A blind spot? Confronting the stigma of hepatitis B virus (HBV) infection - A systematic review [version 2; referees: 2 approved with reservations]

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Abstract

Background: Stigma, poverty, and lack of knowledge present barriers to the diagnosis and treatment of chronic infection, especially in resource-limited settings. Chronic Hepatitis B virus (HBV) infection is frequently asymptomatic, but accounts for a substantial long-term burden of morbidity and mortality. In order to improve the success of diagnostic, treatment and preventive strategies, it is important to recognise, investigate and tackle stigma. We set out to assimilate evidence for the nature and impact of stigma associated with HBV infection, and to suggest ways to tackle this challenge.

Methods: We carried out a literature search in PubMed using the search terms ‘hepatitis B’, ‘stigma’ to identify relevant papers published between 2007 and 2017 (inclusive), with a particular focus on Africa.

Results: We identified a total of 32 articles, of which only two studies were conducted in Africa. Lack of knowledge of HBV was consistently identified, and in some settings there was no local word to describe HBV infection. There were misconceptions about HBV infection, transmission and treatment. Healthcare workers provided inaccurate information to individuals diagnosed with HBV, and poor understanding resulted in lack of preventive measures. Stigma negatively impacted on help-seeking, screening, disclosure, prevention of transmission, and adherence to treatment, and had potential negative impacts on mental health, wellbeing, employment and relationships.

Conclusion: Stigma is a potentially major barrier to the successful implementation of preventive, diagnostic and treatment strategies for HBV infection, and yet we highlight a ‘blind spot’, representing a lack of data and limited recognition of this challenge. There is a need for more research in this area, to identify and evaluate interventions that can be used effectively to tackle stigma.

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Invited Referees 1 2


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2 Herbert Muyinda, Makerere University, Uganda
area, to identify and evaluate interventions that can be used effectively to tackle stigma, and to inform collaborative efforts between patients, clinical services, policy makers, traditional healers, religious leaders, charity organisations and support groups.

**Keywords**

hepatitis B virus, discrimination, stigma, barriers, ethics, funding, elimination, Africa

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Amendments from Version 1

The new version of our article includes an improved description of the nature of the ‘blind spot’, setting out a number of reasons why we have introduced this metaphor for HBV stigma.

The revision includes a PRISMA flow-chart as a main figure panel (previously included as supplementary data), and makes a clear distinction between the outcome of our systematic review of literature surrounding HBV (presented in the results section), vs. triangulation with data from other diseases associated with stigma (presented as discussion points).

Each article identified was appraised by two independent reviewers, and we revised our results tables in order to provide a comprehensive summary of all the data collected from these articles, such that any given point might be linked to multiple citations, thereby adding confidence to the findings.

We added a table to the results section to summarise the 32 papers that were identified, and grouped these by geographical area in order to provide a clearer snapshot of the existing literature, as well as highlighting specifically the lack of data for Africa.

We undertook a quality appraisal of the literature to provide a better insight into the nature of the existing evidence.

We amended the discussion to mention the potential association between stigma and physical disease manifestations.

See referee reports

Abbreviations

- PMTCT – Prevention of mother to child transmission
- TB – Tuberculosis
- HBV – Hepatitis B virus
- HCC – Hepatocellular carcinoma
- WHO – World Health Organization
- HIV – Human Immunodeficiency Virus
- HCWs – Healthcare workers
- THs – Traditional healers
- CHB – Chronic Hepatitis B

Introduction

Stigma is recognised as a challenge in association with many infectious diseases, but has been poorly studied and is inadequately recognised for viral hepatitis infections. Hepatitis B virus (HBV) infection has been reported worldwide, with an estimated burden of 250–290 million cases, and has been associated with high mortality rates resulting from complications including cirrhosis and hepatocellular carcinoma (HCC)1-2. There are effective prevention and treatment strategies available, including vaccination and suppressive antiviral therapy, both of which also contribute to prevention of vertical transmission1. The Global Hepatitis Health Sector Strategy is aiming for the elimination of viral hepatitis as a public health threat by 20301. However, stigma, poverty, and lack of knowledge can be significant barriers to diagnosis, treatment and prevention, especially in resource-limited settings1. These issues sit alongside additional challenges including gaps in vaccine coverage3, limited provision of diagnostic tests and treatment4 and lack of a curative therapy5,6. There is a growing body of personal testimonies providing evidence of stigma associated with HBV6,7. However, there is a very limited literature to describe this. We have therefore used the metaphor of a ‘blind spot’ to describe the current situation for HBV stigma. This reflects a genuine gap in culture or society in which there is no word for the infection, it highlights the paucity of published data, and it describes a problem that is known to exist, but which is often neglected or ignored by current interventions, policy and practice. In light of this, more work is required to understand the nature and impact of stigma for individuals with HBV infection.

Individuals who are stigmatised as a result of illness or infection not only have to contend with potential challenges to health, but may also be denied the opportunities that define quality of life such as education, employment, access to appropriate health care and interaction with a diverse cross-section of society4. Although many diseases are stigmatised, awareness of – and investigation into – stigma is better represented in some areas than others. For example, in HIV, stigma has been shown to limit engagement with services including screening and prevention of mother to child transmission (PMTCT), and uptake of antiretroviral therapy8-10; in tuberculosis (TB) it has been shown to cause diagnostic delays and treatment non-compliance11,12; and in mental illness, stigma has been associated with delays in help-seeking, discontinuation of treatment, suboptimal therapeutic relationships, patient safety concerns, and poorer quality mental and physical care13-17.

Stereotypes and prejudice may stem from physical differences attributable to the condition, misconceptions associated with fear of contagion, and judgements about routes of transmission, all of which may be underpinned by lack of knowledge16-20 and stigma is enhanced by poor of awareness, education and perception21. The importance of physical signs of illness is exemplified for HIV, where those displaying wasting syndrome and certain identifiable opportunistic infections have been described as suffering more stigma compared to those who are asymptomatic2. HIV and TB may also be stigmatised as a result of anxieties about spread of infection, and may be regarded as a punishment for ‘irresponsible’ or ‘immoral’ behaviour.14,22-24. People with mental illnesses may be considered ‘dangerous’ or provoke fear, may lose their autonomy, or be treated as ‘childlike’.25. Understanding why society reacts in a particular way is one way to address stigma14, and could therefore help to guide approaches to tackling stigma in HBV.

HBV infection is highly endemic in Africa, but there are huge challenges in prevention, diagnosis and treatment2. The situation is further complicated by the substantial public health challenge of co-endemic HIV and HBV25. An understanding of the breadth and scope of stigma in HBV, especially in Africa, is an essential part of any strategy that seeks to tackle and eventually eliminate HBV infection as a public health problem. As the improvement of universal availability and accessibility of...
diagnostic, treatment and vaccination options are underway, it is important to ensure that products and services are not only available, but also accessible; people with HBV infection must be able to access education, clinical care, and support from their partners and families, healthcare workers, and members of their communities. The WHO recommends HBV treatment in an environment that minimizes stigma and discrimination.

We set out to assimilate evidence for the nature and impact of stigma on the lives of people with HBV infection and on the community, to describe coping strategies employed by people with HBV, and to suggest ways to tackle stigma and discrimination. Our approach was to gather relevant information regarding HBV stigma from the published literature using a systematic approach, to curate it in order to unify key messages, and to highlight gaps where future work is still needed. We have been able to develop suggestions to address HBV stigma and discrimination from the existing literature, but in light of the paucity of HBV-specific studies, we have also triangulated our approach by drawing on resources from other stigmatised conditions including HIV, TB and mental illness to inform the discussion.

Methods
Search strategy: systematic literature review
In November-December 2017, we undertook a systematic literature search in PubMed; our search strategy focused entirely on the evidence detailing stigma in HBV (Figure 1). The terms of this search are detailed in Supplementary file 1. We carried out two searches: the first search focused on stigma in HBV in Africa, and a second search was not limited to Africa. The two searches yielded 50 and 879 articles, respectively (n=929). We removed 49 duplicate articles (n=880). On reviewing the titles and abstracts, 827 were excluded from search results as they were not on stigma or HBV. Full texts of 53 articles were reviewed by two different individuals, and 19 were excluded (6 articles not primary studies and 13 articles do not address stigma in HBV). A total of 34 articles were therefore downloaded in full. From each publication, we extracted the following: citation, study design, sample size, study population, country, factors associated with stigma, impact of stigma on the lives of people with HBV, and proposed interventions to tackle stigma in the society. We used our research question to group data collated from the included studies into four major themes: factors underpinning stigma in HBV infection, evidence for the impact of stigma, coping strategies for individuals with HBV infection, and interventions proposed to tackle stigma in HBV. There were insufficient data from Africa to focus specifically on that continent, but where possible we have highlighted issues that have been reported in African populations. Data were curated using MS Excel software (Microsoft, Redmond, WA). Ethics approval was not required for this study.

Search strategy: other relevant resources
In order to inform a wider understanding of the potential relevance and impact of stigma in infection and illness, we have
also referred to articles published on other conditions including HIV, TB and mental health to underpin hypotheses set out in the introduction, and to inform discussion. These papers were not identified through a formal systematic review, but were identified as relevant sources from robust, peer reviewed literature.

