

The global prevalence and burden of disease of hepatitis D: a small pathogen with an outsized impact

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Disclosures

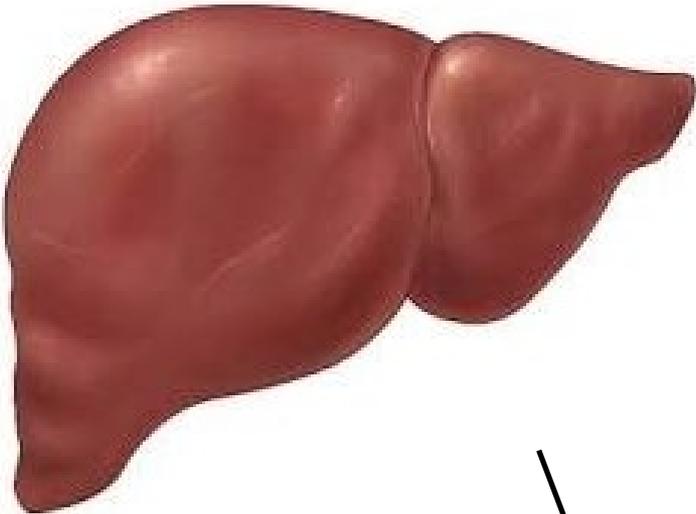
None

Hepatitis D

- Small
- Neglected
- May have underappreciated but important role in viral hepatitis morbidity and mortality



