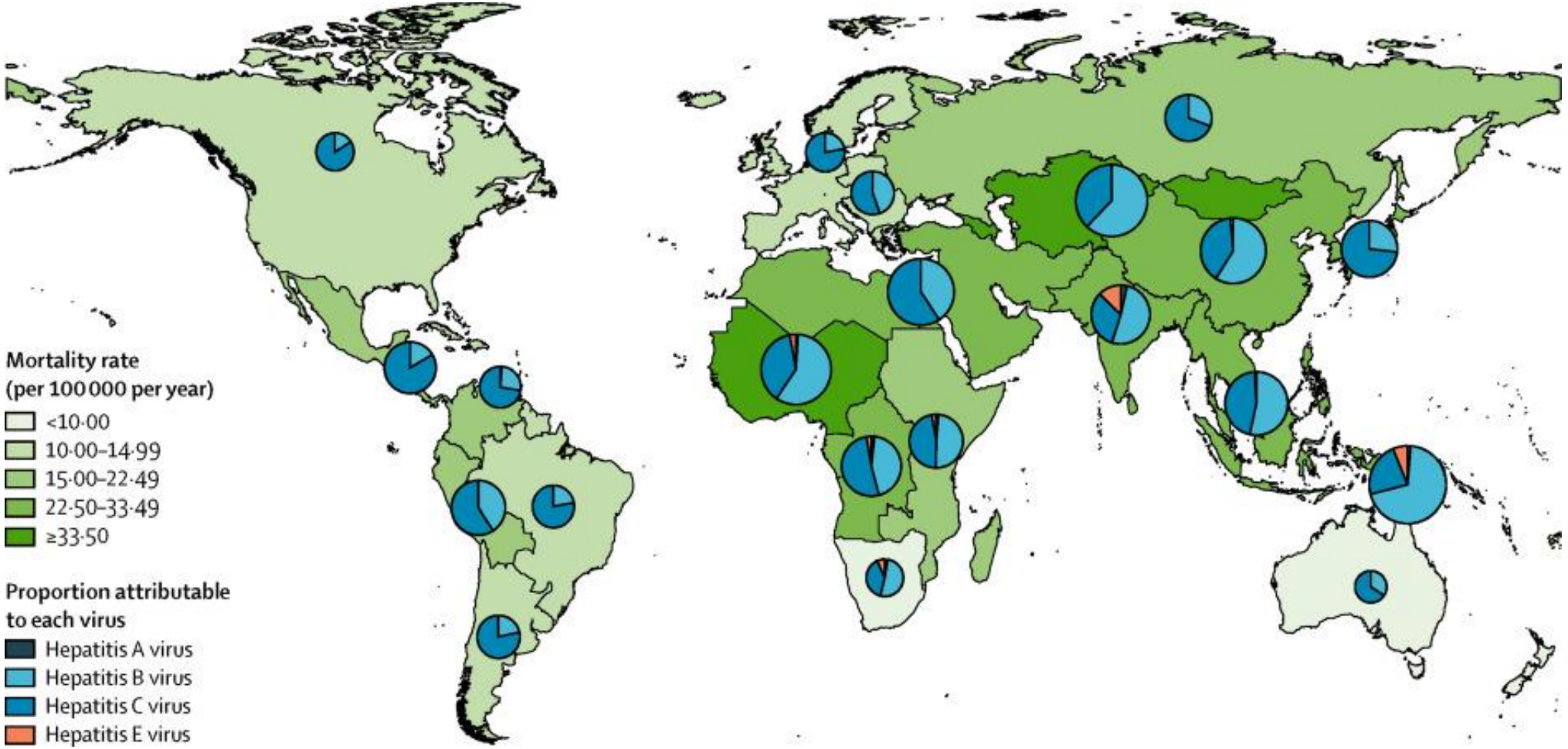




Global burden of viral hepatitis from 1990 to 2013 (Global Burden of Disease Study 2013)

Viral hepatitis-related, age-standardized mortality rate, by GBD region

(Overlaid pie charts indicate each virus type's contribution to the total hepatitis-related mortality;
the size of the pies are proportional to the hepatitis-attributable mortality for that region)

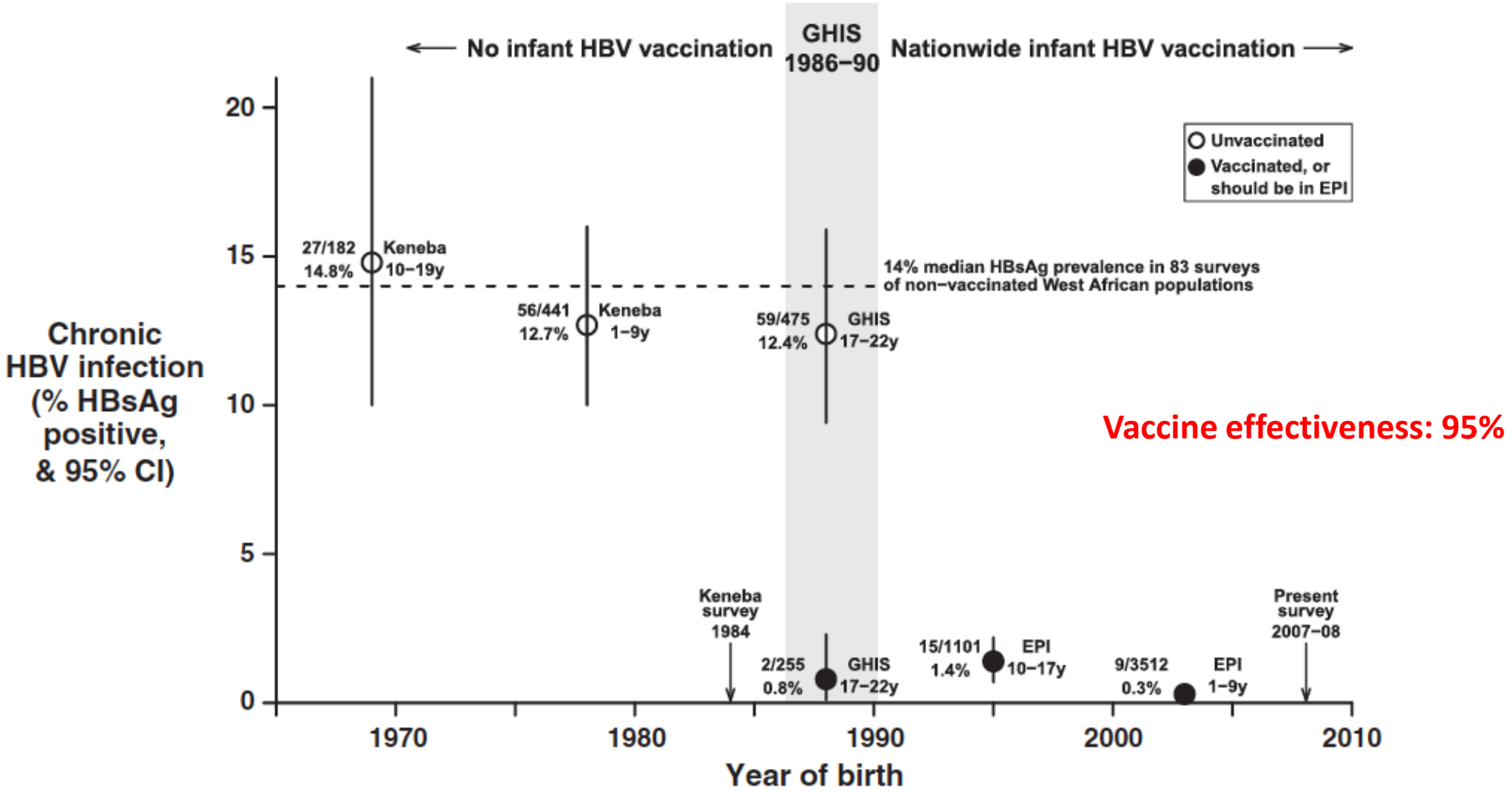


STANAWAY *et al*, Lancet 2016

Tools For Control of HBV

- Interruption of transmission
  - Vaccination
  - Birth dose vaccine + HBIG or analogues
- Treatment
  - Nucleoside/Nucleotide analogues
  - Interferons

