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?
257-296 million (3.5-3.9%) have chronic hepatitis B globally. 
What proportion have HDV infection?
What proportion of liver disease is caused by HDV?

WHO Global Hepatitis Report 2017/2021
Polaris Observatory Lancet Gastroenterol & Hepatol 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. Stockdale¹,², Benno Kreuels³,⁴, Marc Y.R. Henrion²,⁵, Emanuele Giorgi⁶, Irene Kyomuhangi⁶, Catherine de Martel⁷, Yvan Hutin⁸, Anna Maria Geretti¹,*

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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)
2104 potentially eligible studies identified for abstract review from search of PubMed, EMBASE and Scopus after removal of duplicates

1359 studies excluded after abstract review:

- 316 basic science, animal or pre-clinical
- 304 review, comment or editorial
- 196 did not test for hepatitis D
- 160 treatment evaluation
- 99 hepatitis D cohort study
- 74 diagnostic test development
- 52 case report or case series
- 43 acute hepatitis
- 41 genotypic data only
- 24 clinical guidelines
- 17 study of migrants
- 16 histological studies
- 8 liver transplantation cohort
- 6 mathematical modelling
- 3 duplicate data
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 HD Ag 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
Liver disease populations
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
Table 1. Estimated anti-HDV prevalence in general and hepatology clinic HBsAg-positive populations, by WHO region.

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

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.
<table>
<thead>
<tr>
<th>Group</th>
<th>Odds ratio (95% CI)</th>
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<tbody>
<tr>
<td>People who inject drugs</td>
<td>19.00 (12.26, 29.45)</td>
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<tr>
<td>33 samples (I² = 86.7%, τ² = 1.16)</td>
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<tr>
<td>Commercial sex workers</td>
<td>18.70 (6.70, 52.17)</td>
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<td>5 samples (I² = 91.5%, τ² = 1.19)</td>
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<tr>
<td>Men who have sex with men</td>
<td>16.00 (3.94, 64.92)</td>
</tr>
<tr>
<td>2 samples (I² = 0.0%, τ² = 0.0)</td>
<td></td>
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<tr>
<td>Haemodialysis recipients</td>
<td>3.42 (1.38, 8.48)</td>
</tr>
<tr>
<td>11 samples (I² = 21.0%, τ² = 0.49)</td>
<td></td>
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<tr>
<td>HIV, excluding generalised epidemics</td>
<td>6.57 (4.08, 10.59)</td>
</tr>
<tr>
<td>18 samples (I² = 74.4%, τ² = 0.56)</td>
<td></td>
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<tr>
<td>Hepatitis C virus infection</td>
<td>10.02 (5.49, 18.26)</td>
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<tr>
<td>17 samples (I² = 90.7%, τ² = 1.21)</td>
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<tr>
<td>Cirrhosis</td>
<td>6.68 (4.37, 10.20)</td>
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<td>29 samples (I² = 77.2%, τ² = 0.85)</td>
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<tr>
<td>Hepatocellular carcinoma</td>
<td>4.80 (3.18, 7.26)</td>
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<td>20 samples (I² = 38.4%, τ² = 0.26)</td>
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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

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Any questions?