The European Code Against Cancer (ECAC): The need for updating EU Council Recommendations for public and policy makers to prevent HCC

Hepatitis B

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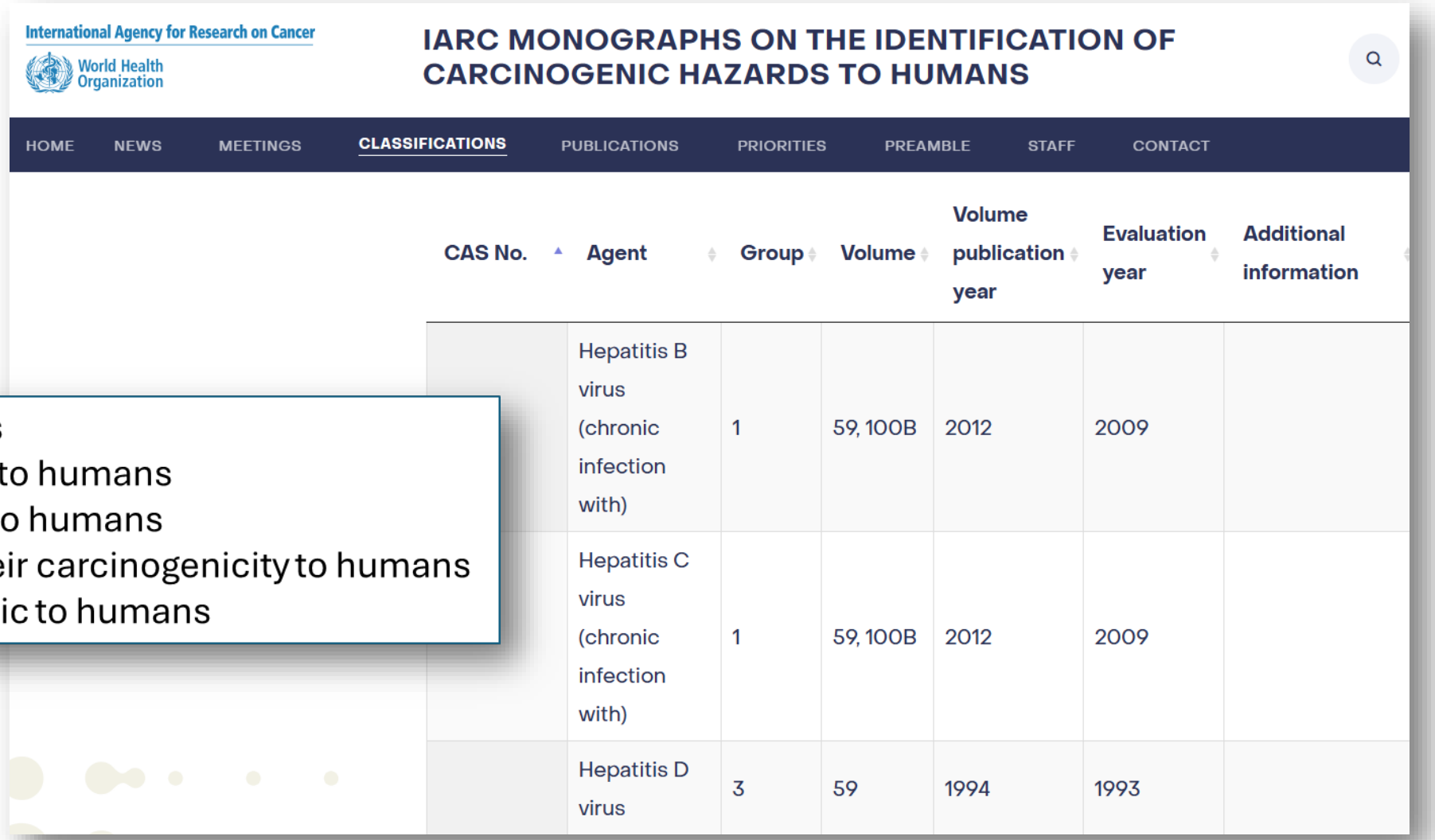
Disclosures: nothing to declare

