Community-based testing of migrants for infectious diseases (COMBAT-ID): impact, acceptability and cost-effectiveness of identifying infectious diseases among migrants in primary care: protocol for an interrupted time-series, qualitative and health economic analysis

Manish Pareek, Helen C Eborall, Fatimah Wobi, Kate S Ellis, Evangelos Kontopantelis, Fang Zhang, Rebecca Baggaley, T Deirdre Hollingsworth, Darrin Baines, Hemu Patel, Pranabashis Haldar, Mayur Patel, Iain Stephenson, Ivan Browne, Paramjit Gill, Rajesh Kapur, Azhar Farooqi, Ibrahim Abubakar, Chris Griffiths

ABSTRACT

Background Migration is a major global driver of population change. Certain migrants may be at increased risk of infectious diseases, including tuberculosis (TB), HIV, hepatitis B and hepatitis C, and have poorer outcomes. Early diagnosis and management of these infections can reduce morbidity, mortality and onward transmission and is supported by national guidelines. To date, screening initiatives have been sporadic and focused on individual diseases: systematic routine testing of migrant groups for multiple infections is rarely undertaken and its impact is unknown. We describe the protocol for the evaluation of acceptability, effectiveness and cost-effectiveness of an integrated approach to screening migrants for a range of infectious diseases in primary care.

Methods and analysis We will conduct a mixed-methods study which includes an observational cohort with interrupted time-series analysis before and after the introduction of routine screening of migrants for infectious diseases (latent TB, HIV, hepatitis B and hepatitis C) when first registering with primary care within Leicester, UK. We will assess trends in the monthly number and rate of testing and diagnosis for latent TB, HIV, hepatitis B and hepatitis C to determine the effect of the policy change using segmented regression analyses at monthly time-points. Concurrently, we will undertake an integrated qualitative sub-study to understand the views of migrants and healthcare professionals to the new testing policy in primary care. Finally, we will evaluate the cost-effectiveness of combined infection testing for migrants in primary care.

Ethics and dissemination The study has received HRA and NHS approvals for both the interrupted time-series analysis (16/SC/0127) and the qualitative sub-study (16/EM/0159). For the interrupted time-series analysis we will only use fully anonymised data. For the qualitative sub-study, we will gain written, informed consent. Dissemination of the results will be through local and national meetings/conferences as well as publications in peer-reviewed journals.

INTRODUCTION

Migration is an important determinant of population change in the UK. Office for National Statistics estimates indicate that between 1991 and 2011, median
annual migration to the UK was 158,000 people (IQR: 76,000–198,000 people) with a median of 57.5% (IQR: 54.7%–65.9%) of migrants arriving from outside the European Union (31.7% from Africa and the Indian subcontinent). Consequently, in 2012, 12.4% of the UK population was born overseas; roughly half (4.5 million) were born outside Europe, North America. Large UK urban conurbations have higher levels of migration and therefore larger overseas-born populations. For example, in Leicester, one of the most ethnically diverse UK cities, approximately 30% of the population is born outside Europe and North America, and individuals from the Indian subcontinent alone make up 15% of the population.

Migrants are a heterogeneous group, characterised by specific language and cultural identities with specific health needs. Although the evidence-base remains limited, data indicate that overseas-born migrants (primarily from Africa and Asia), as compared with the UK born population, are at an increased risk of, and disproportionately affected by, certain communicable diseases—including tuberculosis (TB), HIV, hepatitis B and hepatitis C. Between 1998 and 2012, UK-TB notifications increased by 55% however, most of this increase has been among those born outside the UK, in whom notifications have risen by 106%; foreign-born migrants account for over 70% of UK-TB notifications and have a 20-fold higher TB incidence than UK-born individuals. Overseas-born migrants from certain regions such as sub-Saharan Africa and Southeast Asia are also at increased risk from blood-borne viruses and account for over 50% of newly diagnosed cases of HIV, hepatitis B infected UK blood donors, and 50% of hepatitis C infected UK blood donors. However, sero-prevalence data for these infections among UK migrant populations are limited.

