The Case for Hepatitis D virus (HDV) Reflex Testing

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CDA FOUNDATION

CDA Foundation (CDAF) is a non-profit organization with the goal of assisting countries in achieving WHO hepatitis elimination targets

POLARIS OBSERVATORY

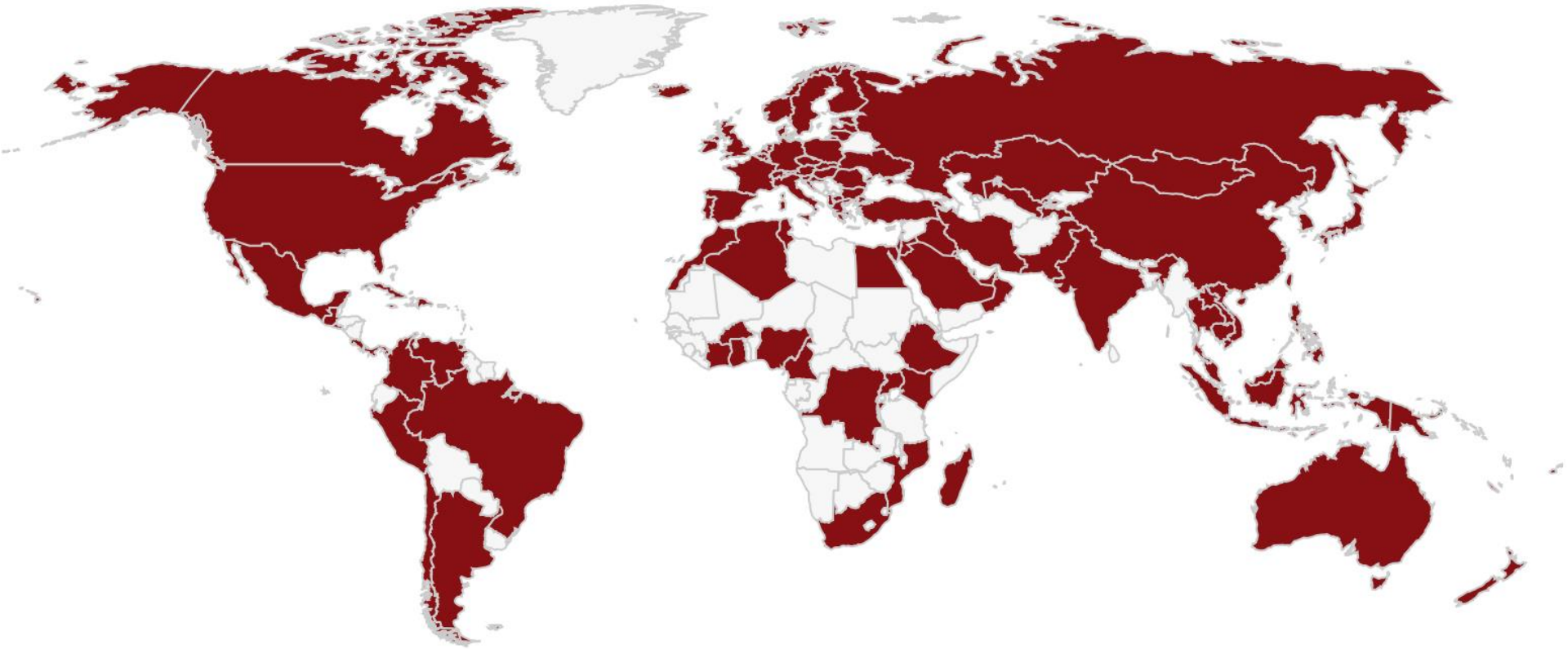
Services

- HCV & HBV disease burden modeling
- HCV & HBV economic impact modeling
- HBV vertical and horizontal transmission modeling
- Cohort analysis
- Hepatitis elimination strategies
- Cost-effectiveness and ROI analyses
- Data and metrics to track progress to elimination

Guiding Principles

- Validate all data/analyses with local experts
- Complement country interviews with literature searches to minimize the burden on country experts
- Facilitate objective, data-driven decisions and policy-making with consideration of each country's unique needs
- Publish key findings with local collaborators
- Function as a platform to provide data, tools and analyses with a user-friendly Microsoft Excel® interface

We have modeled hepatitis disease burden for 132 countries/regions in collaboration with more than 750 country experts



Topics

- HBV burden and cascade of care
- HDV epidemiology
- HDV reflex testing

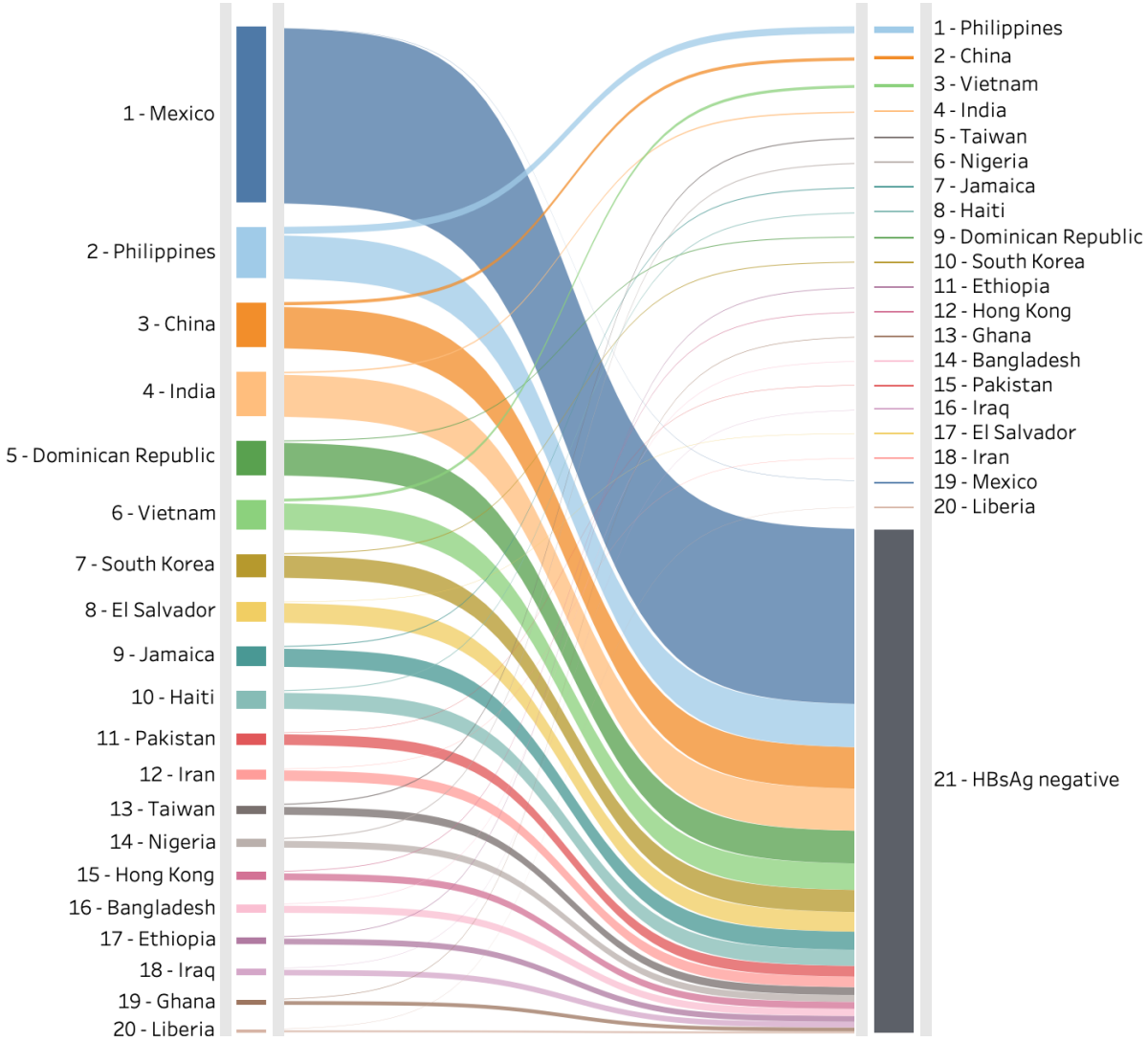
Globally, an estimated 258 million are HBsAg+ with less than 15% diagnosed and 8% of the eligible population treated