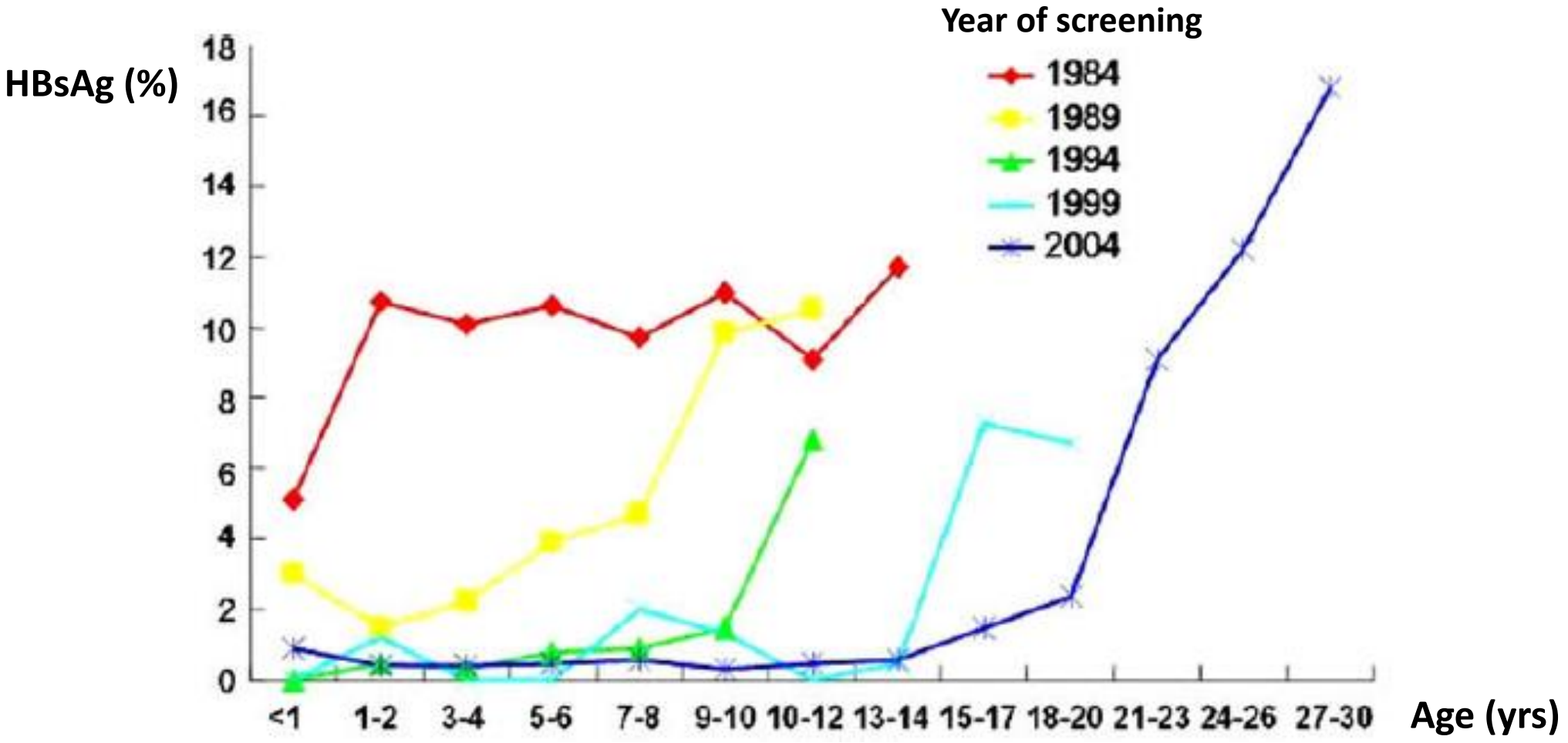
Before and After Vaccination - Gambia



Vaccine effectiveness: 95%

PETO *et al,* BMC Infect Dis 2014

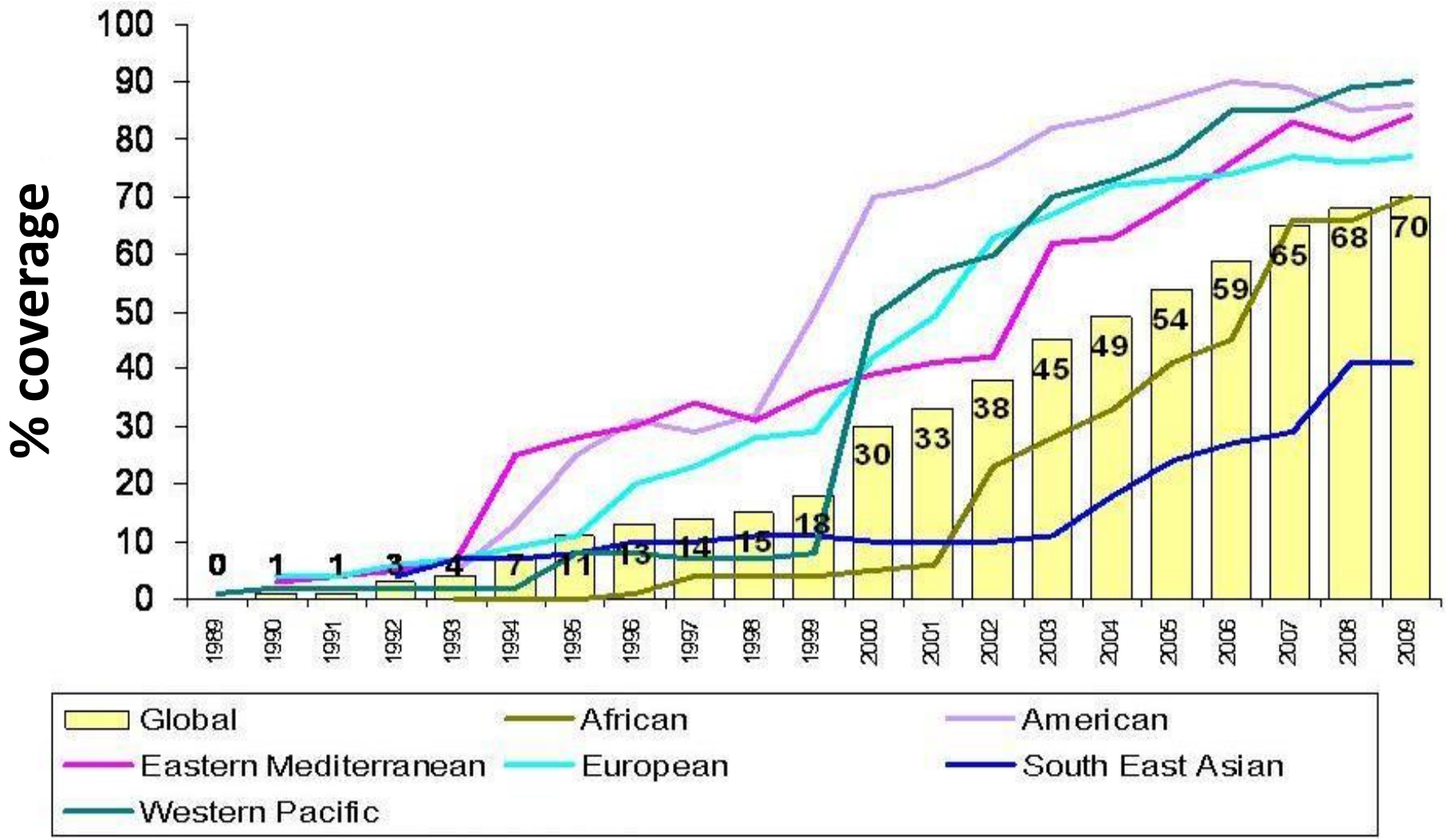
Taiwan: Impact of Comprehensive Coverage



Age-specific HBsAg positive rates in 1984, 1989, 1994, 1999, 2004, and 2009 in Taipei, Taiwan

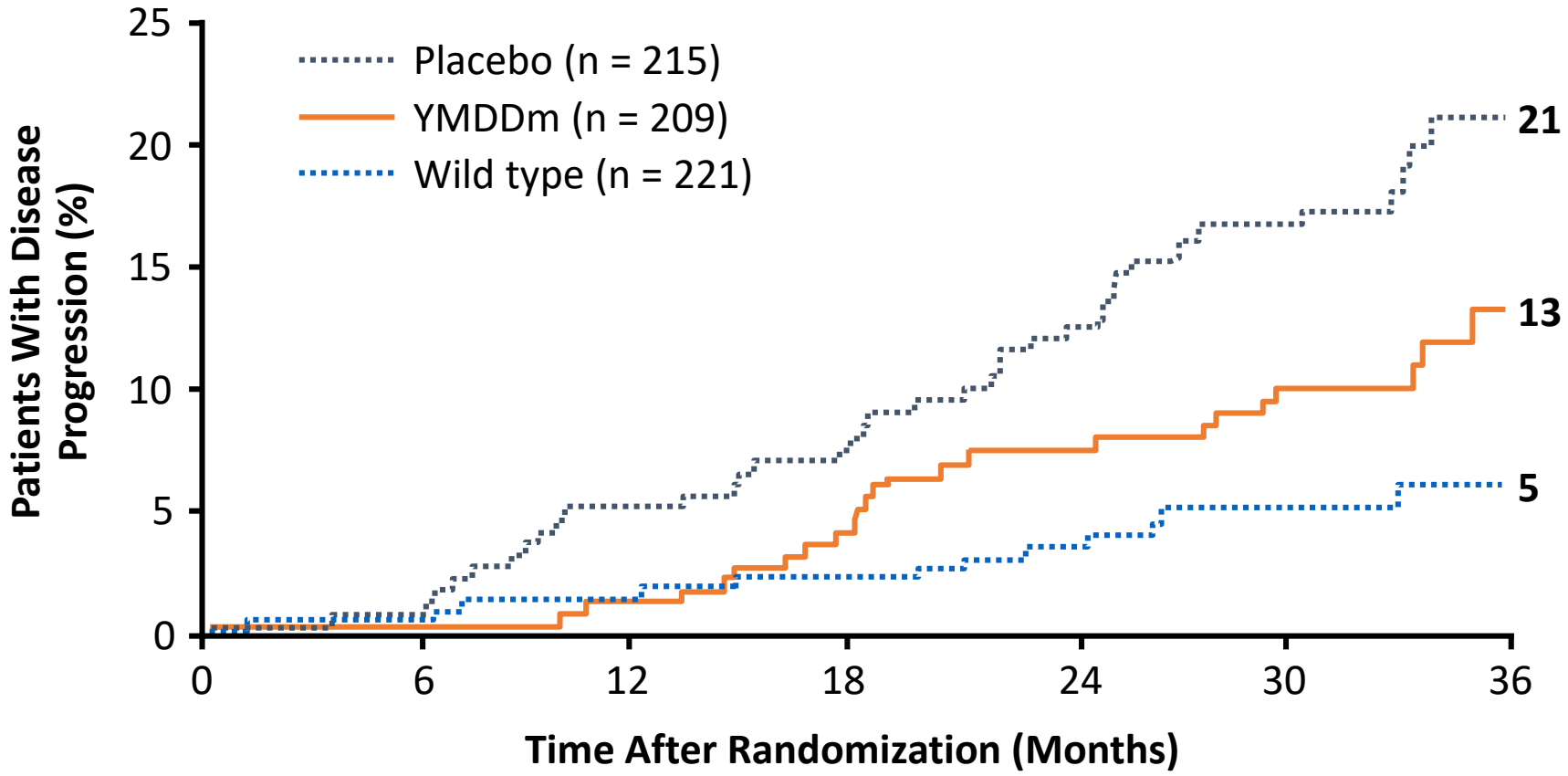
NI *et al*, J Hep 2012

HBV vaccine coverage is still low



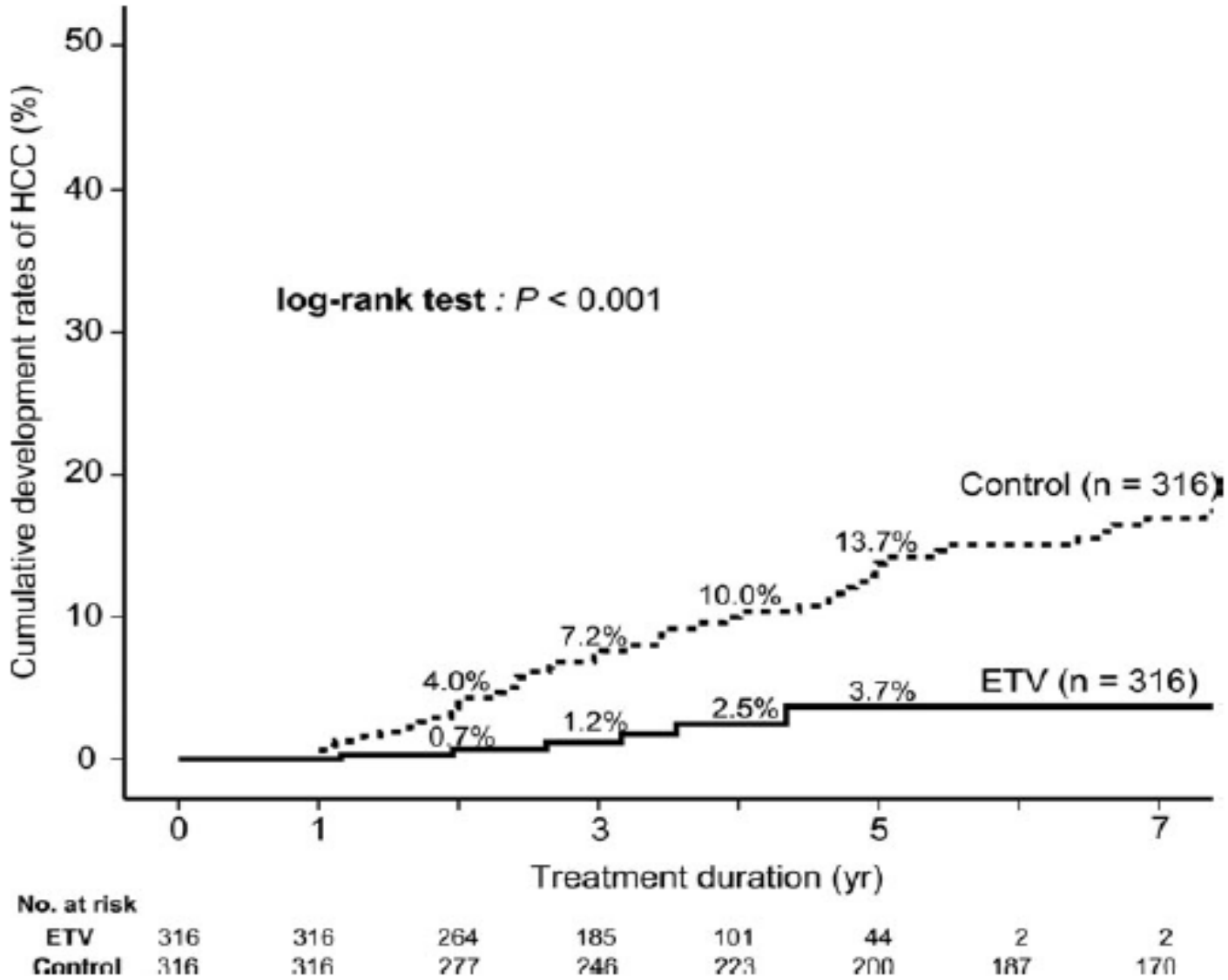
Source: WHO/UNICEF (2010)