Quality of evidence assessment
For the 32 studies included from our systematic review, we performed a risk of bias assessment (Supplementary file 2). For qualitative studies (n=12) we used the qualitative appraisal checklist by NICE public health guidance and for quantitative studies (n=19) we used the Centre of Evidence based Management checklist. One study used a mixed method study design, and we assessed this using each of the two approaches above.

Results
A full list of citations generated from our systematic literature review of HBV stigma is shown in Table 1. We have also provided an expanded version of this table, with details summarising the key information pertinent to stigma, in Supplementary file 2.

Quality of evidence
Asia and North America were best represented by the literature, in contrast to Africa from where we identified only two published studies, both set in Ghana (Table 1). Among the 19 studies that used a quantitative study design, eight used a convenient

<table>
<thead>
<tr>
<th>Citation (Author; Date; PMID), divided by region of origin and presented alphabetically by first author</th>
<th>Country where study took place</th>
<th>Study design</th>
<th>Study participants</th>
<th>Sample size</th>
<th>Recruitment site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjei et al. 2017; PMID: 29102991</td>
<td>Ghana</td>
<td>Qualitative</td>
<td>People with HBV infection</td>
<td>14</td>
<td>Hospital</td>
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<td>Mkandawire et al. 2013; PMID: 23811012</td>
<td>Ghana</td>
<td>Qualitative</td>
<td>Local chiefs, village elders and HCWs</td>
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<td>Community</td>
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<td>Qualitative</td>
<td>West African Immigrants</td>
<td>39</td>
<td>Community</td>
</tr>
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<td>Carabez et al. 2014; PMID: 24395631</td>
<td>USA</td>
<td>Survey</td>
<td>HBV positive Asian Americans</td>
<td>154</td>
<td>Community</td>
</tr>
<tr>
<td>Cheng et al. 2017; PMID: 27770375</td>
<td>USA</td>
<td>Survey</td>
<td>Asian</td>
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<td>Community</td>
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<td>Cotler et al. 2012; PMID: 22239504</td>
<td>USA</td>
<td>Survey</td>
<td>Chinese immigrants</td>
<td>N/A</td>
<td>Community</td>
</tr>
<tr>
<td>Frew et al. 2014; PMID: 25506280</td>
<td>USA</td>
<td>Survey</td>
<td>Vietnamese Americans</td>
<td>316</td>
<td>Community</td>
</tr>
<tr>
<td>Li et al. 2007; PMID: 22993729</td>
<td>Canada</td>
<td>Survey</td>
<td>Canadian Chinese</td>
<td>343</td>
<td>Community</td>
</tr>
<tr>
<td>Russ et al. 2012; PMID: 22440043</td>
<td>USA</td>
<td>Qualitative</td>
<td>Asian Americans</td>
<td>HCWs:23 Individuals with HBV: 17</td>
<td>Hospital</td>
</tr>
<tr>
<td>Wu et al. 2009; PMID: 19172206</td>
<td>Canada</td>
<td>Survey</td>
<td>People with HBV infection</td>
<td>204</td>
<td>Community</td>
</tr>
<tr>
<td>Yoo et al. 2012; PMID: 21748476</td>
<td>USA</td>
<td>Qualitative</td>
<td>Asian American</td>
<td>23</td>
<td>Community</td>
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<tr>
<td>Cochrane et al. 2016; PMID: 26896472</td>
<td>UK</td>
<td>Qualitative</td>
<td>Somali community living in UK</td>
<td>30</td>
<td>Community</td>
</tr>
<tr>
<td>Lee et al. 2017; PMID: 28950835</td>
<td>UK</td>
<td>Qualitative</td>
<td>Chinese immigrants</td>
<td>61</td>
<td>Community</td>
</tr>
<tr>
<td>Sweeney et al. 2015; PMID: 25890125</td>
<td>UK</td>
<td>Qualitative</td>
<td>Immigrant communities and HCWs</td>
<td>118</td>
<td>Community and healthcare centres</td>
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<td>van der Veen et al. 2014; PMID: 23913128</td>
<td>Netherlands</td>
<td>Survey</td>
<td>Turkish-Dutch community</td>
<td>N/A</td>
<td>Community</td>
</tr>
</tbody>
</table>
sampling method which introduces selection bias [3–5, 33, 37, 41, 53–56], two studies did not describe a sampling method [39, 40], five used a random sampling method [46, 47, 50–53], three studies included all intended participants [44, 45, 52], and only one study used a sample size based on pre-study consideration [19]. A participant response rate was presented in 10 studies; in nine of these the response rate was >60%, only one had a 30% response rate [44]. Statistical significance of results was reported in 15/19 studies [42, 43, 50–56]. For the single study that used mixed methodology [40], a convenient sample was used. Participants’ response rate and statistical significance of quantitative data was not reported. In the qualitative question [36, 40–43, 45–46, 53–56], all except two of these [40, 41] clearly described data collection procedure and the research context. Analysis of data may be less robust in four studies [41, 42, 55, 56] since there was no description of how many researchers analysed the results and how differences in extracted themes and codes were resolved between researchers. Two studies did not provide details of ethics approval [45, 54]; seven studies did not report in detail on their study limitations [39, 40, 42, 43, 50–56]. For the single study that used mixed methodology [40], a convenient sample was used. Participants’ response rate and statistical significance of quantitative data was not reported. In the qualitative

<table>
<thead>
<tr>
<th>Citation (Author; Date; PMID), divided by region of origin and presented alphabetically by first author</th>
<th>Country where study took place</th>
<th>Study design</th>
<th>Study participants</th>
<th>Sample size</th>
<th>Recruitment site</th>
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<td><strong>MIDDLE EAST AND ASIA</strong></td>
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<td>Dam et al. 2016; PMID: 2810149815</td>
<td>Vietnam and USA</td>
<td>Survey</td>
<td>General population</td>
<td>1012</td>
<td>Hospital</td>
</tr>
<tr>
<td>Eguchi et al. 2013; PMID: 2408676516</td>
<td>Japan</td>
<td>Survey</td>
<td>Japanese working community</td>
<td>3129</td>
<td>Community</td>
</tr>
<tr>
<td>Eguchi et al. 2014; PMID: 2479209517</td>
<td>Japan</td>
<td>Survey</td>
<td>General population</td>
<td>3000</td>
<td>Community</td>
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<tr>
<td>Huang et al. 2016; PMID: 2720637918</td>
<td>China</td>
<td>Survey</td>
<td>Individuals with HBV and healthy controls</td>
<td>1236</td>
<td>Community</td>
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<tr>
<td>Ishimaru et al. 2016; PMID: 2710864519</td>
<td>Japan</td>
<td>Survey</td>
<td>Nurses</td>
<td>992</td>
<td>Hospital</td>
</tr>
<tr>
<td>Ishimaru et al. 2017; PMID: 2916512520</td>
<td>Japan</td>
<td>Survey</td>
<td>Nurses</td>
<td>400</td>
<td>Hospital</td>
</tr>
<tr>
<td>Leng et al. 2016; PMID: 2704396321</td>
<td>China</td>
<td>Survey</td>
<td>General population</td>
<td>903</td>
<td>Community</td>
</tr>
<tr>
<td>Mohammed et al. 2012; PMID: 2285688922</td>
<td>Malaysia</td>
<td>Survey</td>
<td>People with HBV infection</td>
<td>483</td>
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<td>Ng et al. 2013; PMID: 2180763023</td>
<td>Malaysia</td>
<td>Qualitative study</td>
<td>People with HBV infection</td>
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<td>Hospital</td>
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<tr>
<td>Rafique et al. 2015; PMID: 2566451824</td>
<td>Pakistan</td>
<td>Quantitative and qualitative study</td>
<td>People with HBV infection</td>
<td>140</td>
<td>Hospital</td>
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<tr>
<td>Taheri Ezbarami et al. 2017; PMID: 2908565725</td>
<td>Iran</td>
<td>Qualitative study</td>
<td>People with HBV infection</td>
<td>27</td>
<td>Community</td>
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<tr>
<td>Valizadeh et al. 2016; PMID: 2698966626</td>
<td>Iran</td>
<td>Qualitative study</td>
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<td>18</td>
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<td>Valizadeh et al. 2017; PMID: 2393626227</td>
<td>Iran</td>
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<td>Wada et al. 2016; PMID: 2685000228</td>
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<td>Survey</td>
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</tr>
<tr>
<td>Wai et al. 2005; PMID: 1612405329</td>
<td>Singapore</td>
<td>Survey</td>
<td>People with HBV infection</td>
<td>192</td>
<td>Community</td>
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<tr>
<td>Wallace et al. 2017; PMID: 2876476830</td>
<td>China</td>
<td>Qualitative study</td>
<td>People with HBV infection</td>
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<td>Hospital</td>
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<tr>
<td>Yu et al. 2015; PMID: 2673313331</td>
<td>China</td>
<td>Survey</td>
<td>General population</td>
<td>6538</td>
<td>Community</td>
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<tr>
<td>Drazic et al. 2013; PMID: 2317132432</td>
<td>Australia</td>
<td>Survey</td>
<td>General population</td>
<td>77</td>
<td>Community</td>
</tr>
<tr>
<td>Sievert et al. 2017; PMID: 2812013139</td>
<td>Australia</td>
<td>Survey</td>
<td>Afghan, Rohingya and Sudanese community</td>
<td>26</td>
<td>Community</td>
</tr>
</tbody>
</table>

HBV = hepatitis B virus, HCW = healthcare worker
arm, data collection and analysis was clearly described but it was not stated how many researchers analysed the data and how discrepancies were handled.

