Title

High prevalence of latent tuberculosis and blood borne virus infection in a UK homeless population

Robert W Aldridge, Academic Clinical Lecturer[1,2], Andrew C Hayward, Professor of Inclusion Health[1,2*], Sara Hemming, Research Nurse[1,2,5], Susan Yates, Research Nurse[1,2,5], Gloria Ferenando, Research Nurse[1,2,5], Lucia Possas, Research Assistant[1,2,5], Elizabeth Garber, Programme Manager[1,2,5], John M Watson, Visiting Professor[1], Anna Maria Geretti, Professor of Virology & Infectious Diseases[3], Timothy D McHugh, Professor of Medical Microbiology[4], Marc Lipman, Senior Clinical Lecturer and Consultant in Respiratory Medicine[5,6], Alistair Story, Clinical Lead and Manager for Find&Treat[7]

1. Centre for Public Health Data Science, Institute of Health Informatics, University College London, London, NW1 2DA. UK.
2. The Farr Institute of Health Informatics Research, London, NW1 2DA. UK.
3. Institute of Infection & Global Health, University of Liverpool, Liverpool, L69 7BE. UK.
4. Centre for Clinical Microbiology, Division of Infection and Immunity, University College London, NW3 2QG. UK.
5. Royal Free London NHS Foundation Trust, London, NW3 2QG. UK.
6. UCL Respiratory, Division of Medicine, University College London, London, NW3 2QG. UK.
7. University College London Hospitals, London, NW1 2BU. UK.

*Corresponding Author

Professor Andrew Hayward
Professor of Inclusion Health
Research Department of Infectious Disease Informatics
Farr Institute of Health Informatics Research
University College London
222 Euston Road
London NW1 2DA
Email: a.hayward@ucl.ac.uk
Telephone: +44 20 3549 5489

Word Count: 3341
Key Words: Tuberculosis, latent tuberculosis, HIV, hepatitis B, hepatitis C, homeless

Abstract

Introduction: Urban homeless populations in the UK have been shown to have high rates of active tuberculosis, but less is known about the prevalence of latent tuberculosis infection (LTBI). This study aimed to estimate the prevalence of LTBI among individuals using homeless hostels in London.

Methods: We performed a cross-sectional survey with outcome follow-up in homeless hostels in London. Our primary outcome was prevalence of LTBI. Secondary outcomes were prevalence of hepatitis B, hepatitis C or HIV infections, and outcomes in those referred to healthcare services. Recruitment for the study took place between May 2011 and June 2013. To estimate an LTBI prevalence of 10% with 95% confidence intervals between 8 and 13% we required 500 participants.

Results: 491/804 (61.1%) individuals agreed to be screened. The prevalence of LTBI was 16.5% (81/491; 95%CI:13.2-19.8). In UK-born individuals, a history of incarceration was associated with increased risk of LTBI (odds ratio 3.49; 95%CI:1.10-11.04; p=0.018) after adjusting for age, length of time spent homeless, and illicit drug use. Of the three subjects who met English treatment guidelines for LTBI at the time of the study, none engaged with services after referral for treatment. Prevalence of past hepatitis B infection was 10.4% (51/489; 95%CI:7.7-13.1) and 59.5% (291/489; 95%CI:55.1-63.9) of individuals were non-immune. Prevalence of current hepatitis C infection was 10.4% (51/489; 95%CI:7.8, 13.1).

Conclusions: This study demonstrates the high prevalence of LTBI in homeless people in London, and the associated poor engagement with care. There is a large unmet need for LTBI and hepatitis C infection treatment, and hepatitis B vaccination, in this group.

What is the key question?

What is the prevalence of latent tuberculosis infection (LTBI) and blood borne viral infections among homeless people in London, and what are the outcomes in those referred to healthcare services.

What is the bottom line?

People experiencing homelessness in London have a very high prevalence of LTBI, hepatitis B and hepatitis C infection and co-infection, compounded by poor engagement with care.

Why read on?

We report for the first time on the burden of LTBI and blood borne viruses among homeless people in a metropolitan UK setting. The findings highlight the need to ensure recent improvements in diagnostics and therapeutic can benefit the most vulnerable and excluded populations.

140 character twitter conclusion:

London researchers highlight need for improved access to testing and treatment for tuberculosis infection and viral hepatitis among homeless people.

Introduction

Homeless individuals have high rates of active pulmonary tuberculosis and often present late to healthcare services.[1] Latent tuberculosis infection (LTBI) has been shown to be common in homeless populations in low burden countries[2,3], though limited data are available in the UK.

Homelessness and tuberculosis in homelessness populations are both increasingly significnant problems in London. Using data collected in a multi-agency database about rough sleepers and the wider street population (CHAIN) it is estimated that approximately 8,000 people sleep rough annually in London.[4] This number has doubled from just under 4,000 in 2010, whilst at the same time there has been has been an annual reduction in the number of homeless hostel beds for single people and couples without dependents across England of 43,655 in 2010 to 35,727 in 2016.[5]. In 2014 it was estimated that 3.6% (89/2,498) of cases with social risk factor information available had a history of tuberculosis.[6] A study undertaken to estimate the point prevalence of active tuberculosis estimated that the overall prevalence was 27 per 100 000 and was 788 per 100 000 in homeless people.[1]

Developments in testing and treatment for LTBI and blood borne viruses (BBV) provide new opportunities for effective diagnosis and management.[7,8] Despite these advances, concerns remain about LTBI treatment in this homeless population due to poor treatment adherence and the potential for severe hepatotoxicity exacerbated by high rates of alcohol- or viral related liver disease.[9] It is also important to determine the current ability of health services to successfully treat those homeless people identified with a given infection before a systematic screening and treatment programme is implemented.

Due to uncertainty regarding the prevalence of LTBI and BBVs in homeless populations, doubts remain about the effectiveness and cost-effectiveness of a targeted LTBI and BBV screening strategy in this group. We therefore undertook a cross-sectional survey to estimate the prevalence of LTBI and BBVs among individuals in homeless hostels in London, a group which is broadly representative of the homeless population of the UK. We also examined outcomes of referral to healthcare services after 12 months.