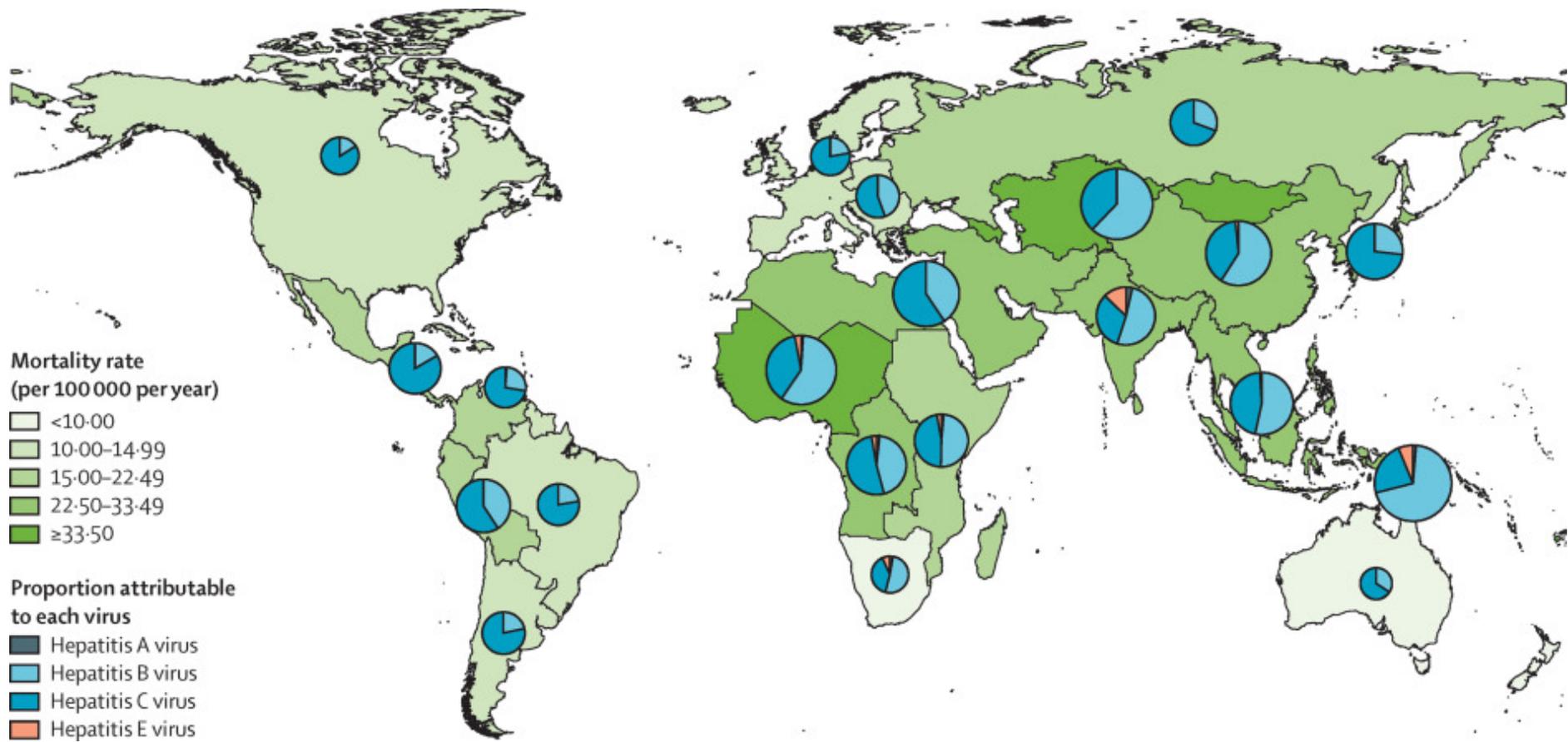
**NORMAL
LIVER**



CIRRHOSIS



HCC



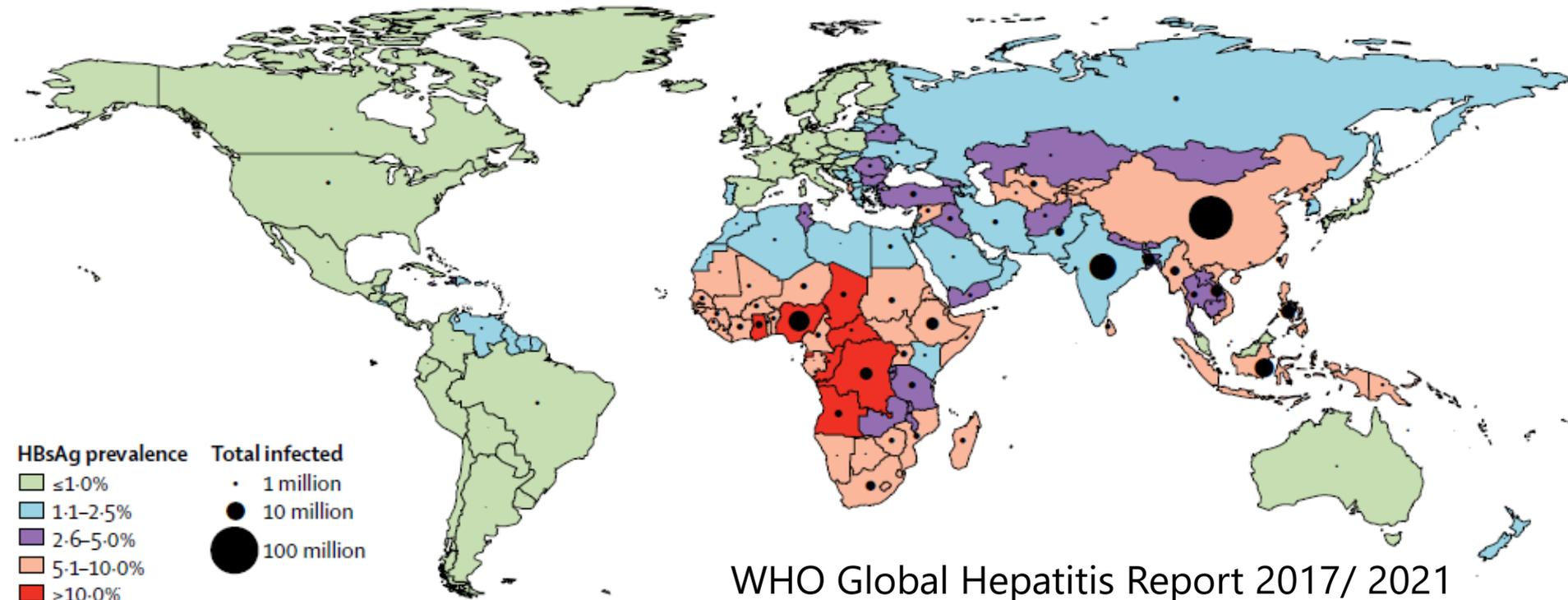
Hepatitis D virus?

Epidemiology of hepatitis B

257- 296 million (3.5-3.9%) have chronic hepatitis B globally

What proportion have HDV infection?

c What proportion of liver disease is caused by HDV?



WHO Global Hepatitis Report 2017/ 2021
Polaris Observatory Lancet Gastroenterol &
Hepatology 2018 3:383-403

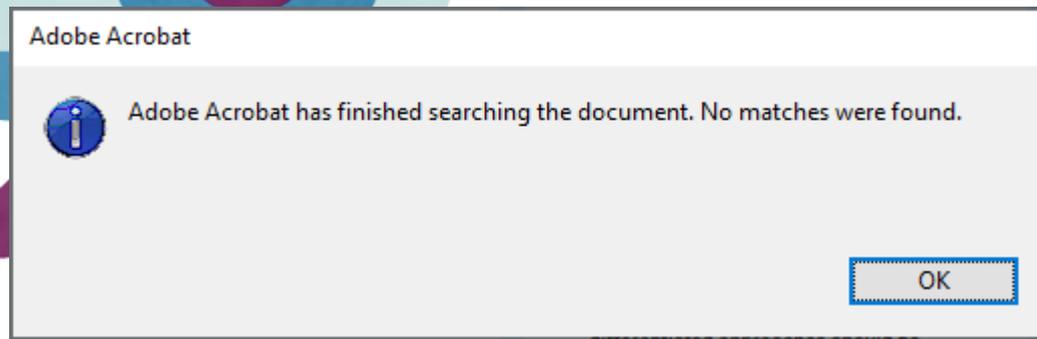
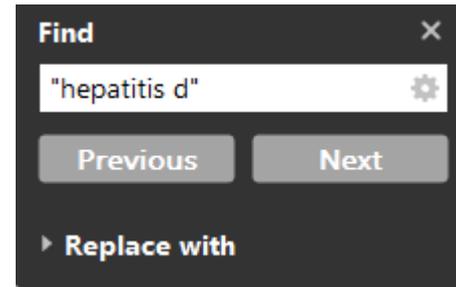
GLOBAL HEALTH SECTOR STRATEGY ON
VIRAL HEPATITIS
2016–2021

TOWARDS ENDING VIRAL HEPATITIS

HDV: 2 references
No epidemiological
data

HCV: 44 references,
epidemiology, specific
targets, strategic plan

Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021



Accountability for the global health
sector strategies 2016–2021: actions
for impact