There was considerable diversity in the size of the population sampled (range 14–6538), but overall, most studies had small sample sizes (median 173), and some were opportunistic in recruiting participants, thus limiting the generalisability of the findings.

Themes
The data that we assimilated from our literature review of 32 systematically identified studies are presented in Table 2–Table 4 below.

Discussion
Through this review, we have been able to identify some key themes including the potentially profound impact of HBV infection on personal wellbeing and mental health, opportunities for education and career, influence on family and relationships, and the role that health care workers can play in either contributing to stigma or dispelling it. Through enhancing consistent insights into these areas, the ‘blind spot’ associated with HBV stigma can start to be reduced. Previous reviews addressing stigma in Asian populations have reported small numbers of relevant publications, but identify the challenges of stigma, poor knowledge, and lack of focus on appropriate interventions. This review demonstrates the lack of data for the whole of the African continent which is particularly striking. A recent report showed that in Africa, hepatocellular carcinoma (HCC) secondary to HBV infection frequently presents at a late stage, where effective treatment would be challenging for any healthcare system, and indeed presentation is too late to allow formal diagnosis or treatment – this illustrates a hidden burden of infection, another aspect of the ‘blind spot’.

Stigma associated with physical disease manifestations
In most cases, HBV infection is asymptomatic and invisible for many decades, so individuals are not likely to be physically stigmatised. However, in acute infection, and again in the latter stages of chronic disease, it may cause jaundice and other manifestations such as abdominal swelling from ascites. We have not found any representation in the literature of stigma associated with specific physical syndromes, but further work is needed to explore this possibility. Importantly, health-related quality of life, including mental health, has been shown to decline in the setting of more severe manifestations of HBV infection.

Relationship between stigma and knowledge or education
Findings in Africa demonstrate a general lack of knowledge on HBV, an inability to define the disease, confusion of HBV with other infections, including malaria, yellow fever and HIV, and the association of HBV symptoms with witchcraft or poisoning. Such negative associations have been described to have the potentially profound impact of ‘spoiling the identity’ of the individual: the individual ceases to be perceived as a normal person but rather one who is tainted and discounted from society. Lack of knowledge or awareness leads to misinformation that feeds stigma and discrimination. Formal education can be important in reducing discrimination and stigma; however, it is interesting to note that this is not always the case. Indeed, higher levels of knowledge or formal education can sometimes be associated with increased stigma. One study describes how specific knowledge - such as recognising sexual contact as a transmission route – can actually increase stigma. In other settings, education level did not have a specific relationship with stigma. A general lack of stigma was reported associated with HBV in the Somali population, but this study reports that the problem of stigma is increasing over time as education increases.

Age may be relevant to knowledge or education, and varying influence of age on stigma has also been reported; in some instances older age and traditional values have been associated with stigma, while in others, there is decreased prejudice among older age. In light of these discrepancies, it is important to design studies with bigger sample sizes and conduct studies in different regions and communities. This will help not only provide a clear explanation of factors associated with stigma in HBV but will also guide in designing interventions that target specific groups of people who might be most vulnerable to the effects of stigma.

Interventions for HBV stigma
Depending on the coping strategies used, not everyone experiencing stigma will necessarily suffer emotional distress or have diminished well-being as a consequence. In HIV, avoiding coping strategies such as denial have been associated with higher levels of depression whereas acceptance of the diagnosis, associated with personal control and self-efficacy, is associated with reduced levels of depression. Among patients with schizophrenia, the ability to use positive coping strategies was associated with reduced self-stigma. Stigma and/or the disease process can contribute to the decline of health-related quality of life and mental health of some individuals living with chronic HBV, however there are few studies that address these issues. In light of this, further studies are needed to explore coping strategies used to deal with HBV stigma, to explore the choice of coping strategy, and to determine outcomes.

As well as individual coping strategies, a variety of other interventions have been proposed to tackle stigma. In many cases, attitudes may improve after realising that infection can be prevented and managed therapeutically. This is in line with a report from the WHO about mental illness, highlighting that stigma can be combated through educational messages representing conditions as illnesses that respond to specific treatment. Counselling can provide several benefits, alleviating anxiety associated with a new diagnosis, as well as providing an opportunity to share factual information regarding treatment, prevention, self-care and overall well-being. This should be delivered sensitively, at a time and in a manner that supports the individual in accepting and processing the information.

There are several strategies that have been used to raise awareness of HIV, many of which could be applied to HBV. Dissemination of factual information through use of radio, television, posters, pamphlets and drama has been widely used to diminish...
### Table 2. Factors underpinning stigma in HBV infection, identified from a systematic literature review.

<table>
<thead>
<tr>
<th>Factor underpinning stigma</th>
<th>Evidence from systematic literature review</th>
</tr>
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</table>
| **Cultural understanding and relevant language**                                           | • Lack of common cultural understanding of HBV is indicated by an absence of any word in local languages to define HBV and ‘hepatitis B’ and ‘carcinoma’ from English vocabulary in migrant populations.  
  • There is confusion between HBV and other infections, including malaria, yellow fever and HIV; HBV may be seen as synonymous with ‘jaundice’, or believed to be associated with nutritional status;  
  • One study describes the assumption that hepatitis A, B and C infections are ranked by letter in order of severity, or represent the chronological development of a single infection. |
| **Knowledge about diagnosis, treatment and symptoms of chronic HBV infection**             | • Poor understanding of the chronic nature of HBV infection, and lack of insight into the asymptomatic nature of HBV infection and its complications, are well described.  
  • There may be an assumption that lack of symptoms correlates with lack of severity;  
  • Poor awareness of treatment options can be associated with a ‘passive’ or ‘fatalistic’ attitude towards treatment;  
  • There are misconceptions that HBV screening tests can be harmful and that HBV infection is not treatable;  
  • A significant correlation is reported between less knowledge and higher stigma scores. However, among individuals with HBV infection, higher levels of HBV knowledge can also be associated with being more worried;  
  • Improved knowledge of HBV infection is associated with higher levels of formal education, and with a close relationship with an individual infected with HBV. |
| **Beliefs and insights into transmission of HBV infection**                               | • Beliefs are widespread that HBV can be transmitted through sharing of utensils, via food and water, or eating together;  
  • There is a belief that smoking tobacco causes HBV;  
  • Some studies report beliefs that HBV infection arises as a result of poor sanitation or could be transmitted by sharing water for bathing;  
  • In some communities, HBV infection is regarded as a genetic trait;  
  • HBV infection is represented as a consequence of immoral behaviour, or as a punishment for sins;  
  • Some communities believe that HBV infection is caused by witchcraft or evil spirits; this can be associated with pursuit of traditional remedies or religious interventions;  
  • Poor insights into transmission are associated with lack of precautions for prevention of transmission;  
  • Awareness of injecting drug use and sexual transmission of HBV can be stigmatising. |
| **Sociodemographic factors**                                                             | • In some studies older age has been associated with increased stigma; however, this is not consistent, as older age has also been associated with decreased levels of stigma;  
  • People strongly defined by traditional values are more likely to stigmatise HBV infection;  
  • Unemployed individuals from rural areas are more likely to experience discrimination;  
  • HBV may be more prevalent in disadvantaged groups who are also stigmatised for other reasons, eg refugees;  
  • Stigma can be reduced by having a family member with HBV infection; in this case it clarifies misconceptions about the disease, humanizes the affected, and can reduce negative attitudes associated with cultural beliefs. |
| **Interactions with HCWs**                                                               | • Lacking or inaccurate information may be provided by HCWs regarding HBV diagnosis or treatment, including inappropriate reassurance, or overemphasis of potential complications;  
  • Some studies describe HCWs expressing discrimination or prejudice towards patients and/or colleagues with HBV infection, which may be more common among those who have poor knowledge or are unfamiliar with providing HBV care;  
  • Diagnosis of HBV infection is presented as ‘bad news’ which can add to anxiety and stigma;  
  • Lack of screening or vaccination may be associated with stigma, although in contrast, HBV-related discrimination is also described as arising in association with diagnostic screening. |
| **Emotional responses**                                                                  | • HBV infection can be associated with anxiety, fear and depression; see Table 3 for further details and references.                                                                                                                     |
Table 3. Evidence for the behavioural, psychological and social impact of HBV infection, identified from a systematic literature review.