Methods

Study population

We performed a cross sectional survey testing for LTBI, hepatitis B, hepatitis C and HIV in residents of homeless hostels in London. The study was conducted alongside the Find and Treat (F&T) service run by the National Health Service. F&T identifies cases of active tuberculosis using digital chest radiography and supports patients to

complete treatment.[20] Recruitment for the study took place between May 2011 and June 2013 and convenience sampling was used as individuals were screened within the F&T programme. Individuals were eligible to participate in the study if they were over 18, resident at a homeless hostel on the day of F&T screening, had a tuberculosis screening chest radiograph by F&T (or elsewhere within the last 6 months that could be proven), and were able to provide written informed consent.

Socio-demographic and risk factor data including self-reported age, sex, history of imprisonment, history of drug and alcohol use, history of homelessness, and country of birth were collected by dedicated research team using a paper-based questionnaire. The questionnaire was piloted and improved with help from homeless hostel users at the start of the study.

Referral to NHS services

In line with NICE guidance, up to March 2012, individuals diagnosed with LTBI were offered advice about tuberculosis symptoms and those co-infected with HIV were referred to local health services.[21] After March 2012, all individuals diagnosed with LTBI that were under the age of 35 years were to be referred to local health services, reflecting new NICE guidance for identifying and managing tuberculosis among hard-to-reach groups.[22] Individuals with current hepatitis B or hepatitis C infection and previously undiagnosed HIV infection were referred to 14 local health services and the outcomes were collected 12 months after referral by the research team phoning and speaking to clinicians and nurses to whom the patients were referred.

The study received approval from the East of England – Essex National Research Ethics Service Committee (number 10/H0302/5).

Laboratory testing

Whole venous blood samples were collected to test for LTBI and BBVs. LTBI was measured using the QuantiFERON-TB Gold gamma interferon release assay (Cellestis, Australia) following the manufacturer's instructions for interpretation (Table 1).

Hepatitis B surface antigen (HBsAg), core total antibody (anti-HBc), surface antibody (anti-HBs) were detected by the Architect immunoassay (Abbott Diagnostics, Germany). Hepatitis B infection was classed as current in subjects that tested positive for HBsAg at screening with confirmation by HBsAg neutralisation. Hepatitis B was classified as confirmed past in those who were HBsAg negative, anti-HBc positive and anti-HBs positive and probable past in those who were HBsAg negative, anti-HBc positive and anti-HBs negative. For all analyses we combine these two groups of confirmed and probable past into one group of past hepatitis B infection and we refer to them as such throughout the rest of the paper. Non-immune hepatitis B status was defined by absence of all hepatitis B markers.

Anti-HCV antibody was detected by the Vitros chemiluminescence assay (Ortho Clinical Diagnostics). Hepatitis C RNA was measured by either an real-time PCR assay based on the method described by Komurian-Pradel et al. [23], or the Abbott M2000 Real-Time hepatitis C assay.[24][23][22][21] Samples reactive for anti-HCV but with undetectable hepatitis C RNA underwent anti-HCV confirmation by the Recombinant Immuno Blot Assay (RIBA, Chiron) or the Line Immunoassay (Inno-Lia, Innogenetics). Hepatitis C infection was classed as current in anti-HCV positive subjects who tested hepatitis C RNA positive, and past in those who showed undetectable hepatitis C RNA with confirmed anti-HCV positivity (Table 1). HIV screening was performed by the Architect combined HIV antibody/p24 antigen chemiluminiscence assay (Abbott Diagnostics).

Analysis

The primary outcome for the study was the proportion of subjects with a positive QuantiFERON-TB Gold assay result. Based on studies in marginalised populations in the United States[2,3,25], we expected a minimum of 10% of participants to test positive for LTBI. To measure this within 95% confidence intervals between 8 and 13%, we required 500 participants. Secondary outcomes were hepatitis B, hepatitis C, and HIV status, and outcomes in those referred to healthcare services for all infections. Data from the paper questionnaires were entered onto a Microsoft Access database created for the study. Categorisation of categorical variables, methods of assessment and treatment of missing data are presented in a supplementary Appendix. A descriptive analysis of baseline variables and their association with primary and secondary outcomes was performed. We considered age, *a priori,* as a confounding variable for LTBI. History of imprisonment, history of drug and alcohol use, history of homelessness and country of birth were considered as exposure variables and a logistic regression model was used to examine the evidence for these as risk factors for LTBI. Data were analysed in Stata version 14.

Results

Study population

After accessing the F&T mobile screening service, 804 individuals were approached by research staff and invited to participate in the study. A total of 542/804 (67.4%) individuals consented to take part (Figure 1). 51 (9.4%) individuals were subsequently excluded, mainly due to a lack of venous access for blood sampling (n=31). A total of 491 individuals were therefore included in the analysis. A majority of participants (437/491, 89.0%) were men aged between 30 and 49 (257/491, 52.3%), born in the UK (305/491, 62.1%) and current tobacco smokers (394/491, 80.2%). Most (443/491, 90.2%) reported to have been homeless for one or more years. Just over half (263/481, 54.7%) had spent time in prison. Drug use was common with 107/491 (21.8%) ever having smoked heroin or crack cocaine and 86/491 (17.5%) ever having injected either crack cocaine or heroin. A large number of individuals (202/477, 42.3%)

had ever been concerned about their drinking, or had had a health worker express concern about their alcohol consumption. Results of testing are shown in Tables 1 and 2 and in Figures 2 and 3.