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 as ***class 1 carcinogen***[1]
- In 2014, IARC emitted recommendations to prevent some infection-related cancers (i.e., HBV-associated cervical cancer and HBV-associated liver cancer) (ECAC4)[2]

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/



CAS No.	Agent	Group	Volume	Volume publication year	Evaluation year	Additional information
	Hepatitis B virus (chronic infection with)	1	59, 100B	2012	2009	
	Hepatitis C virus (chronic infection with)	1	59, 100B	2012	2009	
	Hepatitis D virus	3	59	1994	1993	

1 = Carcinogenic to humans
2A = Probably carcinogenic to humans
2B = Possibly carcinogenic to humans
3 = Not classifiable as to their carcinogenicity to humans
4 = Probably not carcinogenic to humans

https://monographs.iarc.who.int/list-of-classifications

European Code Against Cancer

12 WAYS TO REDUCE YOUR CANCER RISK

- TOBACCO
- SECOND-HAND SMOKE
- HEALTHY BODY WEIGHT
- PHYSICAL ACTIVITY
- DIET
- SUN/UV EXPOSURE
- POLLUTANTS
- RADIATION
- BREASTFEEDING
- HORMONAL THERAPY
- VACCINATION AND INFECTIONS

Ensure your children take part in vaccination programmes for:

- **Hepatitis B (for newborns)**
- **Human papillomavirus (HPV) (for girls).**

Few people associate infection with cancer, but nearly one-fifth of all cancers in the world are caused by infectious agents, including viruses and bacteria. Among the most important infections associated with cancers are human papillomaviruses (HPVs) which can cause most cervical and anal cancers as well as a fraction of oral cancers; hepatitis B virus (HBV) and hepatitis C virus (HCV), which can cause liver cancer; and Helicobacter pylori, which is a bacterium that can cause cancer of the stomach. Human immunodeficiency virus (HIV) infection does not cause cancers directly but people with HIV have a greater risk of developing certain cancers because their immune systems are weakened. Vaccines are the most effective way of preventing some of these infections. Highly effective vaccines against HBV have been available for several decades and most countries include HBV vaccination in their childhood immunization programmes; vaccination is also highly effective in preventing infection with the HPV types that cause the majority of cervical cancers.

https://cancer-code-europe.iarc.fr/index.php/en/

Rationale for the ECAC4 recommendations

Reference	Population	Results
Chiang CJ, et al (2013)	Birth cohort born in 1981-1984 *vs* 1977–1980 (Taiwan)	RR 0.70, 95%CI 0.59–0.83 of HCC mortality RR 0.73, 95%CI 0.63–0.85 of HCC incidence
Sun Z, et al (2013)	Liver cancer incidence rates in 2005-2008 *vs* 1980–1983, Qidong, China	Incidence decreased 1.9-fold at ages 0–19, 14-fold at ages 20–24, 9-fold at ages 25–29, 4-fold at ages 30–34, 1.5-fold at ages 35–39, 1.2-fold at ages 40–44 and 1.4-fold at ages 45–49
Tajiri H, et al (2011)	HCC *vs* hepatoblastoma incidence ratio (2001–2005 *vs*1986–1990) (Japan, nationwide)	Incidence ratio decreased from 0.214 to 0.124 (P = 0.006)
McMahon BJ, et al (2011)	Universal newborn vaccination among Alaskan native people	HCC incidence in persons <20 years of age from 3/100,000 in 1984–1988 to zero in 1995–1999
Mendy M, et al (2013)	Infant HBV vaccination started in two Gambian villages in 1984	24 years after vaccination, vaccine efficacy against chronic HBV infection: 95.1% (95% CI 91.5–97.1%)
Qu C, et al (2014)	RCT of neonatal HBV vaccination, 1983-1990, Qidong County (China)	Risk reduction of the HCC incidence rate 84% (95% CI 23–97%)

The European Code Against Cancer (ECAC) #4

- The role of screening 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]
- Risk factors based on selected 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). This could include the family members, close friends, household contacts or sexual partners of someone known to be chronically infected with hepatitis B
  - 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: U.S. Preventive Services Task Force recommendation statement. Ann Int Med 2014;161:58-66