Data on the outcomes from these communicable diseases suggests that migrants are more likely to present late (e.g., HIV-infection individuals born overseas are significantly more likely to present with CD4 counts <350 cells/mm³), have more aggressive disease processes (HIV and TB) and are likely to transmit to contacts if undiagnosed (in the case of communicable diseases). Early diagnosis and management of communicable diseases can, therefore, result in improved outcomes by preventing morbidity, mortality and onward transmission. This position is supported by several guidelines from the National Institute for Health and Care Excellence (NICE) and other national/international bodies which advocate screening migrants for active and latent TB, HIV (which exemplifies a shift towards universal HIV testing in high prevalence areas [≥2/1000]), hepatitis B and hepatitis C. Operationalising a systematic/co-ordinated method of identifying infectious diseases that are prevalent in migrants, while desirable, has not been undertaken to date with the exception of latent TB with previous UK work showing that identifying latent TB in migrants from countries with an intermediate TB incidence (>150 cases/100,000 population per year) when first registering with primary care would be feasible and cost-effective for the National Health Service (NHS). Recent work from London has shown that identifying viral hepatitis, although in a mixed migrant and non-migrant population, was feasible and cost-effective. Currently, however, routine migrant testing for infectious diseases remains limited despite it being acceptable to migrant communities which may reflect concerns about implementation, costs and resource implications.

Although the new Collaborative Tuberculosis Strategy for England recommends identifying latent TB in migrants (from countries with TB incidence ≥150/100,000 or sub-Saharan Africa) when they first register with primary care, screening migrants for individual conditions (latent TB only) at the time of primary care registration potentially fails to address the range of infectious diseases prevalent in migrant populations. Therefore, there is a need to explore city-wide coordinated testing for a range of infectious diseases in migrant populations at the time of new patient registration with primary care, assess the cost effectiveness of this approach and use qualitative approaches to understand views towards testing. This would, for the first time, allow us to determine the acceptability, effectiveness and cost-effectiveness of such a combined infectious diseases migrant health programme in primary care.

**AIMS AND OBJECTIVES**

1. Determine the impact of screening in primary care for latent TB, HIV, hepatitis B and hepatitis C on the identification of these conditions in migrants.
2. Determine the impact of programmatic routine testing in primary care for latent TB, HIV, hepatitis B and hepatitis C on the number of tests performed on migrants for these conditions.
3. Estimate the prevalence of latent TB, HIV, hepatitis B and hepatitis C in a cohort of migrants.
4. Explore the knowledge, attitudes and practices of primary care staff about testing migrants for a range of infectious diseases in primary care.
5. Explore the knowledge, attitudes and practices of migrants about infectious diseases and the testing programme in primary care.
6. Estimate the cost-effectiveness of primary care based testing of migrants for latent TB, HIV, hepatitis B and hepatitis C.

**METHODS**

**Work package 1: observational cohort study with interrupted time-series analysis (objectives 1–3)**

**Study design**

Observational cohort study utilising primary care data before and after the introduction of a migrant screening
service in primary care in Leicester, UK. Assessment of the screening service’s impact will be with interrupted time-series (ITS) analyses of testing numbers. ITS is a powerful quasi-experimental design used to assess the impact of health/public policy interventions introduced at a specific time-point where random assignment is not possible. We have followed published guidance in designing this study.

**Study setting**

General practices (n=65) in Leicester, UK participating in the migrant screening service. Leicester is among the most ethnically diverse UK cities with 34% of the population (307,000 in 2011) born overseas; individuals from the Indian subcontinent make up 15% of the population.

**Study duration**

48 months.

**Study population**

Adult overseas-born migrants registering with one of the participating practices in Leicester, UK.

- **Participant inclusion criteria**
  - Age ≥16 years.
  - Arrival in the UK ≤5 years.
  - Overseas-born.
  - Country of birth TB incidence ≥150/100 000 or sub-Saharan Africa or Refugee/Asylum seeker.

