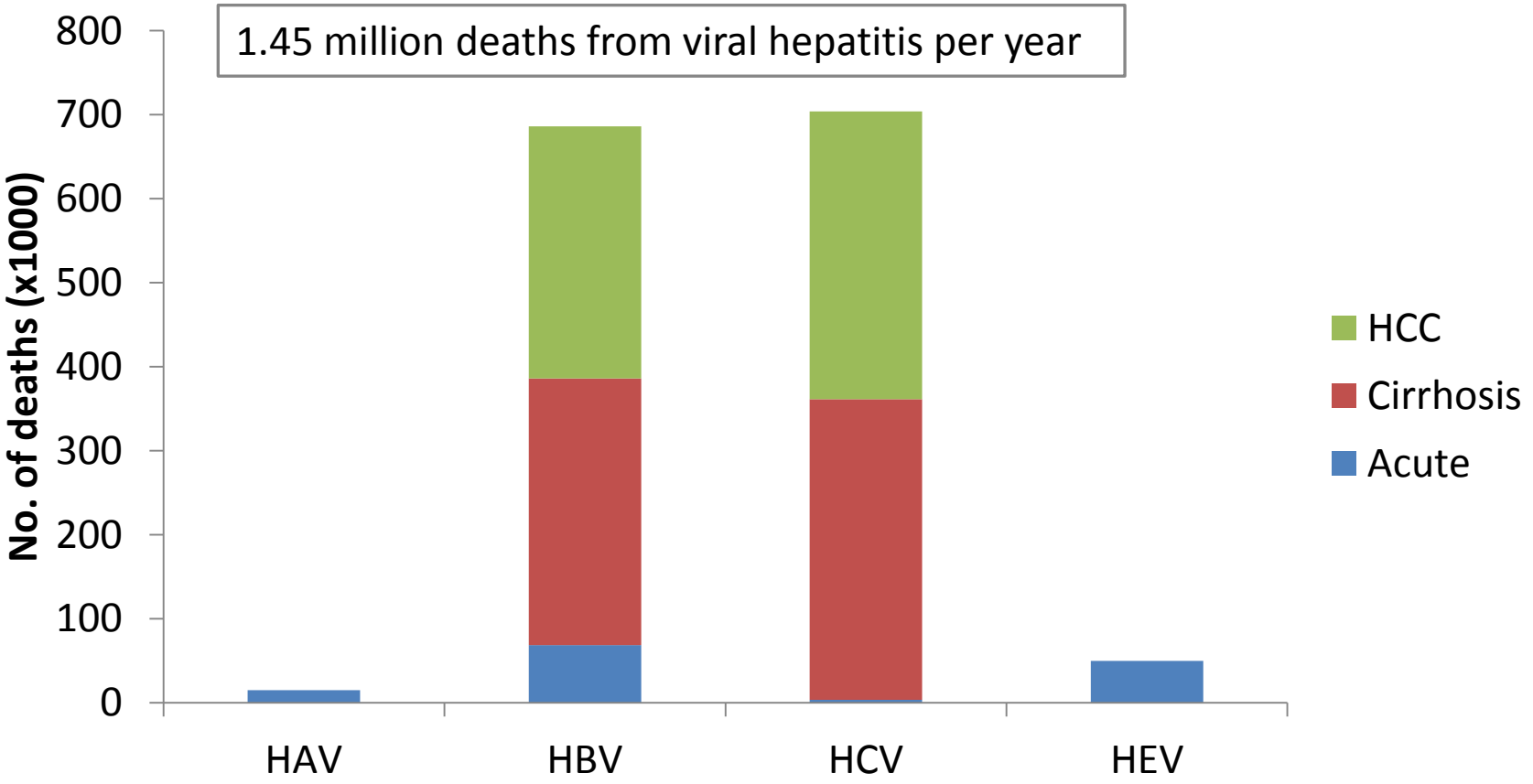
Updates on hepatitis B and C treatment guidelines and overview of hepatitis treatment landscape

