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Corresponding Author: Professor Graham Foster,

Corresponding Author's Institution: QMUL

First Author: Stuart Flanagan

Order of Authors: Stuart Flanagan; Jan Kunkell; Victoria Appleby; Sandra Eldridge; Sharif Ismail; Sulleman Moreea; Christopher Griffiths; Robert Walton; Martin Pitt; Andrew Salmon; Vichithranie Madurasinghe; Eleanor Barnes; Elizabeth Sims; Kosh Agarwal; Graham Foster

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Abstract: Background
The prevalence of chronic viral hepatitis is >2% in low and middle income countries but lower in high income countries. Migrants to high income countries are more likely than their hosts to be infected, and usually live in circumscribed areas. The best way to find and treat such people, both in high and low migrant density areas, is unknown.

Methods
HepFREE was an open cluster randomised controlled clinical trial in 90,250 subjects examining the hypothesis that incentivising and supporting primary care physicians increases screening rates for viral hepatitis in adult migrants in areas of high migrant density (Bradford, Yorkshire and London (North and South East)). Testing uptake rates were calculated on an intention-to-treat basis. In embedded sub-studies we examined whether bespoke invitation letters were beneficial and whether community care increased engagement. We conducted a parallel investigation of screening in a region of low migrant density (Oxford).

Findings
The intervention (incentivised general practitioners) increased screening from 1·7% in control practices with no additional support beyond a single training session to 19·5% in incentivised, supported practices (IRR = 3·7, p = 0·01) and was cost effective. A bespoke invitation letter did not increase uptake. Community care did not improve engagement, with > 85% participant attendance at both standard hospital and community care appointments. In a low migrant density area the screening rate by incentivised doctors was 7·5%. Overall the prevalence of chronic viral hepatitis in people identified in primary care as originating from a country with a high prevalence was 2% (1% HBV, 1% HCV) but only 32% of patients testing positive for hepatitis C antibodies were viraemic.

Interpretation
Screening migrants for viral hepatitis in primary care is effective if doctors are incentivised and supported. Community care is expensive and there is no evidence that this offers benefits in this setting or that bespoke invitation letters add value. The prevalence of patients with hepatitis C viraemia is lower than previously reported.

Funding and registration
NIHR Programme Grant, ISCRTN 54828633

A cluster randomised trial of case finding and therapy for chronic viral hepatitis in primary care (HepFREE).

Stuart Flanagan* MRCP
Jan Kunkel* MD
Victoria Appleby[1]* MRCP
Sandra E Eldridge[2] PhD
Sharif Ismail MFPH
Sulleman Moreea[1] FRCP
Christopher Griffiths[2] FRCP
Robert Walton[2] FRCP
Martin Pitt[3]PhD
Andrew Salmon[3] PhD
Vicithranie Madurasinghe[2]
Eleanor Barnes[4] FRCP
Elizabeth Simms[4] RGN
Kosh Agarwal[5] FRCP
Graham R Foster FRCP

*Joint first author

Barts Liver Centre, Blizard Institute, Queen Mary University of London
[1] Gastroenterology, Bradford Teaching Hospitals NHS Foundation Trust
[2]Blizard Institute, Queen Mary University of London
[3]University of Exeter
[4] Nuffield Department of Medicine and Oxford University NHS Trust
[5] Liver Unit, Kings College Hospital London

Correspondence to:-
Professor Graham R Foster
Barts Liver Centre
The Blizard Institute
4 Newark Street
London E1 4AT
g.r.foster@qmul.ac.uk

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Background

Chronic infection with the hepatitis B or hepatitis C virus (HBV, HCV - referred to as "viral hepatitis" henceforth) is common [1]particularly in low and middle income countries (LMICs) where materno-fetal transmission (HBV) and poorly sterilised medical equipment (HCV) have led to high prevalence with substantial morbidity (e.g. West Africa where HBV may affect up to 15% of the population[2] and Pakistan where HCV prevalence exceeds 20%[3] in some regions). In many high income countries (HICs) the prevalence of viral hepatitis is <1% and screening is encouraged only in those with a history of injecting drug use[4] , although many other groups are known to be infected. Effective therapy is available – all oral therapy for HCV clears the virus in >90% of those treated[5-7] and suppression of HBV replication with oral nucleosides prevents complications and reverses cirrhosis[8,9]. Given the mortality associated with untreated viral hepatitis and the benefits of therapy, the WHO recommends that testing and treatment should be increased to reduce their impact by 2030.

The prevalence of viral hepatitis in migrants is higher than among the general population in many HICs[10-12]. However, migrants may not prioritise viral hepatitis testing and treatment rates following community screening has been low[10]. It is unclear how best to screen and engage with at-risk migrants, and it is unknown whether those registered with primary care physicians can be identified, tested, and treated. Migrants are not evenly distributed and usually concentrate in inner city locations. It is unknown whether testing in areas of low migrant density is effective. HepFREE was designed to determine whether screening for chronic viral hepatitis in migrants living in England, by testing all registered migrants in GP surgeries in low and high prevalence areas, is feasible, effective, and cost effective. We compared testing in incentivised general practices with controls who received no support or incentives, evaluated the impact of an augmented invitation letter and compared treatment engagement in the community compared to hospital care. Cost effectiveness of the intervention was also assessed.

Methods

Study design and participants

HepFREE comprised a main randomised controlled trial of screening, two randomised embedded trials studying an augmented invitation letter and community care as well as a non-randomised sub-study. The main trial investigated the hypothesis that incentivising general practitioners (GPs) to test migrants (identified by electronic record searches) for viral hepatitis is superior to ad hoc testing and is cost effective when compared to unincentivised, unsupported control practices provided with a single training session. A cluster design minimised training and spill over-effects. Clusters consisted of all migrants registered at a practice (or a random subset of such patients) and interventions were delivered at cluster level in parallel interventions. Patients registered with the practice were not informed of the allocation but the practices were aware. Patients were not required to consent to participate in the main trial but gave informed written consent to be tested and have data collected.

The HepFREE main and the two embedded trials took place in Bradford, Yorkshire, South East and North East London, -areas of high migrant density. GPs were invited by letter to participate with a follow up phone call if no response was received. Seventy practices were contacted. In standard screening GPs were given a teaching session on viral hepatitis and asked to test all registered migrants. In enhanced screening GPs were paid a notional sum (£500) for setting up record searches , provided with a 'prompt to test' on eligible patients' electronic records, reimbursed £25 for each signed consent form, and supported by a dedicated clinician (trainee 5 years post qualification) who spent three days a week supporting practices). Costs were derived by negotiation with NIHR with reference to similar studies. Data from qualitative studies examining attitudes to viral hepatitis in migrants[13] were used to develop an enhanced invitation letter (see Appendix p1), validated in focus group sessions and sent to patients in practices cluster randomised to receive an enhanced letter in the main trial. Main trial patients cluster randomised to 'standard letter' practices were sent a standard invitation letter. Since patients are not normally contacted in this way this was not included in the control arm. The impact of the two different letters was assessed, patients tested within 31 days of the letters' dispatch were deemed to have responded to it.