Nucleoside Analogues Prevent Disease Progression



LIAW *et al,* N Engl J Med. 2004;351:1521-1531

Antiviral Therapy Reduces the Risk of HCC



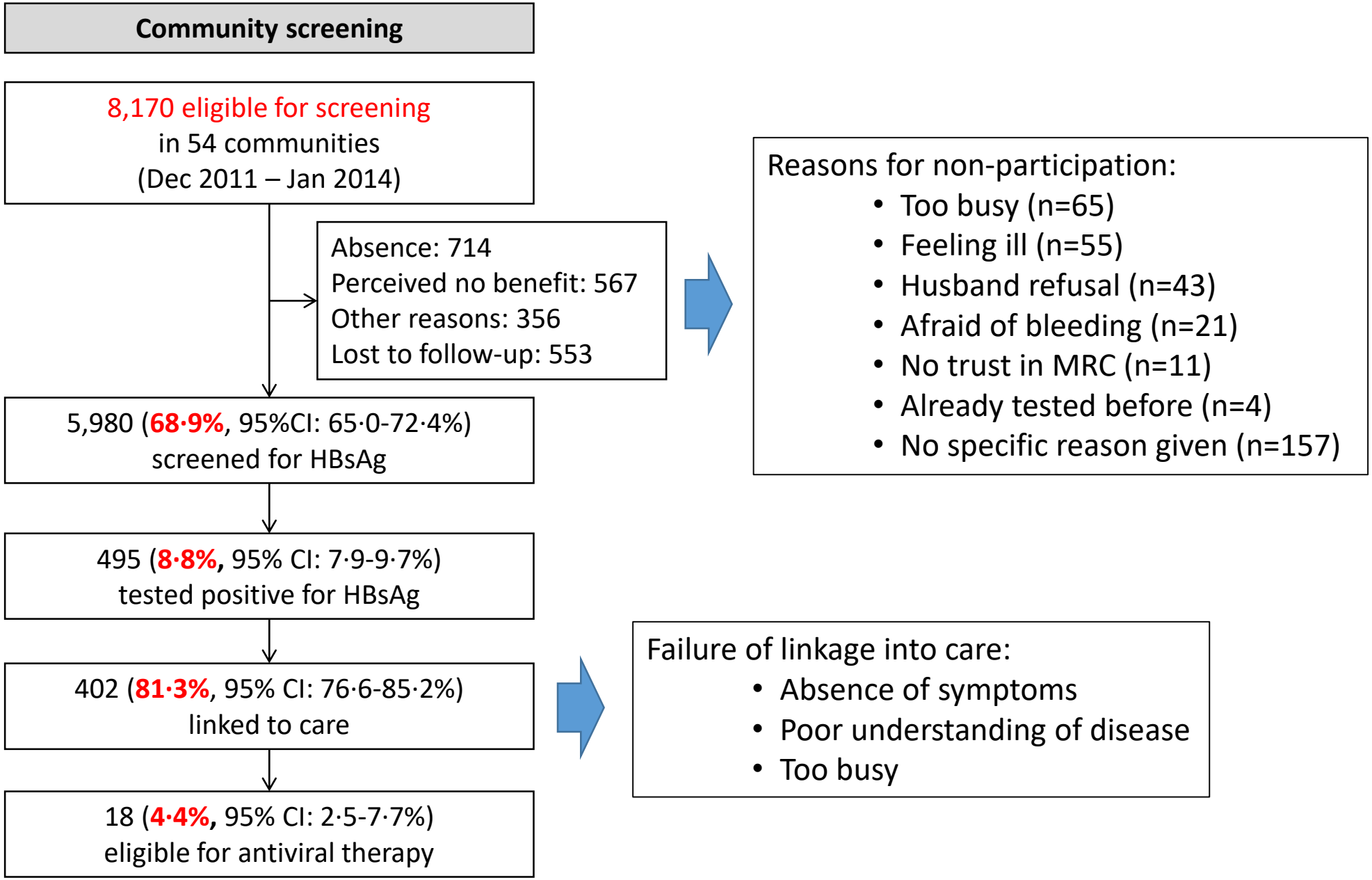
HOSAKA *et al,* Hepatology 2013

Acceptability and feasibility of a screen-and-treat programme for hepatitis B virus infection in The Gambia: the Prevention of Liver Fibrosis and Cancer in Africa (PROLIFICA) study

Maud Lemoine, Yusuke Shimakawa*, Ramou Njie*, Makie Taal, Gibril Ndow, Isabelle Chemin, Sumantra Ghosh, Harr F Njai†, Adam Jeng, Amina Sow, Coumba Toure-Kane, Souleymane Mboup, Penda Suso, Saydiba Tamba, Abdullah Jatta, Louise Sarr, Aboubacar Kambi, William Stanger, Shevanthi Nayagam, Jessica Howell, Liliane Mpabanzi, Ousman Nyan, Tumani Corrah, Hilton Whittle, Simon D Taylor-Robinson, Umberto D'Alessandro, Maimuna Mendy, Mark R Thursz, on behalf of the PROLIFICA investigators*

- Point-of-care HBsAg assay (Alere) offered to randomly selected communities in Western Gambia and potential blood donors in Banjul
- HBsAg screening accepted by 5980 (68·9%) of 8170 community adults and 5559 (81·4%) of 6832 blood donors
- HBsAg detected in 495 (8·8%) individuals in communities and 721 (13·0%) blood donors
- Linkage to care (visit to liver unit) was high in the communities (402/495, 81·3%) but low (300/721, 41·6%) among people screened at the blood bank
- Of those who attended the clinic, 18 (4·4%) patients from the communities and 29 (9·7%) from the blood donors were eligible for treatment (as per EASL guidelines)

LEMOINE *et al,* Lancet Global Health 2016;4:e559-67

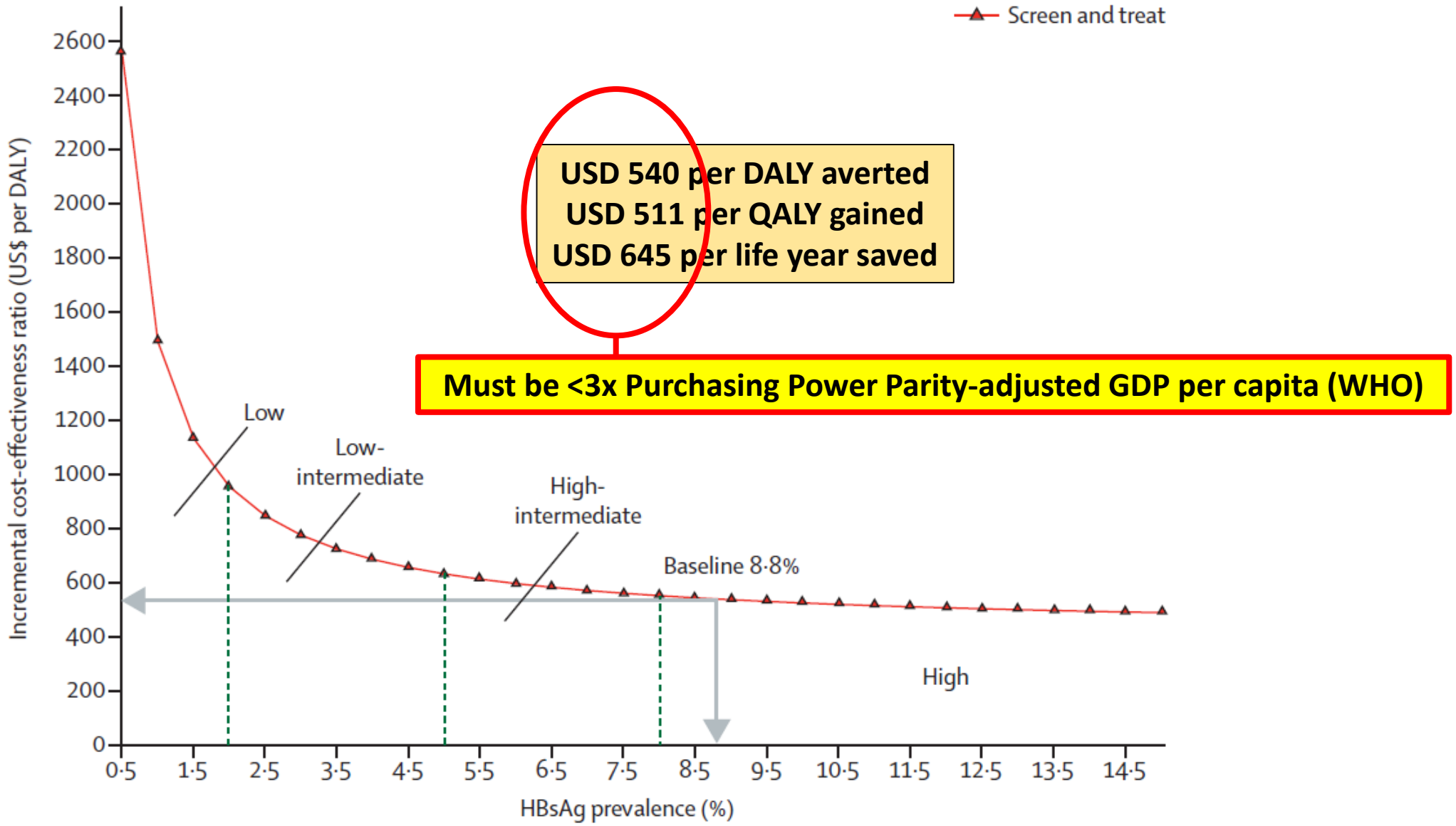


LEMOINE *et al,* Lancet Global Health 2016;4:e559-67

“The high coverage of community-based screening,
the good linkage into care,
and the small proportion of HBsAg carriers who need treatment
suggest that large scale test-and-treat programmes are feasible
in sub-Saharan Africa”

LEMOINE *et al,* Lancet Global Health 2016;4:e559-67

Is screening cost-effective?

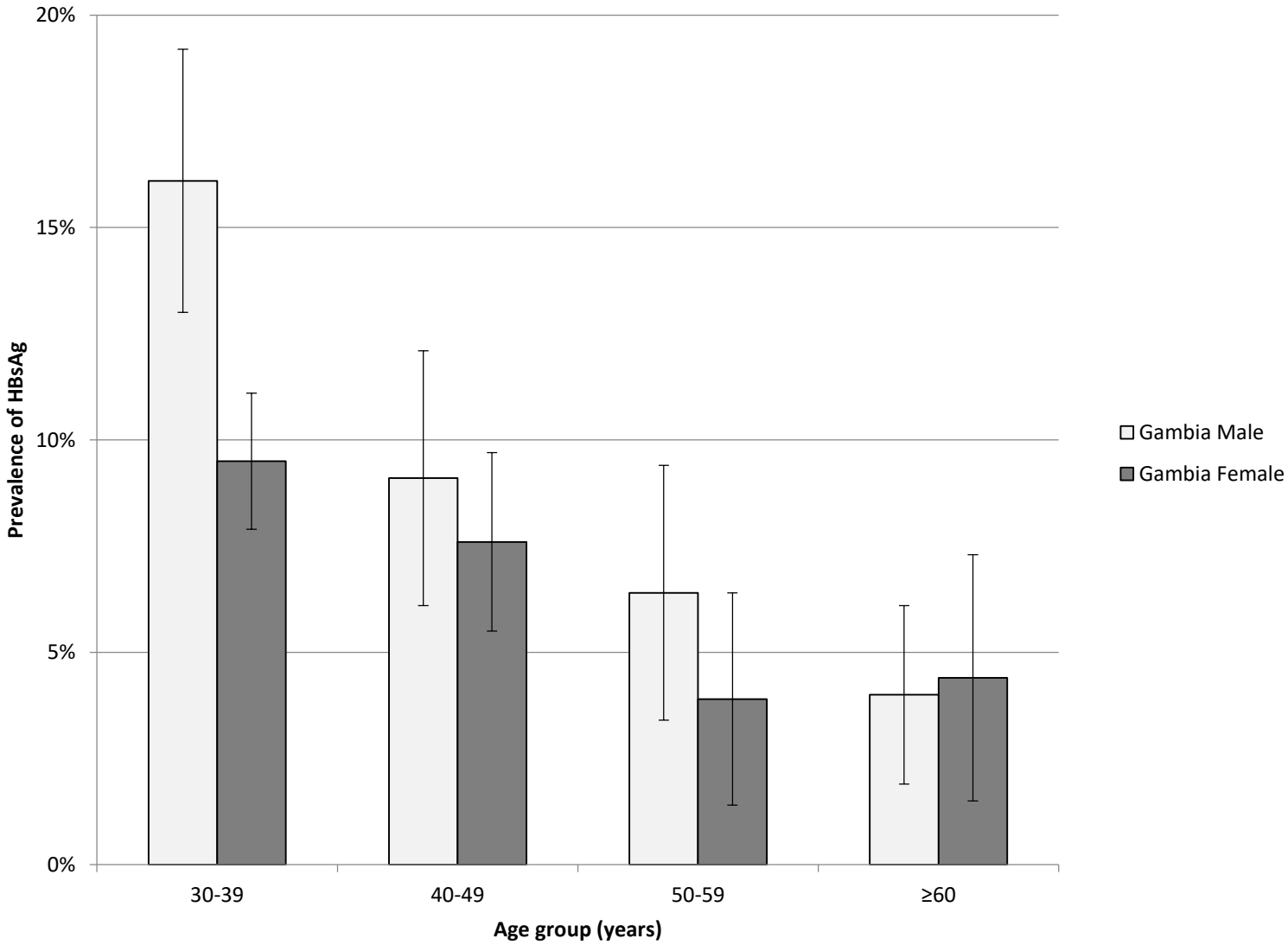


USD 540 per DALY averted
USD 511 per QALY gained
USD 645 per life year saved

Must be <3x Purchasing Power Parity-adjusted GDP per capita (WHO)

