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## Chronic Hepatitis B virus case-finding in populations born abroad in medium or high endemicity countries: an economic evaluation

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Manuscripts

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3 1 **Title: Chronic Hepatitis B virus case-finding in populations born abroad in**  
4  
5 2 **medium or high endemicity countries: an economic evaluation**  
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49 21 research  
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54 23 **Abbreviations:** HBV: Hepatitis B Virus; HBsAg: hepatitis B virus surface antigen;  
55  
56 24 HBeAg: hepatitis B virus e antigen; ALT: alanine transaminase; DNA: deoxyribose  
57  
58 25 nucleic acid  
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### 1   **ABSTRACT**

2   **Objectives:** The majority (>90%) of new or undiagnosed cases of hepatitis B virus  
3 (HBV) in the UK are among individuals born in countries with intermediate or high  
4 prevalence levels. We evaluate the cost-effectiveness of increased HBV case-finding  
5 among UK migrant populations, based on a one-time opt out case-finding approach  
6 in a primary care setting.

7  
8   **Design:** Cost-effectiveness evaluation. A decision model based on a Markov  
9 approach was built to assess the progression of HBV infection with and without  
10 treatment as a result of case-finding. The model parameters, including the cost and  
11 effects of case-finding and treatment, were estimated from the literature. All costs  
12 were expressed in 2017/18 GBPs and health outcomes as quality-adjusted life-years  
13 (QALYs).

14  
15   **Intervention:** HCV case-finding among UK migrant populations in a primary care  
16 setting compared to no intervention (background testing).

17  
18   **Results:** At a 2% hepatitis B surface antigen (HBsAg) prevalence, the case-finding  
19 intervention led to a mean incremental cost-effectiveness ratio (ICER) of £13,625 per  
20 QALY gained which was 87% and 98% likely of being cost-effective at willingness to  
21 pay (WTP) thresholds of £20,000 and £30,000 per additional QALY, respectively.  
22 Sensitivity analyses indicated that the intervention would remain cost-effective under  
23 a £20,000 WTP threshold as long as HBsAg prevalence among the migrant  
24 population is at least 1%. However, the results were sensitive to a number of  
25 parameters, especially the time horizon and probability of treatment uptake.

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4  
5 2 **Conclusions:** HBV case-finding using a one-time opt out approach in primary care  
6  
7 3 settings is very likely to be cost-effective among UK migrant populations with HBsAg  
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9 4 prevalence  $\geq 1\%$  if the WTP for an additional QALY is around £20,000.  
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## 15 6 **Article Summary**

- 16  
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19 8
  - This is a cost-effectiveness evaluation of increased HBV case-finding  
20  
21 9 among UK migrant populations, based on a one-time opt out case-finding  
22  
23 10 approach in a primary care setting.

## 24 25 26 11 **Strengths and limitations of this study**

- 27  
28 12  
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31 13
  - Few studies have evaluated the cost-effectiveness of HBV interventions  
32  
33 14 among populations born abroad in medium to high endemicity countries.
  - Strengths include numerous sensitivity analyses assessing how cost-  
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35 15 effectiveness varies for a range of different prevalences, intervention  
36  
37 16 effect and cost, thus increasing the generalizability of our results to other  
38  
39 17 similar interventions and different settings.
  - Limitations include uncertainty in the exact cost or effect of this  
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45 20 intervention if scaled up to a national level.
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## 1 INTRODUCTION

2 Worldwide, the burden of liver disease continues to rise and remains an urgent  
3 public health problem[1]. It is estimated that viral hepatitis is in the top 10 leading  
4 causes of mortality globally[2], the majority due to infection with hepatitis B virus  
5 (HBV)[3]. Chronic infection with HBV can lead to liver fibrosis, cirrhosis,  
6 hepatocellular carcinoma, and death in the absence of treatment. It is estimated that  
7 over 5% of the world's population are chronic carriers of HBV[4]. Globally, HBV  
8 burden is highest in low-middle income countries in areas such as Sub-Saharan  
9 African and East Asia[3]. HBV is spread through exposure to infected blood or body  
10 fluids, with the majority of chronic infections acquired perinatally or during  
11 childhood[1]. Recently, effective antiviral treatment for HBV has become available  
12 which may achieve long-term viral suppression and slow progression of disease[5,  
13 6].

14  
15 Around 320 cases of acute hepatitis were reported in England in 2015[7]. The  
16 prevalence of chronic hepatitis B (CHB) in the UK is estimated to be 0.4% of all  
17 adults[8]. It is further estimated that 80% to 90% of newly diagnosed chronic HBV  
18 infections are among migrant individuals living in the UK that were born overseas in  
19 countries with intermediate or high HBV prevalence (>2%), such as China or  
20 Pakistan[8-11]. Although uncertain, it is also likely that a considerable number of  
21 people with chronic HBV remain undiagnosed. For example, in one study in Bristol  
22 only 12% of migrants born in countries with endemic prevalence >2% had been  
23 tested for HBV[9].

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3 1 Universal screening of pregnant women to identify and immunize neonates exposed  
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5 2 to infection is highly cost-effective and under some circumstances cost-saving[12].  
6  
7 3 The vast majority of European countries already offer universal immunization against  
8  
9 4 hepatitis B, with six exceptions: Denmark, Finland, Iceland, Norway and Sweden.  
10  
11 5 These countries have a very low HBV endemicity and so it is unlikely to be cost-  
12  
13 6 effective to introduce a separate universal HBV vaccination programme[13]. Recent  
14  
15 7 assessments of the cost-effectiveness of universal childhood HBV vaccination  
16  
17 8 suggest that it may be cost-effective if introduced with other vaccines as a  
18  
19 9 component of a hexavalent vaccine – the UK moved to such a product in 2017[13].  
20  
21 10 Nonetheless, infant vaccination is unlikely to have a great impact on the prevalence  
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23 11 of chronic HBV in countries such as the UK because few transmissions are thought  
24  
25 12 to occur once people have entered the country[14]. For these reasons, there remains  
26  
27 13 a critically important role for case-finding activities. However, while studies have  
28  
29 14 shown the cost-effectiveness of one-time screening programs, where a test offer is  
30  
31 15 mailed to migrant individuals identified through a population registry[15], until  
32  
33 16 recently there has not been a published evaluation from a UK perspective. This  
34  
35 17 changed earlier this year when the results of a randomized controlled trial (Hepfree)  
36  
37 18 showed that incentivized screening of HBV and HCV in first and second-generation  
38  
39 19 migrants in a primary care setting was shown to be effective and cost-effective in the  
40  
41 20 UK [16]. However, in contrast to an incentivized screening approach, pilot data from  
42  
43 21 the UK also indicates that an opt-out HBV case-finding approach in primary care  
44  
45 22 settings was also highly effective, and potentially less expensive[17]. Additionally, it  
46  
47 23 was unclear in the previous analysis for the Hepfree trial how much the cost-  
48  
49 24 effectiveness was driven by HCV versus HBV outcomes, and whether the  
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51 25 intervention was cost-effective for HBV alone. Further, it is unknown how the cost-  
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3 1 effectiveness of HBV case-finding could vary for a range of prevalences (which likely  
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5 2 vary by country of origin), costs, and uptake rates that may occur when the  
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7 3 interventions are rolled out across different settings.  
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11  
12 5 The aim of this paper is to evaluate the cost-effectiveness of increased HBV case-  
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14 6 finding among UK populations born in high or medium endemicity countries, based  
15  
16 7 on a one-time opt out case-finding approach in primary care settings. Importantly, to  
17  
18 8 increase the generalizability of our results to other similar interventions and different  
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20 9 settings, we assess how the cost-effectiveness of HBV case-finding varies for a  
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22 10 range of different prevalences, intervention effect and cost.  
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### 30 13 **METHODS**

31  
32 14 The economic evaluation was undertaken using a Markov approach, where a closed  
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34 15 cohort of individuals move between a set of discrete health states, in this instance on  
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36 16 an annual basis[18, 19]. A UK National Health Service's cost perspective was used.  
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38 17 All costs were displayed in GBP 2017/18 prices and a 40-year time horizon was  
39  
40 18 used. Health outcomes were expressed in terms of Quality-Adjusted Life-Years  
41  
42 19 (QALYs). QALYs and costs were discounted at 3.5% per annum according to UK  
43  
44 20 National Institute for Health and Care Excellence (NICE) recommendations[20].  
45  
46 21 Uncertainty in the results was examined using deterministic and probabilistic  
47  
48 22 sensitivity analysis (PSA); distributions shown in the tables relate to the PSA  
49  
50 23 analysis. Each PSA consisted of 5,000 runs. HBV transmission was not included in  
51  
52 24 the model as most infections are likely to occur in UK migrant populations before  
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54 25 entering the UK[14].  
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## 1 **Intervention and target population**

2 A systematic literature review found few studies evaluating HBV case-finding in  
3 migrant or other high-risk populations, nor have many studies been published since  
4 this review[16, 21]. Our study evaluates the cost-effectiveness of HBV case-finding  
5 in the UK for individuals born in countries with intermediate or high prevalence  
6 levels. The base case analysis uses the results from an uncontrolled study;  
7 Pakistani/British Pakistani people registered at general practices (GPs) in London's  
8 East End were written to and invited to 'opt out' of being tested for hepatitis B and C  
9 infection. Those who did not opt out were telephoned and asked to attend a clinic for  
10 testing[17]. The intervention was designed to increase the likelihood of testing for  
11 each infection, assumed in this analysis to occur over the initial model cycle. After  
12 this time, the intervention effect was assumed to be zero, with the probability of  
13 testing reverting to background levels. The comparator programme or 'no  
14 intervention' was defined as the background likelihood of testing through existing  
15 routes such as GUM clinics, antenatal clinics or primary care[22].

## 17 **Model structure**

18 The Markov model was created to represent HBV disease progression and current  
19 understanding of policies regarding disease management (Figure 1). The natural  
20 history element of the model was largely based on Shepherd et al.[23, 24] The  
21 model starts by creating a cohort of people, a proportion of whom are HBsAg+ (HBV  
22 prevalence). HBsAg- individuals remain in the model with a general population level  
23 of mortality but incurring no HBV-related costs, other than the possibility of being  
24 tested for infection. Known HBsAg+ people were assumed to undergo a full viral

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3 1 profile when initially diagnosed. Acute HBV infection was not included in the model  
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5 2 as it is likely that people would have been infected much longer than 6 months ago.  
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10 4 Mutually exclusive stages of chronic hepatitis B (CHB) that were modelled included:  
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12 5 HBeAg seroconverted (where ALT levels and HBV DNA are both low), active CHB  
13  
14 6 hepatitis B e-antigen positive (HBeAg+) disease, active CHB hepatitis B e-antigen  
15  
16 7 negative (HBeAg-) disease, and inactive CHB HBeAg- (where ALT levels and HBV  
17  
18 8 DNA are both low). Individuals progressed from CHB to compensated cirrhosis,  
19  
20 9 decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), liver transplant, and  
21  
22 10 post-transplant stages if appropriate drug treatment was not initiated or failed. Due to  
23  
24 11 the severity of the disease and likely presentation, the infection status of all  
25  
26 12 individuals with CHB was assumed to become known if / as soon as they developed  
27  
28 13 DC, HCC or required a liver transplant. Individuals could die from non-HBV related  
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30 14 causes from any health state.  
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37 15  
38 16 Individuals who had raised ALT and HBV (active) levels and who were CHB HBeAg+  
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40 17 were assessed for fibrosis and offered treatment with pegylated interferon for the first  
41  
42 18 year, followed by tenofovir until seroconversion is achieved (as per NICE  
43  
44 19 guidelines[25]) or later stage CHB developed. We assumed successful treatment of  
45  
46 20 active CHB individuals normalized ALT and lowers HBV DNA levels, therefore  
47  
48 21 moving active HBV HBeAg+ individuals to the HBeAg seroconverted stage.  
49  
50 22 Individuals with no evidence of compensated cirrhosis stopped treatment at this  
51  
52 23 time[25]. Individuals with active CHB who were HBeAg- also received pegylated  
53  
54 24 interferon for the first year, followed by tenofovir if they had not developed inactive  
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56 25 CHB HBeAg- disease[25]. However, even following the development of inactive  
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3 1 disease, they were assumed to stay on treatment indefinitely to sustain the achieved  
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5 2 level of viral suppression[25]. Individuals with evidence of compensated cirrhosis  
6  
7 3 were assumed to remain on tenofovir as long as no further disease progression was  
8  
9 4 recorded, irrespective of e-antigen status[25]. All individuals were assumed to stop  
10  
11 5 treatment on progression to DC or later stages of disease.  
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17 7 Individuals with CHB whose infection status was unknown and those that tested  
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19 8 HBsAg+, but declined treatment, were assumed to develop progressive disease  
20  
21 9 according to a set of defined transition probabilities. A different set of transition  
22  
23 10 probabilities were used to define CHB disease progression for those who accepted  
24  
25 11 treatment. As the focus of this analysis is on case-finding, we do not model possible  
26  
27 12 adverse events associated with treatment or treatment resistance.  
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### 33 14 **Model parameters**

#### 35 15 *HBV prevalence among migrant populations to the UK*

37 16 There is substantial heterogeneity in HBV burden between different migrant  
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39 17 populations in the UK depending on their country of origin. Additionally, HBV  
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41 18 prevalence among UK migrants may be different compared with their country of  
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43 19 origin; a recent UK study of antenatal testing showed the prevalence in migrants was  
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45 20 generally less than published estimates for the country of origin, with only Eastern  
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47 21 Asia having a higher than expected prevalence[9]. Public Health England (PHE) data  
48  
49 22 on those undergoing routine diagnostic testing suggests that the HBV prevalence  
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51 23 among all Asian or British Asian people in the UK is approximately 2%, however  
52  
53 24 these data do not specify country of origin in any further detail[26]. By contrast, the  
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55 25 HBV prevalence estimates obtained through targeted studies or antenatal testing  
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3 1 have identified a range of prevalence among UK migrants born in countries with  
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5 2 intermediate-high HBV endemicity, such as 17% (Vietnam-born), 7%-10%[27, 28]  
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7 3 (China-born), 3-6% (Somalia-born), 1-3% (Pakistan-born), 0.5-1.5% (Bangladesh-  
8  
9 4 born), 0.7% (Poland-born), and 0.5% (India-born)[14, 29-31]. The recent Hepfree  
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11 5 trial found a lower prevalence of 1.1%, varying by country of origin, although this  
12  
13 6 included second generation migrants that were born in the UK[16].  
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19 8 Due to the uncertainty in prevalence within populations, and the likely wide variation  
20  
21 9 between populations, in the base case, we assume an HBV prevalence (HBsAg+) of  
22  
23 10 2%, but explore a range of values (from 0.05-10%) in the sensitivity analysis.  
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27 11

### 28 12 *Transition probabilities*

29  
30  
31 13 Transition probability values, representing the likelihood of moving between health  
32  
33 14 states, for untreated disease stages were based on those reported in a 2006 UK  
34  
35 15 Health Technology Assessment report (Supplementary Tables 1 and 2)[23].  
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### 39 40 17 *Background testing rate and diagnostic accuracy*

41  
42 18 The background rate of testing for migrants in the absence of the intervention was  
43  
44 19 estimated using data from PHE, indicating a probability of 2.6% per year[22]. The  
45  
46 20 HBsAg diagnostic test was assumed to be 100% accurate.  
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### 50 51 22 *Referral and treatment effect*

