

# The relationship between psychosocial stress, immune function, and tuberculosis risk among migrants

## Background

Tuberculosis (TB) remains an urgent global public health priority, with ~1.7 million deaths worldwide in 2016.<sup>1</sup> The biology of TB infection and disease is well-understood, meaning that, although progress has been slower than was hoped, biomedical advances in diagnostics, antibiotics and vaccines have helped reduce TB morbidity and mortality.<sup>1</sup> Meanwhile, the association between TB and poverty has long been recognised, hence it is termed a “social disease” and “poverty’s penalty”. However, biological and social lines of enquiry have proceeded largely independently. This research gap needs bridging, bringing together the knowledge and methods of social and biomedical disciplines to gain a truly interdisciplinary understanding of TB.

Psychosocial theory postulates that vulnerability to disease is linked to psychological stress, in particular arising from perceptions and experiences of social inequalities. Given the association between TB and poverty, and between poverty and chronic psychosocial stressors and mental disorders, many TB patients are likely exposed to various psychosocial factors that may compromise their immune response prior to the development of active disease. Despite this, no existing research has explored psychosocial influences on TB. During my MSc in Public Health at [removed], I carried out a systematic review of the relationship between mental health and TB, finding that various studies show a high prevalence of mental disorders among TB patients. While the relationship between TB and mental health is complex and bidirectional,<sup>2</sup> several cohort studies indicate that depression often precedes and is therefore likely a risk factor for TB.

Despite such evidence suggesting a relationship between psychosocial stress and TB risk, no study has sought to unpick the mechanisms behind these observations by investigating whether psychosocial factors can modulate immune response to TB. However, this is plausible given evidence for psychosocial influences on immunity to other infectious diseases.<sup>3</sup> For my MSc dissertation, I systematically reviewed literature on the impact of psychosocial factors on the expression of biomarkers of immunity, applying the findings to propose mechanisms by which psychosocial factors could influence immune function in ways relevant to TB. Most studies reviewed found some relationship between psychosocial factors and immune biomarkers, though the direction and strength of associations was mixed. Nevertheless, some overarching patterns emerged; in particular, adverse psychosocial factors such as stress are generally associated with compromised vaccine response and higher antibody titres to herpesviruses, with the reverse true for positive psychosocial factors. Such findings indicate two plausible mechanisms by which psychosocial exposures could modulate immunity in such a way as to influence TB outcomes: one through immune suppression compromising BCG vaccine efficacy and one via immune exhaustion associated with herpesvirus infection. The finding that psychosocial factors can influence immune response to infectious diseases, but in a highly heterogeneous manner, renders the current lack of TB-specific studies a clear hole in the evidence base. In addition, the finding that plausible pathways exist linking psychosocial factors to immunity in relation to TB further justifies the need for primary research.

Migrants are a particularly interesting group in which to explore such relationships for several reasons. In the published work arising out of my undergraduate dissertation at [HEI removed], I explored the reasons for the higher incidence of TB among migrants and ethnic minorities in the UK compared with the UK-born population.<sup>4</sup> While TB rates have been falling slowly across all UK populations since 2011, they remain 15 times higher in the foreign-born than the UK-born population.<sup>5</sup> There is a common misconception that migrants simply ‘import’ TB from high-incidence countries to the UK, which fails to account for the fact

that very few migrants arrive in the UK with active TB, with most cases resulting from reactivation of remotely-acquired latent *M.tb* infection (LTBI) after arrival. There are various biological and social factors that increase the vulnerability of migrants to reactivation of latent *M.tb* infection, including psychosocial stress. Migrants may be exposed to different kinds of psychosocial stressors at different points along the migration trajectory. Prior to migration, refugees and asylum seekers in particular may be exposed to intensely stressful experiences in their country of origin, such as conflict and human rights violations. The process of migrating can also be extremely stressful, although the migratory journeys of legal and undocumented migrants will vary enormously. Upon arrival in their destination country, migrants are likely to face different kinds of stressors, which may be short-term (e.g. finding housing or employment, risk of deportation) or long-term (e.g. social isolation, poverty). No existing research explores whether such psychosocial stressors in migrants could influence immune function and thereby increase risk of infection or precipitate progression from latent to active TB.

## Research question

*Aim:* To understand the relationship between psychosocial stress, immune function and risk of TB infection or reactivation among migrants. The population of interest is migrants to high-income countries (HICs), with a focus on the UK.

*Objectives:*

1. To synthesise existing evidence on the relationship between psychosocial factors, mental health and TB risk among migrants in HICs, through:
  - a. a systematic literature review, and
  - b. a secondary database analysis
2. To conduct a qualitative study to understand experiences of stress in migrant TB patients, and the perspectives of health service providers on stress and mental health in this group
3. To conduct a cross-sectional study to examine the relationship between psychosocial stress, mental health, biomarkers of immunity and TB status among migrants

## Methods

In order to meet the aims and objectives outlined, a mixed-methods approach will be required. My [UG degree removed] at [HEI removed] has given me an understanding of biological and social science disciplines, making me well-placed to integrate approaches from multiple disciplines. Both my BA and MSc in Public Health at [HEI removed] taught me qualitative, quantitative and literature review skills. I will continue to develop these skills in my current role as [removed] at [removed], where I am working at the interface of biological and social sciences to understand how social policy change interacts with genetic makeup to influence dementia risk. I am therefore well-suited to further develop my skills, with the support of the project supervisors, to conduct the research required to meet the above objectives.

### 1. Evidence synthesis

#### a. Systematic review

Bibliographic databases will be used to search for published and grey literature that investigates psychosocial factors and mental health as risk factors for TB among migrants in HICs. This review will be registered with PROSPERO and will be conducted in line with PRISMA guidelines.

*Search strategy:* The databases MEDLINE, EMBASE, Global Health, PsycINFO and PsycEXTRA will be searched, using key terms and subject headings for psychosocial factors or mental health combined with those for TB,

migrants/migration, and HICs. Further supplementary searches will include contacting experts, citation searching and reference list searching.

*Inclusion criteria:* Primary research including original peer-reviewed studies and grey literature looking at the relationship between psychosocial factors/mental health and TB incidence among migrants in HICs will be included.

*Screening, data extraction and critical appraisal:* Any papers identified as being potentially relevant from screening the title and abstract will be read in full to assess their eligibility for inclusion. Data will be extracted using a modified version of the Cochrane EPOC group's data collection form, detailing participants, methods and results of included studies. Study quality will be assessed using CASP checklists for cohort and case-control studies and the AXIS tool for cross-sectional studies. Non-English papers will be translated prior to screening.

*Analysis:* A narrative synthesis will be carried out to explore evidence of relationships between psychosocial factors, mental health and TB among migrant populations in HICs in the published literature. Any suitable data will be subject to meta-analysis using STATA statistical software, and sources of heterogeneity will be explored.

## **b. Secondary database analysis**

Data from a range of sources will be extracted and entered into a database. This will include:

- i. Surveillance data on TB in migrants in EU/EEA countries from the European Centre for Disease Prevention and Control's (ECDC's) The European Surveillance System (TESSy) database, which includes demographic and clinical data
- ii. Danish registry data, which includes data on migrant status, reason for migration, mental health, and TB status
- iii. Retrospective clinical data for TB patients at St George's University Hospital NHS Trust and University Hospitals of Leicester NHS Trust
- iv. Public Health England (PHE) datasets, including TB case notifications to the Enhanced Tuberculosis Surveillance system (ETS) in England and LTBI testing and treatment data
- v. The World Health Organization's (WHO's) global tuberculosis database, which includes TB incidence and mortality estimates for countries worldwide

I will gain access to the above data sources via my supervisors and their collaborators. Data will be analysed using STATA. Initially, descriptive analyses will be used to examine key associations within each data source. For example, for the TESSy database, I will examine the proportion of TB cases occurring in migrants in EU/EEA countries, as well as key associations (e.g. using chi-square, t-test) such as age, sex, country of origin and time since migration. The various datasets may then be aggregated and analysed using multivariate regression and 'Big Data' techniques to examine relationships between migrant status, psychosocial factors, mental health and TB status.

## **2. Qualitative study**

In-depth interviews will be carried out with migrants with experience of active and latent TB, and health service providers. The purpose of the interviews is to understand patients' own experiences of stress prior to, during and after migration to the UK, and also before and after TB diagnosis and the commencement of treatment. In addition, interviews with health service providers will uncover their perceptions of the stressors experienced by migrant TB patients, and their significance for the mental health, TB risk and treatment pathways/outcomes of this group.

*Sample and recruitment:* Patients will be recruited from TB services at St George's University Hospital NHS Trust and University Hospitals of Leicester NHS Trust, and community organisations such as Doctors of the World. Health service providers will be recruited from staff at the above NHS Trusts. Purposive sampling will be used to recruit a diverse group of migrants in relation to country of origin, time since migration, legal status and TB status. Snowball sampling may be used once the study has commenced. Participants will be recruited until theoretical saturation is reached.

*Methods:* The interviews will be conducted in person and will be semi-structured, with flexibility to be guided by the participants. The questions will be developed in conjunction with the Project Advisory Group (see below) and piloted. Oral and written translation will be available where preferred by participants. The interviews will be recorded and transcribed.

*Analysis:* Thematic analysis will be carried out to identify themes relating to stress and mental health among migrant TB patients. Data will be analysed using NVivo software.

### **3. Cross-sectional study**

A cross-sectional study will be carried out to explore the associations between psychosocial factors, mental health, immune function and TB status among migrants in the UK.

*Sample and recruitment:* The study will involve collecting data from migrants with latent and active TB accessing TB services at St George's University NHS Trust and University Hospitals of Leicester NHS Trust. Migrants with no history of TB will be recruited as controls, matched by age, gender, country of origin and reason for migration. These healthy controls will be recruited via community centres and organisations such as Doctors of the World. Based on existing literature, I anticipate that at least 25% of the population of interest will experience a common mental disorder or Post Traumatic Stress Disorder. Therefore, to have sufficient power for a multivariate analysis with four variables (see below), a sample size of at least 160 participants will be required. Purposive sampling will be used to ensure that the sample is representative of the migrant population with TB in England, based on PHE's TB surveillance report for 2018. This will allow for a comparison of migrants of different legal statuses and with variation in time since migration, to explore whether these factors influence psychosocial stress, mental health, immune response and TB risk.

*Methods:* Data will be collected on:

- a. Psychosocial factors, using various questionnaire instruments: Perceived Stress Scale, lifetime and 12 month stressful life events using an additive index, and Medical Outcomes Study Social Support Survey
- b. Mental health, using both medical history and Mini Neuropsychiatric Interview diagnostic screening tool
- c. Immune function, using blood and/or saliva samples to examine biomarkers of immunity associated with *M.tb* infection and TB disease, such as proinflammatory mediators including TNF and IFN $\gamma$  (whose secretion is measured by Luminex), steroid hormone levels, and herpesvirus-specific antibody titres, based on the findings of my MSc literature review

Oral and written translation will be available where preferred by participants.

*Analysis:* Descriptive analyses will be used to examine the association between key variables and latent infection and active TB disease. