APASL STC – Tashkent – June 4, 2025

Test and treat early to prevent cancer
Hepatitis B and Hepatitis C

Francesco Negro

Emeritus Professor

Formerly at the Departments of Medicine and of Pathology and Immunology

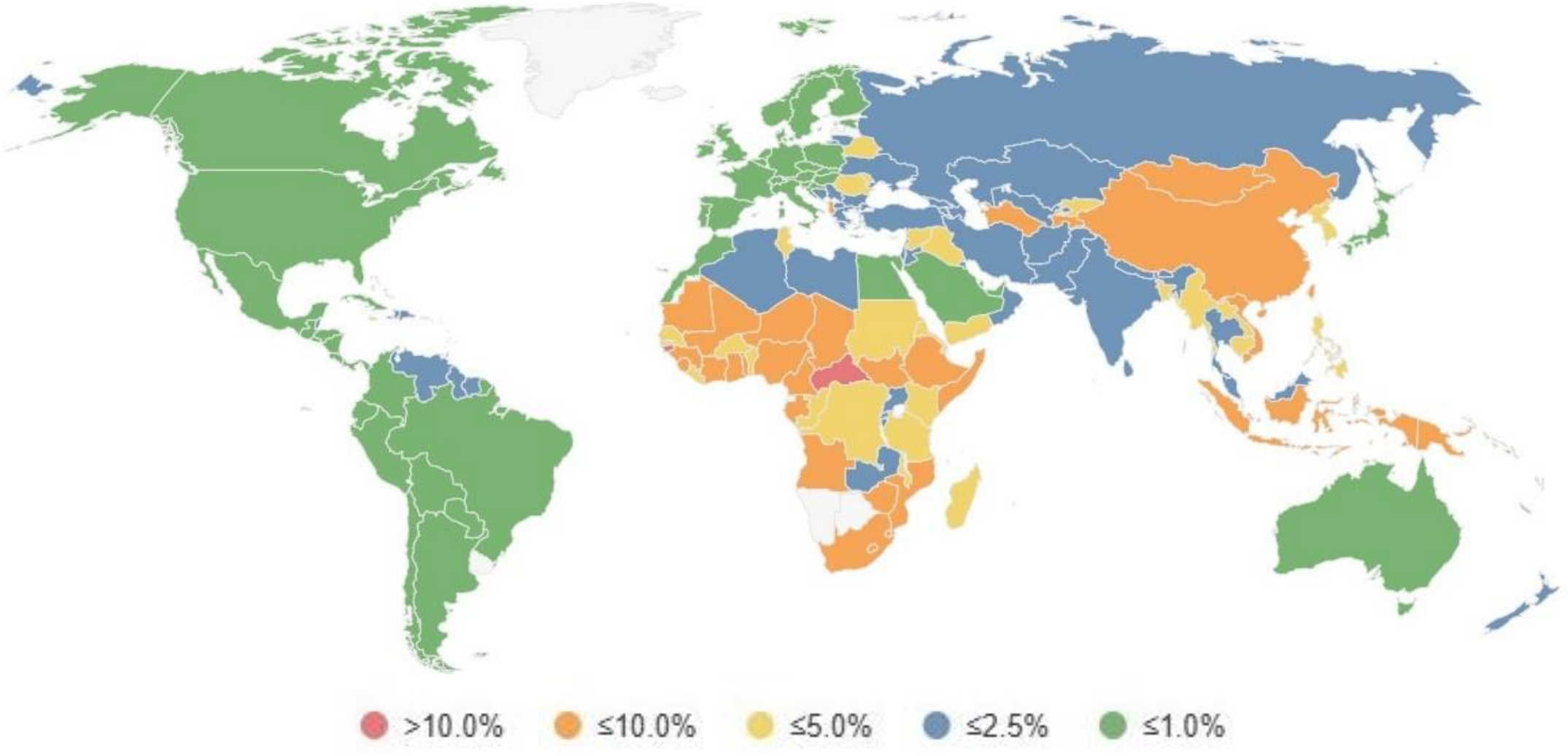
Faculty of Medicine, University of Geneva, Switzerland

Disclosures

- I have nothing to disclose

Global burden of hepatitis B

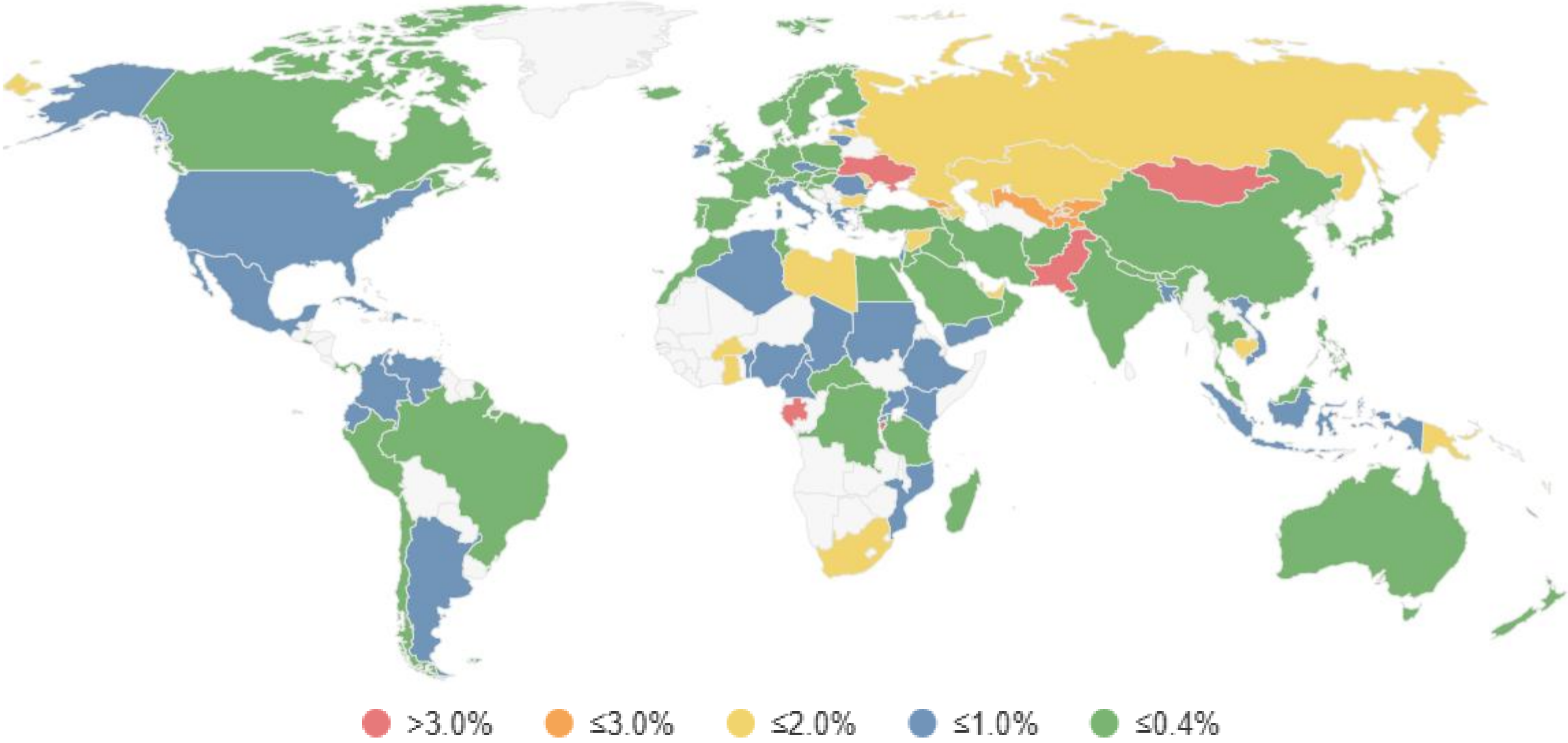
HBsAg prevalence: 3%, or 248 million infected