globalhepatitis programme

Philippa Easterbrook

World Health Organization

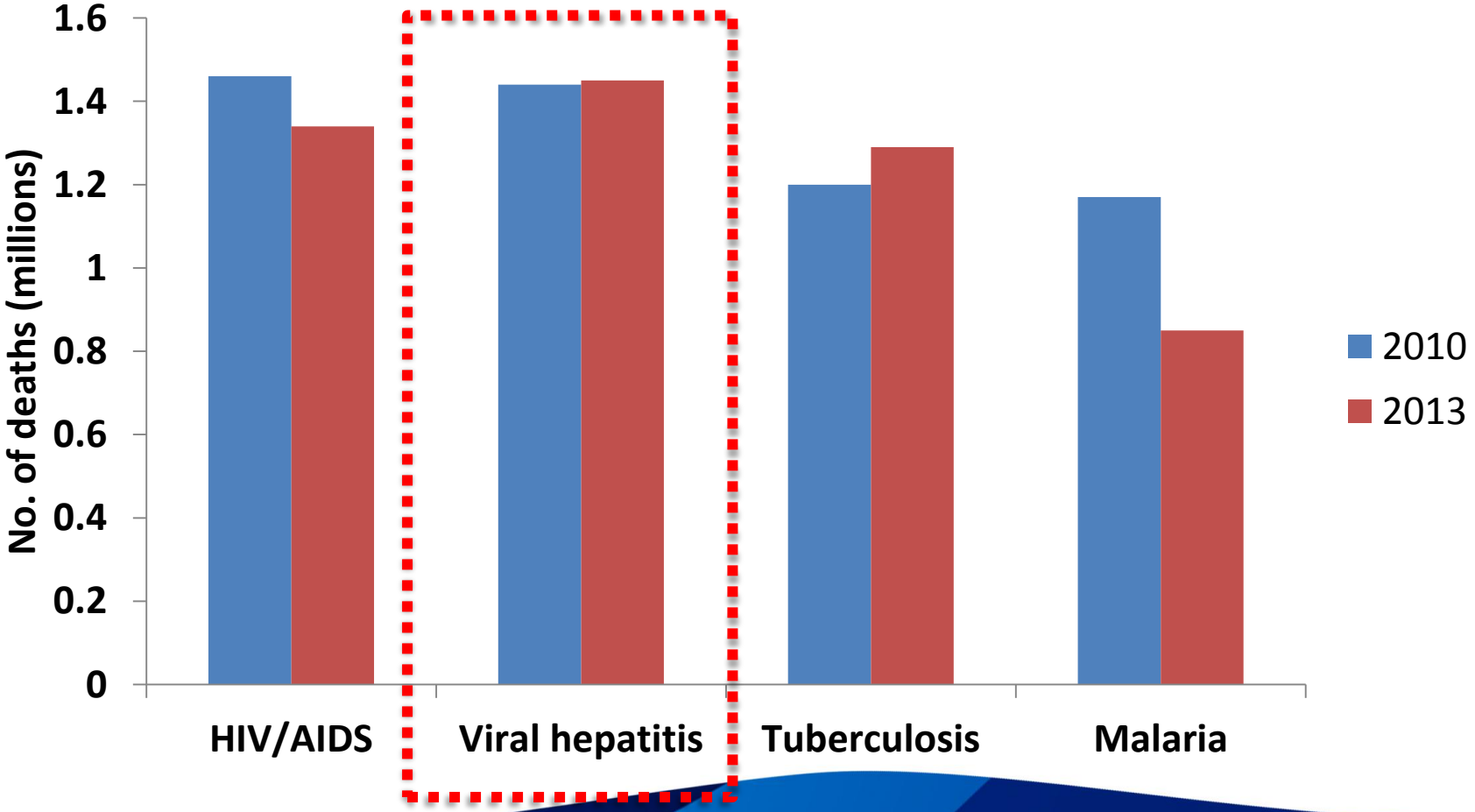
Hepatitis-related mortality, 2013



GBD 2013 Mortality and Causes of Death Study: Lancet 2014

World Health Organization

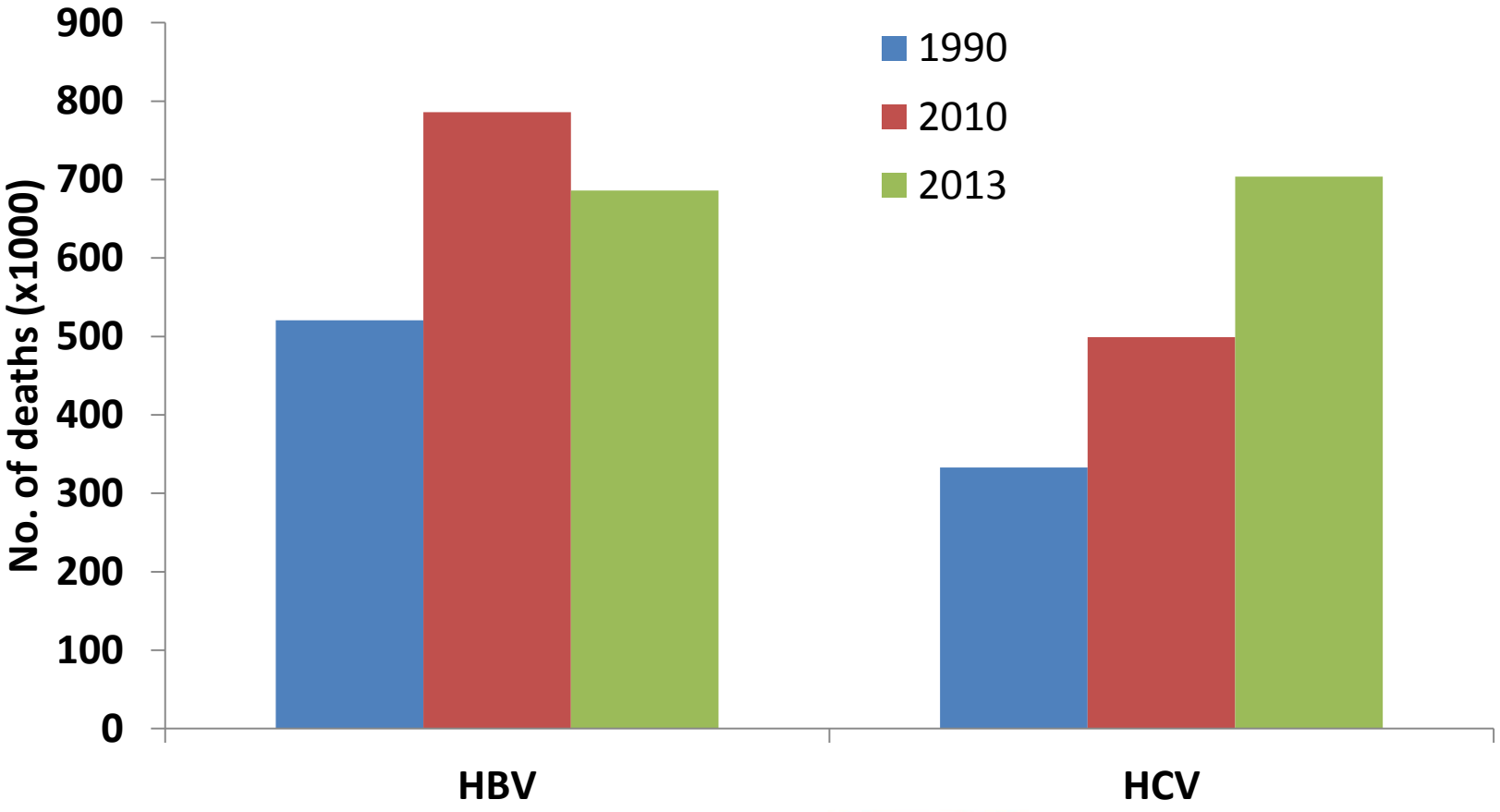
Number of deaths/year from selected conditions, Global Burden of Disease Study 2010 and 2013



GBD 2013 Mortality and Causes of Death Study: Lancet 2014

World Health Organization

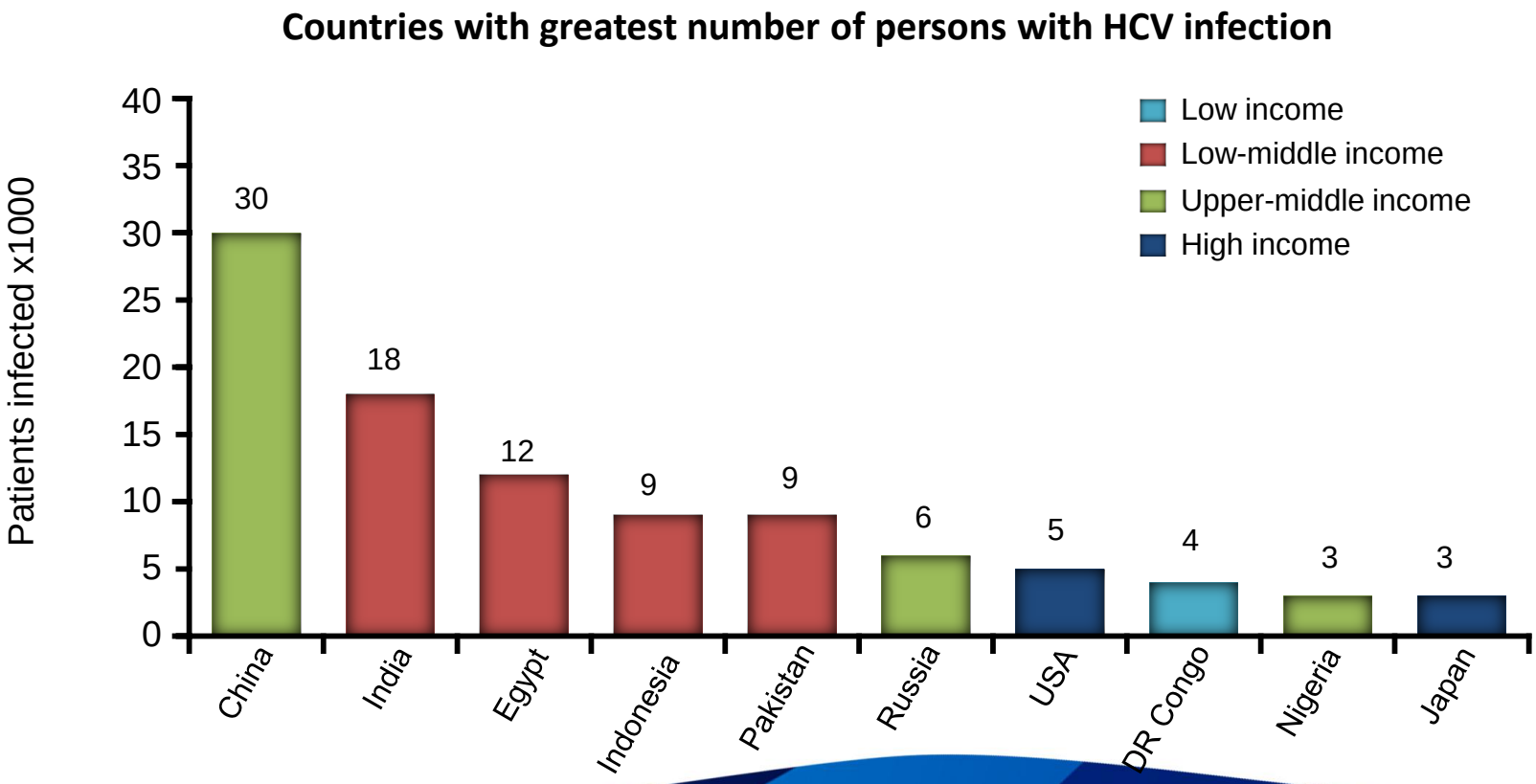
Number of deaths/year from hepatitis B and C, Global Burden of Disease Study 1990, 2010 and 2013



