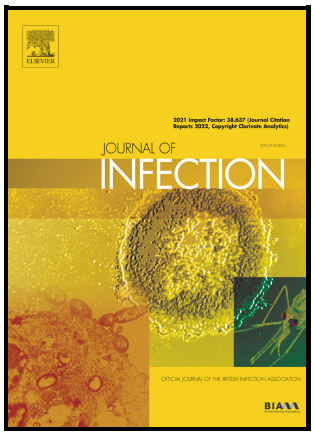

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Hepatitis B virus infection in general practice across England: An analysis of the Royal College of General Practitioners Research and Surveillance Centre real-world database

Anna Maria Geretti[1,2], Harrison Austin[3], Giovanni Villa[4], Colette Smith[5], Caroline Sabin[5,6], Ruby Tsang[7], Julian Sherlock[7], Filipa Ferreira[7], Rachel Byford[7] (TBC), Bernardo Meza-Torres[7], Martin Whyte,[7] Simon de Lusignan[7] (0000-0002-8553-2641)

1. Dept. of Infectious Diseases, Fondazione PTV, University of Rome Tor Vergata, Rome, Italy
2. School of Immunology & Microbial Sciences, King's College London, London, United Kingdom
3. Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, Liverpool, United Kingdom
4. Dept. of Global Health & Infection, Brighton & Sussex Medical School, University of Sussex, Brighton United Kingdom
5. Institute for Global Health, University College London (UCL), London, United Kingdom
6. NIHR HPRU in Blood Borne and Sexually Transmitted Infections at UCL, a partnership with UKSHA, London, United Kingdom.
7. Nuffield Dept. of Primary Care Health Sciences, University of Oxford, Oxford, United Kingdom

Corresponding author:

Prof Anna Maria Geretti

MD, PhD, FRCPath

Dept. of Infectious Diseases

Fondazione PTV, University of Rome Tor Vergata,

Viale Oxford 81, 00133 Rome, Italy

Telephone: +39 06 2090 3440

anna_maria.geretti@kcl.ac.uk

Summar

Objectives. We analysed hepatitis B surface antigen (HBsAg) screening and seropositivity within a network of 419 general practices representative of all regions of England.

Methods. Information was extracted using pseudonymised registration data. Predictors of HBsAg seropositivity were explored in models that considered age, gender, ethnicity, time at the current

practice, practice location and associated deprivation index, and presence of nationally endorsed screen indicators including pregnancy, men who have sex with men (MSM), history of injecting drug use (IDU), close HBV contact or imprisonment, and diagnosis of blood-borne or sexually transmitted infections.

Results. Among 6,975,119 individuals, 192,639 (2.8%) had a screening record, including 3.6- 38.6% of those with a screen indicator, and 8065 (0.12%) had a seropositive record. The odds of seropositivity were highest in London, in the most deprived neighbourhoods, among minority ethnic groups, and in people with screen indicators. Seroprevalence exceeded 1% in people from high prevalence countries, MSM, close HBV contacts, and people with a history of IDU or HIV, HCV, or syphilis diagnosis. Overall, 1989/8065 (24.7%) had a recorded referral to specialist hepatitis care.

Conclusions: In England, HBV infection is associated with poverty. There are unrealised opportunities to promote access to diagnosis and care for those affected.

Introduction

The World Health Organisation (WHO) estimates that in 2019 there were 296 million people living with chronic hepatitis B virus (HBV) infection, defined by seropositivity for the hepatitis B surface antigen (HBsAg).[1] Whilst HBsAg seroprevalence varies substantially by location and population, only approximately 10% of those living with chronic HBV infection have been diagnosed, and 22% of those with a diagnosis receive antiviral treatment.[1] In 2019, 820,000 people died of HBV-related complications, primarily liver cirrhosis and hepatocellular carcinoma (HCC).[1] Although vaccination programmes are effectively reducing HBsAg seroprevalence in children below the age of 5,[2] HBV-related mortality is predicted to continue to exceed 500,000 annually until at least 2070.[3] WHO has called for enhanced efforts to increase awareness of chronic HBV infection, improve the use of prevention strategies, and expand access to testing and care.[4]

In the United Kingdom (UK), the estimated prevalence of chronic HBV infection is between 0.1% and 0.5%,[5,6] although there is a recognised paucity of data.[7] Prevalence is likely to vary regionally and between communities, and estimates may not fully account for substantial underdiagnosis.[8,9] HBsAg screening of pregnant women is part of routine antenatal care, with uptake currently exceeding 99%.[10] Other forms of screening are targeted to specific indicators: in 2013, the National Institute for Health and Care Excellence (NICE) recommended HBsAg testing for people born or brought up in countries with intermediate or high HBV endemicity (HBsAg prevalence ≥2%), those with a history of current or past injecting drug use (IDU), close contacts of people with HBV infection, prisoners, people in residential care, men who have sex with men (MSM) and other people at risk via sexual exposure such as those that report multiple sexual partners or are diagnosed with sexually transmitted infections (STIs).[11] Sentinel surveillance collects data on HBsAg testing performed in approximately 20 designated primary and secondary care services across England. These include sentinel centres within general practice, which between 2008 and 2019 contributed around 28% of surveillance data outside of antenatal care, with an overall HBsAg seroprevalence among those

undergoing testing of 2.1% in 2008-2011,[12] 1.5% in 2012-2016,[13,14] and 1.1% in 2017-2019.[14] Referrals from general practice also account for around 30% of routes to the diagnosis of HCC.[15]