Latent tuberculosis infection

The overall prevalence of LTBI was estimated at 81/491 (16.5%; 95% CI 13.2, 19.8). Prevalence was higher in those born outside of the UK (52/186, 28.0%; 95% CI 21.4, 34.4) relative to those born in the UK (29/305, 9.5%; 95% CI 6.2, 12.8), but both were substantially higher than the 1.6% (95% CI 0.2, 5.7) prevalence found in inflammatory bowel disease patients screened for LTBI before initiation of anti-TNFα therapy in the UK (Figure 2).[26] A multivariable analysis was conducted to identify risk factors for LTBI in those individuals born in the UK. There was evidence that a history of imprisonment was associated with an increased risk of LTBI (OR 3.49; 95% CI 1.10, 11.04; p=0.018) after adjusting for age, length of time spent homeless, and any illicit drug use (Table 3).

Blood borne viruses

Current Hepatitis B as confirmed by HBsAg neutralisation was 7/489 (1.4%; 95% CI 0.4, 2.5). A large proportion of participants (51/489, 10.4%; 95% CI 7.7, 13.1) had evidence of past hepatitis B infection. The number of individuals who were non-immune to hepatitis B was 291/489 (59.5%; 95% CI 55.1, 63.9), and was lower for those who had ever injected drugs (23/85, 27.1%; 95% CI 17.4, 36.7; Figure 3). The majority of individuals that tested non-immune to hepatitis B (226/291, 77.7%) did not recall whether they had been previously vaccinated and 29/291 (10.0%) reported never having received vaccination. 120(41.2%; 120/291) had spent time in a UK prison. Only four non-immune individuals reported being vaccinated against hepatitis B more than once.

Among a total of 64/491 (13.0%; 95% CI 10.0, 16.0) subjects with anti-HCV seropositivity, 51 (10.4%; 95% CI 7.8, 13.1) tested positive for hepatitis C RNA indicating current infection. The remaining 13 subjects (2.7%; 95% CI 1.2, 4.1) showed confirmed anti-HCV reactivity in the absence of hepatitis C RNA, indicating a resolved infection. The number of individuals with past or current hepatitis C was higher in those who had ever injected drugs (46/86, 53.4%; 95% CI 42.4, 64.3). However, those with no injecting drug history (12/405, 3.0; 95% CI 1.3, 4.6) had higher levels than the general population estimates in the UK (0.4%).[27] The highest risk of hepatitis C was found in those individuals who had been injecting drugs for more than 10 years (Figure 4), but there was already an increase in prevalence when comparing injecting for 2-9 years vs. 1 year or less. In those diagnosed with LTBI, the frequency of co-infection with either hepatitis B or hepatitis C (past or current) was 37.0% (95% CI 26.3, 47.8) and co-infection with both hepatitis B and hepatitis C (past or current) was 16.2% (95% CI 9.7, 24.7).

Prevalence of HIV seropositivity was 1.02% (95% CI 0.1, 1.9), all cases were due to HIV-1 and all subjects were previously aware of their diagnosis.

Clinical management and outcome

A total of 81 individuals had a positive LTBI test result, none of whom were co-infected with HIV. Three individuals that were diagnosed with LTBI after March 2012 and the introduction of updated NICE treatment guidelines, were referred to local health services for chemoprophylaxis (Table 4). One subject declined referral, and at twelve months follow up, the remaining two had disengaged with services and had not started treatment.

Among subjects with a current hepatitis B infection, all 7 accepted a referral; 6 of 7 were seen at least once in specialist services, none of whom was deemed to require immediate antiviral therapy over 12 months following diagnosis.

Among the subjects with current hepatitis C infection, 49/51 (96.1%) subjects accepted a referral to specialist services. Two patients initiated interferon-based treatment (3.9%; 2/51) with one having completed treatment and one still on treatment at 12 months follow up. A further 19 (37.3%; 19/51) subjects were seen at least once over 12 months of follow-up and remained under review in the absence of treatment; 28 (54.9%; 28/51) individuals were lost to follow up after referral.

Discussion

This study demonstrates a burden of latent tuberculosis and blood borne virus infections in a London homeless population at levels that are substantially higher than the general population. Although, we found that the greatest risk of LTBI was in those born outside the UK, around 10% of UK-born homeless adults were infected. UK born individuals with a history of imprisonment had more than three times the risk of LTBI compared to other UK born participants. During the study, referral rates for treatment for latent tuberculosis infection were low due to the criteria in operation at the time. Under new 2016 NICE guidelines[19] all those with a positive test under the age of 65 would be referred for treatment. Therefore, instead of three people (4%; 3/81) being referred, 76 (93.8%; 76/81) would now be eligible for treatment.

Significantly higher levels of current and past hepatitis B were seen in this study compared to the general population (1.4% and 10.4% respectively). A history of hepatitis B vaccination was higher in those reporting a history of injecting drug use, possibly as a result of targeted vaccination in this population, but there remained a substantial proportion of this homeless population who were non-immune and who would benefit from vaccination. The levels of hepatitis B are particularly important to address in this population given the risk of onward transmission due to poor living conditions and low immunisation levels. No patients were initiated on treatment,

however, this is not necessarily unexpected given the prolonged clinical assessment (typically 2-3 appointments spaced out by a few months) required before treatment initiation for hepatitis B.

At 13%, the prevalence of hepatitis C infection was high. This was substantially increased in participants reporting injecting drug use, but even those without such a history had higher levels than the general population. Engagement with health services was poor in those diagnosed with current hepatitis C infection, with just over half of those referred either not attending appointments or being lost to follow up. In only a minority of those referred was antiviral therapy initiated within 12 months. Until recently, hepatitis C care in general has been characterised by a small number of treatment initiations relative to the number of people needing and accessing care.[27] The introduction of interferon-free regimens of short duration (typically 12 weeks) has the potential to improve engagement with care in this vulnerable population but the impact remains to be formally investigated. In individuals diagnosed with LTBI, co-infection with either hepatitis B or C (past or current) was high at 37.0%, as was co-infection with both hepatitis B and C at 16.2%. The implications of this for LTBI treatment and risk of hepatotoxicity need to be carefully considered.

There were several strengths to our study including the sample size achieved in a population that is typically described as “hard-to-reach”. We managed to recruit a large number of participants as a result of long established links with homeless services (through F&T). The questionnaires used for the collection of self-reported risk factor data were developed and piloted with the target population, and were improved on the basis of feedback.