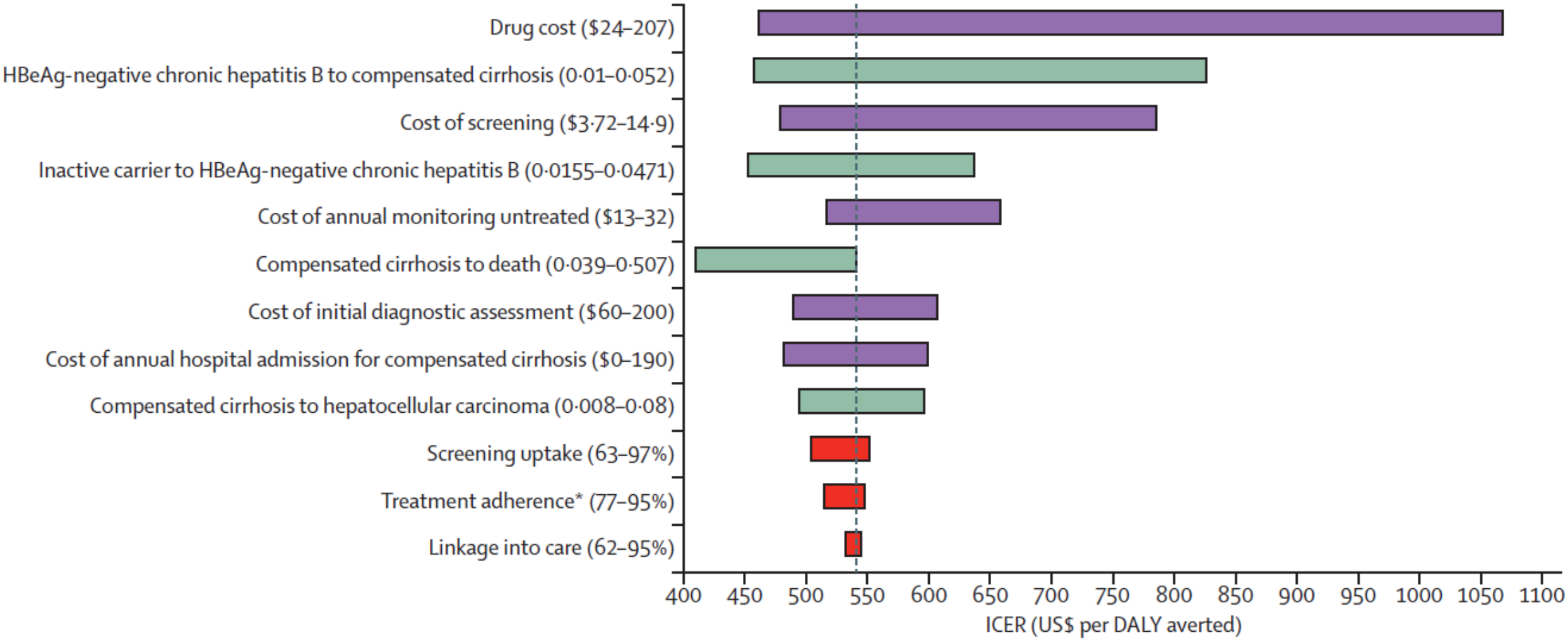
NAYAGAM *et al*, Lancet Global Health 2016;4:e568-78

HBsAg prevalence by age and sex in community screening



LEMOINE *et al,* Lancet Global Health 2016;4:e559-67

Tornado diagram of factors affecting ICER



NAYAGAM *et al,* Lancet Global Health 2016;4:e568-78

A simulation model of the global HBV epidemic

- Dynamic transmission model, incorporating data on the natural history of HBV, prevalence, mortality, vaccine coverage, treatment dynamics, and demographics
- Age, sex and region structured (21 world regions)
- Generate projections for each scenario (i.e. current interventions and scaling up of existing interventions for prevention of infection and introducing wide-scale population screening and treatment interventions) on:
  - Incidence of chronic new infection
  - Prevalence
  - Deaths due to HBV
  - Costs

NAYAGAM *et al,* Lancet Infect Dis 2016 Sep 13 [Epub ahead of print]

Data Inputs and Calibration Strategy

Data	Source
Demography	World Population Prospects
Infant Vaccination coverage	WHO data
Birth dose vaccination coverage	WHO data
Treatment availability/coverage	WHO global policy report on prevention & control of viral hepatitis & assumptions
Natural history parameters	Literature review

Data	Objective	Source
Prevalence patterns of **HBsAg+**	*Informs burden and historic pattern of infection*	OTT *et al,* Vaccine 2012
Prevalence patterns of **HBeAg+**	*Informs patterns of new cases of chronic infection and transmission*	OTT *et al,* BMC Inf Dis 2012
Cancer death estimates	*Informs burden of disease and stages of disease progression for chronically infected*	GLOBOCAN 2012

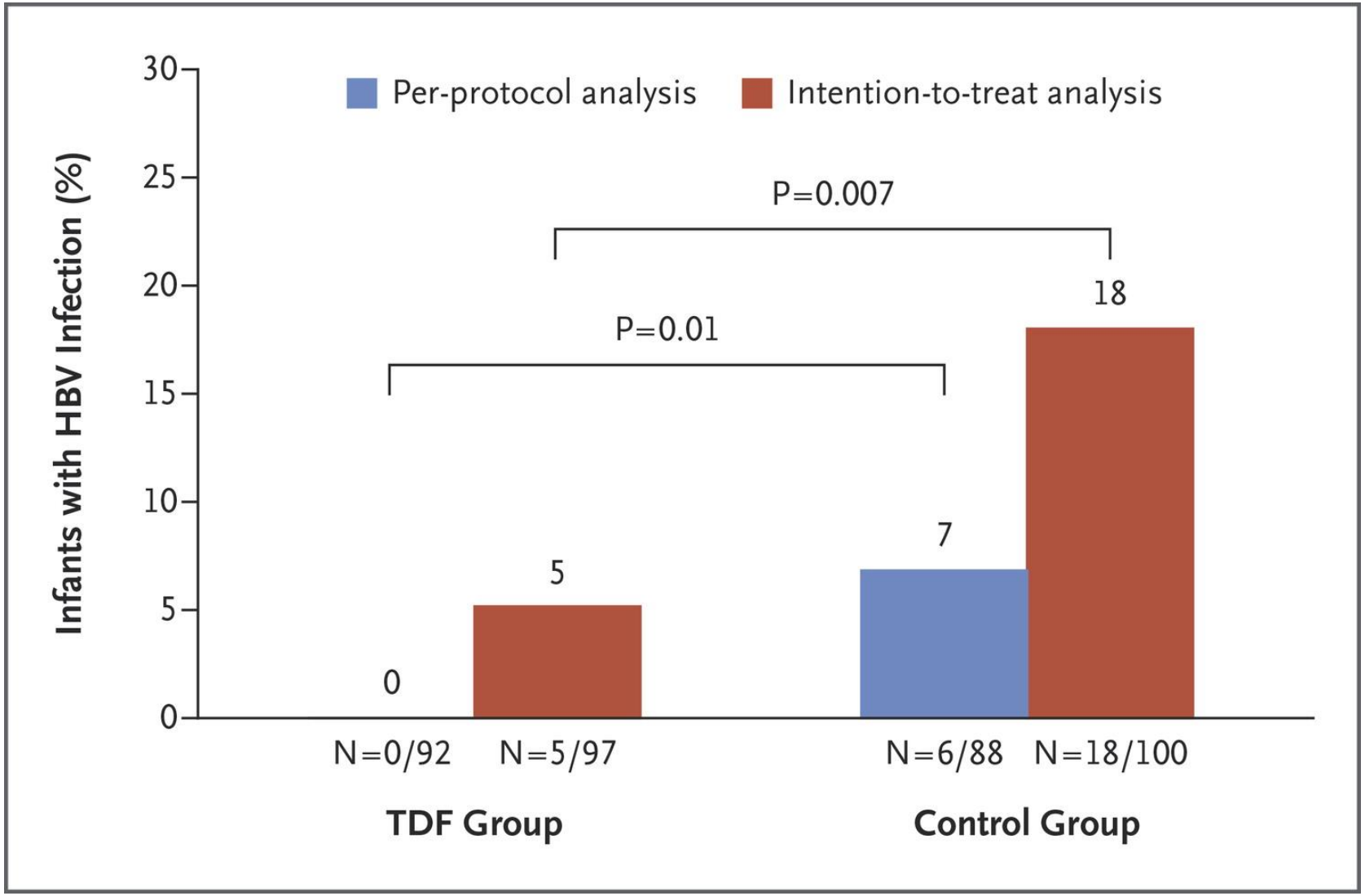
NAYAGAM *et al,* Lancet Infect Dis 2016 Sep 13 [Epub ahead of print]

Public Health Intervention Scenarios

<table>
<tr><th>Intervention Scenarios</th><th>Infant Vaccination Coverage</th><th>Birth Dose Vaccination Coverage</th><th>Coverage of Peri-Partum Treatment (PPT) for HBeAg+ mothers§</th><th>Access to treatment±</th><th>Cure</th></tr>
<tr><td>No Historic Intervention</td><td>None</td><td>None</td><td>None</td><td>None</td><td>No</td></tr>
<tr><td>Status Quo</td><td>Continues at current levels</td><td rowspan="2">Continues at current levels</td><td rowspan="2">No coverage currently</td><td rowspan="3">Continues at current levels (categorised by region)</td><td rowspan="4">No</td></tr>
<tr><td>Infant Vaccination</td><td rowspan="5">90%</td></tr>
<tr><td>Infant Vaccination + BD Vaccination</td><td rowspan="4">80%</td></tr>
<tr><td>Infant Vaccination + BD Vaccination + PPT</td><td rowspan="3">80%</td></tr>
<tr><td>Infant Vaccination + BD Vaccination + PPT + Treatment</td><td rowspan="2">80%</td></tr>
<tr><td>Infant Vaccination + BD Vaccination + PPT + Treatment + Cure</td><td>2025</td></tr>
</table>

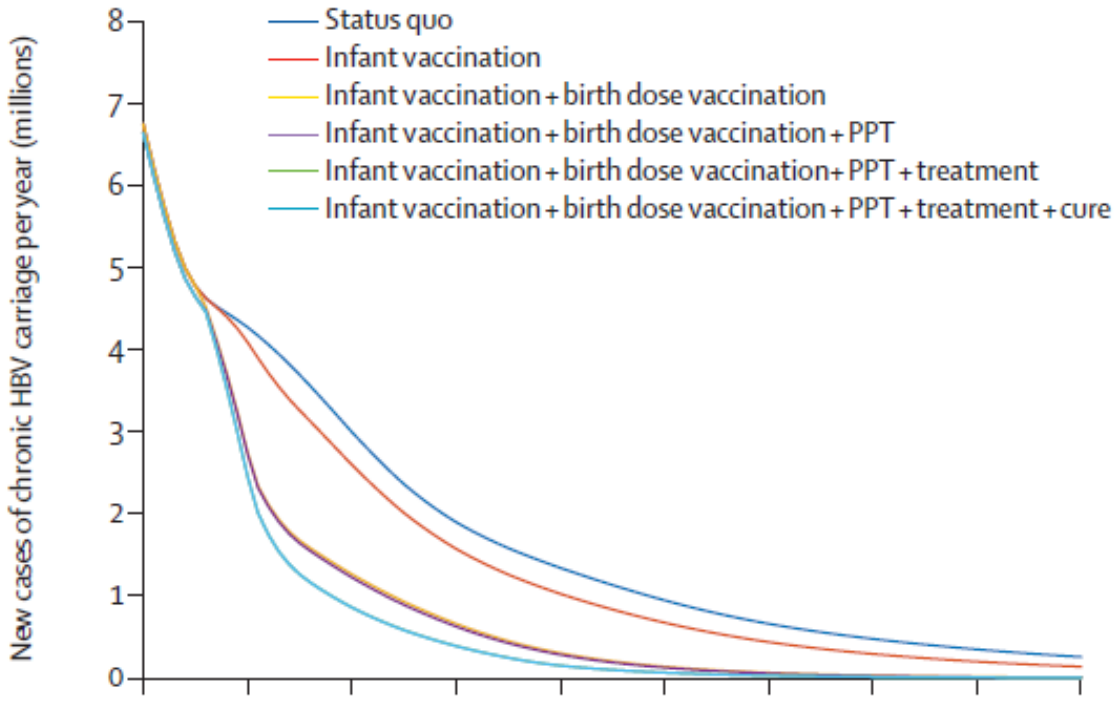
NAYAGAM *et al,* Lancet Infect Dis 2016 Sep 13 [Epub ahead of print]