Published evidence supports the wider adoption of targeted HBsAg screening in healthcare services including general practice.[16] Yet, large gaps remain in our understanding of HBV epidemiology in England and it remains unclear why the large majority of people living with HBV infection remain undiagnosed.[17] To evaluate the patterns of HBsAg seroprevalence in general practice across England, we analysed data from the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC), one of Europe's oldest sentinel network. The RSC is a collaboration with the University of Oxford and the UK Health Security Agency that collects and monitors pseudonymised data from a large network of general practices across all regions of England recruited to be nationally representative.[18]

Methods

Study population

Information from 419 general practices comprising all patients who had a record between January 2008 and July 2019 were extracted using pseudonymised registration data. These include age, gender, socioeconomic status and rurality; the latter are derived from postcodes, which are not subsequently retained. Key clinical data including diagnoses, symptoms, tests, and therapy are recorded in electronic healthcare records coded using the Read Codes version 2 or Clinical Terms version 3 (CTv3).[19] The data extraction included age, gender, time registered at the current general practice, ethnicity, National Health System (NHS) region (London, South, North, Midlands & East), and a record of one or more HBsAg screen indicators. Duplicate records were removed by retaining the most recently active record. Screen indicators were adapted from those in the NICE recommendations[11] according to the availability of suitable codes within the records. They comprised: MSM, origin from a country with intermediate or high HBV endemicity, current or past IDU, close HBV contact, history of imprisonment, and a diagnosis of blood-borne or sexually transmitted infections (BB/STI). The latter included hepatitis C virus (HCV), human immunodeficiency virus (HIV), syphilis, scabies, gonorrhoea, trichomoniasis, genital herpes, and human papillomavirus (HPV). Chlamydia was not included as screening results were not recorded. To take into account that HBsAg screening is routinely performed within antenatal care, we also extracted whether women had a record of pregnancy utilising published ontologies[20], considering pregnancy as a potential screen indicator. Potential screen indicators of interest that did not have suitable codes (e.g., having multiple sexual partners) were not included. Screen indicators were considered if they were recorded prior to or at the same time as HBsAg screening; if there was no record of HBsAg screening, we considered indicators at any time they were recorded. The case definition for HBsAg screening was a (first) record of i) recognition of the need for HBsAg testing, or ii) offer of HBsAg testing. The case definition for HBsAg seropositivity was a (first) record of i) history of HBsAg seropositivity or ii) positive HBsAg test result. Referrals to gastroenterology, infectious diseases, or hepatology clinics for specialist HBV care were also extracted utilising Read Codes v.2 or CTv3.

Socioeconomic and geographical data

Location data, including urban-rural classification, Indices of Multiple Deprivation (IMD) and local super output area (LSOA) were derived from the general practice postcode. IMD is a measure of relative deprivation which considers seven domains: income, employment, education, health, local crime, barriers to housing and services, and living environment.[21] LSOAs are small geographical areas containing approximately 1,500 people which are used to describe national statistics. The map of HBsAg seroprevalence was generated in ArcGIS Pro (version 2.6 API) by matching LSOAs to their corresponding local authority district (LAD) using data available from the office of national statistics.[22] LSOAs that did not match to a LAD in England were removed from this analysis.

Statistical analysis

Variables were summarised as absolute counts with frequencies or as medians with interquartile ranges (IQR) if categorical or continuous, respectively. Confidence intervals (CI) for prevalence were calculated by Wilson binomial test. Temporal trends in HBsAg screening were evaluated by counts per year, normalised by the total number of patients registered within that year. Factors associated with a record of HBsAg seropositivity were explored by logistic regression analysis. Adjustments comprised age, gender, time registered at the current general practice, ethnicity, NHS region, IMD quintile, IDU history, close HBV contact, imprisonment history, and $\geq$1 BB/STI diagnosis. Separate models considered the association of HBsAg seropositivity with each of the eight individual BB/STI diagnoses included in the analysis, all adjusting for age, gender, time registered at the current general practice, ethnicity, IMD quintile, NHS region, IDU history, close HBV contact, and imprisonment history; BB/STIs were not reciprocally adjusted. Cross tabulation was used to detect co-occurrence of BB/STIs. A sensitivity analysis explored the association between HBsAg seropositivity and a record of syphilis after excluding people with both syphilis and HCV records. As registration at the general practice was allowed at any time within the study period, it was possible to adjust for both age and time registered at the current general practice. The models excluded country of birth due to missing data; in the subset with a recorded country of birth, a two-sample Wilcoxon rank-sum test was used to test for trends in HBsAg screening and seropositivity. In this analysis, the country of birth was categorised based on the WHO criteria as having high (>8%), intermediate (2-7%), or low (<2%) HBsAg seroprevalence.[23] Univariate logistic regression analysis was used to explore factors associated with a record of referral to specialist care among people with a record of HBsAg seropositivity. Statistical analyses were carried out in STATA (Version 14.2 College Station, Texas, United States).

