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Evidence Check

Population-level interventions to improve the health outcomes of people living with hepatitis B

An Evidence Check rapid review brokered by the Sax Institute for the NSW Ministry of Health—November 2022

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Disclaimer:

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Population-level interventions to improve the health outcomes of people living with hepatitis B

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Executive summary

Background

An estimated 292 million people are living with chronic hepatitis B virus (HBV) infection globally, including 223,000 people in Australia. HBV diagnosis and linkage of people living with HBV to clinical care is suboptimal in Australia, with 27% of people living with HBV undiagnosed and 77% not receiving regular HBV clinical care. This Evidence Check review aimed to characterise population-level interventions implemented to enhance all components of the HBV care cascade and to analyse the effectiveness of interventions.

Evidence Check questions

Question 1: What population-level interventions, programs or policy approaches have been shown to be effective in reducing the incidence of hepatitis B; and, where they have not yet been fully rolled out or evaluated in Australia, demonstrate early effectiveness or promise in reducing the incidence of hepatitis B?

Question 2: What population-level interventions and/or programs are effective in reducing the disease burden for people in the community with hepatitis B?

Methods

The review team searched four bibliographic databases and 21 grey literature sources. Studies were eligible for inclusion if the study population included people with or at risk of chronic HBV and the study looked at population-level interventions to decrease HBV incidence or disease burden or to enhance any components of the HBV care cascade (i.e. diagnosis, linkage to care, treatment initiation, adherence to clinical care) or HBV vaccination coverage.

Studies published in the past 10 years (since January 2012), with or without comparison groups, were eligible for inclusion. Studies conducting an HBV screening intervention were eligible if they reported the proportion of people participating in screening, the proportion of newly diagnosed HBV cases (the participant was unaware of their HBV status), the proportion of people who received HBV vaccination following screening, or the proportion of participants diagnosed with chronic HBV infection who were linked to HBV clinical care. Studies were excluded if they had fewer than 20 participants, if they included a pharmaceutical or hospital-based intervention, or if the study was implemented in limited clinical services.

Initially, we screened the records by title and abstract, then reviewed the full text of potentially eligible records and selected eligible studies for inclusion.

For each study included in the Evidence Check, we calculated the study outcome and corresponding 95% confidence intervals (95%CIs). Where studies included a comparison group, we calculated the odds ratio (OR) and corresponding 95%CIs. We used random effect meta-analysis models to calculate the pooled study outcome estimates and conducted stratified analyses by study setting, study population and intervention-specific characteristics.

Key findings

A total of 61 studies were included in the Evidence Check. A large majority (study n=48, 79%) were single-arm studies with no concurrent control, with seven (11%) randomised controlled trials and six (10%) non-randomised controlled studies. A total of 109 interventions were evaluated in 61 included studies. The most frequent interventions were on-site or outreach HBV screening and linkage to HBV clinical care coordination, conducted in 27 and 26 studies respectively.

Question 1

We found no studies reporting HBV incidence as the study outcome. One study conducted in a remote area demonstrated that an intervention including education of pregnant women and training village health volunteers enhanced coverage of HBV birth dose vaccination (93% post-intervention, vs. 81% pre-intervention), but no data of HBV incidence among infants were reported.

Question 2

Study outcomes most relevant to the HBV burden for people in the community included HBV diagnosis, linkage to HBV care and HBV vaccination coverage.

Among randomised controlled trials aimed at enhancing HBV screening, there was a meta-analysis of three studies that implemented an intervention including community face-to-face education focused on HBV and/or liver cancer among migrants from high HBV prevalence areas. This analysis demonstrated a significantly higher HBV testing uptake in intervention groups, with the likelihood of HBV testing 3.6 times higher among those participating in education programs compared with the control groups (OR: 3.62, 95% CI 2.72, 4.88).

In another analysis of 25 studies evaluating an intervention to enhance HBV screening, a pooled estimate of 66% of participants received HBV testing following the study intervention (95%CI: 58%–75%), with high heterogeneity across studies (range: 17%–98%; I-square: 99.9%). A stratified analysis by HBV screening strategy demonstrated that in the studies providing participants with on-site HBV testing, the proportion receiving HBV testing (80%, 95%CI: 72%–87%) was significantly higher compared with the studies that referred participants to an external site for HBV testing (54%, 95%CI: 37%–71%).

In the studies implementing an intervention to enhance the linkage of people diagnosed with HBV infection to clinical care, the interventions included different components and varied across studies.

The most common component was post-test counselling followed by assistance in scheduling clinical appointments, conducted in 52% and 38% of the studies respectively. In a meta-analysis, a pooled estimate of 73% of people with HBV infection were linked to HBV clinical care (95%CI: 64%–81%), with high heterogeneity across studies (range: 28%–100%; I-square: 99.2%). A stratified analysis by study population demonstrated that in the studies among the general population in high prevalence countries, 94% of people (95%CI: 88%–100%) who received the study intervention were linked to care, significantly higher than the 72% (95%CI: 61%–83%) in studies among migrants from high prevalence areas living in a country with low prevalence.

In 19 studies, HBV vaccination uptake was assessed after an intervention; one study assessed birth dose vaccination among infants, one assessed vaccination in elementary school children and 17 studies assessed vaccination in adults. Among studies assessing adult vaccination, a pooled estimate of 38% (95%CI: 21%–56%) of people initiated vaccination, with high heterogeneity across studies (range: 0.5%–93%; I-square: 99.9%). A stratified analysis by HBV vaccination strategy demonstrated that in the studies providing on-site vaccination, the uptake was 78% (95%CI: 62%–94%), significantly higher than the 27% (95%CI: 13%–42%) achieved in studies referring participants to an external site for vaccination.

Conclusion

This Evidence Check identified a wide variety of interventions, mostly multi-component interventions, to enhance HBV screening, linkage to HBV clinical care and HBV vaccination coverage. We observed high heterogeneity in the effectiveness of interventions in all three domains: screening, linkage to care and vaccination. Strategies that were found to boost the effectiveness of interventions included providing on-site HBV testing and vaccination (versus referral to off-site locations for testing and vaccination) and community education focused on HBV or liver cancer in an HBV screening program. Further studies are needed to evaluate the effectiveness of more novel interventions (e.g. point of care testing) and interventions specifically including Indigenous populations, people who inject drugs, men who have sex with men and incarcerated people.

Background

An estimated 292 million people were living with chronic hepatitis B virus (HBV) infection in 2016 globally.[1] Chronic HBV infection is also a major cause of advanced liver diseases, liver cancer and liver disease-related mortality in many countries.[2] Currently available HBV antiviral treatments are not able to eradicate the virus in the large majority of people, but treatment is highly effective in suppressing virus replication and controlling liver fibrosis progression, and reducing the risk of liver cancer.[3] Clinical management of chronic HBV includes antiviral therapy in people who have specific eligibility criteria based on viral markers, liver inflammation and liver disease stage, while other people need monitoring of HBV and liver disease markers only.[4, 5] As these criteria can change over time, linkage to HBV clinical care and adherence to care are crucial for people living with HBV, regardless of eligibility for antiviral treatment.

In 2016, the World Health Organisation (WHO) defined specific targets for the elimination of HBV infection as a global public health threat by 2030, including diagnosing 90% of people living with HBV, treating 80% of those eligible and reducing HBV-related mortality by 65%.[6] In Australia, an estimated 223,000 individuals were living with HBV in 2020, with the majority of them born overseas or identifying as Aboriginal or Torres Strait Islander Australians.[7] It was also estimated that 73% of people with HBV had been diagnosed with the disease, only 23% were engaged in clinical care and only 11% were receiving antiviral treatment, which is less than half of the 29.5% of Australians living with hepatitis B who are estimated to be eligible for treatment.[7] Interventions are required to enhance the HBV diagnosis rate and linkage to care.

Several interventions have been suggested to improve various components of the HBV care cascade. A review of interventions to increase the HBV care cascade among migrants included 17 studies.[8] This review described the interventions and reported the individual study outcomes but had no quantitative pooled analysis of study outcomes. A systematic review published in 2016 also reviewed interventions to optimise the HBV care cascade.[9] While the main focus of this review was on HBV educational interventions, it also included interventions targeting specific populations such as patients receiving chemotherapy, limiting the applicability of its findings in the community.

This Evidence Check aimed to characterise population-level interventions implemented to enhance all components of the HBV care cascade and analyse the effectiveness of interventions.

Evidence Check questions

This Evidence Check aimed to address the following questions:

Question 1: What population-level interventions, programs or policy approaches have been shown to be effective in reducing the incidence of hepatitis B; and, where they have not yet been fully rolled out or evaluated in Australia, demonstrate early effectiveness or promise in reducing the incidence of hepatitis B?

Question 2: What population-level interventions and/or programs are effective at reducing the disease burden for people in the community with hepatitis B?

Methods

Eligibility criteria

The Evidence Check review team included studies if they met all the following criteria:

a) Study population included people with or at risk of chronic HBV infection. Main populations at risk of HBV included:
   - People born in high HBV prevalence countries
   - Indigenous people (in Australia, Aboriginal and Torres Strait Islander people)
   - Pregnant women living with HBV and their children
   - People who inject drugs
   - Men who have sex with men
   - People living with HIV

b) Study conducted a population-level intervention in relation to the outcomes specified below

c) Study outcome included HBV incidence, any component of the HBV care cascade (i.e. diagnosis, linkage to care, treatment initiation, adherence to clinical care) HBV vaccination coverage and HBV disease burden.

Studies with or without comparison groups were eligible for inclusion. Population-level intervention was defined as non-pharmaceutical interventions implemented in the community or in a range of clinical and/or non-clinical settings. Based on this definition, we excluded studies evaluating the effectiveness of HBV antiviral treatment or vaccination (as pharmaceutical interventions). However, studies evaluating other interventions to increase treatment uptake or vaccination coverage were included if otherwise eligible. Studies conducted in limited clinical services or studies implementing hospital-based interventions were excluded. Studies with fewer than 20 participants were excluded. Studies conducting an HBV screening intervention were included if they reported the proportion of eligible people participating in screening, the proportion of newly diagnosed HBV cases (participant was unaware of their HBV status), the proportion of people who received HBV vaccination following screening, or the proportion of participants diagnosed with chronic HBV infection who were linked to HBV clinical care. Studies published in the past 10 years (since January 2012) were included. There were no language restrictions.

Information sources

We searched four bibliographic databases for peer-reviewed publications, including MEDLINE (PubMed), Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL).

We searched several resources for studies not published in peer-reviewed journals (grey literature), including conference abstracts of the International Liver Congress™ and The Liver Meeting®, ClinicalTrials.gov (for unpublished or ongoing studies), the latest HBV national and NSW strategies, and the websites of the national and international organisations with activities relevant to viral hepatitis (Table 1). We hand searched reference lists of the relevant review articles.

Table 1: List of organisations whose websites were searched for grey literature.

International
World Health Organisation
NHS Race & Health Observatory
CATIE—Canada's source for HIV and hepatitis C information
Canadian Liver Foundation
United States Department of Health and Human Services
US Centers for Disease Control and Prevention
Family Health International
United Nations Population Fund
NOHep
PRevention Of LIver FIbrosis and Cancer in Africa (PROLIFICA)
World Hepatitis Alliance
The Task Force for Global Health
Coalition for Global Hepatitis Elimination
Médecins du Monde
National
Kirby Institute
Doherty Institute
Burnet Institute
Menzies Institute for Medical Research
Hepatitis Australia
Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine
Multicultural HIV and Hepatitis Service NSW

Search strategy

We used combinations of search terms related to HBV, intervention, incidence, care cascade and diseases burden to develop search strategies. For intervention, we used the broad search term of intervention in addition to several terms in relation to specific interventions to increase the sensitivity of the search strategy. In each search strategy, the search terms were used to search article title, abstract or keywords. In MEDLINE, we also used the relevant medical subject heading (MeSH) terms. The details of the search strategies have been provided in the appendices. The searches were conducted in June 2022.

Study selection and data extraction

The details of the screening and review process are illustrated in Figure 1. Records were initially checked for duplicates. After removal of duplicates, we screened the records by title and abstract, then reviewed the full texts of potentially eligible records and selected eligible studies for inclusion. In the case of multiple publications of one study, we included the one with the most updated data. Repeated studies were only included when each paper reported separate study outcomes.

We reviewed the full texts and supplementary materials of the papers we found eligible for inclusion and extracted the required data. The extracted data included the items related to study design and setting, study population and inclusion criteria, components of the study interventions, participants' demographic characteristics, and study outcomes. Two or more reviewers independently carried out title/abstract screening, full text review and data extraction, with discrepancies discussed in the group to reach consensus.

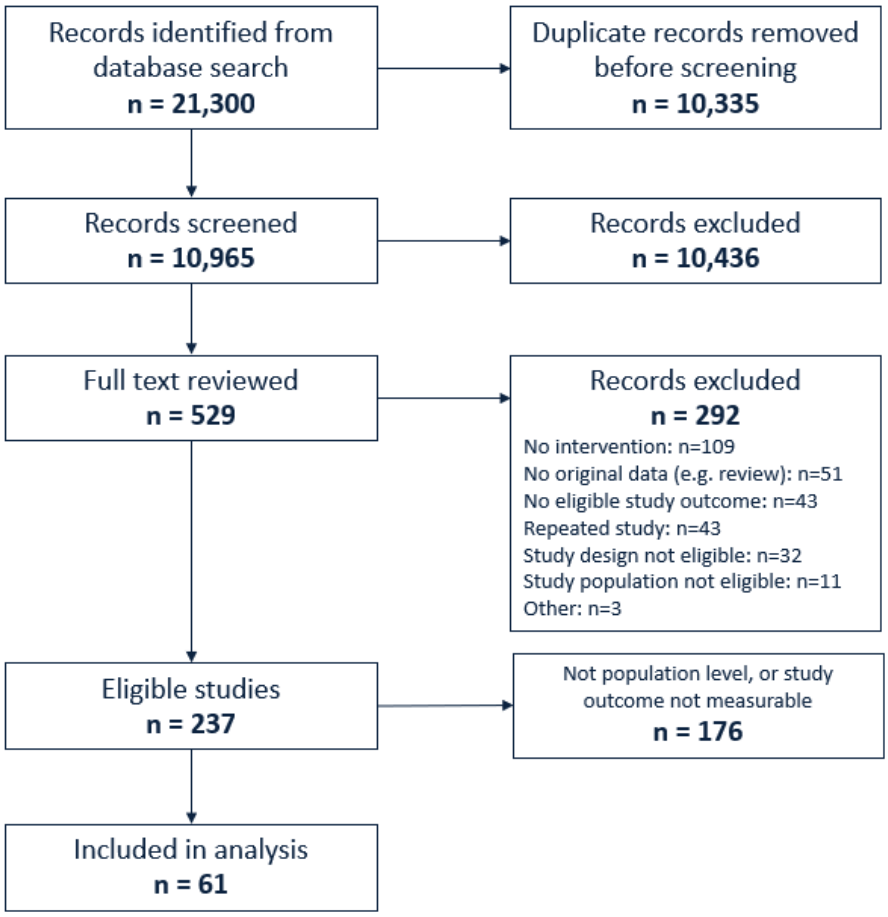


Figure 1: Flow diagram detailing the review process.