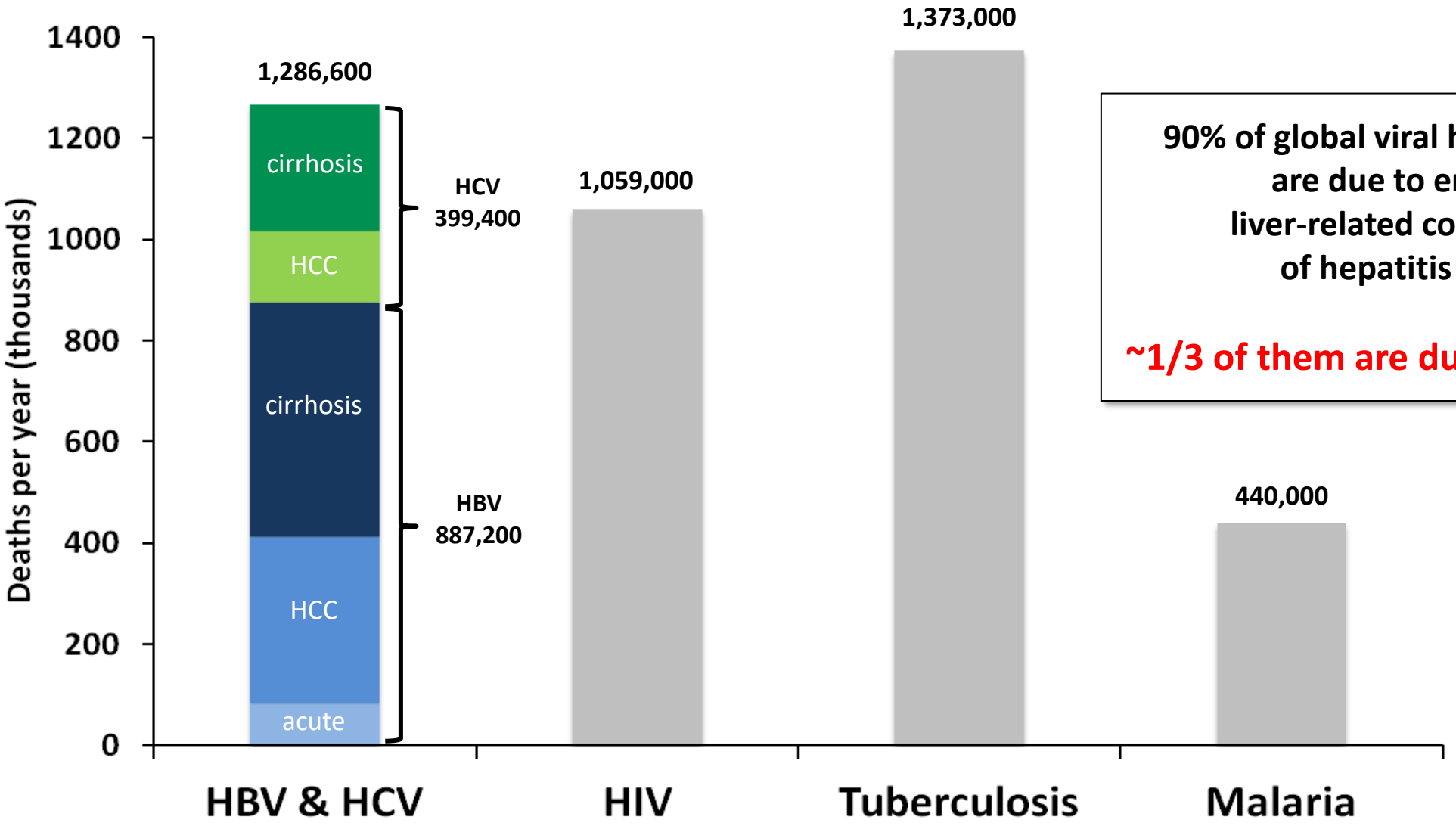
https://cdafound.org/polaris/dashboard/

Global burden of hepatitis C

HCV RNA prevalence: ~1%, or 51.3 million infected



https://cdafound.org/polaris/dashboard/



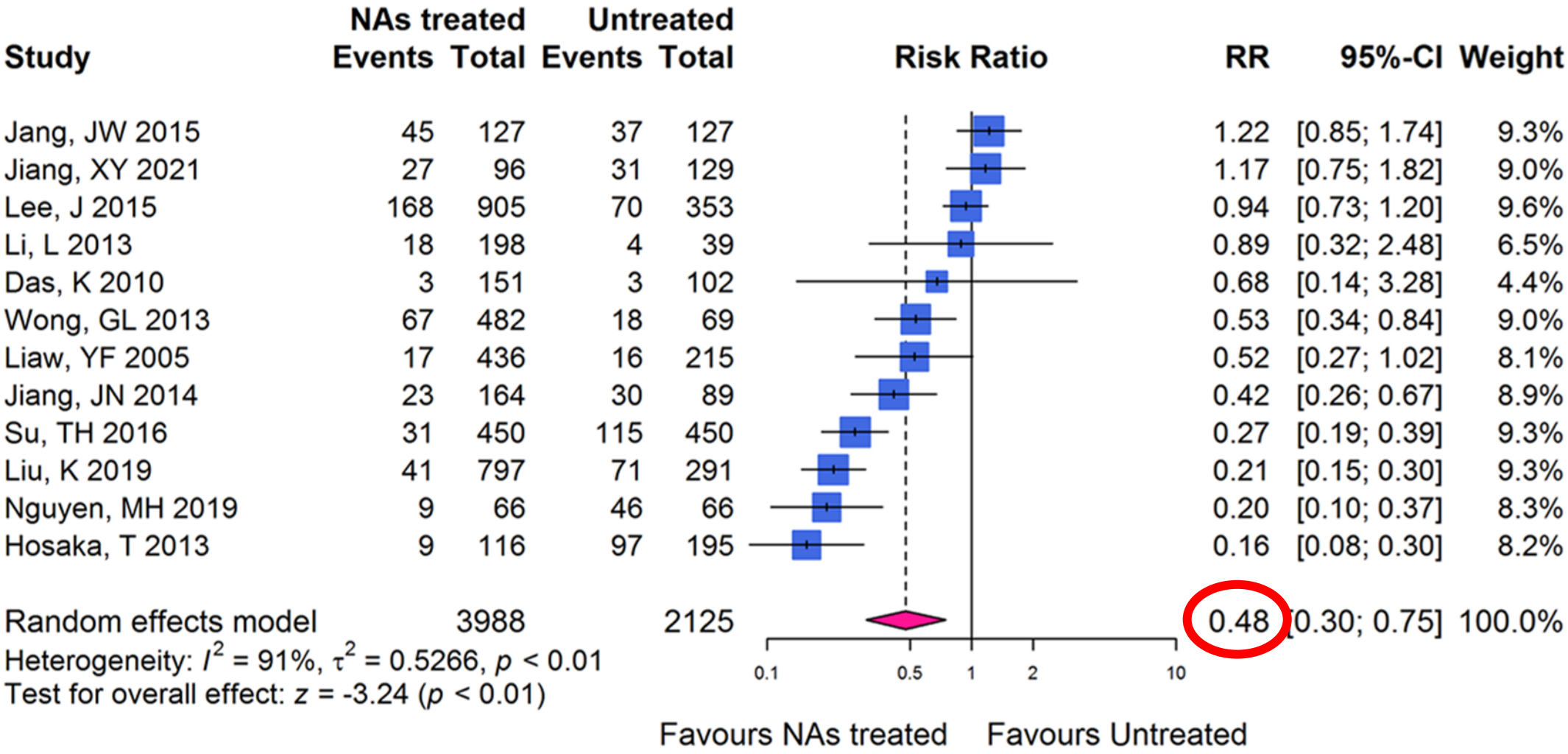