Region/ Country	Modeled HBV Prevalence, 2022	HBV+ Population, 2022 (Thousands)	Treatment Eligible, 2022	Diagnosed, 2022	% Diagnosed, 2022	Treated, 2022	% Treated of Total Eligible, 2022
High income	0.9% (0.7%–1.2%)	11,185 (8,891–14,705)	3,479,000	5,020,000	45%	996,000	29%
Upper middle income	3.8% (3.4%–4.1%)	96,069 (85,791–104,731)	38,561,000	21,636,000	23%	5,279,000	14%
Lower middle income	3.3% (2.7%–4.5%)	114,198 (91,851–154,100)	33,067,000	7,183,000	6%	400,000	1%
Low income	4.8% (4.0%–5.7%)	35,620 (29,694–41,994)	8,037,000	2,165,000	6%	170,000	2%
Total	3.2% (2.7%–4.0%)	257,518 (216,602–316,384)	83,250,000	36,0414,000	14%	6,823,000	8%

Less than 5% of all HBV infections are in high income countries.

Polaris Observatory Collaborators. Global prevalence, cascade of care, and prophylaxis coverage of hepatitis B in 2022: a modelling study. Lancet Gastroenterol Hepatol. 2023 Jul 27:S2468-1253(23)00197-8. doi: 10.1016/S2468-1253(23)00197-8. Epub ahead of print. PMID: 37517414.

Over 76% of all HBV infections in the US are among immigrants



US HBV - NHANES **estimates 0.82 million (0.61–1.1)** vs. to **1.8 million (1.3–2.6)** if immigration is taken into consideration.

A similar analysis in Switzerland found that HBV prevalence is 2x higher than FOPH estimates and 80% of all HBV infections are among foreign born.

Razavi-Shearer D, Gamkrelidze I, Pan CQ, Razavi-Shearer K, Blach S, Estes C, Mooneyhan E, Razavi H. The impact of immigration on hepatitis B burden in the United States: a modelling study. Lancet Reg Health Am. 2023 May 27;22:100516. doi: 10.1016/j.lana.2023.100516. PMID: 37274551; PMCID: PMC10239007.

Topics

- HBV burden and cascade of care
- HDV epidemiology
- HDV reflex testing

Methodology

- Conduct a literature search to identify studies in each country that report HDV prevalence
- Meet with national experts to review the published study and assess:
  - The representativeness of the published study
  - Other studies that have not been published (national serosurveys underway)
  - Access to studies published in the local journals (not found in literature search)
  - Availability of government reports
- Adjust reported prevalence based on geography; study population in consultation with national experts
- Adjust for RNA positivity rate
- Estimate national anti-HDV and RNA+ prevalence

Key observations and limitations

- Quality HDV prevalence data is lacking in most countries
- Published data are often biased
  - » Individuals seeking care or hospitalized (prevalence among cirrhotic individuals – 15-30%, prevalence in patients seeking reimbursement 5-15%)
  - » Age groups with a high HDV prevalence (non-vaccinated)
  - » Geographies or high-risk groups with a high prevalence
- HDV prevalence in the general population is low (national serosurveys $\leq$ 1%)
- There is wide variability in the sensitivity and specificity of the anti-HDV tests – countries use different assays
- No country is doing reflex testing at the national level for HBsAg+ to anti-HDV or for anti-HDV+ to RNA

Key observations and limitations (continued)

- HDV infection is concentrated in specific populations, risk-groups, regions
  - Brazil and Colombia – the Amazon region has a much higher prevalence than other provinces
  - Western Europe – immigrants carry a significant burden of HDV particularly if they emigrate from countries with more recent and/or less robust vaccination programs
  - High risk groups (PWID and sex workers) – high HDV infections in the unvaccinated age groups
- In almost all countries, the prevalence of HDV is thought to be decreasing
  - This is due to longstanding and robust HBV vaccination programs
  - The exceptions were countries in which a significant portion of their HBV cases are the result of immigration (e.g., France, Germany and Italy)

CDA Foundation has been working on quantifying HDV prevalence globally

- We are finding:
  - Much lower prevalence of HDV in the general population
  - Current meta-analyses (Chen 2019, Miao 2020, Stockdale 2020) have found an anti-HDV prevalence of 5-15% globally:
    - Use crude prevalence
    - Use published studies in endemic regions (e.g. Amazon region)
    - Use published studies in high-risk groups
    - Use published studies in hospitalized or patient cohorts
    - Registries primarily including patients suspected of having HDV

Miao Z, Zhang S, Ou X, et al. Estimating the Global Prevalence, Disease Progression, and Clinical Outcome of Hepatitis Delta Virus Infection. J Infect Dis 2020; ***221****(10): 1677-87.*

Stockdale AJ, Kreuels B, Henrion MYR, et al. The global prevalence of hepatitis D virus infection: Systematic review and meta-analysis. J Hepatol 2020; ***73****(3): 523-32.*

Chen HY, Shen DT, Ji DZ, et al. Prevalence and burden of hepatitis D virus infection in the global population: a systematic review and meta-analysis. Gut 2019; ***68****(3): 512-21.*

Study (crude) prevalence is never the same as population prevalence

- 3.2% of the population were anti-HDV+ from 2013-2015 (Lago 2018)
  - » Based on 1240 HBsAg+ individuals from 24 of the 26 states
  - » Does report prevalence by age
- Many meta-analyses and global health organizations make the mistake of using a study prevalence as the prevalence in a population
- The adjusted prevalence from the exact same study is 1.7%

TABLE 1 Demographic and virological characteristics of the study population regarding HBV monoinfection or coinfection with HDV and its distribution among Brazilian regions