<table>
<thead>
<tr>
<th>Factor with impact on HBV infection</th>
<th>Evidence from systematic literature review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access to appropriate health care and treatment compliance</td>
<td>• Stigma is associated with reduced uptake of opportunities for diagnostic screening and clinical care. 35,37,38,42,48,56,57,85; • There is a low rate of disclosure of HBV status among individuals with HBV to family, other acquaintances, and to HCs due to fear of stigma 50,55; • Stigma can lead to disengagement from treatment 86 and reduce treatment adherence 87; • Anxiety about treatment, or the cost of treatment (potentially not just for one individual but also for other family members), can lead to reluctance to seek clinical care and follow-up 32,43,62; • Treatment can be seen as futile 50; • Stigma can lead to negative experiences of health care such as being ‘labelled’, placed in physical isolation, or criticised by HCs 50; • Stigma may influence the priorities of health professionals and commissioners, leading to certain health issues being addressed whilst others are ignored 87.</td>
</tr>
<tr>
<td>Impact on opportunities for education, work and career development</td>
<td>• Discrimination is reported within schools 15,45; • HBV affects employment and education choices 30,80; individuals with HBV infection may be discriminated against at work, lose employment, or be unable to find work 30,34,42,54,56,60; they may also be concerned about missing work due to illness 38, and may be restricted from particular jobs (e.g. food preparation) 37,52; • As a result of discrimination in education and the work-place, HBV can prevent personal goals or potential from being fulfilled 88.</td>
</tr>
<tr>
<td>Impact on mental health</td>
<td>• People with HBV infection may fear psychological consequences of transmission, disease progression and/or treatment side effects 39,51,53, including fear of cancer and death 30,33,51,56; • Individuals in migrant populations may fear deportation 32,38; • A range of emotional responses is described, included shock and grief following initial diagnosis, and subsequently anxiety, sadness, denial, anger and aggression 30,32,51,54,62; • Negative self-image can be associated with infection, associated with feelings of disgrace, guilt and shame, humiliation, embarrassment, or inferiority 30,51,53,34,58,48,52,53,56; • Reactions can also include insomnia and depression 30,53,54,60,62, and suicidal ideation 42,54; • Anxiety is described in association with the economic cost of treatment 50; • A fear of disclosure promotes secrecy and isolation 30,50,60,62.</td>
</tr>
<tr>
<td>Impact on personal interactions</td>
<td>• ‘Fear of contagion’ causes isolation; individuals with infection either avoid or are rejected from social activities, including avoidance of sharing utensils / food / towels / soap 35,37,42,48,51,53,54,56,57,82, and may be banned from participation in sports 88; • Parents may be unwilling to allow their children to socialise with HBV-infected children 31,67; • Anxiety about spreading infection to family members leads to withdrawal from close relationships 30,32,34,52,53,57; and exclusion from social gatherings 88; • Individuals with HBV infection perceive themselves, or are perceived by others, as less desirable as a parent or spouse 31,51,52,54,56,57; • Partner or spouse refuses sexual intercourse or insists on use of condoms 54; • Individuals with HBV infection may seek assistance from traditional healers (THs) or faith leaders, seeking ‘purification’, although this can provide important psychosocial support, there is also the potential for harm and/or delaying presentation to clinical care 96.</td>
</tr>
</tbody>
</table>

Stigma towards HIV in resource limited settings. Multiple educational sessions can also be an effective way of increasing awareness and therefore reducing stigma, as participants have the opportunity to reflect on the concepts learnt in the previous sessions 78. Another successful method for training HCs is perspective-taking and empathy: participation is associated with increased willingness to treat people with certain illnesses, decreased stigma and increased awareness of confidentiality among healthcare workers 78. These approaches could be used to tackle HBV stigma among HCs and community members.

On-line support groups provide a platform for people living with HBV to share their experiences 60,70, and charities can be influential in raising awareness, and promoting important health messages 70. The internet is widely used as a tool for sharing experiences, and as such can raise awareness of stigma 7, as well as uniting individuals and communities as a support network. It is important for HCs to introduce newly diagnosed individuals to these avenues to help people living with HBV. Importantly, more charities and support groups that are well suited for people with HBV infection in Africa are needed.

Limitations and caveats

Only two studies were identified on HBV stigma from Africa 50,51; these studies were both carried out in one country (Ghana). Three other studies included African participants in USA 52, Australia 97 and in UK 51. This highlights the substantial problem of HBV neglect in Africa. However, although we undertook a robust systematic search of the peer-reviewed scientific literature, there may be other sources that are not captured by this scientific style of approach.
**Table 4. Interventions that have been used to tackle stigma in HBV, identified from a systematic literature review.**

<table>
<thead>
<tr>
<th>Category of intervention</th>
<th>Evidence from systematic literature review</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interventions targeting individuals with HBV infection</strong></td>
<td>• Provision of educational opportunities in health care settings, in the individual’s own language, can be valuable to inform patients of the importance of symptoms, treatment, follow-up, prevention and social stigma; improving knowledge regarding the potential for silent complications, and understanding treatment could enhance willingness to access healthcare and reduce fatalism; developing positive coping strategies may include seeking encouragement from spiritual leaders and open dialogue with family members; lifestyle modifications can be helpful, such as reduced intake of alcohol and fatty foods; barriers to interventions should be considered (e.g. remote location, no internet access, language barriers).</td>
</tr>
<tr>
<td><strong>Interventions targeting HCWs</strong></td>
<td>• Education and training for HCWs should be improved, particularly for community doctors in rural settings; this includes training in diagnosis, prevention, treatment and monitoring, and provision of appropriate pre- and post-test counselling. HCWs can be deployed to design interventions to encourage participation in treatment programs and better self-care; education and communication programmes are needed to reduce stigma towards patients and colleagues with HBV infection; championing a positive safety culture, such as strict infection control, may not only protect HCWs but can also improve the quality of patient care.</td>
</tr>
<tr>
<td><strong>Interventions targeting communities and policy makers</strong></td>
<td>• Culturally appropriate education programs are required to improve knowledge on symptoms, modes of transmission and preventative measures, to correct misconceptions and decrease stigma; this could include use of internet, social media, radio, posters in public places (bars, markets, healthcare settings), and should involve schools and religious leaders; public campaigns and awareness raising among individuals with HBV infection, the social implications of the infection, and should prioritise affordability of prevention and treatment.</td>
</tr>
</tbody>
</table>

Sub-Saharan Africa encompasses huge diversity, and as such it would be misleading to assume that we can generalise about culture, beliefs and stigma, or that findings that arise in one setting can be extrapolated to others; the knowledge, manifestations, and experience of stigma is bound to be different between settings. It is frequently the case that local, indigenous knowledge and understanding of disease and/or health conditions is not well reflected in the published literature. Further work will be needed to develop insights that are relevant to particular populations in order to develop the most effective interventions. Referring to specific examples for particular places or countries is currently difficult in the absence of more published data. However, to understand some of the specific challenges of HBV, we have previously collated individual experiences of HBV from patients, researchers and healthcare workers representing different settings across sub-Saharan Africa.

Our description of ‘coping strategies’ is an over-simplification of the complex responses that arise as a result of stigma. We recognise that many individuals who suffer stigma may not be able to deploy specific active coping mechanisms, and indeed may ‘endure’ their situation.

**Future aspiration and challenges**

We see this article as a starting point for this field, as it is currently very difficult to make substantial advances in the absence of better data. By collating the existing literature, we hope to raise the profile of this topic overall, to improve recognition of the problem, to promote dialogue, and to highlight specific areas of neglect. This provides a foundation for healthcare workers and researchers to build on over time.

Studies looking at stigma may benefit from a mixed method study design, providing stronger evidence and increasing generalisability of the findings. It is important to carry out research on stigma with the aim of demonstrating its burden and its effects, while also considering how to establish and evaluate interventions that tackle stigma within communities. We identified only one study that evaluated the effectiveness of stigma reduction programmes among Asians in USA. More studies like this are needed in Africa, in order to provide insights into local understanding and beliefs, as they will also help to deploy resources in the most appropriate and effective ways with particular relevance to individual settings. In addition to raising awareness among individuals with HBV infection, the
general public and HCWs, enhanced communication with policy makers is also crucial. Despite the high burden of HBV in low and middle-income countries, there is limited infrastructure to support diagnosis and treatment, and disproportionately little international research funding for HBV compared to other infectious diseases.

Conclusion
Despite the limited evidence from Africa, the data we have gathered reflect consistent themes in stigma and discrimination affecting individuals with chronic viral hepatitis infection. These may have a wide-reaching influence on physical health (for example inhibiting interaction with clinical services and reducing treatment adherence), psychological well-being (through increasing isolation, anxiety and depression), and interactions with family and the wider society (by limiting relationships, social interactions and employment opportunities). Recognising, understanding and tackling the issue of this stigma in African populations could be a valuable tool to improve population health and to underpin advances towards elimination strategies proposed for the year 2030. Education clearly provides a very important role in reducing discrimination and stigma; it is interesting to note that stigma may drive lack of knowledge, just as lack of knowledge may drive stigma.

There is also a pressing need for more research in this area, to identify and evaluate interventions that can be used effectively to tackle stigma in HBV, and for collaborative efforts between policy makers, HCWs, traditional healers, religious leaders, charity organisations and support groups, to improve awareness and tackle stigma in HBV in Africa.

Data availability
All data underlying the results are available as part of the article and Supplementary files, and no additional source data are required.

Grant information
JM is funded by a Leverhulme Mandela Rhodes Scholarship. PCM is funded by the Wellcome Trust (grant ref. 110110).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Supplementary material
Supplementary file 1: Details of search strategy used to identify studies on stigma in Hepatitis B virus (HBV) infection, from PubMed database. The terms in each row were combined by Boolean operator ‘OR’, the columns were combined by Boolean term ‘AND’. We carried out two searches: the first search focused on stigma in HBV in Africa - we combined all the columns in search strategy (#1 AND #2 AND #3); a second search was not limited to Africa – for this we only combined columns (#1 AND #3).

Click here to access the data.

Supplementary file 2: Full details of 32 studies identified by a systematic literature search of stigma in Hepatitis B virus (HBV) infection published between 2005 and 2017.

Click here to access the data.

Supplementary file 3. Details of risk of bias assessment, using Centre of Evidence based management checklist, on 14 quantitative studies identified by a systematic literature search of stigma in Hepatitis B virus (HBV) infection published between 2005 and 2017.

Click here to access the data.