52  
53 23 Few studies have quantified the number of people diagnosed with CHB who are  
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55 24 subsequently referred on to, and accept, appropriate further clinical investigations for  
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57 25 their infection. However, interruptions in the cascade of care post diagnosis are  
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3 1 known to be an issue in the management of CHB and hepatitis C infection both in  
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5 2 the UK and elsewhere, particularly in migrant populations[32]. We therefore include a  
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7 3 single probability of being referred for specialist care following a HBsAg+ test results,  
8  
9 4 then attending the appointment and starting treatment for those eligible. In the  
10  
11 5 absence of HBV related data, the probability (0.42) was estimated on the basis of  
12  
13 6 2004-2015 data supplied by Public Health England (personal communication with  
14  
15 7 Public Health England staff) for people who were identified using algorithmic  
16  
17 8 approaches as being Asian and tested HCV RNA positive who then received  
18  
19 9 treatment. However, we consider this parameter to be highly uncertain and  
20  
21 10 undertake sensitivity analysis around it using a wide range of alternative values (10%  
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23 11 to 60%).  
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31 13 While a systematic review and meta-analysis of the effects of drug therapy for CHB  
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33 14 is available[33], we chose to estimate the impact of antiviral treatment using  
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35 15 Marcellin et al[34] as it analysed a much longer follow up period, 5 years rather than  
36  
37 16 1 year. For HBeAg+ individuals, it was assumed that 20% would e-antigen  
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39 17 seroconvert after 1-year of treatment with pegylated interferon and 5.4% a year  
40  
41 18 following treatment with tenofovir. Giving a 40% seroconversion rate at year 5. For  
42  
43 19 HBeAg- individuals, the process was similar, only that by year 5, 84% would develop  
44  
45 20 inactive disease. This was assumed to relate to a 75% probability of response  
46  
47 21 following the initial 1-year of pegylated interferon and 2.3% a year following  
48  
49 22 treatment with tenofovir. Irrespective of whether individuals were HBeAg+ or HBeAg-  
50  
51 23 , they were assumed to continue treatment after year 5 with tenofovir until they  
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53 24 responded to it assuming the same constant rate of response.  
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3 1 The probability of responding to treatment was assumed to be the same for people  
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5 2 with or without compensated disease. However, once people developed  
6  
7 3 compensated disease, it was assumed not to regress following treatment, and the  
8  
9 4 costs and disutility associated with it would remain. The only benefit of treatment in  
10  
11 5 this group was slower progression to poorer health states compared with not being  
12  
13 6 treated.  
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### 19 8 *Intervention effect*

20  
21 9 The base case probability of testing for HBsAg in the intervention arm was based on  
22  
23 10 a one-time 'opt out' option within a general practice setting; 223 out of 1,134 (19.7%)  
24  
25 11 eligible tested after being identified using a GP registries database and responding  
26  
27 12 to a written invite[17].  
28  
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### 33 14 *Cohort demographics and initial stage distribution*

34  
35 15 PHE data suggests that the average age at HBV diagnosis in the UK Asian  
36  
37 16 population is approximately 35 years of age[26], which we use as the base-case  
38  
39 17 starting age in our model but vary in the sensitivity analysis. The proportion of people  
40  
41 18 with CHB who were, or were originally, HBeAg+, rather than HBeAg-, was assumed  
42  
43 19 to be 0.14 ([71/490] personal communication with Public Health England staff). The  
44  
45 20 proportion of people who had subsequently seroconverted, or developed inactive  
46  
47 21 disease, before being tested for HBsAg, was assumed to be 80% (personal  
48  
49 22 communication with Public Health England staff). It was further assumed that 44% of  
50  
51 23 people with active HBeAg+ or HBeAg- disease, had already developed compensated  
52  
53 24 cirrhosis[35].  
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### 1 *Health utilities and costs*

2 Utility values related to HBV infection were sourced from the review by Shepherd et  
3 al[23] and Takeda et al[24] (Supplementary Table 3). The costs of HBV  
4 testing/monitoring, antiviral treatment, and health-state specific costs were taken  
5 from a number of published sources[23, 35] (Table 1), inflated to GBP £2017 where  
6 appropriate using the NHS Hospital and Community Health Services Pay and Prices  
7 Index and the Health Service Cost Index[36, 37]. The intervention cost was  
8 estimated at £4 per person eligible for testing. This cost relates to the resources  
9 required to identify and invite each individual for a test and excludes the cost of any  
10 tests and treatments. Thus, if 100 individuals were eligible for testing, the total cost  
11 of the intervention was £400 irrespective of how many people attended for a test.  
12 The importance of this assumption was assessed in the sensitivity analysis given the  
13 extent of uncertainty.

### 15 **Sensitivity analyses**

16 To test the robustness of the results to alternative assumptions, we have undertaken  
17 extensive one-way sensitivity analyses. The results of a probabilistic sensitivity  
18 analysis (PSA) are also reported, in which relevant parameters are simultaneously  
19 sampled 5,000 times. Finally, due to the uncertainty surrounding the intervention  
20 cost and impact if scaled-up to the national level and among different migrant  
21 populations, we undertake a threshold analysis where we evaluate the HBV  
22 prevalence at which the intervention is cost-effective at a willingness to pay (WTP)  
23 ICER threshold of <£20,000 per additional QALY with varying intervention cost  
24 (between £1 and £20, £4 per person eligible at base-case), intervention effect



1 (between 5% and 30%, 19.7% uptake at base-case) and HBsAg prevalence  
2 (between 1% and 10%, 2% base-case) – the results are displayed as a contour map.

3

## 4 **RESULTS**

### 5 *Base-case 2% HBsAg prevalence*

6 At a 2% HBsAg prevalence, the case-finding intervention resulted in mean  
7 incremental costs and QALYs of about £28 and 0.002 respectively over the 5,000  
8 samples, corresponding to an ICER of £13,625 per QALY gained (95% credible  
9 interval £7,121 to £27,588). The intervention was 87% and 98% likely to be cost-  
10 effective at £20,000 and £30,000 WTP per additional QALY thresholds, respectively  
11 (Supplementary Figure 1). Most of the univariate sensitivity analyses produced  
12 ICERs below a £20,000 WTP threshold (Figure 2), including reducing the likelihood  
13 of testing from 19.7% to 5% (£19,323 / QALY gained). However, the exceptions  
14 were assuming a 20-year time horizon instead of 40 years (£22,713 / QALY gained),  
15 discounting QALYs at 6% instead of 3.5% (£21,970 / QALY gained), not discounting  
16 costs instead of 6% (21,521 / QALY gained) and doubling the costs of all drug  
17 treatments from £3,979 / £2,453 to £7,957 / £4,905 (£22,586 / QALY gained).  
18 Decreasing the probability of treatment uptake after testing positive for HBsAg from  
19 0.42 to 0.1 increased the ICER to over £30,000 (£31,340 / QALY gained).

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### 21 *Impact of variation in HBV prevalence and intervention impact (cost, effect and 22 uptake)*

23 Cost-effectiveness is strongly driven by HBV prevalence. Our sensitivity analyses  
24 indicated that the intervention would remain cost-effective under a £20,000 WTP

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3 1 threshold as long as HBV prevalence among the migrant population is equal to or  
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5 2 exceeds 1% (Figure 3).  
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10 4 Due to the uncertainty in cost and intervention impact if scaled-up across the UK and  
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12 5 among different migrant population, we additionally present a sensitivity analysis of  
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14 6 the threshold HBV prevalence which would ensure the intervention is cost-effective  
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16 7 under a £20,000 WTP with varying costs and intervention effects (Figure 4). The  
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18 8 contour map shows that, for example, the intervention would be cost-effective at a  
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20 9 prevalence of 1% if it cost £6 per person and the intervention effect was 20%.  
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22 10 However, it would no longer be cost-effective at a 1% prevalence level and £6 cost if  
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24 11 the intervention effect reduced to 10%.  
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## 31 **DISCUSSION**

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33 14 HBV case-finding using a one-time opt out approach in primary care settings has a  
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35 15 high potential to be cost-effective among UK migrant populations with a HBV  
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37 16 prevalence at or above an average of 1%. However, the results are sensitive to a  
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39 17 number of factors including the intervention effect or cost, rate of treatment uptake,  
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41 18 assuming a much shorter time horizon and (unrealistically) high discount rates and  
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43 19 drug costs.  
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## 49 **Limitations**

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51 22 The main limitation with the analysis is the substantial uncertainty surrounding the  
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53 23 costs of the intervention and its effect if this case-finding intervention were scaled-up  
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55 24 to a national level. Nonetheless, extensive sensitivity analysis shows that the  
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57 25 intervention remained cost-effective across a large range of evaluated scenarios.  
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3 1 Thus, while establishing more robust estimates of the costs and effects of  
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5 2 interventions to find cases of HBV will undoubtedly decrease the uncertainty around  
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7 3 our results, we believe the scope for the modelled intervention to be cost-effective is  
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9 4 extremely high.  
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15 6 Current UK NHS HBV-testing policy is to contact household members once a case  
16  
17 7 has been identified. However, we were unable to include this aspect in our analysis  
18  
19 8 due to a lack of data specific to the target migrant populations on the size and age  
20  
21 9 distribution of households of infected contacts, the probability that contacts were  
22  
23 10 HBsAg+ and the likelihood that contacts could be traced in the first instance. The  
24  
25 11 impact of excluding this process on the ICER we report is difficult to determine. For  
26  
27 12 example, if contact tracing results in a high proportion of people being treated for  
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29 13 CHB the ICER could decrease. Conversely, if many HBsAg- people are vaccinated  
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31 14 against HBV, the ICER could increase as there is already evidence to suggest it is  
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33 15 unlikely to be cost-effective[13].  
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40 17 Finally, we did not model the possibility of simultaneously testing for hepatitis C virus  
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42 18 (HCV), which may increase the cost-effectiveness of the intervention though  
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44 19 evidence on the HCV prevalence among migrants also has uncertainties<sup>19</sup>.  
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## 49 21 **Comparison with other studies**

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51 22 Five studies have examined the cost-effectiveness of screening for HBV among  
52  
53 23 migrant populations. A Dutch study[15] found that screening migrants from countries  
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55 24 with high or intermediate HBV prevalence (assuming a 3.4% chronic infection  
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57 25 prevalence) was highly cost-effective (EUR9000 per QALY gained) at a screening  
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3 1 campaign cost of approximately EUR11 per person eligible and 35% uptake – which  
4  
5 2 is consistent with our sensitivity analysis. Another study explored screening and  
6  
7 3 treatment of migrants from Asian and Pacific Islands in the US[38], finding it to be  
8  
9 4 cost-effective (US\$36,000 per QALY gained) but also assuming a much higher  
10  
11 5 prevalence of HBV (10%), screening uptake (70%) and no screening programme  
12  
13 6 costs aside from the diagnostic tests. Two studies examined the cost-effectiveness  
14  
15 7 of screening all migrants to Canada[39, 40], both finding tenofovir-based treatment  
16  
17 8 moderately cost-effective (CAD\$40,000/QALY [~£22,000]) at 4.8-6.5% chronic  
18  
19 9 infection prevalence's. Our model assumes a lower prevalence of chronic HBV,  
20  
21 10 higher treatment efficacy and lower treatment and screening costs than the North  
22  
23 11 American studies, which may explain the difference in cost-effectiveness estimates.  
24  
25 12 Lastly, our results are partially consistent with findings from the recent Hepfree trial,  
26  
27 13 which was found to be cost-effective (£8,540/QALY) for a similar observed  
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29 14 intervention effect (19.7% uptake of testing compared to 19.5% uptake in our study).  
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31 15 However, Hepfree had higher intervention costs (>£25 per patient compared to £1-  
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33 16 20 in our model), combined HCV and HBV screening and identified patients on basis  
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35 17 of ethnic group rather than country of birth [41].  
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## 19 **Conclusions**

20 Our analysis suggests that interventions to increase HBV case-finding in primary  
21 care among UK migrant populations with a prevalence of at least 1% – such as using  
22 a one-time opt out approach – could be cost-effective – underpinning current  
23 National Institute for Health and Care Excellence guidance[42]. Critically, at a  
24 threshold prevalence above 1% this will encompass migrant populations from most  
25 countries with endemic HBV, even if there is a healthy migrant effect (with migrant  
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1 populations in UK on average at lower risk than people in their country of origin[14]).  
2 These recent results support the recommendation that interventions to increase HBV  
3 case-finding in primary care among UK migrant populations should be expanded, but  
4 needs to be based on screening by country of birth rather than ethnic group.  
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2 **Author contributions:** AM, PV, MH designed the study. AM, AG, JW and NM coded  
3 the analysis. All authors interpreted the data. AM and NM wrote the first draft. All  
4 authors contributed to the manuscript drafting, approved of the final version, and  
5 agreed to authorship.

6  
7 **Data Sharing:** Model code available on request to the corresponding author.  
8

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13 5 **Patient and Public Involvement:** This study was commissioned by the UK National  
14  
15 6 Institute for Health and Care Excellence (<https://www.nice.org.uk/guidance/ph43/>)  
16  
17 7 with representation from lay members on the guidance panel who contributed to  
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20 8 shaping the proposed intervention and interpretation of the study findings and  
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22 9 implications.  
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## 1 **FIGURE LEGENDS**

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3 **Figure 1. HBV model schematic.** The arrows denote possible transitions between states;

4 HBsAg, hepatitis B virus surface antigen; HBeAg: hepatitis b virus e antigen; CHB, chronic hepatitis B  
5 virus; CC, compensated cirrhosis; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT,

6 liver transplant; \*individuals may or may not know their infection status; %individuals with CC

7 responding to treatment were assumed to keep the costs and utility associated with CC, but with

8 disease progression probabilities equivalent to HBeAg seroconversion / inactive disease; "transitions

9 permitted from all health states to death

10

11 **Figure 2: Univariate sensitivity analysis on the ICER with a 2% HBV prevalence**

12 **scenario.** ICER, incremental cost-effectiveness ratio; Y-axis indicates the base case ICER of

13 £21,400 per QALY gained; \*halves or doubles all baseline drug costs where relevant

14

15 **Figure 3. Mean incremental cost-effectiveness ratio (ICER) of HBV screening**

16 **by varying HBsAg prevalence**

17

18 **Figure 4. Contour map showing for a range of costs (horizontal axis) and**

19 **intervention effects (vertical axis), the threshold HBV prevalence (contours)**

20 **where the intervention ICER falls under a £20,000 willingness to pay threshold.**

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Table 1: Annual costs in 2017/18 UK prices (£)

Cost	Mean	95% interval of sampled range <sup>^</sup>	Source
Intervention cost per person eligible for testing*	4	-	Assumption
HBsAg test (laboratory)	10	-	Assumption
Pegylated interferon	3,979	-	BNF[43]
Tenofovir	2,453	-	BNF[43]
ALT and ultrasound	77	-	Assumption[43]
Full viral profile	432	-	Assumption[43]
HBeAg+ seroconverted / HBeAg- ALT/DNA low <sup>a</sup>	335	240-446	Shepherd[23]
HBeAg+ / HBeAg- active disease <sup>b</sup>	674	480-896	Shepherd[23]
Compensated cirrhosis	1,606	1,052-2,283	Crossan[35]
Decompensated cirrhosis	38,212	21,848-60,645	Crossan[35]
Hepatocellular carcinoma	38,212	21,848-60,645	Crossan[35]
Liver transplant (first year)	67,698	57,301-79,287	Crossan[35]
Liver transplant (subsequent years)	17,231	5,415-35,399	Crossan[35]

\*Indicates a one off cost; <sup>^</sup>Sampled values from the probabilistic sensitivity analysis using a gamma distribution; <sup>b</sup>costs are additional to<sup>a</sup>