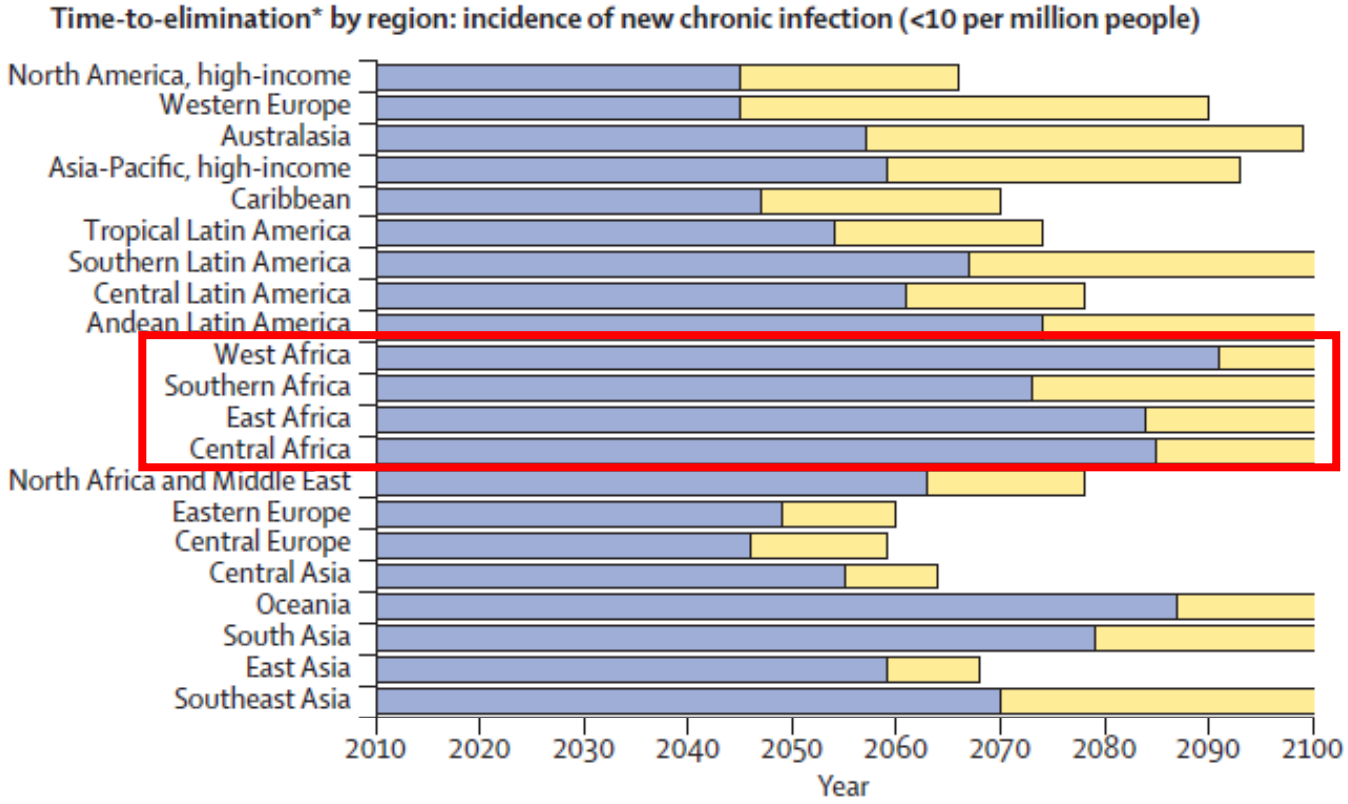
Tenofovir for prophylaxis of mother-to-child transmission (PMTCT)



PAN *et al,* N Engl J Med 2016;374:2324-34

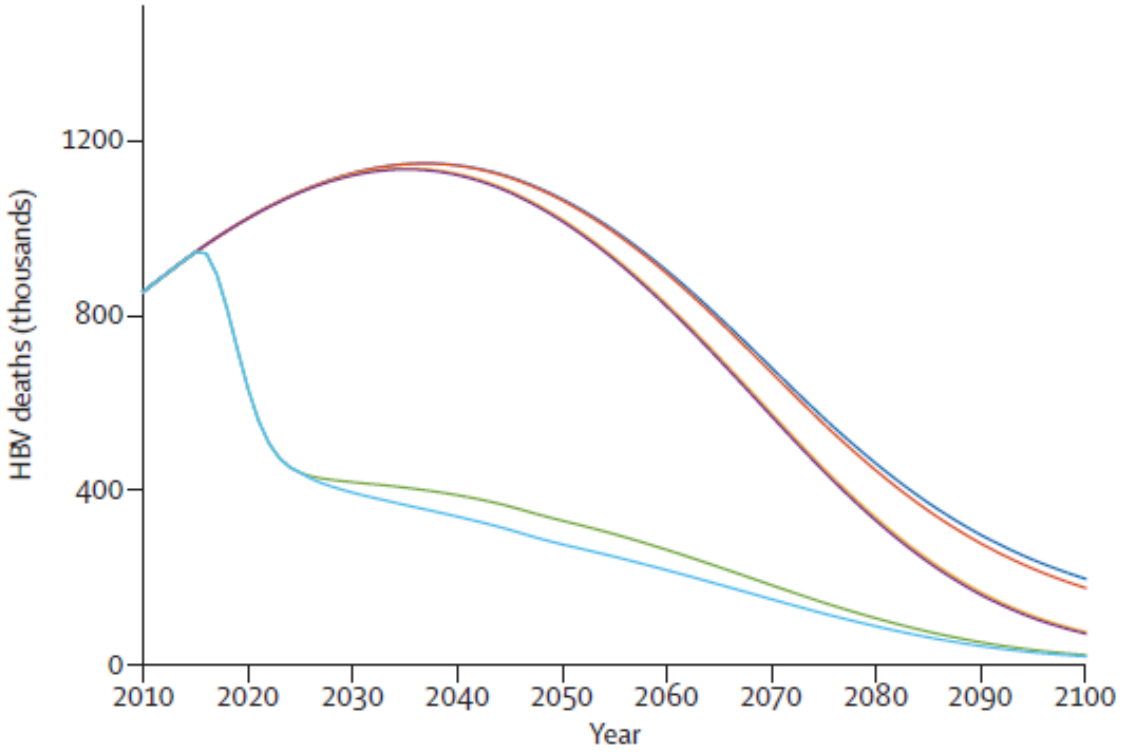
Control of incidence of new chronic HBV carriage

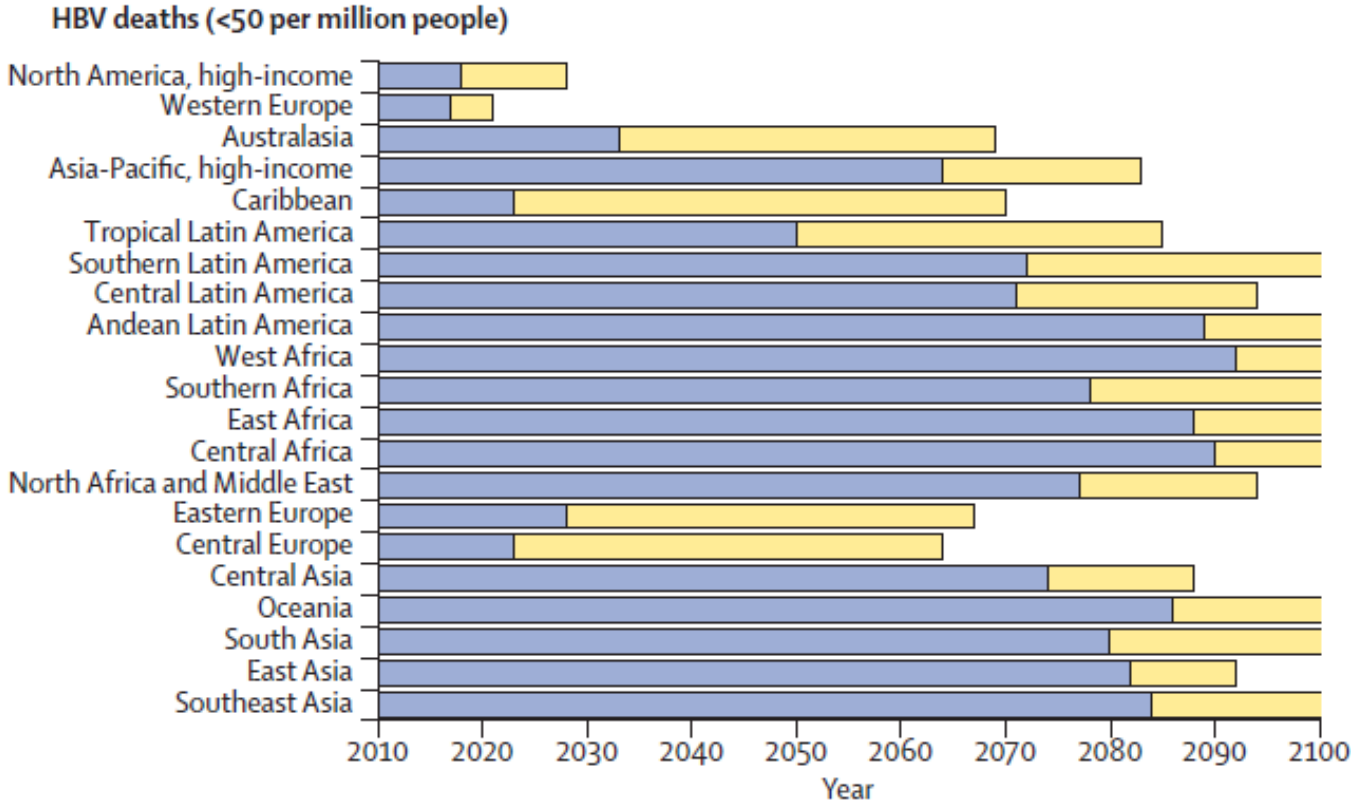




NAYAGAM *et al,* Lancet Infect Dis 2016 Sep 13 [Epub ahead of print]

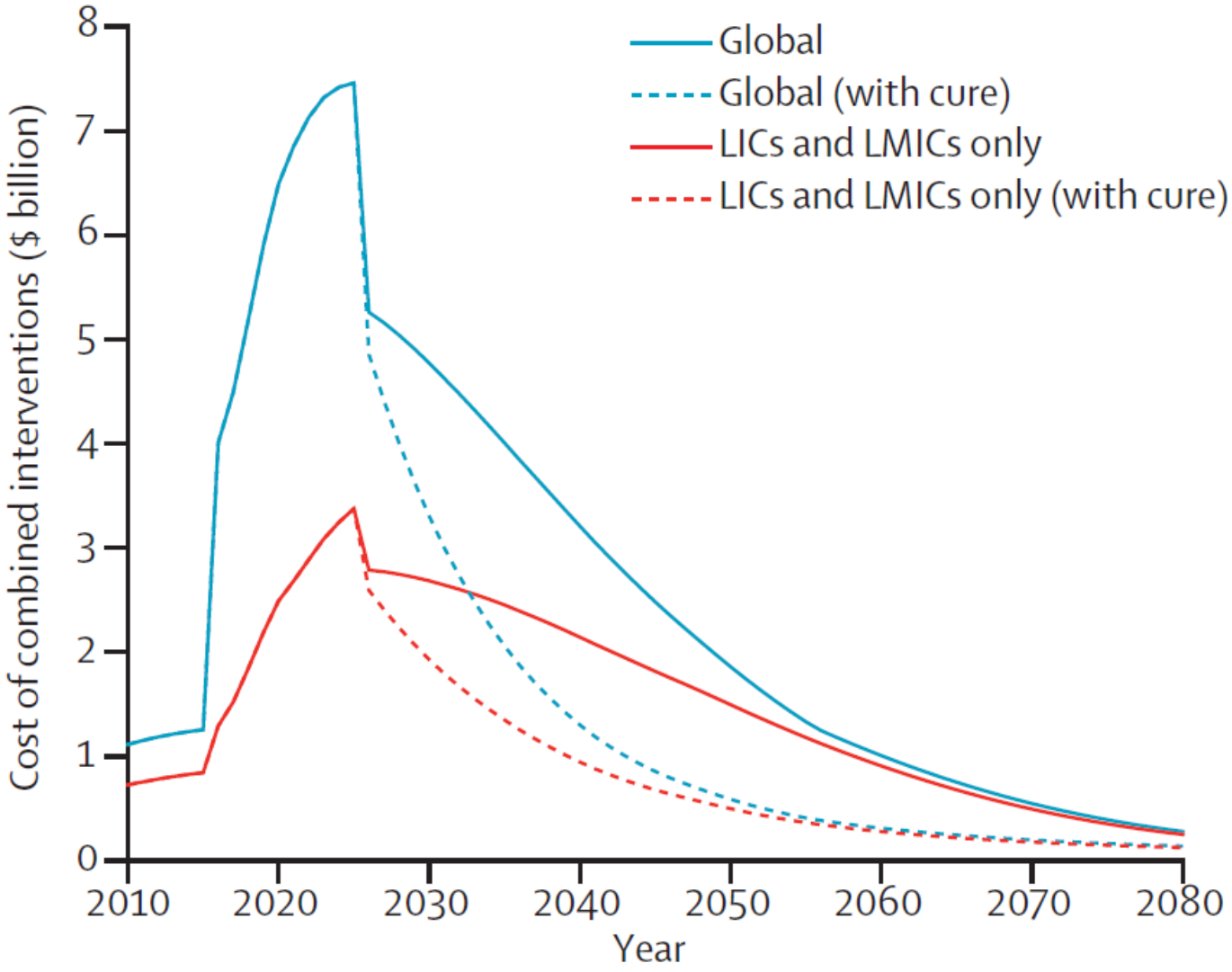
Control of Mortality





NAYAGAM *et al,* Lancet Infect Dis 2016 Sep 13 [Epub ahead of print]