Supplementary file 4. Details of risk of bias assessment, using NICE public health guidance qualitative appraisal checklist, on 20 quantitative studies identified by a systematic literature search of stigma in Hepatitis B virus (HBV) infection published between 2005 and 2017.

Click here to access the data.

References


70. Hepatitis B Foundation. Reference Source
Open Peer Review

Current Referee Status:  ?  ?

Version 1

Referee Report 05 June 2018

doi:10.21956/wellcomeopenres.15534.r32085

Herbert Muyinda
Child Health and Development Centre, College of Health Sciences, Makerere University, Kampala, Uganda

1. Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes: The article addresses the important health aspect of HBV stigma. It states that there is minimal recognition of the challenge stigma poses especially in Africa, yet it is a potentially major barrier to the successful delivery and access to care. The authors set out to fully understand [assimilate] the evidence for the nature and impact of stigma on the lives of people with HBV infection, and on the community, and to suggest ways to tackle stigma and discrimination.

1. Are sufficient details of the methods and analysis provided to allow replication by others?
Partly: This was a systematic literature review using a search in PubMed focusing on information published between 2007 and 2017, with a particular focus on Africa. However, although the target area of analysis was ‘Africa’, in the limitations section they state that there were only two studies conducted in Africa, in fact in the abstract they state that it was only one. This paucity of published information on the subject matter would call for triangulation – additional sources of information would be sought to supplement the one or two published articles reviewed.

1. Are the conclusions drawn adequately supported by the results presented in the review?
Partly: While this topic is important and merits careful analysis, this article presents over generalized already known assertions regarding stigma, with hardly new contribution to the topic. The authors approach the topic by posing a question in their title: “A blind spot? …” The implication here is that the article should explicitly articulate the nature of ‘blindspotness’ of HBV stigma. Non-availability or presence of few articles of published work on this particular topic may not be enough to make it a blind spot. To satisfy such a claim, it would be useful to address some of these questions: Do people (particularly in Africa) know what Hepatitis B disease is? What are some of the local names/labels/terminologies used in describing it? What are the individual and collective experiences of the disease, and what are the common social responses? In other words, a more detailed description and analysis of how stigma manifests itself and experienced by the affected individuals (in Africa) would be the way to illustrate the social (in)visibility and/or extent/magnitude of the ‘blindspotness’ of HBV stigma, as referred to in the article.

First of all, focusing on Africa as a whole (as a target population) is one of the main challenges of the paper. Africa is too diverse to have such generalized ‘lack of knowledge’, ‘misconceptions and prejudices’ regarding HBV. The Moslem North and part of west Africa, the Sub-Saharan Africa, and the relatively wealthy South Africa are different cultures and the knowledge, manifestations, and experience of stigma is bound to be different. The paper can benefit from referring to examples, references in particular places
or countries.

While the article states the intention to assimilate the available evidence for the nature and impact of stigma on the lives of people with HBV infection and on the community, this does not seem to have been effectively achieved. The paper states very generalized and quite obvious views, which makes it difficult to find new contribution the paper makes to the topic of HBV stigma.

There is a general tendency to be unspecific regarding manifestation and experience of stigma, by referring to experiences in other conditions – HIV and AIDS, and mental illness, and areas outside Africa. For instance, the authors emphasized lack of knowledge of HBV among different players (health workers, people with HBV infection themselves, community) as potent driver of stigma, and then link the negative effects thereof to prevention, treatment seeking and provision of care. On pg. 3 the authors state that “stereotypes and prejudice may stem from physical differences attributable to the condition, misconceptions associated with fear of contagion, and judgements about routes of transmission, all of which may be underpinned by lack of knowledge … arises from lack of awareness, lack of education and lack of perception … and that healthcare workers provided inaccurate information to those diagnosed by HBV.” While these assertions may be true, the kind of ‘knowledge’ being referred to as lacking in this case, is not clear. First, if there was ‘lack of knowledge’, then what would shape the HBV stigma stated in the paper? The fact that there was stigma, means that there was some form of knowledge; probably ‘inappropriate’ but some knowledge. Quite often, there is a tendency to disregard local/indigenous (African) knowledge and understanding of disease and/or health conditions including HBV, and emphasis placed on the biomedical knowledge and quoting sources from the Western World.

Further, generally stigma is known to be characterized by labelling, and social constructs and actions that discount one’s identity (see Goffman: Notes on spoilt Identity). For example, it is not clear what knowledge of HBV bodily signs and symptoms people have, their local names/labels/terminologies, and how this knowledge shapes different forms of stigma. All these seem to have been missing in the literature, which makes it difficult to conclude from the review that people with HBV (in Africa) were actually being stigmatized, leave alone HBV stigma being a blind spot. In other words, the paper does not explicitly show whether or how HBV related stigma (in Africa), is blind spot.

**Other comments:**

- Coping strategies and interventions for HBV stigma” (Table 3)

  The coping strategies listed in the table and discussed in the paper assume existence of particular forms of stigma, that have not been shown to be evident or experienced in Africa. The paper can be improved by linking particular ‘coping’ strategies to particular forms of stigma (in Africa). In fact, in some cases the stigmatized hardly cope, but just endure, and the boundary between coping, and endurance is so blurred.

**Discussion:**

The claim in the paper, that the data gathered reflect consistent themes of stigma and discrimination … is not adequately illustrated in the results section. Most of the examples given were from Asia and other areas other than Africa, and of other conditions – mental illness and HIV and AIDS, and not HBV, which hardly reflects any consistency at stated.

**Limitations:**

The limitations as stated, considerably weakens the paper. Given the paucity of data, a ‘blind spot on HBV stigma in Africa would be verified by triangulation of information clearly showing what is (in)visible/blindspot, rather than simply interpreting it as lack of literature on the subject matter.

**Are the rationale for, and objectives of, the Systematic Review clearly stated?**

Yes
Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?
Partly

**Competing Interests:** No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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Author Response 14 Aug 2018

Philippa Matthews, Nuffield Department of Medicine, Peter Medawar Building for Pathogen Research, University of Oxford, UK

REVIEWER: Are sufficient details of the methods and analysis provided to allow replication by others? **Partly:** This was a systematic literature review using a search in PubMed focusing on information published between 2007 and 2017, with a particular focus on Africa. However, although the target area of analysis was ‘Africa’, in the limitations section they state that there were only two studies conducted in Africa, in fact in the abstract they state that it was only one.

RESPONSE: We have corrected this statement in the abstract, this now reads” We identified a total of 32 articles, of which only two studies were conducted in Africa”. As per responses to reviewer 1, this information has also been presented more clearly in the form of a new table 1.

REVIEWER: This paucity of published information on the subject matter would call for triangulation – additional sources of information would be sought to supplement the one or two published articles reviewed.

RESPONSE: We agree that additional sources of information are required, and this provides the justification for drawing on the literature for HIV, TB and mental health to provide more insights than can be gained from the HBV literature alone. In response to comments from reviewer 1, we have adopted a clearer stance on which sections of the manuscript draw on just the HBV literature, and which sections have included reference to wider sources. Please see our comments to reviewer 1 for more details.

REVIEWER: While this topic is important and merits careful analysis, this article presents over generalized already known assertions regarding stigma, with hardly new contribution to the topic. The authors approach the topic by posing a question in their title: “A blind spot? …” The implication here is that the article should explicitly articulate the nature of ‘blindspotness’ of HBV stigma. Non-availability or presence of few articles of published work on this particular topic may not be enough to make it a blind spot. To satisfy such a claim, it would be useful to address some of these questions: Do people (particularly in Africa) know what Hepatitis B disease is? What are some of the local names/labels/terminologies used in describing it? What are the individual and collective
experiences of the disease, and what are the common social responses? In other words, a more detailed description and analysis of how stigma manifests itself and experienced by the affected individuals (in Africa) would be the way to illustrate the social (in)visibility and/or extent/magnitude of the ‘blindspotness’ of HBV stigma, as referred to in the article.

RESPONSE: We believe our work is a new contribution to the topic, as no prior attempt has been made to review the existing literature in a systematic way. To explain the use of the ‘blind spot’ metaphor in the title, we have added some text to the introduction to explain the use of this metaphor as a way of describing the lack of recognition (including lack of local words to describe the infection), the paucity of existing data, and a neglect of the problem to date. We also return to this point in the discussion, to emphasise the consequences of the blind spot through missed or late diagnosis. The questions posed by the reviewer cannot be completely addressed, due to missing data, but our results do incorporate the lack of missing words to describe the infection in certain languages and the individual and collective responses to infection. These points are more clearly presented as a result of the more robust structure to the results section that we have undertaken in response to feedback from reviewer 1.

REVIEWER: First of all, focusing on Africa as a whole (as a target population) is one of the main challenges of the paper. Africa is too diverse to have such generalized ‘lack of knowledge’, ‘misconceptions and prejudices’ regarding HBV. The Moslem North and part of west Africa, the Sub-Saharan Africa, and the relatively wealthy South Africa are different cultures and the knowledge, manifestations, and experience of stigma is bound to be different. The paper can benefit from referring to examples, references in particular places or countries.