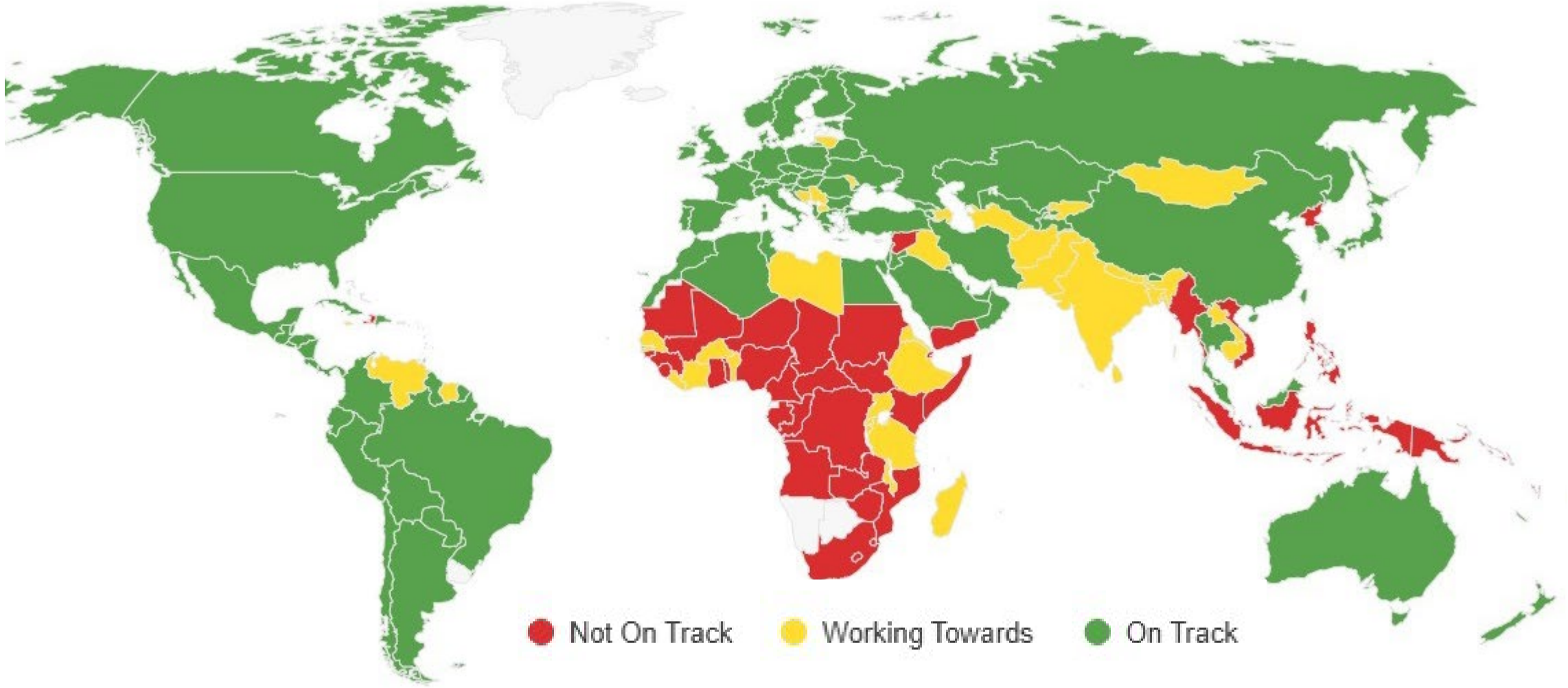
Hepatitis B Cascade of Care, per WHO Region: Prevalence, Diagnosis and Immunization Rates (2022)