GBD Mortality and Causes of Death Study: Lancet 2014

World Health Organization

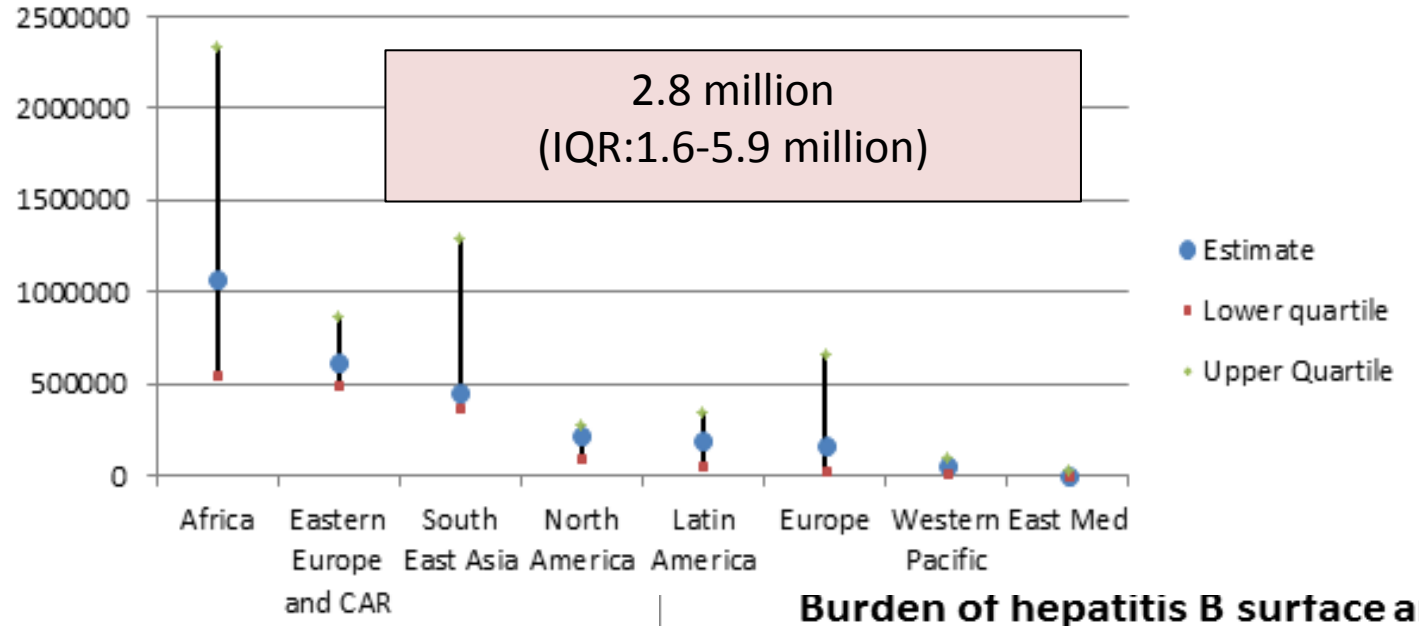
Most people with chronic HCV live in middle-income countries



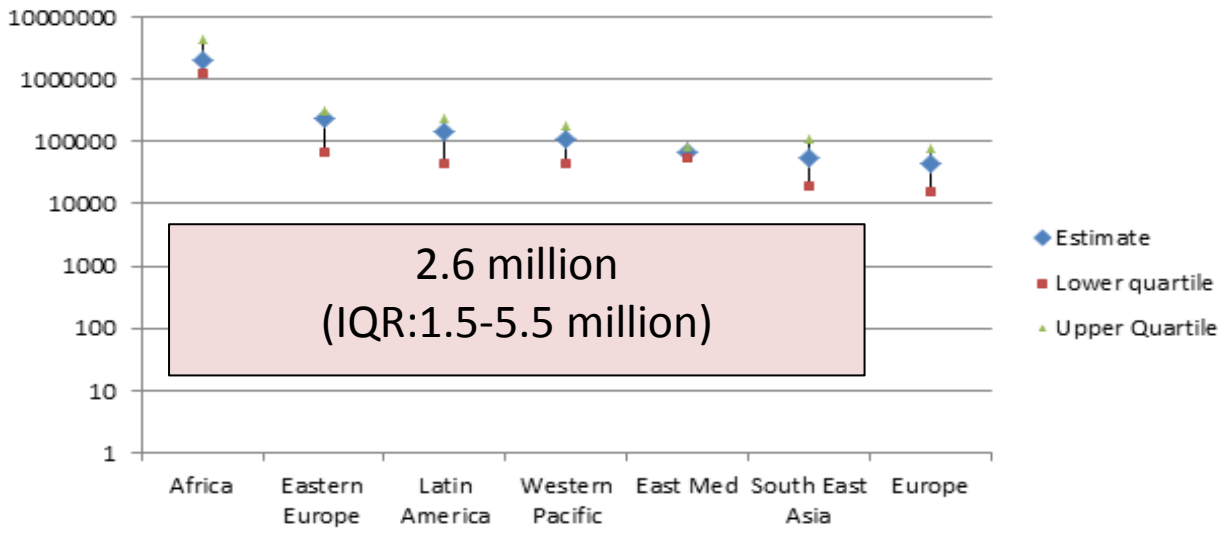
Source: Hill A, et al. Clin Infect Dis 2014;58:928–36