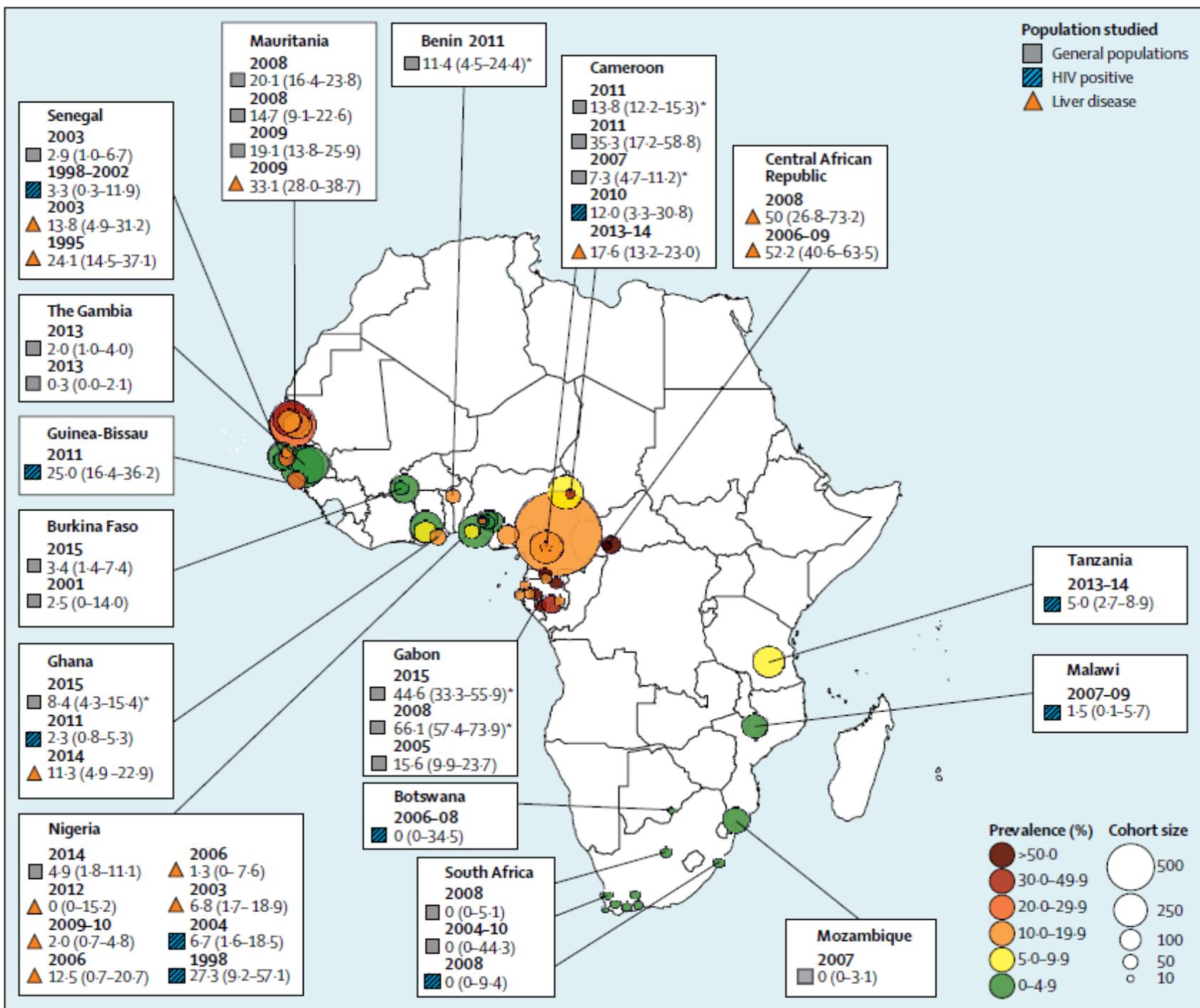
Prevalence of hepatitis D virus infection in sub-Saharan Africa: a systematic review and meta-analysis



Alexander J Stockdale, Mas Chaponda, Apostolos Beloukas, Richard Odame Phillips, Philippa C Matthews, Athanasios Papadimitropoulos, Simon King, Laura Bonnett, Anna Maria Geretti

- Included 30 studies
- Primary data from HIV cohorts in Malawi and Ghana
- Method: searches of pubmed, embase and scopus
- General, HIV positive, Liver disease populations
- Pooled proportions by DerSimonian Laird Random effects model

Lancet Global Health 2017; 5: e992-1003



Findings

General Populations:

West Africa: 7.3% (95% CI: 3.6 – 12.2)

Central Africa: 25.6% (12.1 – 42.0)

Southern Africa: 0.1% (0.0 – 1.8)

Liver Disease Populations:

West Africa: 9.6% (2.3 - 20.4)

Central Africa: 37.8% (12.1- 67.5)

Southern Africa: No data

Summary: HDV in sub-Saharan Africa

- High endemicity in central > west Africa
- Limited data in southern/east Africa
- HDV may be an important contributor to HBV-associated disease in sub-Saharan Africa





Challenges: HDV epidemiology

- Large sample sizes (especially if low HBV prevalence)
- Variable awareness, selection or referral bias
- Rarely tested in LMIC, especially outside tertiary centres
- Bias may be compounded by HBV and HDV selection
- Resampling of high prevalence regions
- Consideration of population weighting
- Importance of well-characterised liver disease populations
- underestimation from general populations
- Lack of historical standardisation of HDV PCR assays