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%

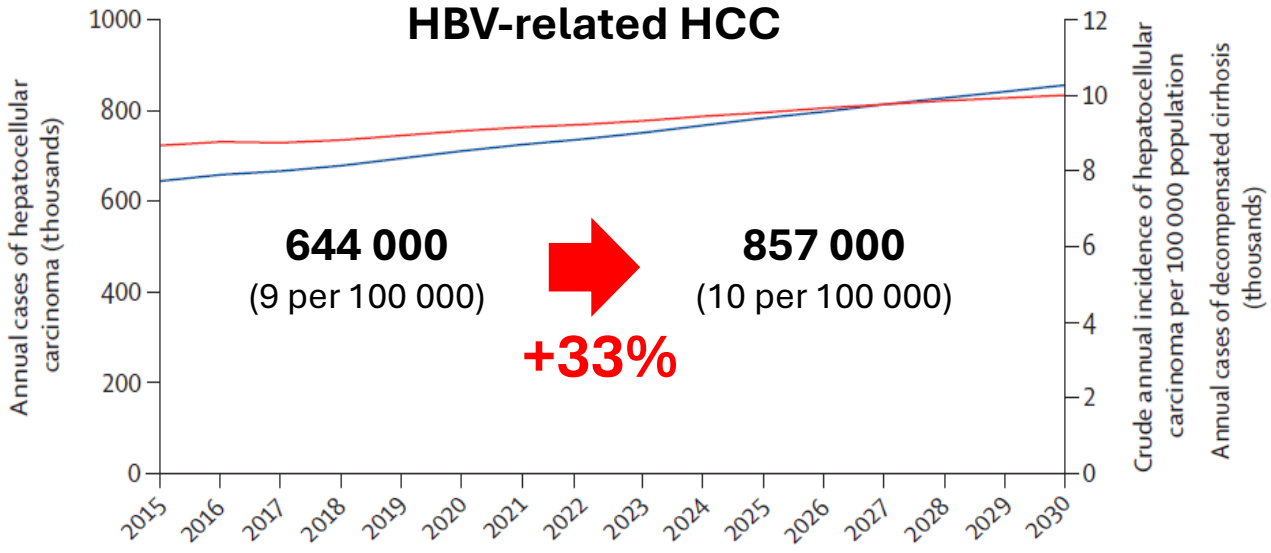
Polaris Observatory Collaborators. Lancet Gastroenterol Hepatol 2023;8(10):879-907

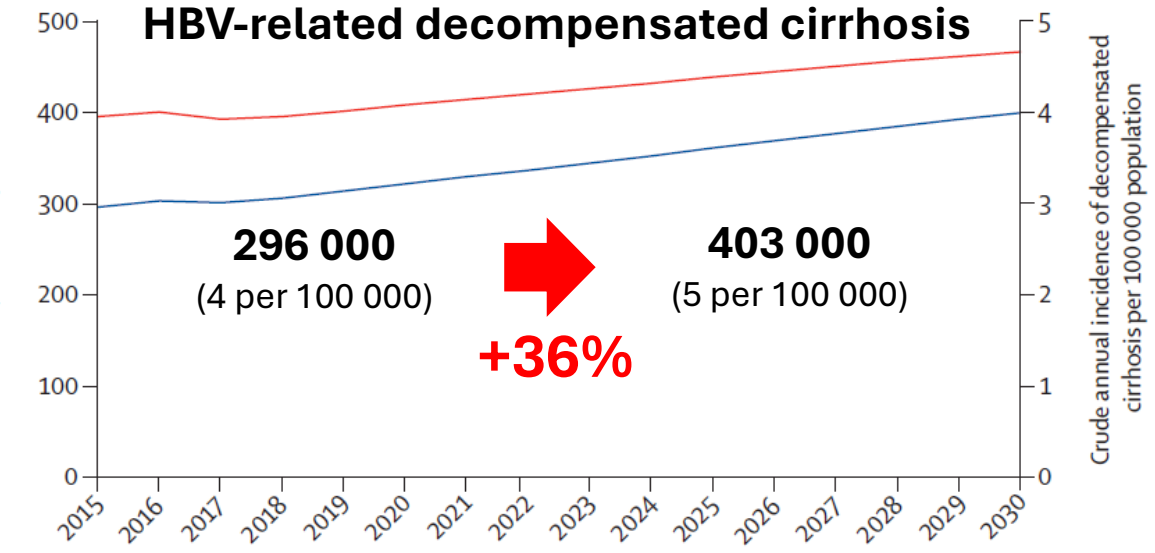
Countries on track to achieve WHO HBV elimination targets in ≤5 years old
(0.1% prevalence)