## References

1. World Health Organisation. *Global hepatitis report, 2017*. 2017 04/08/2017]; Available from: <http://apps.who.int/iris/bitstream/10665/255016/1/9789241565455-eng.pdf?ua=1>.
2. Cooke, G.S., M. Lemoine, M. Thursz, C. Gore, T. Swan, A. Kamarulzaman, et al., *Viral hepatitis and the Global Burden of Disease: a need to regroup*. J Viral Hepat, 2013. **20**(9): p. 600-1.
3. Lozano, R., M. Naghavi, K. Foreman, S. Lim, K. Shibuya, V. Aboyans, et al., *Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010*. The Lancet, 2012. **380**(9859): p. 2095-2128.
4. World Health Organisation, *Hepatitis B fact sheet*. 2014.
5. Rajbhandari, R. and R.T. Chung, *Treatment of Hepatitis B: A Concise Review*. Clinical and Translational Gastroenterology, 2016. **7**(9): p. e190.
6. World health Organisation. *Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection*. Guidelines 2015 16/06/2017]; Available from: [http://apps.who.int/iris/bitstream/10665/154590/1/9789241549059\\_eng.pdf?ua=1&ua=1](http://apps.who.int/iris/bitstream/10665/154590/1/9789241549059_eng.pdf?ua=1&ua=1).
7. Public Health England, *Acute hepatitis B (England): annual report 2017*. 2018.
8. Health Protection Agency, *Migrant Health: Infectious diseases in non-UK born populations in the UK. An update to the baseline report*. 2011.
9. Cochrane, A., I. Evlampidou, C. Irish, S.M. Ingle, and M. Hickman, *Hepatitis B infection prevalence by country of birth in migrant populations in a large UK city*. J Clin Virol, 2015. **68**: p. 79-82.
10. Hahne, S., M. Ramsay, K. Balogun, W.J. Edmunds, and P. Mortimer, *Incidence and routes of transmission of hepatitis B virus in England and Wales, 1995-2000: implications for immunisation policy*. J Clin Virol, 2004. **29**(4): p. 211-20.
11. Evlampidou, I., M. Hickman, C. Irish, N. Young, I. Oliver, S. Gillett, et al., *Low hepatitis B testing among migrants: a cross-sectional study in a UK city*. British Journal of General Practice, 2016.
12. Edmunds, W.J. and R. Ramsay, *The estimated cost-effectiveness of vaccination in infants born to hepatitis B positive mothers*, in *NICE Public Health Guidance no. 21*. 2009.
13. Siddiqui, M.R., N. Gay, W.J. Edmunds, and M. Ramsay, *Economic evaluation of infant and adolescent hepatitis B vaccination in the UK*. Vaccine, 2011. **29**(3): p. 466-475.
14. Uddin, G., D. Shoeb, S. Solaiman, R. Marley, C. Gore, M. Ramsay, et al., *Prevalence of chronic viral hepatitis in people of south Asian ethnicity living in England: the prevalence cannot necessarily be predicted from the prevalence in the country of origin*. Journal of Viral Hepatitis, 2010. **17**: p. 327-335.
15. Veldhuijzen, I.K., M. Toy, S.J.M. Hahné, G.A. De Wit, S.W. Schalm, R.A. de Man, et al., *Screening and Early Treatment of Migrants for Chronic Hepatitis B Virus Infection Is Cost-Effective*. Gastroenterology, 2010. **138**(2): p. 522-530.

16. Flanagan, S., J. Kunkel, V. Appleby, S.E. Eldridge, S. Ismail, S. Moreea, et al., *Case finding and therapy for chronic viral hepatitis in primary care (HepFREE): a cluster-randomised controlled trial*. *Lancet Gastroenterol Hepatol*, 2019. **4**(1): p. 32-44.
17. Lewis, H., K. Burke, S. Begum, I. Ushiro-Limb, and G.R. Foster, *What is the best method of case finding for chronic viral hepatitis in migrant communities?* *Gut*, 2011. **Vol 60 Suppl 2**: p. A26.
18. Beck, J.R. and S.G. Pauker, *The Markov process in medical prognosis*. *Medical Decision Making*, 1983. **3**(4): p. 419-458.
19. Sonnenberg, F.A. and J.R. Beck, *Markov models in medical decision making: a practical guide*. *Medical Decision Making*, 1993. **13**(4): p. 322-338.
20. National Institute for Health and Care Excellence, *Guide to the methods of technology appraisal*. 2013.
21. Jones, L., G. Bates, E. McCoy, C. Beynon, J. McVeigh, and M. Bellis. *A systematic review of the effectiveness & cost-effectiveness of interventions aimed at raising awareness and engaging with groups who are at an increased risk of hepatitis B and C infection*. 2011 23/03/2017]; Available from: <https://www.nice.org.uk/guidance/ph43/evidence/evidence-review-2-69062510>.
22. Health Protection Agency, *Sentinel Surveillance of Hepatitis Testing in England - Hepatitis B and D 2010 Report - Analysis of testing between 2007 and 2010*. 2011: Collindale, UK.
23. Shepherd, J., J. Jones, A. Takeda, P. Davidson, and A. Price, *Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation*. *Health Technology Assessment*, 2006. **10**(28).
24. Takeda, A., J. Jones, J. Shepherd, P. Davidson, and A. Price, *A systematic review and economic evaluation of adefovir dipivoxil and pegylated interferon-alpha-2a for the treatment of chronic hepatitis B*. *Journal of Viral Hepatitis*, 2007. **14**: p. 75-88.
25. National Institute for Health and Care Excellence. *Hepatitis B (chronic): diagnosis and management*. 2013 24/03/2017]; Available from: <https://www.nice.org.uk/guidance/Cg165>.
26. Public Health England. *Annual report from the sentinel surveillance study of blood borne virus testing in England: data for January to December 2015*. *Health protection report 2016* 02/06/2017]; Available from: [https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/540332/hpr2416\\_bbvs.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/540332/hpr2416_bbvs.pdf).
27. McPherson, S., M. Valappil, S. Moses, G. Eltringham, C. Miller, K. Baxter, et al., *CHASE-B (Chinese hepatitis awareness, surveillance, and education): A pilot of targeted case finding for hepatitis B virus (HBV) in the British-Chinese community*. *Gut*, 2010. **60**: p. A25-A26.
28. Kawsar, M.T. and B.T. Goh, *Hepatitis B virus infection among Chinese residents in the United Kingdom*. *Sexually Transmitted Infections*, 2002. **78**: p. 166-168.

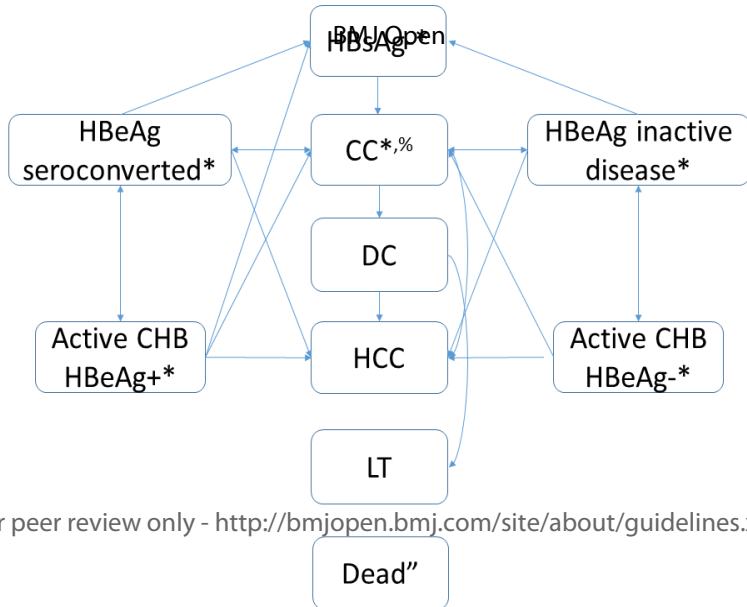
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29. Aweis, D., B.J. Brabin, N.J. Beeching, J.E. Bunn, C. Cooper, K. Gardner, et al., *Hepatitis B prevalence and risk factors for HBsAg carriage amongst Somali households in Liverpool*. *Commun Dis Public Health*, 2001. **4**(4): p. 247-52.
30. Brabin, B., N.J. Beeching, J.E. Bunn, C. Cooper, K. Gardner, and C.A. Hart, *Hepatitis B prevalence among Somali households in Liverpool*. *Arch Dis Child*, 2002. **86**(1): p. 67-8.
31. McPherson, S., M. Valappil, S.E. Moses, G. Eltringham, C. Miller, K. Baxter, et al., *Targeted case finding for hepatitis B using dry blood spot testing in the British-Chinese and South Asian populations of the North-East of England*. *J Viral Hepat*, 2013. **20**(9): p. 638-44.
32. Vedio, A., E.Z.H. Liu, A.C.K. Lee, and S. Salway, *Improving access to health care for chronic hepatitis B among migrant Chinese populations: A systematic mixed methods review of barriers and enablers*. *Journal of Viral Hepatitis*, 2017. **24**(7): p. 526-540.
33. Woo, G., G. Tomlinson, Y. Nishikawa, M. Kowgier, M. Sherman, D.K. Wong, et al., *Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses*. *Gastroenterology*, 2010. **139**(4): p. 1218-1229.
34. Marcellin, P., E. Gane, M. Buti, N. Afdhal, W. Sievert, I.M. Jacobson, et al., *Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study*. *Lancet*, 2013. **381**(9865): p. 468-75.
35. Crossan, C., E.A. Tsochatzis, L. Longworth, K. Gurusamy, B. Davidson, M. Rodriguez-Peralvarez, et al., *Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease: systematic review and economic evaluation*. *Health Technol Assess*, 2015. **19**(9): p. 1-409, v-vi.
36. Curtis, L. and A. Burns. *Unit costs of health and social care 2015*. 2015 [27/03/2017]; Available from: <http://www.pssru.ac.uk/project-pages/unit-costs/2015/>.
37. Curtis, L. and A. Burns. *Unit costs of health and social care 2018*. 2018 [18/12/2018]; Available from: <https://www.pssru.ac.uk/pub/uc/uc2018/sources-of-information.pdf>.
38. Hutton, D.W., D. Tan, S.K. So, and M.L. Brandeau, *Cost-effectiveness of screening and vaccinating Asian and Pacific Islander adults for hepatitis B*. *Ann Intern Med*, 2007. **147**(7): p. 460-9.
39. Rossi, C., K. Schwartzman, O. Oxlade, M.B. Klein, and C. Greenaway, *Hepatitis B screening and vaccination strategies for newly arrived adult Canadian immigrants and refugees: a cost-effectiveness analysis*. *PLoS One*, 2013. **8**(10): p. e78548.
40. Wong, W.W.L., G. Woo, E. Jenny Heathcote, and M. Krahn, *Cost effectiveness of screening immigrants for hepatitis B*. *Liver International*, 2011. **31**(8): p. 1179-1190.
41. Hickman, M., S. Mandel, P. Vickerman, A. Miners, and N. Martin, *Hepatitis case finding among migrants in primary care*. *Lancet Gastroenterol Hepatol*, 2019. **4**(1): p. 3-4.

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42. National Institute for Health and Clinical Excellence. *Hepatitis B and C - ways to promote and offer testing*. 2012; Available from: <http://publications.nice.org.uk/hepatitis-b-and-c-ways-to-promote-and-offer-testing-to-people-at-increased-risk-of-infection-ph43>.
  43. Royal Pharmaceutical Society. *British National Formulary no. 71*. 2016 01/08/2016]; Available from: [www.bnf.org](http://www.bnf.org).
  44. Briggs, A., M. Sculpher, and K. Claxton, *Decision modelling for health economic evaluation*. Handbooks in health economic evaluation series, ed. A. Gray and A. Briggs. 2006, Oxford: Oxford University Press.

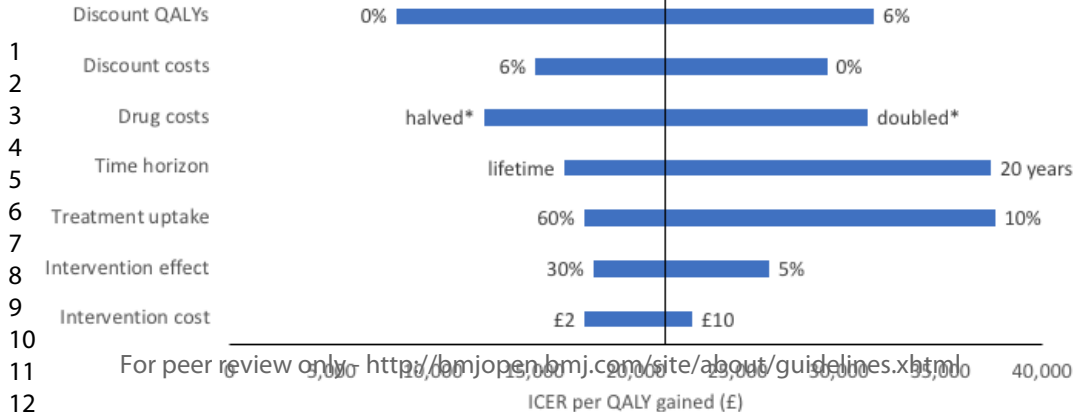
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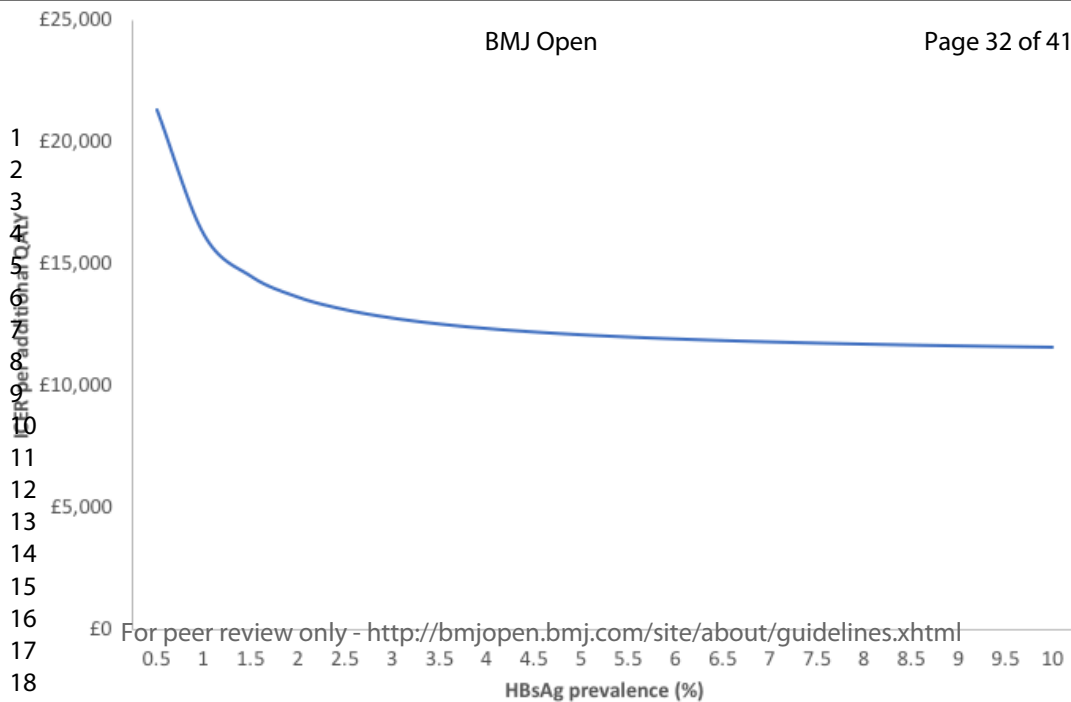
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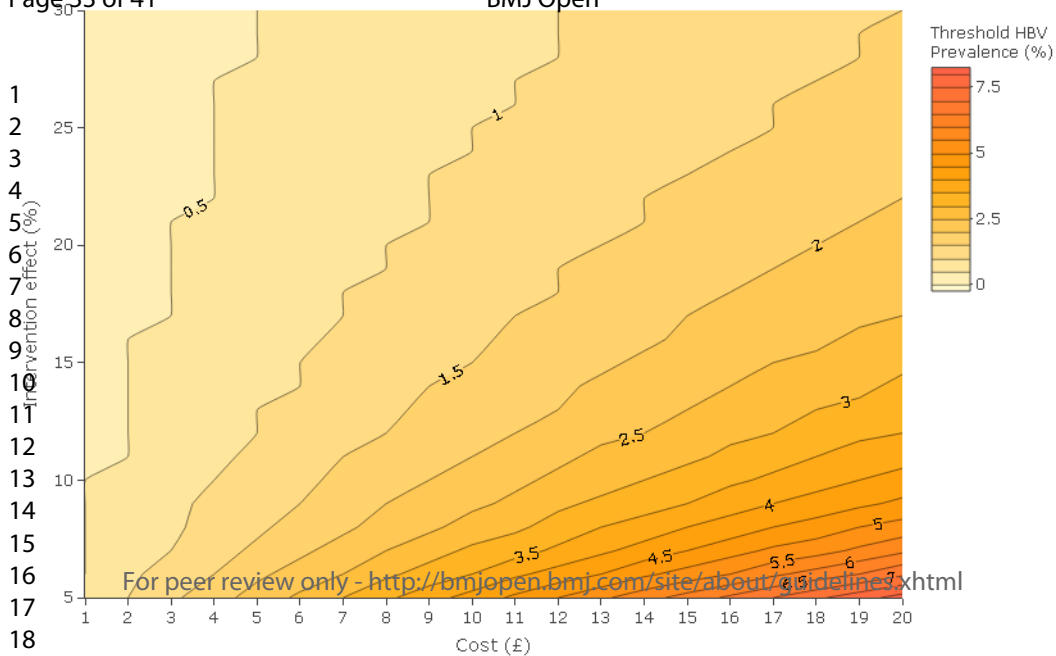
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## Supplementary Materials