We initially planned to test all eligible patients in each practice. However there were more eligible patients in each practice than estimated (500) due to practice mergers creating larger practices. To avoid over-recruitment and strain on resources a protocol modification 'capped' the number of patients to 500 at some practices whilst allowing others to recruit all eligible patients so that we could assess the feasibility of testing everyone. The pre-specified primary aims were a) to determine whether interventional screening is more cost-effective than control screening in detecting viral hepatitis in migrants in primary care, b) to determine the screening uptake in intervention practices compared to controls and c) to determine whether provision of an enhanced patient information invitation letter increased screening compared to a standard letter.

To examine engagement with diagnostic and therapeutic procedures we conducted a second, embedded, trial (patient flow shown in Appendix p4) to determine whether community based therapy is superior to conventional delivery of treatment (hospital based) as measured by engagement with management.

To determine whether screening migrants in an area of low immigrant density was effective we conducted a parallel observational, non-randomised sub-study with identical procedures and outcome measures in Oxford. Public Health England guidance to commissioners in 2017 indicated a prevalence of immigrants of Asian ethnicity of 34% in Newham, East London compared to 3·4% in Oxford. We selected Oxford as a region with a lower number of migrants than our other sites.

Eligible patients were > 18 years old, they or their parents were born in a country with prevalence of viral hepatitis >2% (World Health Organisation - listed in Protocol), and had no previous documented test for HBV and HCV. In the main study recruitment and testing ran from 31st October 2013 to 4th February 2017 with each practice recruiting over 18 consecutive calendar months. In Oxford, recruitment and testing took place over 18 calendar months between 22nd May 2015 and 16th April 2017. Eligible patients were identified by review of GP electronic records (EMIS or SystmOne) using a bespoke algorithm to identify coded ethnicity, language, country of birth and previous viral hepatitis testing and diagnosis. We did not distinguish foreign born from English born children of migrants For practices where the number of patients was 'capped', 500 patients from the eligible population were selected using the random number facility on the electronic records system. These patients formed the eligible cohort. For practices where no cap applied, all identified patients formed the eligible cohort. Patients who were not on the eligible list but who were tested as part of routine care

were excluded. At the end of the intervention period, in control and 'uncapped' practices the eligibility search was repeated and eligible patients who joined the practice during the study (present on final but not initial eligibility lists) were included as 'new registrants'. We had no data on patients who registered and left the practice within the 18 month study period.

Sample size calculation

We originally calculated sample size assuming 500 potential (i.e. high risk because of country of birth/ethnicity) patients per practice, on average. We assumed an intra-cluster correlation co-efficient of 0.05 for all outcomes and a coefficient of variation of cluster size of 0·65. The sample size is driven by the embedded treatment trial since this involves a smaller number of practices and patients. We assume that 40% of 500 patients will be screened and 3% will test positive - approximately 6 patients per practice. To detect a difference from 50% to 70% engaged with 90% power at the 5% significance level requires 134 patients in each arm without taking account of clustering. With clustering this increases to 185 patients, 31 clusters, in each arm of the embedded treatment trial. We increased this to 32 to allow for drop out. This would give us 32 practices in each arm for the enhanced vs standard invitation letter comparison giving us a 88% power to detect a 10% difference in testing rates (32% to 42%) between the two arms.

As practice recruitment progressed it was clear that the number of eligible patients in some practices could be 3 to 4 times (approximately 2000 eligible patients) more than anticipated. Following this realisation we agreed to cap the number of patients recruited in some practices to prevent overstretch of the study team. We allowed some practices (15) to approach all eligible participants to assess the feasibility of contacting all patients (estimated 2000). We revised our original calculations accordingly.

We continued to assume an intra-cluster correlation coefficient (ICC) of 0·05 for all outcomes, a coefficient of variation of cluster size of 0·65, and that 40% of eligible patients would be screened and 3% would test positive. This would give us 24 participants per practice from 15 practices screening 2000 eligible participants for the embedded treatment trial; once allowed for clustering the effective number of patients from these practices is 9 participants per practice, and 136 in total. This meant to detect a difference from 50% to 70% engaged with 90% power at the 5% significance level requires 132 further patients without accounting for clustering and 182 patients accounting for clustering. This is an additional 30 practices screening 500 eligible patients and a total of 45 practices.

For the main screening trial, with this number of practices in standard care/community care arms, and again using an ICC of 0·05, we require 6 practices in the control arm to detect an increase in screening from 15% to 40% with 90% power. We increased the number of practices needed to 56 overall to allow for drop outs.

We did not undertake a formal sample size calculation for the embedded trial comparing different intervention letters but with this sample size, we had sufficient power to detect a difference in screening rate of 19% to 36%. The ICC for our primary outcome in the main trial was 0·08, slightly higher than that assumed by the sample size calculation, but the baseline screening rate was much lower at 1·7% which considerably increased our power to detect a 20% difference in screening rates between intervention and control arms.

Intervention

Eligible patients were sent a letter inviting them to attend for viral hepatitis testing and patients were tested following an appointment made after responding or when they attended the practice for other reasons. Eligible patients had an electronic prompt attached to their records visible whenever they attended. Patients provided written consent via a Research Ethics Committee approved form to share their information prior to testing and details were recorded electronically in the GP records. Testing for viral hepatitis was performed when a bespoke request form was sent to local virology laboratories where standard tests for HBV and HCV were performed. A testing algorithm (Appendix p5) was deployed with re-tests for indeterminate results and patients were determined to have chronic hepatitis B (Hepatitis B surface antigen (HBsAg) positive or test positive for chronic hepatitis C antibody (anti-HCV)). The test result was provided to the GP practice for entry on the patient's records. Patients who

tested positive for anti-HCV were either automatically tested for viraemia (HCV RNA) (Bradford) or recalled for a further test for viraemia (London). Anonymised results were provided to the trial researchers to facilitate data checking. Data collection from practices was performed monthly by electronic data capture. After 18 months the intervention ceased.

Randomisation and blinding

Practices were randomly allocated to targeted or opportunistic ('controls') screening and within target screening to four groups (standard care, standard invitation letter; standard care, enhanced invitation letter; community care, standard invitation letter; community care, enhanced invitation letter) Thus there were five treatment arms, first stratified by area (Bradford, East and South London) and then minimised by number of eligible patients per practice. This method was used in preference to minimisation with a random element which has drawbacks when it is required to allocate different numbers of clusters to different trial groups as in this case. Practices were divided into three groups according to the number of eligible patients: <1600, 1600-3300, >3300. The randomisation was performed using an online minimisation system developed and hosted at the Pragmatic Clinical Trials Unit (PCTU), Queen Mary University of London.