RESPONSE: We agree with this important point, and have added to the discussion accordingly: ‘Sub-Saharan Africa encompasses huge diversity, and as such it would be misleading to assume that we can generalise about culture, beliefs and stigma, or that findings that arise in one setting can be extrapolated to others; the knowledge, manifestations, and experience of stigma is bound to be different between settings. Further work will be needed to develop insights that are relevant to particular populations in order to develop the most effective interventions. Referring to specific examples for particular places or countries is currently difficult in the absence of more published data. However, to understand some of the specific challenges of HBV, we have previously collated individual experiences of HBV from patients, researchers and healthcare workers representing different settings across sub-Saharan Africa (O’Hara et al, doi: 10.1371/journal.pntd.0005842).

REVIEWER: While the article states the intention to assimilate the available evidence for the nature and impact of stigma on the lives of people with HBV infection and on the community, this does not seem to have been effectively achieved. The paper states very generalized and quite obvious views, which makes it difficult to find new contribution the paper makes to the topic of HBV stigma.

RESPONSE: We agree with the frustrations expressed here; it is indeed difficult to make advances in the absence of a better literature. However, we see the publication of this article as providing important advocacy for the future development of this field. Although the data may seem ‘generalised and obvious’, they have not currently been translated into any consistent recognition or action. We have added this specifically to the discussion (section headed ‘future aspirations and challenges’) as follows: ‘We see this article as a starting point for this field, as it is currently very difficult to make substantial advances in the absence of better data. By collating the existing literature, we hope to raise the profile of this topic overall, and to highlight specific areas of neglect. This provides a foundation for clinicians and researchers to build on over time.’
REVIEWER: There is a general tendency to be unspecific regarding manifestation and experience of stigma, by referring to experiences in other conditions – HIV and AIDS, and mental illness, and areas outside Africa. For instance, the authors emphasized lack of knowledge of HBV among different players (health workers, people with HBV infection themselves, community) as potent driver of stigma, and then link the negative effects thereof to prevention, treatment seeking and provision of care.

RESPONSE: In keeping with comments also raised by reviewer 1, we have improved the clarity around evidence that is HBV-specific, vs. insights that have been gained from sources pertaining to other diseases/infections. The results now contain only HBV-specific findings based on a systematic approach.

REVIEWER: The authors state that “stereotypes and prejudice may stem from physical differences attributable to the condition, misconceptions associated with fear of contagion, and judgements about routes of transmission, all of which may be underpinned by lack of knowledge … arises from lack of awareness, lack of education and lack of perception … and that healthcare workers provided inaccurate information to those diagnosed by HBV.” While these assertions may be true, the kind of ‘knowledge’ being referred to as lacking in this case, is not clear. First, if there was ‘lack of knowledge’, then what would shape the HBV stigma stated in the paper? The fact that there was stigma, means that there was some form of knowledge; probably ‘inappropriate’ but some knowledge.

RESPONSE: We have expanded table 2 content regarding ‘lack of knowledge’ to be specific about the gaps in knowledge/understanding, e.g. lack of knowledge ‘about transmission routes’, ‘about treatment availability’, ‘about chronic and asymptomatic nature of HBV infection’, and specific misconceptions e.g. that tobacco causes HBV infection. In this way, we recognise that the lack of knowledge is not absolute but that specific gaps in knowledge can be detrimental.

REVIEWER: Quite often, there is a tendency to disregard local/indigenous (African) knowledge and understanding of disease and/or health conditions including HBV, and emphasis placed on the biomedical knowledge and quoting sources from the Western World.

RESPONSE: Thank you for highlighting this omission. As above, we have added specific reference to our previous publication (O’Hara et al, doi: 10.1371/journal.pntd.0005842) in which local experiences are better individually represented. Although most of us currently have affiliations in the UK, it is noteworthy that our authorship list represents personal and individual experience from Uganda, South Africa, Kenya and Zimbabwe. It is difficult to add more robust representation of local beliefs as this is just not apparent in the literature, but we agree that this is a crucial aspiration, and we have therefore added to the discussion to highlight this point, as follows: ‘It is frequently the case that local, indigenous knowledge and understanding of disease and/or health conditions is not well reflected in the published literature’, and subsequently ‘More studies like this are needed in Africa, in order to provide insights into local understanding and beliefs, as they will also help to deploy resources in the most appropriate and effective ways with particular relevance to individual settings’.

REVIEWER: Further, generally stigma is known to be characterized by labelling, and social constructs and actions that discount one’s identity (see Goffman: Notes on spoilt Identity). For example, it is not clear what knowledge of HBV bodily signs and symptoms people have, their local
names/labels/terminologies, and how this knowledge shapes different forms of stigma. All these seem to have been missing in the literature, which makes it difficult to conclude from the review that people with HBV (in Africa) were actually being stigmatized, leave alone HBV stigma being a blind spot. In other words, the paper does not explicitly show whether or how HBV related stigma (in Africa), is blind spot.

RESPONSE: We agree that these are important aspirations for ongoing research. We have expanded on the ways in which the ‘blind spot’ metaphor is pertinent (see point above). We have added the reference to Goffman in order to support the point raised about identity, and have expanded the discussion as follows: ‘Findings in Africa demonstrate a general lack of knowledge on HBV, an inability to define the disease, confusion of HBV with other diseases such as malaria and yellow fever, and the association of HBV symptoms with witchcraft or poisoning. Such negative associations have been described to have the potential to ‘spoil the identity’ of the individual: the individual ceases to be perceived as a normal person but rather one who is tainted and discounted from society. Lack of knowledge or awareness leads to misinformation that feeds stigma and discrimination.’

REVIEWER: The coping strategies listed in table 3 and discussed in the paper assume existence of particular forms of stigma, that have not been shown to be evident or experienced in Africa. The paper can be improved by linking particular ‘coping’ strategies to particular forms of stigma (in Africa). In fact, in some cases the stigmatized hardly cope, but just endure, and the boundary between coping, and endurance is so blurred.

RESPONSE: In the results section, we have improved the layout of this table to reduce duplication (see feedback to reviewer 1). Within the discussion section entitled ‘limitations and caveats’, we have added as follows: ‘Our description of ‘coping strategies’ is an over-simplification of the complex responses that arise as a result of stigma. We recognise that many individuals who suffer stigma may not be able to deploy specific active coping mechanisms, and indeed may simply ‘endure’ their situation’.

REVIEWER: Discussion: The claim in the paper, that the data gathered reflect consistent themes of stigma and discrimination … is not adequately illustrated in the results section. Most of the examples given were from Asia and other areas other than Africa, and of other conditions – mental illness and HIV and AIDS, and not HBV, which hardly reflects any consistency at stated.

RESPONSE: We have removed the use of the description of our results as identifying ‘consistent themes’, and simply state that ‘the data we have gathered reflect stigma and discrimination affecting individuals with chronic viral hepatitis infection’. The new table 1 provides the reader with a clearer oversight regarding the geographical origin of the dataset we have used.

REVIEWER: Limitations: The limitations as stated, considerably weakens the paper. Given the paucity of data, a ‘blind spot on HBV stigma in Africa would be verified by triangulation of information clearly showing what is (in)visible/blindspot, rather than simply interpreting it as lack of literature on the subject matter.

RESPONSE: We have addressed this point through our specific responses to individual points raised earlier in both reviews. Specifically, this includes a clear comment in the introduction and methods about triangulation of data sources, drawing on HIV, TB and mental illness, and
expanded introduction and discussion to include a better description of the ‘blind spot’. It is an interesting point that the blind spot is not as simple as merely a lack of data.

**Competing Interests:** No competing interests were disclosed.

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**Summary:** The article presents findings from a systematic review on HBV stigma. The authors recognize the large burden of HBV globally and the potential for stigma to hamper prevention, diagnosis and treatment. They unpack the lack of knowledge underpinning the stigmatization of HBV as well as some factors associated with stigmatization of HBV. They also present findings on how HBV stigma impacts health care, familial and social relationships, employment, mental health, and behavior. The authors also describe strategies individuals use to cope with or manage HBV stigma and interventions to address HPV stigma. Finally, the authors conclude by identifying gaps in the literature, particularly a paucity of research conducted in Africa, and provide guidance for future research.

**Specific Comments to explain ratings:**

**With respect to rating for Question 1 (partly):** The rationale for the paper is clear, however the objectives of this paper are less clear. We are uncertain what the word assimilate means with respect to the literature. Did the authors mean to use this term? If so, it may be helpful to explain it further. As well, it’s unclear if the authors are going to abstract suggestions to address stigma and discrimination from the included articles or if they are going to use their findings to provide suggestions, drawing on literature from other stigmatized conditions. It is also unclear from the results section, and in particular the literature included in the tables, if this literature review is restricted to HBV stigma, or also includes HIV and mental health stigma (in which case the review is not extensive enough). The supplementary material showing the search strategy indicates it is restricted to HBV stigma, yet the results section suggests otherwise. The paper would be strengthened by a clearer statement of the objectives and then ensuring that those objectives are adhered to throughout.

**With respect to rating for Question 2 (partly):** The authors do not include their specific inclusion/exclusion criteria, which relates to the point above with respect to the mixing of what looks like included literature from the search, with other literature from HIV and Mental Health in the results section. It is also unclear how “factors associated with stigma,” “impact of stigma on the lives of people with HBV,” and “proposed interventions to tackle stigma in the society” were systematically captured. There is one article included in the data abstraction supplementary file (Cochrane et al 2016) for which “not/applicable” is listed for all of the data abstraction categories related to stigma. It is unclear why this article is included.