Ethical considerations

This study was approved by the RCGP-University Joint Research and Surveillance Centre (JRSCC) and regulated by a data sharing agreement between the JRSCC and the University of Liverpool. The analysis was made using pseudonymised data, with researchers having no access to individual level

data. Release of the data from the Oxford-RCGP trusted research environment goes through a process of statistical disclosure control.

Results

Study population

A total of 6,975,119 unique individual pseudonymised records were extracted spanning the period between January 2008 and July 2019 (Table 1). The population comprised similar proportions of men and women, had a median age of 38 years, and was ethnically diverse, largely urban, and distributed across England and IMD quintiles. The most commonly recorded BB/STI diagnoses were scabies, HPV, and genital herpes. HCV and HIV had a recorded seroprevalence of 0.04% (95% CI 0.04-0.04) and 0.002% (95% CI 0.001-0.002), respectively. Demographic and socioeconomic characteristics by the screen indicators MSM, close HBV contact, IDU history, imprisonment history, and each BB/STI diagnosis are shown in Supplementary Table 1. When considering individual BB/STI diagnoses, syphilis and scabies were recorded in nearly similar proportions of men and women; gonorrhoea, HCV, and HIV were more common in men; and genital herpes, trichomoniasis and HPV were more common among women. Women with a pregnancy record had a higher prevalence of STIs than women without a record, and most commonly had a diagnosis of scabies, HPV, or genital herpes.

HBsAg screening

A record of HBsAg screening was found in 192,639/6,975,119 (2.8%) people (Table 1). HBsAg screening increased between 2008 and 2014 and remained essentially stable in subsequent years (Supplementary Figure 1). Proportions with a screening record exceeded 10% among close HBV contacts (38.6%), MSM (19.0%), women with a pregnancy record (14.3%), people with a history of IDU (11.6%), and those with a diagnosis of syphilis (10.2%) (Table 1). Proportions ranged between 5% and 10% among those with an imprisonment history (5.0%) and the BB/STI diagnoses HCV (9.3%), gonorrhoea (6.0%), trichomoniasis (8.2%), and genital herpes (5.6%). Geographically, proportions with a screening record were highest among those attending practices in London and those resident in the most deprived neighbourhoods of England (Table 1).

HBsAg seropositivity

A record of HBsAg seropositivity was found in 8065/6,975,119 people (Table 1), yielding a seroprevalence of 0.12% (95% CI 0.11-0.12). The proportion with a seropositive record was highest among people with HCV (6.5%; 95% CI 5.7-7.5) and exceeded 1% among MSM (1.1%; 95% CI 0.6-1.9), those with an IDU history (1.3%; 95% CI 1.1-1.6), close HBV contacts (2.7%; 95% CI 2.1-3.5), people with a diagnosis of syphilis (2.1%; 95% CI 1.5-2.9), and the few with a recorded HIV diagnosis (4.5%; 95% CI 1.9-10.1). The logistic regression analysis indicated that the odds of HBsAg seropositivity were highest among MSM, people whose recorded ethnicity was black, Asian, mixed, or other (vs. white), people with an IDU history, close HBV contacts, and people with a record of

HCV, HIV, or syphilis (Table 2). Smaller increases were detected among woman with a pregnancy record, people with an imprisonment history, and those with a record of scabies, whereas women without a pregnancy record had substantially reduced odds of HBsAg seropositivity (Table 2). Geospatial data (n= 5944/8065; 73.7%) were used to map the distribution of HBsAg seropositivity across England by each local authority (Figure 1). Geographically, HBsAg seropositivity was most common in people attending GP practices located in London and in the most deprived neighbourhoods of England. Adjusting for age, gender, time registered at the current general practice, ethnicity, IMD quintile, NHS region, IDU history, close HBV contact, imprisonment history, and ≥1 BB/STI diagnosis cumulatively did not significantly change the univariable estimates (Table 3). Separate analyses that considered individual BB/STI diagnoses confirmed that, after adjusting for age, gender, time registered at the current general practice, ethnicity, IMD quintile, NHS region, IDU history, close HBV contact, and imprisonment history, the odds of HBsAg seropositivity were significantly increased with a record of HCV, HIV, and syphilis, and marginally with a record of scabies (Table 3). There were no associations with other STIs (Supplementary Table 2). Among those with both a record of HBsAg seropositivity and a record of syphilis (n=37), 1 also had a recorded diagnosis of genital herpes, 1 of scabies and 3 of HCV, whereas none had a record of gonorrhoea, trichomoniasis, HPV, or HIV. In a sensitivity analysis that excluded the 3 people with both syphilis and HCV, a recorded diagnosis of syphilis remained independently associated with increased odds of HBsAg seropositivity, with an adjusted OR of 5.57 (95% CI 3.97-7.82; p<0.001), and with no changes to other findings (not shown).

Population with recorded country of birth

In total, 292,099/6,975,119 (4.2%) individuals had a recorded country of birth, including 49,170 (16.8%) and 9523 (3.3%) who were from countries with intermediate (mainly the South-East Asian and Eastern European regions) and high (mainly the African region) HBsAg prevalence, respectively (Supplementary Table 3). Among these, 4211/49,170 (8.6%) and 916/9523 (9.6%) respectively had a record of HBsAg screening, which compared with 9431/233,406 (4.0%) among those from a low prevalence country (p<0.01). HBsAg seropositivity was 290/233,406 in those from low prevalence countries (0.12%; 95% CI 0.11%-0.14%), 460/49,170 in those from intermediate prevalence countries (0.94%; 95% CI 0.85%-1.02%), and 182/9523 in those from high prevalence countries (1.91%; 95% CI 1.65%-2.20) (p<0.01).