Supplementary Table 1: Annual transition probability matrix for people who enter the model as HBsAg+ and HBeAg+ derived from Shepherd(1) and Marcellin(2)

From:	To:	HBsAg seroconverted	HBeAg seroconverted	CHB HBeAg+ active disease	CC	DC	HCC	LT1	LT2	Dead <sup>+</sup>
HBsAg seroconverted		#	0	0	0	0	0.00005	0	0	0
HBeAg seroconverted		0.02	#	0.03	0.01	0	0.005	0	0	0
CHB HBeAg+ active disease no treatment		0.0175	0.05	#	0.05	0	0.005	0	0	0.0035
CHB HBeAg+ active disease or CC on treatment										
Treatment response with pegylated interferon		0.0175	0.20	#	0.05	0	0.005	0	0	0.0035
Treatment response with tenofovir		0.0175	0.054	#	0.05	0	0.005	0	0	0.0035
Compensated cirrhosis (CC) no treatment		0	0.05	0	#	0.05	0.025	0	0	0.051
Decompensated cirrhosis (DC)		0	0	0	0	#	0.025	0.03	0	0.39
Hepatocellular carcinoma (HCC)		0	0	0	0	0	#	0	0	0.56
Liver transplant – first year (LT1)		0	0	0	0	0	0	#	0	0.21
Liver transplant – subsequent years (LT2)		0	0	0	0	0	0	0	#	0.057

\*an age-adjusted general population mortality is added to this amount; #, indicates the residual row probability; all values are converted to a Dirichlet distribution by assuming an effective sample size of 200 for each row(3)

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**Supplementary Table 2: Annual transition probability matrix for people who enter the model as HBsAg+ and HBeAg-derived from Shepherd(1) and Marcellin(2)**

From:	To:	HBsAg seroconverted	HBeAg seroconverted	CHB HBeAg-active disease	CC	DC	HCC	LT1	LT2	Dead <sup>+</sup>
HBsAg seroconverted		#	0	0	0	0	0.00005	0	0	0
HBeAg seroconverted		0.0175	#	0.03	0.01	0	0.005	0	0	0
CHB HBeA- active disease no treatment		0	0.015	#	0.05	0	0.005	0	0	0.0035
CHB HBeAg- active disease or CC on treatment										
Treatment response with peglyated interferon		0	0.75	#	0.05	0	0.005	0	0	0.0035
Treatment response with tenofovir		0	0.023	#	0.05	0	0.005	0	0	0.0035
Decompensated cirrhosis (DC)		0	0	0	0	#	0.025	0.03	0	0.39
Hepatocellular carcinoma (HCC)		0	0	0	0	0	#	0	0	0.56
Liver transplant – first year (LT1)		0	0	0	0	0	0	#	0	0.21
Liver transplant – subsequent years (LT2)		0	0	0	0	0	0	0	#	0.057

<sup>+</sup>an age-adjusted general population mortality is added to this amount; #, indicates the residual row probability; all values are converted to a Dirichlet distribution by assuming an effective sample size of 200 for each row(3)

Review only

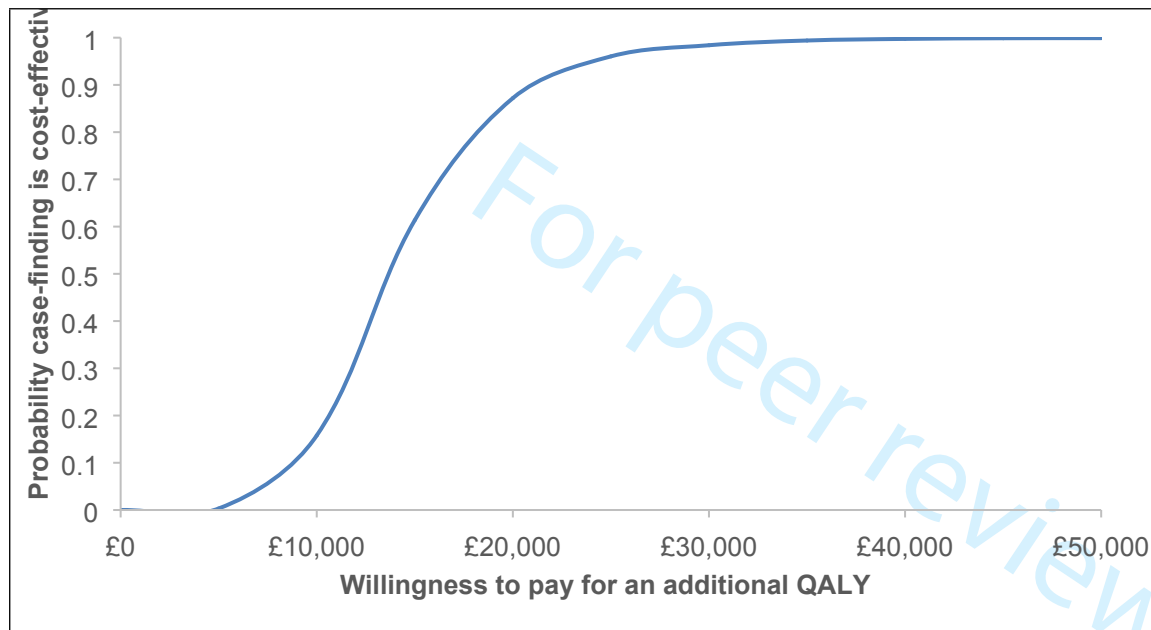
**Supplementary Table 3: Utility values from Shepherd(1) and Takeda(4)**

<b>Utility</b>	<b>Mean decrement</b>	<b>95% interval of sampled range<sup>^</sup></b>
<b>Age</b>		-
<b>0-44</b>	0.09	-
<b>45-54</b>	0.15	-
<b>55-64</b>	0.20	-
<b>65-74</b>	0.22	-
<b>75+</b>	0.27	-
<b>HBsAg-</b>	0	-
<b>HBeAg+ seroconverted / HBeAg- ALT/DNA low</b>	0	-
<b>HBeAg+ / HBeAg- active disease</b>	0.04	0.023-0.062
<b>Compensated cirrhosis</b>	0.44	0.34-0.55
<b>Decompensated cirrhosis</b>	0.54	0.43-0.73
<b>Hepatocellular carcinoma</b>	0.54	0.43-0.73
<b>Liver transplant (first year)</b>	0.54	0.43-0.73
<b>Liver transplant (subsequent years)</b>	0.32	0.22-0.43

Utility values are calculated by subtracting appropriate decrements from 1; <sup>^</sup>Sampled values from the probabilistic sensitivity analysis using a beta distribution

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**Supplementary Figure 1. Cost-effectiveness acceptability curve for the base-case 2% HBsAg prevalence.**



## Reference

1. Shepherd J, Jones J, Takeda A, Davidson P, Price A. Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation. *Health Technology Assessment*. 2006;10(28).
2. Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet*. 2013 Feb 9;381(9865):468-75. PubMed PMID: 23234725. Epub 2012/12/14. eng.
3. Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation. Gray A, Briggs A, editors. Oxford: Oxford University Press; 2006.
4. Takeda A, Jones J, Shepherd J, Davidson P, Price A. A systematic review and economic evaluation of adefovir dipivoxil and pegylated interferon-alpha-2a for the treatment of chronic hepatitis B. *Journal of Viral Hepatitis*. 2007;14:75-88.



## CHEERS Checklist

### Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: <http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp>

Section/item	Item No	Recommendation	Reported on page No/line No
<b>Title and abstract</b>			
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	_____
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	_____
<b>Introduction</b>			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	_____
<b>Methods</b>			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	_____
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	_____
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	_____
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	_____
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	_____
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	_____
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	_____
Measurement of effectiveness	11a	<i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	_____



1	11b	<p><i>Synthesis-based estimates:</i> Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.</p>	
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4	12	<p>If applicable, describe the population and methods used to elicit preferences for outcomes.</p>	
5	13a	<p><i>Single study-based economic evaluation:</i> Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.</p>	
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8	13b	<p><i>Model-based economic evaluation:</i> Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.</p>	
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15	14	<p>Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.</p>	
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28	15	<p>Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.</p>	
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32	16	<p>Describe all structural or other assumptions underpinning the decision-analytical model.</p>	
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34	17	<p>Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.</p>	
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49	18	<p>Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.</p>	
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54	19	<p>For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.</p>	
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**Results**

Study parameters

Incremental costs and outcomes

Characterising uncertainty



1			of methodological assumptions (such as discount rate, study	
2			perspective).	
3				
4		20b	<i>Model-based economic evaluation</i> : Describe the effects on the	
5			results of uncertainty for all input parameters, and uncertainty	
6			related to the structure of the model and assumptions.	
7	Characterising	21	If applicable, report differences in costs, outcomes, or cost-	
8	heterogeneity		effectiveness that can be explained by variations between	
9			subgroups of patients with different baseline characteristics or	
10			other observed variability in effects that are not reducible by	
11			more information.	
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13	<b>Discussion</b>			
14	Study findings,	22	Summarise key study findings and describe how they support	
15	limitations,		the conclusions reached. Discuss limitations and the	
16	generalisability, and		generalisability of the findings and how the findings fit with	
17	current knowledge		current knowledge.	
18				
19	<b>Other</b>			
20	Source of funding	23	Describe how the study was funded and the role of the funder	
21			in the identification, design, conduct, and reporting of the	
22			analysis. Describe other non-monetary sources of support.	
23				
24	Conflicts of interest	24	Describe any potential for conflict of interest of study	
25			contributors in accordance with journal policy. In the absence	
26			of a journal policy, we recommend authors comply with	
27			International Committee of Medical Journal Editors	
28			recommendations.	
29				

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: <http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp>

The citation for the CHEERS Task Force Report is:

Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. *Value Health* 2013;16:231-50.



# BMJ Open

## Chronic Hepatitis B virus case-finding in UK populations born abroad in intermediate or high endemicity countries: an economic evaluation

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-030183.R1
Article Type:	Research
Date Submitted by the Author:	03-May-2019
Complete List of Authors:	Martin, Natasha; University of California San Diego; University of Bristol, Population Health Sciences Vickerman, Peter; University of Bristol, Population Health Sciences Khakoo, Salim; University of Southampton Ghosh, Anjan; NHS London Borough of Bexley Ramsay, Mary; Public Health England, immunisation; London School of Hygiene and Tropical Medicine, Epidemiology Hickman, M; University of Bristol, Population Health Sciences Williams, Jack; London School of Hygiene and Tropical Medicine Miners, Alec; London School of Hygiene and Tropical Medicine
<b>Primary Subject Heading</b>:	Health economics
Secondary Subject Heading:	Health economics, Infectious diseases
Keywords:	Hepatology < INTERNAL MEDICINE, hepatitis b virus, HEALTH ECONOMICS, economic evaluation, case-finding, health services research

SCHOLARONE™  
Manuscripts

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3 1 **Title: Chronic Hepatitis B virus case-finding in UK populations born abroad in**  
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5 2 **intermediate or high endemicity countries: an economic evaluation**  
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10 4 **Authors:** Natasha K Martin<sup>1,2</sup>, Peter Vickerman<sup>1</sup>, Salim Khakoo<sup>3</sup>, Anjan Ghosh<sup>4</sup>,  
11  
12 5 Mary Ramsay<sup>5</sup>, Matthew Hickman<sup>2</sup>, Jack Williams<sup>6</sup> and Alec Miners<sup>6</sup>  
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47 20 **Keywords:** Hepatitis B virus, economic evaluation, case-finding and health services  
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49 21 research  
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54 23 **Abbreviations:** HBV: Hepatitis B Virus; HBsAg: hepatitis B virus surface antigen;  
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56 24 HBeAg: hepatitis B virus e antigen; ALT: alanine transaminase; DNA: deoxyribose  
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16  
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19 Merck. MH reports personal fees from Gilead, Abbvie, and MSD. AM, SK, AG, MR,  
20 JW have no disclosures.

21  
22  
23 **Word Count:** 3392 not including references.

24 **Figures:** 4

25  
26 **Tables:** 1

1  
2  
3 **1 ABSTRACT**  
4

5 **2 Objectives:** The majority (>90%) of new or undiagnosed cases of hepatitis B virus  
6  
7 (HBV) in the United Kingdom (UK) are among individuals born in countries with  
8  
9 intermediate or high prevalence levels ( $\geq 2\%$ ). We evaluate the cost-effectiveness of  
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11 increased HBV case-finding among U.K. migrant populations, based on a one-time  
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13 opt out case-finding approach in a primary care setting.  
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19 **8 Design:** Cost-effectiveness evaluation. A decision model based on a Markov  
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21 approach was built to assess the progression of HBV infection with and without  
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23 treatment as a result of case-finding. The model parameters, including the cost and  
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25 effects of case-finding and treatment, were estimated from the literature. All costs  
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27 were expressed in 2017/18 GBPs and health outcomes as quality-adjusted life-years  
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29 (QALYs).  
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35 **15 Intervention:** HCV case-finding among U.K. migrant populations born in countries  
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37 with intermediate or high prevalence levels ( $\geq 2\%$ ) in a primary care setting compared  
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39 to no intervention (background testing).  
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45 **19 Results:** At a 2% hepatitis B surface antigen (HBsAg) prevalence, the case-finding  
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47 intervention led to a mean incremental cost-effectiveness ratio (ICER) of £13,625 per  
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49 QALY gained which was 87% and 98% likely of being cost-effective at willingness to  
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51 pay (WTP) thresholds of £20,000 and £30,000 per additional QALY, respectively.  
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53 Sensitivity analyses indicated that the intervention would remain cost-effective under  
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55 a £20,000 WTP threshold as long as HBsAg prevalence among the migrant  
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1 population is at least 1%. However, the results were sensitive to a number of  
2 parameters, especially the time horizon and probability of treatment uptake.