Synthesis of results

The primary outcomes from the studies included in this Evidence Check consisted of the proportion of eligible people who received HBV testing (screening), the proportion of people with newly diagnosed HBV (i.e. participant had been unaware of their HBV status), the proportion of participants diagnosed with HBV who were linked to HBV clinical care after diagnosis and the proportion of people eligible for HBV vaccination who received HBV vaccination following screening.

For each study, we calculated the proportion with the study outcome and corresponding 95% confidence intervals (95%CIs). For studies including a comparison group, we calculated the odds ratio (OR) and corresponding 95%CIs. We assessed heterogeneity across studies using the I square statistic, with an I square >75% considered as high heterogeneity. Random effect meta-analysis models were used to calculate the pooled study outcome estimates. We conducted stratified analyses by study setting, study population and intervention-specific characteristics. Analyses were performed using Stata 14.0.

Levels of evidence were defined using the NHMRC recommended categories (Appendix Table A1).

Findings

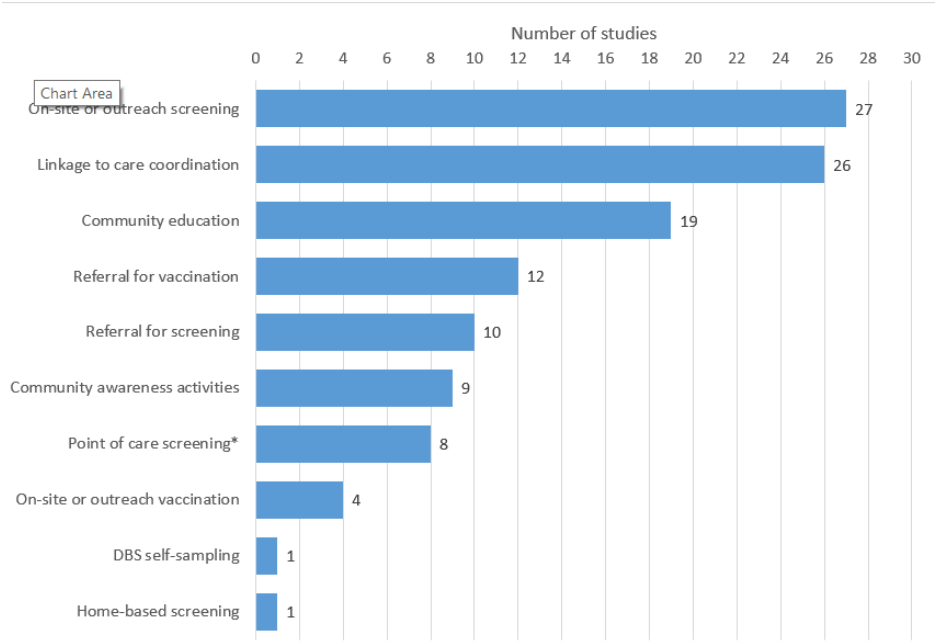
Overall findings

Levels of evidence and study interventions

A total of 61 studies were included in the analysis (Appendix Table A2)[10–70], including 59 peer-reviewed journal articles and two conference abstracts (grey literature).

Level of evidence was defined based on the NHMRC recommended categories (Appendix Table A1). A large majority of studies provided level III-3 evidence and included single-arm studies with no concurrent control (study n=48, 79%). Only seven studies (12%) were randomised controlled trials providing level II evidence. Other studies included pre-intervention versus post-intervention comparison studies (study n=4, 7%) and non-randomised trials (study n=2, 3%). The characteristics of included studies have been summarised in Appendix Table A2.

A total of 109 interventions conducted in 61 studies were included in this analysis (Figure 2 and Appendix Table A2). On-site or outreach HBV screening and linkage to care coordination were the most frequent interventions, conducted in 27 and 26 studies respectively. These interventions were conducted to enhance HBV diagnosis (study n=41), linkage to HBV clinical care (study n=27) and HBV vaccination coverage (study n=19; Appendix Table A2).



.* A subgroup of on-site screening

Figure 2: Frequency of interventions conducted in studies included in the analysis.

Question 1:

We found no studies reporting HBV incidence as the study outcome. One remote area study demonstrated that an intervention including education of pregnant women and training village health volunteers enhanced coverage of HBV birth dose vaccination (93% post-intervention vs. 81% pre-intervention)[49], but no data of HBV incidence among infants were reported.

Question 2:

Study outcomes most relevant to the HBV burden of people in the community living with the disease included HBV diagnosis, linkage to HBV clinical care and HBV vaccination. Accordingly, the study interventions aimed to enhance the coverage of HBV screening, linkage to care and vaccination.

HBV screening

A total of 41 studies conducted an HBV screening intervention and reported an eligible outcome, including the proportion of people who received HBV testing (study n=25) and/or proportion of people newly diagnosed with HBV (study n=21). They included nine studies with a control population (Appendix Table A3) and 31 studies with no control populations (Appendix Table A4).

Proportion of people who received HBV testing

Nine studies with control populations evaluated interventions that aimed to enhance the coverage of HBV screening (Appendix Table A3). Interventions included HBV or cancer education (study n=6), a media campaign promoting HBV screening (study n=2), and point of care testing (study n=1). Given the differences in study designs, study interventions and study populations, we did not include all studies in the meta-analysis. In six studies the intervention included one session of face-to-face education focused on HBV and/or liver cancer and the study population consisted of migrants from high HBV prevalence areas.[12, 22, 42, 51, 52] All these studies demonstrated a significantly higher proportion of HBV testing among the intervention population compared with the control population (Appendix Table A3). For the meta-analysis, two studies[42, 43] were excluded as outliers to stabilise the variance, given the unusually large odds ratios (OR≥100). The results of the meta-analysis indicated that the likelihood of HBV testing was more than three times higher among those participating in education programs compared with the control groups (OR: 3.62, 95% CI 2.72, 4.88; Figure 3).

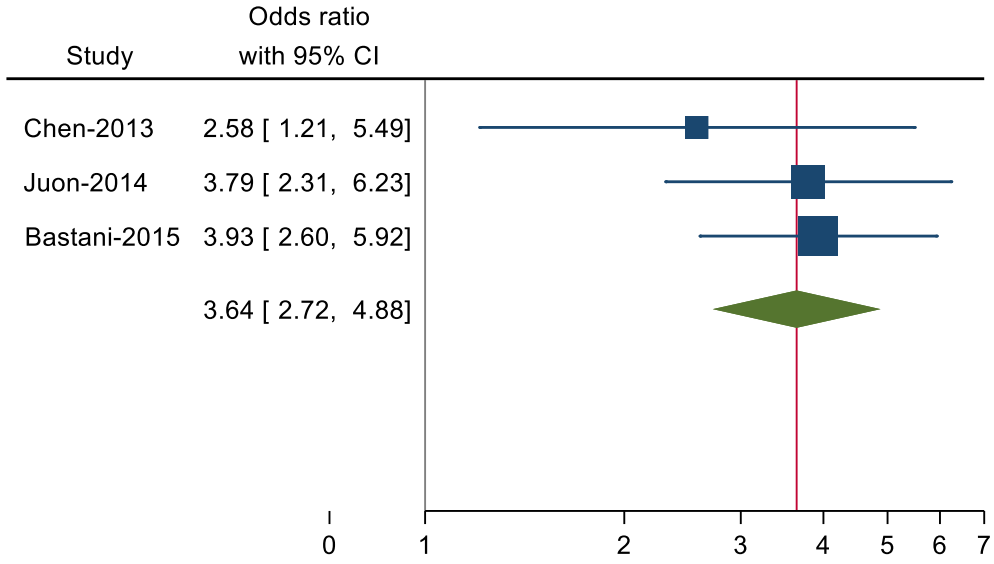


Figure 3: Pooled estimate of the proportion of people receiving HBV testing in the controlled trials evaluating the effectiveness of a community education intervention to enhance HBV screening.

In another analysis, we included all studies that implemented an intervention that aimed to enhance the coverage of HBV screening and reported the proportion of participants receiving HBV testing. They included the studies with no control group in addition to the intervention arms of the controlled trials. Twenty-five studies were included in this analysis. Most studies were conducted in the US or European countries (88%), were conducted in the community (68%) and recruited migrants from high HBV prevalence areas as study population (68%; Table 2).

Table 2: Distribution of study characteristics and pooled estimates of outcomes of studies that implemented an intervention to enhance the coverage of HBV screening and reported the proportion of participants receiving HBV testing.

	Study n (%)	Study population n	Pooled estimate of percentage of participants receiving HBV testing (95%CI)	I square
Region				
Europe/US	22 (88)	45,965	64.1 (52.8, 75.4)	99.9%
Other (Africa, South Asia)	3 (12)	54,003	82.9 (66.5, 99.4)	NA
Study setting				
Community	17 (68)	54,234	58.8 (45.7, 71.9)	>99.9%
Clinical and non-clinical	3 (12)	2011	71.0 (43.2, 98.8)	NA
Clinical	2 (8)	8641	NA	NA
Non-clinical refugee services	2 (8)	34,496	NA	NA
Homeless services	1 (4)	586	NA	NA
Study population				
Migrants from high prevalence area	17 (68)	16,601	61.5 (50.9, 72.1)	99.8%
General population in high prevalence countries	2 (8)	25,951	NA	NA

Refugees	2 (8)	34,496	NA	NA
People in remote areas	1 (4)	11,818	NA	NA
People experiencing homelessness	1 (4)	586	NA	NA
Multiple populations	2 (8)	10,516	NA	NA
HBV screening strategy				
On-site testing	12 (48)	68,736	79.7 (72.3, 87.1)	99.8%
Referral for testing	11 (44)	12,594	53.6 (36.8, 70.5)	99.9%
Other or not reported*	2 (8)	18,638	NA	NA
HBV testing method among studies using on-site testing				
Phlebotomy	7 (58)	19,518	76.5 (64.9, 88.1)	99.9%
DBS or point-of-care testing	3 (25)	42,404	77.5 (73.6, 81.4)	NA
Other or not reported*	2 (17)	6814	NA	NA
Participants received incentives				
No	22 (88)	99,182	66.7 (57.9, 75.4)	99.9%
Yes	3 (12)	786	64.0 (17.4, 99.9)	NA

NA: Not applicable
* Including mixed strategy/method in one study and not reported strategy/method in one study

The meta-analysis showed a pooled estimate of 66% of participants received HBV testing following the study intervention (95%CI: 58%–75%), with very high heterogeneity across studies (range: 17%–98%; I-square: 99.9%; Figure 4). In studies conducted in the US or Europe (with health systems and HBV epidemics more similar to Australia) a pooled estimate of 64% of participants (95%CI: 53%–75%) received HBV testing following the study intervention (Table 2).

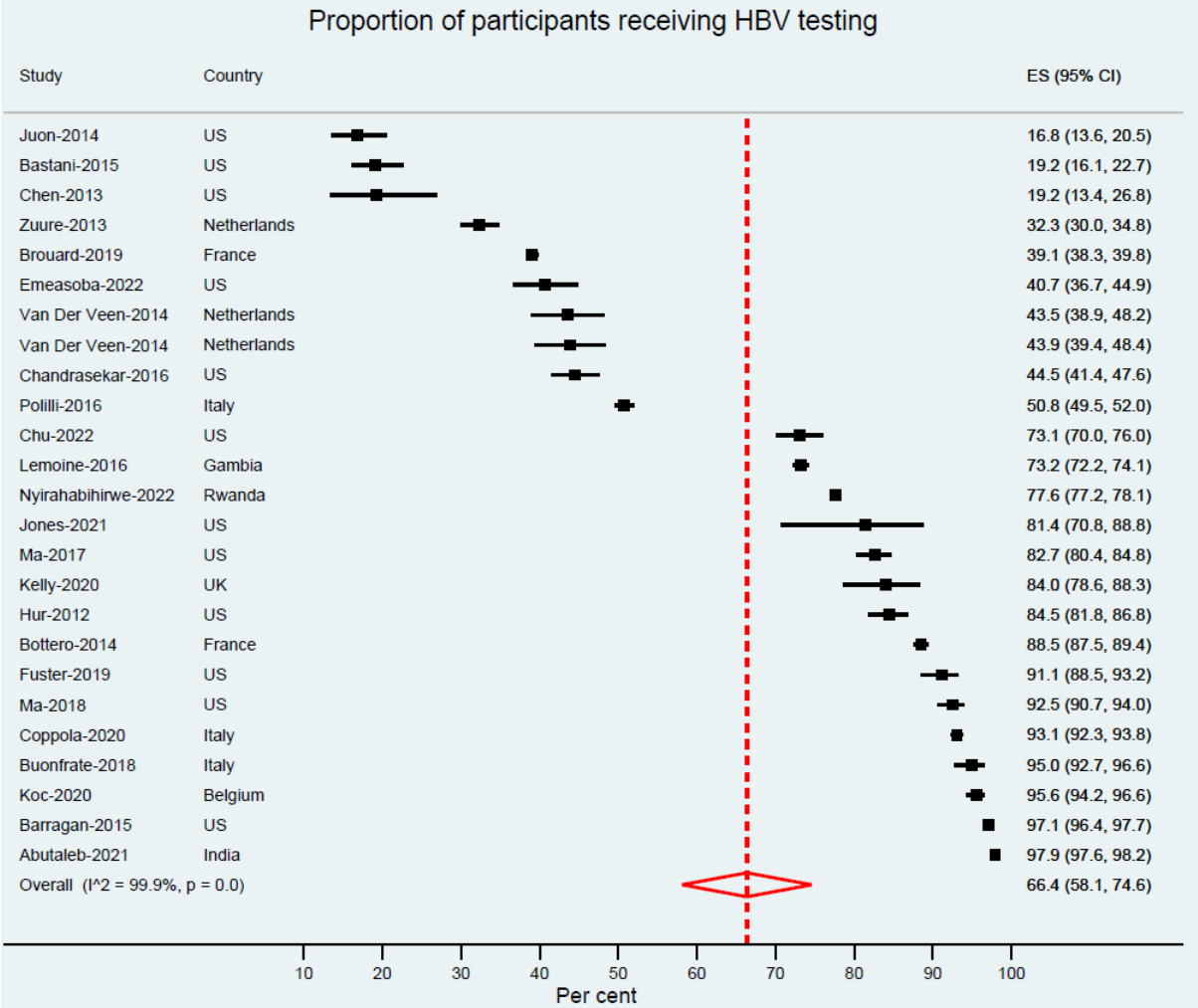


Figure 4: Pooled estimates of the outcomes of studies that implemented an intervention to enhance HBV screening coverage and reported the proportion of participants receiving HBV testing.