90% of global viral hepatitis deaths are due to end-stage liver-related complications of hepatitis B and C

~1/3 of them are due to liver cancer

WHO 2017 Global Hepatitis Report

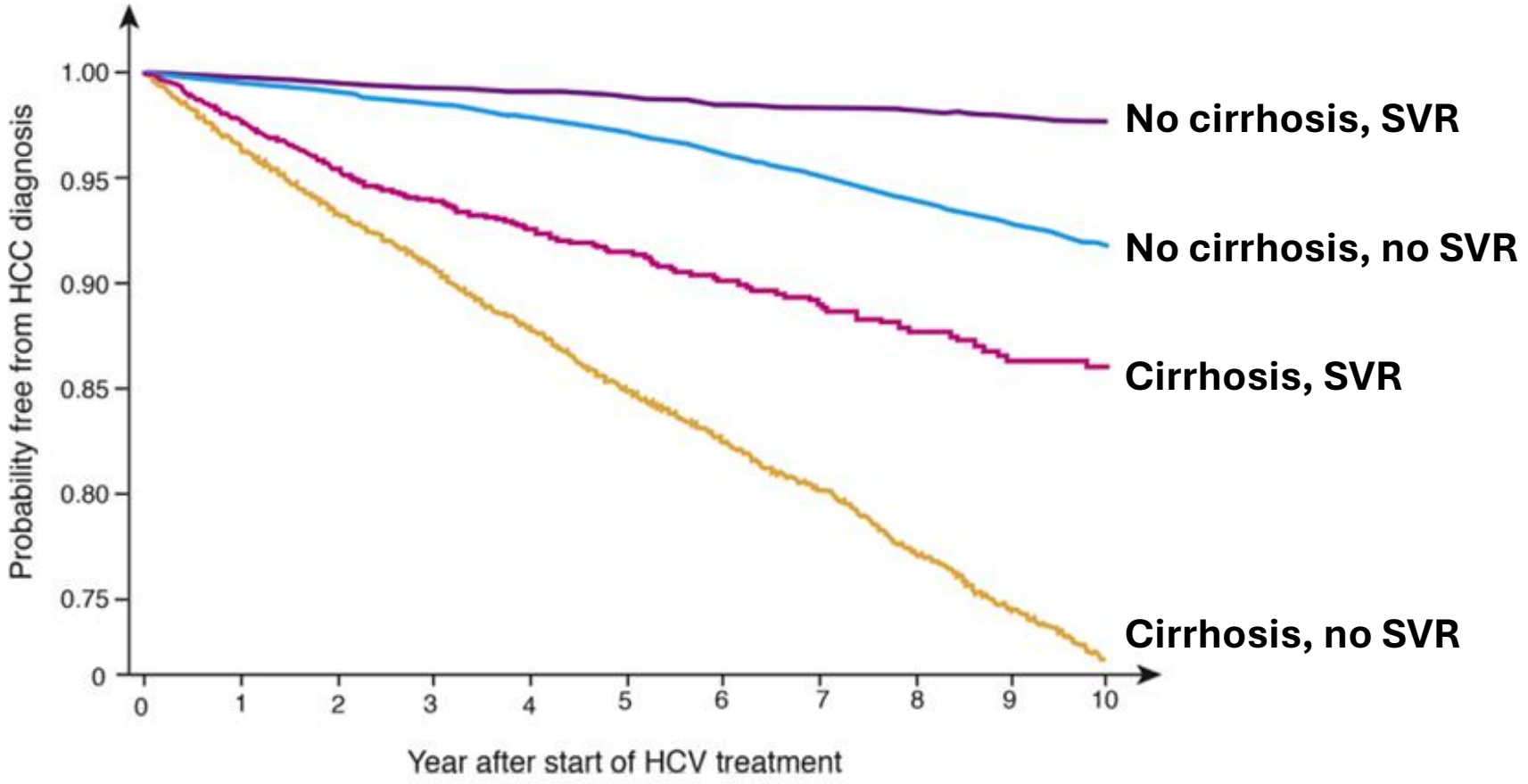
HCC incidence in nucleos(t)ide analogue-treated *vs* untreated hepatitis B