The project co-ordinator e-mailed the details of GP practice(s) to be randomised directly to an independent PCTU statistician who used the randomisation software to allocate the practice and the project co-ordinator was then notified by e-mail of the allocation arm. The analysis team were blinded to the nature of the allocation arm. Patients who tested positive for viral hepatitis were not informed of the arm to which their practice was allocated until after they consented to enter the embedded trial of community versus standard care.

Embedded trial of community versus standard care

All patients who tested positive for viral hepatitis in the screening trial were eligible for enrolment in a second, embedded, trial comparing standard hospital-based care to community care. Interventional screening practices were cluster randomised to standard or community care. Following a diagnosis of viral hepatitis patients were referred to the local hospital when they were asked to consent to participate in a trial of standard or community care by a clinician blinded to practice allocation. Following consent patients were informed of the allocation of their practice and treated in the community at one of nine GP surgeries by a visiting hospital nurse/doctor (community care), or at hospital outpatients (standard care). Community care was delivered at GP surgeries that were not necessarily the surgery where the patient was normally seen. Patients who did not consent to community care or who were tested before community care was established were given standard care.

All patients were asked to complete a fibrosis evaluation (liver biopsy or fibroscan) and were offered NHS treatment. For active HBV infection therapy was interferon or nucleotide-based and for HCV this was interferon-based initially but latterly was with all oral therapy (initially for patients with genotype 1 and later genotype 3). Given the evolving complexity of management options we adopted pragmatic criteria for engagement based on attendance. Engagement with diagnostic and prognostic assessment was defined as completion of three events (diagnostic assessment, fibrosis assessment with fibroscan and/or ultrasound and clinical management according to local policy). For patients who were HCV antibody positive but HCV RNA negative attending a diagnostic visit on two occasions was deemed 'engaged'. Following engagement patients were asked to adhere to a treatment plan of either monitoring (inactive HBV or HCV not prioritised for therapy) or antiviral therapy. Adherence among monitored patients was defined as attending at least one visit within six months. Patients prescribed medication were deemed adherent if the clinical staff reported <20% of medication was unused at clinic review. A successful outcome was defined as sustained virologic response (SVR) 12 weeks after treatment completion (HCV) or a reduction in viral load to <80% of starting value within 12 weeks (HBV).

Outcomes and statistical analyses

The primary endpoints of the study were the proportion of potential participants tested in control GP practices compared to the proportion tested in intervention practices along with the proportion of patients tested within 31 days of receiving an invitation letter (standard compared to enhanced invitation). The third primary endpoint was the proportion of potential participants testing positive for viral hepatitis who engaged in therapy in the different treatment arms (community care vs hospital

based care). The secondary endpoints were the proportion of tested patients who were positive for viral hepatitis along with the number of new registrants who agreed to undergo testing for viral hepatitis and the proportion of viral hepatitis positive participants that complied with the clinical diagnostic and prognostic assessment in secondary care, along with the proportions who adhered to therapy and responded to treatment.

We calculated testing uptake rates on an intention-to-treat basis and used these to derive incidence rate ratios (IRRs) adjusted for site and number of eligible patients over the 18 month trial recruitment period. To determine whether a bespoke invitation letter improved testing we defined tested in response to the invitation letter as 'testing within 31 days of the letter's dispatch' and evaluated IRR. Testing rates were modelled using Poisson regression, with the number of patients tested in each practice as the dependent variable. The, number of eligible patients was fitted as the exposure variable, practice was fitted as a random effect and site and the number of eligible patients grouped into three categories (see previous) included as covariates. Generalised estimating equations (xtgee command in Stata) using logit link with exchangeable correlation matrix and robust standard errors were used to model engagement rates. Site, number of eligible patients category , age and sex were included as covariates. Model based ICCs were derived. If ICCs were found to be negative, the intervention effects from the analysis not adjusting for clustering are presented. Analysis was carried out using Stata version 14·1. A 5% significance level (two-sided) was used for all significance tests. We also calculated proportion who tested positive

In the embedded trial on treatment engagement among infected patients, we assessed engagement with the diagnostic and prognostic assessment.

For the economic evaluation, the incremental cost per quality-adjusted life year (QALY) of the HepFREE programme, compared with standard practice, was estimated using a modified decision tree /Markov model structure. Model structure and the simplifying assumptions used are outlined in Cost Effectiveness Supplementary data (See Appendix p12). Initial screening of patients was modelled using a decision tree structure which estimates the cost differential of the intervention compared with usual care as well as the modelled disease state of the patients with regard to long term follow up. Patient recruitment, clinical assessment and treatment costs were modelled using data from this project (Appendix p14-23). Patients in the usual care arm of the model were assumed to follow the same pathway as in the intervention arms. The number of positive cases reported in the control arm was used to estimate the year on year case finding of both arms of the model during long term follow up. In this phase patients are also assumed to present symptomatically with end stage liver disease. In the base case scenario, treatment regimen allocation was on an intention-to-treat-basis, modelling a combination of interferon and all-oral treatment regimes. Clinical outcomes for patients still undergoing treatment at trial end were imputed using published efficacy data. Modelled patients were followed over a lifetime horizon. Long term follow up of HBV cases was based on previous models and annual transition probabilities [13](CES4). The Markov model for HCV used transition probabilities from the Thein meta-regression of disease progression[14]. Post-transplant survival was estimated from UK transplantation service 2016 data. Costs of treatment were estimated from British National Formulary (Appendix p15) and did not include negotiated discounts. Scenarios with a range of discounts were modelled to allow an assessment of likely benefits for different prices. Costs of disease management were calculated from NHS national tariff bundles (Appendix p15). Quality of life data was based on Levy (HBV)[15] and Wright (HCV)[16] (Appendix p23) and discount rates of 3·5% were applied in line with guidance from the National Institute of Health Care Excellence. Sensitivity of the base case results to parameter variation was extensively tested by one-way parameter variation and probabilistic sensitivity analysis (PSA) using Monte Carlo simulation. Patient recruitment variability was assessed at the cluster level.

Registration, role of the funding source

This study was funded by a National Institute for Health Research Programme Grant. The funder played no part in the design, conduct or analysis of the study. The trial was registered with NIHR on their publically accessible database from contract start date 01/01/2012 - CPMS ID 14034. Ethics committee approval was confirmed on 24/12/2012 and patient recruitment started 07/02/2014 with ISTCRN registration (54828633) on 22/01/2015 before trial treatments commenced on 07/02/2015. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Seventy practices were approached and asked to participate and 63 general practices in three areas of high immigrant density agreed to participate. Five withdrew before contributing data and fifty eight were randomised - 50 intervention practices and eight controls. Fifteen intervention practices were asked to invite all eligible patients ('uncapped') and 35 were 'capped' to 500 eligible patients. Nine practices in Oxford took part in the parallel observational sub-study. Practice allocation and eligible patient numbers in each arm are detailed in Figure 1. Allocated groups were well matched in terms of practice and population characteristics (Table 1). There were slightly fewer patients from Pakistan amongst newly registered patients and capped practices. In Oxford the population differed from the other sites with fewer people from the Indian sub-continent.