The results of the stratified meta-analyses by study characteristics were reported in Table 2. A pooled estimate was generated in the subgroups with more than two studies. The stratified analysis by HBV screening strategy demonstrated that in studies providing participants with on-site HBV testing, the proportion receiving HBV testing (80%, 95%CI 72%–87%) was significantly higher than in the studies referring participants to an external site for HBV testing (54%, 95%CI 37%–71%; Figure 5).

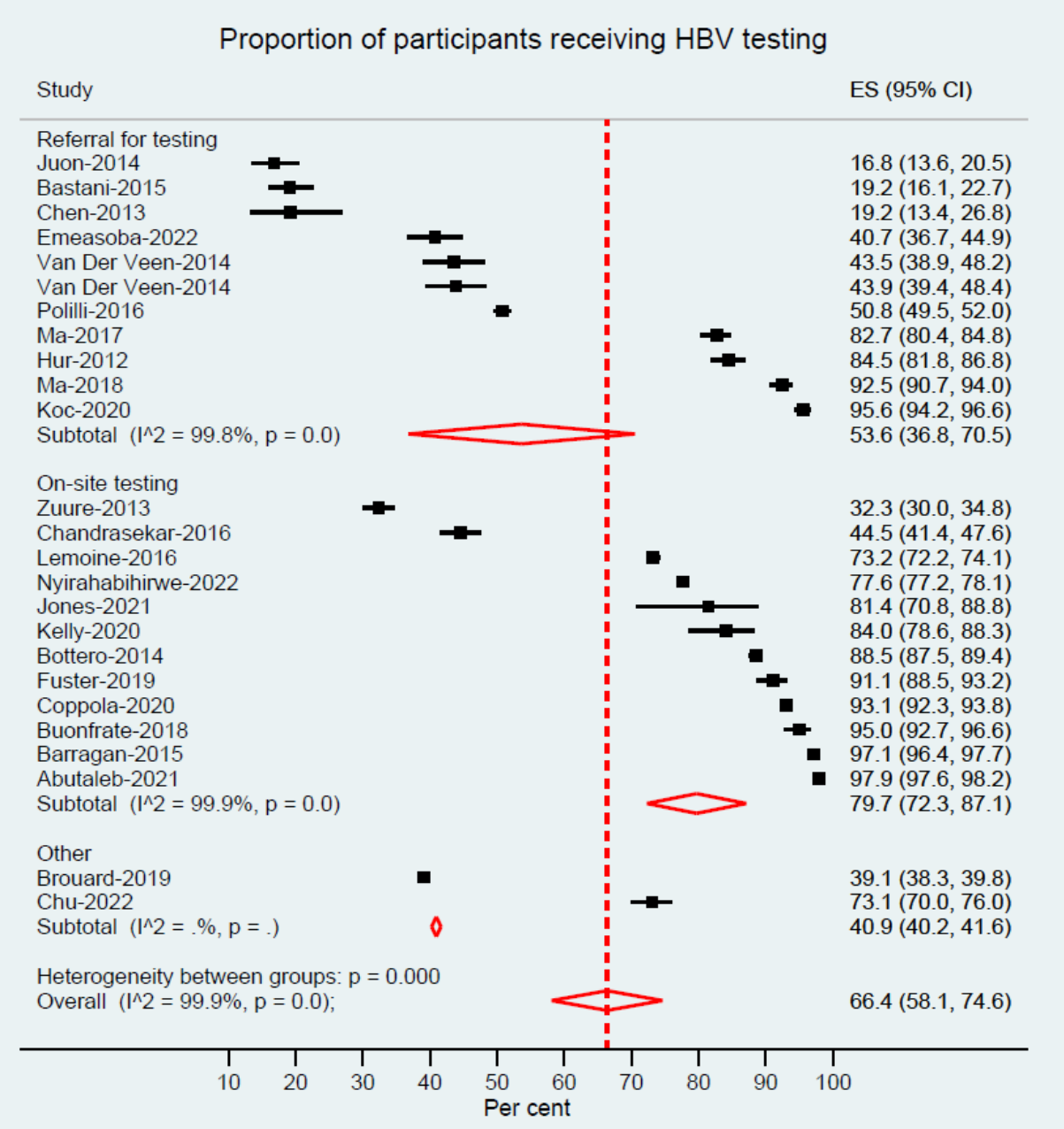


Figure 5: Pooled estimates of the proportion of participants receiving HBV testing, by HBV testing strategy.

Prevalence of newly diagnosed HBV infection

Twenty-one studies reported the prevalence of newly diagnosed HBV infection following HBV screening. Newly diagnosed HBV was defined as an HBsAg positive test result in a person who was not aware of their HBV status before screening. The meta-analysis demonstrated a pooled estimate of newly diagnosed HBV of 4.0% (95%CI 2.9%–5.0%) with a very high heterogeneity across studies (range: 0.2%–10.4%; I-square: 98.9%; Figure 6). In studies conducted in the US or Europe, the pooled estimate of newly diagnosed HBV was 3.3% (95%CI 2.3%–4.3%) with very high heterogeneity across studies (I-square: 98.1%; Table 3).

Table 3: Distribution of study characteristics and pooled estimates of outcomes of studies that implemented an intervention to enhance the coverage of HBV screening and reported the prevalence of newly diagnosed HBV.

	Study n (%)	Study population n	Pooled estimate of prevalence of newly diagnosed HBV (95%CI)	I square
Region				
Europe/US	18 (86)	30,983	3.3 (2.3, 4.3)	98.1%
Other (Africa, South Asia)	3 (14)	30,829	7.8 (2.5, 13.2)	NA
Study setting				
Community	14 (67)	23,938	3.9 (2.5, 5.3)	98.4%
Clinical	3 (14)	8267	4.1 (0.0, 8.4)	NA
Clinical and non-clinical	2 (10)	2315	NA	NA
Non-clinical refugee services	1 (5)	26,406	NA	NA
Prison	1 (5)	886	NA	NA
Study population				
Migrants from high prevalence areas	13 (62)	18,320	4.4 (2.8, 5.9)	97.4%
General population in high prevalence countries	3 (14)	11,368	6.8 (0.0, 14.7)	NA
Refugees	1 (5)	26,406	NA	NA
People incarcerated	1 (5)	886	NA	NA
Multiple populations	3 (14)	4832	1.1 (0.0, 2.3)	NA

NA: Not applicable

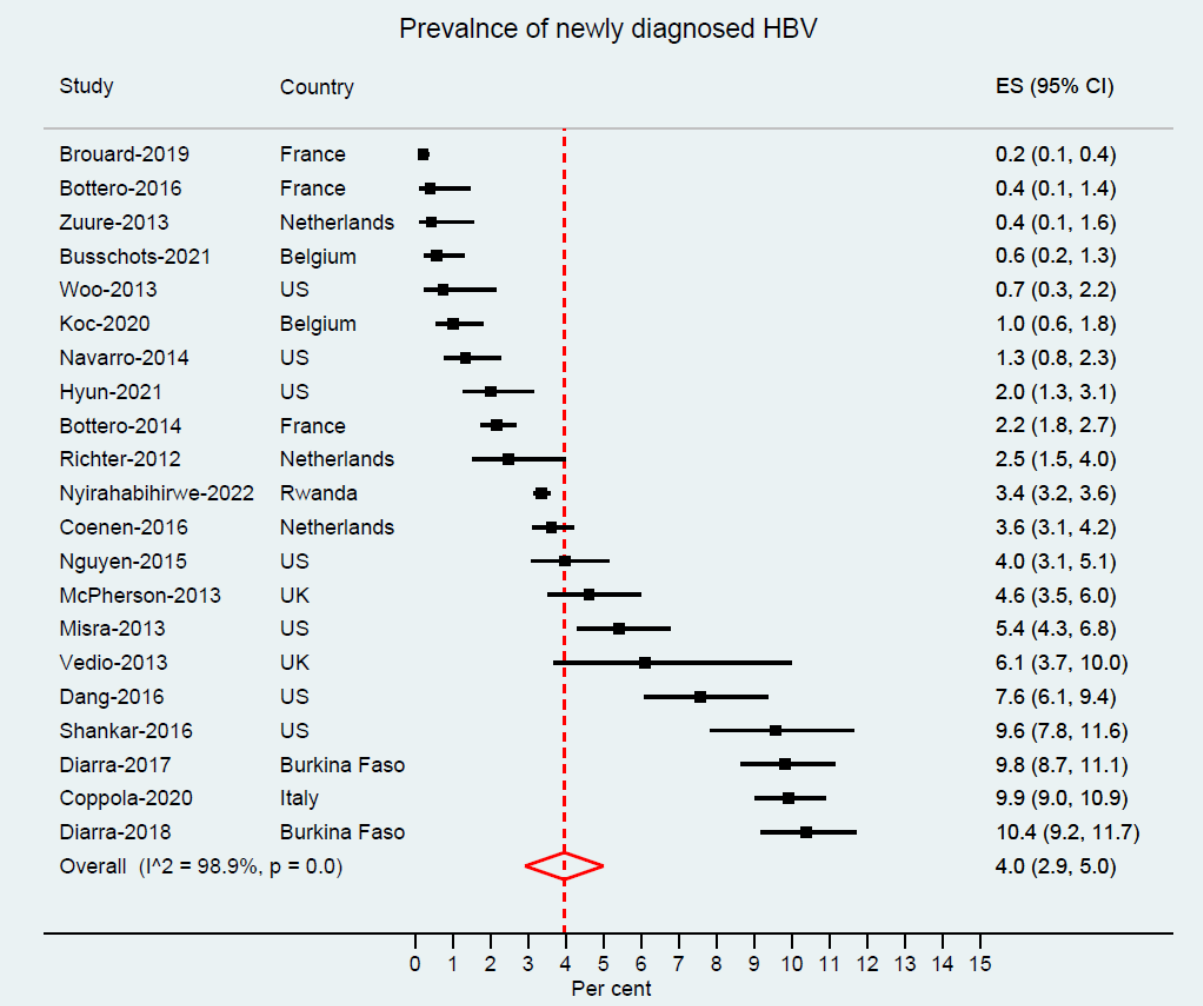


Figure 6: Pooled estimates of the prevalence of newly diagnosed HBV infection following population-based HBV screening.

Linkage to HBV clinical care

Twenty-seven studies implemented interventions aimed at enhancing the linkage of people diagnosed with HBV infection (i.e. HbsAg positive) to HBV clinical care services, among which 21 studies had a study population of >20 and reported the intervention outcome and were included in the analysis (Appendix Table A5). Linkage to care was defined as attending a clinical appointment with an HBV care provider in primary care or specialist services in 19 studies, initiating HBV treatment in one study and receiving post-test counselling in one study.

The interventions included different components and varied across studies. The structured distributions of intervention components are summarised in Table 4. The most common component was post-test counselling, followed by assistance with scheduling clinical appointments, implemented in 52% and 38% of the studies, respectively.

Table 4: Distribution of study characteristics, intervention components and pooled estimates of outcomes of studies that implemented an intervention to enhance linkage to HBV clinical care.

	Study n (%)	Study population n	Pooled estimate of proportion of participants who linked to HBV clinical care services (95%CI)	I square
Region				
Europe/US	17 (81)	3910	70.0 (59.9, 80.2)	98.3%
Other (Africa, South Asia)	4 (19)	1180	82.7 (71.4, 94.1)	99.4%
Study setting				
Community	15 (71)	2584	78.3 (71.9, 84.6)	98.3%
Clinical and non-clinical	4 (19)	2197	64.3 (43.7, 85.0)	98.8%
Clinical	1 (5)	230	NA	NA
Homeless services	1 (5)	79	NA	NA
Study population				
Migrants from high prevalence areas	14 (67)	3362	71.6 (60.6, 82.7)	97.4%
General population in high prevalence countries	3 (14)	761	93.8 (87.6, 100.0)	NA
People in remote areas	1 (5)	419	NA	NA
People experiencing homelessness	1 (5)	79	NA	NA
Multiple populations	2 (10)	469	NA	NA
Components of linkage to care co-ordination interventions				
Post-test counselling				
No	10 (48)	1557	71.2 (55.9, 86.6)	99.4%
Yes	11 (52)	3533	73.6 (60.4, 86.7)	98.9%
Assistance with scheduling clinical appointment				
No	13 (62)	2173	74.1 (65.8, 82.3)	98.9%
Yes	8 (38)	2917	70.9 (57.1, 84.7)	98.4%
Linkage to care co-ordinator spoke in patient's language				
No	14 (67)	2552	71.0 (62.7, 79.3)	98.9%
Yes	7 (33)	2538	76.2 (58.6, 93.8)	99.1%
Sending reminder about clinical appointments				
No	19 (90)	4814	NA	NA
Yes	2 (10)	276	NA	NA
Assistance with transportation				
No	19 (90)	4625	NA	NA
Yes	2 (10)	465	NA	NA
GP training				
No	20 (95)	4860	NA	NA
Yes	1 (5)	230	NA	NA

NA: Not applicable

In the meta-analysis, a pooled estimate of 73% of people with HBV infection were linked to HBV clinical care (95%CI: 64%–81%), with very high heterogeneity across studies (range: 28%–100%; I-square: 99.2%; Figure 7). In 17 studies conducted in Australia, the US or Europe, there was a pooled estimate of 70% participants (95%CI: 60%–80%) linked to care, with a high heterogeneity across studies (I-square: 98%; Table 4).