Due to the nature of the population and the fact that this study was conducted alongside a busy NHS clinical service, we were not able to use a formal sampling framework for the recruitment of patients, and so utilised convenience sampling. The requirement for individuals to be able to consent meant that our results do not include individuals who were intoxicated (by drugs or alcohol); and therefore is likely to under-represent those at highest risk of blood borne virus infection.

Although it was not possible to collect data on individuals unable to consent or who were approached for screening and refused to take up the offer, the homeless population taking part in this study included a high proportion of previous rough sleepers and people with either current or previous high risk drug and harmful and hazardous alcohol use. Males are overrepresented among homeless hostel residents and the population sampled are broadly demographically comparable to homeless populations nationally according to F&T data collected from extensive screening outside London and Homeless Link’s health needs audit.[28]

We are not aware of other published data estimating the prevalence of LTBI in a large representative homeless population in the UK. Previous studies in other high income countries (including Italy, Japan, South Korea and USA) have reported LTBI

prevalence in homeless populations and found rates varying from 16% to 75.9%.[3,29–32] Comparability with our findings is complicated by highly heterogeneous populations, differences between studies, including definition of homelessness used, eligibility criteria, uptake, and the test used to diagnose latent tuberculosis.

A recent systematic review and meta-analysis of active tuberculosis and blood borne viruses in homeless populations internationally found the prevalence of hepatitis C virus infection ranged from 3·9% to 36·2%, and for HIV from 0·3% to 21·1%.[33] None of the studies testing for HIV were conducted in the UK, but one hepatitis C study, which recruited homeless individuals from shelters, special projects, and medical centres in Oxford, found 26.5% of individuals positive based upon oral fluid testing.[34]

Our results highlight the potential value of early intervention for prevention given the increasing risk of blood borne viruses associated with greater length of time injecting drugs. Every opportunity should therefore be taken to maximize vaccination uptake including improving healthcare interventions to those in prison. This finding is consistent with our previous work demonstrating the inverse care law with respect to influenza vaccination.[35] Our data demonstrated that homeless people's eligibility for influenza vaccination due to clinical risk factors was 38.9% compared with 13.0% of the general population, but only 23.7% of those eligible were vaccinated compared to national levels of 53.2%. Given this unmet need we believe there is a strong rationale for offering universal provision of hepatitis B vaccination to homeless people through existing services engaged with this group.[36] Individuals who tested HBsAg positive generally engaged with services after referral, whereas those diagnosed with hepatitis C infection showed suboptimal engagement. Further studies are required to determine whether expanded availability of interferon-free regimens of short duration will increase engagement in this population.

Homelessness has increased dramatically in the UK since 2010 and the number of people seen rough sleeping has doubled nationally.[37,38] These populations represent the extreme end of health inequalities in high-income countries and experience a high burden of preventable morbidity and mortality from infectious and non-infectious disease.[39,40] Our study demonstrates for the first time the high prevalence of undiagnosed LTBI, hepatitis B and C, in homeless populations in the UK and a large unmet need for hepatitis B vaccination. Our findings also clearly illustrate the requirement for intensive case management and ongoing support to ensure that testing can translate into treatment opportunities. The very high rates of co-infection demonstrated highlight the importance of service integration through combined testing and treatment pathways.[41] NICE now recommend that persons accessing targeted mobile radiology should be offered tests for BBV[19] and our data provide the basis to estimate the cost effectiveness of this approach. The recent national collaborative TB strategy[42] commits to new investment in a national outreach service in line with the proven Find & Treat outreach model.[20] Our findings

reinforce the need for an integrated screening and treatment support model, whilst highlighting the ongoing complexity found in this population plus the support they will require through such services.

Funding

The study funders had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. This work presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (Reference Number RP-PG-0407-10340). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. RWA is funded by a Wellcome Trust research training fellowship (097980/Z/11/Z). We also acknowledge the support from The Farr Institute of Health Informatics Research. The Farr Institute is supported by a 10-funder consortium: Arthritis Research UK, the British Heart Foundation, Cancer Research UK, the Economic and Social Research Council, the Engineering and Physical Sciences Research Council, the Medical Research Council (K006584/1), the National Institute of Health Research, the National Institute for Social Care and Health Research (Welsh Assembly Government), the Chief Scientist Office (Scottish Government Health Directorates), the Wellcome Trust.

Contributors

ACH and AS proposed the hypothesis and idea for study. All authors contributed substantially to the conception, design and acquisition of data. RWA performed the analyses and wrote the first draft of the report. All authors helped interpret the data and revised and edited the manuscript. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Competing interests

RWA, ACH, SH, LP, GF, EG, AMG, ML, TMcH declare that they have no relevant conflicts of interest. AS is clinical lead for the Find and Treat service including the mobile digital X-ray unit.

References

1 Story A, Murad S, Roberts W, *et al.* Tuberculosis in London: the importance of homelessness, problem drug use and prison. *Thorax* 2007;**62**:667–71. doi:10.1136/thx.2006.065409

2 Gelberg L, Panarites CJ, Morgenstern H, *et al.* Tuberculosis skin testing among homeless adults. *J Gen Intern Med* 1997;**12**:25–33.

3 Dewan PK, Grinsdale J, Liska S, *et al.* Feasibility, acceptability, and cost of tuberculosis testing by whole-blood interferon-gamma assay. *BMC Infect Dis* 2006;**6**:47. doi:10.1186/1471-2334-6-47

4 Crisis - Homelessness Monitor. Crisis. https://www.crisis.org.uk/ending-homelessness/homelessness-knowledge-hub/homelessness-monitor/ (accessed 3 Jul 2017).

5 Annual review of single homelessness support in England. Homeless Link. http://www.homeless.org.uk/facts/our-research/annual-review-of-single-homelessness-support-in-england (accessed 3 Jul 2017).