3  
4 **Conclusions:** HBV case-finding using a one-time opt out approach in primary care  
5 settings is very likely to be cost-effective among UK migrant populations with HBsAg  
6 prevalence  $\geq 1\%$  if the WTP for an additional QALY is around £20,000.

### 7 8 **Strengths and limitations of this study**

- 9
- 10 • Our cost-effectiveness evaluation is one of few studies evaluating HBV  
11 case-finding among populations born abroad in intermediate to high  
12 endemicity countries.
  - 13 • Strengths include numerous sensitivity analyses assessing how cost-  
14 effectiveness varies for a range of different prevalences, intervention  
15 effect and cost, thus increasing the generalizability of our results to other  
16 similar interventions and different settings.
  - 17 • A key limitations is uncertainty in the exact cost or effect of this  
18 intervention if scaled up to a national level.
  - 19 • The model, due to a lack of available data, did not incorporate any  
20 additional impact of household contact tracing of diagnosed cases.
  - 21 • The model also does not incorporate the possibility of simultaneous  
22 testing for hepatitis C virus.
- 23



## 1 INTRODUCTION

2 Worldwide, the burden of liver disease continues to rise and remains an urgent  
3 public health problem<sup>1</sup>. It is estimated that viral hepatitis is in the top 10 leading  
4 causes of mortality globally<sup>2</sup>, the majority due to infection with hepatitis B virus  
5 (HBV)<sup>3</sup>. Chronic infection with HBV can lead to liver fibrosis, cirrhosis, hepatocellular  
6 carcinoma, and death in the absence of treatment. It is estimated that over 5% of the  
7 world's population are chronic carriers of HBV<sup>4</sup>. Globally, HBV burden is highest in  
8 low-middle income countries in areas such as Sub-Saharan African and East Asia<sup>3</sup>.  
9 HBV is spread through exposure to infected blood or body fluids, with the majority of  
10 chronic infections acquired perinatally or during childhood<sup>1</sup>. Recently, effective  
11 antiviral treatment for HBV has become available which may achieve long-term viral  
12 suppression and slow progression of disease<sup>5 6</sup>.

13  
14 The United Kingdom (UK) has a low burden of HBV, with an estimated 0.4% of  
15 adults infected with chronic hepatitis B (CHB)<sup>7</sup>, and only approximately 320 cases of  
16 acute HBV reported in England in 2015<sup>8</sup>. The vast majority (80% to 90%) of newly  
17 diagnosed chronic HBV infections are among migrant individuals living in the UK that  
18 were born overseas in countries with intermediate (2-7%) or high HBV prevalence  
19 ( $\geq 8\%$ ) as defined by the World Health Organization<sup>9</sup>, such as China or Pakistan<sup>10-12</sup>.  
20 Although uncertain, it is also likely that a considerable number of people with chronic  
21 HBV remain undiagnosed. For example, in one study in Bristol only 12% of migrants  
22 born in countries with endemic prevalence  $>2\%$  had been tested for HBV<sup>10</sup>. Due to  
23 the often asymptomatic nature of chronic infection<sup>13</sup>, individuals with HBV infection  
24 can often remain undiagnosed until they develop advanced liver disease. It is critical,

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3 1 therefore, that increased case-finding among UK migrant populations is enhanced to  
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5 2 ensure timely treatment and follow-up to prevent complications from liver disease.  
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10 4 The UK, like many countries worldwide, recommends universal screening of  
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12 5 pregnant women to identify and immunize neonates exposed to HBV infection, which  
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14 6 has been shown to be highly cost-effective and under some circumstances cost-  
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16 7 saving<sup>14</sup>. However, the UK is one of only six countries in Europe which does not  
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18 8 offer universal immunization against hepatitis B (along with Denmark, Finland,  
19  
20 9 Iceland, Norway and Sweden). These countries have a very low HBV endemicity and  
21  
22 10 so it is unlikely to be cost-effective to introduce a separate universal HBV vaccination  
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24 11 programme<sup>15</sup>. Recent assessments of the cost-effectiveness of universal childhood  
25  
26 12 HBV vaccination suggest that it may be cost-effective if introduced with other  
27  
28 13 vaccines as a component of a hexavalent vaccine – the UK moved to such a product  
29  
30 14 in 2017<sup>15</sup>. Nonetheless, infant vaccination is unlikely to have a great impact on the  
31  
32 15 prevalence of chronic HBV in countries such as the UK because few transmissions  
33  
34 16 are thought to occur once people have entered the country<sup>16</sup>. For these reasons,  
35  
36 17 there remains a critically important role for case-finding activities.  
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44 19 While studies in The Netherlands have shown the cost-effectiveness of one-time  
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46 20 screening programs (where a test offer is mailed to migrant individuals identified  
47  
48 21 through a population registry<sup>17</sup>), until recently there has not been a published  
49  
50 22 evaluation from a UK perspective. This changed earlier this year when the results of  
51  
52 23 a randomized controlled trial (HepFREE) showed that incentivized screening of HBV  
53  
54 24 and HCV in first and second-generation migrants in a primary care setting was  
55  
56 25 shown to be effective and cost-effective in the UK; the incentive included a startup  
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3 1 payment of £500 per general practice, £25 for each enrolled participant and support  
4  
5 2 from a dedicated clinician 3 days a week<sup>18</sup>. However, in contrast to an incentivized  
6  
7 3 screening approach, pilot data from the UK also indicates that an opt-out HBV case-  
8  
9 4 finding approach in primary care settings without incentives was also highly effective,  
10  
11 5 and potentially a less expensive approach<sup>19</sup>. Additionally, it was unclear in the  
12  
13 6 previous analysis for the HepFREE trial how much the cost-effectiveness was driven  
14  
15 7 by HCV versus HBV outcomes, and whether the intervention was cost-effective for  
16  
17 8 HBV alone. Further, it is unknown how the cost-effectiveness of HBV case-finding  
18  
19 9 could vary for a range of prevalences (which likely vary by country of origin), costs,  
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21 10 and uptake rates that may occur when the interventions are rolled out across  
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23 11 different settings.  
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31 13 The aim of this paper is to evaluate the cost-effectiveness of increased HBV case-  
32  
33 14 finding among UK migrant populations born in intermediate or high endemicity  
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35 15 countries, based on a one-time opt out case-finding approach in primary care  
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37 16 settings. Importantly, to increase the generalizability of our results to other similar  
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39 17 interventions and different settings, we assess how the cost-effectiveness of HBV  
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41 18 case-finding varies for a range of different prevalences, intervention effect and cost.  
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## 49 21 **METHODS**

50 22 The economic evaluation was undertaken using a Markov approach, where a closed  
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52 23 cohort of U.K. individuals born in countries with intermediate or high prevalence  
53  
54 24 levels ( $\geq 2\%$ ) move between a set of discrete health states representing HBV  
55  
56 25 infection stage<sup>20 21</sup>. A UK National Health Service's cost perspective was used. All  
57  
58 26 costs were displayed in GBP 2017/18 prices and a 40-year time horizon was used  
59  
60

1 with an annual time step. Health outcomes were expressed in terms of Quality-  
2 Adjusted Life-Years (QALYs). QALYs and costs were discounted at 3.5% per  
3 annum according to UK National Institute for Health and Care Excellence (NICE)  
4 recommendations<sup>22</sup>. Uncertainty in the results was examined using deterministic and  
5 probabilistic sensitivity analysis (PSA); distributions shown in the tables relate to the  
6 PSA analysis. Each PSA consisted of 5,000 runs. HBV transmission was not  
7 included in the model as most infections are likely to occur in UK migrant populations  
8 before entering the U.K.<sup>16</sup>. Ethical approval was not required for this study as it is an  
9 economic modelling exercise utilising published evidence and aggregate data from  
10 Public Health England.

## 12 **Intervention and target population**

13 A systematic literature review found few studies evaluating HBV case-finding in  
14 migrant or other high-risk populations, nor have many studies been published since  
15 this review<sup>18 23</sup>. Our study evaluates the cost-effectiveness of HBV case-finding in  
16 the U.K. for individuals born in countries with intermediate or high prevalence levels  
17 ( $\geq 2\%$ ). The base case analysis uses the results from an uncontrolled study in which  
18 Pakistani/British Pakistani people registered at general practices (GPs) in London's  
19 East End were written to and invited to 'opt out' of being tested for hepatitis B and C  
20 infection. Those who did not opt out were telephoned and asked to attend a clinic for  
21 testing<sup>19</sup>. The intervention was designed to increase the likelihood of testing for each  
22 infection, assumed in this analysis to occur over the initial model cycle of one year.  
23 After this time, the intervention effect was assumed to be zero, with the probability of  
24 testing reverting to background levels. The comparator programme or 'no  
25 intervention' was defined as the background likelihood of testing through existing

1 routes such as sexual health or genitourinary medicine clinics, antenatal clinics or  
2 primary care<sup>24</sup>. Although we base our analysis on data from a study among  
3 Pakistani/British Pakistani individuals in London, we evaluate the potential impact of  
4 this intervention in populations with a range of HBV prevalences as observed among  
5 UK migrants born in countries with intermediate or high prevalence levels ( $\geq 2\%$ ).

### 7 **Model structure**

8 The Markov model was created to represent HBV disease progression and current  
9 understanding of policies regarding disease management (Figure 1). The natural  
10 history element of the model was largely based on a model developed by Shepherd  
11 et al.<sup>25 26</sup> The model simulates a cohort of people, a proportion of whom are positive  
12 for hepatitis B surface antigen (HBsAg+). For this analyses, we refer to “HBV  
13 prevalence” as the proportion of individuals who are HBsAg+. Individuals who are  
14 negative for hepatitis B surface antigen.(HBsAg-) remain in the model with a general  
15 population level of mortality but incurring no HBV-related costs, other than the  
16 possibility of being tested for infection. Known HBsAg+ people were assumed to  
17 undergo a full viral profile when initially diagnosed. Acute HBV infection was not  
18 included in the model as it is likely that people would have been infected much  
19 longer than 6 months ago.

20  
21 Among HBsAg+ individuals, the model stratifies by mutually exclusive stages of  
22 chronic hepatitis B (CHB), including: HBeAg seroconverted (where ALT levels and  
23 HBV DNA are both low), active CHB hepatitis B e-antigen positive (HBeAg+)  
24 disease, active CHB hepatitis B e-antigen negative (HBeAg-) disease, and inactive  
25 CHB HBeAg- (where ALT levels and HBV DNA are both low). Individuals progressed

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3 1 from CHB to compensated cirrhosis, decompensated cirrhosis (DC), hepatocellular  
4  
5 2 carcinoma (HCC), liver transplant, and post-transplant stages if appropriate drug  
6  
7 3 treatment was not initiated or failed. Due to the severity of the disease and likely  
8  
9 4 presentation, the infection status of all individuals with CHB was assumed to become  
10  
11 5 known when they developed DC, HCC or required a liver transplant. Individuals  
12  
13 6 could die from non-HBV related causes from any health state.  
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19 8 Individuals who had raised ALT and HBV (active) levels and who were CHB HBeAg+  
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21 9 were assessed for fibrosis and offered treatment with pegylated interferon for the first  
22  
23 10 year, followed by tenofovir until seroconversion is achieved (as per NICE  
24  
25 11 guidelines<sup>27</sup>) or later stage CHB developed. We assumed successful treatment of  
26  
27 12 these individuals resulted in normalization of ALT and lowering of HBV DNA levels,  
28  
29 13 therefore resulting in transition to the HBeAg seroconverted stage. Individuals with  
30  
31 14 no evidence of compensated cirrhosis stopped treatment at this time<sup>27</sup>. Individuals  
32  
33 15 with active CHB who were HBeAg- also received pegylated interferon for the first  
34  
35 16 year, followed by tenofovir if they had not developed inactive CHB HBeAg-  
36  
37 17 disease<sup>27</sup>. However, even following the development of inactive disease, they were  
38  
39 18 assumed to stay on treatment indefinitely to sustain the achieved level of viral  
40  
41 19 suppression<sup>27</sup>. Individuals with evidence of compensated cirrhosis were assumed to  
42  
43 20 remain on tenofovir as long as no further disease progression was recorded,  
44  
45 21 irrespective of e-antigen status<sup>27</sup>. All individuals were assumed to stop treatment on  
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47 22 progression to DC or later stages of disease.  
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56 24 Individuals with CHB whose infection status was unknown and those that tested  
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58 25 HBsAg+, but declined treatment, were assumed to develop progressive disease  
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3 1 according to a set of defined transition probabilities, with different probabilities used  
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5 2 for those who accepted treatment. (Supplementary Tables 1 and 2). As the focus of  
6  
7 3 this analysis is on case-finding, we do not model possible adverse events associated  
8  
9 4 with treatment or treatment resistance.  
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## 15 6 **Model parameters**

### 17 7 *HBV prevalence among migrant populations to the UK*

19 8 There is substantial heterogeneity in HBV burden between different migrant  
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21 9 populations in the UK depending on their country of origin. Additionally, HBV  
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23 10 prevalence among UK migrants may be different compared with their country of  
24  
25 11 origin; a recent UK study of antenatal testing showed the prevalence in migrants was  
26  
27 12 generally less than published estimates for the country of origin, with only Eastern  
28  
29 13 Asia having a higher than expected prevalence<sup>11</sup>. Public Health England (PHE) data  
30  
31 14 on those undergoing routine diagnostic testing suggests that the HBV prevalence  
32  
33 15 among all Asian or British Asian people in the UK is approximately 2%, however  
34  
35 16 these data do not specify country of origin in any further detail<sup>28</sup>. By contrast, the  
36  
37 17 HBV prevalence estimates obtained through targeted studies or antenatal testing  
38  
39 18 have identified a range of prevalence among UK migrants born in countries with  
40  
41 19 intermediate-high HBV endemicity, such as 17% (Vietnam-born), 7%-10%<sup>29 30</sup>  
42  
43 20 (China-born), 3-6% (Somalia-born), 1-3% (Pakistan-born), 0.5-1.5% (Bangladesh-  
44  
45 21 born), 0.7% (Poland-born), and 0.5% (India-born)<sup>16 31-33</sup>. The recent HepFREE trial  
46  
47 22 found a lower prevalence of 1.1%, varying by country of origin, although this included  
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49 23 second generation migrants that were born in the UK<sup>18</sup>.  
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3 1 Due to the uncertainty in prevalence within populations, and the likely wide variation  
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5 2 between populations, in the base case, we assume an HBV prevalence (HBsAg+) of  
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7 3 2%, but explore a range of values (from 0.05-10%) in the sensitivity analysis.  
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9 4

#### 10 *Transition probabilities*

11  
12 5  
13 6 Transition probability values, representing the likelihood of moving between health  
14  
15 7 states, for untreated disease stages were based on those reported in a 2006 UK  
16  
17 8 Health Technology Assessment report (Supplementary Tables 1 and 2)<sup>25</sup>.  
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19 9

#### 20 *Background testing rate and diagnostic accuracy*

21  
22 10  
23 11 The background rate of testing for migrants in the absence of the intervention was  
24  
25 12 estimated using data from PHE, indicating a probability of 2.6% per year<sup>24</sup>. The  
26  
27 13 HBsAg diagnostic test was assumed to be 100% accurate.  
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29 14