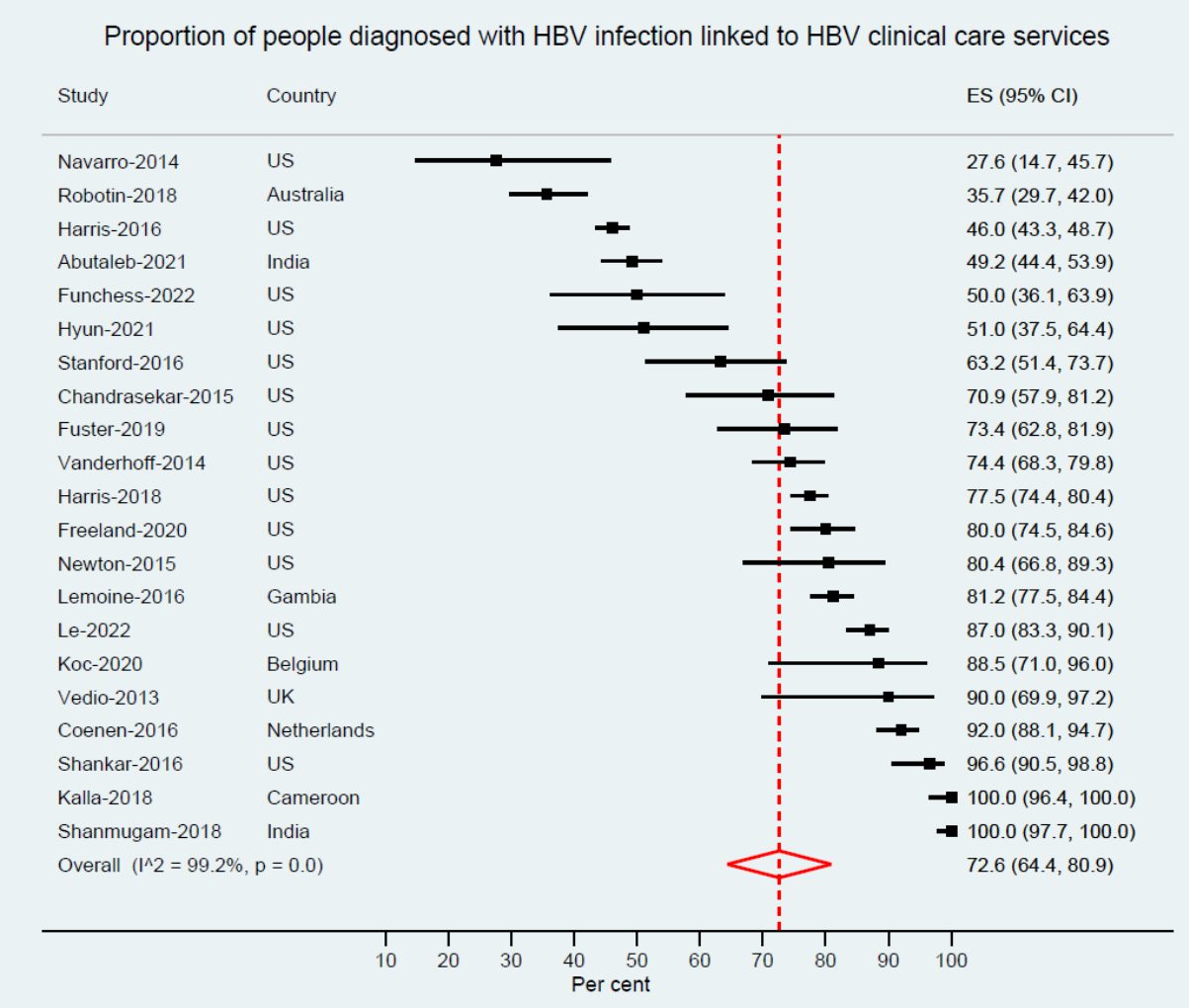


Figure 7: Pooled estimate of proportion of people with HBV infection who were linked to HBV clinical care.

The results of the stratified meta-analyses by study characteristics are reported in Table 4. A stratified analysis by study population demonstrated that in the studies among the general population in high prevalence countries, 94% of people with HBV who received the study intervention (95%CI: 88%–100%) were linked to care, significantly higher than the 72% (95%CI: 6183%) achieved in studies among migrants from high prevalence areas living in a country with low prevalence (Figure 8).

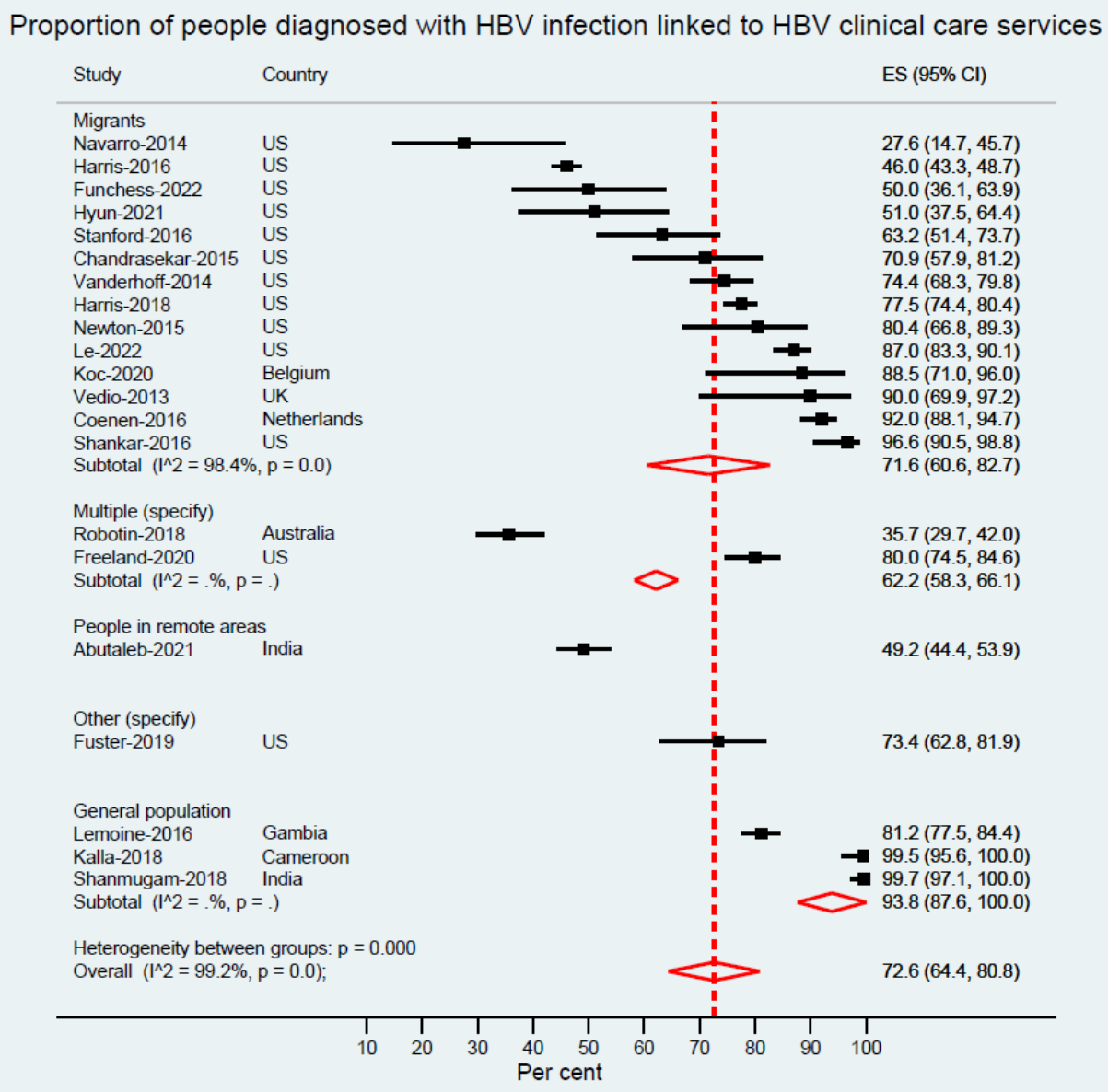


Figure 8: Pooled estimate of proportion of people with HBV infection who were linked to HBV clinical care, by study population.

HBV vaccination

In 19 studies, HBV vaccination uptake was assessed as the primary or secondary outcome of the study; among these, one study assessed birth dose vaccination among infants, one assessed vaccination in children and 17 studies assessed vaccination in adults.

One study from Kiribati (Asia Pacific) implemented an intervention that included one-to-one education of pregnant women about HBV vaccination by health workers and village health volunteers and training village health volunteers. Coverage of timely birth dose vaccination significantly increased from 81% (n=505/570) during the 12 months before the intervention to 93% (n=292/306) during the six months after the intervention.[49] In another study conducted in 311 elementary schools in remote areas of China, an HBV education program was conducted for students that included 45-minute

classes, an educational song and cartoon posters. All students were offered on-site HBV vaccination. Of 55,010 students, 99% (n=54,610) completed their full three-dose vaccination.[21]

In the other 17 studies a population-based HBV screening intervention was implemented among adults during which vaccination was offered to eligible people (Appendix Table A6). Eligibility for vaccination varied across studies, defined as negative test results for all three markers of HBsAg, anti-HBc and anti-HBs (study n=6), negative test results for HBsAg and anti-HBs (study n=6), HBsAg negative (n=2), and negative test results for HBsAg and anti-HBc (study n=1). Two studies did not report the definition of eligibility for vaccination.

Vaccination initiation

Sixteen studies reported uptake of a first dose of vaccine (vaccination initiation), while seven studies reported uptake of the full three doses.

Among 15 studies reporting uptake of the first dose of vaccine (one study was excluded given the small sample size), meta-analysis demonstrated that a pooled estimate of 38% (95%CI 21%–56%) initiated vaccination, with very high heterogeneity across studies (range: 0.5%–93%; I square: 99.9%; Figure 9). In studies from the US and Europe, the pooled vaccination initiation estimate was 33% (95%CI: 15%–51%), with high heterogeneity across studies (I square: 99.8%; Table 5).

Table 5: Distribution of the study characteristics and pooled estimates of HBV vaccination uptake.

	Study n (%)	Study population n	Pooled estimate of proportion of people starting HBV vaccination (95%CI)	I square
Region				
Europe/US	11 (73)	4196	32.8 (14.6, 51.1)	99.8%
Other (Africa, South Asia, East Asia)	4 (27)	37,585	53.6 (26.5, 80.6)	>99.9%
Study setting				
Community	11 (73)	39,587	42.8 (22.6, 63.0)	>99.9%
Clinical	2 (13)	1411	NA	NA
Clinical and non-clinical	2 (13)	783	NA	NA
Study population				
Migrants from high prevalence areas	9 (60)	2785	38.9 (12.5, 65.2)	99.9%
General population in high prevalence countries	3 (20)	26,432	43.7 (29.5, 57.9)	NA
People in remote areas	1 (7)	11,153	NA	NA
Multiple populations	2 (13)	1411	NA	NA
HBV vaccination strategy				
On-site vaccination	3 (20)	13,269	77.8 (61.5, 94.0)	NA
Referral for vaccination	11 (73)	10,226	27.3 (12.5, 42.0)	99.8%
Mixed strategy	1 (7)	18,286	NA	NA