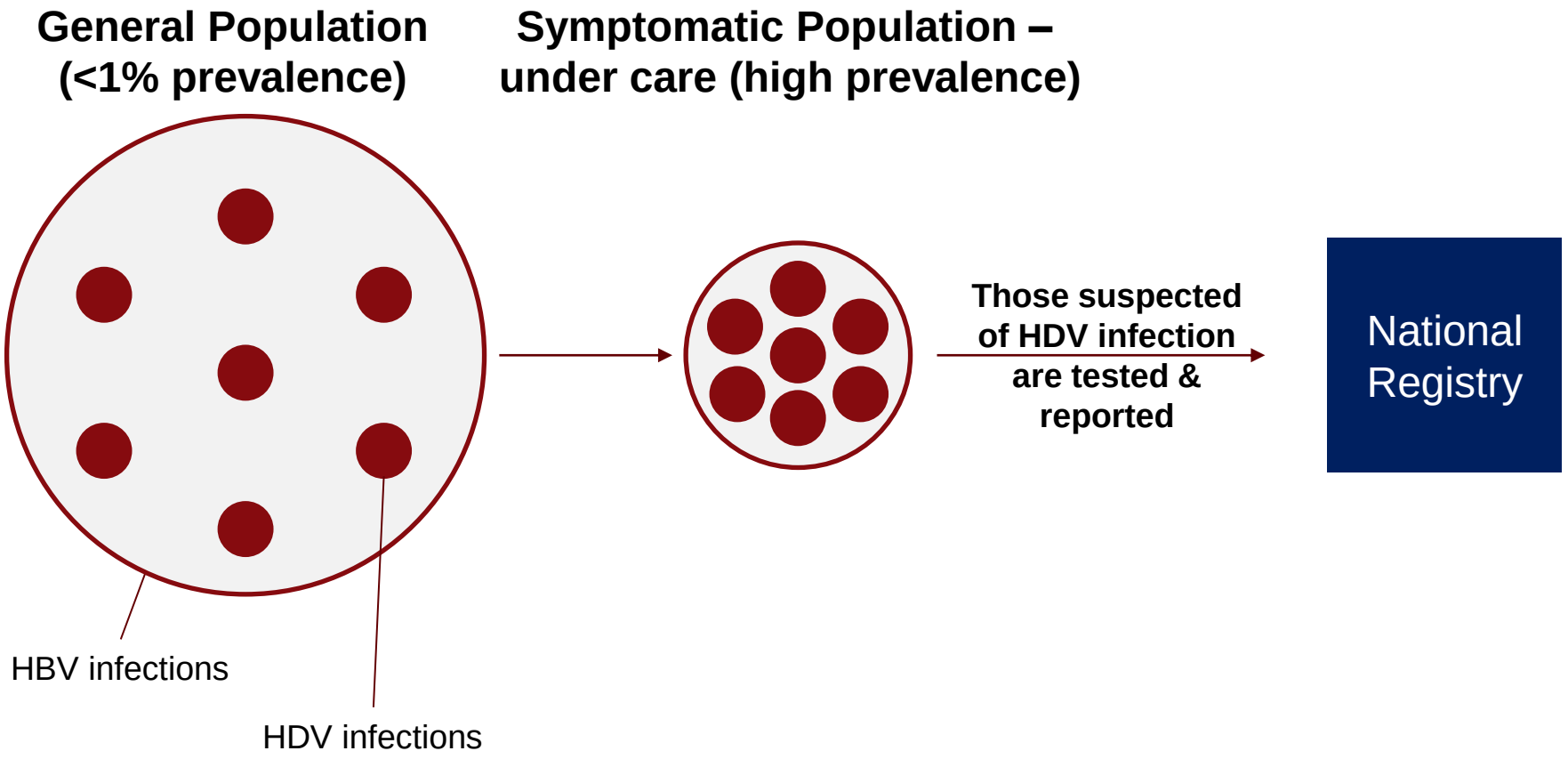
	HBV/HDV coinfection (*n* = 40)	HBV monoinfection (*n* = 1200)	*P*-value
Gender[a]			
Male	19	591	0.303
Female	21	501	
Age[a]			
0-20	6	18 (25%)	<0.0001
21-40	11	339 (3.1%)	
41-60	17	349 (4.6%)	
>61	1	95 (1.0%)	
HBV viral load (UI/mL)[a]			
Median	2.5 + E03	3.7 + E03	0.431
Min	3.7 + E02	9.9	
Max	3.2 + E07	1.0 + E09	
Brazilian regions			
North	28	302 (8.5%)	<0.001
Northeast	3	353 (0.8%)	
Central-West	3	119 (2.5%)	
Southeast	6	343 (1.7%)	
South	0	83 (0.0%)	

[a]Informations from available data.

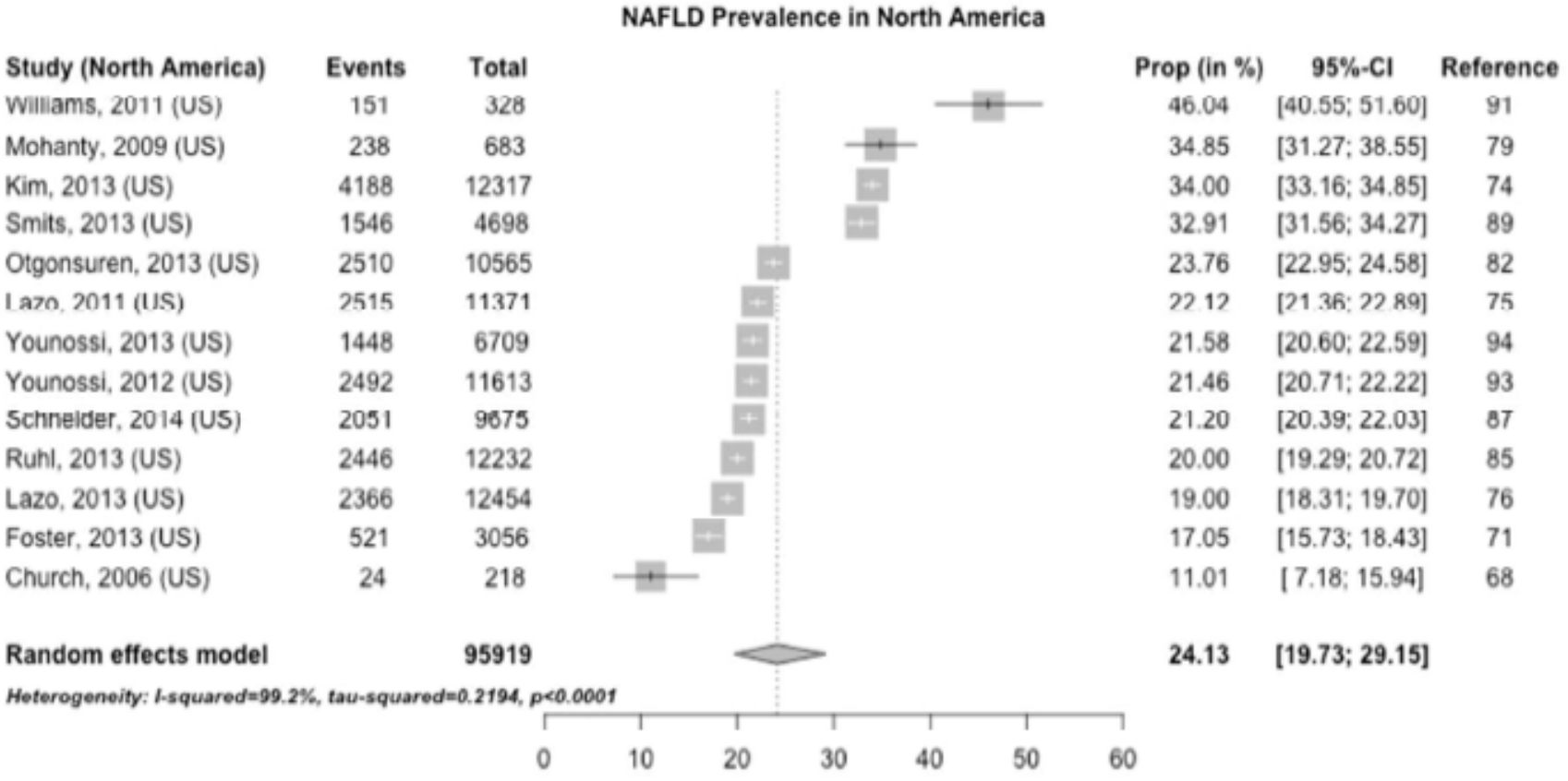
HDV prevalence drops in older ages (higher mortality rate).