World Health Organization

Burden of co-infection with HIV and HCV by region, 2013



Burden of hepatitis B surface antigen and HIV by region, 2013

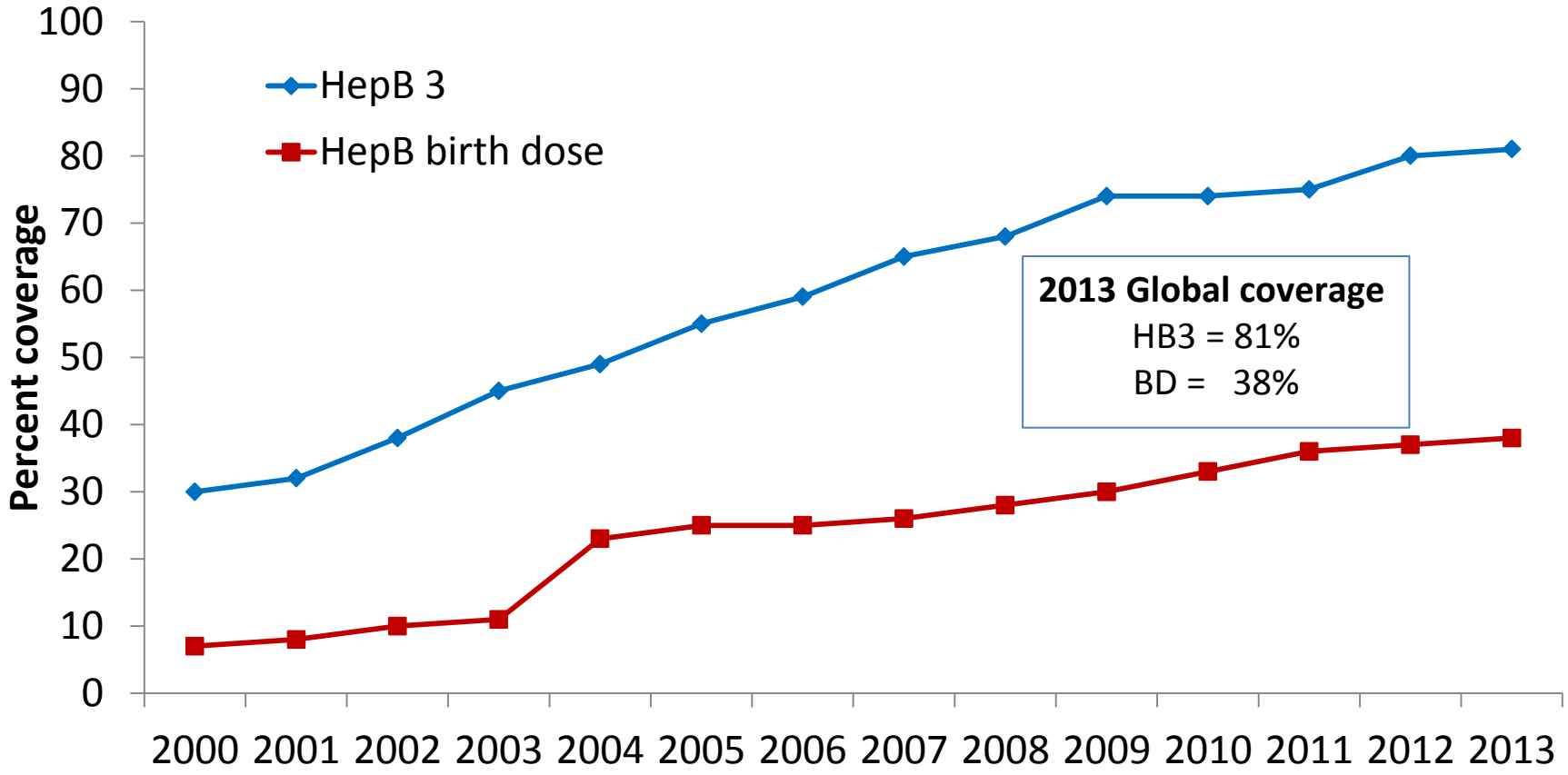


Source: Easterbrook et al. Methodological challenges in the conduct of a global systematic review and meta-analysis of the seroprevalence of HBV and HCV infection in HIV-infected persons. Abstract MOPE191 presented at the 2014 International AIDS Conference.

The Global Hepatitis Response

World Health Organization

Continued success in HBV immunization: Global HepB3 & BD coverage, 2000-2013

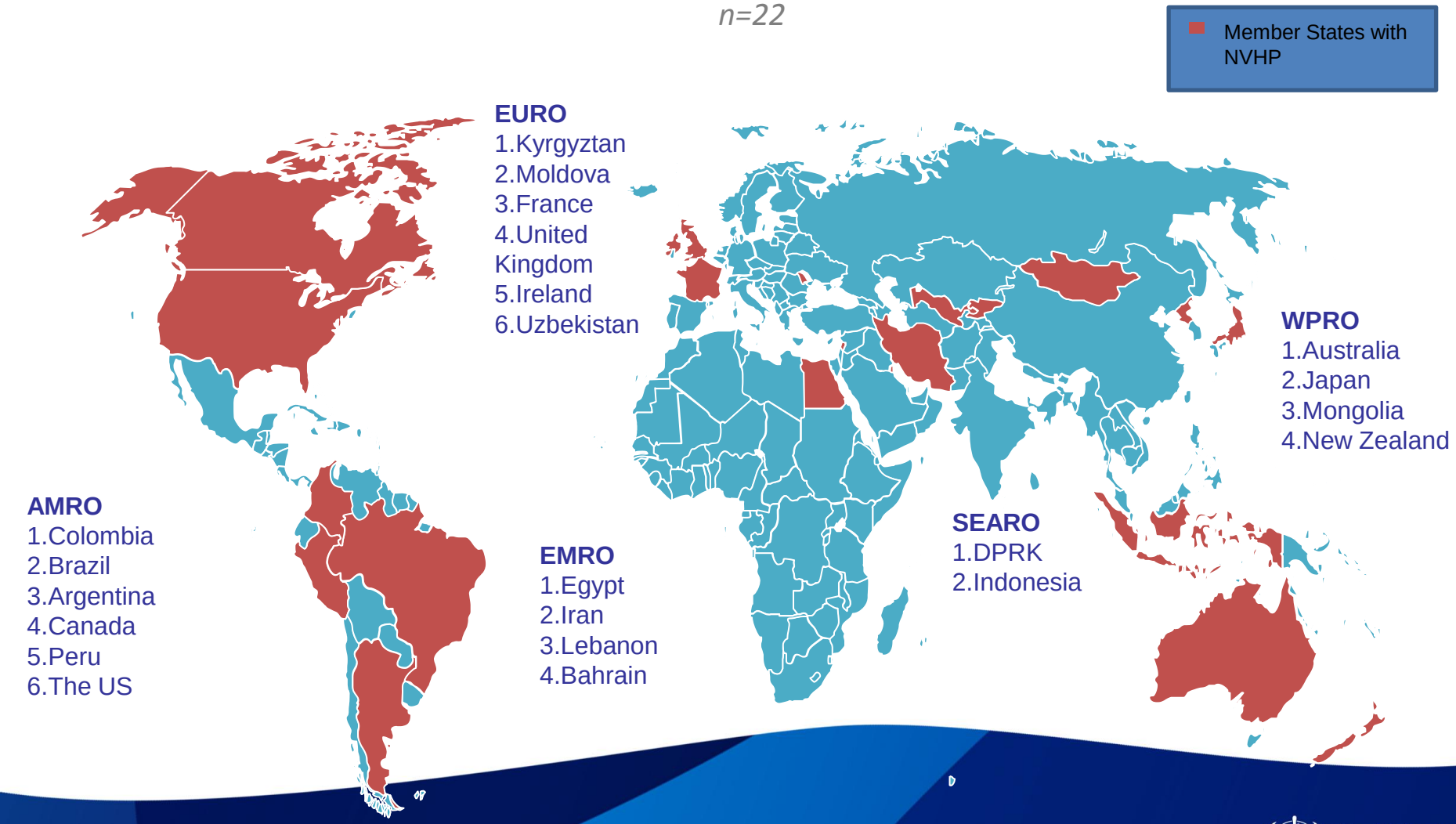


Source: WHO/UNICEF coverage estimates 2013 revision. July 2014
Immunization Vaccines and Biologicals, (IVB), World Health Organization.
194 WHO Member States.