NA: Not applicable

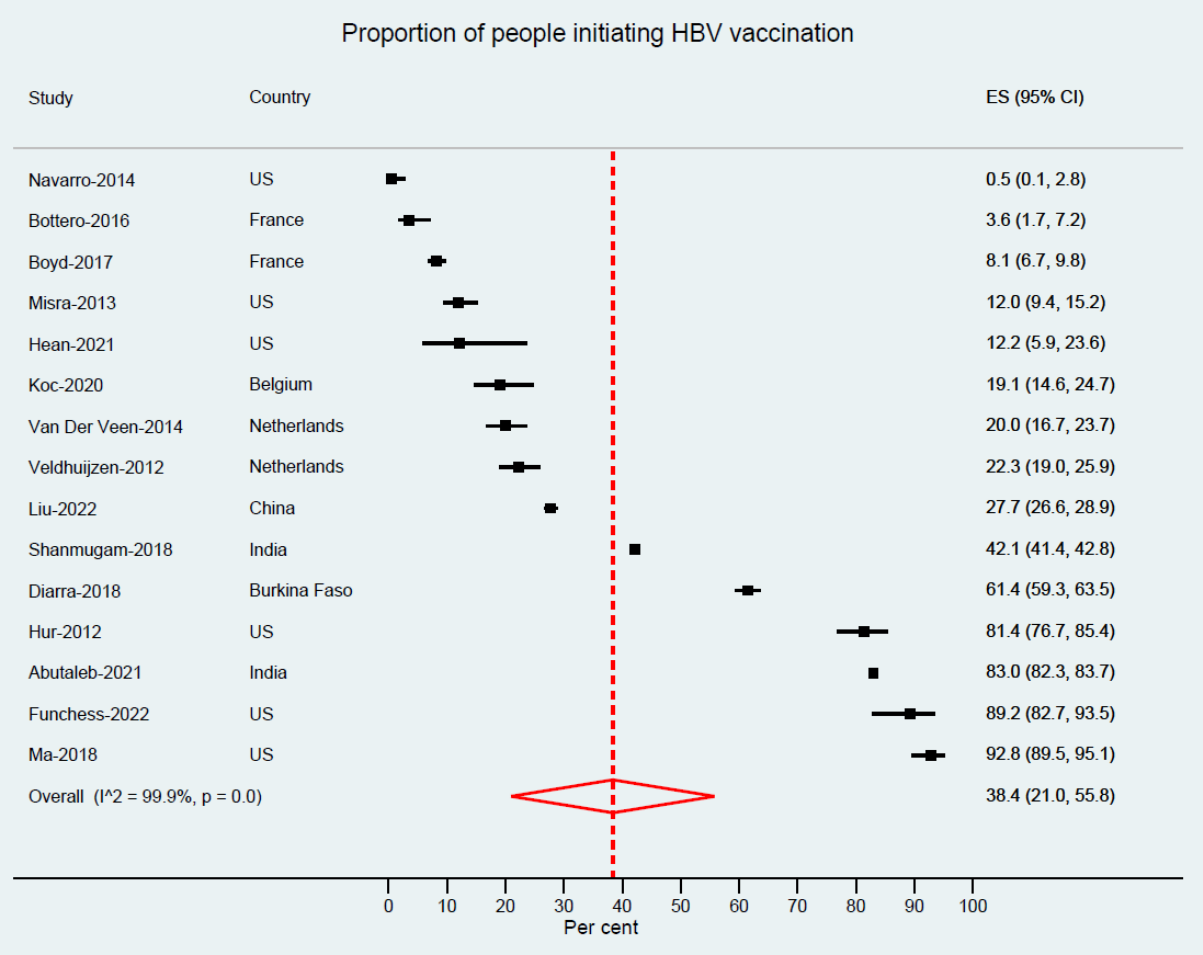


Figure 9: Pooled estimate of proportion of people initiating HBV vaccination (received the first dose).

The results of the stratified meta-analyses by study characteristics are summarised in Table 5. A stratified analysis by HBV vaccination strategy demonstrated that in the studies providing the participants with on-site HBV vaccination, uptake was 78% (95%CI: 62%–94%), significantly higher than the 27% (95%CI 13%–42%) achieved in studies referring participants to an external site for vaccination (Figure 10).

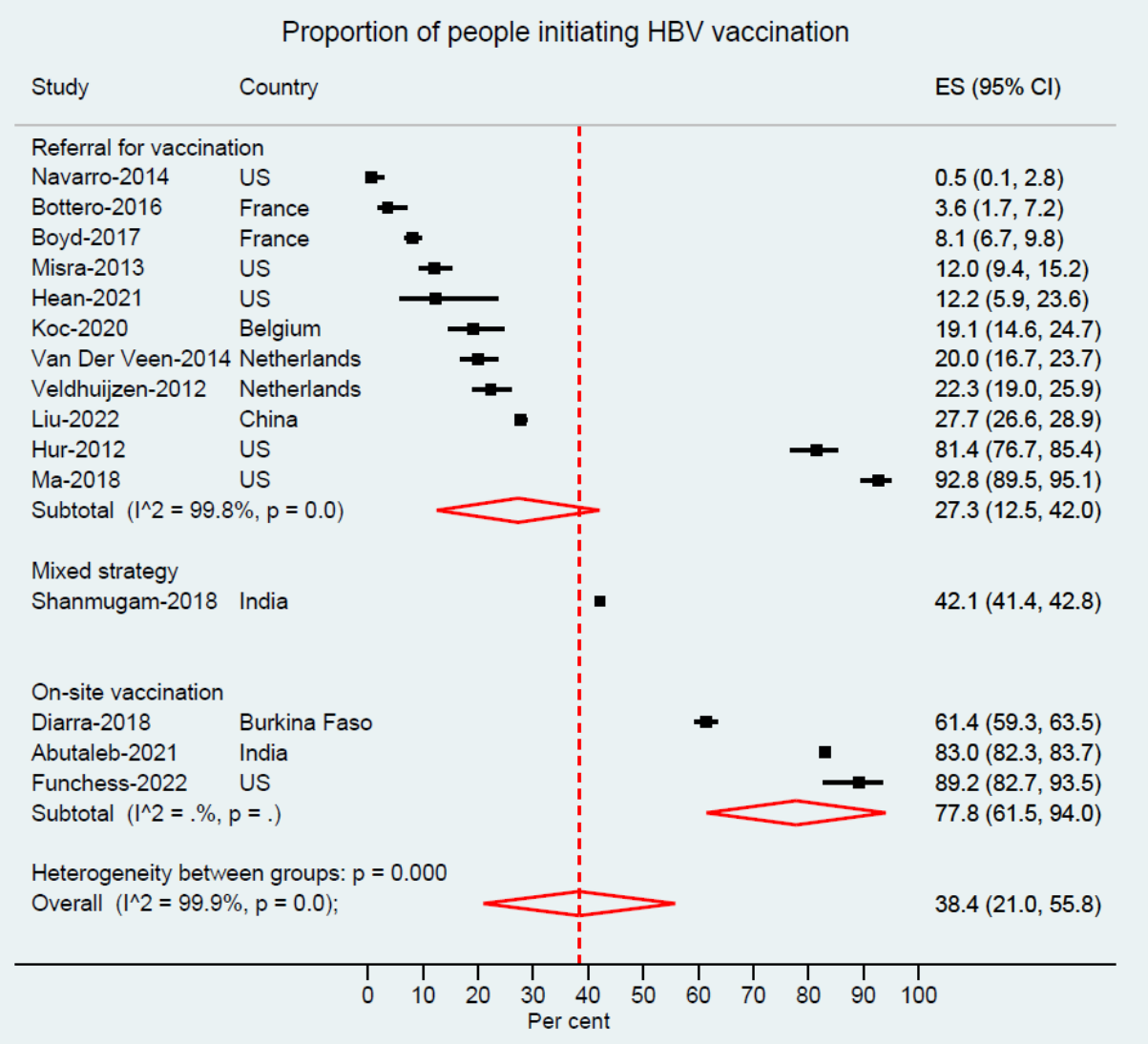
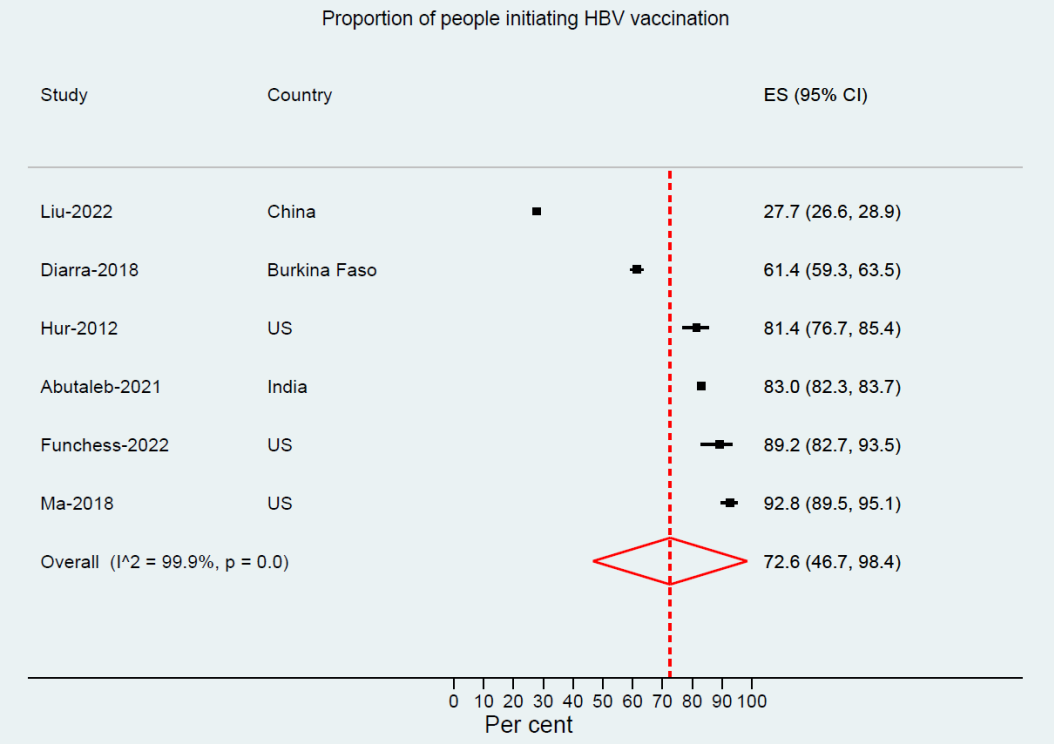


Figure 10: Pooled estimate of proportion of people initiating HBV vaccination (received the first dose), by vaccination strategy.

Vaccination completion

Six studies reported uptake of both the first dose (initiation) and the full three doses of vaccine (completion). In these studies, a pooled estimate of 73% (95%CI 47%–98%) initiated vaccination and 58% (95%CI 42%–75%) completed vaccination (Figure 11).

A.



B.

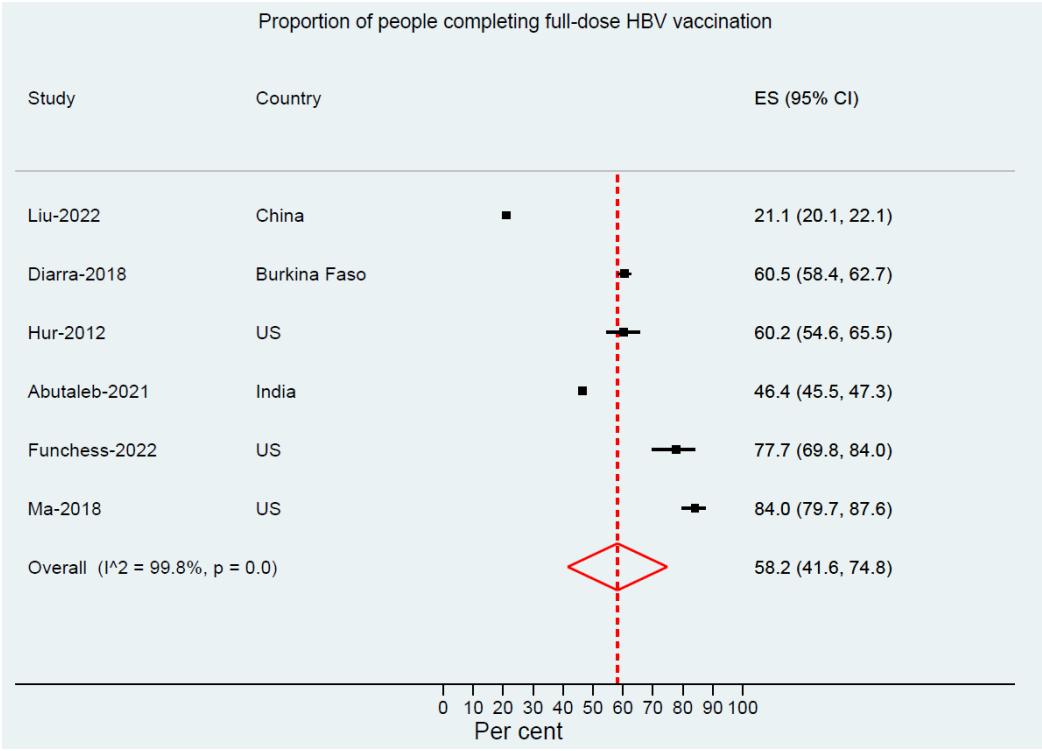


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Figure 11: Pooled estimates of the proportion of people who initiated (A) and those who completed (B) HBV vaccination in studies reporting both measures.

Gaps in the evidence

Level of evidence

A large majority of studies (79%) were single-arm studies with no concurrent control, providing low grade evidence. Seven studies (12%) were randomised controlled trials, among which only three studies were included in the meta-analysis of the measure of effects given major differences in study interventions or concerns of biases.

HBV incidence

We found no studies reporting HBV incidence as the study outcome. One study demonstrated that an intervention that included education of pregnant women and training village health volunteers enhanced coverage of HBV birth dose vaccination, but no data were reported of HBV incidence among infants.

Study population

Aboriginal and Torres Strait Islander people in Australia and Indigenous populations in several other countries experience a higher prevalence of chronic HBV infection. However, we found no studies evaluating a population-level intervention to enhance the HBV care cascade for these populations. Although we searched a wide range of sources for grey literature, our search may have not captured some studies. We also found only one study with pregnant women as the study population. Some other priority populations such as people who inject drugs or men who have sex with men were included in seven studies as a part of a heterogeneous study population of people at risk of HBV or sexually transmitted infections. However, we found no studies that evaluated an intervention specifically targeting people who inject drugs or men who have sex with men. There were studies evaluating interventions targeting people who inject drugs, but they did not meet our definition of population-level interventions.[71]

We found only one study from Australia in which linkage to care was assessed following a multi-component program in primary care services. Although data from other countries with a health system and HBV epidemic similar to Australia may be useful, Australian studies are still needed as more representative evidence.

Study intervention

Among studies implementing HBV screening interventions and providing data of the proportion of participants who received testing, most studies used traditional phlebotomy sampling, while only three studies used other sampling/testing methods, including two studies using point of care finger prick testing and one study using self-collected dried blood spot sampling. Given the existing evidence demonstrating the effectiveness of point of care testing in increasing testing uptake for other infections such hepatitis C[72], and the evidence identified here that on-site testing (whether through phlebotomy or point of care testing) was associated with increased uptake, further controlled studies are needed to evaluate the impact of this new technology on HBV testing uptake in various settings and populations.