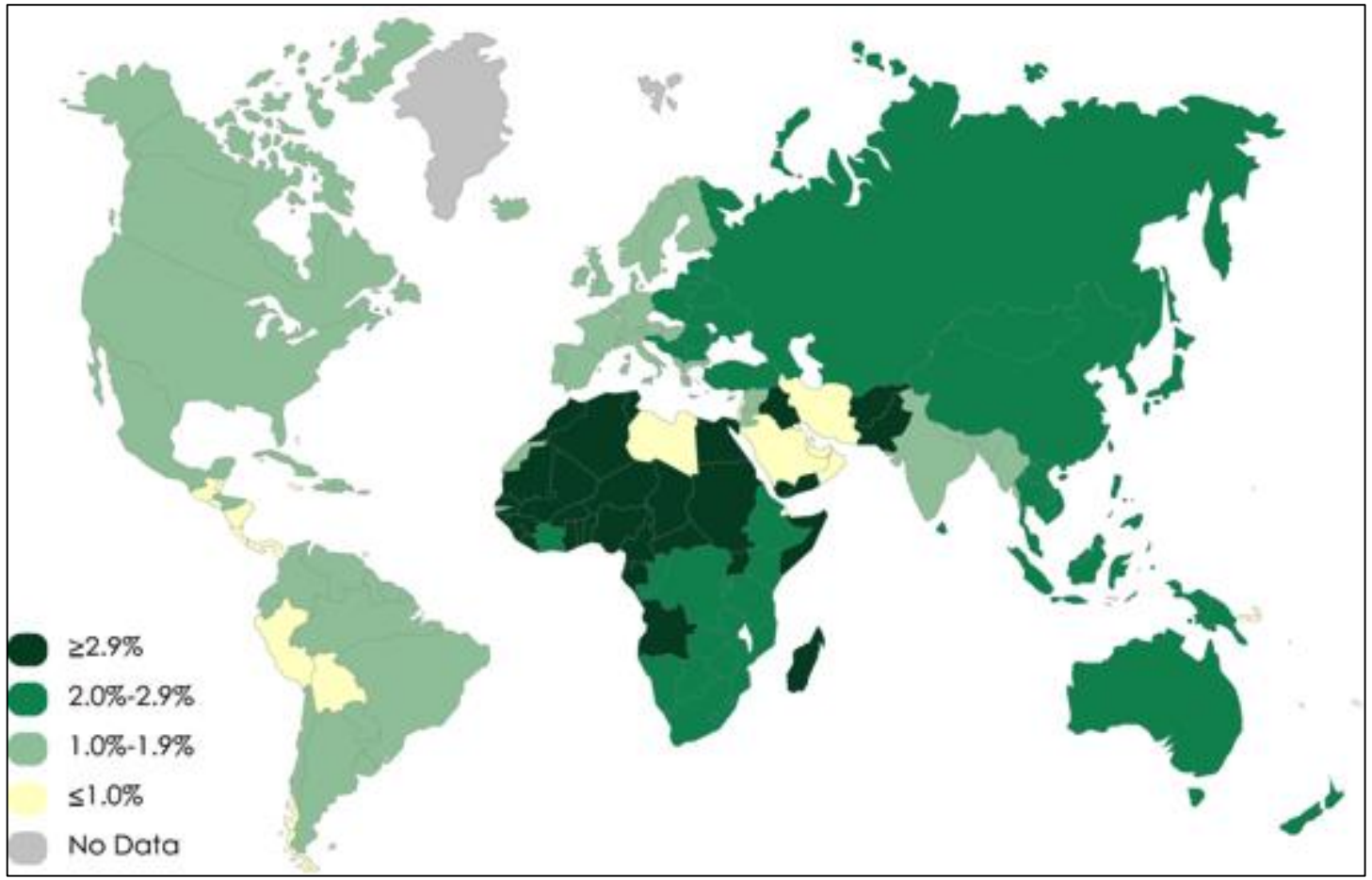
How Much Would it Cost?



NAYAGAM *et al,* Lancet Infect Dis 2016 Sep 13 [Epub ahead of print]

Epidemiology of Hepatitis C

130–170 million persons are infected with hepatitis C virus (HCV)



- ~ 350 000 people die annually of HCV-related diseases
- Highest prevalence in Central and East Asia and North Africa
- Bloodborne virus
  - Injecting drug use
  - Inadequate sterilization of medical equipment
  - Transfusion of unscreened blood
- Currently no vaccine
- Very powerful, safe antivirals

Lavanchy D *Clin Microbiol Infect* 2011; 17: 107–115
Averhoff FM, et al. *Clin Infect Dis.* 2012;55(S1):S10-S15.
Global Burden of Hepatitis C Working Group. *Journal of Clinical Pharmacology.* 2004;44:20-29

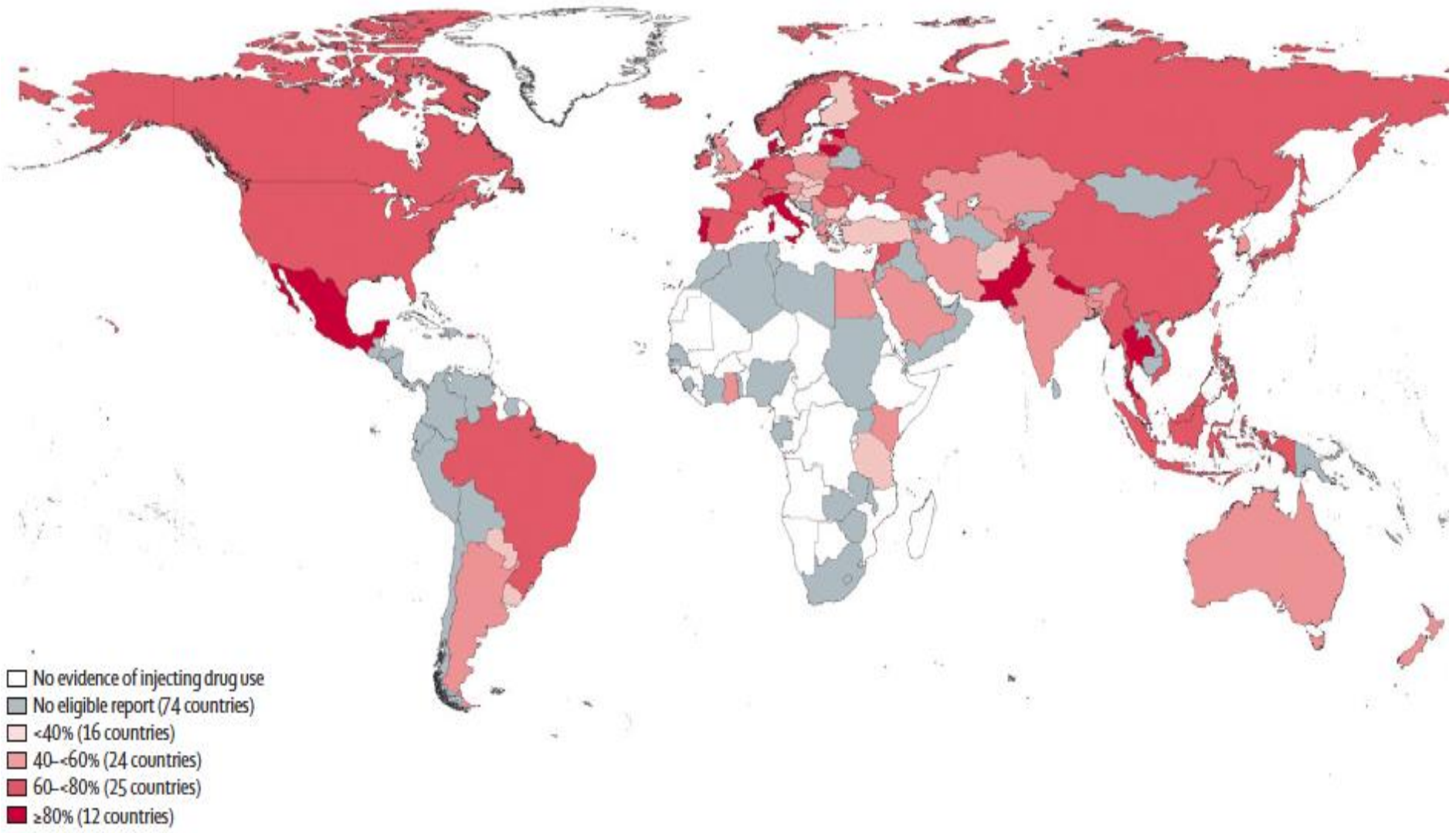
HCV is a hidden epidemic, especially in developing countries

- ✓ **Most hepatitis cases in low & middle income countries**
- ✓ **Insufficient/No surveillance systems**
- ✓ **No systematic screening of key populations**
- ✓ **Stigmatization**
- ✓ **Penalization**
- ✓ **Expensive diagnostic tools**

LEMOINE *et al,* J Hepatol 2015

PWIDs are a key population

HCV seroprevalence among PWIDs worldwide (~50% of 16,000,000)



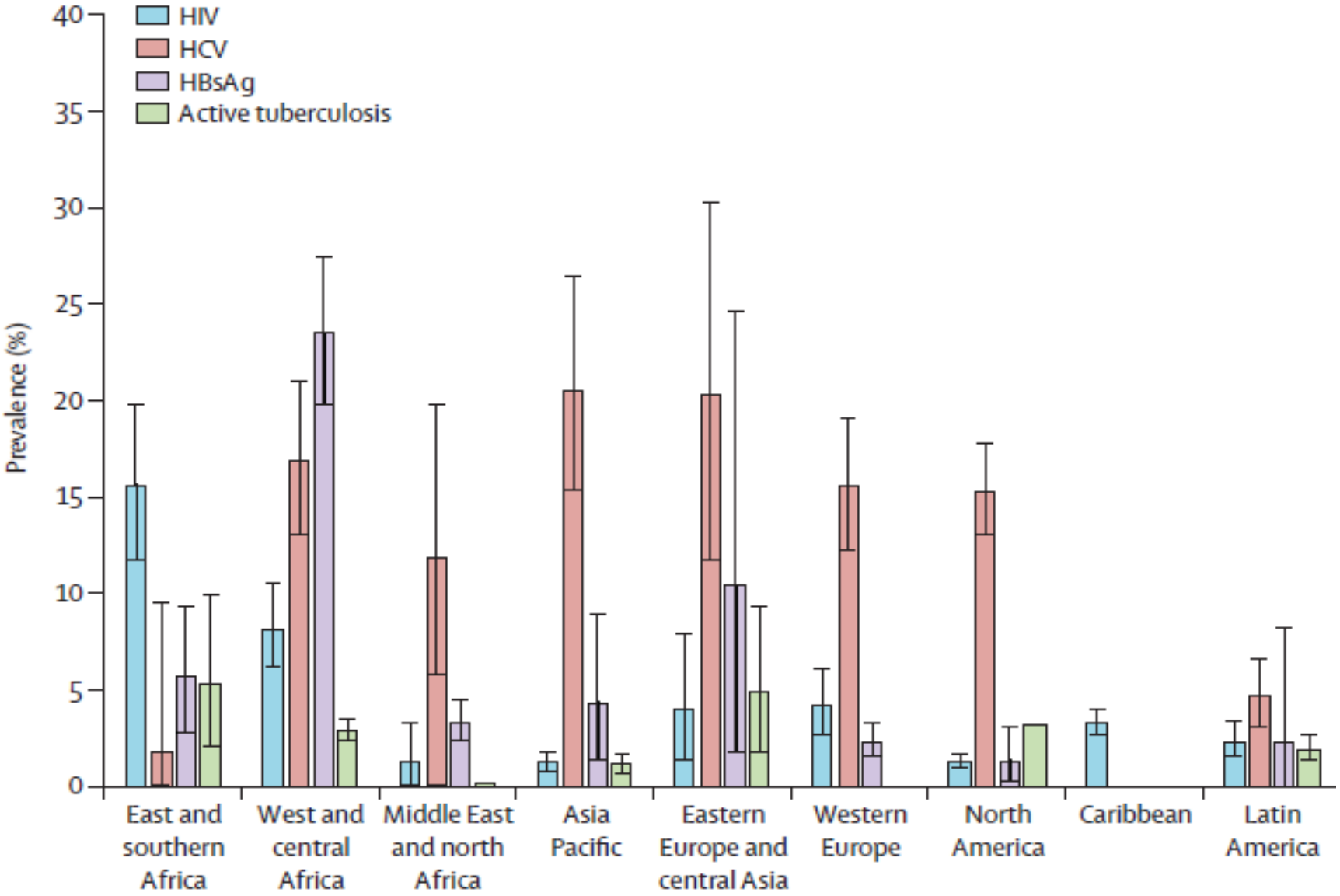
GREBELY & DORE, Antiviral Res 2014; NELSON *et al,* Lancet 2011

Also people in Africa inject drugs!