6 Tuberculosis (TB): regional and devolved administration reports - GOV.UK. https://www.gov.uk/government/publications/tuberculosis-tb-regional-reports (accessed 3 Jul 2017).

7 Menzies D, Al Jahdali H, Al Otaibi B. Recent developments in treatment of latent tuberculosis infection. *Indian J Med Res* 2011;**133**:257–66.

8 Sterling TR, Villarino ME, Borisov AS, *et al.* Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med* 2011;**365**:2155–66. doi:10.1056/NEJMoa1104875

9 Saukkonen JJ, Cohn DL, Jasmer RM, *et al.* An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006;**174**:935–52. doi:10.1164/rccm.200510-1666ST

10 Department of Health. Immunisation against infectious disease - GOV.UK. https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book (accessed 11 Jul 2016).

11 Ghany MG, Gara N. QUEST for a cure for hepatitis C virus: the end is in sight. *The Lancet* 2014;**384**:381–3. doi:10.1016/S0140-6736(14)60807-2

12 Lawitz E, Mangia A, Wyles D, *et al.* Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013;**368**:1878–87. doi:10.1056/NEJMoa1214853

13 Afdhal N, Zeuzem S, Kwo P, *et al.* Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 2014;**370**:1889–98. doi:10.1056/NEJMoa1402454

14 Afdhal N, Reddy KR, Nelson DR, *et al.* Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med* 2014;**370**:1483–93. doi:10.1056/NEJMoa1316366

15 Kowdley KV, Gordon SC, Reddy KR, *et al.* Ledipasvir and Sofosbuvir for 8 or 12 Weeks for Chronic HCV without Cirrhosis. *N Engl J Med* 2014;**370**:1879–88. doi:10.1056/NEJMoa1402355

16 Poordad F, Hezode C, Trinh R, *et al.* ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med* 2014;**370**:1973–82. doi:10.1056/NEJMoa1402869

17 NICE. Hepatitis C | Guidance and guidelines | NICE. https://www.nice.org.uk/guidance/indevelopment/gid-cgwave0666 (accessed 11 Jul 2016).

18 People who inject drugs: HIV and viral hepatitis monitoring - Publications - GOV.UK. https://www.gov.uk/government/statistics/people-who-inject-drugs-hiv-and-viral-hepatitis-monitoring (accessed 11 Jul 2016).

19 NICE. Tuberculosis | Guidance and guidelines | NICE guidelines [NG33]. https://www.nice.org.uk/guidance/ng33 (accessed 11 Jul 2016).

20 Jit M, Stagg HR, Aldridge RW, *et al.* Dedicated outreach service for hard to reach patients with tuberculosis in London: observational study and economic evaluation. *BMJ* 2011;**343**:d5376–d5376. doi:10.1136/bmj.d5376

21 National Institute for Health and Clinical Excellence. Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control (clinical guideline 33). http://guidance.nice.org.uk/CG33 (accessed 18 Dec 2009).

22 Tuberculosis: identification and management in under-served groups | Guidance and guidelines | NICE. https://www.nice.org.uk/guidance/ph37 (accessed 11 Jul 2016).

23 Komurian-Pradel F, Perret M, Deiman B, *et al.* Strand specific quantitative real-time PCR to study replication of hepatitis C virus genome. *J Virol Methods* 2004;**116**:103–6.

24 Abbott. Abbott m2000 RealTime System. Abbott M2000 Realt. Syst. 2015.https://www.abbottmolecular.com/us/products/instrumentation-automation/realtime-pcr/m2000-sp-rt.html (accessed 11 Jul 2016).

25 Lobato MN, Leary LS, Simone PM. Treatment for latent TB in correctional facilities: a challenge for TB elimination. *Am J Prev Med* 2003;**24**:249–53.

26 Greveson K, Goodhand J, Capocci S, *et al.* Yield and cost effectiveness of mycobacterial infection detection using a simple IGRA-based protocol in UK subjects with inflammatory bowel disease suitable for anti-TNFα therapy. *J Crohns Colitis* 2013;**7**:412–8. doi:10.1016/j.crohns.2012.08.010

27 Hepatitis C in the UK - Publications - GOV.UK. https://www.gov.uk/government/publications/hepatitis-c-in-the-uk (accessed 11 Jul 2016).

28 Homeless Link. Homelessness and health research | Homeless Link. http://www.homeless.org.uk/facts/our-research/homelessness-and-health-research (accessed 5 Aug 2016).

29 Laurenti P, Bruno S, Quaranta G, *et al.* Tuberculosis in sheltered homeless population of Rome: an integrated model of recruitment for risk management. *ScientificWorldJournal* 2012;**2012**:396302. doi:10.1100/2012/396302

30 Lee C-H, Jeong Y-J, Heo EY, *et al.* Active pulmonary tuberculosis and latent tuberculosis infection among homeless people in Seoul, South Korea: a cross-sectional study. *BMC Public Health* 2013;**13**:720.

31 McAdam JM, Bucher SJ, Brickner PW, *et al.* Latent tuberculosis and active tuberculosis disease rates among the homeless, New York, New York, USA, 1992-2006. *Emerg Infect Dis* 2009;**15**:1109–11. doi:10.3201/eid1507.080410

32 Tabuchi T, Takatorige T, Hirayama Y, *et al.* Tuberculosis infection among homeless persons and caregivers in a high-tuberculosis-prevalence area in Japan: a cross-sectional study. *BMC Infect Dis* 2011;**11**:22. doi:10.1186/1471-2334-11-22

33 Beijer U, Wolf A, Fazel S. Prevalence of tuberculosis, hepatitis C virus, and HIV in homeless people: a systematic review and meta-analysis. *Lancet Infect Dis* 2012;**12**:859–70. doi:10.1016/S1473-3099(12)70177-9

34 Sherriff LCH, Mayon-White RT. A survey of hepatitis C prevalence amongst the homeless community of Oxford. *J Public Health Med* 2003;**25**:358–61.