Discussion

This Evidence Check review identified a wide variety of interventions implemented to enhance HBV screening, linkage to HBV clinical care and HBV vaccination coverage. Interventions usually included a multi-component program. Several studies implemented HBV screening interventions, conducting a community education program[12, 22, 31 ,39, 42, 44, 45, 51, 52, 59, 65, 67, 70] or a community awareness campaign[23, 24, 28–30] before HBV screening. Even among studies conducting community education, the education modalities varied, such as one-to-one education[22], group education[12, 42, 51, 52] or web-based education.[59, 65] This wide variation in study interventions partly explains the high heterogeneity found in HBV testing uptake across studies. Using stratified analysis, we explored some of the factors contributing to this heterogeneity. We found a higher testing uptake in studies using on-site HBV testing compared with studies referring people to an external site for HBV testing. Randomised trials demonstrated improved HBV testing uptake following community education focused on HBV or liver cancer.

Among 25 studies that implemented HBV screening interventions and reported data of the proportion of participants who received testing, most studies used traditional testing including phlebotomy sampling and sending samples to a centralised lab for serology testing. Only three studies used other sampling or testing methods, including two studies using point of care finger prick testing and one study using self-collected dried blood spot sampling. Other studies have demonstrated that point of care testing improved the uptake of HCV[72] and HIV testing.[73] In our Evidence Check, we found a randomised trial comparing HBV testing uptake using point of care finger prick testing with standard of care serology testing.[13] This study found no significant difference in testing uptake between the two methods. However, in this study point of care testing results had to be confirmed by standard of care serology testing before notifying participants, which hampered the benefit of point of care testing through providing rapid results. Given the high accuracy of HBsAg point of care testing[74], it can be used as a stand-alone test in HBV screening.

Three studies used financial incentives as part their interventions, including one randomised trial[22] and two studies with no control groups.[34, 41] We could not to evaluate the effectiveness of the incentives, given that, first, they were used in combination with other interventions and, second, there were no control groups in two studies while in the randomised trial the incentive was used in both study arms.

Linkage to care is essential to realising improvements in the cascade of care for HBV in Australia and globally. Linkage to care co-ordination interventions were also multi-components of most studies. Post-test counselling, the most common component, was included in only half the studies (52%), demonstrating the high variance in interventions implemented across studies. In 17 studies assessing linkage to care conducted in Australia, the US or Europe (where the epidemiology of hepatitis B is similar and significantly influenced by migration), a pooled estimate of 70% of participants were linked to care, with high heterogeneity across studies.

In stratified analysis no particular component (i.e. post-test counselling, assistance with scheduling clinical appointments, linkage to care co-ordinator using patient's language) was associated with increased linkage to care. However, these findings should be interpreted cautiously. Given the small number of studies using some of the intervention components (e.g. sending reminders of clinical appointments, assistance with transportation, GP training), we did not do stratified analysis for those subgroups. Moreover, several studies did not fully explain the details of the intervention conducted, which may have introduced misclassification bias in this analysis.

Our findings indicated that in the studies among the general population in high prevalence countries, a significantly higher proportion of participants who received the study intervention were linked to care, compared with the studies among migrants from high prevalence areas living in a country with low prevalence. One explanation could be related to the cost of clinical care services or other logistical issues. For example, in one US study HBV screening was offered free of charge but participants needed health insurance to access HBV care services after screening.[33] In another US study, although uninsured people with HBV were referred to a 'low-cost clinic' to receive HBV clinical care services, they had to pay a 'discounted total fee' of $326 for the hepatology consultation, which is not affordable for most low socioeconomic status patients.[55]

Our findings demonstrated a pooled estimate of 38% of people initiating vaccination following intervention, with very high heterogeneity across studies ranging from >1% to 93%. A part of this heterogeneity can be explained by the HBV vaccine strategy used in studies. Our findings demonstrated a significantly higher vaccination uptake in studies providing the participants with on-site HBV vaccination compared with studies referring participants to an external site for vaccination. Cost of vaccination could be another barrier for vaccination in some studies. Although most studies provided free vaccination, in some studies people had to pay for the vaccine. For example, in a US study people were referred to a 'low-cost HBV vaccination clinic', where they had to pay $108 for the full-dose vaccination.[55]

In studies included in this Evidence Check, most interventions in all domains of HBV screening, linkage to HBV clinical care and HBV vaccination targeted migrant populations, which reflects the most common population affected by HBV in Australia. Further studies are required to evaluate interventions targeting other HBV priority populations.

Conclusion

This Evidence Check identified a wide variety of interventions, mostly multi-component interventions, to enhance HBV screening, linkage to HBV clinical care and HBV vaccination coverage. We observed high heterogeneity in the effectiveness of interventions in all three domains—screening, linkage to care and vaccination—meaning the effectiveness of the interventions was highly variable across studies. Some strategies were identified that boosted the effectiveness of interventions, including providing on-site HBV testing and vaccination (versus referral for testing and vaccination) and community education focused on HBV or liver cancer in an HBV screening program. Further studies are needed to evaluate the effectiveness of more novel interventions (e.g. point of care testing) and interventions specifically targeting Indigenous populations, people who inject drugs, men who have sex with men and incarcerated people.

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Appendices

Search strategies

PubMed

5 June 2022

#1
("HBV"[Title] OR "hepatitis B"[Title] OR “hep B”[Title] OR "Hepatitis B"[MeSH Terms])

#2
("intervention*"[Title/Abstract] OR "strateg*"[Title/Abstract] OR "program*"[Title/Abstract] OR "policy"[Title/Abstract] OR "policies"[Title/Abstract] OR "campaign*"[Title/Abstract] OR "engage*"[Title/Abstract] OR "communit*"[Title/Abstract] OR "educat*"[Title/Abstract] OR "awareness*"[Title/Abstract] OR "discriminat*"[Title/Abstract] OR "stigma*"[Title/Abstract] OR “screen*”[Title/Abstract] OR "health policy"[MeSH Terms] OR "health planning"[MeSH Terms] OR "health promotion"[MeSH Terms] OR "health education"[MeSH Terms] OR "social stigma"[MeSH Terms] OR "social discrimination"[MeSH Terms] OR “mass screening” [MeSH Terms])

#3
("inciden*"[Title/Abstract] OR “prevent*”[Title/Abstract] OR "diagnos*"[Title/Abstract] OR “tested”[Title/Abstract] OR “testing”[Title/Abstract] OR “linking”[Title/Abstract] OR “linkage”[Title/Abstract] OR "treat*"[Title/Abstract] OR "therap*"[Title/Abstract] OR "monitor*"[Title/Abstract] OR “retain*”[Title/Abstract] OR “retention”[Title/Abstract] OR “adhere*”[Title/Abstract] OR "Cirrhosis"[Title/Abstract] OR "HCC"[Title/Abstract] OR "Hepatocellular"[Title/Abstract] OR "Hepatoma"[Title/Abstract] OR "liver cancer"[Title/Abstract] OR "transplant*"[Title/Abstract] OR "death*"[Title/Abstract] OR "Mortality"[Title/Abstract] OR "Morbidity"[Title/Abstract] OR "Cost"[Title/Abstract] OR "life year*"[Title/Abstract] OR "life year*"[Title/Abstract] OR "DALY"[Title/Abstract] OR "QALY"[Title/Abstract] OR "incidence"[MeSH Terms] OR “Preventive Health Services”[MeSH Terms] OR "diagnosis"[MeSH Terms] OR "treatment adherence and compliance"[MeSH Terms] OR "liver cirrhosis"[MeSH Terms] OR "liver neoplasms"[MeSH Terms] OR "liver transplantation"[MeSH Terms] OR "Mortality"[MeSH Terms] OR "Morbidity"[MeSH Terms] OR "quality adjusted life years"[MeSH Terms] OR "disability adjusted life years"[MeSH Terms])

#4
2012/01/01:3000/12/31[Date - Publication] AND (humans[Filter])

#5
#1 AND #2 AND #3 AND #4

Scopus:

5 June 2022

TITLE (HBV OR "hepatitis B" OR “hep B”)

AND

TITLE-ABS-KEY (intervention* OR strateg* OR program* OR policy OR policies OR campaign* OR engage* OR educat* OR communit* OR awareness* OR discriminat* OR stigma* OR screen*)

AND

TITLE-ABS-KEY (inciden* OR prevent* OR diagnos* OR tested OR testing OR linking OR linkage OR treat* OR therap* OR monitoring OR retain* OR retention OR adhere* OR cirrhosis OR hcc OR hepatocellular OR hepatoma OR "liver cancer" OR transplant* OR death* OR mortality OR morbidity OR cost OR life-year* OR "life year*" OR daly OR qaly)

AND

PUBYEAR > 2011

TITLE-ABS-KEY: title, abstract and keywords

Web of Science

5 June 2022

#1
TI=(HBV OR "hepatitis B" OR “hep B”)

#2
TS=(intervention* OR strateg* OR program* OR policy OR policies OR campaign* OR engage* OR educat* OR communit* OR awareness* OR discriminat* OR stigma* OR screen*)

#3
TS=(inciden* OR prevent* OR diagnos* OR tested OR testing OR linking OR linkage OR treat* OR therap* OR monitoring OR retain* OR retention OR adhere* OR cirrhosis OR hcc OR hepatocellular OR hepatoma OR "liver cancer" OR transplant* OR death* OR mortality OR morbidity OR cost OR life-year* OR "life year*" OR daly OR qaly)

#4
DOP=2012-01-01/2023-01-01

#5
#1 AND #2 AND #3 AND #4

TS: Title, Abstract, Author Keywords, and Keywords Plus® within a record

Cochrane Central Register of Controlled Trials (CENTRAL)

5 June 2022

#1
(HBV OR "hepatitis B" OR “hep B”):ti

#2
(intervention* OR strateg* OR program* OR policy OR policies OR campaign* OR engage* OR educat* OR communit* OR awareness* OR discriminat* OR stigma* OR screen*):ti,ab,kw

#3
(inciden* OR prevent* OR diagnos* OR tested OR testing OR linking OR linkage OR treat* OR therap* OR monitoring OR retain* OR retention OR adhere* OR cirrhosis OR hcc OR hepatocellular OR hepatoma OR "liver cancer" OR transplant* OR death* OR mortality OR morbidity OR cost OR life-year* OR "life year*" OR daly OR qaly):ti,ab,kw

Limit: with Cochrane Library publication date from Jan 2012 to Jun 2022

ti,ab,kw: Title, Abstract, and Keywords

Table A1: NHMRC levels of evidence

Level of evidence	Study design
I	A systematic review of Level II studies.
II	A randomised controlled trial
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls (i.e. non-randomised experimental trials, cohort studies, case-control studies, interrupted time series studies with a control group)
III-3	A comparative study without concurrent controls (i.e. historical control study, two or more single-arm studies, interrupted time series studies without a parallel control group)
IV	Case series with either post-test or pre-test/post-test outcomes

Table A2: Main characteristics of the studies included in the analysis

First author, year (country)	Study design	Study setting	Study population	Intervention(s)	Main inclusion criteria	Study outcome reported
Abutaleb, 2021 (India)[10]	Interventional, no control	Community, remote area (5 districts)	People living in remote area	Outreach screening Linkage to care coordination Outreach vaccination	General population living in study villages	HBV testing Linkage to care Vaccination
Barragan, 2015 (US)[11]	Interventional, no control	Community (one city)	Migrants	On-site screening Linkage to care coordination	Migrant	HBV testing
Bastani, 2015 (US)[12]	Cluster randomised trial	Community (one city)	Migrants	Community education Referral for screening	Korean background; 18–64 yr old	HBV testing
Bottero, 2014 (France)[14]	Interventional, no control	Clinical—primary care (one city)	Multiple groups of people at risk of HBV	On-site screening	Eligible for HBV screening; covered by national healthcare insurance; ≥18 yr old	HBV testing
Bottero, 2016 (France)[13]	Randomised controlled trial	Clinical—primary care (one city)	Multiple groups of people at risk of HBV	Point of care screening Referral for vaccination Linkage to care coordination	Eligible for HBV screening; covered by national healthcare insurance; ≥18 yr old	HBV testing Linkage to care Vaccination
Boyd, 2017 (France)[15]	Interventional, no control	Clinical—primary care (one city)	Multiple groups of people at risk of HBV	On-site screening Referral for vaccination	Eligible for HBV screening; covered by national healthcare insurance; ≥18 yr old	Vaccination
Brouard, 2019 (France)[16]	Interventional, no control	Community (national)	General population	Dried blood spot self-sampling	Covered by health insurance; 18–75 yr old	HBV testing
Busschots, 2021 (Belgium)[18]	Interventional, no control	Prison (national)	People in prison	Prison-based point of care screening	Incarcerated in study prisons; ≥18 yr old	HBV testing
Buonfrate, 2018 (Italy)[17]	Interventional, no control	Non-clinical refugee services	Refugees	Outreach screening	Asylum seekers arriving in the past 6 months; >14 yr old	HBV testing
Chandrasekar, 2015 (US)[19]	Interventional, no control	Clinical and non-clinical settings (one city)	Mostly migrants (some refugee)	Community education On-site screening	Migrants and refugees from Asia and Africa	Vaccination