#### 30 *Referral and treatment effect*

31  
32 15  
33 16 Few studies have quantified the number of people diagnosed with CHB who are  
34  
35 17 subsequently referred to, and accept, appropriate further clinical investigations for  
36  
37 18 their infection. However, interruptions in the cascade of care post-diagnosis are  
38  
39 19 known to be an issue in the management of CHB and hepatitis C virus (HCV)  
40  
41 20 infection both in the U.K. and elsewhere, particularly in migrant populations<sup>34</sup>. We  
42  
43 21 therefore include a single probability of being referred for specialist care following a  
44  
45 22 HBsAg+ test result, attending the appointment, and starting treatment for those  
46  
47 23 eligible. In the absence of HBV related data, the we utilize data on the proportion of  
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49 24 individuals who ho were identified using algorithmic approaches as being Asian and  
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51 25 who tested positive and subsequently received treatment for chronic HCV from  
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3 1 2004-2015 (0.42, based on data supplied by Public Health England, personal  
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5 2 communication with Public Health England staff). However, we consider this  
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7 3 parameter to be highly uncertain and undertake sensitivity analysis around it using a  
8  
9 4 wide range of alternative values (10% to 60%).  
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12 5  
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15 6 While a systematic review and meta-analysis of the effects of drug therapy for CHB  
16  
17 7 is available<sup>35</sup>, we estimated the impact of antiviral treatment using data from a study  
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19 8 which a much longer follow up period (5 years rather than 1 year)<sup>36</sup>. For HBeAg+  
20  
21 9 individuals, we assumed 20% would e-antigen seroconvert after 1-year of treatment  
22  
23 10 with pegylated interferon and 5.4%/year following treatment with tenofovir, resulting  
24  
25 11 in 40% having seroconverted by 5 years. For HBeAg- individuals, we assumed a  
26  
27 12 75% probability of response (development of inactive disease) following the initial 1-  
28  
29 13 year of pegylated interferon and 2.3%/year following treatment with tenofovir  
30  
31 14 Therefore, we assumed that 84% would develop inactive disease by 5 years.  
32  
33 15 Irrespective of whether individuals were HBeAg+ or HBeAg-, they were assumed to  
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35 16 continue treatment after year 5 with tenofovir until they responded to it assuming the  
36  
37 17 same constant rate of response.  
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45 19 The probability of responding to treatment was assumed to be the same for people  
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47 20 with or without compensated disease. However, once people developed  
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49 21 compensated disease, it was assumed not to regress following treatment, and the  
50  
51 22 costs and disutility associated with it would remain. The only benefit of treatment in  
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53 23 this group was slower progression to poorer health states compared with not being  
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55 24 treated.  
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### 1 *Intervention effect*

2 The base case probability of testing for HBsAg in the intervention arm was based on  
3 a one-time 'opt out' option within a general practice setting; 223 out of 1,134 (19.7%)  
4 eligible tested after being identified using a GP registries database and responding  
5 to a written invite<sup>19</sup>.

### 7 *Cohort demographics and initial stage distribution*

8 PHE data suggests that the average age at HBV diagnosis in the UK Asian  
9 population is approximately 35 years of age<sup>28</sup>, which we use as the base-case  
10 starting age in our model but vary in the sensitivity analysis. The proportion of people  
11 with CHB who were HBeAg+ in our starting cohort was assumed to be 0.14 ([71/490]  
12 personal communication with Public Health England staff). The proportion of people  
13 who had seroconverted, or developed inactive disease, before being tested for  
14 HBsAg, was assumed to be 80% (personal communication with Public Health  
15 England staff). It was further assumed that 44% of people with active HBeAg+ or  
16 HBeAg- disease, had already developed compensated cirrhosis<sup>37</sup>.

### 18 *Health utilities and costs*

19 Utility values related to HBV infection were sourced from the review by Shepherd et  
20 al<sup>25</sup> and Takeda et al<sup>26</sup> (Supplementary Table 3). The costs of HBV  
21 testing/monitoring, antiviral treatment, and health-state specific costs were taken  
22 from a number of published sources<sup>25 37</sup> (Table 1), inflated to GBP £2017 where  
23 appropriate using the NHS Hospital and Community Health Services Pay and Prices  
24 Index and the Health Service Cost Index<sup>38 39</sup>. The intervention cost was estimated at  
25 £4 per person eligible for testing. This cost relates to the resources required to

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2  
3 1 identify and invite each individual for a test and excludes the cost of any tests and  
4  
5 2 treatments. Thus, if 100 individuals were eligible for testing, the total cost of the  
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7 3 intervention was £400 irrespective of how many people attended for a test. The  
8  
9 4 importance of this assumption was assessed in the sensitivity analysis given the  
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11 5 extent of uncertainty.  
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## 17 Main outcomes

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19 8 Our main results incorporate a probabilistic sensitivity analysis (PSA), in which  
20  
21 9 relevant parameters are simultaneously sampled 5,000 times to represent underlying  
22  
23 10 uncertainty, including the costs, utilities probabilities and disease progression  
24  
25 11 parameters. We present total and incremental costs, QALYs, and incremental cost-  
26  
27 12 effectiveness ratios (ICERs). Mean and 2.5-97.5% centile (95% CI) results are  
28  
29 13 presented. We additionally present the proportion of simulations which are cost-  
30  
31 14 effective under £20,000 and £30,000 WTP thresholds.  
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## 38 Sensitivity analyses

39  
40 17 To test the robustness of the results to alternative assumptions, we undertook  
41  
42 18 extensive one-way sensitivity analyses on starting age, discount rate, drug cost, time  
43  
44 19 horizon, treatment uptake, intervention effect, and intervention cost. Finally, due to  
45  
46 20 the uncertainty surrounding the intervention cost and impact if scaled-up to the  
47  
48 21 national level and among different migrant populations, we undertook a threshold  
49  
50 22 analysis where we evaluated the minimum HBV prevalence at which the intervention  
51  
52 23 remains cost-effective at a willingness to pay (WTP) threshold of <£20,000 per QALY  
53  
54 24 gained with varying intervention cost (between £1 and £20, £4 per person eligible at  
55  
56 25 base-case), intervention effect (between 5% and 30%, 19.7% uptake at base-case)  
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1 and HBsAg prevalence (between 1% and 10%, 2% base-case). We displayed the  
2 results of this sensitivity analysis as a contour map.

## 5 RESULTS

### 6 *Base-case 2% HBsAg prevalence*

7 At a 2% HBsAg prevalence, the HBV case-finding intervention resulted in mean  
8 incremental costs and QALYs of about £28 and 0.002 respectively over the 5,000  
9 samples, corresponding to an ICER of £13,625 per QALY gained (95%CI £7,121-  
10 27,588). The intervention was 87% and 98% likely to be cost-effective at £20,000  
11 and £30,000 WTP per additional QALY thresholds, respectively (Supplementary  
12 Figure 1). Most of the univariate sensitivity analyses produced ICERs below a  
13 £20,000 WTP threshold (Figure 2), including reducing the likelihood of testing from  
14 19.7% to 5% (£19,323/QALY gained). However, the exceptions were assuming a  
15 20-year time horizon instead of 40 years (£22,713/QALY gained), discounting  
16 QALYs at 6% instead of 3.5% (£21,970/QALY gained), not discounting costs instead  
17 of 6% (21,521/QALY gained) and doubling the costs of all drug treatments from  
18 £3,979/£2,453 to £7,957/ £4,905 (£22,586/QALY gained). Decreasing the  
19 probability of treatment uptake after testing positive for HBsAg from 0.42 to 0.1  
20 increased the ICER to over £30,000 (£31,340/QALY gained).

### 22 *Impact of variation in HBV prevalence and intervention impact (cost, effect and 23 uptake)*

24 Cost-effectiveness of HBV case-finding was strongly driven by HBV prevalence. Our  
25 sensitivity analyses indicated that the intervention would remain cost-effective under

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2  
3 1 a £20,000 WTP threshold as long as HBV prevalence among the migrant population  
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5 2 is equal to or exceeds 1% (Figure 3).  
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10 4 Due to the uncertainty in cost and intervention impact if scaled-up across the U.K.  
11  
12 5 and among different migrant population, we additionally present a sensitivity analysis  
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14 6 of the threshold HBV prevalence which would ensure the intervention is cost-  
15  
16 7 effective under a £20,000 WTP with varying costs and intervention effects (Figure 4).  
17  
18 8 The contour map shows that, for example, the intervention would be cost-effective at  
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20 9 a prevalence of 1% if it cost £6 per person and the intervention effect was 20%.  
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22 10 However, it would no longer be cost-effective at a 1% prevalence level and £6 cost if  
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24 11 the intervention effect reduced to 10%.  
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## 33 13 **DISCUSSION**

34 14 HBV case-finding using a one-time opt out approach in primary care settings has a  
35  
36 15 high potential to be cost-effective among U.K. migrant populations with a HBV  
37  
38 16 prevalence at or above an average of 1%. However, the results are sensitive to a  
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40 17 number of factors including the intervention effect or cost, rate of treatment uptake,  
41  
42 18 assuming a much shorter time horizon and (unrealistically) high discount rates and  
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44 19 drug costs.  
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## 49 21 **Limitations**

50  
51 22 The main limitation with the analysis is the substantial uncertainty surrounding the  
52  
53 23 costs of the intervention and its effect if this case-finding intervention were scaled-up  
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55 24 to a national level. Nonetheless, extensive sensitivity analysis shows that the  
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57 25 intervention remained cost-effective across a large range of evaluated scenarios.  
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3 1 Thus, while establishing more robust estimates of the costs and effects of  
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5 2 interventions to find cases of HBV will undoubtedly decrease the uncertainty around  
6  
7 3 our results, we believe the scope for the modelled intervention to be cost-effective is  
8  
9 4 extremely high.  
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14 6 Current U.K. NHS HBV-testing policy is to contact household members once a case  
15  
16 7 has been identified. However, we were unable to include this aspect in our analysis  
17  
18 8 due to a lack of data specific to the target migrant populations on the size and age  
19  
20 9 distribution of households of infected contacts, the probability that contacts were  
21  
22 10 HBsAg+ and the likelihood that contacts could be traced in the first instance. The  
23  
24 11 impact of excluding this process on the ICER we report is difficult to determine. For  
25  
26 12 example, if contact tracing results in a high proportion of people being treated for  
27  
28 13 CHB the ICER could decrease. Conversely, if many HBsAg- people are vaccinated  
29  
30 14 against HBV, the ICER could increase as there is already evidence to suggest it is  
31  
32 15 unlikely to be cost-effective<sup>15</sup>.  
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49 17 Finally, we did not model the possibility of simultaneously testing for hepatitis C virus  
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51 18 (HCV), which may increase the cost-effectiveness of the intervention though  
52  
53 19 evidence on the HCV prevalence among migrants also has uncertainties<sup>19</sup>.  
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### 21 **Comparison with other studies**

22 22 Five studies have examined the cost-effectiveness of screening for HBV among  
23  
24 23 migrant populations. A Dutch study<sup>17</sup> found that screening migrants from countries  
25  
26 24 with high or intermediate HBV prevalence (assuming a 3.4% chronic infection  
27  
28 25 prevalence) was highly cost-effective (EUR9000 per QALY gained) at a screening  
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3 1 campaign cost of approximately EUR11 per person eligible and 35% uptake – which  
4  
5 2 is consistent with our sensitivity analysis. Another study explored screening and  
6  
7 3 treatment of migrants from Asian and Pacific Islands in the US<sup>40</sup>, finding it to be cost-  
8  
9 4 effective (US\$36,000 per QALY gained) but also assuming a much higher  
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11 5 prevalence of HBV (10%), screening uptake (70%) and no screening programme  
12  
13 6 costs aside from the diagnostic tests. Two studies examined the cost-effectiveness  
14  
15 7 of screening all migrants to Canada<sup>41 42</sup>, both finding tenofovir-based treatment  
16  
17 8 moderately cost-effective (CAD\$40,000/QALY [~£22,000]) at 4.8-6.5% chronic  
18  
19 9 infection prevalence's. Our model assumes a lower prevalence of chronic HBV,  
20  
21 10 higher treatment efficacy and lower treatment and screening costs than the North  
22  
23 11 American studies, which may explain the difference in cost-effectiveness estimates.  
24  
25 12 Lastly, our results are partially consistent with findings from the recent HepFREE  
26  
27 13 trial, which was found to be cost-effective (£8,540/QALY) for a similar observed  
28  
29 14 intervention effect (19.7% uptake of testing compared to 19.5% uptake in our study).  
30  
31 15 However, HepFREE had higher intervention costs (>£25 per patient compared to £1-  
32  
33 16 20 in our model), combined HCV and HBV screening and identified patients on basis  
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35 17 of ethnic group rather than country of birth<sup>43</sup>.  
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## 19 **Conclusions**

20 Our analysis suggests that interventions to increase HBV case-finding in primary  
21 care among UK migrant populations with a prevalence of at least 1% – such as using  
22 a one-time opt out approach – could be cost-effective, underpinning current National  
23 Institute for Health and Care Excellence guidance<sup>44</sup>. Critically, at a threshold  
24 prevalence above 1% this will encompass migrant populations from most countries  
25 with endemic HBV, even if there is a healthy migrant effect (with migrant populations

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2  
3 1 in UK on average at lower risk than people in their country of origin<sup>16</sup>). These recent  
4  
5 2 results support the recommendation that interventions to increase HBV case-finding  
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7 3 in primary care among U.K. migrant populations should be expanded, but needs to  
8  
9 4 be based on screening by country of birth rather than ethnic group.  
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**Author contributions:** AM, PV, MH designed the study. AM, AG, JW and NM coded the analysis. All authors (AM, PV, MH, AG, JW, SK, MR, NM) interpreted the data. AM and NM wrote the first draft. All authors (AM, PV, MH, AG, JW, SK, MR, NM) contributed to the manuscript drafting, approved of the final version, and agreed to authorship.

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**Data Sharing:** Model code available on request to the corresponding author.