Testing was uncommon in control practices 543 of 31,738 patients (1·7%) and was higher in intervention practices 11,386 of 58,512 patients (19·5%, IRR 3·7 (95% CI:1.3 to10.5), $p = 0·01$ – Table 2A). The difference was more marked in patients initially registered with the practice: 10,524 of 51,773 (20·3%) tested in intervention practices compared to 271 of 26,406 (1%) in controls (IRR 5·2, 95% CI: 1·9 to14·3, $p< 0·01$) whereas in newly registered patients 862 of 6,739 patients (12·8%) were tested in intervention practices compared to 272 of 5,692 (4·8%) (IRR 1·5, 95% CI:0·3-8·4, 01) in controls p=0·63).Characteristics of untested and tested patients are shown in Table 1 - testing was more common in people >40 years old compared to younger patients and this was noted in both initially registered and newly registered patients (5,905 of 20,840 people >40 years of age (28·0%) vs 4,619 of 30,993 young patients (14·9%) and 330 of 1,557 (21·2%) vs 532 of 5182 young patients (10·3%) respectively). Testing was most common in migrants from the Indian sub-continent, in particular Pakistan. In tested people in intervention practices 6,814 of 11,386 (59·9%) were from Pakistan whilst only 19,001 of 58,512 (32·5%) of those eligible for testing were of this ethnicity. Overall 6,814 of 19,001 (36·0%) of eligible patients from Pakistan were screened. People of Chinese or African origin were rarely tested. Testing in response to a letter from the practice showed that an enhanced invitation letter did not increase attendance (standard letter testing rates were 720 of 15,844 (4·5%) vs 1,032 of 28,095 (3·7%) with the enhanced letter, IRR = 0·7, 95% CI: 0·4 to 1·3, $p = 0·26$, Table 2B). Screening rates within 31 days of dispatch of the letter were reduced 1,752 of 43,939 (4%) when compared to overall testing rates 10,524 of 51,773 (20·3%). In the 9 practices from an area of low immigrant density, 515 of 6854 (7·5%) eligible patients were tested and a similar trend was observed with older patients from the Indian sub-continent being most likely to attend.

Table 3 shows the characteristics of the 238 of 11,929 (2%) of patients testing positive. In the 111 of 11,929 (0·93%) of patients who had antibodies against HCV only 36 of 111 (30% - 0·3% of the total) were viraemic. We noted an increase in positive tests in patients screened in control practices (17 of 543, 3·1%) compared to 220 of 11386 (1·9%) in intervention practices and a similar increase was noted in newly registered patients - 29 of 1134 (2·6%) compared to registered patients 271 of 10,795 (1·9%). In an area of low immigrant density 7 of 515 (1·4%) of patients were infected and all had HBV.

A total of 220 people had HBsAg or HCV antibodies detected in serum and were eligible to enrol in the second, embedded, trial to assess engagement and adherence. The CONSORT diagram and patient characteristics are described in Supplementary information (Appendix p6) which shows that the groups were well matched. The majority of infected patients (129) were allocated to 'community care', 91 to 'standard care'. There was no significant difference in engagement with the diagnostic and prognostic assessment between the two groups (80 of 91 (87·9%) patients in standard care engaged compared to 105 of 129 (81·4%) in community care – IRR 0·76, 95% CI: 0·2 to 2·5, $p = 0·65$) by strict ITT analysis of all patients who tested positive for viral hepatitis.

Of the 220 patients who tested positive for viral hepatitis in the intervention arms, 9 were known to services and 21 did not attend for a diagnostic assessment. Of the 190 patients who attended for a diagnostic assessment one patient died before completion of the tests and nine patients did not attend for all of the tests. Fifty two patients who were HCV antibody positive were not viraemic leaving 128 patients who engaged (Appendix p7). Ten patients did not attend for therapy and the outcomes in the 118 treated patients are shown in Appendix p8 (HBV) and p9 (HCV). Seventy eight patients declined to consent for the embedded study (the majority because they were unwilling to defer therapy until community care was available). The logistics of community therapy may thereby have reduced

engagement in this trial. Of the 13 HBV patients randomised to hospital care 12 (92%) complied with recommended management (observation in all) compared to 22 of 25 (88%) patients randomised to community care – one required therapy. In the 55 patients who declined to be randomised and were treated in the hospital setting 49 (89%) complied with the recommended regimen. Of the 35 patients HCV patients who were viraemic 8 were treated in the community care arm and all (100%) were adherent. Twenty-seven patients were treated in standard hospital settings (4 in the trial arm allocated to this setting and 23 by default). All (100%) were adherent. By strict per protocol analysis 89·7% of patients managed in the hospital setting complied with treatment compared to 88% in the community (Appendix p11). In the Oxford parallel study all HBV infected patients identified adhered to therapy in the hospital setting.

Of the 93 patients with HBsAg who completed a diagnostic assessment 2 (2%) had Delta virus infection, 5 were HBeAg positive and 7 (7%) had severe fibrosis or cirrhosis on liver biopsy. For the 45 patients with chronic HCV infection 40 (88%) had genotype 3 and 5 (11%) had cirrhosis. During the intervention phase one patient developed thyroiditis, no other trial related harms were noted during the study.

In the base case, the intervention was cost-effective at willingness to pay thresholds in excess of £8,540 per QALY (Appendix p23). Treatment with pure DAA regimes for HCV made the joint intervention cost-effective at willingness to pay (WTP) thresholds between £6,935 and £18,185 per QALY (Appendix p25-27) depending on pricing and the regime/treatment duration applied. Treatment of over 40s (mean age 50) was cost-effective at WTP thresholds in excess of £15,696 (CES8). Screening based on ethnic background was cost-effective for Pakistani ethnicity at WTP thresholds in excess of £9,523 per QALY (Appendix p29). The intervention was unlikely to be cost-effective for cohorts with mean age greater than 56. Results from the PSA indicated that the intervention is likely to be cost-effective in the vast majority of scenarios (Appendix p29), with a mean incremental cost-effectiveness ratio (ICER) of £5,292. This result is lower than the deterministic mean, in part because the probabilistic analysis adjusts for the poor screening performance of some larger GP practices. This issue appears to have predominantly affected practices where HBV was the more prevalent infection.

Discussion

We completed a large scale trial of testing for viral hepatitis in primary care in England. The strength of the study was the size of the cohort (over 90,000 patients) and the multiple GPs involved in four different locations alongside cluster randomisation to allow comparisons with and without the intervention. The very low rates of testing in control practices was unexpected and reduced the value of our power calculation but the observation that testing for viral hepatitis is miniscule without incentives will need to be considered in any viral hepatitis elimination programme. We compared testing in areas of high immigrant prevalence with an area of much lower prevalence but we accept that there may be other factors influencing testing in different regions. We included in the study a trial of a bespoke invitation letter which is, to our knowledge, the first large scale randomised study of tailored testing invitations in this setting. We undertook a second embedded trial of community care versus hospital care, the first such study in viral hepatitis with this group of patients. However the value of this study was reduced by the reluctance of patients to be randomised to community care.