35 Story A, Aldridge RW, Gray T, *et al.* Influenza vaccination, inverse care and homelessness: cross-sectional survey of eligibility and uptake during the 2011/12 season in London. *BMC Public Health* 2014;**14**:44. doi:10.1186/1471-2458-14-44

36 Story A, Aldridge RW, Abubakar I, *et al.* Active case finding for pulmonary tuberculosis using mobile digital chest radiography: an observational study. *Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis* 2012;**16**:1461–7. doi:10.5588/ijtld.11.0773

37 Statutory homelessness January to March 2016 and homelessness prevention and relief 2015 to 2016: England - Publications - GOV.UK. https://www.gov.uk/government/statistics/statutory-homelessness-january-to-march-2016-and-homelessness-prevention-and-relief-2015-to-2016-england (accessed 5 Aug 2016).

38 Rough sleeping in England: autumn 2015 - Publications - GOV.UK. https://www.gov.uk/government/statistics/rough-sleeping-in-england-autumn-2015 (accessed 5 Aug 2016).

39 Story A. Slopes and cliffs in health inequalities: comparative morbidity of housed and homeless people. *The Lancet* 2013;**382**, **Supplement 3**:S93. doi:10.1016/S0140-6736(13)62518-0

40 Morrison DS. Homelessness as an independent risk factor for mortality: results from a retrospective cohort study. *Int J Epidemiol* Published Online First: 21 March 2009. doi:10.1093/ije/dyp160

41 Fenton KA, Aquino GA, Dean HD. Program collaboration and service integration in the prevention and control of HIV infection, viral hepatitis, STDs, and tuberculosis in the U.S.: lessons learned from the field. *Public Health Rep Wash DC 1974* 2014;**129 Suppl 1**:1–4.

42 Tuberculosis (TB): collaborative strategy for England - Publications - GOV.UK. https://www.gov.uk/government/publications/collaborative-tuberculosis-strategy-for-england (accessed 8 May 2015).

43 QIAGEN. Interpretation criteria for QuantiFERON-TB Gold (Table 4). QuantiFERON-TB Gold. 2016.http://www.quantiferon.com/irm/content/quantiferon-tb-gold1.aspx?RID=300 (accessed 11 Jul 2016).

44 Health D of. Getting ahead of the curve: a strategy for combating infectious diseases (including other aspects of health protection). 2002.http://webarchive.nationalarchives.gov.uk/+/dh.gov.uk/en/publicationsandstatistics/publications/publicationspolicyandguidance/dh_4007697 (accessed 11 Jul 2016).

Tables

Table 1. Definitions of classifications used for latent tuberculosis infection, hepatitis B, hepatitis C, and HIV

Infection (number screened)	Classification status	Definition	Number classified(%[a])
Latent Tuberculosis (N=489) [c]	Positive[b]	TB specific antigen response >0.35 IU/ml, and no evidence of active disease on clinical assessment	81 (16.5)
	Negative	TB specific antigen response <0.35 IU/ml	408 (83.1)
Hepatitis B (N=489)[c]	Current	HBsAg positive, anti-HBc negative, anti-HBs negative	7 (1.4)
	Past	HBsAg negative, anti-HBc positive, anti-HBs positive (confirmed; N=43) Or HBsAg negative, anti-HBc positive, anti-HBs negative (probable past; N=8)	51 (10.4)
	Immune probably through vaccination[d]	HBsAg negative, anti-HBc negative[e], anti-HBs positive	140 (28.7)
	Non-immune	HBsAg, anti-HBc, anti-HBs negative	291 (59.5)
Hepatitis C (N=491)	Current	Anti-HCV positive and HCV RNA positive	51 (10.4)
	Past	Anti-HCV positive, HCV RNA negative, and RIBA positive	13 (2.7)
	Uncertain past history	Anti-HCV positive or equivocal, HCV RNA negative and no RIBA or insufficient sample for testing	3 (0.6)
	Negative	Anti-HCV and HCV RNA negative	424 (86.4)
HIV (N=491)	Seropositive	Anti-HIV/p24 antigen positive	5 (1.0)
	Seronegative	Anti-HIV/p24 antigen positive	486 (99.0)

[a] Denominator for each percentage is number screened, in first column

[b] Further details available from Cellestis, Australia, including interpretation of controls.[43]

[c] Two missing LTBI results as indeterminate, and two missing hepatitis B test results due to insufficient sample for testing.
[d] Median anti-HBs levels were 195 IU/L (IQR 46-945).
[e] Three subjects had equivocal anti-HBc and negative anti-HBe.

Table 2. Baseline demographic and clinical characteristics for participants stratified by test results for latent tuberculosis infection, hepatitis B and C.

	All	Quantiferon Positive		Hep B Positive[a]		Hep C Positive[b]	
	N	N	%	N	%	N	%
All	491	81	16.5	58	11.9	64	13.0
Age [years]							
18-29	69	8	11.6	6	8.7	3	4.3
30-49	257	39	15.2	28	10.9	43	16.7
50+	165	34	20.6	24	14.5	18	10.9
Sex							
Female	54	4	7.4	5	9.3	3	5.6
Male	437	77	17.6	53	12.1	61	14.0
Born in the UK							
Yes	305	29	9.5	29	9.5	50	16.4
No	186	52	28.0	29	15.6	14	7.5
Total time spent homeless							
<1year	48	8	16.7	6	12.5	4	8.3
1 year	135	18	13.3	16	11.9	13	9.6
2-3 years	141	28	19.9	19	13.5	11	7.8
>3 years	167	27	16.2	17	10.2	36	21.6
Has ever spent time in prison							
No	218	35	16.1	27	12.4	12	5.5
Yes	263	45	17.1	30	11.4	50	19.0
Missing	10	1		1		2	
Illicit drug usage							
Neither	298	44	14.8	27	9.1	13	4.4
Has ever smoked heroin / crack	107	20	18.7	14	13.1	5	4.7
Has ever injected drugs	86	17	19.8	17	19.8	46	53.5
Case currently smokes cigarettes							
No	97	18	18.6	10	10.3	2	2.1
Yes	394	63	16.0	48	12.2	62	15.7
Participant or health worker ever been concerned about drinking							
No	275	51	18.5	30	10.9	24	8.7
Yes	202	28	13.9	25	12.4	36	17.8
Missing	14	2		3		4	

[a] Sum of current and past hepatitis B

[b] Sum of current and past hepatitis C

Note: HIV data not included to reduce risk of deductive disclosure.