Specialist care

Among those with a record of HBsAg seropositivity, 1989/8065 (24.7%) had a recorded referral to specialist HBV care. By univariate analysis, the odds of a specialist care record were lower in women, those living outside London, and those from the most deprived neighbourhoods (Table 4).

Discussion

We studied nearly 7 million unique patient records from 419 GP surgeries across England and found that 2.8% had a record of HBsAg screening. Screening rates increased in 2014 relative to 2008 and remained essentially stable in subsequent years. HBsAg screening appeared to be more likely in several populations for whom screening is recommended,[10,11] including women with a pregnancy record, MSM, close HBV contacts, people with a history of IDU or imprisonment, and those with ≥1 BB/STI diagnosis, especially HCV and syphilis. Whilst data on country of origin were incomplete, there was evidence of increased screening among people whose recorded ethnicity was Asian, African, mixed, or other, compared with those of white ethnicity. Of note though, among all of the populations with HBsAg screen indicators, only a minority had a screening record: the highest proportions were found among close HBV contacts (39%) and MSM (19%), but proportions fell below 15% in all other eligible populations. When considering the small subset for whom the country of origin was recorded (4% of the total population), only 8.7% of those from countries with intermediate or high HBV endemicity had a HBsAg screening record. There were geographical differences in HBsAg screening, with higher screening occurring in London relative to all other regions of England. There were also differences by socio-economic status, with higher screening occurring in the first and second IMD quintiles, reflecting areas with the highest levels of deprivation.

It is estimated that a large fraction of people living with HBV in the UK are undiagnosed and thus at risk of presenting to care with advanced liver disease, including liver failure and HCC.[8,9,17] They also pose a risk of onward transmission to close contacts, including family and household members and sexual partners. Screening people at increased risk of HBV infection was recommended by NICE in 2013[11] and shown to be cost-effective for populations with HBsAg seroprevalence ≥1%.[8] Missed opportunities for screening have been previously highlighted. A study in Bristol found that between 2006 and 2013, among 82,561 people from countries of intermediate or high HBV endemicity attending general practice, 12% had undergone HBsAg testing.[9] Recognised barriers to test provision include incomplete knowledge of HBV among both practitioners and patients, performance pay structure, limited time, and language or cultural challenges.[24-26] It is to be acknowledged that, in addition to routine HBsAg screening within antenatal care, certain populations may access HBsAg screening outside of general practice, including in sexual health clinics, speciality services for liver disease, needle exchange and drug misuse clinics, or within prison healthcare. The British Association for Sexual Health and HIV (BASHH) recommends hepatitis B testing in MSM, sex workers, those with an IDU history, people living with HIV, sexual assault victims, people from countries where hepatitis B is endemic, needlestick victims, and sexual partners of people with HBV or at-risk patients; hepatitis B vaccination is also recommended for non-immune MSM.[27] It is not known how widely the guidelines are adopted within sexual health services. One study of 1497 MSM sampled in England in 2016 found that only 30% had serological evidence of immunisation, whereas HBsAg seroprevalence was 0.2%.[28] Nonetheless, there may be the expectation that for many eligible populations HBsAg screening will take place outside of general practice. In such cases, both the need for a test and any test result may not be recorded in the patients' files, illustrating the difficulty of characterising HBV epidemiology in the absence of linkage of HBV data across systems.[17] As an additional barrier, the need for HBsAg screening may not identified unless risk factors are elicited

and recorded.[29] To this point, the proportion of MSM in our study was underestimated based on national Census data,[30] and proportions with a recorded HCV or HCV infection fell below estimated prevalence rates.[31,32]

HBsAg seroprevalence in the overall population was 0.12%, which falls within the wide range of national estimates (0.1-0.5%).[5,6] There were significant geographical differences, with the highest seroprevalence rates found in London (0.29%) relative to all other regions of England. Seroprevalence also varied by ethnic background and was lowest among people of white ethnicity (0.06%) and highest among those of black ethnicity (0.83%) followed by people of Asian ethnicity (0.39%). This is consistent with surveillance data.[12-14] HBsAg seroprevalence was similarly 0.9% in an ethnically diverse population attending the Emergency Department of an East London hospital in 2015-2016.[33] There were also significant differences by socio-economic status, with the highest rates found in areas of greatest deprivation. Correspondingly, national data show that both acute HBV infection[34] and HCC[15] are more common in the most deprived population quintiles. HBsAg seroprevalence reached 0.94% in those from countries of intermediate HBV endemicity and 1.9% in those from high endemicity countries. While lower than anticipated based on WHO estimates,[23] these figures should be interpreted with caution given the incomplete information on country of origin.