Modelling and small scale studies have indicated that screening migrants for viral hepatitis is likely to be clinically and cost effective [17]. Such studies typically involve motivated clinicians and suggest that a large proportion of people will be tested and referred for therapy. A study in the Netherlands estimated that 39-75% of patients would be tested and referred[17]. Based on these studies many screening guidelines advocate testing migrants and in 2012 the English National Institute for Health and Care Excellence (NICE) issued guidance recommending testing of migrants for viral hepatitis in primary care settings [18]. The impact of these guidelines and the benefits of widespread testing have not been assessed. HepFREE was a large scale national trial to examine screening rates in migrants by primary care practitioners who were either encouraged to screen by providing an educational programme (controls) or incentivised to screen with funding and support. We find that testing for viral hepatitis was much less common than expected - very few people were tested in control practices and supported, incentivised GPs tested 20% of eligible patients, substantially lower than the testing rates used in

previous models. People from Pakistan were most likely to be tested, which may reflect the enthusiasm of primary care physicians in the sites with a high prevalence of such patients (chiefly Bradford) but in all sites testing in other ethnicities was poor. Older patients were more likely to attend for testing, perhaps reflecting more contact with primary care. We were surprised to find that a tailored letter was of little value with relatively few patients responding to a letter. This is a costly intervention and we suggest that this approach is not pursued. Engagement following diagnosis was excellent in patients treated in both hospital and community settings, and there is no evidence that expensive, community, care is beneficial, in contrast to other populations at risk of hepatitits, such as injection drug users, where community therapy may be advantageous [19]. Given the increase in testing and its cost effectiveness when general practitioners were incentivised to test migrants for viral hepatitis we suggest that this be introduced into future hepatitis elimination programmes. However the limitations of this strategy need to be considered as only a minority of patients attended. We suggest that further interventions, such as a targetted advertising campaign, be considered to increase testing further.

The prevalence of viral hepatitis was approximately 2% and in our study only 30% of patients with HCV antibodies were viraemic, substantially lower than previous reports [20]. This finding has implications for future hepatitis C elimination programmes - there may be fewer patients with treatment-requiring HCV than believed. Our previous community based screening studies in the same geographical areas[14] found a higher prevalence of viraemia and it is possible that older viraemic patients have either died, retired to their country of birth or sought treatment, perhaps outside the NHS using generic drugs widely available in Pakistan. Further work will be required in migrant communities at risk of infection to confirm these observations.

We attempted to conduct a randomised trial of community versus hospital-based care. However setting up treatment in the community proved challenging with complex logistics reducing the availability of easy access, community treatment. When patients were given the option of waiting for an opportunity to undergo treatment close to home or receive immediate care in the hospital they invariably opted for hospital treatment. On a per-protocol analysis it was clear that adherence to hospital based care was excellent and although our trial was technically unsatisfactory due to poor uptake of the intervention it seems likely that for this population community based care is not required. Although our study does not provide definitive evidence of equity in community and hospital settings the very high compliance rate in the hospital setting indicates that any benefits of community care will be hard to identify.

The cost effectiveness analysis indicates that the intervention is cost effective at current thresholds even when the listed drug price was used. Negotiations by NHSE and other health care payers have led to significant reductions in the price of antivirals for HCV and the expiration of the patents for the common HBV drugs has led to cost reductions. The intervention is therefore highly cost effective in current settings. Interestingly, cost effectiveness was less marked in the elderly – a result driven by the reduction of the time horizon needed to recoup the benefits. Joint screening for HBV and HCV coupled with lower than expected test costs meant that the intervention might be cost-effective at disease prevalence as low as 0.3%, however this result also benefitted from a high uptake of treatment and a low proportion of patients lost to follow up. Variation in disease management costs and utility of individual disease states did not significantly influence the result in terms of proximity to recognised WTP thresholds.

In summary we find that interventions to increase GP testing for chronic viral hepatitis in primary care settings are clinically and cost effective. The large scale nature of the trial persuades us that these findings are likely to be broadly applicable to migrant testing but we do not believe that the results can be extended to other populations, such as people who inject drugs. Given the WHO's challenging goal to reduce the burden of these infections screening migrant populations for these infections is likely to form an important part of campaigns to reduce the disease burden. However the finding that only 20% of patients attended for screening even with the interventions in this trial indicates that further measures will be required to eliminate viral hepatitis as a health care concern.

Declaration of interests

Professors Foster and Agarwal have received speaker and consultancy fees from companies that market drugs for the treatment of viral hepatitis, specifically AbbVie, Gilead and Merck. Professor Barnes is

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Author contributions

SF was clinical fellow for the final two years of the project. Contributed to data collection, analysis and co-authored the paper
JK was clinical fellow for two years – le the trial initiation and early data collection and analysis
VA contributed to co-ordinating the HepFree trial in one centre (Bradford), data collection.
SE contributed to oversight of design and analysis
SI set up the Oxford site and initiated the study in London. Involved in data collection and analysis and writing the manuscript
SM contributed to data collection and review of the manuscript
CG contributed to the study design, data collection, analysis and writing up of the MS
RW contributed to study design and oversight at the Oxford site
MP supervised and oversaw the cost effectiveness modelling and analysis. Contributed to the interpretation of the outputs of the cost effectiveness analysis and its implications in terms of the outputs as a whole
AS conducted the cost effectiveness analysis and authored the cost effectiveness section of the manuscript
VM provided recommendations for the trial protocol, wrote the analysis plan, and conducted the data analysis.
EB helped with the design and execution of the study and critically read the manuscript.
ES managed and led the Oxford sub-study, collected the data and helped write the manuscript
KA contributed to study design, data collection, analysis and writing of manuscript
GRF was the principal investigator who initiated and ran the study and guarantees the data

Legends to Figures

Figure 1
CONSORT diagram of the main HepFREE trial.
General practices from areas of high immigrant density (Bradford, NE and SE London) were randomised to act as controls or take part in interventional screening. Interventional screening practices were randomised to either standard or community care and a standard invitation or enhanced invitation letter, giving four possible allocations, as shown. In a parallel study in Oxford practices were asked to undertake interventional screening with standard care. Some practices (capped practices) had a limit on the number of patients who could be enrolled (N=500) and others attempted to test all patients. Patients registered with the practice (shown in standard text) as well as newly registered patients (shown *in brackets in italics labelled +xxx)* were offered screening and numbers screened are indicated. Patients who tested positive were eligible to enroll in a second trial to assess the value of community based treatment compared to hospital care.

Table 1
Demographics, gender, ethnicity (recorded by the general practice) and age is shown for the eligible population as well as those screened. Percentages are the percent of the total relevant population.

Table 2
Primary end-points of the HepFREE study.
2A shows IRRs for interventional vs standard screening and 2B shows screening rates in response to an invitation letter.

Table 3
Proportion of patients testing positive for HBV (HBsAg positive) or HCV (antibody and RNA detected by PCR testing).