Table 3. Logistic regression results of risk factors for latent tuberculosis infection in UK born homeless

Risk Factor	Univariable Odds Ratio (95%CIs)	Multivariable Odds Rati (95%CIs)	p-value*
Age			
<30	1.0	1.0	
30-49	1.36 (0.61, 3.07)	0.69 (0.14, 3.51)	
50+	1.98 (0.86, 4.53)	2.04 (0.41, 10.05)	0.07
Total time spent homeless			
<1year	1.0	1.0	
1 year	0.77 (0.31, 1.91)	0.32 (0.06, 1.79)	
2-3 years	1.24 (0.52, 2.94)	0.79 (0.18, 3.44)	
>3 years	0.96 (0.41, 2.29)	0.82 (0.20, 3.32)	0.43
Has ever been to prison			
No	1.0	1.0	
Yes	1.08 (0.67, 1.75)	3.49 (1.10, 11.04)	0.018
Illicit drug usage			
Neither	1.0	1.0	
Has ever smoked heroin / crack	1.33 (0.74, 2.37)	1.44 (0.49, 4.22)	
Has ever injected drugs	1.42 (0.77, 2.64)	2.65 (0.92, 7.62)	0.20

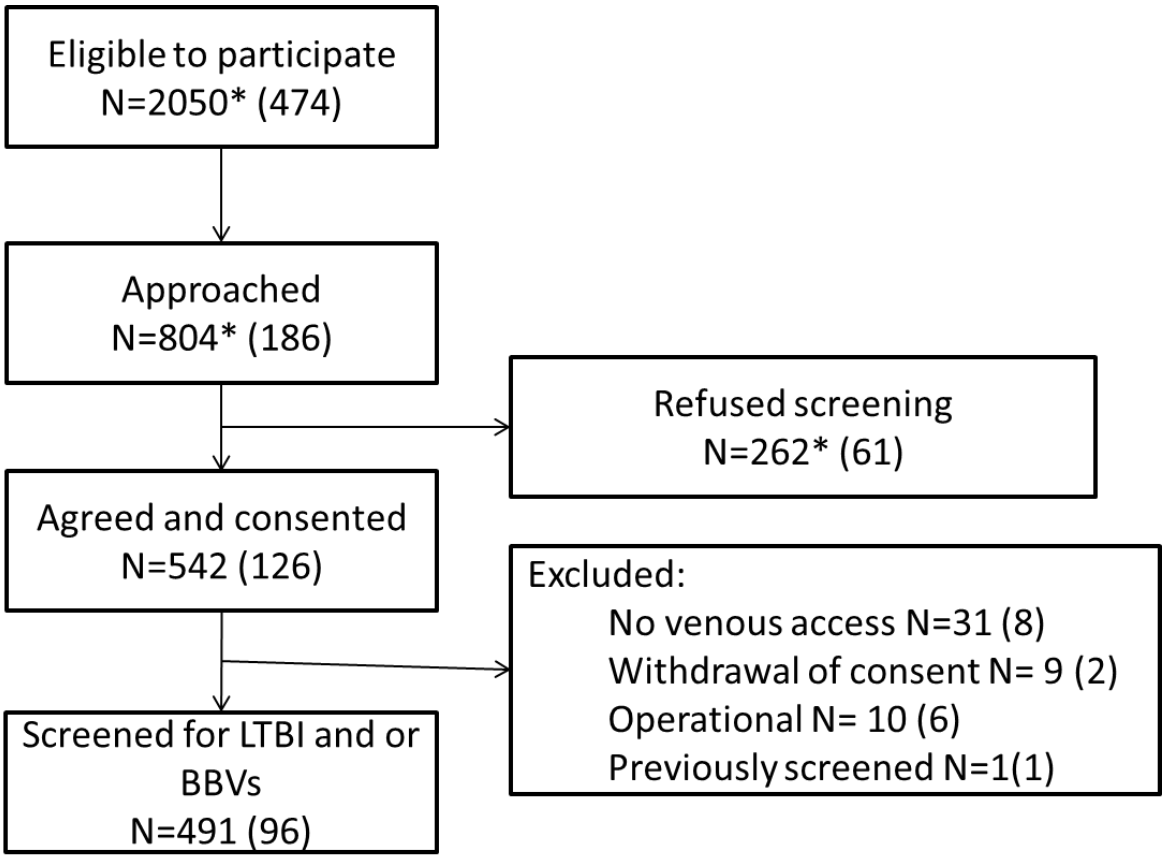
*Likelihood ratio test; 2 indeterminate IGRA results grouped with negative results.

Table 4. Outcomes of referral to clinical services for positive cases of latent tuberculosis, hepatitis B and hepatitis C.

Outcome at 12 months	LTBI positive N (%)	HBV positive N (%)	HCV positive N (%)
Diagnosed and eligible for referral	3 (100.0)	7 (100.0)	51 (100.0)
Treatment started			
On treatment	0 (0)	0 (0)	1 (2.0)
Completed treatment	0 (0)	0 (0)	1 (2.0)
Incomplete treatment	0 (0)	0 (0)	0 (0)
Engaged with services, no treatment			
Seen, discharged, no treatment required	0 (0)	6 (85.7)	0 (0)
Under review, no treatment at present	0 (0)	0 (0)	19 (29.4)
No engagement with services			
DNA, discharged/ LFU	2 (66.6)	1 (14.3)	28 (49.0)
Declined referral	1 (33.3)	0 (0)	2 (3.9)