Diagnosis of HDV

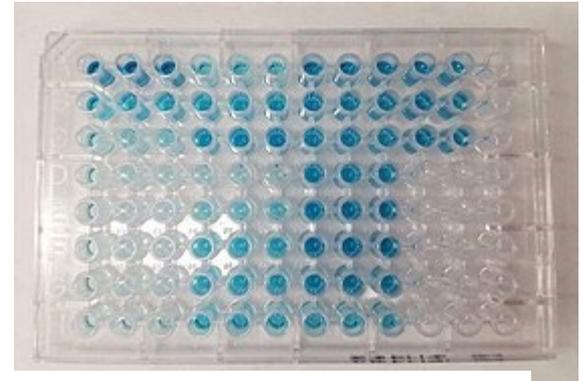
Exposure

Anti-HDV



Infection

HDV RNA





The global prevalence of hepatitis D virus infection: Systematic review and meta-analysis

Alexander J. Stockdale^{1,2}, Benno Kreuels^{3,4}, Marc Y.R. Henrion^{2,5}, Emanuele Giorgi⁶,
Irene Kyomuhangi⁶, Catherine de Martel⁷, Yvan Hutin⁸, Anna Maria Geretti^{1,*}

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J Hepatol 2020; 73:523-532

Global HDV prevalence: Methods

Primary outcome: Total or IgG anti-HDV in 3 key populations

1. General populations
2. Liver disease populations
3. At risk groups

WHO region/ country level

Inclusion criteria

- Studies or abstracts reporting anti-HDV which described the **geographic** and **clinical** setting of participants
- All eligible consenting participants tested, or representative subset

Exclusions

- Studies <1988 (>20 years ago)
- Anti-HDV IgM or HDAG
- HDV RNA unselected, without testing for anti-HDV
- Acute hepatitis
- Repeat blood donors
- Remunerated blood donors
- Migrant populations
- Children <18 months (maternal Ab transfer)
- Liver transplant recipients or registers
- Duplicate or overlapping data

Search

- EMBASE, Pubmed, Scopus
- Broad search terms: HDV and diagnostic/ epidemiological terms
- Grey literature: Global Health data exchange, Ministry of Health/ Public Health Organisation websites, UNICEF multiple cluster surveys, DHS programmes

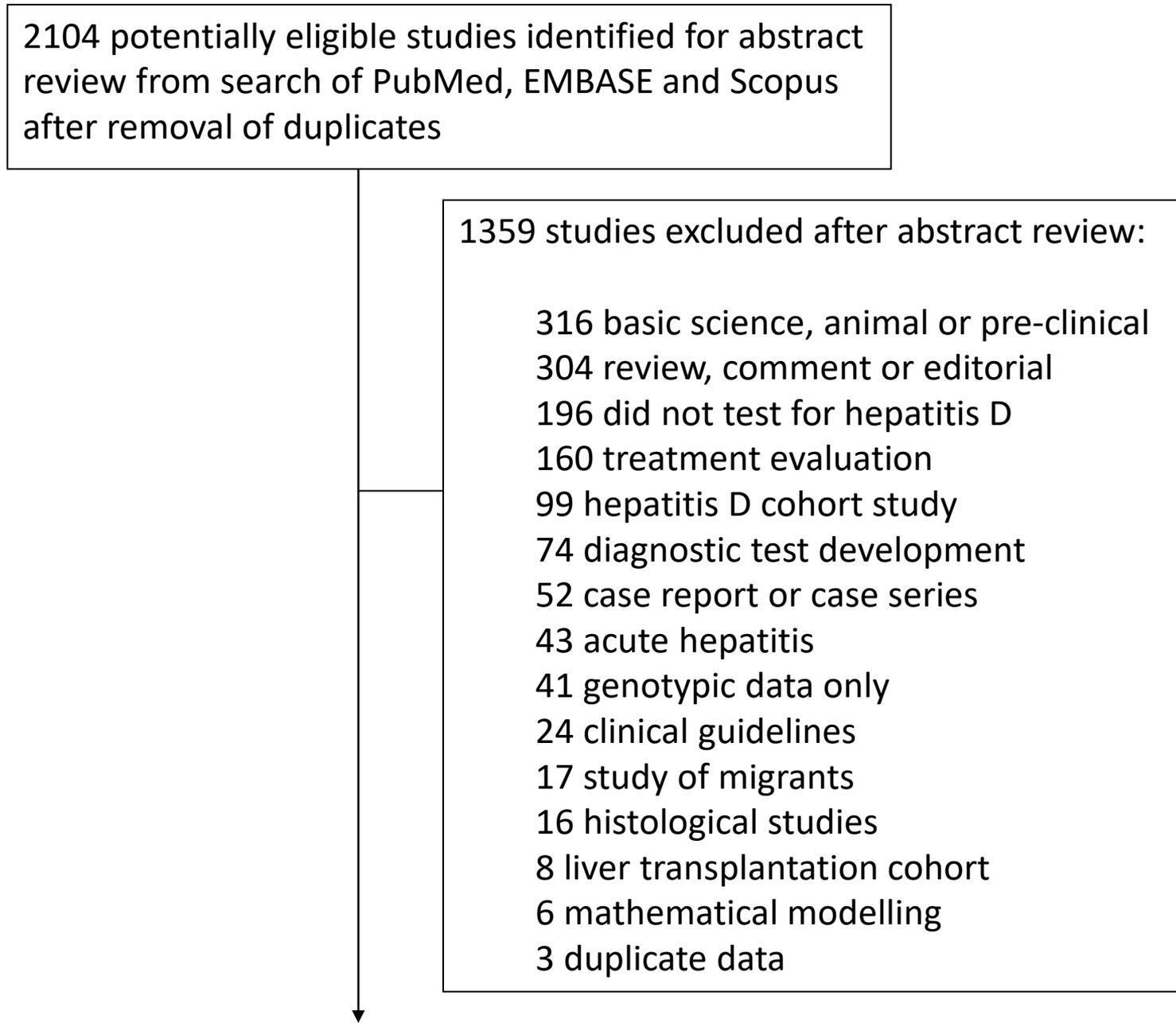
Quality assessment

1. Adequacy of description of inclusion/exclusion criteria
2. Recruitment methodology
3. Assessment of risk of bias

Statistical methods

- HDV prevalence among HBsAg carriers modelled using a binomial mixed model
- Principle component analysis derived quality score used to weight the likelihood function
- Predictions for HDV prevalence: weighting for quality and size of the represented population
- Provisional population attributable fraction estimate=
Prevalence (cases) * (OR-1/ OR) (cases vs controls)