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Figure

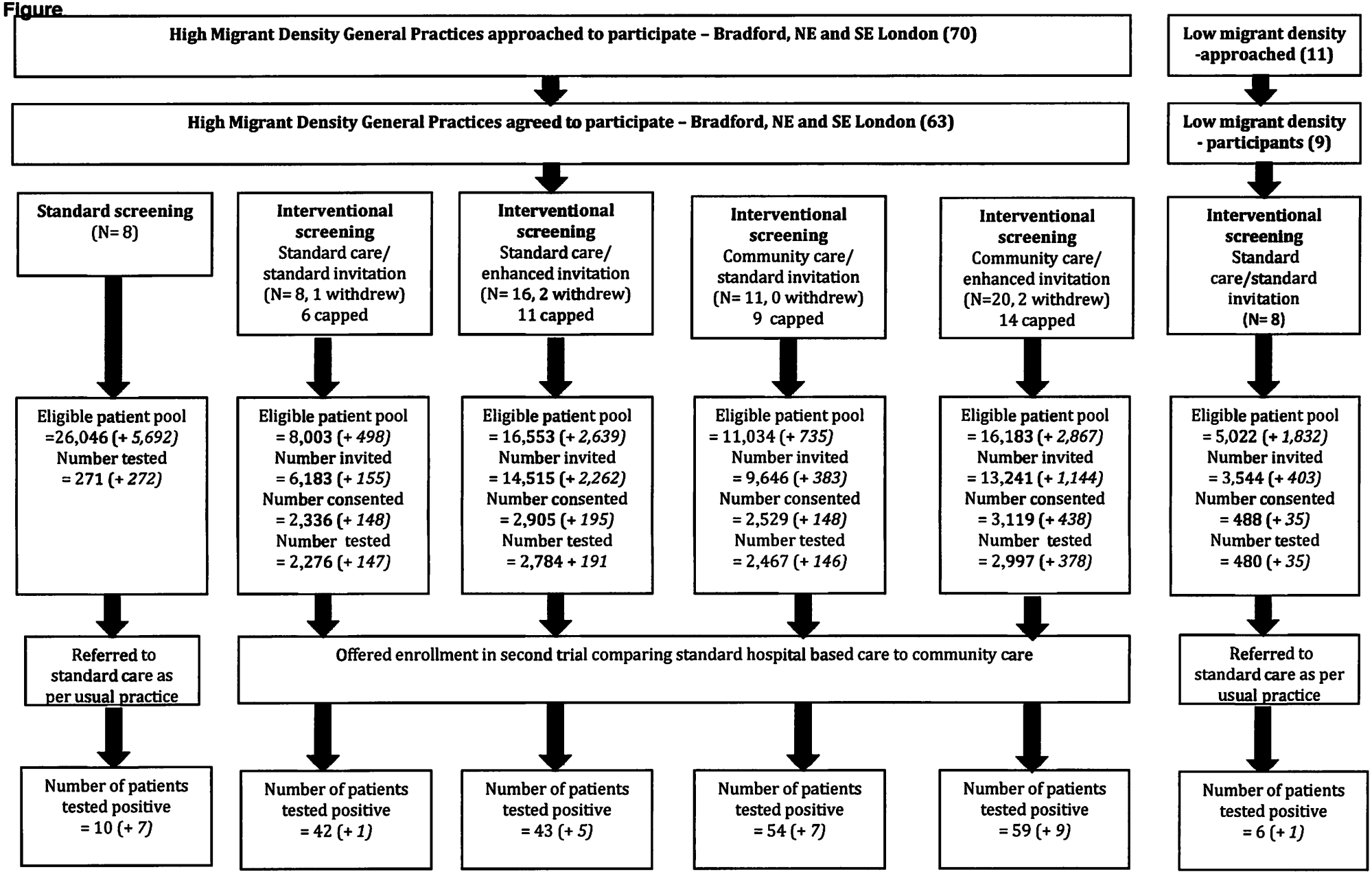
High Migrant Density General Practices approached to participate – Bradford, NE and SE London (70)
Low migrant density -approached (11)
High Migrant Density General Practices agreed to participate – Bradford, NE and SE London (63)
Low migrant density - participants (9)
Standard screening (N= 8)
Interventional screening Standard care/ standard invitation (N= 8, 1 withdrew) 6 capped
Interventional screening Standard care/ enhanced invitation (N= 16, 2 withdrew) 11 capped
Interventional screening Community care/ standard invitation (N= 11, 0 withdrew) 9 capped
Interventional screening Community care/ enhanced invitation (N=20, 2 withdrew) 14 capped
Interventional screening Standard care/standard invitation (N= 8)
Eligible patient pool =26,046 (+ 5,692) Number tested = 271 (+ 272)
Eligible patient pool = 8,003 (+ 498) Number invited = 6,183 (+ 155) Number consented = 2,336 (+ 148) Number tested = 2,276 (+ 147)
Eligible patient pool = 16,553 (+ 2,639) Number invited = 14,515 (+ 2,262) Number consented = 2,905 (+ 195) Number tested = 2,784 + 191
Eligible patient pool = 11,034 (+ 735) Number invited = 9,646 (+ 383) Number consented = 2,529 (+ 148) Number tested = 2,467 (+ 146)
Eligible patient pool = 16,183 (+ 2,867) Number invited = 13,241 (+ 1,144) Number consented = 3,119 (+ 438) Number tested = 2,997 (+ 378)
Eligible patient pool = 5,022 (+ 1,832) Number invited = 3,544 (+ 403) Number consented = 488 (+ 35) Number tested = 480 (+ 35)
Referred to standard care as per usual practice
Offered enrollment in second trial comparing standard hospital based care to community care
Referred to standard care as per usual practice
Number of patients tested positive = 10 (+ 7)
Number of patients tested positive = 42 (+ 1)
Number of patients tested positive = 43 (+ 5)
Number of patients tested positive = 54 (+ 7)
Number of patients tested positive = 59 (+ 9)
Number of patients tested positive = 6 (+ 1)