A meta-analysis on 12 studies



Kong Y, *et al.* Hepatol Int 2022;16:1052–1063

Residual risk of HCC after HCV eradication (SVR) in 25,424 Veterans treated with direct-acting antivirals, by cirrhosis status



DAA-induced SVR is associated with a 71% reduction in HCC risk

Ioannou GN, Feld JJ. Gastroenterology 2019;156:446-460.e2

The European Code Against Cancer (ECAC) #4

- In 2012, the International Agency for Research on Cancer (IARC) (an authoritative intergovernmental agency belonging to the WHO) classified HBV and HCV as ***class 1 carcinogens***[1]
- In 2014, IARC emitted recommendations to prevent HPV-associated cervical cancer and HBV-associated liver cancer through ***vaccination*** (ECAC4)[2]
- Current ECAC4 do not include preventive or treatment measures for hepatitis C

1. IARC. List of Classifications: Agents classified by the IARC Monographs. Available from: https://monographs.iarc.who.int/list-of-classifications
2. IARC: European Code Against Cancer (2014). Available from: https://cancer-code-europe.iarc.fr/index.php/en/

The European Code Against Cancer (ECAC) #4

- The role of testing to prevent chronic HBV infection and its long-term sequelae was not considered in the recommendations, although the Discussion section mentioned that persons ***at risk of chronic HBV*** should seek medical advice about testing and ***treated if indicated***[1]
- **HBV risk factors** were based on international guidelines:[2-4]
  - People born or brought up in a country with an intermediate or high prevalence (≥2%) of chronic hepatitis B
  - Babies born to mothers who are HBV carriers
  - People who have ever injected drugs
  - Men who have sex with men
  - Anyone who has ever had unprotected sex
  - Anyone (especially babies and children under the age of 10) subject to close contacts with carriers (i.e., where there is a risk of transmitting the infection through blood or body fluids, including family members, close friends, household contacts or sexual partners
  - Healthcare workers

1. Villain P, et al. European Code against Cancer 4th Edition: Infections and Cancer. Cancer Epidemiol 2015;39 Suppl 1:S120-38
2. Hepatitis B and C Testing: People at Risk of Infection, NICE Guidelines: https://www.nice.org.uk/guidance/ph43
3. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. J Hepatol 2012;57:167-185
4. M.L. LeFevre. Screening for hepatitis B virus infection in nonpregnant adolescents and adults: USPSTF recommendation statement. Ann Int Med 2014;161:58-66

What about testing for HCV?

- International recommendations have traditionally promoted three screening strategies:
  - ➢Risk-based[1,2]
    - Typically, all those at risk of blood borne infections
    - High-risk sexual activities
    - Newborns of anti-HCV-positive mothers
    - People born in HCV endemic countries
  - ➢Birth cohort-based[3-6]
    - US: baby boomer "birth cohort" of individuals born 1945-1965, covering ~75% of HCV infections in the USA despite representing only 27% of the general population (irrespective of symptoms or risk factors)
  - ➢Opportunistic screening (e.g., colonoscopy, ED)[6]

1. https://iris.who.int/; 2. https://www.ecdc.europa.eu/
3. Smith BD, *et al*. Ann Intern Med 2012;157:817–822; 4. Smith BD, *et al*. MMWR Recomm Rep 2012;61:1–32
5. Moyer VA, *et al*. Ann Intern Med 2013;159:349–357; 6. Tsay CJ, Lim JK. J Clin Transl Hepatol 2020;8:25-41

Hepatitis B Cascade of Care, per WHO Region: Prevalence, Diagnosis and Immunization Rates (2022)

WHO Region	Modelled prevalence	HBsAg+ population	Diagnosed	Prevalence of HBsAg+ in children (<5 yrs)	Timely birth dose	3 doses <1 year of age
Africa	5·4%	64 778 000	2 610 000 (4%)	**1·7%**	**14%**	82%
Eastern Mediterranean	1·9%	15 200 000	2 332 000 (15%)	**0·4%**	**35%**	87%
Europe	1·2%	11 554 000	2 293 000 (20%)	**<0·1%**	57%	91%
Americas	0·5%	5 101 000	1 066 000 (21%)	**<0·1%**	54%	80%
Southeast Asia	3·0%	61 391 000	1 678 000 (3%)	**0·6%**	65%	83%
Western Pacific	5·1%	99 494 000	26 062 000 (26%)	**0·3%**	80%	90%

Globally: ~14%

Polaris Observatory Collaborators. Lancet Gastroenterol Hepatol 2023;8(10):879-907

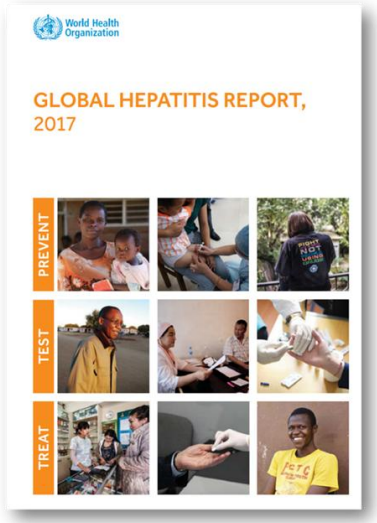
Hepatitis C Cascade of Care, per WHO Region: Prevalence and Diagnosis Rate (2023)