First author, year (country)	Study design	Study setting	Study population	Intervention(s)	Main inclusion criteria	Study outcome reported
				Linkage to care coordination		
Chandrasekar, 2016 (US)[20]	Interventional, no control	Clinical and non-clinical settings (one city)	Mostly migrants (some refugee)	Community education On-site screening Linkage to care coordination On-site vaccination	African background	HBV testing
Chen, 2012 (China)[21]	Interventional, no control	Elementary schools in remote area (villages)	People in remote area	Community education Outreach vaccination	Elementary school students; 5–12 yr old	Vaccination
Coppola, 2020 (Italy)[25]	Interventional, no control	Clinical—primary care (5 cities)	Mostly migrants (some refugee)	On-site screening Linkage to care coordination Referral for vaccination	Undocumented migrant, asylum seeker, or refugee	HBV testing
Chen, 2013 (US)[22]	Randomised controlled trial	Community (one city)	Migrants	Community education Referral for screening	Hmong background; never been tested for HBV	HBV testing
Chu, 2022 (US)[23]	Controlled before and after study	Community (9 cities)	Migrants	Community awareness	Vietnamese background; 18–64 yr old	HBV testing
Coenen, 2016 (Netherlands)[24]	Interventional, no control	Community (5 cities)	Migrants	Community awareness On-site screening Linkage to care coordination Referral for vaccination	Chinese background	HBV testing Linkage to care
Dal, 2013 (Turkey)[26]	Controlled before and after study	Community (4 towns)	People in remote areas	Community awareness	No recruitment	Vaccination
Dang, 2016 (US)[27]	Interventional, no control	Clinical and non-clinical settings (one city)	Migrants	On-site screening Linkage to care coordination	Chinese, Hmong, Korean or Vietnamese background; never tested for HBV; ≥18 yr old	HBV testing
Diarra, 2017 (Burkina Faso)[28]	Interventional, no control	Community (one city)	General population	Community awareness Point of care screening On-site vaccination	General population	HBV testing
Diarra, 2018 (Burkina Faso)[29]	Interventional, no control	Community (one city)	General population	Community awareness Point of care screening On-site vaccination	General population	HBV testing Vaccination

First author, year (country)	Study design	Study setting	Study population	Intervention(s)	Main inclusion criteria	Study outcome reported
Eguchi, 2021 (Japan)[30]	Controlled before and after study	Community (one city)	General population	Community awareness	No recruitment	HBV testing
Emeasoba, 2022 (US)[31]	Interventional, no control	Community (one city)	Migrants	Community education Referral for screening Linkage to care coordination	West African background	HBV testing
Freeland, 2020 (US)[32]	Interventional, no control	Community (one city)	Multiple groups of people at risk of HBV	On-site screening Linkage to care coordination Referral for vaccination	Born in regions with HBV prevalence ≥2%, people who inject drugs, men who have sex with men, people with HIV, or household or sexual contacts of people with HBV; ≥18 yr old	Vaccination
Funchess, 2022 (US)[33]	Interventional, no control	Community (one city)	Migrants	On-site screening Linkage to care coordination On-site vaccination	Vietnamese background	Vaccination
Fuster, 2019 (US)[34]	Interventional, no control	Homelessness services (one city)	People experiencing homelessness	Outreach screening Linkage to care coordination	Experiencing homelessness; ≥18 yr old	HBV testing Linkage to care
Harris, 2016 (US)[36]	Interventional, no control	Clinical and non-clinical settings	Mostly migrants (some refugee)	On-site screening Linkage to care coordination	Born in countries with HBV prevalence >2%; ≥18 yr old	Vaccination
Harris, 2018 (US)[35]	Interventional, no control	Multiple—Clinical and non-clinical settings	Mostly migrants (some refugee)	On-site screening Linkage to care coordination	Born in countries with HBV prevalence >2%; ≥18 yr old	Vaccination
Hean, 2021 (US)[37]	Interventional, no control	Community (one city)	Migrants	Community education On-site screening Linkage to care coordination Referral for vaccination	Hmong background; ≥18 yr old	Vaccination
Ho, 2020 (Belgium)[38]	Non-randomised	Community (3 cities)	Migrants	Point of care screening Linkage to care coordination	First- or second-generation migrant from Asia; birth date <1999	Vaccination

First author, year (country)	Study design	Study setting	Study population	Intervention(s)	Main inclusion criteria	Study outcome reported
	controlled study					
Hur, 2012 (US)[39]	Interventional, no control	Clinical and non-clinical settings (one city)	Migrants	Community education Referral for screening Referral for vaccination Linkage to care coordination	Asian or Latino background; ≥18 yr old	HBV testing Vaccination
Hyun, 2021 (US)[40]	Interventional, no control	Community (one city)	Migrants	On-site screening Linkage to care coordination	Born in China; 20–79 yr old	HBV testing Linkage to care
Jones, 2021 (US)[41]	Interventional, no control	Community (one city)	Migrants	Home-based screening	Exit from a parent trial; Haitian background; 50–64 yr old	HBV testing
Juon, 2014 (US)[42]	Cluster randomised trial	Community (5 cities)	Migrants	Community education Referral for screening	Asian background; ≥ 18 yr old	HBV testing
Kalla, 2018 (Cameroon)[43]	Interventional, no control	Community (>1 cities)	General population	On-site screening Linkage to care coordination	General population	Linkage to care
Kelly, 2020 (UK)[44]	Interventional, no control	Clinical and non-clinical settings (2 cities)	Migrants	Community education Point of care screening	First-generation migrant from South Asia; ≥18 yr old old	HBV testing
Koc, 2020 (Belgium)[45]	Interventional, no control	Community (one city)	Migrants	Community education Referral for screening Linkage to care coordination Referral for vaccination	Turkish migrants; ≥18 yr old	HBV testing Linkage to care Vaccination
Le, 2022 (US)[46]	Interventional, no control	Community (one city)	Migrants	On-site screening Linkage to care coordination Referral for vaccination	Foreign-born; ≥18 yr old	Vaccination
Legoupil, 2017 (France)[47]	Interventional, no control	Community (one city)	Mostly people who inject drugs, sex workers and people experiencing homeless	Outreach screening	At risk of HBV	HBV testing

First author, year (country)	Study design	Study setting	Study population	Intervention(s)	Main inclusion criteria	Study outcome reported
Lemoine, 2016 (Gambia)[48]	Interventional, no control	Community (2 urban and 6 rural areas)	General population	Point of care screening Linkage to care coordination	≥ 30 yr old	HBV testing Linkage to care
Li, 2017 (Kiribati)[49]	Controlled before and after study	Clinical—primary care (one city)	Pregnant women in remote area	Community education Training health volunteers	Pregnant women	Vaccination
Liu, 2022 (China)[50]	Non-randomised controlled study	Community (one city)	General population	On-site screening Referral for vaccination	≥18 yr old	Vaccination
Ma, 2017 (US)[51]	Cluster randomised trial	Community (3 cities)	Migrants	Community education Referral for screening Linkage to care coordination	≥18 yr old; never enrolled in any HBV programs; not aware of their HBV status	HBV testing
Ma, 2018 (US)[52]	Cluster randomised trial	Community (2 cities)	Migrants	Community education Referral for screening Linkage to care coordination Referral for vaccination	≥18 yr old old; never enrolled in any HBV programs; not aware of their HBV status	HBV testing Vaccination
McPherson, 2013 (UK)[53]	Interventional, no control	Community (2 cities)	Migrants	Point of care screening Linkage to care coordination	Chinese or South Asian background	HBV testing
Misra, 2013 (US)[54]	Interventional, no control	Community and clinics (one city)	Migrants	On-site screening Linkage to care coordination Referral for vaccination	Racially diverse; ≥18 yr old	HBV testing Vaccination
Navarro, 2014 (US)[55]	Interventional, no control	Community (one city)	Migrants	On-site screening Linkage to care coordination Referral for vaccination	First-generation migrants from Korea; ≥18 yr old	HBV testing Vaccination
Newton, 2015 (US)[56]	Interventional, no control	Community	Migrants	On-site screening Linkage to care coordination	Asian, Pacific Islander or African background	Vaccination
Nguyen, 2015 (US)[57]	Interventional, no control	Community (one city)	Migrants	On-site screening	Vietnamese background	HBV testing Linkage to care Vaccination

First author, year (country)	Study design	Study setting	Study population	Intervention(s)	Main inclusion criteria	Study outcome reported
Nyirahabihirwe, 2022 (Rwanda)[58]	Interventional, no control	Refugee camp (one city)	Refugees	Point of care screening Point of care Linkage to care coordination	Refugee; >15 yr old	HBV testing
Polilli, 2016 (Italy)[59]	Interventional, no control	Community (one region)	People at high risk of HIV and other sexually transmitted infections	Web-based community education Referral for screening	General population with access to internet	HBV testing
Richter, 2012 (Netherlands)[60]	Interventional, no control	Community (one city)	Migrants	Community education On-site screening	First-generation migrants from Turkey	HBV testing Linkage to care
Robotin, 2018 (Australia)[61]	Interventional, no control	Clinical—primary care (one city)	People with HBV or migrants	Linkage to care coordination	Confirmed HBV diagnosis or born in HBV-endemic countries; > 35 yr old	Vaccination
Shankar, 2016 (US)[62]	Interventional, no control	Community (one city)	Migrants	On-site screening Linkage to care coordination	African-born; ≥18 yr old	HBV testing Linkage to care
Shanmugam, 2018 (India)[63]	Interventional, no control	Community (14 districts)	General population	Community awareness Point of care screening Linkage to care coordination Referral for vaccination	General population	Vaccination
Standford, 2016 (US)[64]	Interventional, no control	Community and clinical (one city)	Mostly migrants (some refugees)	Community awareness On-site screening Linkage to care coordination	Migrant from countries with HBV prevalence ≥2%	Vaccination
Van Der Veen, 2014 (Netherlands)[65]	Randomised controlled trial	Community	Migrants	Web-based community education Referral for screening Referral for vaccination	Born in Turkey; 16–40 yr old	HBV testing Vaccination
Vanderhoff, 2014 (US)[66]	Interventional, no control	Community (one city)	Migrants	On-site screening Linkage to care coordination	Migrant from countries with HBV prevalence ≥2%	Vaccination
Vedio, 2013 (UK)[67]	Interventional, no control	Community (one city)	Migrants	Community education On-site screening Linkage to care coordination	Chinese background	HBV testing Linkage to care

First author, year (country)	Study design	Study setting	Study population	Intervention(s)	Main inclusion criteria	Study outcome reported
Veldhuijzen, 2012 (Netherlands)[68]	Interventional, no control	Community (one city)	Migrants	Community awareness On-site screening Linkage to care coordination Referral for vaccination	Migrants from countries with HBV prevalence ≥2%	Vaccination
Woo, 2013 (US)[69]	Interventional, no control	Community (one city)	Multiple groups of people at risk of HBV	On-site screening	18–65 yr old	HBV testing
Zuure, 2013 (Netherlands)[70]	Interventional, no control	Community (one city)	Migrants	Community education On-site screening Linkage to care coordination	Born in Egypt; ≥18 yr old	HBV testing Linkage to care

Table A3: Characteristics and outcomes of controlled trials evaluating an HBV screening intervention

First author, year (country)	Study design (population)	Intervention group				Control group				Odds Ratio (95%CI)	
		Intervention	Participant n (% men)	Age mean or median	Received testing n (%)	Control	Participant n (% men)	Age mean or median	Received testing n (%)	Unadjusted	Adjusted
Bastani, 2015 (US)[12]	Cluster randomised trial (migrants)	One small-group HBV-focused education session Referral for testing	543 (33)	46	104 (19)	Physical activity and nutrition-focused education Referral for testing	580 (37)	45	33 (6)	3.9 (2.6, 6.1)	NR
Bottero, 2016 (France)[13]	Randomised controlled trial (people at risk of HBV)	Point of care testing with confirmatory standard of care serology testing	499 (46)	41	185 (37)[a]	Standard of care serology testing	496 (50)	40	197 (40)[a]	0.9 (0.7, 1.2)	NR
Chen, 2013 (US)[22]	Randomised controlled trial (migrants)	Home-based one to one HBV-focused education session Referral for testing	130 (39)	30–49	25 (19)	Physical activity and nutrition-focused education Referral for testing	130 (42)	30–49	11 (9)	2.6 (1.2, 6.1)	3.5 (1.3, 9.2)
Chu, 2022 (US)[23]	Before and after study (migrants)	Media campaign promoting HBV screening	857 (39)	48	626 (73)	Before campaign assessment	871 (41)	46	569 (65)	1.4 (1.2, 1.8)	0.9 (0.7,1.3)[b]
Eguchi, 2021 (Japan)[30 c]	Before and after study (general population)	1- Media campaign promoting HBV screening 2- Free HBV test at routine health check-up of workers	NR	NR	1- 1589 2- 7298	Before interventions	NR	NR	1- 345 2- 786	NR	NR
Juon, 2014 (US)[42]	Cluster randomised trial (migrants)	One group education focused on liver cancer Referral for testing	441 (42)	47	74 (17)	Educational brochure Referral for testing	436 (40)	43	22 (5)	3.8 (2.3, 6.5)	5.1 (3.1, 8.3)[d]
Ma, 2017 (US)[51]	Cluster randomised trial (migrants)	One group education focused on HBV Referral for testing	1131 (41)	55	935 (83)	General cancer education Referral for testing	1206 (44)	56	55 (4.6)	99.8 (72.5, 138.5)	18.6 (13.7, 25.3)[e]
Ma, 2018 (US)[52]	Cluster randomised trial (migrants)	One group education focused on HBV Referral for testing	972 (42)	50	899 (92)	General cancer education Referral for testing	862 (40)	54	47 (5.5)	213.5 (143.9, 317.9)	512.3 (105.2, 1344.5)[f]
Van Der Veen, 2014 (Netherlands)[65 g]	Randomised controlled trial (migrants)	Web-based HBV education: 1- Behaviourally tailored	1- 432 (45) 2- 472 (48)	1- 34 2- 34	1- 188 (44) 2- 207 (44)	Web-based HBV education: Generic information	496 (41)	34	228 (46)	1- 0.65 (0.88-1.1) 2- 0.94 (0.6-1.2)	NR

		2- Behaviourally & culturally tailored Referral for testing									

NR: Not reported

a. People returned to receive their HBV test results

b. Included another before and after survey (with no exposure to intervention) as control. OR were adjusted for group (intervention vs. comparison), time (post- vs. pre-intervention), sociodemographic, and health and healthcare access

c. Study included assessment of 2 interventions. For each intervention, the study output was reported as the number of HBV tests post- vs. pre-intervention

d. Adjusted for age, ethnicity and clustering

e. Relative risk adjusted for age, income, employment, health insurance, having regular physician, speaking English, participation in social gathering and clustering

f. Adjusted for age, income, having regular physician, speaking English and clustering

g. Study evaluated web-based education tailored on social-cognitive determinants of screening and included 2 interventions: 1-Behaviourally tailored; and 2-Behaviourally and culturally tailored education. Web-based education including generic HBV information was used as control.