*Lago BV, Mello FCA, Barros TM, et al. Hepatitis D infection in Brazil: Prevalence and geographical distribution of anti-Delta antibody. J Med Virol 2018; **90**(8): 1358-63.*

The national registries and cohort studies are very likely to have a high prevalence since only those suspected of HDV infection are tested & reported



Why are meta-analyses very dangerous?



Six of these studies came from the same original source – US NHANES study.

Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016 Jul;64(1):73-84. doi: 10.1002/hep.28431. Epub 2016 Feb 22. PMID: 26707365.

Anti-HDV prevalence is lower in vaccinated cohorts, but this study also highlights the impact of immigration in Europe

Characteristic	Year of observation 1987 Ref. [2]	1992 Ref. [3]	1997 Ref. [4]	2001 Ref. [5]	2019 Present study
Sex ratio (M/F)	3.1	2.8	3.5	2.9	1.0
Age distribution					
0-29 y	34.1%	24.9%	14.5%	8.7%	2.6%
30-49 y	43.6%	43.8%	56.5%	46.6%	37.2%
>49 y	21.3%	31.3%	29.0%	44.7%	60.3%
Mean age (y)	38.1	NA	NA	46.5	51.7
Percentages of cirrhosis	35.7%	42.6%	43.5%	43.4%	53.9%
Prevalence of anti-HDV in Italian natives	NA	NA	NA	7.4%	6.4%
Prevalence of anti-HDV in people born abroad	NA	NA	NA	12.2%	26.4%

Abbreviations: NA, not available.

TABLE 5 Changing pattern of some characteristics of anti-delta-positive subjects in Italy over more than three decades (1987-2019)

Impact of HBV vaccination

Impact of immigration

- Brancaccio 2019 found that average age of infected Italian was 55 (7%) while the average age of infected immigrant was 25 (11%)

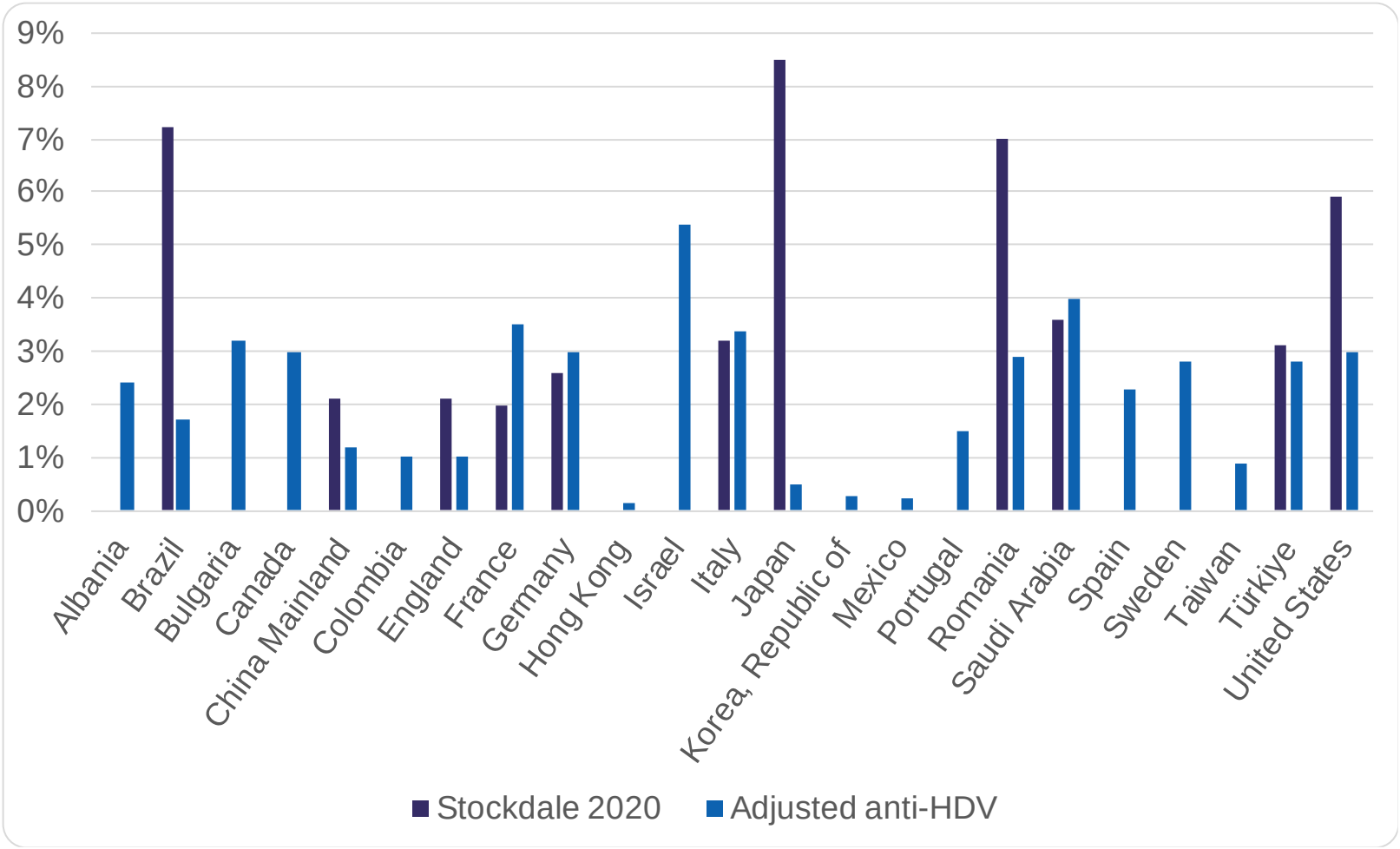
Stroffolini T, Ciancio A, Furlan C, et al. Migratory flow and hepatitis delta infection in Italy: A new challenge at the beginning of the third millennium. J Viral Hepat. 2020 Sep;27(9):941-947. doi: 10.1111/jvh.13310. Epub 2020 May 11. PMID: 32338810.
Brancaccio, G., et al.. (2019). The present profile of chronic hepatitis B virus infection highlights future challenges: An analysis of the Multicenter Italian MASTER-B cohort. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver, 51(3), 438–442. https://doi.org/10.1016/j.dld.2018.09.008

Anti-HDV+ immigrants from countries with less robust vaccination programs have a lower average age than non-foreign-born individuals

- Brancaccio 2019 found that Italians had a prevalence of 7% while immigrants had a prevalence of 11%
  - » Average age of infected Italian was 55
  - » Average age of infected immigrant was 25

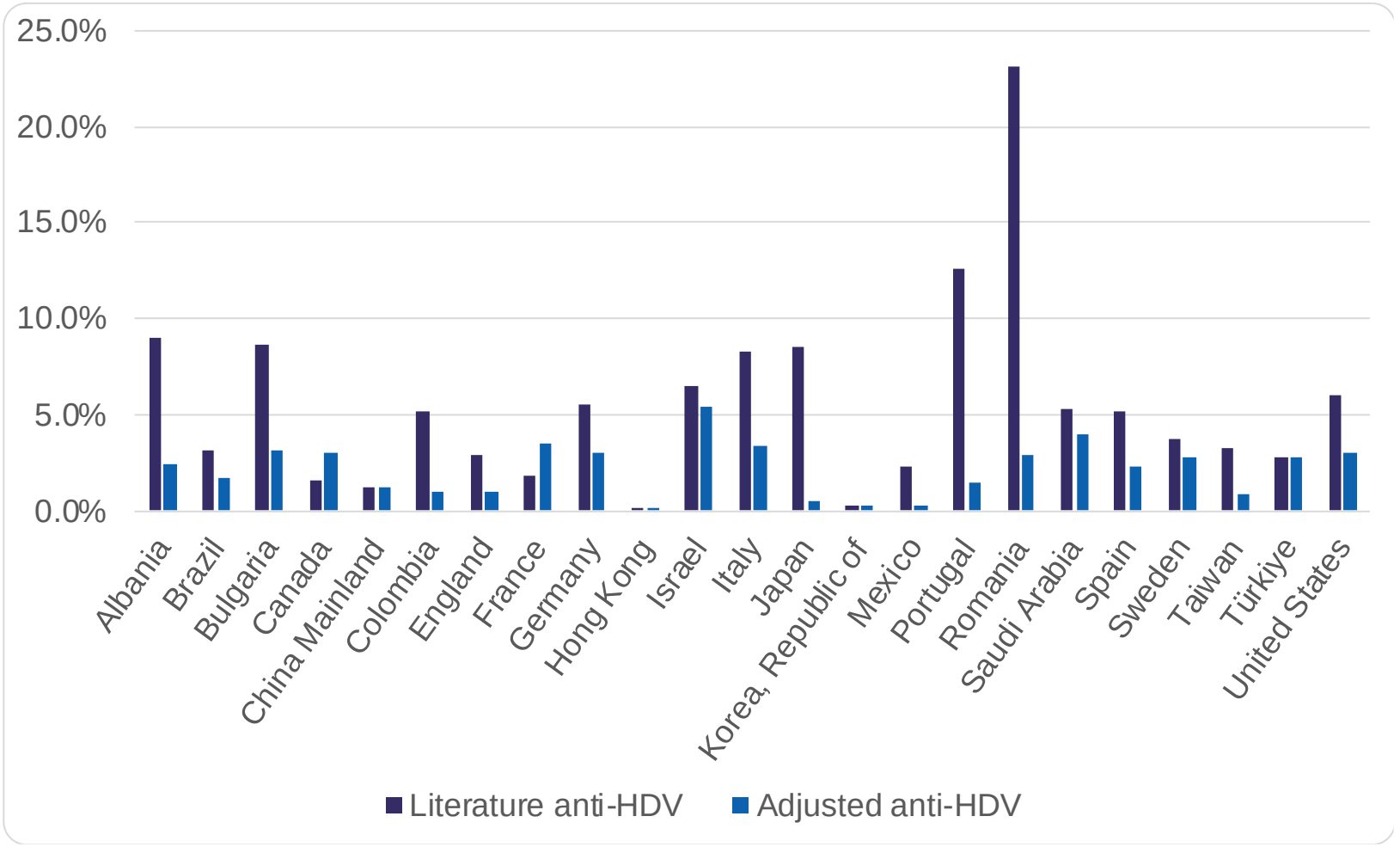
Brancaccio, G., Nardi, A., Madonia, S., Fasano, M., Verucchi, G., Massari, M., Maimone, S., Contini, C., Levantesi, F., Alfieri, A., Gavrila, C., Andreone, P., Milella, M., & Gaeta, G. B. (2019). The present profile of chronic hepatitis B virus infection highlights future challenges: An analysis of the Multicenter Italian MASTER-B cohort. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver, 51(3), 438–442. https://doi.org/10.1016/j.dld.2018.09.008