WHO Region	Prevalence	Anti-HCV+	Diagnosed
AFRO	1%	8 722 941	**9%**
EMRO	2%	12 073 671	**25%**
EURO	1%	8 714 800	**24%**
SEARO	<1%	9 369 609	**9%**
PAHO	1%	5 383 703	**22%**
WPRO	<1%	7 050 173	**40%**

Global diagnosis rate: ~21%

https://cdafound.org/polaris/dashboard/

Interim progress towards global viral hepatitis targets (2022)



Indicator	2015	2020	2022	2025 target	2030 target
New HBV infections, py	**N/A**	**1,500,000**	**1,230,000**	**850,000**	**170,000**
New HCV infections, py	**1,750,000**	**1,030,000**	**980,000**	**670,000**	**240,000**
HBV deaths, py	**904,000**	**820,000**	**1,100,000**	**530,000**	**310,000**
HCV deaths, py	**390,000**	**290,000**	**244,000**	**170,000**	**100,000**

Global hepatitis report 2024. Geneva: WHO 2024

Viral hepatitis: finding the missing ones to prevent liver cancer

- Risk-based strategies have failed to identify most chronic hepatitis B and C patients, even in high income countries
- Most chronic HBV infections are established at birth or during the first 5 years of life, thus excluding birth cohort screening strategies for HBV
- Birth cohort screening strategies for HCV have identified most infected persons only in specific settings
- Given the current efficacy and safety of antiviral therapies, is universal screening a feasible, alternative strategy?

The evidence from Cost-Effectiveness Analyses

At an estimated **0.24% prevalence** of undiagnosed chronic hepatitis B, universal HBsAg screening in US adults aged 18-69 years is **cost-saving**

(Markov model, compared to current practice, with a treatment drug costs <894 USD/year)

Table 2. Clinical Outcome and Cost-Effectiveness of 1-Time Universal Hepatitis B Surface Antigen Screening for Chronic Hepatitis B Compared With Current Practice for a Population of 100 000 Persons Aged 18–69 Years

Scenarios	Cirrhosis	Decompensated Cirrhosis	Hepatocellular Carcinoma	Transplants	Hepatitis B Virus Deaths	Cost[a]	Quality-Adjusted Life-Years	Incremental Cost-Effectiveness Ratio
CP	24.9	7.6	23.9	8.0	38.0	8 747 703	2 062 384	-
CP + 1-time universal screening	17.5	4.3	18.4	6.1	27.7	8 484 846	2 062 521	-
Difference	−7.4	−3.3	−5.5	−1.9	−10.3	−262 857	+137	Cost-saving

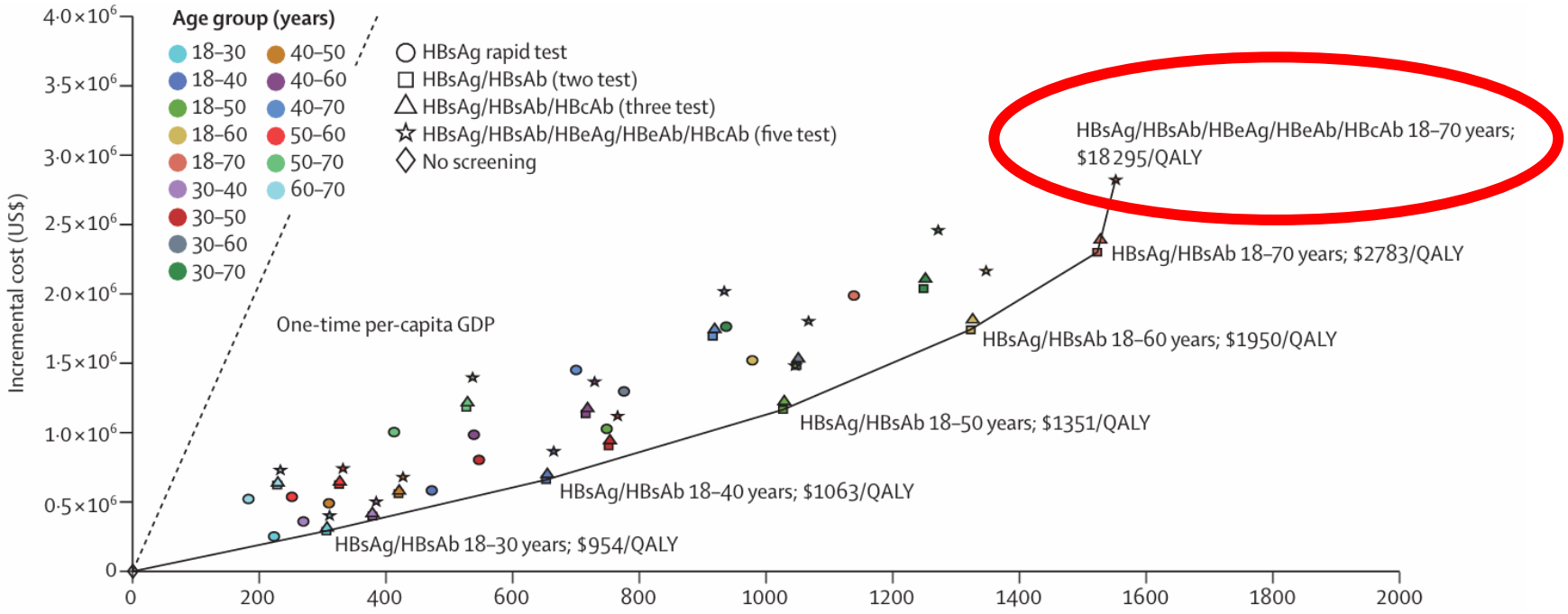
Abbreviation: CP, current practice.