World Health Organization

Member States with National Viral Hepatitis Plans (NVHP)

n=22

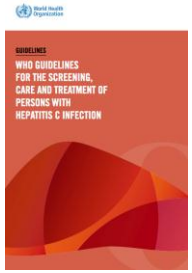


World Health Organization

The Global Hepatitis Response: key issues

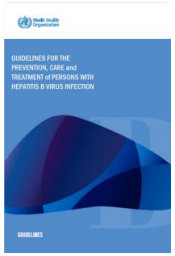
- Few national plans but increasing
- Progress in regions on HBV elimination
- Low treatment scale-up

TIMELINES OF HEPATITIS GUIDANCE



LAUNCH OF HEPATITIS C GUIDELINES
EASL Conference

HBV GUIDELINES MEETING
June 2014

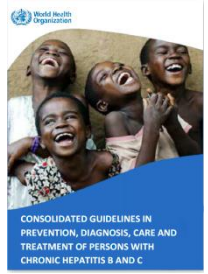


LAUNCH OF HEPATITIS B GUIDELINES
APASL Conference

HEPATITIS TESTING GUIDELINES MEETING
June 2015
HEPATITIS C TREATMENT UPDATE GUIDELINES MEETING
June 2015

RELEASE OF HEPATITIS TESTING GUIDELINES

RELEASE OF HEPATITIS C TREATMENT UPDATE GUIDELINES



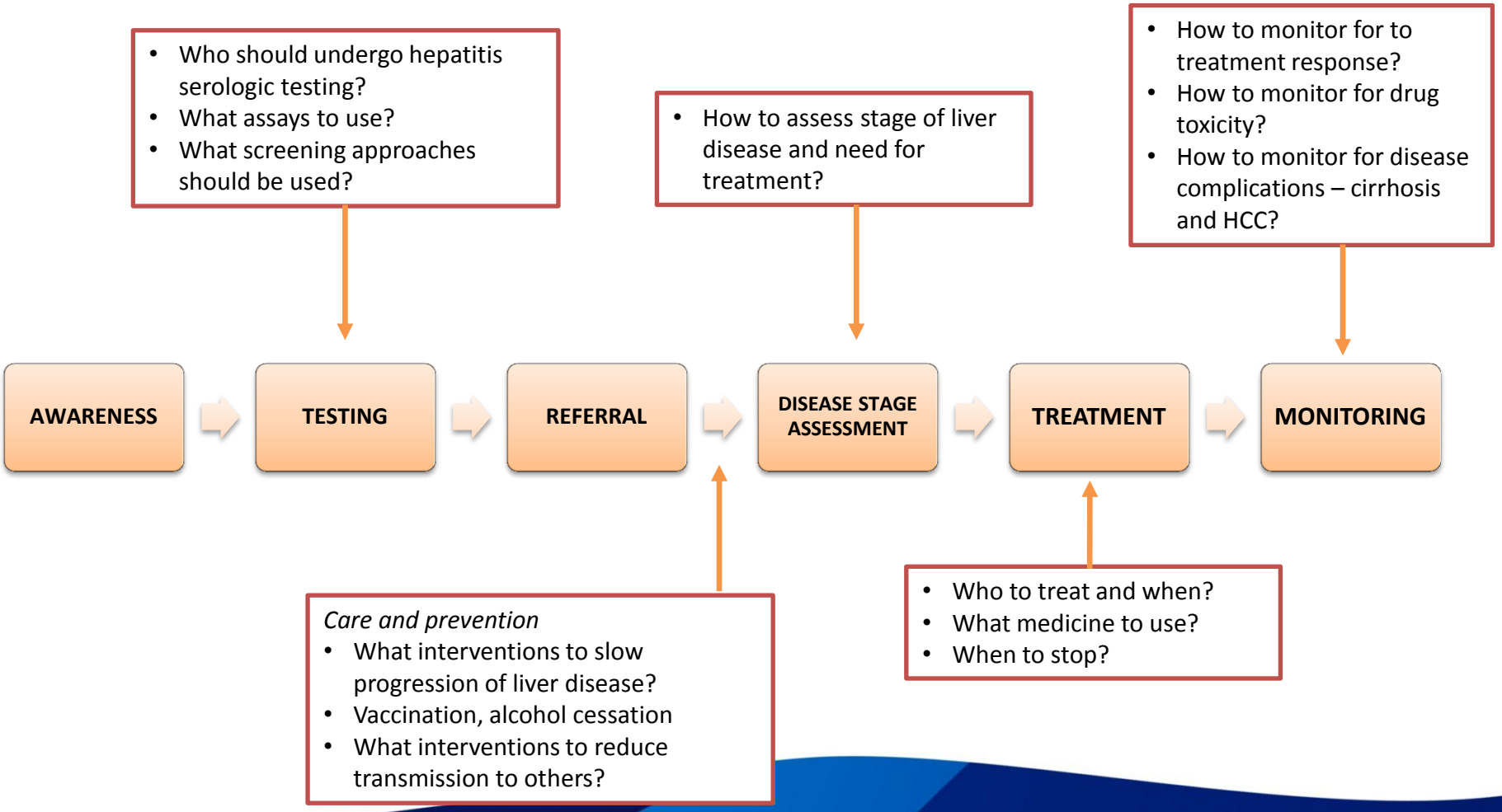
LAUNCH OF CONSOLIDATED HEPATITIS GUIDELINES (2016)

APRIL · JUNE · DECEMBER · MARCH · APRIL · JUNE · SEPTEMBER · OCTOBER · DECEMBER · JANUARY · MARCH · JULY

2014 · 2015 · 2016

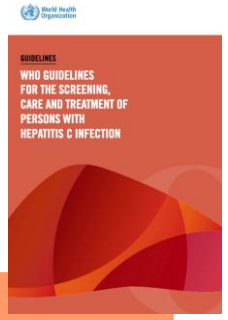
World Health Organization

HBV AND HCV TESTING, CARE AND TREATMENT GUIDELINES ALONG CONTINUUM OF CARE



World Health Organization

HCV GUIDELINE RECOMMENDATIONS (2014)



Topic	Recommendation
Diagnosis	▪ HCV Ab testing offered to individuals with high HCV prevalence or history of HCV-risk exposure / behaviour ▪ RNA testing following positive HCV Ab test to establish diagnosis of active infection and for treatment evaluation
Staging	▪ Use non-invasive tests (APRI or FIB4) for assessment of liver fibrosis
Prevention	▪ Alcohol-intake assessment + offer of behavioural alcohol reduction intervention for persons with moderate-high alcohol intake
Treatment	▪ Assessment of all adults and children with chronic HCV, including PWID for antiviral treatment – PEG-IFN + Ribavirin rather than standard non PEG-IFN + Ribavirin – Telaprevir or boceprevir in GT 1 – Sofosbuvir + Ribavirin ± PEG-IFN in GT 1, 2, 3 and 4 – Simeprevir + PEG-IFN + Ribavirin in GT 1