Among women with a pregnancy record, HBsAg seroprevalence was 0.3%, which is consistent with surveillance data from antenatal testing in England, showing seroprevalence rates of 0.5-0.6% in 2008-2012, 0.3-0.4% in 2013-2018, and 0.2% in 2019.[12-14] Seroprevalence was 1.1% in MSM, which is higher than previously reported in England among 325 MSM tested in 2014 (0.3%)[35] and among 1497 MSM tested in 2016 (0.2%).[28] This points to a possible selective recording of MSM sexual orientation combined with the offering of HBsAg screening to people with recognised risks of HBV infection. HBsAg seroprevalence was 1.3% overall in people with a current or past IDU history. Reflecting the marked increase in the uptake of the hepatitis B vaccine, since 2003 incidence of HBV infection has declined in the IDU population; HBsAg seroprevalence estimates fell from 0.9% in 2012 to around 0.3% in 2019.[36,37] HBsAg seroprevalence was higher among close HBV contacts (2.7%). It is unclear to what extent seroprevalence in this group may reflect ongoing HBV transmission versus the sharing of other factors such as country of origin.[38] The data emphasise the importance of offering HBsAg screening (and if indicated vaccination) to family and household members and sexual partners of people with chronic HBV infection.

Among people with a BB/STI diagnosis, HBsAg seroprevalence increased in association with a record of HCV (6.5%), HIV (4.5%), or syphilis (2.1%). The association between HBV and both HCV and HIV is well recognised.[39,40] Interestingly, a record of syphilis was associated with a six-fold increase in the odds of HBsAg seropositivity. The association was confirmed after adjustment for variables including gender, age, ethnicity, history of IDU, close HBV contact or imprisonment, and after excluding people with both HCV and syphilis. A previous systematic review explored the association between HBsAg seropositivity and a diagnosis of syphilis, chlamydia, gonorrhoea or an unspecified STI.[41]

Although the meta-analysis suffered from high heterogeneity, the pooled risk ratio for HBsAg seropositivity was 2.36 with past syphilis (95% CI 1.36-4.08), 6.76 with current syphilis (95% CI 2.10, 21.76), and 1.65 with a past unspecified STI (95% CI 1.08-2.52). In contrast, there was no significant association with a diagnosis of chlamydia or gonorrhoea. We confirm the unique association between HBsAg seropositivity and syphilis by demonstrating that there was also no significant association with a diagnosis of trichomoniasis, genital herpes, or HPV, whereas there was a borderline association with a diagnosis of scabies. In England, cases of syphilis tripled between 2010 and 2019; increases have been seen in large urban centres and among MSM, but also among heterosexual men and women.[42] In 2018 there were 381 reported cases of acute or possible acute HBV infection in England, yielding an annual incidence of 0.68 per 100,000 populations overall and increasing to 1.52 per 100,000 among men aged 45-54 years.[43] Although the dataset was incomplete, among 110 cases with recorded exposure, 50% were likely exposed via heterosexual intercourse and 17% were in MSM. These data support the inclusion of syphilis as a specific indicator for HBsAg screening regardless of disclosed sexual orientation.

One strength of this study was the utilisation of data collected from a large and nationally representative network of GP practices, thus enriching with more details the outputs of sentinel surveillance. The RSC is one of the largest sentinel research networks in Europe. A previous study of common chronic diseases found that its database was overall representative of the population of England, with only a small overrepresentation of younger ages and underrepresentation of white ethnicity and deprived people.[44] There are however limitations to this study. The inclusion of screen indications was dictated by the availability of representative Read Codes v.2 and CTv3 within the dataset; therefore, only screen indicators with appropriate coding could be included. There is no requirement to record country of birth in primary care records. Country of birth may have been recorded as a surrogate for ethnicity, which since the time of this study practices are encouraged to record[45]. However, this is an important area for improvement as highlighted by campaigns to improve migrant health care.[46] There was likely underestimation of certain screen indicators such as MSM or HIV status, and we were also unable to obtain details of the stage of the syphilis diagnoses. Although the association between HBV seropositivity and deprivation was independent of all other modelled factors, we were not able to consider what proportion of migrants from countries of intermediate or high HBV endemicity were living in these areas, which may be significant.[47] Importantly, we were not able to confirm whether HBsAg seropositivity was indicative of a chronic or acute infection; data indicate that incidence of acute HBV infection in England has halved between 2008 and 2018, with the large majority of cases of HBsAg seropositivity being indicative of chronic HBV infection.[48]

In summary, in this large dataset from primary care in England, the recorded presence of HBsAg screen indicators appeared to increase the likelihood of HBsAg screening; however, there were large gaps in both the recording of such indicators and the screening offered. In 2013-2017, a randomised controlled trial demonstrated that incentivising and supporting general practices in areas with a high density of migrants (Bradford, Yorkshire, and northeast and southeast London) effectively increased the numbers of first- or second-generation adult migrants screened for viral hepatitis.[16] Within

screen indicators that can be routinely coded within general practice datasets, key groups that would benefit from routine HBsAg screening, in addition to those from countries with intermediate and especially high HBV endemicity, include MSM, those with a history of IDU, close HBV contacts, and those with a diagnosis of HCV, HIV, or syphilis, all of whom showed HBsAg seroprevalence >1%. Across England, HBV infection is largely a disease of poverty, with the highest prevalence found in the most deprived neighbourhoods. Socioeconomic deprivation also affects HBV-related health outcomes, with higher incidence of HCC in poorest areas than in more affluent areas reported in England.[49] Thus, general practices located in deprived areas play a key role in promoting HBsAg screening. Checking children born to mothers with HBV is an additional task, given that a large proportion of women with a record of pregnancy and HBsAg seropositivity were registered at general practices located in highly deprived areas. Guidelines from specialist societies can be strengthened in terms of emphasising the importance of HBsAg screening for people with a diagnosis of syphilis, regardless of gender and sexual orientation. Finally, whilst acknowledging that referral records might have been incomplete, only approximately 1 in 4 of people with a record of HBsAg seropositivity also had a specialist referral record, with some evidence of uneven availability based on gender, socio-economic status, and place of residence. Care pathways for chronic HBV infection need strengthening to ensure equity of access.

