# *ACE Latent Tuberculosis Infection Study*

## *A. Summary of the project*

This study is focused upon early diagnosis, referral and treatment of latent tuberculosis (LTBI), which has two key purposes: 1) preventing individuals from getting active tuberculosis (TB); 2) contributing to disease control in public health terms by preventing further spread.

Accident and Emergency (A&E) Departments are an important point of testing and referral for hospital attendees who constitute those at greatest risk of active tuberculosis, as for many this will be their only interaction with the health service. Currently, about 20% of patients with TB are diagnosed in A&E Departments. The majority of these individuals are more likely to have presented with symptoms indicative of TB disease, compared to those attending for other reasons who would have been unlikely to have been tested or referred. Similarly many individuals at risk of LTBI would only have contact with an A&E department and not other parts of the health system. There are therefore potential missed opportunities to diagnose latent and active tuberculosis among high risk individuals in A&E departments.

This study will seek to evaluate specific measures currently being undertaken by Public Health England and the NHS to control TB as well as investigate whether case finding for active TB in A&E departments would improve TB control (see separate protocol for ACE active TB). This study is linked by the NIHR funded PREDICT study (Prognostic value of Interferon Gamma Release Assays in predicting active tuberculosis among individuals with, or at risk of, latent tuberculosis infection). The economic impact of these interventions will be evaluated, providing a measure of their value for money.

## *B. Planned Investigation*

### *1.0 Background*

Tuberculosis (TB) is a major cause of disease burden worldwide. The UK has seen a resurgence of TB since the late 1980s and there are currently over 8000 new cases each year (1). Most cases occur in major cities, particularly in London, and an increasing proportion occur in persons born abroad (currently two-thirds of TB cases and higher still in London) and other groups with specific risk factors. Control measures have traditionally relied on the prompt diagnosis of active TB cases and ensuring that patients complete their treatment.

The majority of TB cases in the UK arise due to reactivation of latent infection (1). Among immigrant groups, the infection is likely to have been acquired abroad whereas among the elderly UK-born population, the infection is likely to have been acquired in earlier years when TB was highly prevalent in the UK. Identifying those in high risk groups for TB, evaluating signs and symptoms of active TB and referring individuals for testing and management as well as detecting LTBI in those at high risk of progression to active TB are key to disease control efforts. Early diagnosis and treatment may have the greatest impact by interrupting transmission.

Diagnosis of TB is complex as it requires consideration of many factors. A potential mechanism to identify and test individuals at high risk of TB is to offer testing in A&E Departments. Of TB cases reviewed in a pan-London audit, 21% were diagnosed in A&E with less diagnostic delay compared to patients referred via other routes. If a successful system for undertaking testing in high risk groups attending A&E is developed, this would significantly improve the ability to diagnose a greater proportion of individuals at high risk of TB and complement current efforts to set up primary care based screening for active TB.

**Identification of latent tuberculosis infection**

It is estimated that about one-third of the world's population is latently infected with the tubercle bacterium and widely accepted that, among those with latent TB, there is an approximately 10% lifetime chance of progression to active TB. Until recently, the tuberculin skin test (TST) was the only tool for the diagnosis of latent TB. TST assesses the delayed type hypersensitivity response to a purified protein derivative (PPD - which contains antigens shared by several mycobacteria and *Mycobacterium bovis* BCG) by measuring the size of the skin induration following the injection of the antigen. Limitations to the validity (sensitivity and specificity) of TST as a measure of latent infection have been recognised for many years. These are partly due to variability in the quality of administration and interpretation of the test; as well as the state of host immunity and a lack of specificity for *M. tuberculosis* (positive results can be due to infection with other mycobacteria or vaccination with BCG).

**Interferon Gamma Release Assays**

Interferon Gamma Release Assays (IGRA) are based on the detection of *Mycobacterium tuberculosis* complex specific region of difference (RD1) antigens such as Early Secretory Antigenic Target 6 (ESAT-6), Culture Filtrate Protein 10 (CFP-10) and other TB specific antigens. Two commercial assays have been developed using these *M. tuberculosis* antigens, QuantiFERON TB Gold In Tube (Cellestis, Australia) – which uses an ELISA format – and T Spot TB (Oxford Immunotec, UK).

## 1.1 National and International Guidelines and Policy Context

### 1.1.1 National Policy

The national policy for the control of tuberculosis is based on the collaborative TB strategy for England, published in January 2015. Following the publication of the strategy, a national primary care based latent TB screening programme of migrants funded by NHS England has been launched.

### 1.1.2 Guidelines

The national guidelines for the clinical and public health management of TB were published by the National Institute for Health and Care Excellence (NICE) in January 2016. These guidelines include recommendations on the diagnosis and management of active and latent TB infection including the use of IGRA tests and the tuberculin skin test.

## 2.0 Objectives

### 2.1 Primary objectives

To evaluate the effectiveness and cost effectiveness of screening patients at high-risk of LTBI within hospital Accident and Emergency departments (A&E).

### 2.2 Secondary objectives

To measure the prevalence of LTBI in high-risk patients attending A&E Departments.

To assess the proportion of patients with LTBI that would not have been diagnosed if testing is limited to primary care.

## 3.0 Method

### 3.1 Design

#### 3.1.1 Setting, population and disease burden

This prospective study will recruit individuals aged 16 years or older, who are attending A&E Departments and are: (a) new entrants from high incidence countries in sub-Saharan Africa or Asia, or Eastern European countries, who have arrived in the UK within the past 5 years, or (b) people who have ever been homeless or in prison, or used drugs

The work will take place across a network of hospitals in London. These hospitals have been selected based on the high incidence of TB (located in areas with over 40 TB cases per 100,000 population per year, including several, such as Newham and Brent, with rates comparable to those seen in low-income countries). There is also considerable socioeconomic deprivation and ethnic diversity in these boroughs reflecting the population of TB cases nationally. All study sites will be coordinated from UCL.

#### 3.1.2 Recruitment and inclusion criteria

New entrants from high incidence countries including those in sub-Saharan Africa, south Asia and parts of eastern Europe and people who have ever been homeless or in prison, or used drugs, attending A&E departments, will be invited to take part.

Those born in high incidence countries who entered the UK more than five years ago, but have spent more than one year (cumulative) in the past five years in a high incidence country as per the study's defined list, will be invited to take part.

In order to assess their basic eligibility before directing patients to the research nurse, patients will be asked the following questions:

How long they have been living in the UK?

Which country were they born in?

If they were born in a country with high TB incidence and have been in the U.K. for less than 5 years, are they happy to take part in the study?

Do they have a history of homelessness / prison / drug use?

Following this initial eligibility screening, a study nurse will further assess eligibility and provide eligible persons with written information sheets (translated as appropriate). Written informed consent will be obtained (with the help of a translator where appropriate) from all patients willing to take part. The research nurse will complete a baseline assessment questionnaire including demographic and clinical information (see details of variables and data collection process below in section 3.2). As this is a pragmatic assessment of the use of these assays, the process is very similar to standard practice with the only differences being obtaining formal consent, systematic collection of data and offer of IGRA test at this stage.

Samples and transportation: A blood specimen will be collected for an IGRA test and transported to a laboratory for testing.

### 3.1.4 Test results and further action

Clinicians (A&E and GP) will be informed of all test results by the testing laboratory. Subsequent action after testing will follow existing NICE guidance. Where appropriate, patients will be referred to a TB clinic for treatment of LTBI and data on subsequent treatment will be collected from the clinic.

## 3.2 Data Collection

Data will be collected through an interview by trained research nurses for the baseline study data, supplemented by clinic and primary care records, for results and outcome data. All data will be imported into a purpose-built database maintained at UCL.

Data items to be collected from participants include age, gender, country of birth and date of entry to the UK for non UK born persons, ethnicity, duration of residence in the UK,

social risk factors (including history of homelessness, prison and drug use) current employment, details of any previous TB contact, history of previous TB including treatment, results of previous TST and chest radiographic findings, BCG vaccination status (scar and record), associated medical diagnoses or use of immunosuppressive agents, drugs used for

the treatment of latent infection and simple measures of compliance with, and adverse effects of, chemoprophylaxis (i.e. treatment of latent infection).

HIV status will be determined at the end of the follow-up period through pseudo-anonymised record linkage with the national HIV surveillance system, which has been demonstrated to be a reliable mechanism for identifying infected cases.

### 3.3 Outcome measures and definitions

#### 3.3.1 Primary Outcome:

a. Number and proportion of screened patients with a positive IGRA test

b. Cost of screening high-risk patients for LTBI in A&E per quality-adjusted life year

c. Proportion of those with LTBI (i.e. a positive IGRA) who would not have been detected through primary care.

#### 3.3.1 Secondary Outcome

a. Cost per quality adjusted life year

### 3.4 Analysis Plan

Prevalence of LTBI will be calculated and a multivariable logistic regression model will be built to identify risk factors for the primary and secondary outcomes. We will also determine the proportion of participants who are not registered with a GP and those who have not had contact with the GP in the previous year.

Economic analysis will follow standard NICE recommended methods.

### 3.5 Sample Size

Approximately 800 participants will be needed to estimate an LTBI prevalence of 20% (Pareek 2011) with a 95% confidence interval 11 percentage points wide. With a study duration of 24 months, we would therefore need to recruit on average 8 participants per week.

## 5.0 Ethics and Research Governance

Multi Centre NHS Research Ethics Committee (MREC) approval has been obtained for this study.

All study data will be held in accordance with NHS data protection principles including the use of secure password protected systems. UCL will be the nominated sponsor.