Figure 1: Study flowchart



745 studies reviewed in full and 5 additional studies identified from review of references

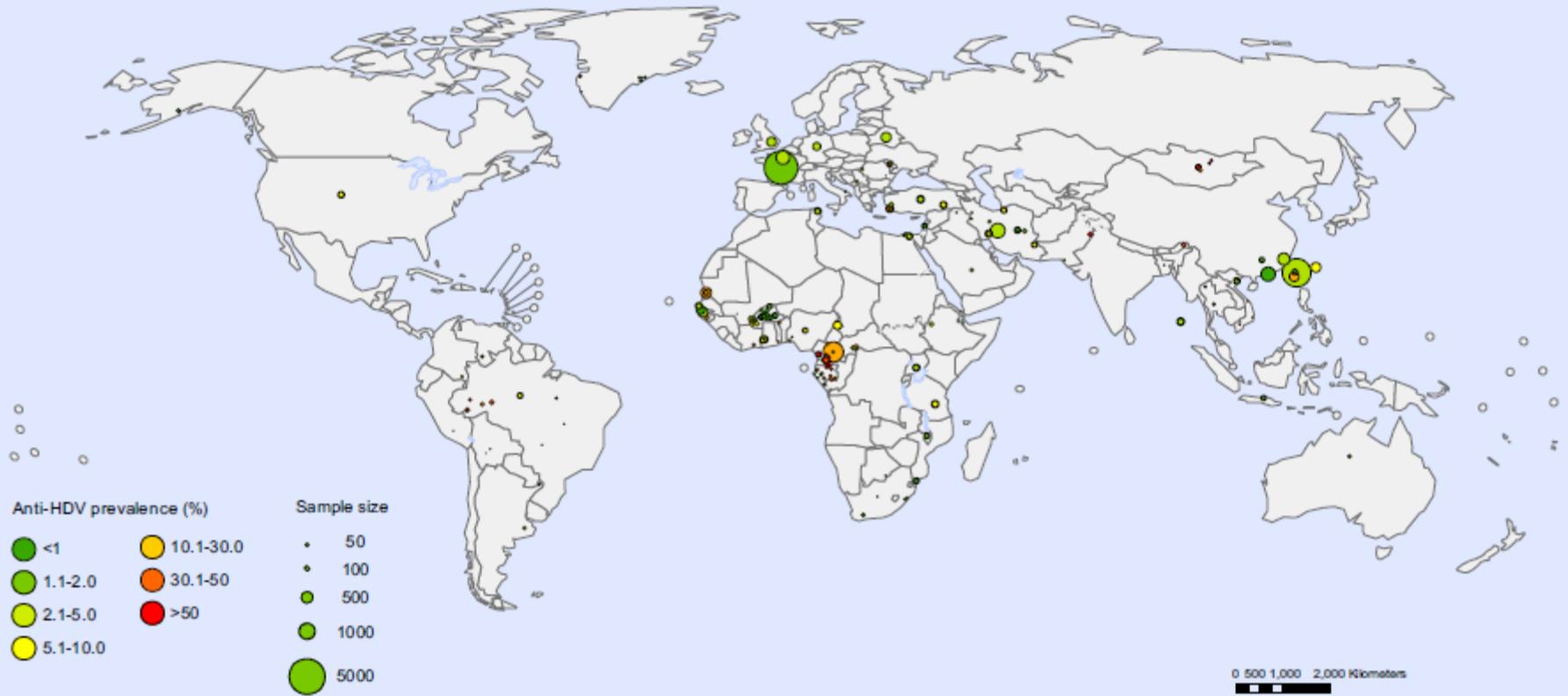
462 studies excluded after in-depth screening:

- 109 duplicate or overlapping data
- 92 insufficient data provided
- 76 non-random or unrepresentative sample
- 42 review, comment or editorial
- 32 hepatitis D cohort or case-control
- 25 did not test for hepatitis D
- 21 IgM or HDAG or HDV RNA only used
- 17 genotypic data only
- 17 liver transplantation
- 16 acute hepatitis
- 6 did not test people with HBsAg
- 4 required detectable HBV DNA
- 2 study of migrants
- 2 conducted prior to 1990
- 1 mathematical model

283 studies eligible for inclusion

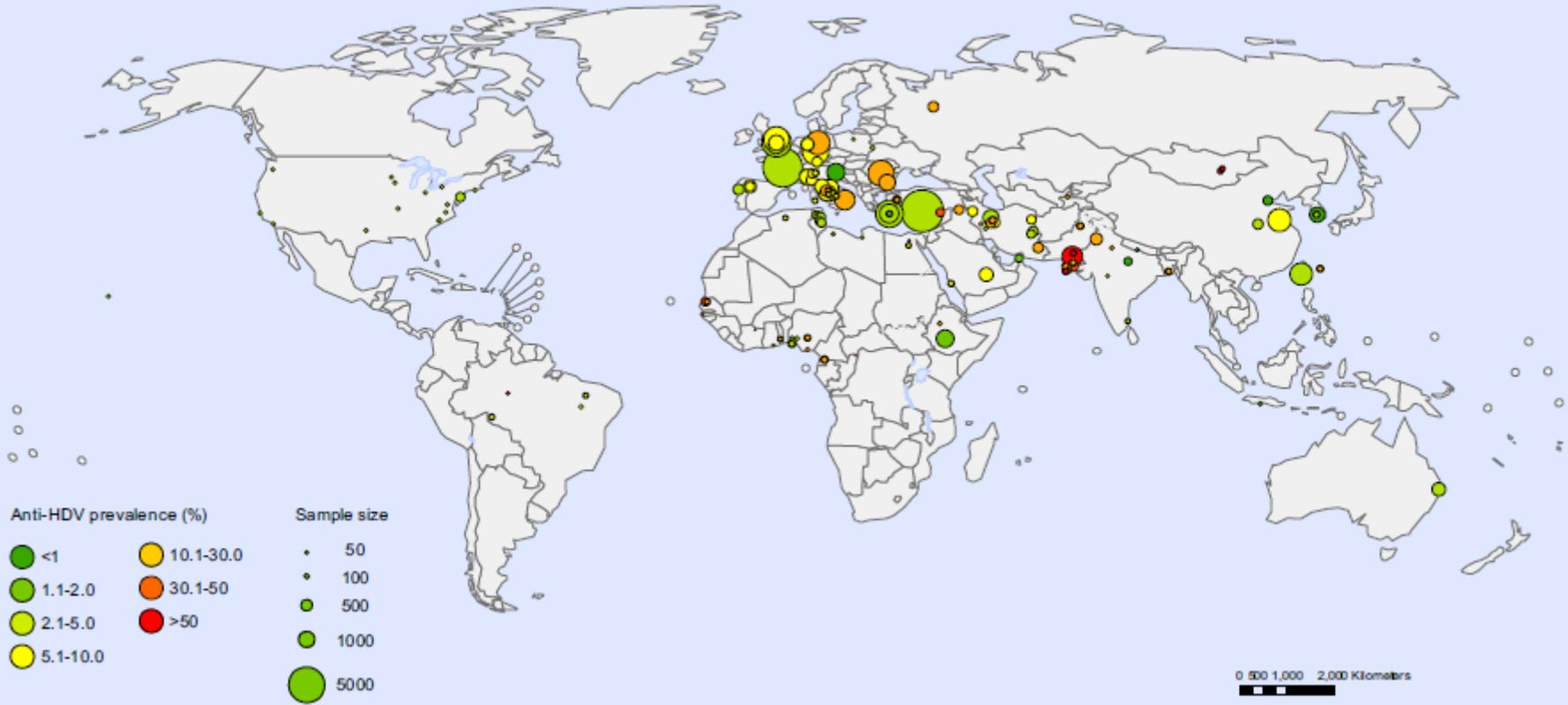
General populations

A



Liver disease populations

B

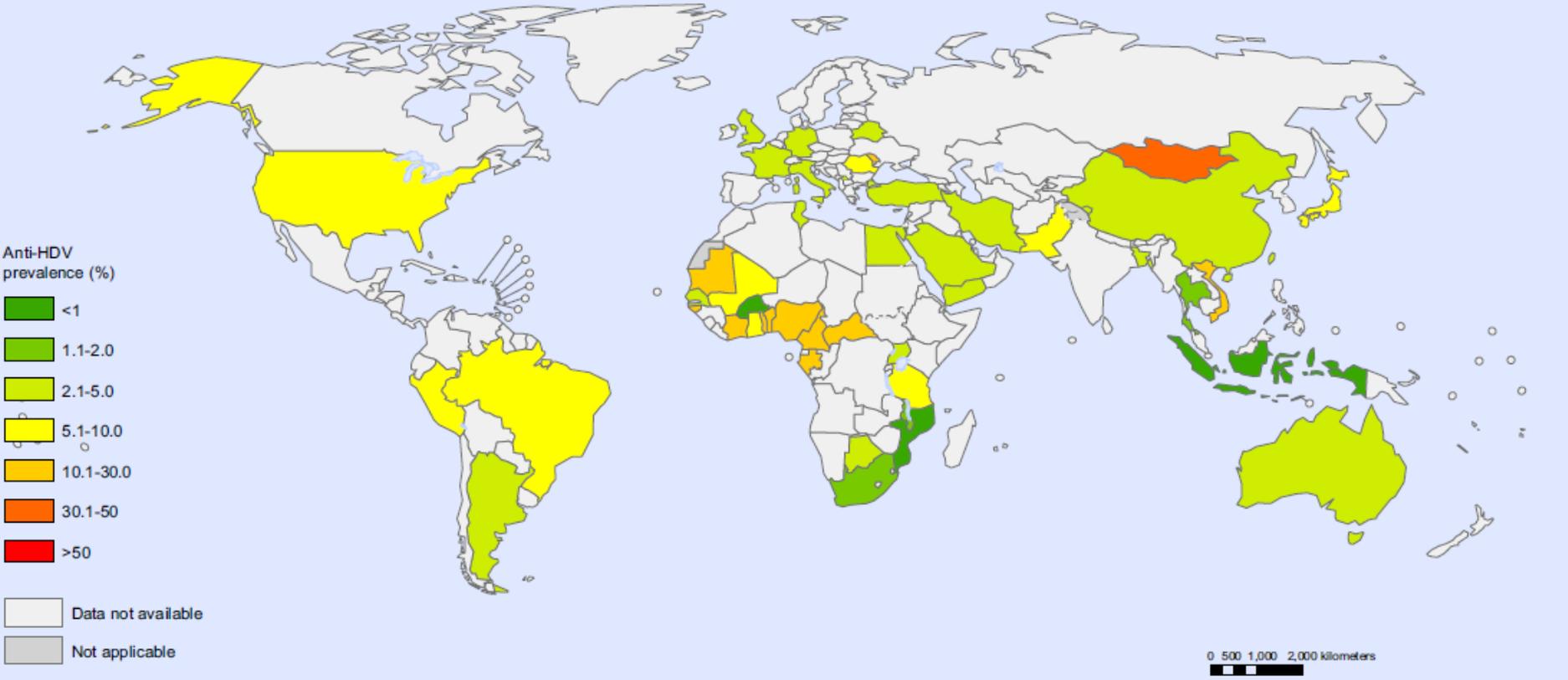


Included studies

- 376 samples from 95 countries:
 - 155 general populations
 - 137 hepatology clinics
 - 85 selected risk groups
 - 19 isolated populations
- 120,293 people with HBsAg tested for anti-HDV
- 5065 anti-HDV positive people tested for HDV RNA by PCR

General Population estimates

A



Hepatology clinic populations

B

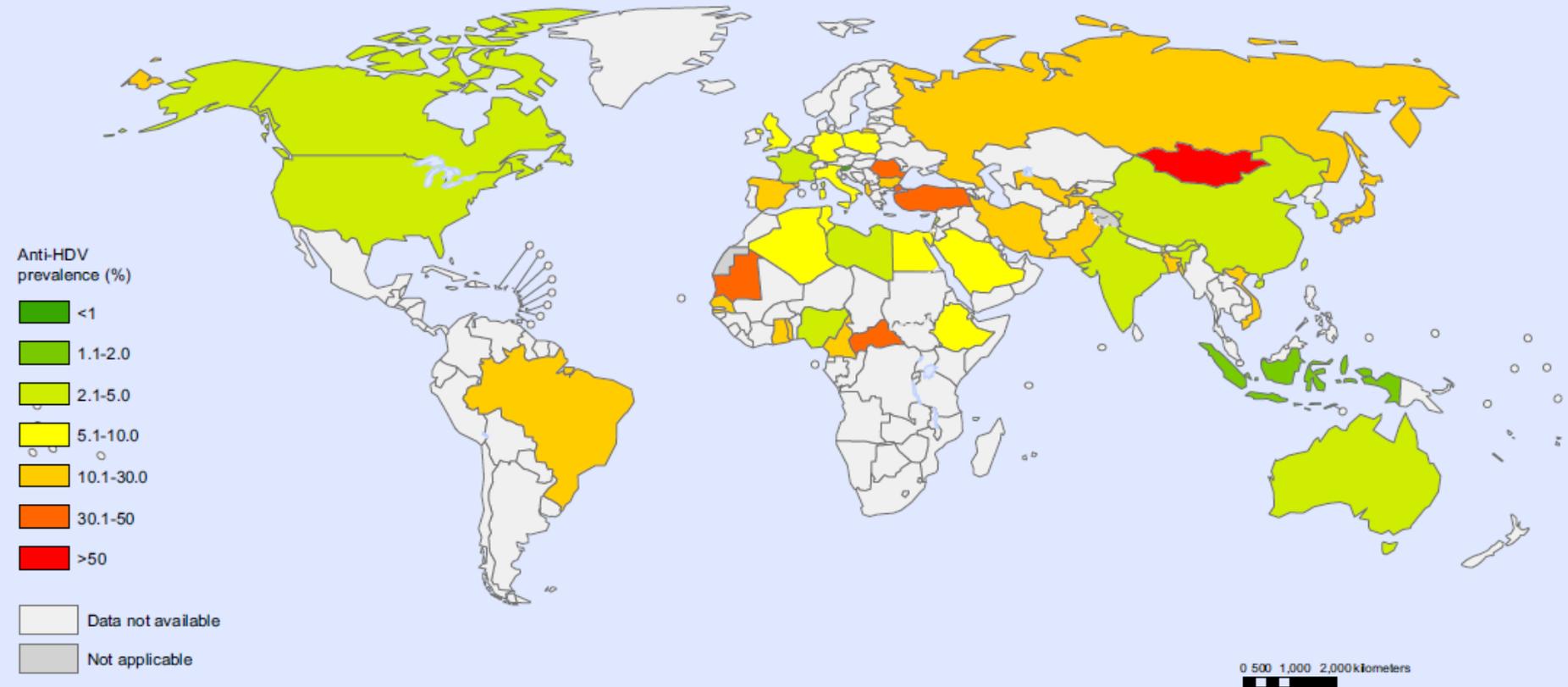
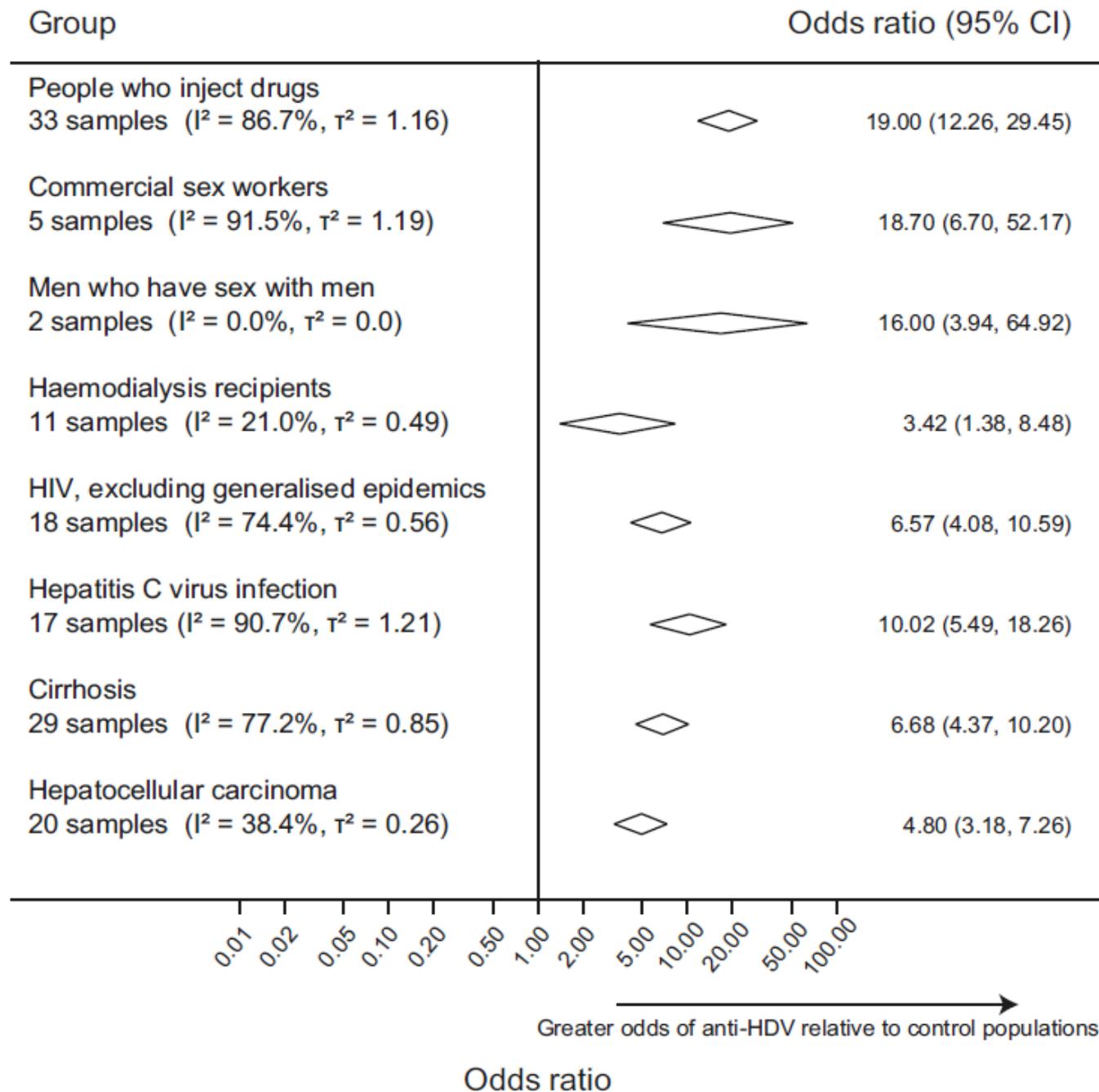