- **Participant exclusion criteria**
  - Tourists visiting the UK.
  - Migrants aged <16 years.

**Study synopsis/investigative plan**

**Proposed migrant screening service in Leicester**

As part of NHS care, general practices in Leicester commenced migrant screening for latent TB, HIV, hepatitis B and hepatitis C from April 2016. This will be the standard-of-care whereby overseas-born individuals aged 16–65 with UK arrival within the last 5 years from a country with TB incidence ≥150/100 000 or from sub-Saharan Africa or a refugee/asylum seeker will be identified by staff at the time of general practice (GP) registration/new patient health check (using template prompts) and offered blood-tests for HIV, hepatitis B and hepatitis C. Migrants aged 16–55 will also be offered an interferon gamma release assay (IGRA) blood-test (QuantiFERON Gold in-tube) for latent TB. No other interventions are planned during this period.

Laboratory results will be sent to the participant’s general practitioner. Migrants testing positive for any of the infectious diseases will be referred to secondary care for further management using standard referral pathways.

**Measurements and data collection**

To ensure data collection complies with information governance processes Leicester City Clinical Commissioning Group and the Arden and Greater East Midlands-Commissioning Support Unit (AGEM-CSU) are involved. The GEM-CSU is a designated Data Services for Commissioners Regional Office for primary and secondary care data (approved safe haven).

Prior to data collection, we will work with the AGEM-CSU to ensure data-sharing agreements are in place with participating practices to provide pseudonymised/anonymised patient data.

Following data-sharing agreements and approvals, we will collect GP registration/consultation data on a monthly basis for 87 time-points in total: 60 time-points (5 years at monthly-intervals) before the screening-service (intervention) commenced (retrospective data collection—January 2011 to March 2016) and 30 time-points (2 years and 3 months at monthly-intervals) after the screening-service (prospective data collection—April 2016 to October 2018). As the screening service commences in April 2016, the 3-month period following this (April–June 2016) will be considered a transition/lag period and excluded from data analysis (thus 27 time-points will be analysed in the post-intervention period).

Data will be downloaded from practices by the AGEM-CSU. Primary care searches will be linked to Flag-4 indicators which allows one to identify new migrants. All data will then be anonymised with no personal identifiable details. Data will be encrypted prior to being supplied (by secure nhs.net email) to the analysts. Data storage will comply with the European Union General Data Protection Regulation.

Variables that will be collected from GP registration/consultation data for all migrants registering with primary care and eligible for the screening-service will include: practice-level data, demographics (age, gender, country of birth, dates of arrival and registration), which tests were performed (communicable diseases testing: latent TB, HIV, hepatitis B and hepatitis C; non-communicable disease testing: haemoglobin, kidney function [GFR and serum creatinine], vitamin D, lipid profile, HbA1c, glucose, height/weight/body mass index, blood pressure), and the results of these tests. This will therefore provide information on the numbers of eligible migrants registering with primary care, the numbers of migrants tested with the different tests and the number of positive tests (and therefore diagnoses) in the cohort. As a control, over the same time-periods, we will collect migrant testing and diagnosis data for syphilis which is not included in the screening service.

**Statistical analysis**

**Power and sample size calculations**

Sample size/power calculations in an ITS design are based on the number of time-points at which data will be collected. Generally, 10–12 time-points before and after the introduction of the intervention are required. We will have 60 time-points before and 27 (24 excluding the 3-month lag period) time-points after the screening-service is introduced which should allow sufficient power.

Since no closed-form expressions are available for ITS methods, we also conducted simulations to estimate power with the following parameters for the change in

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the outcome rates: outcomes assessed 60 months before and 27 months after screening-service commenced:
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- An expected sudden level change.
- 0.5 positive autocorrelation.
- $\alpha=0.05$.

Under these assumptions, we have more than 86% power with an expected effect size of over 2 (monthly latent TB diagnostic rate increasing from 100/1000 tested/month to 200/1000 tested/month). In addition, large numbers (3500/year) of registering migrants will be eligible for testing and approximately 20%–40% of those tested will have latent TB. We selected latent TB diagnoses as the primary outcome as the prevalence is high and it is a public-health concern; the study is suitably powered for this evaluation.