Our estimates are also significantly different than the Stockdale 2020 study

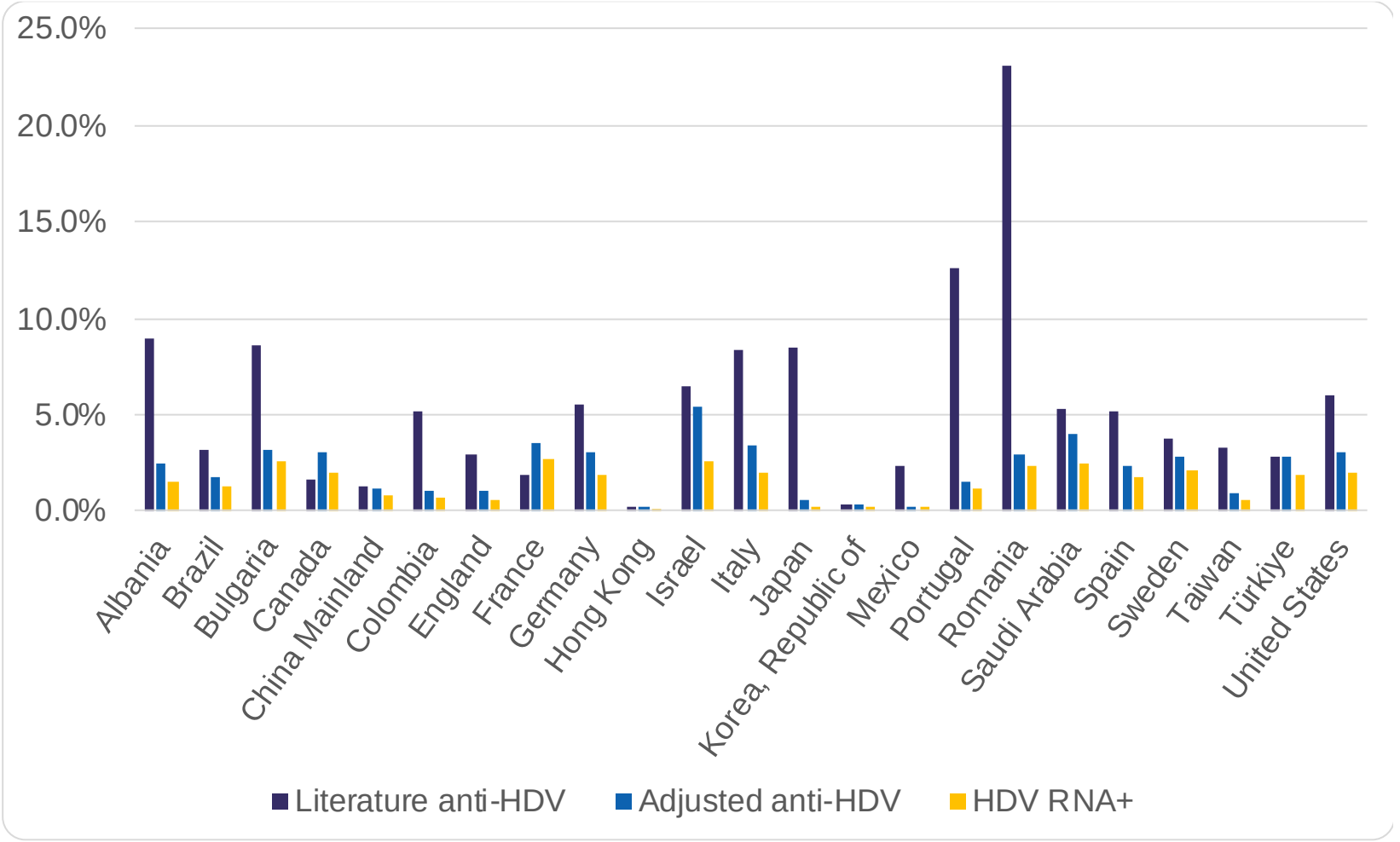


*Stockdale AJ, Kreuels B, Henrion MYR, et al. The global prevalence of hepatitis D virus infection: Systematic review and meta-analysis. J Hepatol 2020; **73**(3): 523-32.*

In discussions with experts we have found lower HDV prevalence that reported in the literature



This impact is even larger when the viremic portion (RNA+) of the anti-HDV population is considered



In almost all countries the prevalence of HDV was thought to be decreasing

- This is due to the longstanding and robust vaccination programs in these countries
- The exceptions were countries in which a significant portion of their HBV cases are the result of immigration
  - » France, Germany and Italy

Topics

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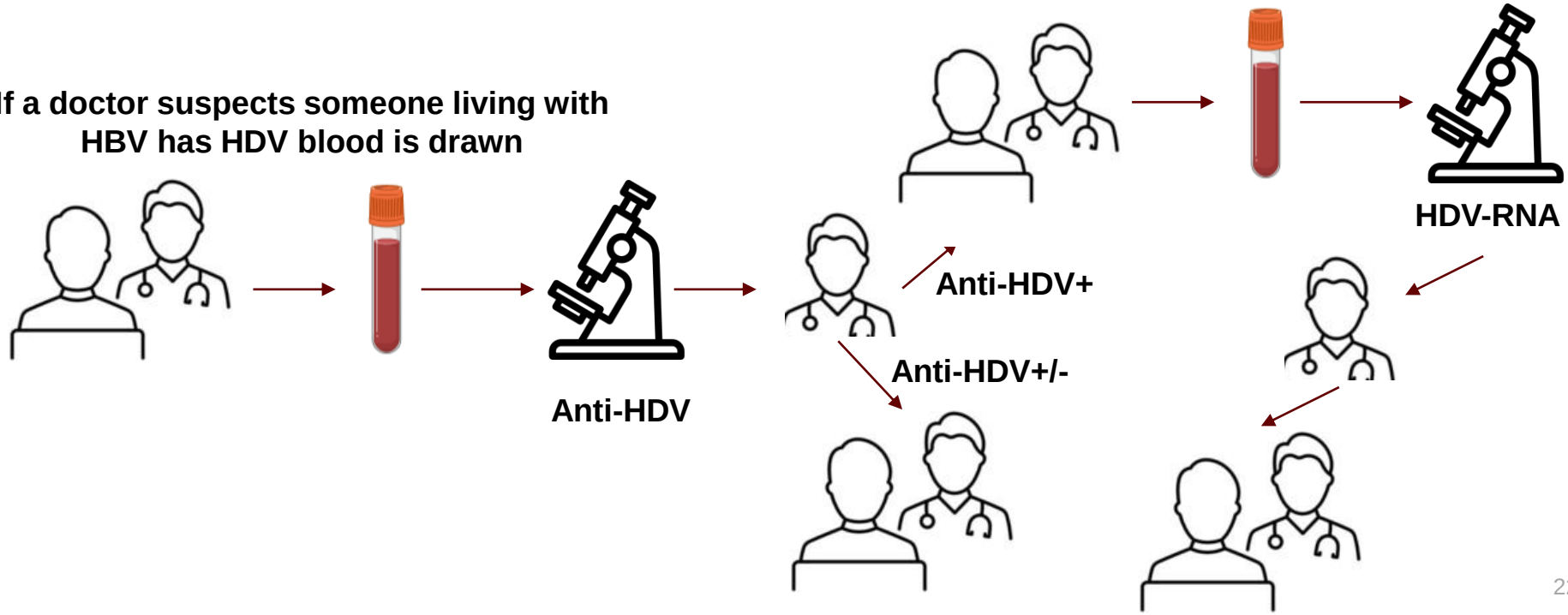
- HDV epidemiology
- HDV reflex testing

The current process for HDV diagnosis is stepwise, based on a doctor's decision, and takes a considerable number of visits

If a doctor suspects someone of having HBV of blood is drawn

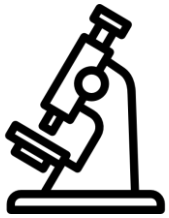
HBsAg/anti-HBc/anti-HBs

If a doctor suspects someone living with HBV has HDV blood is drawn



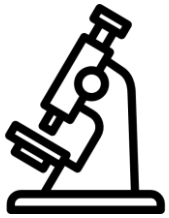
Reflex testing greatly simplifies the process for providers and patients

If a doctor suspects someone of having HBV of blood is drawn



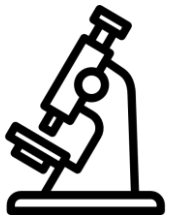
HBsAg/anti-HBc/anti-HBs

HBsAg+



anti-HDV

anti-HDV+



HDV-RNA

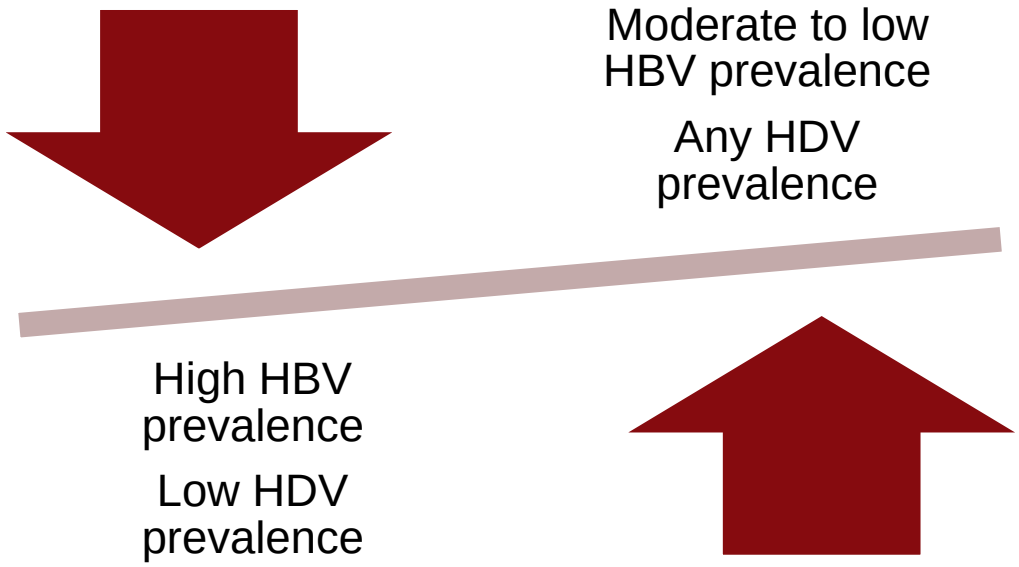
Laboratory reflex testing can be implemented to better understand the burden of HDV