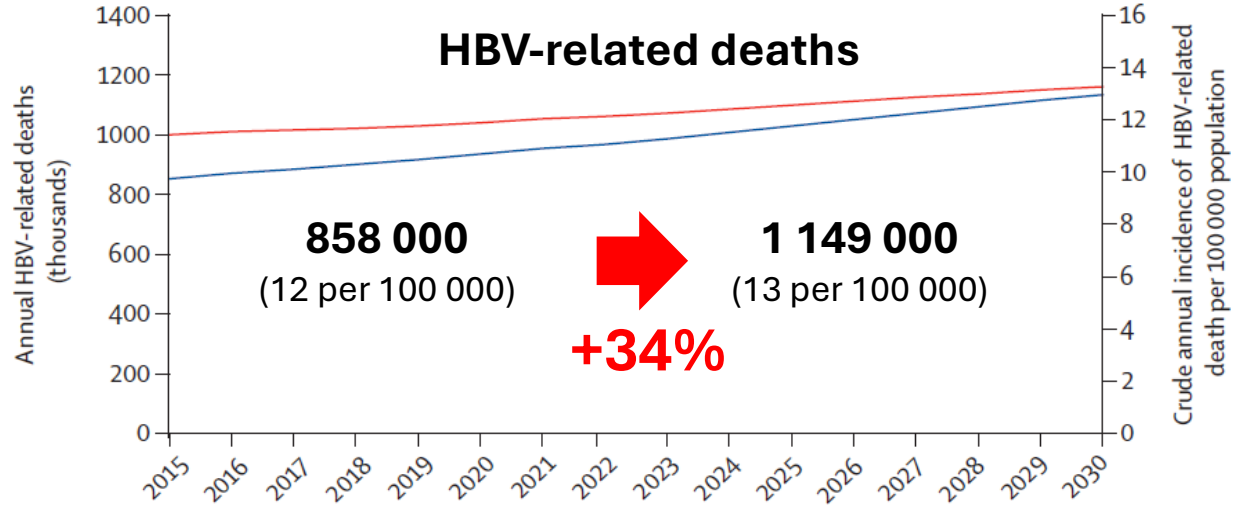


https://cdafound.org/polaris/dashboard/

The burden of HBV: the future cost of status quo







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

Hepatitis B: finding the missing ones (~86%)

Risk-based strategies have failed to identify most chronic hepatitis B 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

Universal screening?

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.

Screen for hepatitis B screening at least once during a lifetime all adults aged ≥18 years

Extend risk groups: persons (formerly) incarcerated, or with (history of) STD/multiple sex partners, and/or HCV

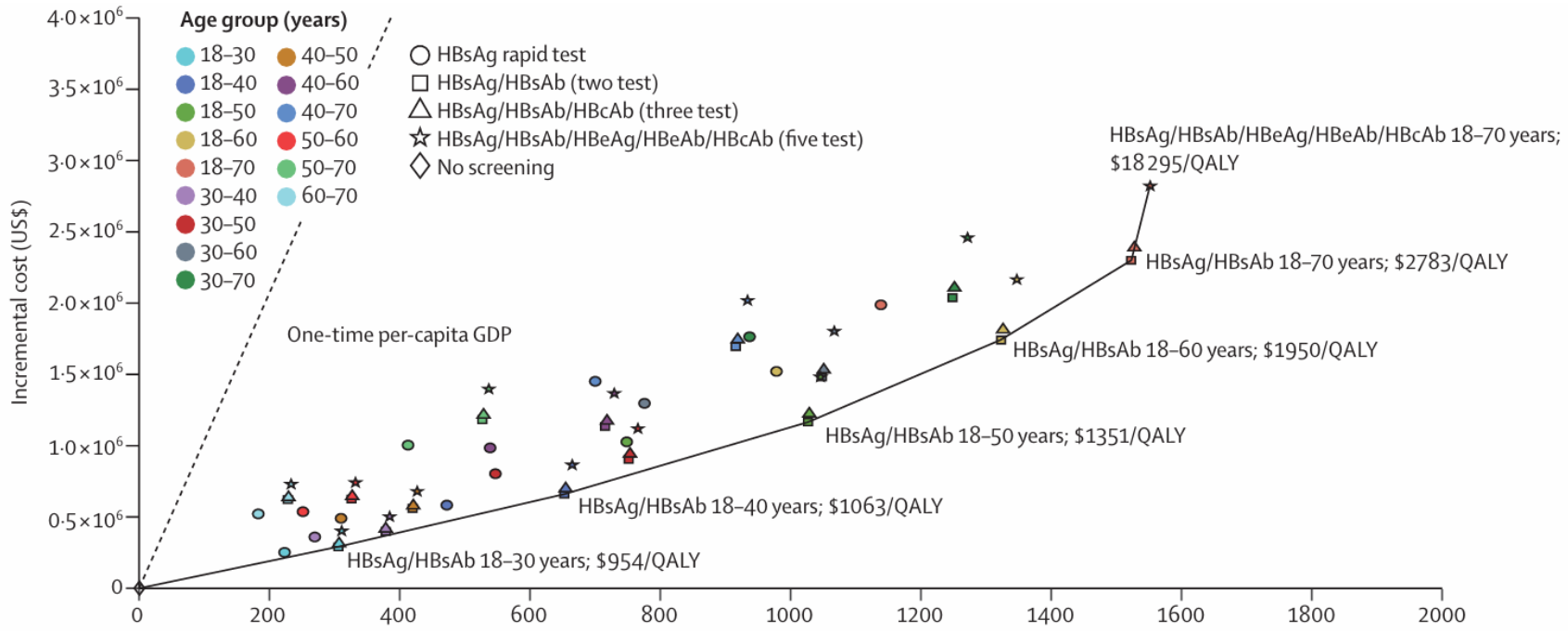
Anyone who requests HBV testing should receive it, regardless of disclosure of risk