Table 1 –
Panels 1, 2 and 3 for assembly

	Control					
	Total		Registered		New registrants	
	Eligible	Screen	Eligible	Screen	Eligible	Screen
	31,738	543 (1·7%)	26,046	271 (1·0%)	5,692	272 (4·8%)
Female	16,549 (52·1%)	304 (56·0%)	13,351 (51·3%)	142 (52·4%)	3,198 (56·2%)	162 (59·6%)
Ethnicity						
Black	3,142 (9·9%)	112 (20·6%)	2,619 (10·1%)	67 (24·7%)	523 (9·2%)	45 (16·5%)
Bang·	3,289 (10·4%)	61 (11·2%)	2,837 (10·9%)	47 (17·3%)	452 (7·9%)	14 (5·1%)
Indian	4,269 (13·5%)	25 (4·6%)	3,506 (13·5%)	13 (4·8%)	763 (13·4%)	12 (4·4%)
Pak·	8,771 (27·6%)	38 (7·0%)	7,874 (30·2%)	24 (8·9%)	897 (15·8%)	14 (5·1%)
Other Asian	2,857 (9·0%)	55 (10·1%)	2,376 (9·1%)	28 (10·3%)	481 (8·5%)	27 (9·9%)
Eastern Cauc·	1,309 (4·1%)	9 (1·7%)	965 (3·7%)	1 (0·4%)	344 (6·0%)	8 (2·9%)
Other	8,101 (25·5%)	243 (44·8%)	5,869 (22·5%)	91 (33·6%)	2,232 (39·2%)	152 (55·9%)
Age						
18-19	882 (2·8%)	6 (1·1%)	882 (3·4%)	6 (2·2%)	0 (0·0%)	0 (0·0%)
20-29	9,523 (30·0%)	180 (33·1%)	7,107 (27·3%)	56 (20·7%)	2,416 (42·4%)	124 (45·6%)
30-39	10,023 (31·6%)	185 (34·1%)	8,035 (30·8%)	94 (34·7%)	1,988 (34·9%)	91 (33·5%)
40-49	5,413 (17·1%)	113 (20·8%)	4,681 (18·0%)	66 (24·4%)	732 (12·9%)	47 (17·3%)
50-59	2,846 (9·0%)	38 (7·0%)	2,550 (9·8%)	30 (11·1%)	296 (5·2%)	8 (2·9%)
60-69	1,602 (5·0%)	17 (3·1%)	1,472 (5·7%)	16 (5·9%)	130 (2·3%)	1 (0·4%)
>70	1,449 (4·6%)	4 (0·7%)	1319 (5·1%)	3 (1·1%)	130 (2·3%)	1 (0·4%)

Intervention High Immigrant Density														
Total		Standard letter		Enhanced letter		Registered		New registrants		Capped		Uncapped		
Eligible	Screen	Eligible	Screen	Eligible	Screen	Eligible	Screen	Eligible	Screen	Eligible	Screen	Eligible	Screen	
58,512	11386 (19·4%)	19,037	4743 (24·9%)	32,736	5781 (17·6%)	51,773	10,524 (20·3%)	6,739	862 (12·8%)	16,970	3173 (18·7%)	41,542	8213 (19·8%)	
30,187 (51·6%)	6,537 (57·4%)	9,524 (50·0%)	2,632 (55·5%)	17,024 (52·0%)	3,427 (59·3%)	26,548 (51·3%)	6,059 (57·6%)	3,639 (54·0%)	478 (55·5%)	8,608 (50·7%)	1,870 (58·9%)	21,579 (51·9%)	4,667 (56·8%)	
6,866 (11·7%)	545 (4·8%)	2,727 (14·3%)	209 (4·4%)	3,723 (11·4%)	328 (5·7%)	6,450 (12·5%)	537 (5·1%)	416 (6·2%)	8 (0·9%)	3,419 (20·1%)	372 (11·7%)	3,447 (8·3%)	173 (2·1%)	
3,357 (5·7%)	905 (8·0%)	1,480 (7·8%)	412 (8·7%)	1,668 (5·1%)	409 (7·1%)	3,148 (6·1%)	821 (7·8%)	209 (3·1%)	84 (9·7%)	1,835 (10·8%)	363 (11·4%)	1,522 (3·7%)	542 (6·6%)	
5,499 (9·4%)	1,148 (10·1%)	957 (5·0%)	254 (5·4%)	3,986 (12·2%)	770 (13·3%)	4,943 (9·5%)	1,024 (9·7%)	556 (8·3%)	124 (14·4%)	1,382 (8·1%)	306 (9·6%)	4,117 (9·9%)	842 (10·3%)	
19,001 (32·5%)	6,814 (59·9%)	7,215 (37·9%)	3,224 (68·0%)	10,482 (32·0%)	3,190 (55·2%)	17,697 (34·2%)	6,414 (61·0%)	1,304 (19·4%)	400 (46·4%)	3,920 (23·1%)	1,352 (42·6%)	15,081 (36·3%)	5,462 (66·5%)	
4,790 (8·2%)	350 (3·1%)	1,011 (5·3%)	93 (2·0%)	2,898 (8·9%)	231 (4·0%)	3,909 (7·6%)	324 (3·1%)	881 (13·1%)	26 (3·0%)	1,264 (7·4%)	139 (4·4%)	3,526 (8·5%)	211 (2·6%)	
3,126 (5·3%)	406 (3·6%)	501 (2·6%)	87 (1·8%)	1,930 (5·9%)	219 (3·8%)	2,431 (4·7%)	306 (2·9%)	695 (10·3%)	100 (11·6%)	642 (3·8%)	72 (2·3%)	2,484 (6·0%)	334 (4·1%)	
15,873 (27·1%)	1,218 (10·7%)	5,146 (27·0%)	464 (9·8%)	8,049 (24·6%)	634 (11·0%)	13,195 (25·5%)	1,098 (10·4%)	2,678 (39·7%)	120 (13·9%)	4,508 (26·6%)	569 (17·9%)	11,365 (27·4%)	649 (7·9%)	
1,619 (2·8%)	223 (2·0%)	686 (3·6%)	122 (2·6%)	933 (2·9%)	101 (1·7%)	1,619 (3·1%)	223 (2·1%)	0 (0·0%)	0 (0·0%)	352 (2·1%)	27 (0·9%)	1,267 (3·0%)	196 (2·4%)	
16,816 (28·7%)	2,029 (17·8%)	4,864 (25·6%)	823 (17·4%)	9,068 (27·7%)	942 (16·3%)	13,932 (26·9%)	1,765 (16·8%)	2,884 (42·8%)	264 (30·6%)	4,374 (25·8%)	448 (14·1%)	12,442 (30·0%)	1,581 (19·2%)	
17,680 (30·2%)	2,899 (25·5%)	5,391 (28·3%)	1,268 (26·7%)	9,991 (30·5%)	1,363 (23·6%)	15,382 (29·7%)	2,631 (25·0%)	2,298 (34·1%)	268 (31·1%)	4,922 (29·0%)	746 (23·5%)	12,758 (30·7%)	2,153 (26·2%)	
10,457 (17·9%)	2,606 (22·9%)	3,640 (19·1%)	1,054 (22·2%)	5,974 (18·2%)	1,397 (24·2%)	9,614 (18·6%)	2,451 (23·3%)	843 (12·5%)	155 (18·0%)	3,393 (20·0%)	754 (23·8%)	7,064 (17·0%)	1,852 (22·5%)	
5,967 (10·2%)	1,703 (15·0%)	2,196 (11·5%)	682 (14·4%)	3,365 (10·3%)	924 (16·0%)	5,561 (10·7%)	1,606 (15·3%)	406 (6·0%)	97 (11·3%)	1,992 (11·7%)	545 (17·2%)	3,975 (9·6%)	1,158 (14·1%)	
3,133 (5·4%)	1,130 (9·9%)	1,175 (6·2%)	470 (9·9%)	1,766 (5·4%)	612 (10·6%)	2,941 (5·7%)	1,082 (10·3%)	192 (2·8%)	48 (5·6%)	1,030 (6·1%)	389 (12·3%)	2,103 (5·1%)	741 (9·0%)	
2,840 (4·9%)	796 (7·0%)	1,085 (5·7%)	324 (6·8%)	1,639 (5·0%)	442 (7·6%)	2,724 (5·3%)	766 (7·3%)	116 (1·7%)	30 (3·5%)	907 (5·3%)	264 (8·3%)	1,933 (4·7%)	532 (6·5%)	