Analysis plan
The primary analysis will be the change in the number and rate of new latent TB diagnoses in the migrant population following the introduction of programmatic infectious disease testing in migrants when registering with primary care. This will be undertaken using segmented regression. The unit of analysis will be the individual patient.

Data will be analysed in several steps:
1. We will describe the cohort focusing on the numbers of migrants registering and their demographics.
2. We will compute the absolute numbers, proportion (number of migrants tested for each infectious disease divided by the number of eligible migrants registering) and rate (average number of eligible migrants tested/1000 migrants registering/year) of migrants tested for each of the infectious diseases of interest (latent TB, HIV, hepatitis B and hepatitis C) separately. Data will be calculated for the overall study period and separately for the pre-intervention and post-intervention periods. To ascertain the impact of coordinated testing, we will calculate the numbers and proportions of eligible migrants who accept testing for all of the infectious diseases in the different time periods.
3. We will calculate, at each monthly time-point, the absolute numbers, proportion (number of migrants tested divided by the number of eligible migrants registering in the month) and testing rate (average number of eligible migrants tested in the month/1000 migrants registering/month) for each of the infectious diseases.
4. For each infectious disease we will compute the absolute numbers, proportion positive (number of migrants testing positive divided by the number of eligible migrants tested; this will be the prevalence of the individual diseases in the migrant cohort) and rate (average number of positive tests/1000 migrants tested/year) of migrants diagnosed with latent TB, HIV, hepatitis B and hepatitis C (separately). Data will be calculated for the overall study period and separately for the pre-intervention and post-intervention periods. Co-infection (testing positive for more than one infectious disease) will also be calculated (numbers and rate).
5. We will calculate, at each monthly time-point, the absolute numbers of new diagnoses, proportion of positive test results (number of migrants testing positive divided by the number of eligible migrants tested in the month) and monthly positive diagnosis rate (average number of positive test results in the month/1000 migrants tested/month) for each of the infectious diseases.
6. To investigate factors associated with accepting testing, and testing positive, for each/any of the infectious diseases we will undertake logistic regression modelling.
7. To determine the effect of the screening-service, trends in the monthly number and rate of testing and diagnoses for latent TB, HIV, hepatitis B and hepatitis C (separately) will be examined using ITS analyses. As a control we will also analyse trends in the monthly number and rate of migrant testing and diagnosis for syphilis. The study period will be eighty-seven calendar months: 60 time-points before and 27 time-points (24 excluding the 3-month lag period between January and March 2016) after the screening-service is introduced. The effect of the new testing policy will be assessed using segmented regression analyses. Correlation will be assessed with the Durbin-Watson statistic and if significant, we will use autoregressive integrated moving average models.
8. We will use the data from the fully anonymised infectious diseases testing (including TB, HIV, hepatitis B and hepatitis C) to estimate the yields for testing from different countries and levels of infection prevalence. We will then go on to undertake logistic regression modelling to assess factors associated with test positivity. In addition, we will use the data on test positivity to develop theoretical testing algorithms and subsequently assess their sensitivity and specificity to identify infections. We will not be implementing the theoretical algorithms in clinical practice as part of this work.
We will use the non-communicable disease testing data (in conjunction with the communicable/infectious diseases testing data) to estimate the prevalence of multimorbidity with communicable and non-communicable diseases in a cohort of migrants.
Analyses will use Stata V.15.0 (StataCorp). Tests are two tailed; $p$ values $\leq 0.05$ significant.

Work package 2: qualitative study of the views of primary care staff and migrants (Objectives 4 and 5)
In order to evaluate the screening programme’s feasibility and acceptability to those involved a concurrent qualitative study is essential.

Study duration
48 months.

Design and methodology
This iterative qualitative study will progress through three phases, with each phase informing the next.
Phase 1
Focus groups will be conducted with people from a range of migrant groups, typical to Leicester’s diverse population. Notably, these individuals do not need to have been invited to the testing programme. Purposive sampling will seek to reach migrants from each relevant country-of-origin who have been offered screening (including those who accepted and declined) and widening to include further participants from each migrant group. Recruitment methods will include invitation via practices (direct/postal), posters/leaflets, community contacts and snowballing where necessary for hard-to-reach groups. We will liaise with local healthcare and third sector organisations to recruit participants. Staff from these organisations and translators (when needed) will assist our focus group moderators with facilitation and translation of focus groups. We anticipate a sample size of 32–80 (8–10 focus groups of 4–8 participants).

The aim of the focus groups is to explore the views and experiences of people from the likely migrant population groups in Leicester that may be invited to be tested, about (any) health screening checks that they are aware, or have experience of, and their (hypothetical) views about attending the combined diseases testing programme and, if time, the four specific diseases. Focus groups will be loosely informed around a topic guide, while recognising the need to be flexible, particularly when levels of English language are likely to be variable. Focus group discussions are likely to inform subsequent focus groups, by highlighting salient issues to be further explored. Further, the findings may inform the topics and issues explored in phases 2 and 3.

Phase 2
Individual interviews will be conducted with staff working in healthcare—directly or indirectly involved in part of the testing pathway. Purposive sampling will seek to reach a range of staff in terms of professional role and stage of pathway (eg, primary care [testing], secondary care [treatment] and public health). Recruitment will be via direct invitation (with accompanying information leaflet and opt-in reply slip). We anticipated a sample size of 20–30.

The semi-structured interviews will be informed by a flexible topic guide to explore their views and experiences of the testing programme, including feasibility issues.

Phase 3
Individual interviews will be conducted with individuals receiving treatment, having tested positive for one or more of the conditions through the testing programme. Purposive sampling will seek to reach a range of participant in terms of demographics. Individuals attending clinics will be recruited by a research nurse while in clinic.

Semi-structured interviews will be informed by a flexible topic guide and will explore the participant’s views and experience of the testing programme and views about the four specific diseases. Notably, the interviewer will not know the health status of the interviewee; the interviewee will choose how much to disclose.

We anticipate a sample size of approximately 20.

The final sample size for all three phases will depend on reaching saturation in terms of key themes.

Analysis
With participants’ consent, all focus groups and interviews will be audio-recorded and fully transcribed (with simultaneous translation where necessary). Analysis will be informed by the constant comparative process, which involves reading and rereading of transcripts, identification of themes and patterns, translation of themes into codes, then coding of the dataset, with continuous refinement of the coding framework.

Work package 3: integrated health-economic analysis of migrant testing in primary care (Objective 6)
The economic evaluation integrated into this clinical study consists of:
1. Costing study in practices.
2. Evidence synthesis.
3. Economic modelling.

Costing study
Using site-interviews at individual practices and in secondary care, we will record resource use linked to screening and subsequent management of migrants testing positive for any of the diseases. We will record activity in natural units (staff-time, facility-costs) and use national price-weights to produce costs for each activity. These will then be summed to create total costs per practice which will be used to create an average cost per patient. The perspective taken will be that of the NHS; national price-weights will ensure results are applicable to the whole NHS. The data will inform the modelling process.

Evidence synthesis
We will use relevant literature to collect data on costs, outcomes, model structure and parameters for our decision model. In addition, we will elicit expert opinion on the study results and literature analysis. Once we have estimates for costs, outcomes, model structure and key parameters, we will begin the modelling process.

Economic modelling
Study data and outcomes of the evidence synthesis will inform our modelling to generate cost-effectiveness estimates for the intervention. We envisage adopting a Markov modelling approach, given the long-term nature of many of the outcomes, but final choice of model structures will be informed by the evidence synthesis exercise. Independent models will be designed and constructed for each of the four infectious diseases, aligned in structure as much as possible, and model outputs will be analysed separately and then in combination, to assess the effectiveness and cost-effectiveness of the entire programme. The models will evaluate outcomes including quality-adjusted

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life years (QALYs) gained by earlier diagnosis of infections as a result of the intervention, and infection-specific outcomes such as number of active TB cases prevented, and numbers of HIV and TB transmissions averted. The models will each simulate the screening of a hypothetical cohort of migrants for infectious diseases and analyse outcomes over a 20-year time horizon and beyond. Effectiveness estimates will be generated by comparing these outcomes to simulations modelling the status quo that is, in the absence of the intervention. Models will be populated with costs, outcomes and probabilities taken directly from the study, supplemented by data and evidence from the literature and expert opinion. Costs and health outcomes will be discounted at an annual rate of 3.5% which reflects NICE recommendations. Economic evaluation allows comparison of all relevant options, and so in addition we will evaluate the cost-effectiveness of targeted screening of migrants (including choice of infections to screen/test) according to their countries of origin. We will present the results as incremental cost-effectiveness ratios and use cost-effectiveness acceptability curves to present visually a comparison of our estimates of the cost-effectiveness of the intervention against possible values of the threshold of cost-effectiveness (in particular NICE recommendations for cost-effectiveness). Multi-variable sensitivity analysis will be employed to explore uncertainty ranges for each model output (such as QALYs gained) and will be expressed as 95% uncertainty intervals. The impact of uncertainty in model inputs will be further explored using both one-way and probabilistic uncertainty analysis, to evaluate the impact that changes in parameters (eg, sensitivity and specificity of diagnostic tests) will have on estimates of costs, effects and associated incremental cost-effectiveness ratios (ICERs).

Analysis and results

Policy recommendations informed by effectiveness and cost-effectiveness estimates and sensitivity analysis results will be made along with suggestions for further research. The cost-effectiveness model will be constructed and analysed, using R (The R Foundation for Statistical Computing). Cost-effectiveness analyses will be reported as per EVEREST guidelines.

Patient and public involvement

We have undertaken group discussions with migrants to get their views on this topic and how we should undertake the work. They have been very supportive and provided important information about how to take the work forward, which topics to concentrate on and how to involve people in the study. During the course of the project we continue to work with migrants to guide and advise us about the work. We have also been working with GPs in Leicester to get their views on this testing programme and they have also been highly supportive.

Author affiliations

1Department of Respiratory Sciences, University of Leicester, Leicester, UK

2Department of Infection and HIV Medicine, University Hospitals of Leicester NHS Trust, Leicester, UK

3Department of Health Sciences, University of Leicester, Leicester, UK

4Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

5Centre for Primary Care, NIHR School for Primary Care Research, Manchester, UK

6Department of Population Medicine, Harvard Pilgrim Health Care, Wellesley, Massachusetts, USA

7Department of Infectious Disease Epidemiology, Imperial College London, London, UK

8Department of Global Health and Development, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK

9Big Data Institute, University of Oxford, Oxford, UK

10Department of Accounting, Finance & Economics, Bournemouth University, Poole, UK

11Department of Clinical Microbiology, University Hospitals of Leicester NHS Trust, Leicester, UK

12Department of Respiratory Medicine, University Hospitals of Leicester NHS Trust, Leicester, UK

13NHS Leicester City Clinical Commissioning Group, NHS Leicester City Clinical Commissioning Group, Leicester, UK

14Department of Public Health, Leicester City Council, Leicester, UK

15Academic Unit of Primary Care, University of Warwick, Warwick, UK

16Institute of Global Health, University College London, London, UK

17Barts Institute of Population Health Sciences, Barts and The London School of Medicine and Dentistry, London, UK

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Patient consent for publication Not required.

Ethics approval The study protocol has received HRA and NHS approvals for both the interrupted time-series analysis (16/SC/0127) and the qualitative sub-study (16/EM/0159). For the interrupted time-series analysis we will be using fully anonymised data. For the qualitative sub-study we will gain written, informed, consent before any study procedures are conducted. Dissemination of the results will be through local and national meetings/conferences as well as publications in peer-reviewed journals.

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