Table A4: Characteristics and outcomes of studies conducting an HBV screening intervention with no control population

First author, year (country)	Study population (Study venue)	Testing strategy and sampling method	Number invited or eligible for participation	Participants (tested)			HBsAg positive, n (%)	
				Number	Proportion of men	Age mean or median	Total	Unaware of their HBV
Abutaleb, 2021 (India)[10]	People in remote area (Buddhist monastery, village square)	On-site, phlebotomy	11,818	11,572	47%	27	419 (3.6)	NR
Barragan, 2015 (US)[11]	Migrants (26 community health events)	NR	2298	2232	39%	NR	159 (7.1)	NR
Bottero, 2014 (France)[14]	Mixed (10 primary care centres)	On-site, sampling varied: point of care and phlebotomy	4516	NR	NR	33	85 (2.1)	85 (2.1)
Brouard, 2019 (France)[16]	General population (home-based self-collected dried blood spot sampling)	Dried blood spot self-sampling	17,781	6945	3382	31–60	18 (0.3)	15 (0.2)
Busschots, 2021 (Belgium)[18]	People in prison (11 prisons)	Finger prick point of care	NR	886	NR	41	7(0.8)	5 (0.6)
Buonfrate, 2018 (Italy)[17]	Refugees (14 refugee shelters)	Outreach, phlebotomy	481	457	NR	24	53 (0.1)	NR
Chandrasekar, 2016 (US)[20]	Migrants (clinical: community health centres, physician practices, hospitals, refugee clinic; non-clinical: health fairs, community and faith-based events)	On-site, phlebotomy	1000	445	NR	33	35 (7.9)	NR
Coppola, 2020 (Italy)[25]	Migrants (seven clinical centres)	On-site, phlebotomy	4125	3839	84%	28	381 (9.9)	381 (9.9)
Coenen, 2016 (Netherlands)[24]	Migrants (Chinese community centres, schools and churches)	On-site, phlebotomy	NR	4423	NR	NR	264 (5.9)	160 (3.6)
Dang, 2016 (US)[27]	Migrants (Asian clinic, Vietnamese Cancer Awareness Society,	NR	NR	1004	37%	NR	76(7.6)	76 (7.6)

First author, year (country)	Study population (Study venue)	Testing strategy and sampling method	Number invited or eligible for participation	Participants (tested)			HBsAg positive, n (%)	
				Number	Proportion of men	Age mean or median	Total	Unaware of their HBV
	Hmong community organisation, Korean churches)							
Diarra, 2017 (Burkina Faso)[28]	General population (several localities)	Finger prick point of care	NR	2207	44%	31	217 (9.8)	217 (9.8)
Diarra, 2018 (Burkina Faso)[29]	General population (12 districts)	Finger prick point of care	NR	2216	45%	30	230 (10.3)	230 (10.3)
Emeasoba, 2022 (US)[31]	Migrants (West African faith-based organisations: 3 churches and 6 mosques)	Referral, phlebotomy	550	224	NR	NR	NR	NR
Fuster, 2019 (US)[34]	People experiencing homelessness (19 shelters and 22 free meal programs)	Outreach, phlebotomy	586	534	NR	NR	79 (14.8)	NR
Hur, 2012 (US)[39]	Migrants (clinical: community health centres; non-clinical: local ethnic community centres, churches, temples, health fairs, schools)	Referral, phlebotomy	792	669	46%	47	53 (7.9)	NR
Hyun, 2021 (US)[40]	Migrants (churches, community centres, health fairs)	On-site, phlebotomy	NR	898	37%	54	49 (5.5)	18 (2.0)
Jones, 2021 (US)[41]	Migrants (participants' homes; n=9 in community sites)	Home-based, phlebotomy	70	57	26%	59	0 (0)	NR
Kelly, 2020 (UK)[44]	Migrants (14 venues: religious venues, community centres, primary care facilities)	On-site, dried blood spot	NR	219	47%	NR	2 (0.9)	NR
Koc, 2020 (Belgium)[45]	Migrants (Islamic mosques)	Referral, phlebotomy	1131	1081	44%	44	26 (2.4)	11 (1.0)

First author, year (country)	Study population (Study venue)	Testing strategy and sampling method	Number invited or eligible for participation	Participants (tested)			HBsAg positive, n (%)	
				Number	Proportion of men	Age mean or median	Total	Unaware of their HBV
Lemoine, 2016 (Gambia)[48]	General population (~54 rural and urban communities)	Finger prick point of care	8170	5980	39%	43	495 (8.3)	NR
McPherson, 2013 (UK)[53]	Migrants (community organisations, churches, community centres, mosques)	On-site, dried blood spot	ND	1126	68%	46	62 (5.5)	52 (4.6)
Misra, 2013 (US)[54]	Migrants (health fairs, restaurants, public health clinic, churches, temple)	On-site, phlebotomy	ND	1311	42%	51	72 (5.5)	71 (5.4)
Navarro, 2014 (US)[55]	Migrants (9 Korean churches)	On-site, phlebotomy	ND	973	39%	50	29 (2.9)	13 (1.3)
Nguyen, 2015 (US)[57]	Migrants (health fair)	On-site, phlebotomy	ND	1405	45%	51	124 (8.8)	56 (3.9)
Nyirahabihirwe, 2022 (Rwanda)[58]	Refugees (refugee camp: community locations and schools)	Finger prick point of care	34,015	26,498	46%	NR	1006 (3.8)	888 (3.3)
Polilli, 2016 (Italy)[59]	Mixed (website-based education targeting people living in study area)	Referral, phlebotomy	6000	3046	NR	NR	56 (1.8)	NR
Richter, 2012 (Netherlands)[60]	Migrants (community centres and mosques)	On-site, phlebotomy	NR	647	41%	43	18 (2.8)	16 (2.5)
Shankar, 2016 (US)[62]	Migrants (community centres, places of worship, sites of employment)	On-site, phlebotomy	NR	919	75%	45	88 (9.6)	88 (9.6)
Vedio, 2013 (UK)[67]	Migrants (Chinese community centres, church, school, wholesalers)	On-site, dried blood spot	NR	229	45%	47	20 (8.7)	14 (6.1)
Woo, 2013 (US)[69]	Migrants (Asian Culture Festival)	On-site, phlebotomy	NR	404	NR	NR	4 (0.9)	3 (0.7)
Zuure, Netherlands (2013)[70]	Migrants (church, mosques, Egyptian community organisation, Egyptian trade	On-site, phlebotomy	1438	465	NR	43	5 (1.1)	2 (0.4)

First author, year (country)	Study population (Study venue)	Testing strategy and sampling method	Number invited or eligible for participation	Participants (tested)			HBsAg positive, n (%)	
				Number	Proportion of men	Age mean or median	Total	Unaware of their HBV
	organisation, Islamic school, supermarket)							

NR: Not reported

Table A5: Characteristics and outcomes of studies implementing an intervention to enhance linkage to HBV clinical care among people diagnosed with HBV infection

First author, year (country)	Definition of linkage to care among people HBsAg positive	Intervention component(s)	People HBsAg positive			Linked to care, n (%)
			Number	Proportion of men	Age mean or median	
Abutaleb, 2021 (India)[10]	Attending clinical appointment	Referral; assistance with scheduling clinical appointment and transportation	419	60%	NR	206 (49)
Chandrasekar, 2015 (US)[19]	Attending clinical appointment	Referral; post-test counselling; assistance with scheduling clinical appointment	55	NR	NR	39 (71)
Coenen, 2016 (Netherlands)[24]	Received post-test counselling	Referral; linkage to care; coordinator spoke in participant's preferred language; post-test counselling	264	NR	NR	243 (92)
Freeland, 2020 (US)[32]	Attending clinical appointment	Referral; assistance with scheduling clinic appointment	239	49%	NR	191 (80)
Funchess, 2022 (US)[33]	Attending clinical appointment	Referral; linkage to care; coordinator spoke in participant's preferred language (or interpreter services provided); assistance with scheduling clinical appointment and transportation; reminder about appointment	46	NR	NR	23 (50)
Fuster, 2019 (US)[34]	Received post-test counselling and attending clinic	Referral; post-test counselling; assistance with scheduling clinical appointment	79	NR	NR	58 (73)
Harris, 2016 (US)[36]	Received post-test counselling and attending clinic	Referral; post-test counselling; linkage to care; coordinator spoke in participant's preferred language (some sites); assistance with scheduling clinical appointment	1317	60%	47	606 (46)
Harris, 2018 (US)[35]	Attending clinical appointment and	Referral; post-test counselling; linkage to care; coordinator spoke	757	55%	40	587 (78)

First author, year (country)	Definition of linkage to care among people HBsAg positive	Intervention component(s)	People HBsAg positive			Linked to care, n (%)
			Number	Proportion of men	Age mean or median	
	tested for HBV DNA and liver function tests	in participant's preferred language (some sites); assistance with scheduling clinical appointment				
Hyun, 2021 (US)[40]	Attending clinical appointment	Referral	49	NR	58	25 (51)
Kalla, 2018 (Cameroon)[43]	Attending clinical appointment	Referral	104	NR	NR	104 (100)
Koc, 2020 (Belgium)[45]	Attending clinical appointment	Referral	26	NR	NR	23 (88)
Le, 2022 (US)[46]	Attending clinical appointment	Referral; assistance with scheduling clinical appointment	378	NR	NR	329 (87)
Lemoine, 2016 (Gambia)[48]	Attending clinical appointment	Referral; post-test counselling	495	NR	NR	402 (81)
Navarro, 2014 (US)[55]	Attending clinical appointment	Referral; post-test counselling	29	66%	NR	8 (28)
Newton, 2015 (US)[56]	Attending clinical appointment	Referral; assistance with scheduling clinical appointment; linkage to care; coordinator spoke in participant's preferred language	46	NR	NR	37 (80)
Robotin, 2018 (Australia)[61]	Attending clinical appointment	Referral; training of general practitioners; nurse educator for patient education; reminder for appointment	230	NR	NR	82 (36)
Shankar, 2016 (US)[62]	Attending clinical appointment	Referral; post-test counselling; linkage to care; coordinator spoke in participant's preferred language	88	82%	40	85 (97)
Shanmugam, 2018 (India)[63]	Initiated HBV treatment	Post-test counselling; referral to specialist; blood collection for further testing	162	NR	NR	162 (100)
Standford, 2016 (US)[64]	Attending clinical appointment	Referral; post-test counselling	68	NR	NR	43 (63)
Vanderhoff, 2014 (US)[66]	Attending clinical appointment	Referral; post-test counselling	219	NR	NR	163 (74)

First author, year (country)	Definition of linkage to care among people HBsAg positive	Intervention component(s)	People HBsAg positive			Linked to care, n (%)
			Number	Proportion of men	Age mean or median	
Vedio, 2013 (UK)[67]	Attending clinical appointment	Referral; linkage to care; coordinator spoke in participant's preferred language	20	50%	38	18 (90)

NR: Not reported

Table A6: Characteristics and outcomes of studies implementing a population-level HBV screening intervention in adults followed by HBV vaccination for those eligible for vaccination

First author, year (country)	Study population	Definition of eligibility for vaccination	Vaccination strategy	Eligible for vaccination			Received vaccination, n (%)	
				Number	Proportion of men	Age Mean or Median	First dose	Full dose
Abutaleb, 2021 (India)[10]	People living in remote area	HBsAg negative	On-site vaccination	11,153	NR	NR	9253 (83)	5176 (46)
Boyd, 2017 (France)[15]	Multiple groups of people at risk of HBV	HBsAg, HBcAb, HBsAb negative	Referral for vaccination	1215	58%	36	99 (8)	NR
Bottero, 2016 (France)[13]	Multiple groups of people at risk of HBV	HBsAg, HBcAb, HBsAb negative	Referral for vaccination	196	NR	NR	7	NR
Diarra, 2017 (Burkina Faso)[28]	General population	HBsAg, HBcAb, HBsAb negative	On-site vaccination	1990	43%	NR	NR	628 (32)
Diarra, 2018 (Burkina Faso)[29]	General population	HBsAg, HBcAb, HBsAb negative	On-site vaccination	1986	43%	35	1220 (61)	1202 (60)
Funchess, 2022 (US)[33]	Migrants	HBsAg, HBsAb negative	On-site vaccination	130	NR	NR	116 (89)	101 (78)
Hean, 2021 (US)[37]	Migrants	HBsAg, HBsAb negative	Referral for vaccination	53	44%	42	6 (12)	NR
Hur, 2012 (US)[39]	Migrants	HBsAg, HBsAb negative	Referral for vaccination	307	48%	NR	250 (81)	185 (60)
Koc, 2020 (Belgium)[45]	Migrants	HBsAg, HBcAb, HBsAb negative	Referral for vaccination	230	NR	NR	44 (19)	NR
Liu, 2022 (China)[50]	General population	NR	Referral for vaccination	6160	34%	NR	1708 (28)	1300 (21)
Ma, 2018 (US)[52]	Migrants	HBsAg, HBsAb negative	Referral for vaccination	332	NR	NR	308 (93)	279 (84)
Misra, 2013 (US)[54]	Migrants	HBsAg, HBsAb negative	Referral for vaccination	476	NR	NR	57 (12)	NR
Navarro, 2014 (US)[55]	Migrants	HBsAg, HBcAb, HBsAb negative	Referral for vaccination	196	NR	NR	1 (0.5)	NR
Shanmugam, 2018 (India)[63]	General population	HBsAg negative	Mixed strategy	18,286	NR	NR	770 (42)	NR

Vanderhoff, 2014 (US)[66] [a]	Migrants	NR	Referral for vaccination	9	NR	NR	7 (78)	NR
Van Der Veen, 2014 (Netherlands)[65]	Migrants	HbsAg, HBsAb negative	Referral for vaccination	505	NR	NR	101 (20)	NR
Veldhuijzen, 2012 (Netherlands)[68]	Migrants	HBsAg, HBcAb negative	Referral for vaccination	556	NR	NR	124 (22)	NR

NR: Not reported

a. Not included in the analysis given small study population size