Oxford	
Eligible	Screen
6,854	515 (7·5%)
3,786 (55·2%)	316 (61·4%)
580 (8·5%)	48 (9·3%)
110 (1·6%)	11 (2·1%)
653 (9·5%)	54 (10·5%)
313 (4·6%)	20 (3·9%)
1,027 (15·0%)	105 (20·4%)
674 (9·8%)	43 (8·3%)
3,497 (51·0%)	234 (45·4%)
110 (1·6%)	2 (0·4%)
1,649 (24·1%)	49 (9·5%)
2,532 (36·9%)	167 (32·4%)
1,344 (19·6%)	134 (26·0%)
643 (9·4%)	76 (14·8%)
324 (4·7%)	53 (10·3%)
252 (3·7%)	34 (6·6%)

Table

Table 2A Incidence rate ratios for interventional versus standard screening for all participants and those registered at the start of the study

	Type of screening (number of practices)	Numbers screened		Incidence rate ratio* [95% confidence interval]	p – value
		Number	%		
All participants**	Standard (8) Interventional (50)	543 / 31,738 11,386 / 58,512	1·7% 19·5%	3·697 [1.301 to 10·507]	0·014
Participants present at start of study**	Standard (8) Interventional (50)	271 / 26,046 10,524 / 51,773	1·0% 20·3%	5·201 [1·887 to 14·34]	0·001

*adjusted for site and number of eligible patients
**Intracluster Correlation Coefficients, all participants = 0·028 (95% CI: 0·018 to 0·039)
**Intracluster Correlation Coefficients, participants present at start of study = 0·029 (95% CI: 0·018 to 0·039)
Screening rates were modelled using Poisson regression models. Dependent variable is number of patients screened in each GP practice. The number of eligible patients included as the exposure and practice as a random effect. The stratification factor - area and minimisation factor - number of eligible patients included as covariates in the model.

Table 2B: Screening rates: standard invitation vs enhanced invitation – analysis

Type of invitation	Numbers screened within 31 days of an invitation been sent		Incidence rate ratio* [95% confidence interval]	P - value
	Number	%		
Standard invitation *(number of practices = 18)*	720 / 15,844	4·5%		
Enhanced invitation *(number of practices = 32)*	1,032 / 28,095	3·7%	0·703 [0·378 to 1.306]	0·265

Intracluster Correlation Coefficients = 0·057 (95% CI: 0·035 to 0·078)

Table

Table 3

	Total				High Immigrant Density (Bradford, NE, SE london)							Oxford	
					Control			Intervention					
	Number tested	HBsAg	HCV abod +ve	HCV RNA +ve	Number tested	HBsAg +ve	HCV Abod +ve*	Number tested	HBsAg +ve	HCV Abod +ve	HCV RNA +ve	Number tested	HBsAg +ve
Total	11,929	127 (1·06%)	111 (0·93%)	36 (0·30%)	543	12 (2·21%)	5 (0·92%)	11,386	115 (1·01%)	106 (0·93%)	36 (0·32%)	515	7 (1·36%)
Gender													
Female	6,841	41 (0·6%)	63 (0·92%)	20 (0·29%)	304	4 (1·32%)	5 (1·64%)	6,537	37 (0·57%)	58 (0·89%)	20 (0·31%)	316	2 (0·63%)
Male	5,087	86 (1·69%)	48 (0·94%)	16 (0·31%)	239	8 (3·35%)	0	4,848	78 (1·68%)	48 (0·99%)	16 (0·33%)	199	5 (2·51%)
Ethnicity													
Black	657	9 (1·37%)	2 (0·3%)	0	112	2 (1·79%)	1 (0·89%)	545	7 (1·28%)	1 (0·18%)	0	48	1 (2·08%)
Bangladesh	966	10 (1·04%)	3 (0·31%)	0	61	2 (3·28%)	0	905	8 (0·88%)	3 (0·33%)	0	11	0
Indian	1,173	7 (0·60%)	4 (0·34%)	2 (0·17%)	25	0	0	1,148	7 (0·71%)	4 (0·35%)	2 (0·17%)	54	1 (1·85%)
Pakistan	6,852	53 (0·77%)	89 (1·3%)	32 (0·47%)	38	2 (5·26%)	2 (5·26%)	6,814	51 (0·75%)	87 (1·28%)	32 (0·47%)	20	0
Other Asian	405	11 (2·72%)	1 (0·25%)	0	55	1 (1·82%)	1 (1·82%)	350	10 (2·86%)	0	0	105	2 (1·90%)
Eastern Cauc·	415	8 (1·93%)	4 (0·96%)	2 (0·48%)	9	1 (11·11%)	0	406	7 (1·72%)	4 (0·99%)	2 (0·49%)	43	1 (2·33%)
Other	1,461	29 (1·98%)	8 (0·55%)	0	243	4 (1·65%)	1 (0·41%)	1,218	25 (2·05%)	7 (0·57%)	0	234	2 (0·85%)
Age													
18-19	229	0	0	0	6	0	0	223	0	0	0	2	0
20-29	2,209	18 (1·81%)	8 (0·36%)	5 (0·23%)	180	3 (1·67%)	1 (0·56%)	2,029	15 (0·74%)	7 (0·34%)	5 (0·25%)	49	1 (2·04%)
30-39	3,084	34 (1·10%)	35 (1·13%)	16 (0·52%)	185	8 (4·32%)	1 (0·54%)	2,899	26 (0·90%)	34 (1·17%)	16 (0·55%)	167	0
40-49	2,719	32 (1·18%)	34 (1·25%)	7 (0·26%)	113	0	2 (1·77%)	2,606	32 (1·23%)	32 (1·23%)	7 (0·27%)	134	3 (2·24%)
50-59	1,741	20 (1·15%)	19 (1·09%)	5 (0·29%)	38	1 (2·63%)	1 (2·63%)	1,703	19 (1·12%)	18 (1·06%)	5 (0·29%)	76	1 (1·32%)
60-69	1,147	17 (1·48%)	8 (0·70%)	1 (0·09%)	17	0	0	1,130	17 (1·50%)	8 (0·71%)	1 (0·09%)	53	2 (3·77%)
>70	800	6 (0·75%)	7 (0·88%)	2 (0·25%)	4	0	0	796	6 (0·75%)	7 (0·88%)	2 (0·25%)	34	0

* all patients were HCV RNA undetected