HCV medicines pipeline: 2014 and beyond

Feb 2014
Sofosbuvir

Aug 2014
Daclatasvir

Jan 2015
3D Abbvie
Ombitasvir
Paritaprevir
Dasabuvir

2016?
MSD
Grazoprevir
Elbasvir
....buvir

May 2014
Simeprevir

Nov 2014
STR Gilead
Sofosbuvir
Ledipasvir

2015?
BMS Trio
Daclatasvir
Asunaprevir
Beclabuvir

2016?
SOF/GS-5816

Courtesy of Mark Thursz

World Health Organization

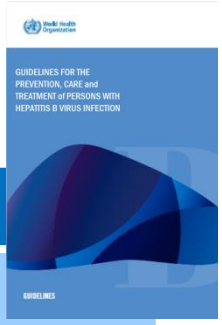
PLANNED UPDATED HCV TREATMENT RECOMMENDATIONS (2015)

- For new medicines:
  - Asunaprevir, Daclatasvir,
  - Ledipasvir/Sofosbuvir,
  - Paritaprevir/ritonavir+Ombitasvir+Dasabuvir

- Recommendations on preferred combinations based on network meta-analysis and cost-effectiveness analysis

- Completion date 4th quarter 2015

HBV GUIDELINE RECOMMENDATIONS (2015)



Topic	Recommendation
Staging/ non-invasive test (NIT)	▪ APRI preferred NIT to assess for the presence of cirrhosis
Who to treat	▪ Decompensated cirrhosis or cirrhosis (clinical criteria or APRI score >2), regardless of ALT levels, HBeAg, or HBV DNA. ▪ No cirrhosis but persistently abnormal ALT levels +/- ongoing HBV replication, (HBV DNA >20,000 IU/mL *or* HBeAg +ve).
First line treatment	▪ Drugs with a high barrier to resistance (TDF or ETV). ▪ ETV in children aged 2-11 years.
Treatment failure	▪ Switch to TDF if evidence of resistance to 3TC, ETV, ADF, TBV.
Treatment discontinuation	▪ Never discontinue in persons with cirrhosis. ▪ If no cirrhosis, discontinuation on case-by-case basis (persistent HBeAg and/or HBsAg loss or undetectable HBV DNA)
Monitoring (treatment response/toxicity)	▪ *On or pre-treatment:* ALT + HBV DNA (HBsAg, HBeAg + APRI pre-treatment) annually. More frequent monitoring with cirrhosis. ▪ Assessment of baseline renal function prior to treatment initiation.
Monitoring for HCC	▪ Ultrasound + AFP every 6 months in persons with cirrhosis and/or family history of HCC.

What treatment to use?

	RECOMMENDATION	STRENGTH	EVIDENCE QUALITY
FIRST-LINE	**NAs with a high barrier to drug resistance** (tenofovir or entecavir) are recommended in all adults, adolescents and children (≥12 years) in whom antiviral therapy is indicated. - Entecavir is recommended in children 2–11 years.	Strong	Moderate
FIRST-LINE	**NAs with a low barrier to resistance** (lamivudine, adefovir or telbivudine) can lead to drug resistance and **are not recommended**.	Strong	Moderate
SECOND-LINE	In persons with confirmed or suspected antiviral resistance (i.e. history of prior exposure or primary non-response) to lamivudine, entecavir, adefovir or telbivudine, **a switch to tenofovir is recommended**. - Use of entecavir is not recommended	Strong	Low

EVIDENCE

Systematic reviews

- **Three in Rx naïve**
  - Comparative studies: 7 existing reviews (49 trials)
  - Long-term effectiveness and safety of entecavir/tenofovir (n=12)
  - HIV coinfection (n=23)
- **One in Rx experienced:** 1 existing review (5 RCTs, 3 non-RCTs) and 7 RCTs

Network meta-analyses

- 21 RCTs (eAg+);16 RCT (eAg-)
- 7 RCTs (eAg+) and 6 RCT (771 eAg -)

RATIONALE

Evidence

- **Potent inhibitors of HBV replication**.
- **Most effective therapies** to achieve undetectable HBV DNA and ALT normalization (reviews and NMA)
- **High genetic barrier:** very low rates of drug resistance
- **Safe and effective in children and** pregnancy

Drug	% HBV DNA <300c/ml	
	NA naive	NA experienced
Tenofovir	94.1% (74.7-98.9)	89% (51.8-98.2)
Entecavir	64.5% (49.1-80.5)	21.4% (10.0-44.6)
ADF+LMV	36.9% (12.3-70.3)	31.3% (13.4-60.8)

Strong operational/programmatic advantages

- **Convenient** – one pill once a day
- **Well tolerated** - low rates of side-effects; minimal requirement for toxicity monitoring
- **Simplifies drug procurement** (HIV programmes)
- **Affordability**

Who to treat?

RECOMMENDATION	STRENGTH	EVIDENCE QUALITY
As a priority, **treat all** with clinical evidence of compensated or decompensated **cirrhosis** (or APRI score >2 in adults), regardless of age, HBeAg status, ALT or HBV DNA levels.	Strong	Moderate
If no evidence of cirrhosis (or APRI score ≤2 in adults): Treat if >30 years, and **persistently abnormal ALT levels** and **high level HBV replication** (HBV DNA >20 000 IU/mL), regardless of HBeAg status.	Strong	Moderate

EVIDENCE

Two systematic reviews

- Identifying HBeAg+/- at high and low risk of HCC and cirrhosis
  - 22 observational studies (4 population-based)
  - SE Asia, Europe, N. America; 1 HIV
- Impact of treatment in advanced liver disease (4 studies)

Participant characteristic	Incidence rate of HCC (x 100 000 person-years)	Adjusted RR (95%CI)
Sex		
Female	178	Reference
Male	530	3.0 (2.0–4.5)
Age (years)		
30–39	111	Reference
40–49	399	3.6 (2.0–6.4)
50–59	566	5.1 (2.0–8.9)
>60	901	8.3 (4.6–15.0)
Baseline HBV DNA (copies/mL) [a]		
<300	108	Reference [b]
300–9999	111	NS
10 000–99 999	297	2.7 (1.3–5.6)
100 000–999 999	962	8.9 (4.6–17.5)
>1 million	1152	10.7 (5.7–20.1)
Baseline ALT (U/L)		
<45	337	Reference
>45	1342	4.1 (2.8–6.0)
HBeAg serostatus		
HBeAg-negative	264	Reference

RATIONALE

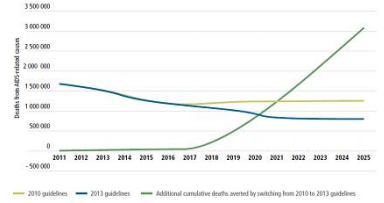
Treat as priority those with cirrhosis:

- **High risk of life-threatening complications**
- **Treatment can halve disease progression and** deaths + fibrosis regression.
- Targeting treatment is **cost- effective**
- **Treatment safe** even with decompensated cirrhosis

Treat: those without cirrhosis

- **Consistent evidence** of increased HCC and cirrhosis risk (age, ALT, HBV DNA)
- **Uncertainties** in specific thresholds
  - Abnormal ALT level varies by lab
  - Age >30 yr based on Asian pop.