The number of newly diagnosed HBV individuals is less than 2 million per year globally, with half of the total newly diagnosed in China

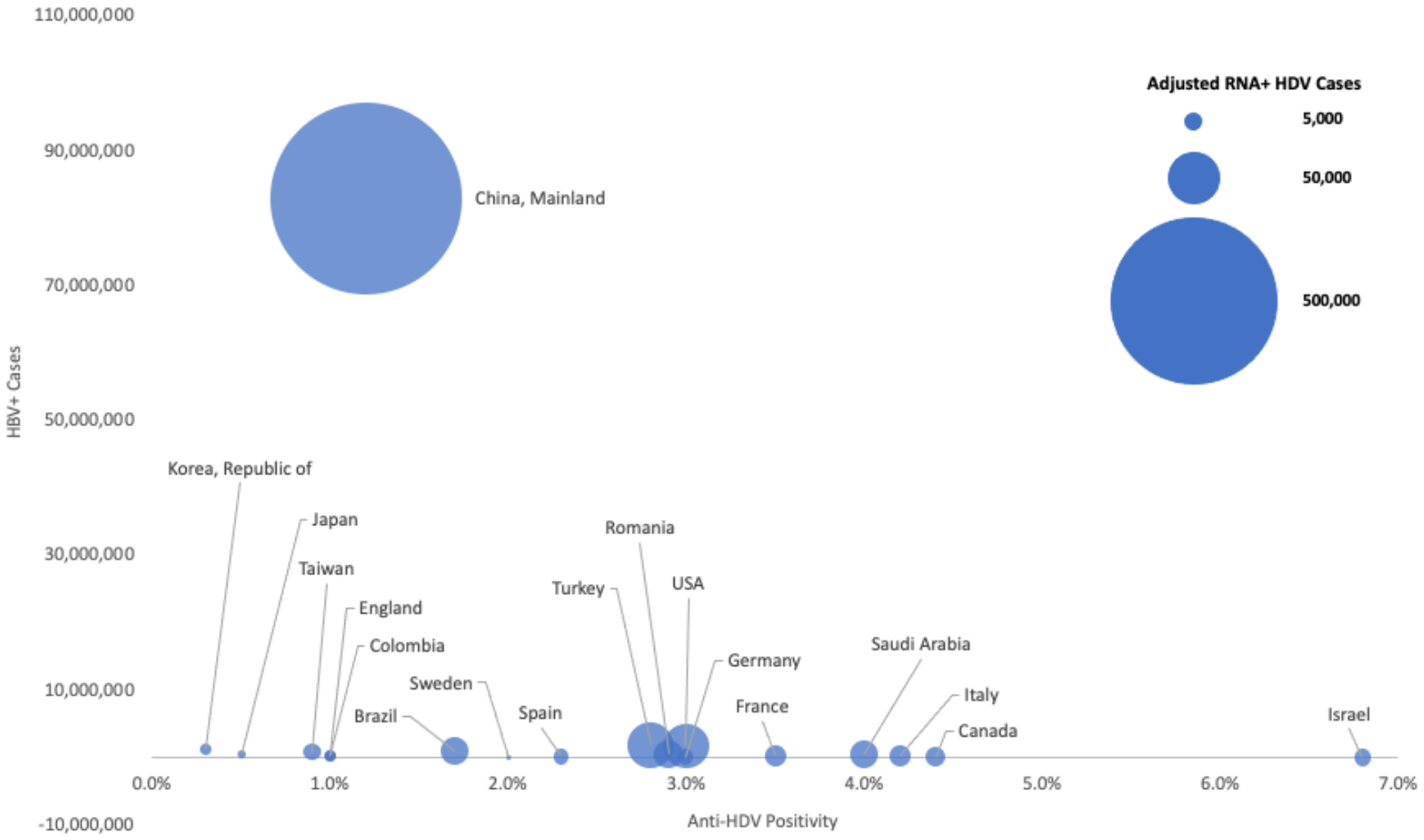
Regions/Countries	Newly Diagnosed HBsAg infections, 2021
Global	1,994,000
Regions by Income Groups	
High income	114,000
Upper middle income	1,128,000
Lower middle income	631,000
Low income	119,000
Regions by Continent	
Africa	187,000
Asia	1,694,000
Australia	6,000
Europe	66,000
North America	22,000
Oceania	1,000
South America	19,000
European Union	35,000
China, Mainland	1,000,000

Razavi HA, Buti M, Terrault NA, Zeuzem S, et. al. Hepatitis D double reflex testing of all hepatitis B carriers in low-HBV- and high-HBV/HDV-prevalence countries. J Hepatol. 2023 Aug;79(2):576-580. doi: 10.1016/j.jhep.2023.02.041. Epub 2023 Apr 6. PMID: 37030400.

The costs associated with reflex testing are highly dependent on the country specific disease burden