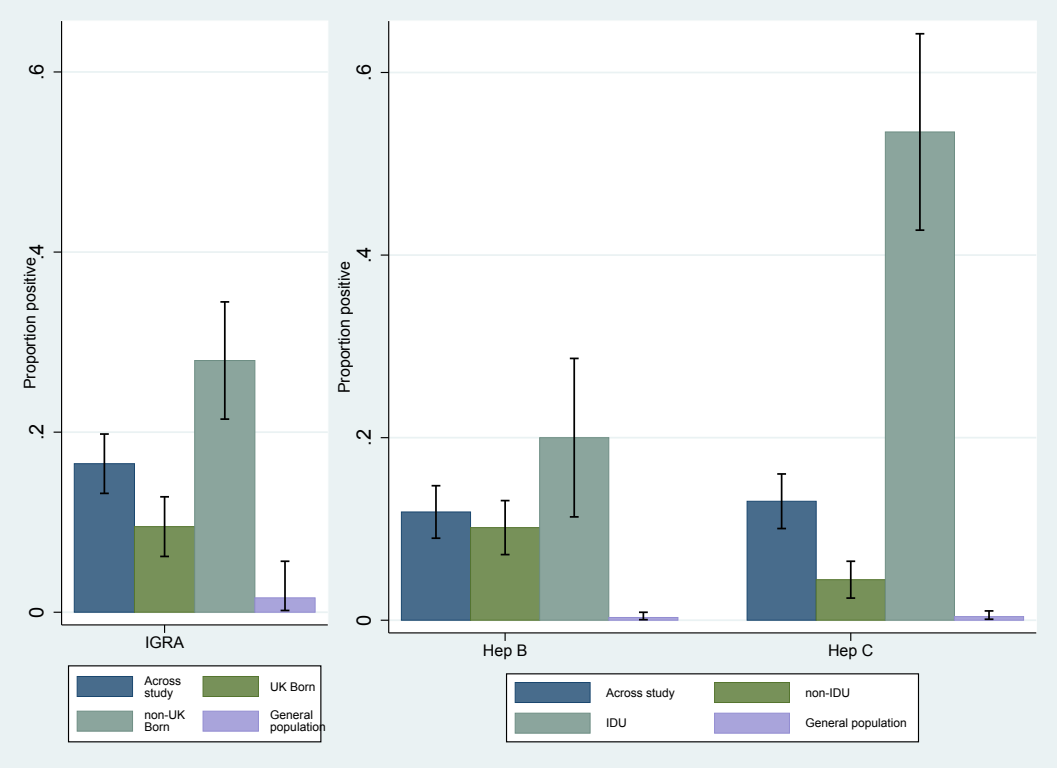
Figures

Figure 1. Recruitment flow chart



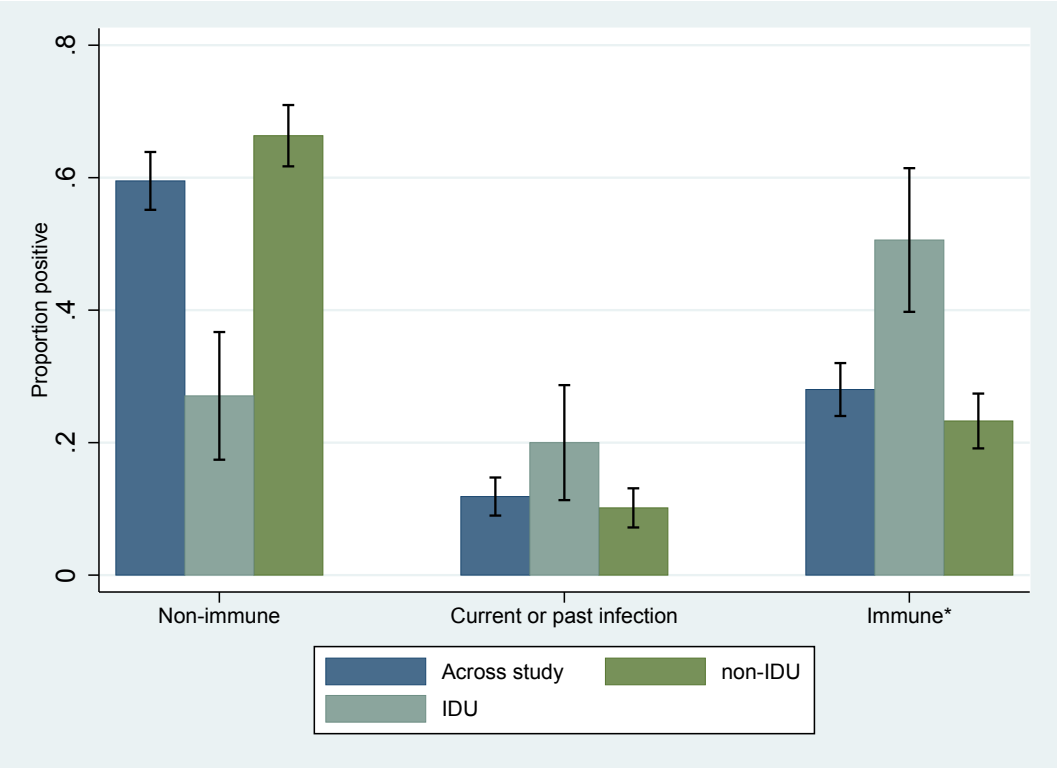
* It was operationally extremely intensive to collect data on the number of individuals who were eligible, approached and refused screening, therefore these data were only collected at the start of the study. These numbers are therefore estimated on the basis of data collected at the start of study (numbers in parenthesis).

Figure 2. Prevalence of latent tuberculosis infection, hepatitis B and hepatitis C, compared to nationally representative samples



General population comparators taken from published sources: LTBI[26]; Hepatitis B[44]; Hepatitis C[27]. Hepatitis B & C results from current study were sum of current and past hepatitis B or C.

Figure 3. Immunity to Hep B across study and by history of injecting drug use.



* Immune due to hepatitis B vaccination

Figure 4. Risk of hepatitis B and C with increasing time of injecting drug use.