HEPATITIS B AND C TESTING GUIDELINES (2015)

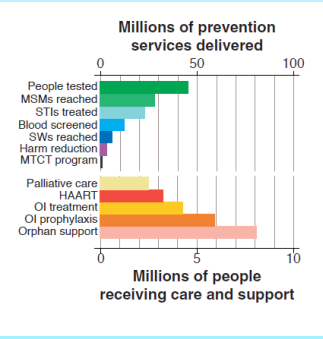


Who to screen? (MODELLING)

- Modelling of impact, cost, and cost-effectiveness of different HBV and HCV testing strategies and scenarios (gen popn and risk group)

How to screen? (SYSTEMATIC REVIEW)

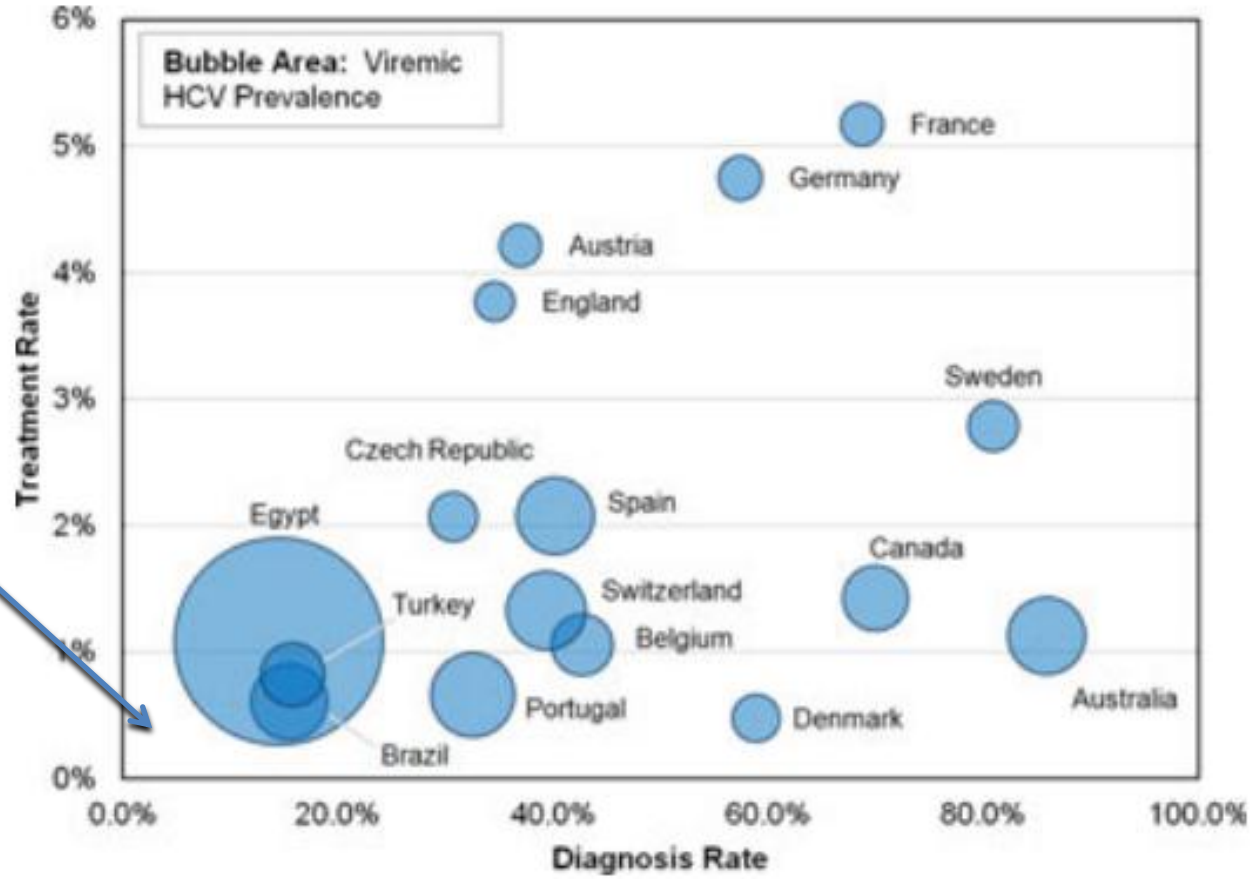
- Diagnostic accuracy and performance of RDTs;
- One test vs. two test strategy
- Core Ag vs. HCV RNA



Improving access to diagnosis/treatment HQ ongoing and planned activities

Activity	Components	Date
1. Normative Guidance	HCV HBV Screening	April 2014 March 2015 4thQ 2015
3. Drugs - WHO Essential Medicines list	Sofosbuvir SOF-Ledipasvir Daclatasvir Paritaprevir+Ombitasvir+Dasabuvir Entecavir Tenofovir (HBV)	June 015
4. Drugs – EoI and PQ of generics	Sofosbuvir Entecavir	Aug 2014
5. Diagnostics - PQ	HCV and HBV RDTs + molecular	Ongoing
6. Drugs/ Diagnostics – Global Price Reporting Mechanism/ Demand Forecasting	TCO/HIV	Ongoing