The US CDC has recommended
to screen for hepatitis B at least once during a lifetime all adults aged ≥18 years

Toy M, *et al.* Clin Infect Dis 2022;74:210–7
Testing for Hepatitis B Virus Infection: CDC Recommendations - US, 2023. MMWR Recomm Rep 2023;72:1-25

Based on a **5.1% prevalence, universal HBV screening** in people aged 18-70 years during the next 10 years, is **cost-effective**

(Markov model, compared to status quo, WTP 3xGDP per capita = 30 828 USD)



CSH/CSM/CSID: HBsAg screening should be performed in the general population, especially in those at high-risk and women of pregnancy or childbearing age

Su S, *et al.* Lancet Glob Health 2022;10:e278-e287

You H, *et al,* Chinese Society of Hepatology, Chinese Medical Association; Chinese Society of Infectious Diseases, Chinese Medical Association. J Clin Transl Hepatol 2023;11:1425-1442

Universal screening for HBV is **cost-effective**, provided that the cost of testing is low and that >50% of patients are properly managed

(Markov model, compared to current practice)

Outcome	Current practice	Test cost low 50% managed
Care cascade for people with chronic hepatitis B (2030): proportion (IQR)		
Diagnosed	82% (80–86%)	90% (88–93%)
Receiving appropriate clinical management	35% (33–38%)	50% (47–52%)
Health impact (IQR)		
New hepatocellular carcinoma cases (2030)	633 (457–802)	593 (426–741)
Deaths attributed to chronic hepatitis B (2030)	709 (548–912)	649 (506–830)
Cumulative HBV-related deaths (2020–2030)	6093 (5634–8235)	5788 (5372–7818)
HBV-related deaths averted (*v* scenario 1)	—	315 (211–454)
Reduction in HBV-attributable mortality (*v* scenario 1)	—	5% (4–6%)
Incremental cost effectiveness ratio (cost per QALY gained)	—	$47 341 (32 643–58 200)

Xiao Y, et al. Med J Aust 2023;218:168-173

In the US, universal screening for HCV followed by DAA treatment is cost-effective (at a prevalence of 0.07%)

Table 2. Results of Base-Case Analysis of Sofosbuvir/Velpatasvir

Strategy	Cost, $	Effectiveness, QALYs	Incremental cost, $	Incremental effectiveness, QALYs	Incremental cost effectiveness, $/QALY
Discount, 3%/y					
Birth cohort screening	363.15	17.7441			
Universal screening	388.19	17.7463	25.04	0.0022	11,378.00
Do not screen	426.81	17.7362	38.62	-0.0101	Dominated
Results of base-case analysis: glecaprevir/pibrentasvir					
Birth cohort screening	405.65	17.7441			
Do not screen	426.81	17.7362	21.16	-0.0079	Dominated
Universal screening	433.23	17.7463	27.58	0.0022	12,515.87

Cost of anti-HCV 19.57 USD; HCV RNA 58.76 USD; SOF/VEL 3 mos. = 24,270 USD; GLE/PIB 3 mos. = 29,490 USD

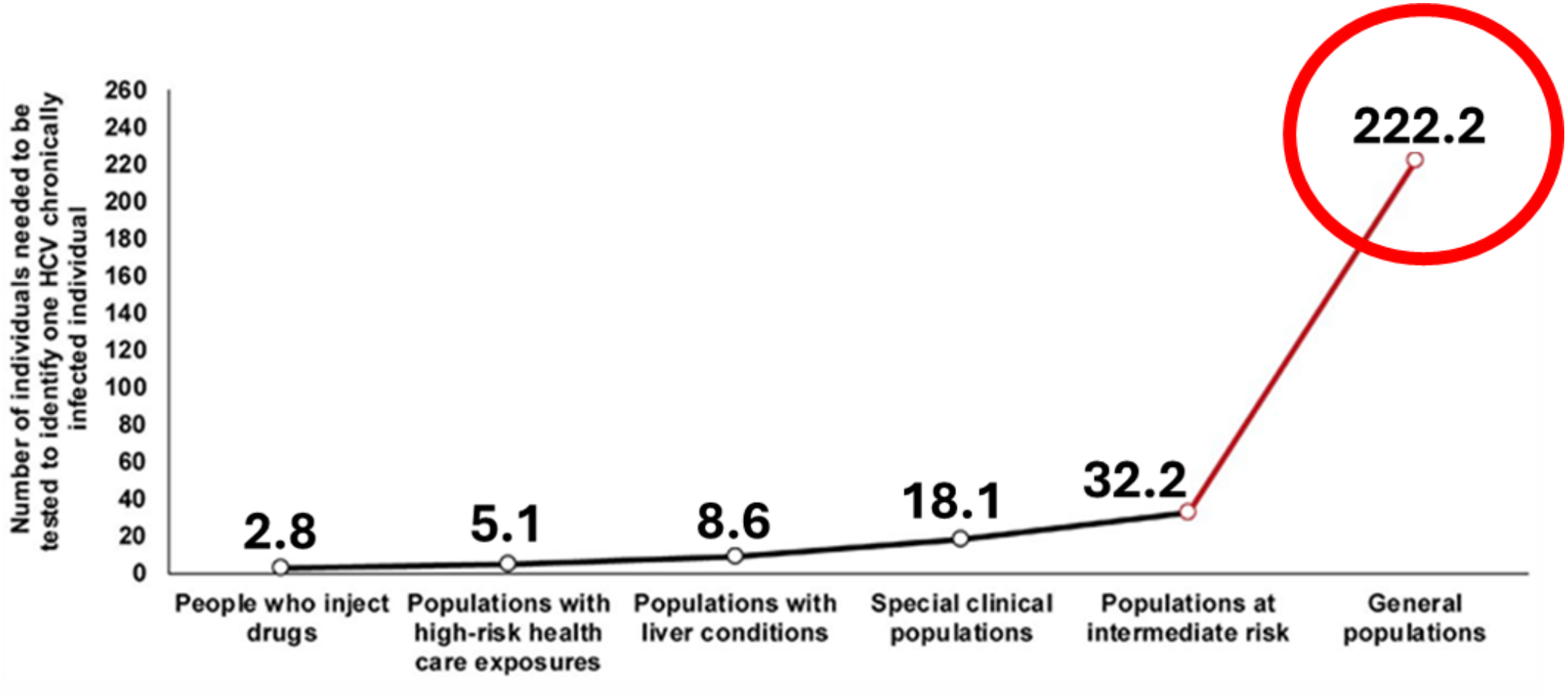
The US CDC has recommended to screen for hepatitis C at least once during a lifetime all adults and all those who request it (irrespectively of risk factors)

Eckman MH, *et al.* Clin Gastroenterol Hepatol 2019;17:930-939.e9

Can we spin universal HBV and HCV screening?