	Senegal	Tanzania	Kenya
Estimated number of IDUs	1,323 (Dakar)	15,000 (Dar el Salaam)	20 - 30,000
HCV prevalence	39%	28%	39-59%

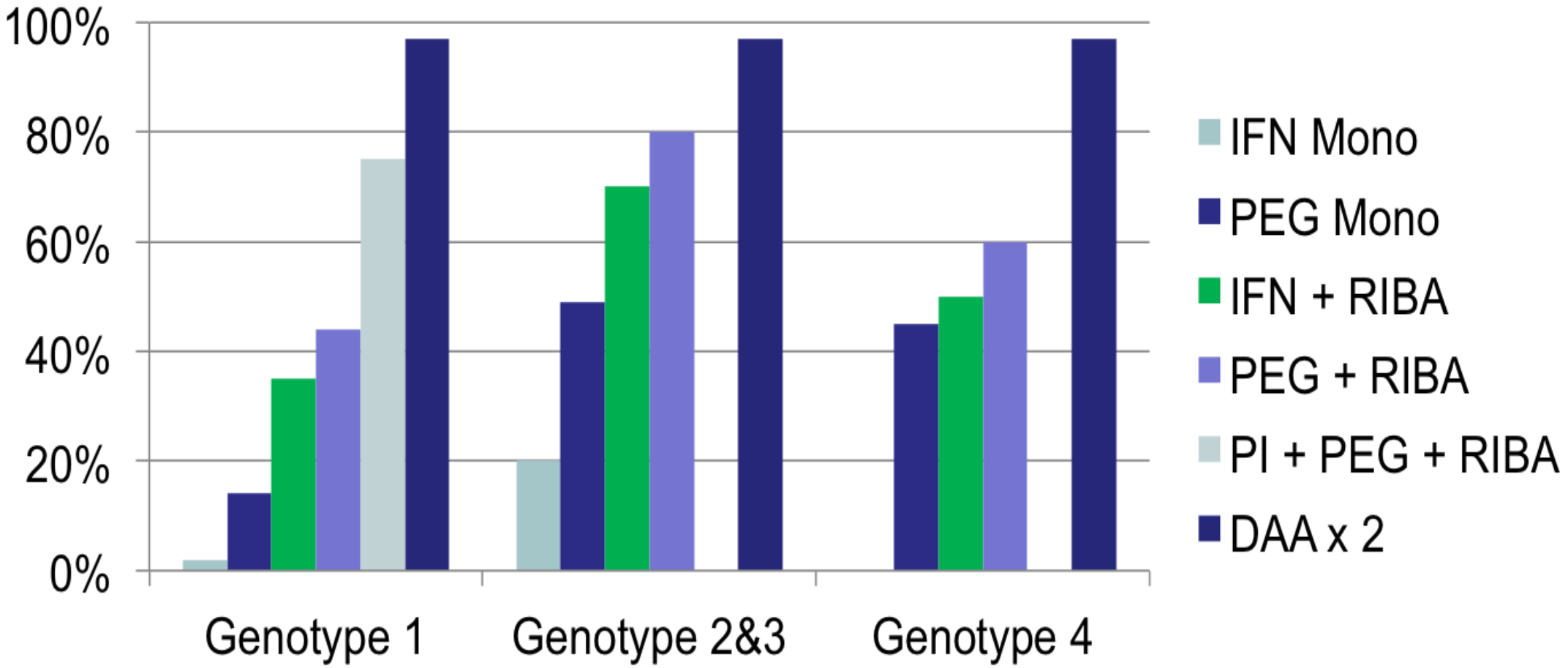
LEPRETRE et al, J AIDS 2015; BOWRING et al, 2013; SHAH et al (unpublished data)
LEPRETRE & LEMOINE (personal communication)

15% of worldwide prisoners are anti-HCV+

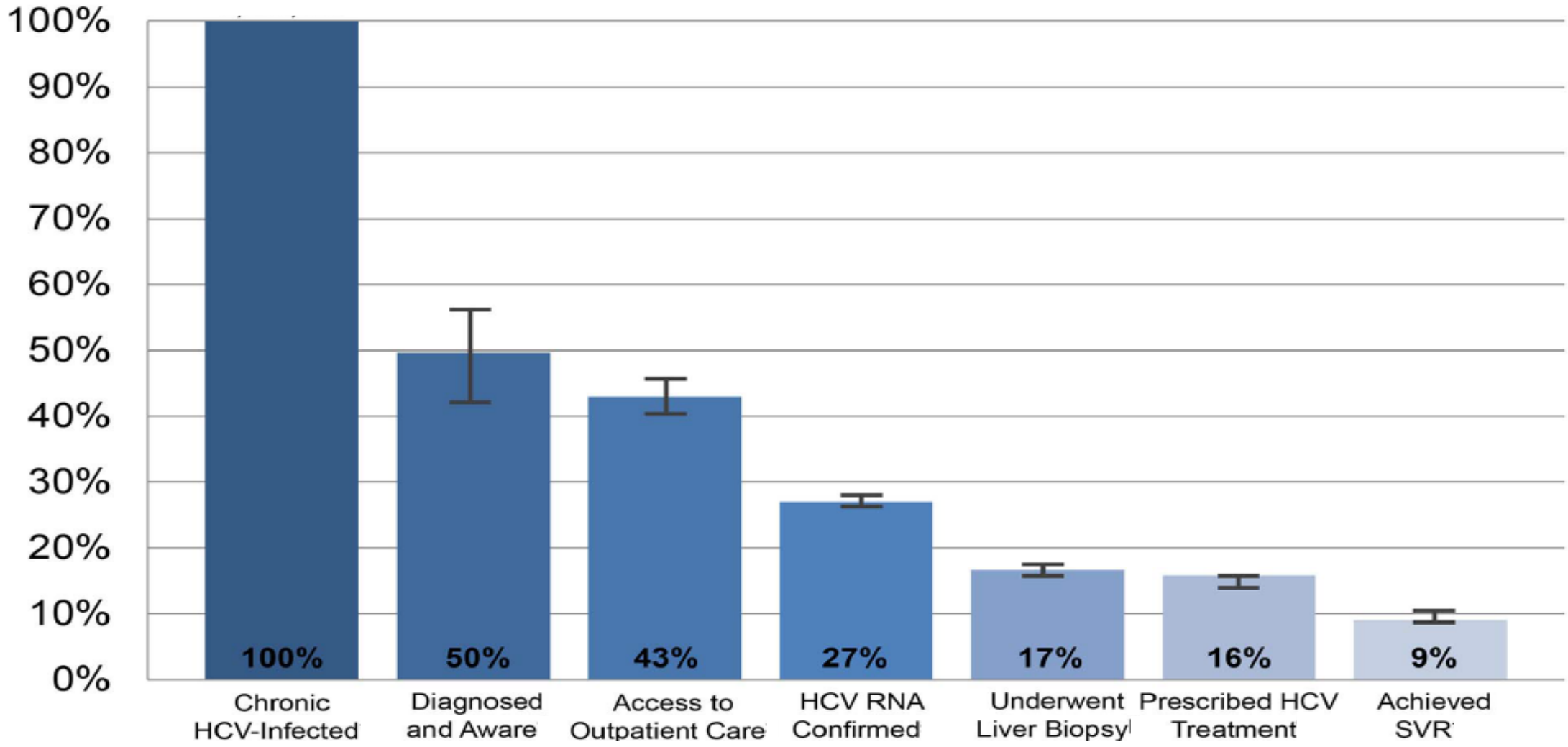


DOLAN *et al*, Lancet 2016

Evolution of HCV Treatment



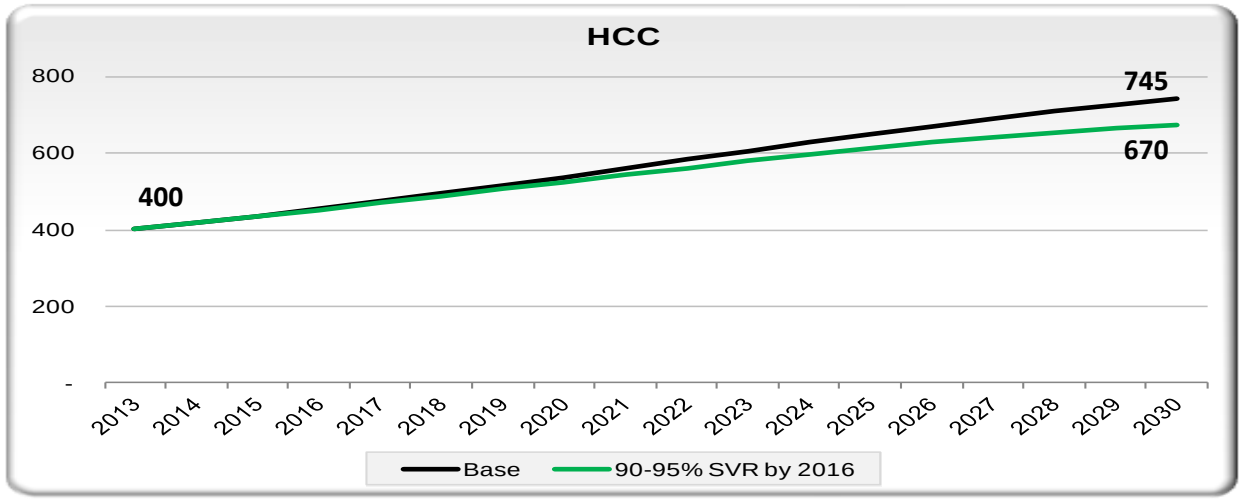
The treatment *cascade* in the US: a meta-analysis

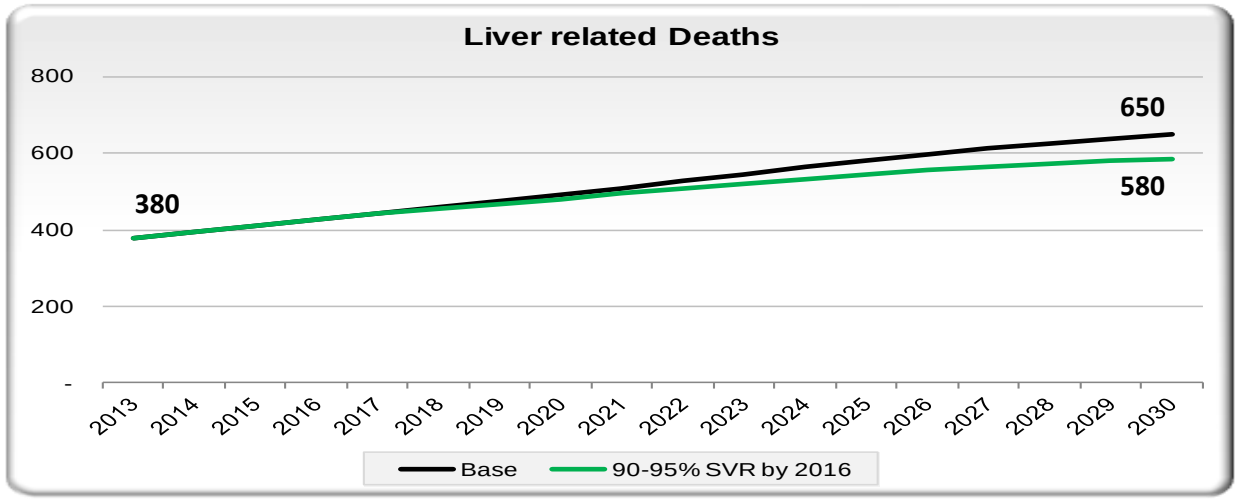


YEHIA *et al,* PLoS One 2014;9:e101554

The Swiss model: assuming a SVR rate of 95% in 2016 and a constant number of treated patients (1,100 per year), the incidence of HCC and liver-related deaths in 2030