More detail is needed on the process of reviewing and selecting which abstracts went to full review and then which articles were included. Was this done by one person? Two people who then compared results with a third as tie breaker in cases of disagreement? This information will help the reader assess the strength of the review.
A standard figure showing the two searches graphically would be helpful for the reader (how many initial abstracts, how many of those went to full review and then how many of those were included).

With respect to rating for Question 4 (partly): The manuscript would benefit from the authors including a discussion on risk of bias in their process and review. They do not mention bias or describe any methods used for assessing risk of bias of individual included studies. Other limitations that need to be mentioned include that many of the findings presented in the results section come from a single article (e.g. in most of the tables, each point often only has one reference attached to it, and in some cases not even a reference from the search itself).

Other comments:

Abstract: The authors state that only one study was conducted in Africa, while in the limitations it states that two studies were conducted in Africa.

Overall language comment: Please do not use HIV/AIDS, it is considered stigmatizing. UNAIDS language guidelines recommend using HIV, HIV and AIDS, or HIV or AIDS, depending on the context. Using HIV/AIDS implies HIV=AIDS and that one cannot live a long, healthy and productive life with HIV.

Methods: See comment above on explanation for rating for Question 2.

Results: The results section would be strengthened by presenting only the results of the search in the results section and keeping discussion (and inclusion of non-HBV stigma literature) to the discussion section. The results section often seems more like a discussion section and it is sometimes difficult to tell what findings are coming from the HBV stigma literature review, versus what are coming from other articles not included in the review (e.g. some of the findings presented in tables are from HIV, mental health or general stigma literature), or are views/conclusion the authors have drawn. For example, in the 4th paragraph of the “Factors associated with creating or perpetuating stigma for individuals with HBV Infection” section, the authors hypothesize about why a certain trend is observed. As well, the “coping strategies and interventions for HBV stigma” section is almost entirely a discussion of coping strategies that have been used to tackle stigma in other fields or interventions that have been used to address stigma related to diseases other than HBV. While pertinent, this information probably belongs in the discussion section.

The results section would benefit from a clearer organizational structure and ensuring only results from the HBV literature are included. For example,

- “Factors associated with creating or perpetuating stigma for individuals with HBV Infection”
  - It seems the first section is trying to unpack factors driving or causing stigma and factors associated with higher levels of stigma. However, this section also includes some behavioral impacts, such as pursing traditional or religious intervention at the individual level, which could be considered “impact on access to care”
  - At the health care level, providing inaccurate information and the provision of inappropriate reassurance or over emphasis of potential complications seem to be the result of lack of knowledge, rather than evidence of lack of knowledge, that could be considered “impact on access to care” or “impact on quality of care.”
  - The text notes stigma among policy makers can be problematic, but this isn’t supported by evidence in the table.
Table 1: Unclear if these factors are actually coming from the HBV literature or not, given the inclusion of HIV articles in the table that from the supplementary material describing the literature search, were not included. For example references 40, 41.

Table 2:

1. The “Impact on mental health” section of the table seems to have some redundant items, particularly around guilt and shame

2. The “Impact on social behavior” section of the table seems to largely encompass manifestations of stigma, but not necessarily social behaviors. It is unclear what is meant by “suffer feelings of “passivity” because of lack of treatment, or cost of treatment, which results in missing…”

3. The “relationship with education/knowledge” section seems to almost entirely overlap with the previous table, highlighting factors associated with stigma. However, it is interesting to highlight that stigma may drive lack of knowledge just as lack of knowledge may drive stigma. However, this might be better said in the text.

4. All references to articles that were not part of the actual HBV stigma review should be removed. This includes references 40, 41, 57, 58, 59. The articles should instead be referred to in the discussion section if the authors feel they are important to discuss around a key result.

Coping strategies and interventions for HBV stigma

Table 3

1. The title “Coping strategies associated with negative influence” is unclear. It seems like this bullet is for interventions.

2. All references that are not coming directly from the review need to be removed. Specifically, #’s 40, 48, 57, 58, 70

The table included in the supplementary material showing the articles should be included within the body of the article in a reduced format, given it is central to the review process.

Discussion: The discussion section paragraph reads more like a conclusion paragraph, while there is much discussion embedded in the results section. Moving the discussion from the results into the discussion section will strengthen both the results and discussions section and also make clearer to the reader what is emanating directly from the review of the HBV literature versus what the authors are supplementing from other fields, because of the sparse HBV stigma literature. The discussion section could be expanded by discussing what the gaps are that were found—and then using the literature from other fields to suggest how those gaps might be filled etc.

Limitations: In addition to comments above to Q.4, it would be appropriate to discuss the strength of findings/quality of included articles. Was any rating of the quality of articles conducted? We also find the statement at the end of the limitations section that literature from HIV, TB and mental illness was drawn on, because of the limitations of the literature found to be confusing. The fact that this was done, muddies
the methods and results sections. If the literature review is only focused on HBV stigma, no matter how scarce the literature is, only this literature should be drawn on/presented in the results section. Other literature can/should be discussed in the discussion section. This is conflating of the results coming from the search itself, with ‘supplementary’ literature from other fields in the result section is problematic. Please move all discussion of other literature not coming from the literature search on HBV to the discussion section.

Conclusions: The conclusions state stigma may disrupt adherence, however, adherence to treatment is not discussed in the results. However, hampered adherence is listed as an impact of stigma in the abstraction table for the Huang et al 2016 article.

References

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Partly

Are sufficient details of the methods and analysis provided to allow replication by others?
Partly

Is the statistical analysis and its interpretation appropriate?
Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?
Partly

Competing Interests: No competing interests were disclosed.

We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.
literature, to curate it in order to be able to unify key messages, and to highlight gaps where future work is still needed'. By strengthening our consistent adherence to the principles of a systematic literature review throughout the paper (addressed in more detail in the points below), our objectives are now set out in a more transparent way.

REVIEWER: As well, it's unclear if the authors are going to abstract suggestions to address stigma and discrimination from the included articles or if they are going to use their findings to provide suggestions, drawing on literature from other stigmatized conditions.

RESPONSE: We have used the reviewer's suggested text at the end of the introduction, to describe both of these approaches, adding: 'We have been able to develop suggestions to address HBV stigma and discrimination from the existing literature, but in light of the paucity of HBV-specific studies, we have also drawn on literature from other stigmatized conditions'.

REVIEWER: It is also unclear from the results section, and in particular the literature included in the tables, if this literature review is restricted to HBV stigma, or also includes HIV and mental health stigma (in which case the review is not extensive enough). The supplementary material showing the search strategy indicates it is restricted to HBV stigma, yet the results section suggests otherwise. The paper would be strengthened by a clearer statement of the objectives and then ensuring that those objectives are adhered to throughout.

RESPONSE: The primary focus of our review is HBV stigma, however in the absence of clear literature on this topic we have also drawn on wider literature about stigma in other conditions. We agree that this was not sufficiently clear or consistent as an approach in our initial version, and have amended the article accordingly as follows:

1. Introduction: we have amended the final paragraph to set out the approach more clearly, describing a systematic approach, curation to unify key themes, and highlighting gaps where future work is still needed. We also explain the need to triangulate our approach by drawing on resources from other stigmatized conditions including HIV, TB and mental illness to inform the discussion.

2. Methods: we have made a clear distinction between the systematic literature review undertaken for HBV stigma, versus a more general use of literature on other conditions to provide additional breadth and context.

3. Results: these are now clearly presented as pertaining only to the systematic literature review, reflecting HBV-specific data (see opening sentence of results section).

4. Discussion: we have used this section to reference the wider literature on stigma, using HIV, mental health and TB as examples.

REVIEWER: The authors do not include their specific inclusion/exclusion criteria, which relates to the point above with respect to the mixing of what looks like included literature from the search, with other literature from HIV and Mental Health in the results section.

RESPONSE: We have tackled this in a number of ways:

1. We have improved a description of our search strategy to make clear the specific focus on HBV stigma. This expanded section now reads as follows: 'we undertook a systematic literature search in PubMed; our search strategy focused entirely on the evidence surrounding stigma in HBV'.

2. We have moved the PRISMA flow diagram into the paper as Fig 1, thus providing the reader with a clear summary of our approach.
3. We have divided our methods surrounding the literature search into two sections, first ‘Search strategy: systematic literature review’, and second ‘Search strategy: other relevant resources’. This makes a distinction between the HBV component of the research, that has been conducted as a robust systematic literature review, versus other supporting references that were not identified through a formal systematic review, but were identified as relevant sources from robust, peer reviewed literature.'

REVIEWER: It is also unclear how “factors associated with stigma,” “impact of stigma on the lives of people with HBV,” and “proposed interventions to tackle stigma in the society” were systematically captured. There is one article included in the data abstraction supplementary file (Cochrane et al 2016) for which “not/applicable” is listed for all of the data abstraction categories related to stigma. It is unclear why this article is included.

RESPONSE: We have included a description of representing our results as a number of themes. This now reads 'We used our research question to group data into four major themes: factors underpinning stigma in HBV infection; evidence for the impact of stigma; coping strategies for individuals with HBV infection'. We have revised the metadata for all included studies: Cochrane et al 2016 does meet our inclusion criteria and we have included information on stigma extracted from this study in the results.

REVIEWER: More detail is needed on the process of reviewing and selecting which abstracts went to full review and then which articles were included. Was this done by one person? Two people who then compared results with a third as tie breaker in cases of disagreement? This information will help the reader assess the strength of the review.