Playing in favor	Playing against
Cost-effective, based on Markov models Effective treatments (and future medicines for HBV may lead to functional cure) People do not like to share stigmatizing behaviors (risk factors for HBV and HCV) Tests are simple and can be easily integrated in other screening strategies	Lack of empirical evidence Sensitive to prevalence, cost of diagnostics and antivirals, and treatment uptake Hyperbolic discounting bias (significant upfront costs vs uncertain benefits in the distant future) Unaccounted costs: awareness campaigns and GP education for proper counseling Inefficient testing program yields in low-risk population segments

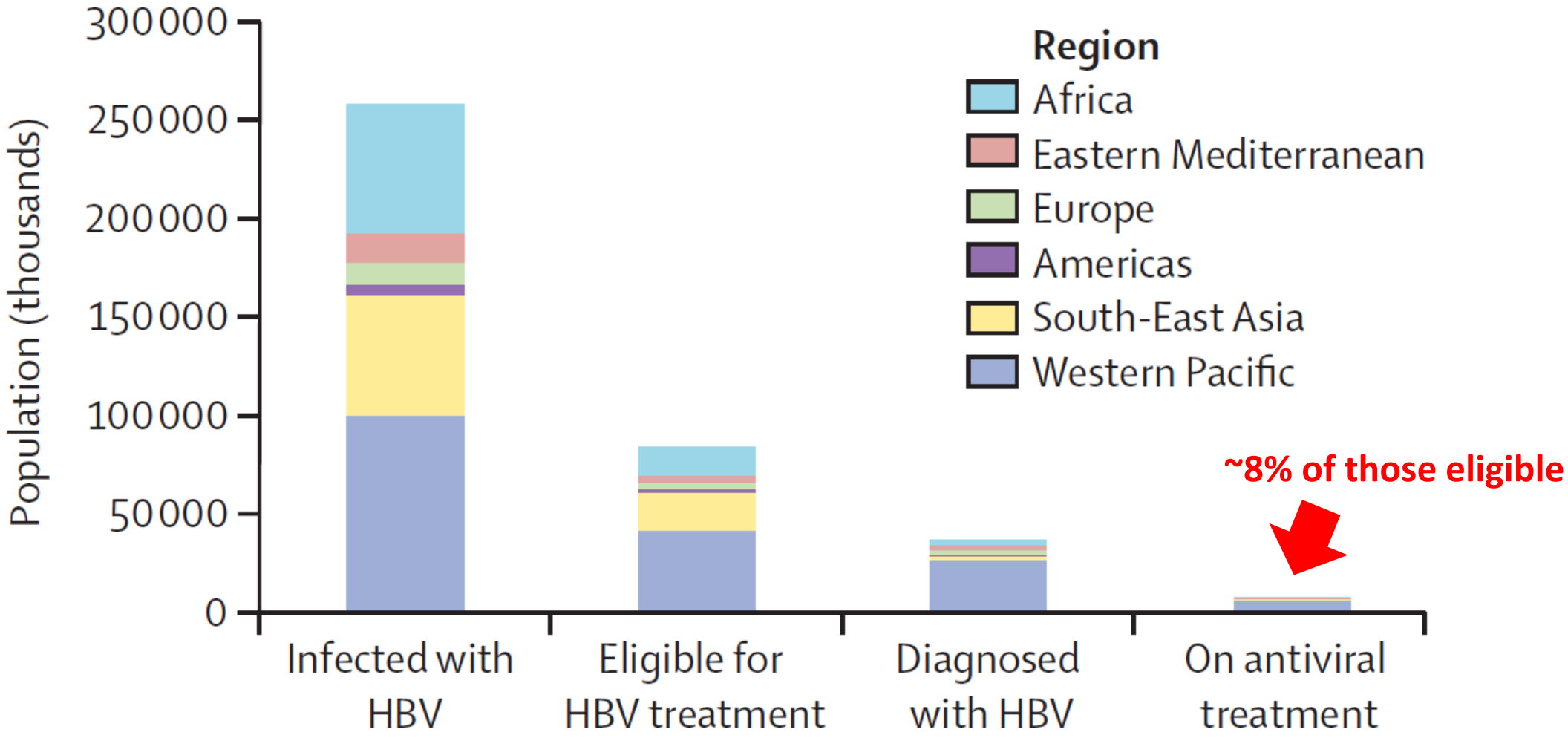
In low prevalence countries (e.g., <3%), the Number Needed To Test (testing yield) may be TOO HIGH to find all HCV-infected patients



Chemaitelly H, *et al.* Hepatol Commun 2019;3:325-339

OK about testing, and then?