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15 6 **Patient and Public Involvement:** This study was commissioned by the UK National  
16  
17 7 Institute for Health and Care Excellence (<https://www.nice.org.uk/guidance/ph43/>)  
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19 8 with representation from lay members on the guidance panel who contributed to  
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## 1 **FIGURE LEGENDS**

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3 **Figure 1. HBV model schematic.** The arrows denote possible transitions between states;

4 HBsAg, hepatitis B virus surface antigen; HBeAg: hepatitis b virus e antigen; CHB, chronic hepatitis B  
5 virus; CC, compensated cirrhosis; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT,  
6 liver transplant; \*individuals may or may not know their infection status; %individuals with CC  
7 responding to treatment were assumed to keep the costs and utility associated with CC, but with  
8 disease progression probabilities equivalent to HBeAg seroconversion / inactive disease; “transitions  
9 permitted from all health states to death

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11 **Figure 2: Univariate sensitivity analysis on the ICER with a 2% HBV prevalence**

12 **scenario.** ICER, incremental cost-effectiveness ratio; Y-axis indicates the base case ICER of  
13 £21,400 per QALY gained; \*halves or doubles all baseline drug costs where relevant

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15 **Figure 3. Mean incremental cost-effectiveness ratio (ICER) of HBV screening**  
16 **by varying HBsAg prevalence**

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18 **Figure 4. Contour map showing for a range of costs (horizontal axis) and**  
19 **intervention effects (vertical axis), the threshold HBV prevalence (contours)**  
20 **where the intervention ICER falls under a £20,000 willingness to pay threshold.**

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Table 1: Annual costs in 2017/18 UK prices (£)

Cost	Mean	95% interval of sampled range <sup>^</sup>	Source
Intervention cost per person eligible for testing <sup>*</sup>	4	-	Assumption
HBsAg test (laboratory)	10	-	Assumption
Pegylated interferon	3,979	-	BNF <sup>45</sup>
Tenofovir	2,453	-	BNF <sup>45</sup>
ALT and ultrasound	77	-	Assumption <sup>45</sup>
Full viral profile	432	-	Assumption <sup>45</sup>
HBeAg+ seroconverted / HBeAg- ALT/DNA low <sup>a</sup>	335	240-446	Shepherd <sup>25</sup>
HBeAg+ / HBeAg- active disease <sup>b</sup>	674	480-896	Shepherd <sup>25</sup>
Compensated cirrhosis	1,606	1,052-2,283	Crossan <sup>37</sup>
Decompensated cirrhosis	38,212	21,848-60,645	Crossan <sup>37</sup>
Hepatocellular carcinoma	38,212	21,848-60,645	Crossan <sup>37</sup>
Liver transplant (first year)	67,698	57,301-79,287	Crossan <sup>37</sup>
Liver transplant (subsequent years)	17,231	5,415-35,399	Crossan <sup>37</sup>

<sup>\*</sup>Indicates a one off cost; <sup>^</sup>Sampled values from the probabilistic sensitivity analysis using a gamma distribution; <sup>b</sup>costs are additional to<sup>a</sup>

## References

1. World Health Organisation. Global hepatitis report, 2017 [Available from: <http://apps.who.int/iris/bitstream/10665/255016/1/9789241565455-eng.pdf?ua=1> accessed 04/08/2017].
2. Cooke GS, Lemoine M, Thursz M, et al. Viral hepatitis and the Global Burden of Disease: a need to regroup. *J Viral Hepat* 2013;20(9):600-1. doi: 10.1111/jvh.12123
3. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet* 2012;380(9859):2095-128. doi: 10.1016/S0140-6736(12)61728-0
4. World Health Organisation. Hepatitis B fact sheet 2014 [Available from: <http://www.who.int/mediacentre/factsheets/fs204/en/2014> accessed 29/04/2019].
5. Rajbhandari R, Chung RT. Treatment of Hepatitis B: A Concise Review. *Clin Transl Gastroenterol* 2016;7(9):e190. doi: 10.1038/ctg.2016.46
6. World health Organisation. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva. 2015 [Available from: [http://apps.who.int/iris/bitstream/10665/154590/1/9789241549059\\_eng.pdf?ua=1&ua=1](http://apps.who.int/iris/bitstream/10665/154590/1/9789241549059_eng.pdf?ua=1&ua=1) accessed 16/06/2017].
7. Health Protection Agency. Migrant Health: Infectious diseases in non-UK born populations in the UK. An update to the baseline report 2011 [Available from: [https://web.archive.nationalarchives.gov.uk/20140714091407/http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb\\_C/1317131996733](https://web.archive.nationalarchives.gov.uk/20140714091407/http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1317131996733) accessed 24/09/2019].
8. Public Health England. Acute hepatitis B (England): annual report 2017 [Available from: [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/736145/hpr3118\\_hepB.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/736145/hpr3118_hepB.pdf) accessed 29/04/2019].
9. World Health Organisation. Hepatitis B. Geneva. 2002 [Available from: [https://apps.who.int/iris/bitstream/handle/10665/67746/WHO\\_CDS\\_CSR\\_LYO\\_2002.2\\_HEPATITIS\\_B.pdf;jsessionid=F89A0070DDEE2B34F204EC538ECD248D?sequence=1#page=1&zoom=auto,-149,603](https://apps.who.int/iris/bitstream/handle/10665/67746/WHO_CDS_CSR_LYO_2002.2_HEPATITIS_B.pdf;jsessionid=F89A0070DDEE2B34F204EC538ECD248D?sequence=1#page=1&zoom=auto,-149,603) accessed 29/04/2019].
10. Evlampidou I, Hickman M, Irish C, et al. Low hepatitis B testing among migrants: a cross-sectional study in a UK city. *Br J Gen Pract* 2016 doi: 10.3399/bjgp16X684817
11. Cochrane A, Evlampidou I, Irish C, et al. Hepatitis B infection prevalence by country of birth in migrant populations in a large UK city. *J Clin Virol*. 2015;68:79-82.
12. Hahne S, Ramsay M, Balogun K, et al. Incidence and routes of transmission of hepatitis B virus in England and Wales, 1995-2000: implications for immunisation policy. *J Clin Virol*. 2004;29:211-20.
13. Fattovich G. Natural history of hepatitis B. *J Hepatol* 2003;39:50-58. doi: 10.1016/S0168-8278(03)00139-9
14. Edmunds WJ, Ramsay R. The estimated cost-effectiveness of vaccination in infants born to hepatitis B positive mothers 2009 [Available from:

- 1  
2  
3  
4 <https://www.nice.org.uk/guidance/ph21/evidence/economic-analysis-3-full-report-371340255> accessed 29/04/2019].
- 5  
6 15. Siddiqui MR, Gay N, Edmunds WJ, et al. Economic evaluation of infant and  
7 adolescent hepatitis B vaccination in the UK. *Vaccine* 2011;29(3):466-75.
- 8  
9 16. Uddin G, Shoeb D, Solaiman S, et al. Prevalence of chronic viral hepatitis in  
10 people of south Asian ethnicity living in England: the prevalence cannot  
11 necessarily be predicted from the prevalence in the country of origin. *J Viral*  
12 *Hepat* 2010;17:327-35.
- 13  
14 17. Veldhuijzen IK, Toy M, Hahné SJM, et al. Screening and Early Treatment of  
15 Migrants for Chronic Hepatitis B Virus Infection Is Cost-Effective.  
16 *Gastroenterology* 2010;138(2):522-30. doi: 10.1053/j.gastro.2009.10.039
- 17  
18 18. Flanagan S, Kunkel J, Appleby V, et al. Case finding and therapy for chronic viral  
19 hepatitis in primary care (HepFREE): a cluster-randomised controlled trial.  
20 *Lancet Gastroenterol Hepatol*. 2019;4(1):32-44. doi: 10.1016/s2468-  
21 1253(18)30318-2
- 22  
23 19. Lewis H, Burke K, Begum S, et al. What is the best method of case finding for  
24 chronic viral hepatitis in migrant communities? *Gut* 2011;Vol 60 Suppl 2:A26.
- 25  
26 20. Beck JR, Pauker SG. The Markov process in medical prognosis. *Med Decis Making*  
27 1983;3(4):419-58.
- 28  
29 21. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical  
30 guide. *Med Decis Making* 1993;13(4):322-38.
- 31  
32 22. National Institute for Health and Care Excellence. Guide to the methods of  
33 technology appraisal 2013 [Available from:  
34 <https://www.nice.org.uk/process/pmg9/chapter/foreword> accessed  
35 29/04/2019].
- 36  
37 23. Jones L, Bates G, McCoy E, et al. A systematic review of the effectiveness & cost-  
38 effectiveness of interventions aimed at raising awareness and engaging with  
39 groups who are at an increased risk of hepatitis B and C infection: Liverpool  
40 John Moores University, Centre for Public Health; 2011 [Available from:  
41 <https://www.nice.org.uk/guidance/ph43/evidence/evidence-review-2-69062510>  
42 accessed 23/03/2017].
- 43  
44 24. Health Protection Agency. Sentinel Surveillance of Hepatitis Testing in England -  
45 Hepatitis B and D 2010 Report - Analysis of testing between 2007 and 2010  
46 2011 [Available from:  
47 [https://webarchive.nationalarchives.gov.uk/20140714073050/http://www.hpa.org.uk/webc/HPAwebFile/HPAweb\\_C/1313155292332](https://webarchive.nationalarchives.gov.uk/20140714073050/http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1313155292332)  
48 accessed  
49 29/04/2019].
- 50  
51 25. Shepherd J, Jones J, Takeda A, et al. Adefovir dipivoxil and pegylated interferon  
52 alfa-2a for the treatment of chronic hepatitis B: a systematic review and  
53 economic evaluation. *Health Technol Assess* 2006;10(28)
- 54  
55 26. Takeda A, Jones J, Shepherd J, et al. A systematic review and economic  
56 evaluation of adefovir dipivoxil and pegylated interferon-alpha-2a for the  
57 treatment of chronic hepatitis B. *J Viral Hepat* 2007;14:75-88.
- 58  
59 27. National Institute for Health and Care Excellence. Hepatitis B (chronic): diagnosis  
60 and management 2013 [Available from:  
<https://www.nice.org.uk/guidance/Cg165> accessed 24/03/2017].

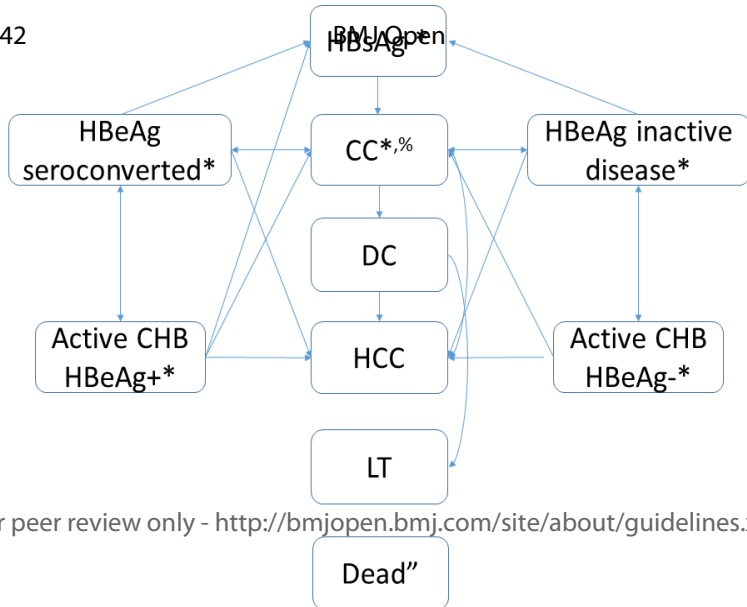
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28. Public Health England. Annual report from the sentinel surveillance study of blood borne virus testing in England: data for January to December 2015 2016 [Available from: [https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/540332/hpr2416\\_bbvs.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/540332/hpr2416_bbvs.pdf) accessed 02/06/2017].
29. McPherson S, Valappil M, Moses S, et al. CHASE-B (Chinese hepatitis awareness, surveillance, and education): A pilot of targeted case finding for hepatitis B virus (HBV) in the British-Chinese community. *Gut* 2010;60:A25-A26.
30. Kawsar MT, Goh BT. Hepatitis B virus infection among Chinese residents in the United Kingdom. *Sex Transm Infect* 2002;78:166-68.
31. Aweis D, Brabin BJ, Beeching NJ, et al. Hepatitis B prevalence and risk factors for HBsAg carriage amongst Somali households in Liverpool. *Commun Dis Public Health*. 2001;4(4):247-52.
32. Brabin B, Beeching NJ, Bunn JE, et al. Hepatitis B prevalence among Somali households in Liverpool. *Arch Dis Child*. 2002;86(1):67-8.
33. McPherson S, Valappil M, Moses SE, et al. Targeted case finding for hepatitis B using dry blood spot testing in the British-Chinese and South Asian populations of the North-East of England. *J Viral Hepat* 2013;20(9):638-44. doi: 10.1111/jvh.12084
34. Vedio A, Liu EZH, Lee ACK, et al. Improving access to health care for chronic hepatitis B among migrant Chinese populations: A systematic mixed methods review of barriers and enablers. *J Viral Hepat* 2017;24(7):526-40. doi: 10.1111/jvh.12673
35. Woo G, Tomlinson G, Nishikawa Y, et al. Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses. *Gastroenterology* 2010;139(4):1218-29.
36. Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet* 2013;381(9865):468-75. doi: 10.1016/s0140-6736(12)61425-1
37. Crossan C, Tsochatzis EA, Longworth L, et al. Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease: systematic review and economic evaluation. *Health Technol Assess* 2015;19(9) doi: 10.3310/hta19090
38. Curtis L, Burns A. Unit costs of health and social care 2015 [Available from: <http://www.pssru.ac.uk/project-pages/unit-costs/2015/> accessed 27/03/2017].
39. Curtis L, Burns A. Unit costs of health and social care 2018 [Available from: <https://www.pssru.ac.uk/pub/uc/uc2018/sources-of-information.pdf> accessed 18/12/2018].
40. Hutton DW, Tan D, So SK, et al. Cost-effectiveness of screening and vaccinating Asian and Pacific Islander adults for hepatitis B. *Ann Intern Med* 2007;147(7):460-9.
41. Rossi C, Schwartzman K, Oxlade O, et al. Hepatitis B screening and vaccination strategies for newly arrived adult Canadian immigrants and refugees: a cost-effectiveness analysis. *PLoS One* 2013;8(10) doi: 10.1371/journal.pone.0078548



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42. Wong WWL, Woo G, Jenny Heathcote E, et al. Cost effectiveness of screening immigrants for hepatitis B. *Liver Int* 2011;31(8):1179-90. doi: 10.1111/j.1478-3231.2011.02559.x
43. Hickman M, Mandel S, Vickerman P, et al. Hepatitis case finding among migrants in primary care. *Lancet Gastroenterol Hepatol*. 2019;4(1):3-4. doi: 10.1016/s2468-1253(18)30385-6
44. National Institute for Health and Clinical Excellence. Hepatitis B and C - ways to promote and offer testing 2012 [Available from: <http://publications.nice.org.uk/hepatitis-b-and-c-ways-to-promote-and-offer-testing-to-people-at-increased-risk-of-infection-ph43>].
45. Royal Pharmaceutical Society. British National Formulary no. 71 2016 [Available from: [www.bnf.org](http://www.bnf.org) accessed 01/08/2016].