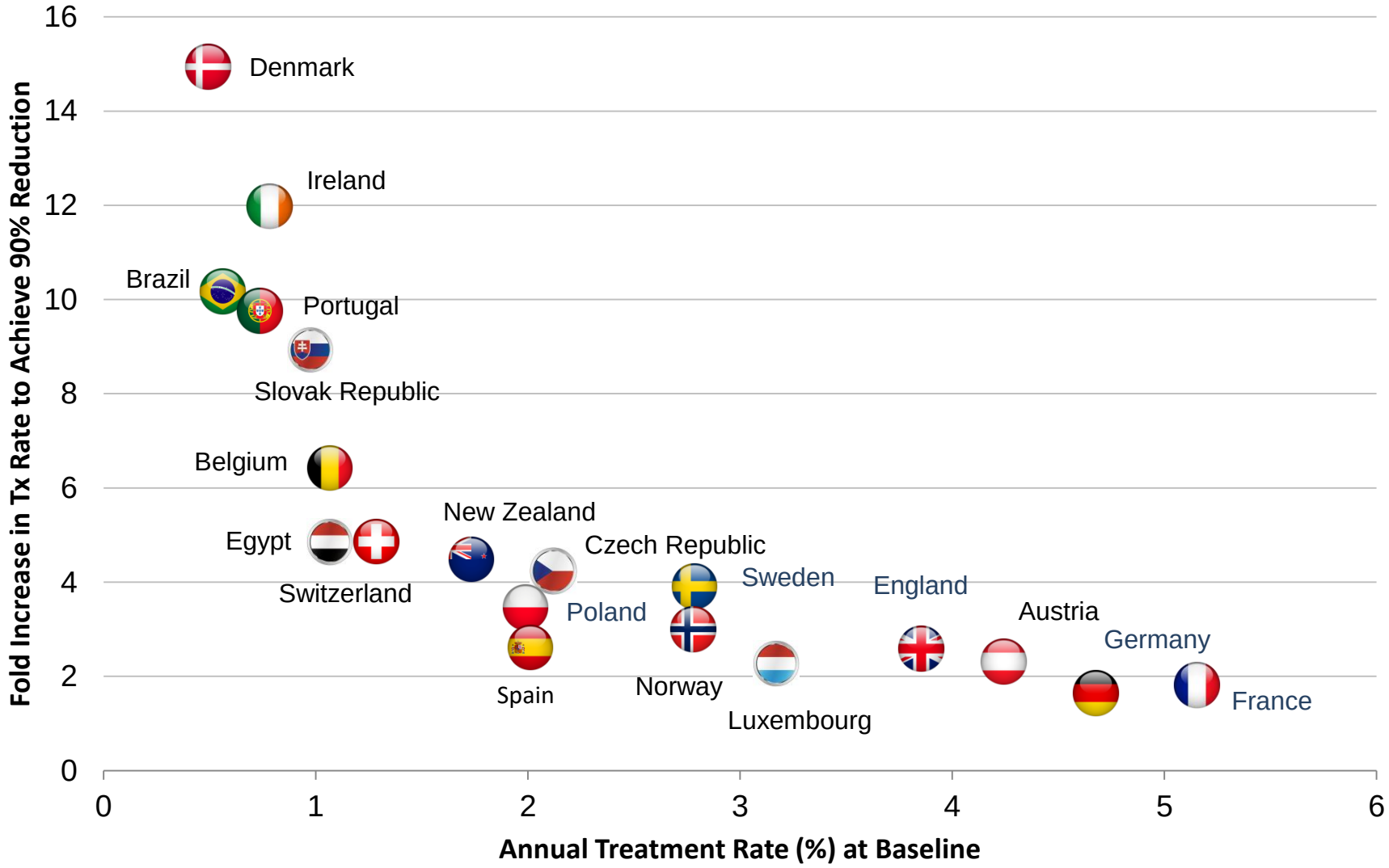
will decrease by ~10% only





MÜLLHAUPT *et al,* PLoS One 2015;10:e0125214

Estimated increase of treatment rate to reduce prevalence by 90% in 2030



PPP-adjusted financial impact of treatment coverage for *all* patients with HCV

Country	Adult Population Infected with Viraemic HCV			Cost of Treatment Coverage (in Millions of PPP Dollars)					
				Sofosbuvir			Ledipasvir/Sofosbuvir		
	Point Estimate	Lower Estimate	Upper Estimate	Point Estimate	Lower Estimate	Upper Estimate	Point Estimate	Lower Estimate	Upper Estimate
United States	2,575,000	2,377,000	4,754,000	$166,551	$153,744	$307,489	$187,370	$172,962	$345,925
Japan	1,252,000	423,000	1,899,000	$47,539	$16,062	$72,106	$61,672	$20,836	$93,542
Italy	768,000	615,000	2,805,000	$35,101	$28,108	$128,202	$39,001	$31,232	$142,447
Turkey	434,000	274,000	959,000	$30,524	$19,271	$67,448	Price not available		
Spain	472,000	109,000	719,000	$22,595	$5,218	$34,419	$25,285	$5,839	$38,516
Poland	196,000	134,000	259,000	$19,808	$13,542	$26,175	$23,276	$15,913	$30,757
Brazil	1,939,000	1,371,000	2,008,000	$18,824	$13,310	$19,494	Price not available		
Egypt	5,623,000	3,940,000	6,885,000	$17,524	$12,279	$21,457	$22,558	$15,807	$27,621

123.5% of total PPP-adjusted pharmaceutical expenditure

IYENGAR *et al,* PLoS Med 2016;13:e1002032

Towards the Elimination of Hepatitis B and C by 2030

The draft WHO Global Hepatitis Strategy, 2016-2021 and global elimination targets

World Health Organization

What does elimination mean?

Elimination: the reduction of an infectious disease's incidence in a regional population to zero, or the reduction of the global prevalence to a negligible amount

Eradication: the reduction of an infectious disease's incidence in the global population to zero

Requirements for elimination

1. No **animal** reservoir

2. The disease should be clearly **identifiable/accurate diagnostic tools** should exist

3. Country, region and global **surveillance systems**

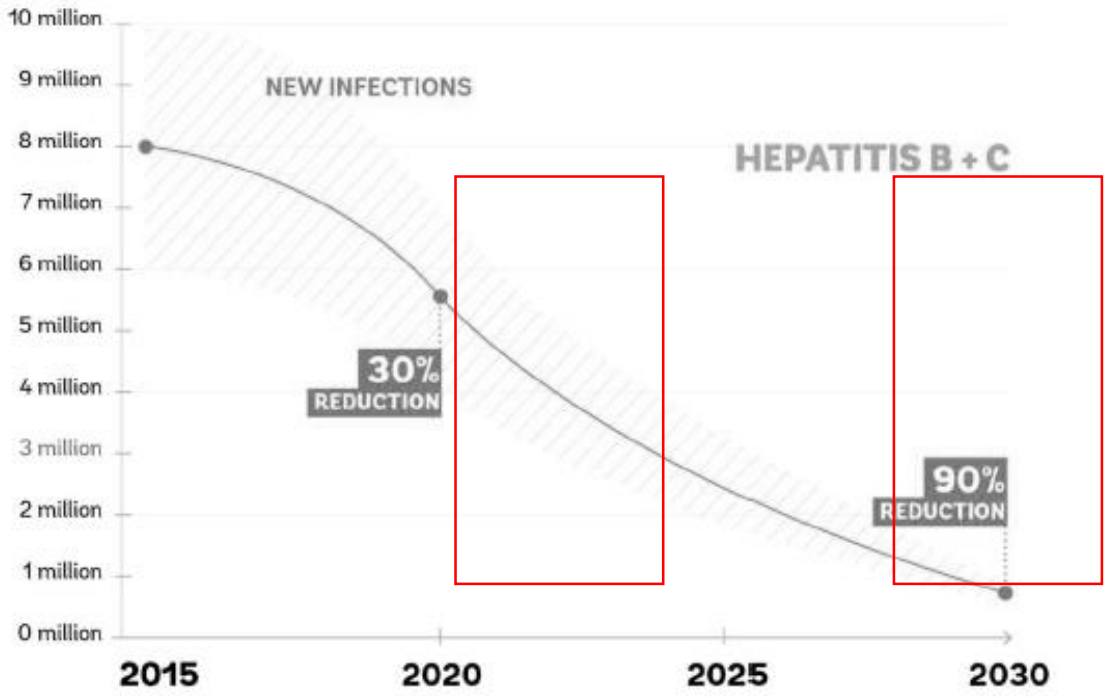
4. An efficient and practical intervention must be available to **interrupt transmission**

5. **Economic considerations** as well as societal and political support and commitment

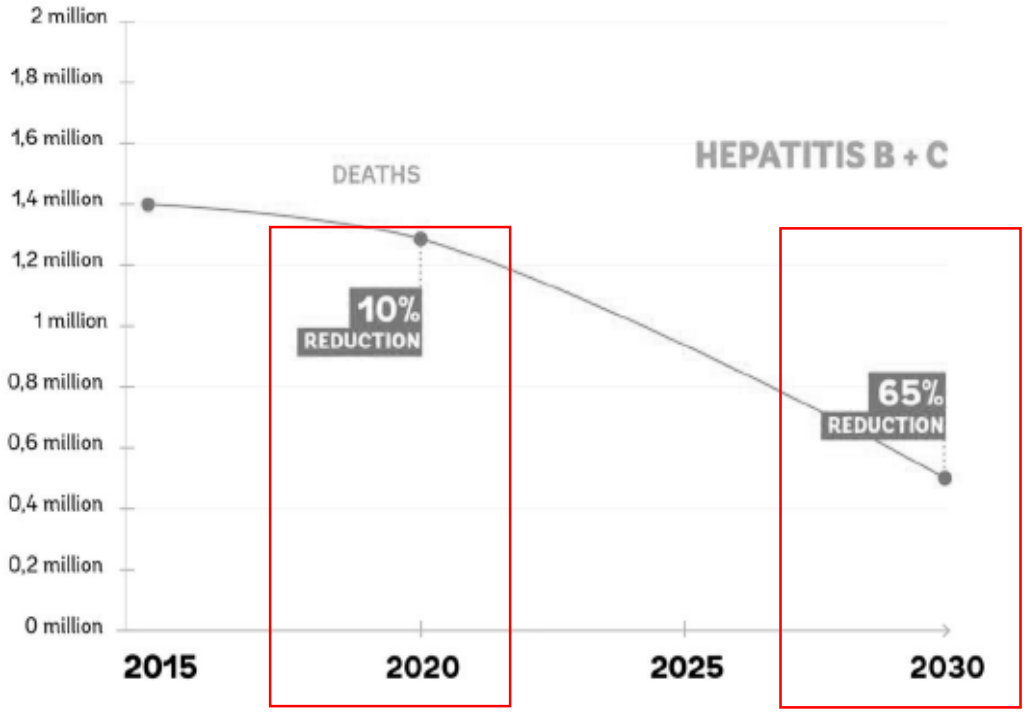
DOWDLE *et al,* Bull World Health Organ 1998

The WHO impact targets for elimination

90% reduction in new cases of of chronic HBV and HCV infection



65% reduction in deaths from chronic HBV and HCV



Courtesy of Stefan Wiktor, WHO 2016

Hepatitis awareness is poor

Mombassa (Kenya):

Out of 400 IDUs (59% anti-HCV+) **369 (92%)** did not know their HCV status as they had never been tested

(LEMOINE, personal communication)

Gambia (West Africa):

Out of 489 participants screened in 2013 for HBV, **only two persons (0.4%)** had heard about HBV infection and had been tested for HBV in the past

None of the positive individuals were previously tested and knew their status

LEMOINE *et al,* Lancet Global Health 2016

Summary

- HBV & HCV are under-appreciated causes of mortality in LMIC
- Awareness about hepatitis in some geographical areas is very low
- Vaccination is effective at prevention of new chronic cases of HBV
- PMTCT required for elimination of HBV
- Mortality cannot be controlled in the foreseeable future without screening and increased treatment uptake
- Current costs of HCV drugs makes elimination programs unaffordable even for rich countries