Table 1. Estimated anti-HDV prevalence in general and hepatology clinic HBsAg-positive populations, by WHO region.

WHO region	HBsAg-positive populations			
	General		Hepatology clinics	
	%	(95% CI)	%	(95% CI)
AFR	5.97	(4.98–7.24)	12.26	(10.13–14.70)
AMR	5.91	(3.02–9.71)	3.34	(2.58–4.21)
EMR	3.54	(2.10–6.28)	17.36	(11.15–26.34)
EUR	3.00	(2.09–4.21)	19.48	(17.31–21.76)
SEAR	3.20	(0.36–12.4)	4.00	(3.09–5.15)
WPR	4.09	(3.47–4.77)	8.07	(7.50–8.64)
Global	4.49	(3.57–5.68)	16.42	(14.58–18.56)

AFR, African Region; AMR, Region of the Americas; EMR, Eastern Mediterranean Region; EUR, European Region; SEAR, South-East Asian Region; WHO, World Health Organisation; WPR, Western Pacific Region.



Population attributable fraction

- Provisional estimates:
- Cirrhosis = 18% (95% CI 10 – 26)
- (29 samples, 19 countries)

- HCC = 20% (95% CI 8 – 33)
- (20 samples, 13 countries)

Conclusions

- Small virus, big impact
- HDV epidemiology is challenging
- High HDV endemicity in Central Europe, Central and West Africa, Mongolia, Pakistan, Amerindian populations
- HDV strongly associated with cirrhosis and HCC
- Limited temporal data
- Need for improved surveillance of HDV particularly in North and East/ Southern Africa, Americas

Recommendations

- Reflex testing for anti-HDV in new diagnosis of HBV
 - Improve epidemiological estimates
 - Correct classification of HBV disease
- Genotype specific data
- Need for improved surveillance of HDV particularly in North America, South America, North and Southern Africa

Acknowledgements

Dr Benno Kreuels, University of Hamburg, Germany

Dr Marc Henrion, Liverpool School of Tropical Medicine, UK

Dr Emanuele Giorgi, University of Lancaster, UK

Dr Irene Kyomuhangi, University of Lancaster, UK

Dr Yvan Hutin, World Health Organisation

Dr Catherine de Martel, IARC, Lyon, France

Prof Anna Maria Geretti, University of Liverpool, UK



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Any questions?