RESPONSE: The initial review of abstracts was performed by one individual according to prospectively agreed, objective criteria, as set out in the PRISMA document. Two individuals contributed to the next stage of the review; this is now included in methods.

REVIEWER: A standard figure showing the two searches graphically would be helpful for the reader (how many initial abstracts, how many of those went to full review and then how many of those were included).

RESPONSE: This was originally in supplementary data, but we have now included a PRISMA flow diagram as fig 1 in the manuscript, as well as adding the relevant numbers to the text.

REVIEWER: The manuscript would benefit from the authors including a discussion on risk of bias in their process and review. They do not mention bias or describe any methods used for assessing risk of bias of individual included studies.

RESPONSE: We have now added a ‘risk of bias assessment’ approach; for qualitative studies we used the qualitative appraisal checklist by NICE public health guidance and for quantitative studies we used the Centre of Evidence based Management checklist. This has been added to the methods, and has informed a new paragraph in the results entitled ‘quality of. We have added new suppl tables 3 and 4 containing the detailed results of this assessment for each paper. Under the section of limitations/ caveats, we also describe some of the shortfalls of the included studies, recognising the paucity of the literature overall and in particular for Africa.

REVIEWER: Other limitations that need to be mentioned include that many of the findings
presented in the results section come from a single article (e.g. in most of the tables, each point often only has one reference attached to it, and in some cases not even a reference from the search itself).

RESPONSE: We have rectified this. The all results presented in the tables include only studies on HBV stigma identified from our systematic literature search. Where possible, we have added more than one reference for each point that is included; this now represents a comprehensive summary of all 34 included studies. However, we recognise that the literature is limited and therefore some points can only be supported by only one citation.

REVIEWER: Abstract: The authors state that only one study was conducted in Africa, while in the limitations it states that two studies were conducted in Africa.

RESPONSE: We have corrected accordingly (two studies were conducted in Africa). We have also improved the clarity of this in the new table 1, by dividing the literature by geographical region so it is easy to pick out the studies that are set in any given location.

REVIEWER: Please do not use HIV/AIDS, it is considered stigmatizing. UNAIDS language guidelines recommend using HIV, HIV and AIDS, or HIV or AIDS, depending on the context. Using HIV/AIDS implies HIV=AIDS and that one cannot live a long, healthy and productive life with HIV.

RESPONSE: Thank you for this feedback, we have corrected accordingly (although please note that several of our references use this abbreviation in their titles).

REVIEWER: The results section would be strengthened by presenting only the results of the search in the results section and keeping discussion (and inclusion of non-HBV stigma literature) to the discussion section. The results section often seems more like a discussion section and it is sometimes difficult to tell what findings are coming from the HBV stigma literature review, versus what are coming from other articles not included in the review (e.g. some of the findings presented in tables are from HIV, mental health or general stigma literature), or are views/conclusion the authors have drawn. For example, in the 4th paragraph of the “Factors associated with creating or perpetuating stigma for individuals with HBV Infection” section, the authors hypothesize about why a certain trend is observed.

RESPONSE: We have taken a careful approach to improving this; our results tables now cite only references that are derived from the systematic literature review. We have now moved all hypotheses and references to other diseases into the discussion section.

REVIEWER: As well, the “coping strategies and interventions for HBV stigma” section is almost entirely a discussion of coping strategies that have been used to tackle stigma in other fields or interventions that have been used to address stigma related to diseases other than HBV. While pertinent, this information probably belongs in the discussion section.

RESPONSE: We agree; we have trimmed the inclusion of coping strategies out of the results section and now feature more of this text in the discussion.

REVIEWER: The results section would benefit from a clearer organizational structure and ensuring only results from the HBV literature are included. For example,
“Factors associated with creating or perpetuating stigma for individuals with HBV Infection”

It seems the first section is trying to unpack factors driving or causing stigma and factors associated with higher levels of stigma. However, this section also includes some behavioral impacts, such as pursing traditional or religious intervention at the individual level, which could be considered “impact on access to care”

At the health care level, providing inaccurate information and the provision of inappropriate reassurance or over emphasis of potential complications seem to be the result of lack of knowledge, rather than evidence of lack of knowledge, that could be considered “impact on access to care” or “impact on quality of care.”

The text notes stigma among policy makers can be problematic, but this isn’t supported by evidence in the table.

RESPONSE: As per our responses to points above, we have improved the results section to make it more consistent and relating only to the HBV literature in the papers we identified through a systematic approach. Most of the additional text has been relocated to the discussion section. We have revisited the classification of each individual point into four different themes (represented by tables 2-5), although there is naturally some cross-referencing between these closely related areas. We have removed the inclusion of stigma among policy makers as we agree it is not sufficiently supported by the literature that we have identified.

REVIEWER: Table 1: Unclear if these factors are actually coming from the HBV literature or not, given the inclusion of HIV articles in the table that from the supplementary material describing the literature search, were not included. For example references 40, 41.

RESPONSE: We have corrected the tables, all the information included are from studies on HBV stigma identified from systematic literature review, and provided table 1 to summarise the literature on which we have based all other results tables.

REVIEWER: Table 2: The “Impact on mental health” section of the table seems to have some redundant items, particularly around guilt and shame.

RESPONSE: We agree, and have collated the relevant points and references into a single statement supported by several references.

REVIEWER: The “Impact on social behavior” section of the table seems to largely encompass manifestations of stigma, but not necessarily social behaviors. It is unclear what is meant by “suffer feelings of ‘passivity’ because of lack of treatment, or cost of treatment, which results in missing…”

RESPONSE: We have changed this sub-heading from ‘impact on social behaviour’ to ‘impact on social interactions’ which better encompasses the points that follow. We have also rephrased the statement to describe instead a ‘passive’ attitude towards treatment.

REVIEWER: Table 2: The “relationship with education/knowledge” section seems to almost entirely overlap with the previous table, highlighting factors associated with stigma. However, it is interesting to highlight that stigma may drive lack of knowledge just as lack of knowledge may drive stigma. However, this might be better said in the text.

RESPONSE: We agree that the sections referring to knowledge and education in Tables 1 and 2
can be assimilated, and have moved all of this into a single section in Table 1. We agree with this interesting reflection raised by the reviewer, which we have added to the discussion as follows: ‘Education clearly provides a very important role in reducing discrimination and stigma; it is interesting to note that stigma may drive lack of knowledge, just as lack of knowledge may drive stigma.’

REVIEWER: All references to articles that were not part of the actual HBV stigma review should be removed. This includes references 40, 41, 57, 58, 59. The articles should instead be referred to in the discussion section if the authors feel they are important to discuss around a key result.

RESPONSE: As above, we have removed any references that are not HBV-specific from the tables.

REVIEWER: Coping strategies and interventions for HBV stigma - Table 3:1. The title “Coping strategies associated with negative influence” is unclear. It seems like this bullet is for interventions.

RESPONSE: We agree this was not clearly presented; we have changed this table to remove the first rows and to remove the idea of ‘coping strategies associated with negative influence’. The point we made here is now included in the previous table, listed simply as ‘emotional responses including grief, denial, anger and aggression’.

REVIEWER: All references that are not coming directly from the review need to be removed. Specifically, #’s 40,48, 57, 58, 70

RESPONSE: This has been done, as per responses to points above.

REVIEWER: The table included in the supplementary material showing the articles should be included within the body of the article in a reduced format, given it is central to the review process.

RESPONSE: Thank you – this is a good suggestion. We have added a reduced version of this table as Table 1 in the results section, grouping the results by geographical area. We have also retained the link to a Suppl data file in order to provide interested readers with further details.

REVIEWER: Discussion: The discussion section paragraph reads more like a conclusion paragraph, while there is much discussion embedded in the results section. Moving the discussion from the results into the discussion section will strengthen both the results and discussions section and also make clearer to the reader what is emanating directly from the review of the HBV literature versus what the authors are supplementing from other fields, because of the sparse HBV stigma literature. The discussion section could be expanded by discussing what the gaps are that were found—and then using the literature from other fields to suggest how those gaps might be filled etc.

RESPONSE: We have taken a careful approach to dividing the results and discussion. The results are now condensed largely into a series of tables, presenting only objective findings from the systematic literature review. Other points, building on literature for other diseases, have now all been moved into the discussion.

REVIEWER: Limitations: In addition to comments above, it would be appropriate to discuss the
strength of findings/quality of included articles. Was any rating of the quality of articles conducted? We also find the statement at the end of the limitations section that literature from HIV, TB and mental illness was drawn on, because of the limitations of the literature found to be confusing. The fact that this was done, muddies the methods and results sections. If the literature review is only focused on HBV stigma, no matter how scarce the literature is, only this literature should be drawn on/presented in the results section. Other literature can/should be discussed in the discussion section. This is conflating of the results coming from the search itself, with ‘supplementary’ literature from other fields in the result section is problematic. Please move all discussion of other literature not coming from the literature search on HBV to the discussion section.

RESPONSE: As above, this has been done.

REVIEWER: **Conclusions:** The conclusions state stigma may disrupt adherence, however, adherence to treatment is not discussed in the results. However, hampered adherence is listed as an impact of stigma in the abstraction table for the Huang *et al* 2016 article.

RESPONSE: Specific reference to treatment adherence is now included in the results section (table 3), supported by relevant references. These do not now include the paper by Huang *et al*, as this study did not provide primary data on adherence (it is mentioned briefly as a discussion point only, supported by other references).

**Competing Interests:** No competing interests were disclosed.