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Conflicts of interest

AMG served as expert scientist for Roche Pharma Research and Early Development, which included research on the development of curative interventions for chronic HBV infection and received funding in support of HBV biomarker research (through her institution) from Roche pRED and Roche Diagnostics. SdeL has received funding for vaccine-related research (through his institution) from AstraZeneca, GSK, Sanofi, Seqirus and Takeda (the GSK award relates to hepatitis related research);

has been a member of influenza and COVID-19 advisory boards for AstraZeneca, Pfizer, Sanofi and Seqirus; and is Director of the Oxford-RCGP RSC as part of his academic post. HA, GV, CoS, CaS, RB, JS, FF, RB, BM-T and MW have no conflict of interest to declare.

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Table 1. Characteristics of the study population according to recorded HBsAg screening and seropositivity

		Total population	With record of HBsAg screening	With record of HBsAg seropositivity
Total number (%)		6,975,119 (100)	192,639 (2.8)	8,065 (0.12)
Gender, n (%)	Women, all	3,537,583 (50.7)	138,108 (3.9)	3,879 (0.11)
	Women, no pregnancy[a]	2,870,055 (41.2)	42,787 (1.5)	1,895 (0.07)
	Women, pregnancy[a]	667,528 (9.6)	95,321 (14.3)	1,984 (0.30)
	Men, all	3,437,536 (49.3)	54,531 (1.6)	4,185 (0.12)
	Men, non MSM	3,436,356 (49.3)	54,307 (1.6)	4,173 (0.12)
	Men, MSM	1,180 (0.02)	224 (19.0)	13 (1.1)
Age, median years (IQR)		38 (24-57)	39 (32-48)	44 (36-54)
Time at general practice, median years (IQR)		10 (5-18)	10 (6-18)	8 (4-12)
Ethnicity, n (%)	White	4,175,022 (59.9)	122,032 (2.9)	2,510 (0.06)
	Asian	519,692 (7.5)	22,044 (4.2)	2,045 (0.39)
	Black	236,529 (3.4)	11,565 (4.9)	1,965 (0.83)
	Mixed	107,967 (1.6)	3,108 (2.9)	309 (0.29)

	Other	99,176 (1.4)	3,806 (3.8)	357 (0.36)
	Unknown	1,836,733 (26.3)	30,084 (1.6)	879 (0.05)
Location, n (%)	Urban	5,427,827 (77.8)	156,683(2.9)	7,398 (0.14)
	Rural	1,315,162 (18.9)	29,654 (2.3)	507 (0.04)
	Unknown	232,130 (3.3)	6,302 (2.7)	160 (0.07)
NHS region, n (%)	London	1,259,823 (18.1)	56,570 (4.5)	3,679 (0.29)
	South	2,601,848 (37.3)	65,714 (2.5)	1,813 (0.07)
	North	1,853,917 (26.6)	42,235 (2.3)	1,553 (0.08)
	Midlands & East	1,259,531 (18.1)	28,120 (2.2)	1,020 (0.08)
IMD quintile[b], n (%)	First	1,257,585 (18.0)	47,118 (3.7)	2,986 (0.24)
	Second	1,265,469 (18.1)	38,118 (3.0)	2,022 (0.16)
	Third	1,292,007 (18.5)	31,858 (2.5)	1,166 (0.09)
	Fourth	1,415,766 (20.3)	34,492 (2.4)	889 (0.06)
	Fifth	1,505,634 (21.6)	34,719 (2.3)	837 (0.06)
	Unknown	238,658 (3.4)	6,334 (2.7)	165 (0.07)
IDU, n (%)		9,261 (0.13)	1,077 (11.6)	124 (1.3)
Close HBV contact, n (%)		2,270 (0.03)	876 (38.6)	62 (2.7)
Imprisonment, n (%)		1,151 (0.02)	57 (5.0)	4 (0.35)
>1 BB/STI diagnosis, n (%)		187,242 (2.7)	8,708 (4.7)	277 (0.15)
	HCV, n (%)	2,785 (0.04)	258 (9.3)	182 (6.5)
	HIV, n (%)	111 (0.00)	4 (3.6)	5 (4.5)
	Syphilis, n (%)	1,750 (0.03)	179 (10.2)	37 (2.1)
	Scabies, n (%)	107,686 (1.5)	4,390 (4.1)	140 (0.13)
	Gonorrhoea, n (%)	1,282 (0.02)	77 (6.0)	2 (0.16)
	Trichomoniasis, n (%)	6,806 (0.10)	556 (8.2)	14 (0.21)
	Genital herpes, n (%)	36,630 (0.53)	2,043 (5.6)	38 (0.10)
	HPV, n (%)	37,357 (0.54)	1738 (4.7)	50 (0.13)

[a]Refers to the presence of a pregnancy record in the dataset; [b]IMD, first, most deprived to fifth, least deprived. HBsAg= Hepatitis B surface antigen; MSM= Men who have sex with men; IQR= Interquartile range; NHS= National health service; IMD= Index of multiple deprivation; IDU= Injecting drug use; HBV= Hepatitis B virus; BB/STI= Blood borne or sexually transmitted infection; HCV= Hepatitis C virus; HIV= Human immunodeficiency virus; HPV= Human papillomavirus.