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

A five-test universal HBV screening strategy in people aged 18-70 years, implemented within the next 10 years, is cost-effective in China

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



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

Screening the general Australian population for HBV is cost-effective, provided that the cost of testing is low, and at least 50% of patients receive proper management

(Markov model, compared to current practice)

Outcome	Scenario 1	Scenario 2	Scenario 3
Care cascade for people with chronic hepatitis B (2030): proportion (IQR)			
Diagnosed	82% (80–86%)	90% (88–93%)	90% (88–93%)
Receiving appropriate clinical management	35% (33–38%)	37% (35–39%)	50% (47–52%)
Health impact (IQR)			
New hepatocellular carcinoma cases (2030)	633 (457–802)	625 (452–788)	593 (426–741)
Deaths attributed to chronic hepatitis B (2030)	709 (548–912)	697 (535–896)	649 (506–830)
Cumulative HBV-related deaths (2020–2030)	6093 (5634–8235)	6013 (5553–8101)	5788 (5372–7818)
HBV-related deaths averted (*v* scenario 1)	—	80 (41–127)	315 (211–454)
Reduction in HBV-attributable mortality (*v* scenario 1)	—	1% (1–2%)	5% (4–6%)
Incremental cost effectiveness ratio (cost per QALY gained)	—	$104 921 (49 587–107 952)	$47 341 (32 643–58 200)

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

Can we spin universal HBV screening?

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

Criteria to be met for screening hepatitis B and C at the population level (WHO)

Criterion	Hepatitis B	Hepatitis C
Important health problem (irrespective of prevalence)	Yes	Yes
An accepted treatment affecting prognosis is available	Yes	Yes
Facilities for diagnosis and treatment are available	Yes	Yes
Asymptomatic phase	Yes	Yes
Test is suitable	Yes	Yes
Tests are acceptable by the population	Yes	Yes
The natural history of the condition is known and understood	Yes	Yes
Existing treatment guidelines	Yes	Yes
Costs of diagnosis and treatment are balanced vs overall health costs	Yes	Yes
Case finding should be a continuous process rather than a one-time project	Yes	Yes

Wilson JMG, Jungner G, World Health Organization. Principles and practice of screening for disease (1968)
Available from: https://iris.who.int/handle/10665/37650

The need to update screening recommendations

Risk-based strategies have failed to identify ~86% of chronic hepatitis B patients globally

Since most chronic HBV infections are established at birth or during the first 5 years of life, birth cohort screening strategies are futile

CEAs (but not empirical evidence) support the extension of screening to all adults, irrespective of risk factors, to prevent HCC:

- Even in low-prevalence settings (e.g., US, est. 0.24%)
- Provided that at least 50% of HBsAg-positive persons receive proper clinical management