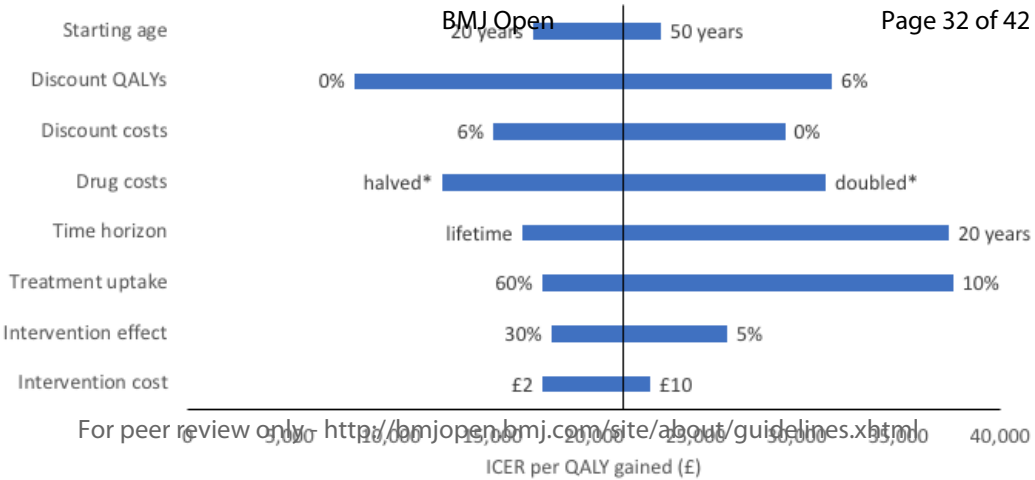
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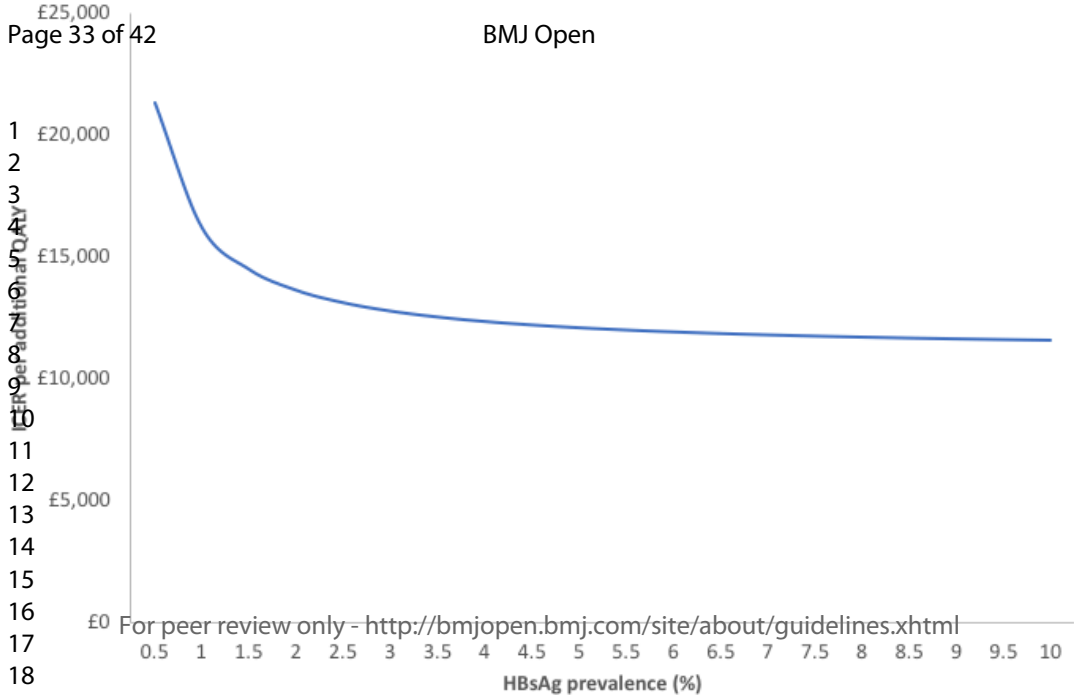
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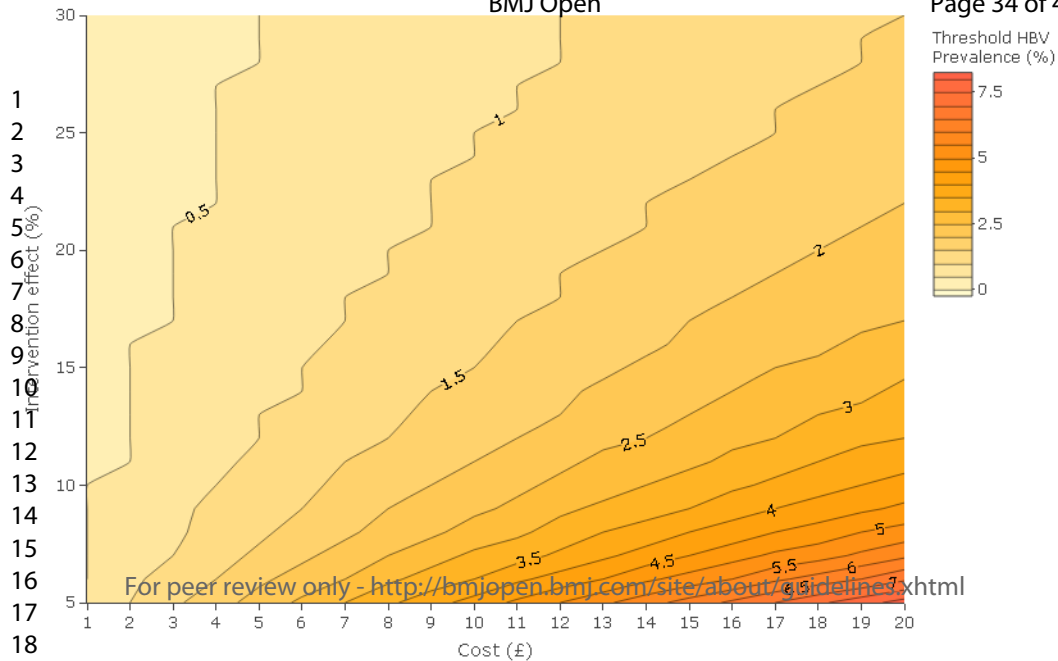


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Supplementary Materials

Supplementary Table 1: Annual transition probability matrix for people who enter the model as HBsAg+ and HBeAg+ derived from Shepherd(1) and Marcellin(2)

From:	To:	HBsAg seroconverted	HBeAg seroconverted	CHB HBeAg+ active disease	CC	DC	HCC	LT1	LT2	Dead <sup>+</sup>
HBsAg seroconverted		#	0	0	0	0	0.00005	0	0	0
HBeAg seroconverted		0.02	#	0.03	0.01	0	0.005	0	0	0
CHB HBeAg+ active disease no treatment		0.0175	0.05	#	0.05	0	0.005	0	0	0.0035
CHB HBeAg+ active disease or CC on treatment										
Treatment response with peglyated interferon		0.0175	0.20	#	0.05	0	0.005	0	0	0.0035
Treatment response with tenofovir		0.0175	0.054	#	0.05	0	0.005	0	0	0.0035
Compensated cirrhosis (CC) no treatment		0	0.05	0	#	0.05	0.025	0	0	0.051
Decompensated cirrhosis (DC)		0	0	0	0	#	0.025	0.03	0	0.39
Hepatocellular carcinoma (HCC)		0	0	0	0	0	#	0	0	0.56
Liver transplant – first year (LT1)		0	0	0	0	0	0	#	0	0.21
Liver transplant – subsequent years (LT2)		0	0	0	0	0	0	0	#	0.057

<sup>+</sup>an age-adjusted general population mortality is added to this amount; #, indicates the residual row probability; all values are converted to a Dirichlet distribution by assuming an effective sample size of 200 for each row(3)

Review only

**Supplementary Table 2: Annual transition probability matrix for people who enter the model as HBsAg+ and HBeAg-derived from Shepherd(1) and Marcellin(2)**

From:	To:	HBsAg seroconverted	HBeAg seroconverted	CHB HBeAg-active disease	CC	DC	HCC	LT1	LT2	Dead <sup>†</sup>
HBsAg seroconverted		#	0	0	0	0	0.00005	0	0	0
HBeAg seroconverted		0.0175	#	0.03	0.01	0	0.005	0	0	0
CHB HBeA- active disease no treatment		0	0.015	#	0.05	0	0.005	0	0	0.0035
CHB HBeAg- active disease or CC on treatment										
Treatment response with peglyated interferon		0	0.75	#	0.05	0	0.005	0	0	0.0035
Treatment response with tenofovir		0	0.023	#	0.05	0	0.005	0	0	0.0035
Decompensated cirrhosis (DC)		0	0	0	0	#	0.025	0.03	0	0.39
Hepatocellular carcinoma (HCC)		0	0	0	0	0	#	0	0	0.56
Liver transplant – first year (LT1)		0	0	0	0	0	0	#	0	0.21
Liver transplant – subsequent years (LT2)		0	0	0	0	0	0	0	#	0.057

<sup>†</sup>an age-adjusted general population mortality is added to this amount; #, indicates the residual row probability; all values are converted to a Dirichlet distribution by assuming an effective sample size of 200 for each row(3)



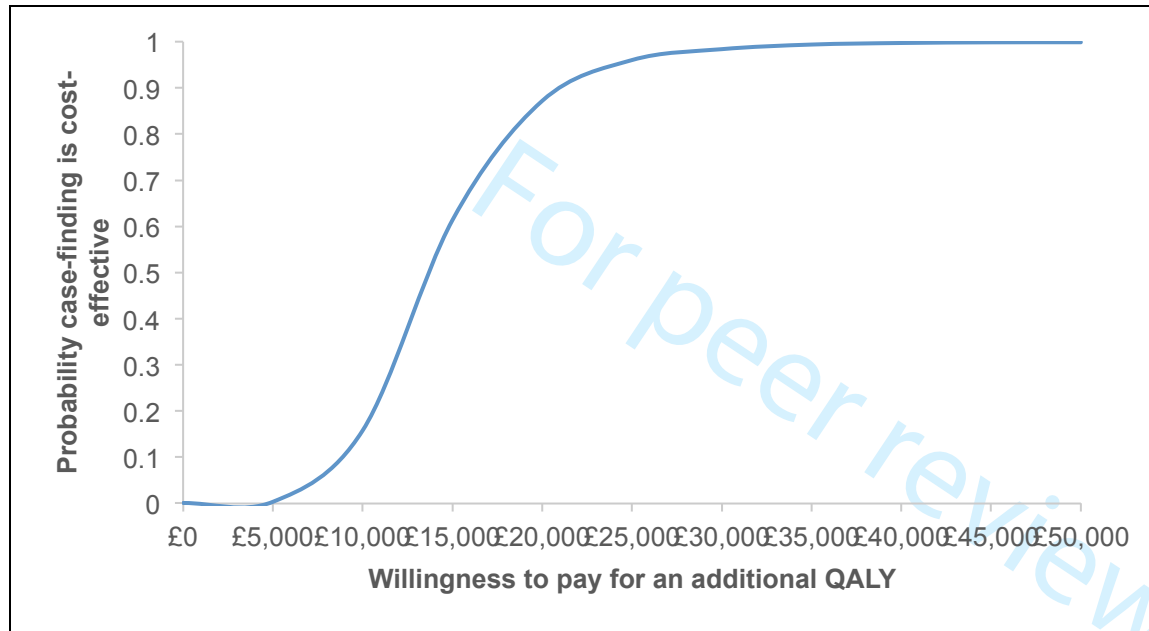
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**Supplementary Table 3: Utility values from Shepherd(1) and Takeda(4)**

<b>Utility</b>	<b>Mean decrement</b>	<b>95% interval of sampled range<sup>^</sup></b>
<b>Age</b>		-
<b>0-44</b>	0.09	-
<b>45-54</b>	0.15	-
<b>55-64</b>	0.20	-
<b>65-74</b>	0.22	-
<b>75+</b>	0.27	-
<b>HBsAg-</b>	0	-
<b>HBeAg+ seroconverted / HBeAg- ALT/DNA low</b>	0	-
<b>HBeAg+ / HBeAg- active disease</b>	0.04	0.023-0.062
<b>Compensated cirrhosis</b>	0.44	0.34-0.55
<b>Decompensated cirrhosis</b>	0.54	0.43-0.73
<b>Hepatocellular carcinoma</b>	0.54	0.43-0.73
<b>Liver transplant (first year)</b>	0.54	0.43-0.73
<b>Liver transplant (subsequent years)</b>	0.32	0.22-0.43

Utility values are calculated by subtracting appropriate decrements from 1; <sup>^</sup>Sampled values from the probabilistic sensitivity analysis using a beta distribution

**Supplementary Figure 1. Cost-effectiveness acceptability curve for the base-case 2% HBsAg prevalence.**



## Reference

1. Shepherd J, Jones J, Takeda A, Davidson P, Price A. Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation. *Health Technology Assessment*. 2006;10(28).
2. Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet*. 2013 Feb 9;381(9865):468-75. PubMed PMID: 23234725. Epub 2012/12/14. eng.
3. Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation. Gray A, Briggs A, editors. Oxford: Oxford University Press; 2006.
4. Takeda A, Jones J, Shepherd J, Davidson P, Price A. A systematic review and economic evaluation of adefovir dipivoxil and pegylated interferon-alpha-2a for the treatment of chronic hepatitis B. *Journal of Viral Hepatitis*. 2007;14:75-88.

**CHEERS Checklist**

**Items to include when reporting economic evaluations of health interventions**

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: <http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp>

Section/item	Item No	Recommendation	Reported on page No/line No
<b>Title and abstract</b>			
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	_____
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	_____
<b>Introduction</b>			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	_____
<b>Methods</b>			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	_____
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	_____
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	_____
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	_____
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	_____
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	_____
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	_____
Measurement of effectiveness	11a	<i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	_____



1		11b	<i>Synthesis-based estimates:</i> Describe fully the methods used for	
2			identification of included studies and synthesis of clinical	
3			effectiveness data.	
4				
5	Measurement and	12	If applicable, describe the population and methods used to	
6	valuation of preference		elicit preferences for outcomes.	
7	based outcomes			
8	Estimating resources	13a	<i>Single study-based economic evaluation:</i> Describe approaches	
9	and costs		used to estimate resource use associated with the alternative	
10			interventions. Describe primary or secondary research methods	
11			for valuing each resource item in terms of its unit cost.	
12			Describe any adjustments made to approximate to opportunity	
13			costs.	
14				
15		13b	<i>Model-based economic evaluation:</i> Describe approaches and	
16			data sources used to estimate resource use associated with	
17			model health states. Describe primary or secondary research	
18			methods for valuing each resource item in terms of its unit	
19			cost. Describe any adjustments made to approximate to	
20			opportunity costs.	
21				
22	Currency, price date,	14	Report the dates of the estimated resource quantities and unit	
23	and conversion		costs. Describe methods for adjusting estimated unit costs to	
24			the year of reported costs if necessary. Describe methods for	
25			converting costs into a common currency base and the	
26			exchange rate.	
27				
28	Choice of model	15	Describe and give reasons for the specific type of decision-	
29			analytical model used. Providing a figure to show model	
30			structure is strongly recommended.	
31				
32	Assumptions	16	Describe all structural or other assumptions underpinning the	
33			decision-analytical model.	
34	Analytical methods	17	Describe all analytical methods supporting the evaluation. This	
35			could include methods for dealing with skewed, missing, or	
36			censored data; extrapolation methods; methods for pooling	
37			data; approaches to validate or make adjustments (such as half	
38			cycle corrections) to a model; and methods for handling	
39			population heterogeneity and uncertainty.	
40				
41				
42	<b>Results</b>			
43	Study parameters	18	Report the values, ranges, references, and, if used, probability	
44			distributions for all parameters. Report reasons or sources for	
45			distributions used to represent uncertainty where appropriate.	
46			Providing a table to show the input values is strongly	
47			recommended.	
48				
49	Incremental costs and	19	For each intervention, report mean values for the main	
50	outcomes		categories of estimated costs and outcomes of interest, as well	
51			as mean differences between the comparator groups. If	
52			applicable, report incremental cost-effectiveness ratios.	
53				
54	Characterising	20a	<i>Single study-based economic evaluation:</i> Describe the effects	
55	uncertainty		of sampling uncertainty for the estimated incremental cost and	
56			incremental effectiveness parameters, together with the impact	
57				
58				
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1			of methodological assumptions (such as discount rate, study	
2			perspective).	
3		20b	<i>Model-based economic evaluation</i> : Describe the effects on the	
4			results of uncertainty for all input parameters, and uncertainty	
5			related to the structure of the model and assumptions.	
6				
7	Characterising	21	If applicable, report differences in costs, outcomes, or cost-	
8	heterogeneity		effectiveness that can be explained by variations between	
9			subgroups of patients with different baseline characteristics or	
10			other observed variability in effects that are not reducible by	
11			more information.	
12				
13	<b>Discussion</b>			
14	Study findings,	22	Summarise key study findings and describe how they support	
15	limitations,		the conclusions reached. Discuss limitations and the	
16	generalisability, and		generalisability of the findings and how the findings fit with	
17	current knowledge		current knowledge.	
18				
19	<b>Other</b>			
20	Source of funding	23	Describe how the study was funded and the role of the funder	
21			in the identification, design, conduct, and reporting of the	
22			analysis. Describe other non-monetary sources of support.	
23				
24	Conflicts of interest	24	Describe any potential for conflict of interest of study	
25			contributors in accordance with journal policy. In the absence	
26			of a journal policy, we recommend authors comply with	
27			International Committee of Medical Journal Editors	
28			recommendations.	
29				

31 For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT  
 32 statement checklist  
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 35 The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item  
 36 CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the  
 37 ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices  
 38 webpage: <http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp>  
 39

40  
 41 The citation for the CHEERS Task Force Report is:  
 42 Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards  
 43 (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication  
 44 guidelines good reporting practices task force. *Value Health* 2013;16:231-50.  
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