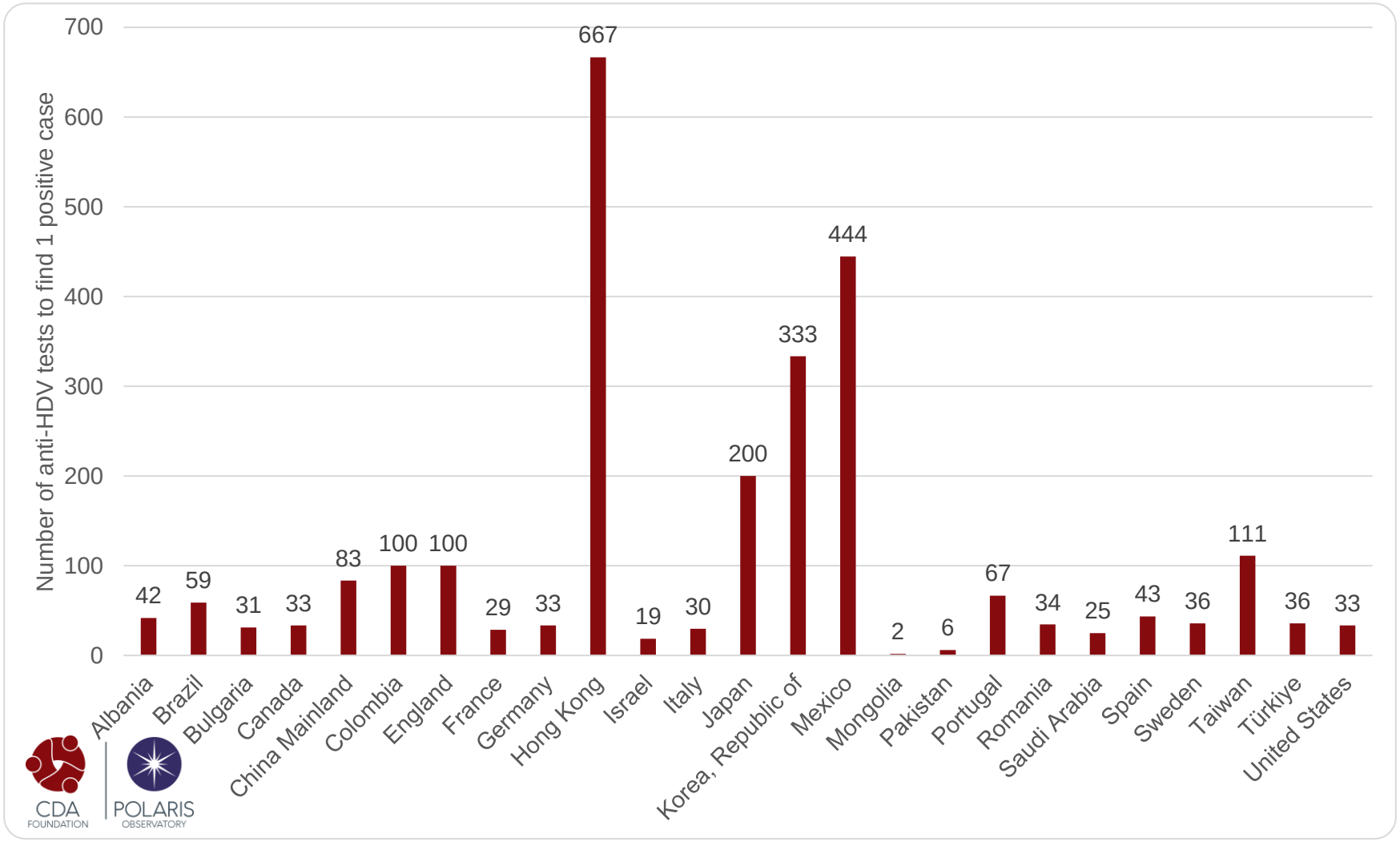
Outside of China, Korea, Japan and Taiwan, HDV double reflex testing makes logical sense



Korea has to screen almost 2 times as many HBV+ individuals to find 13% of the number of cases as the United States

Country	Newly Diagnosed HBV 2020	Number of anti-HDV tests	% Anti-HDV+	Number of HDV RNA tests	% HDV RNA+	Number of HDV RNA+ cases newly diagnosed
Israel	1,400	1,400	5.4%	75	60%	45
Colombia	2,600	2,600	1.0%	30	70%	20
Korea, Republic of	19,600	**19,600**	0.3%	60	54%	**30**
Mainland China	1,000,000	1,000,000	1.2%	12,000	66.6%	8,000
Taiwan	17,100	17,100	0.9%	150	60%	90
United States	11,600	**11,600**	3.0%	350	66%	**230**

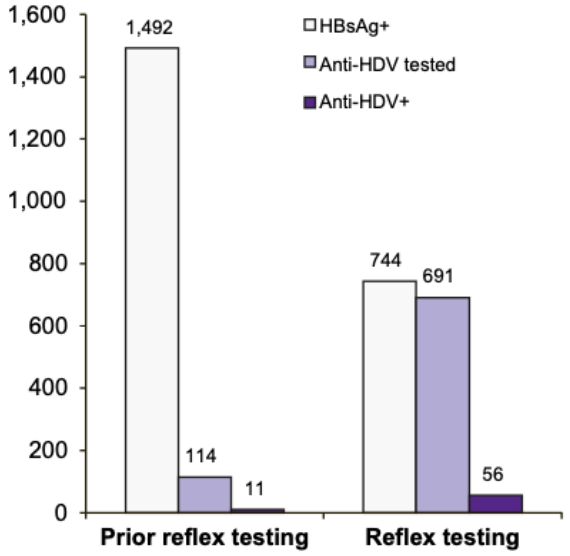
Another way to examine the impact of reflex texting is the number of HBV+ individuals needed to be tested to find one anti-HDV positive case



Reflex testing greatly increases the absolute number of anti-HDV positives identified and overcomes suboptimal risk factor screening

To assess the impact of **anti-HDV reflex testing** implementation in all HBsAg+ samples detected in a central laboratory that receives samples from an academic hospital and primary care centers

Anti-HDV screening prior and after reflex testing



Baseline characteristics of anti-HDV+ according to HDV-RNA detectability

	Anti-HDV+ with HDV-RNA determination (N = 54)	HDV-RNA detectable (n = 35)*	HDV-RNA undetectable (n =19)*	*p* value
Age, years	44 (35-56)	44 (35-54)	46 (38-57)	0.244
Male, n (%)	32 (59%)	19 (54%)	13 (68%)	0.237
Caucasian, n (%)	33 (59%)	23 (66%)	10 (53%)	0.085
Risk factors, n (%)				0.053
Blood-borne (+PWID)	11 (20%)	11 (31%)	0 (0%)	
HDV endemic origin	11 (20%)	8 (23%)	3 (16%)	
Unknown	32 (60%)	16 (46%)	16 (84%)	
ALT, IU/ml	49 (27.5-78)	64 (49-119)	28 (19-38)	<0.001
Liver cirrhosis, n (%)*	19 (35%)	17 (49%)	2 (11%)	0.014
HBsAg, log IU/ml	3.7 (3.4-4.1)	3.9 (3.5-4.2)	3.2 (2.3-3.5)	0.001

- **Anti-HDV reflex testing quintupled** the absolute **diagnoses** of chronic hepatitis D.
- 60% of the anti-HDV and HDV-RNA positive patients did not have any risk factor.
- **Screening by risk factors is suboptimal.**

Palom A, Rando-Segura A, Vico J, Pacín B, Vargas E, Barreira-Díaz A, Rodríguez-Frías F, Riveiro-Barciela M, Esteban R, Buti M. Implementation of anti-HDV reflex testing among HBsAg-positive individuals increases testing for hepatitis D. JHEP Rep. 2022 Jul 21;4(10):100547. doi: 10.1016/j.jhepr.2022.100547. PMID: 36052219; PMCID: PMC9425021.

Conclusions

- Quality HDV prevalence data is lacking in most countries, but available data suggest certain trends across all countries:
  - HDV infection is concentrated in specific populations, risk-groups, regions and age groups
  - Faster HDV disease progression is leading to a lower prevalence in older ages – much more deadly infections than HBV or HCV
  - In almost all countries, the prevalence of HDV is decreasing as the result of vaccination
  - In Western countries, the prevalence of HDV may be increasing due to immigration
- There is wide variability in the sensitivity and specificity of the anti-HDV tests – countries use different assays

Conclusions

- No country is doing reflex testing at the national level for HBsAg+ to anti-HDV or for anti-HDV+ to RNA but there is a strong desire to change this
- In most settings the cost would be limited
  - » Cost-effectiveness studies needed in high HBV and low HDV prevalence settings
- Increase the data available for HDV estimates
  - » Laboratory based reflex testing is less biased that current standards
- Earlier diagnosis for people living with HDV