Estimated chronic HCV prevalence, diagnosis and treatment rates in 2013

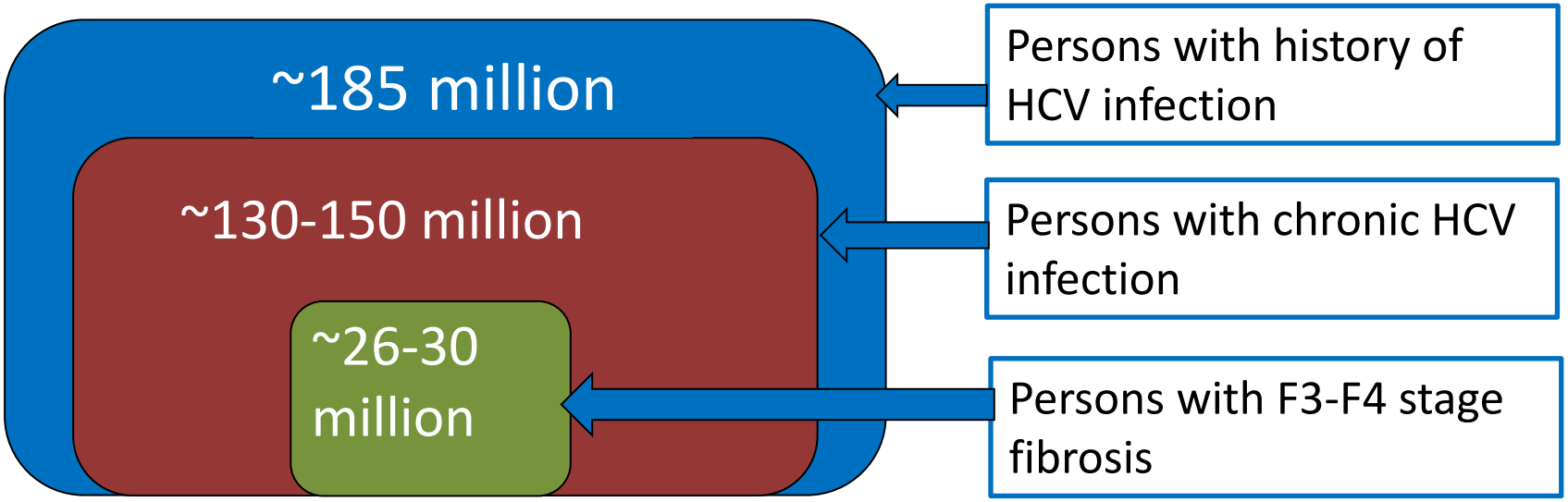


Most low- and Middle-income countries

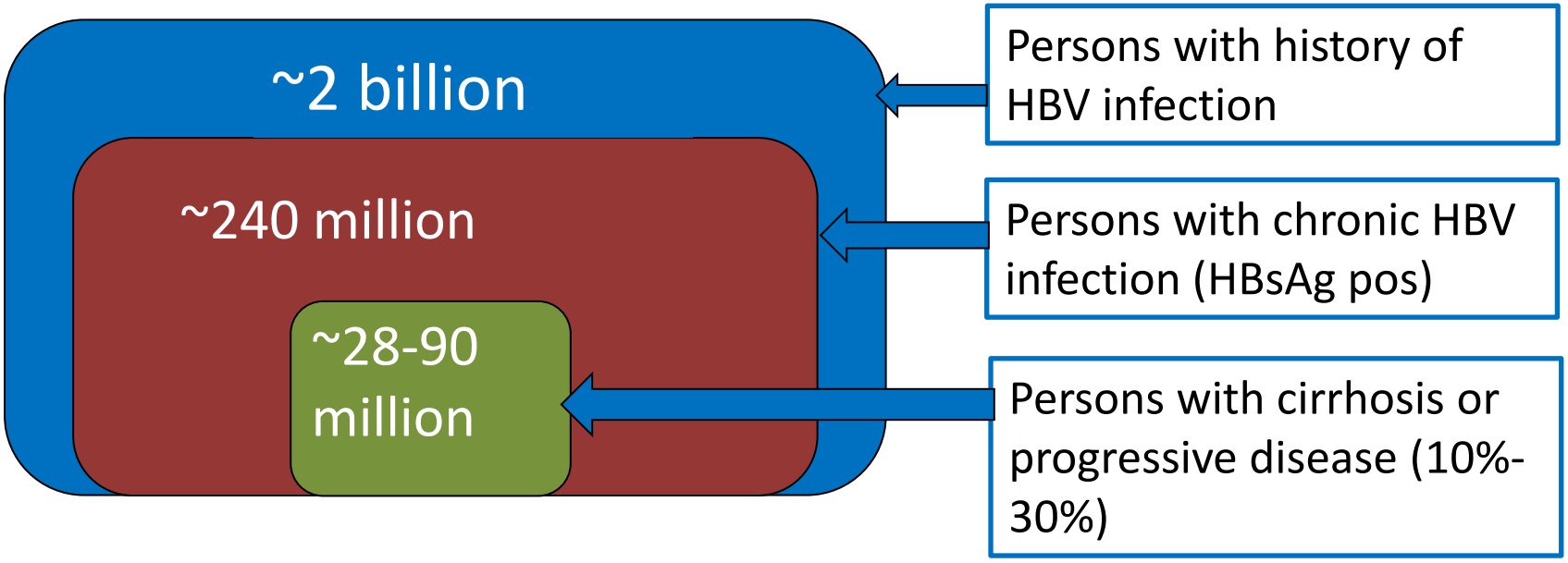
Dore J al. J Viral Hep (2014),

World Health Organization

How many persons need HCV treatment?



How many persons need HBV treatment?



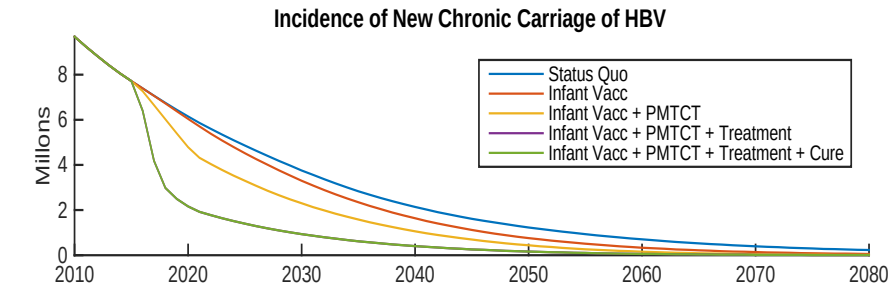
What could be the impact?

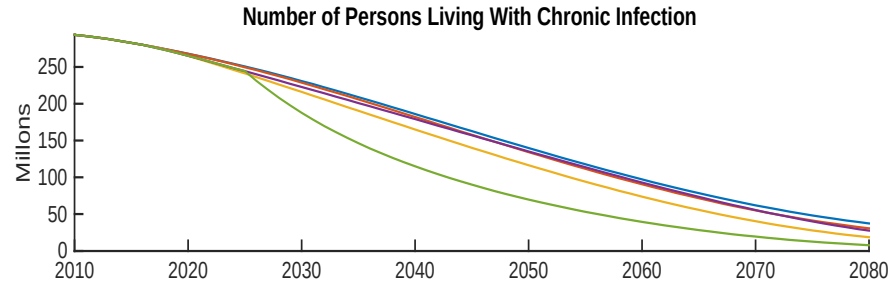
IMPACT
(Incidence, Mortality)

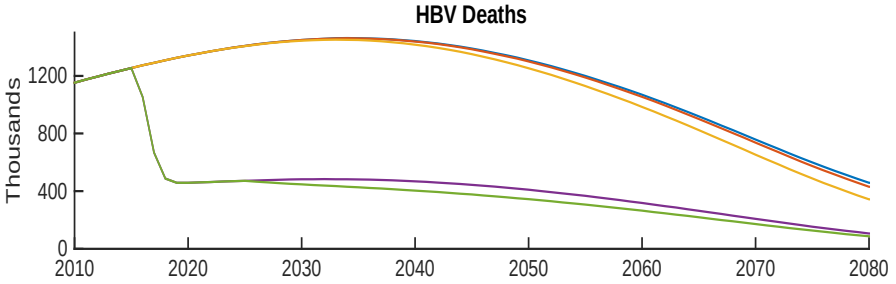
- Modelling of impact of integrated treatment + prevention package on incidence and mortality

- Based on high coverage for:-
  - Infant vaccination + universal access to blood and injection safety + harm reduction
  - Scale-up of diagnosis and treatment

- **Feasible targets by 2030?**
  - 90% reduction in new cases of chronic infection
  - 65% reduction in HBV deaths
  - 13M deaths averted, 6M cancers







World Health Organization

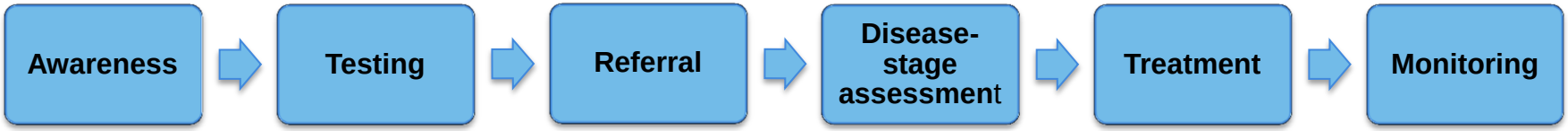
Hepatitis in 2015: where are we now?

- Hepatitis is getting on the agenda (e.g., SDGs)
- Advances in treatment resulting in greater awareness of viral hepatitis and access issues
- Continued limited global and country funding
- So much to do: we have just started scratching the surface
- First time global hepatitis targets are being developed: vision towards elimination by 2030

WHO's role in improving access

World Hepatitis Day
Assistance with national planning
Improved prevalence estimates

Treatment Guidelines
Prequalification of medicines
Essential Medicines List
Price Reporting Mechanism
Advocacy, guidance and technical assistance for improved treatment access



Prequalification of diagnostics
Screening/ testing guidelines

Prevention, including
Injection safety
Hospital infections
Safe blood products
Needle sharing programmes

World Health Organization