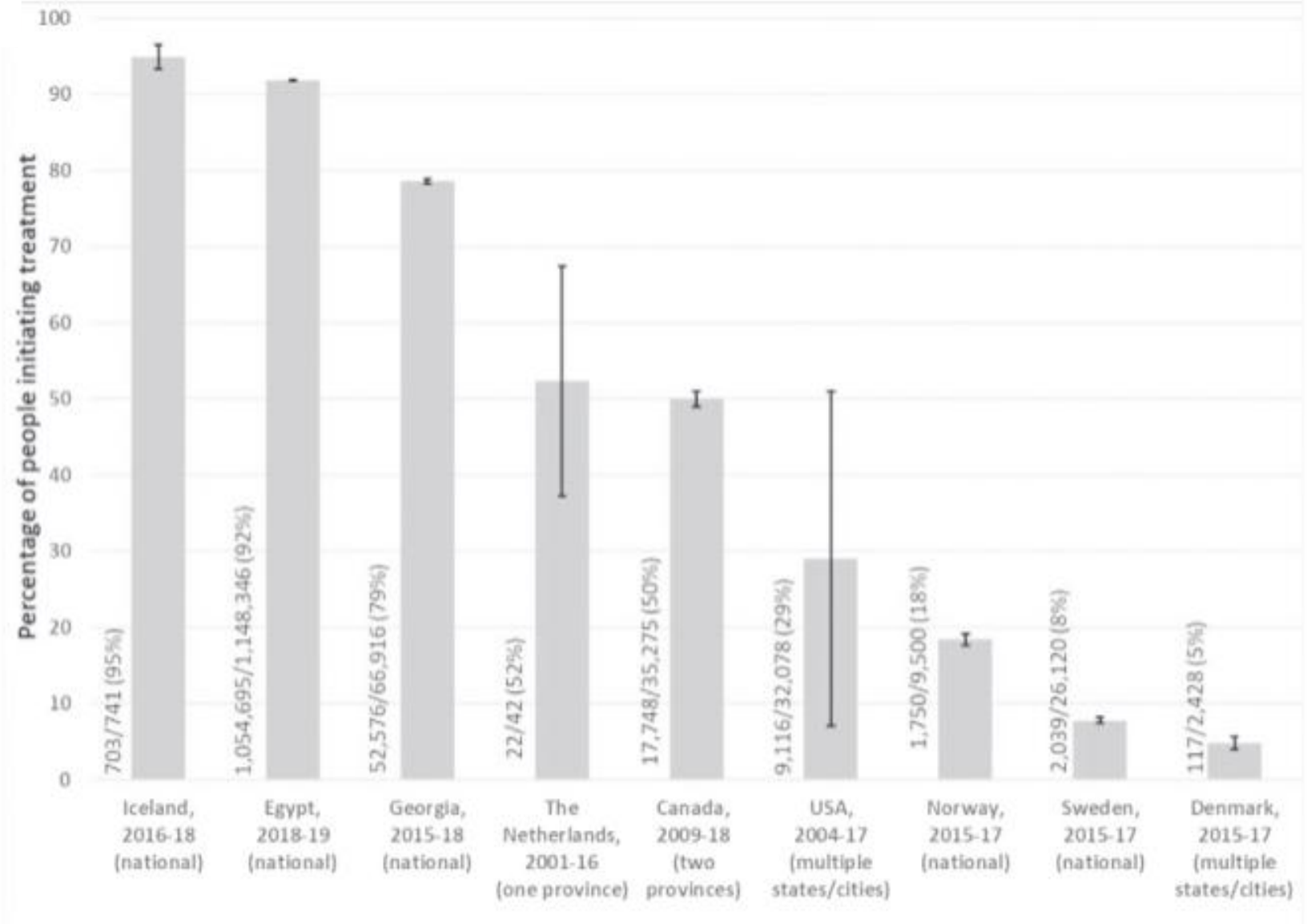
Global and regional HBV infection cascade of care, 2022



Polaris Observatory Collaborators. Lancet Gastroenterol Hepatol 2023;8(10):879-907

The continuum-of-care conundrum

Proportion of individuals diagnosed with HCV who received DAA treatment among the general population



Yousafzai MT, *et al*. J Viral Hepat 2021;28:1340-1354

What about alternative test-and-treat models?

- Four-phase program among migrants

Coppola N, *et al.* Infect Dis Poverty 2024;13:39

- One-site one-visit, test-and-treat community program for HBV and HCV

Shiha G, *et al.* J Viral Hepat 2020;27:593-601

- Same day test-and-treat for HCV among high-risk settings (PWID, prison inmates, homeless, HIV+ MSM)

Suan MAM, *et al.* BMC Public Health 2025;25:1152; Rajkumar N, *et al.* Harm Reduct J 2024;21:98

Morris MD, *et al.* JAMA Netw Open 2023;6:e2338792; Grebely J, *et al.* Int J Drug Policy 2023;114:103982

Forns X, *et al.* J Viral Hepat 2022;29:227-230; Supanan R, *et al.* J Acquir Immune Defic Syndr 2021;88:465-469

Strong political will at work: the case of Egypt

- HCV elimination plan launched in 2014[1]
  - Awareness campaign
  - Comprehensive national program to screen the entire adult population (~62.5 million) and teenage school-children in middle and high schools (~12 million)
  - WHO pre-qualified rapid assay for anti-HCV (USD 0.56/assay) on capillary blood
  - Locally produced, low cost generic DAAs
- HCV prevalence decreased from 6% (2015) to 0.5% in 2021[2]
- HCC attributable to HCV from ~4,800 py (2018) to 2,200 py (2024)[3]
- Mortality attributable to HCV from ~27,000 py (2018) to ~11,000 py (2025)[3]

1. Waked I. Antivir Ther 2022;27:13596535211067592
2. Gomaa A, *et al*. Pathogens 2024;13(8):681
3. Hassany M. EASL/WHO/ECDC Symposium, Amsterdam, May 8, 2025 (easl.eu)

In a high prevalence country, treatment initiation is sub-optimal and may impact elimination programs

HepFreePak observational study, n=25,000, free SOF/DAC plus incentives to attend visits

Site	Model	Tested	HCV RNA+	Started therapy	Came to check SVR	Achieved SVR
Malir	Door-to-door case finding	14,612	930 (6.4%)	713 (77%)	633 (89%)	563 (89%) **(60.5% of HCV+)**
Karachi	Urban clinic and community testing events	2,828	242 (8.6%)	227 (94%)	157 (69%)	151 (96%) **(62.4% of HCV+)**
Gujranwala	Community camp test-and-treat	3,609	246 (6.8%)	178 (72%)	76 (42%)	72 (95%) **(29.3% of HCV+)**

Hasnain A, *et al.* EASL 2025, J Hepatol 2025;82(S1):S687

Reinfection rate 12 months after SVR12: 1/530 (0.18%), 3/189 (1.6%), 8/94 (8.5%)

Niaz S, *et al.* EASL 2025, J Hepatol 2025;82(S1):S708

WHAT IS TO BE DONE?

- Risk-based strategies have failed to identify the majority of chronic hepatitis B and C patients globally
- The availability of low-cost diagnostics and very effective antivirals should prompt more aggressive screening strategies
- CEAs (but not empirical evidence) support the extension of screening to all adults, irrespective of risk factors, to prevent HCC
- Low prevalence, poor testing yield, and high costs of diagnostics and treatments are playing against policy
- Integrated screening may be more efficient and acceptable
- The cascade of care remains a challenge