Table 2. Univariate analysis of factors associated with a record of HBsAg seropositivity

Factor		HBsAg seropositivity		
		OR	95% CI	p
Gender	Men, non MSM	REF		<0.01
	Men, MSM	9.16	5.30-15.84	
	Women, pregnancy[a]	2.45	2.32-2.59	
	Women, no pregnancy[a]	0.52	0.51-0.57	
Age	per 5-year older	1.05	1.05-1.06	<0.01
Time at general practice	Per 5-year longer	0.82	0.81-0.83	<0.01
Ethnicity	White	REF		<0.01
	Asian	6.57	6.19-6.96	
	Black	13.93	13.13-14.78	
	Mixed	4.77	4.24-5.37	
	Other	6.01	5.37-6.71	
	Unknown	0.80	0.74-0.86	
NHS Region	London	REF		<0.01
	South	0.24	0.23-0.25	
	North	0.29	0.27-0.30	
	Midlands & East	0.28	0.26-0.30	
IMD Quintile[b]	First	REF		<0.01
	Second	0.67	0.64-0.71	
	Third	0.38	0.35-0.41	

	Fourth	0.26	0.24-0.28	
	Fifth	0.23	0.22-0.25	
	Unknown	0.29	0.25-0.34	
IDU	Yes vs No record	11.89	9.95-14.22	<0.01
Close HBV contact	Yes vs No record	24.43	18.97-31.48	<0.01
Imprisonment	Yes vs No record	3.01	1.13-8.05	<0.01
BB/STI diagnosis	≥1 vs No record	1.29	1.14-1.45	<0.01
HCV	Yes vs No record	61.77	53.07-71.91	<0.01
HIV	Yes vs No record	40.77	16.62-100.00	<0.01
Syphilis	Yes vs No record	18.74	13.5-25.97	<0.01
Scabies	Yes vs No record	1.78	1.05-3.01	0.03
Gonorrhoea	Yes vs No record	1.35	0.34-5.41	0.67
Trichomoniasis	Yes vs No record	1.13	0.95-1.33	0.16
Genital herpes	Yes vs No record	0.90	0.65-1.23	0.50
HPV	Yes vs No record	1.15	0.88-1.53	0.29

[a]Refers to the presence of a pregnancy record in the dataset; [b]IMD, first, most deprived to fifth, least deprived; HBsAg= Hepatitis B surface antigen; OR= Odds ratio; CI= Confidence interval; MSM= Men who have sex with men; NHS= National health service; IMD= Index of multiple deprivation; IDU= Injecting drug use; HBV= Hepatitis B virus; BB/STI= Blood borne or sexually transmitted infection; HCV= Hepatitis C virus; HIV= Human immunodeficiency virus; HPV= Human papillomavirus.

Table 3. Multivariable analysis of factors associated with a record of HBsAg seropositivity

Factor		Model 1			Model 2			Model 3			Model 4			Model 5		
		OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Gender	Men, non MSM	REF		<0.01	REF		<0.01	REF		<0.01	REF		<0.01	REF		<0.01
	Men,	6.83	3.91-11.9		7.26	4.17-		6.39	3.64-11.2		6.82	3.91-11.8		6.85	3.92-11.9	

	MSM		2		12.64		4		9		5			
	Women, no pregnancy [a]	0.56	0.53-0.59	0.56	0.53-0.59	0.56	0.53-0.59	0.56	0.53-0.59	0.56	0.53-0.59			
	Women, pregnancy [a]	2.23	2.12-2.35	2.25	2.13-2.38	2.24	2.12-2.37	2.24	2.12-2.37	2.24	2.12-2.37			
Age	per 5-year older	1.16	1.15-1.17	<0.01	1.16	1.15-1.16	<0.01	1.16	1.15-1.17	<0.01	1.16	1.15-1.17	<0.01	1.16	1.15-1.17	<0.01
Time at general practice	per 5-year longer	0.82	0.81-0.83	<0.01	0.82	0.81-0.84	<0.01	0.82	0.81-0.83	<0.01	0.82	0.81-0.83	<0.01	0.82	0.81-0.83	<0.01
Ethnicity	White	REF		<0.01	REF		<0.01	REF		<0.01	REF		<0.01	REF		<0.01
	Asian	5.54	5.20-5.89		5.58	5.24-5.94		5.52	5.19-5.88		5.51	5.18-5.87		5.52	5.18-5.88	
	Black	9.33	8.72-9.99		9.46	8.84-10.13		9.31	8.69-9.96		9.25	8.64-9.90		9.33	8.71-9.98	
	Mixed	4.77	4.22-5.38		4.79	4.24-5.41		4.76	4.22-5.37		4.75	4.21-5.35		4.77	4.22-5.38	
	Other	4.93	4.40-5.52		4.97	4.43-5.57		4.91	4.38-5.51		4.90	4.38-5.49		4.92	4.39-5.51	
	Unknown	1.09	1.00-1.17		1.08	1.00-1.17		1.08	1.00-1.17		1.08	1.00-1.17		1.08	1.00-1.17	
NHS Region	London	REF		<0.01	REF		<0.01	REF		<0.01	REF		<0.01	REF		<0.01
	South	0.74	0.69-0.79		0.74	0.69-0.79		0.74	0.69-0.79		0.74	0.69-0.79		0.74	0.69-0.79	
	North	0.70	0.66-0.75		0.68	0.64-0.73		0.70	0.66-0.75		0.70	0.66-0.75		0.70	0.66-0.75	
	Midlands & East	0.68	0.63-0.73		0.67	0.62-0.72		0.68	0.63-0.73		0.68	0.63-0.73		0.78	0.63-0.73	
IMD Quintile [b]	First	REF		<0.01	REF		<0.01	REF		<0.01	REF		<0.01	REF		<0.01
	Second	0.75	0.71-		0.76	0.71-		0.75	0.71-		0.75	0.71-		0.75	0.71-	

			0.80			0.80			0.80			0.80			0.80	
	Third	0.61	0.57-0.66		0.62	0.58-0.67		0.61	0.57-0.66		0.61	0.57-0.66		0.61	0.57-0.66	
	Fourth	0.53	0.49-0.57		0.53	0.49-0.58		0.52	0.48-0.57		0.53	0.49-0.57		0.53	0.48-0.57	
	Fifth	0.49	0.45-0.53		0.50	0.46-0.53		0.49	0.45-0.53		0.49	0.45-0.53		0.49	0.45-0.53	
	Unknown	0.57	0.48-0.66		0.55	0.47-0.64		0.57	0.48-0.66		0.57	0.48-0.66		0.57	0.48-0.66	
IDU	Yes vs no record	11.14	9.26-13.40	<0.01	5.31	4.30-6.55	<0.01	11.20	9.32-13.47	<0.01	11.21	9.32-13.48	<0.01	11.20	9.32-13.46	<0.01
Close HBV contact	Yes vs no record	12.27	9.44-15.95	<0.01	12.30	9.46-15.99	<0.01	12.25	9.42-15.92	<0.01	12.22	9.40-15.88	<0.01	12.25	9.42-15.92	<0.01
Imprisonment	Yes vs no record	1.71	0.63-4.61	0.29	0.54	0.20-1.51	0.24	1.72	0.64-4.65	0.29	1.71	0.63-4.64	0.29	1.71	0.63-4.62	0.29
BB/STI diagnosis[c]	≥1 vs no record	1.22	1.08-1.38	<0.01												
HCV	Yes vs no record				39.46	33.03-47.14	<0.01									
HIV	Yes vs no record							12.93	4.99-33.46	<0.01						
Syphilis	Yes vs no record										5.57	3.97-7.82	<0.01			
Scabies	Yes vs no record													1.17	0.99-1.39	0.06

[a]Refers to the presence of a pregnancy record in the dataset; [b]IMD, first, most deprived to fifth, least deprived; [c]Adjustments for a record of gonorrhoea, trichomoniasis, genital herpes, or HPV are shown in Supplementary Table 2. HBsAg= Hepatitis B surface antigen; OR= Odds ratio; CI= Confidence interval; MSM= Men who have sex with men; NHS= National health service; IMD= Index of multiple deprivation; IDU= Injecting drug use; HBV= Hepatitis B virus; BB/STI= Blood borne or sexually transmitted infection; HCV= Hepatitis C virus; HIV= Human immunodeficiency virus; HPV= Human papillomavirus.

Table 4. Univariate analysis of factors associated with a record of referral to specialist care among people with a record of HBsAg seropositivity

Factor		Specialist care referral		
		OR	95% CI	p
Gender	Female vs. male	0.8	0.7-0.9	<0.01
Age	per 5-year older	0.9	0.9-1.0	0.97
Time at general practice	per 5-year longer	0.9	0.9-1.0	0.93
Ethnicity	Non-white vs. white	0.9	0.9-1.1	0.70
NHS Region	London vs. other	1.2	1.1-1.3	<0.01
IMD Quintile[a]	First vs other	0.8	0.7-0.9	<0.01
MSM	Yes vs. no	0.6	0.1-2.5	0.44
IDU	Yes vs. no	0.8	0.5-1.3	0.34
Close HBV contact	Yes vs. no	1.2	0.7-2.0	0.61
Imprisonment	Yes vs. no	3.1	0.4-21.7	0.26
BB/STI diagnosis	≥1 vs. none	1.1	0.8-1.4	0.70

[a]IMD, First, most deprived. HBsAg= Hepatitis B surface antigen; OR= Odds ratio; CI= Confidence interval; NHS= National health service; IMD= Index of multiple deprivation; MSM= men who have sex with men; IDU= Injecting drug use; HBV= Hepatitis B virus; BB/STI= Blood borne/sexually transmitted infection.

Figure 1. Geospatial analysis of recorded HBsAg seropositivity by Local Authority District, normalised by the total number of persons recorded as being in each LAD within the cohort.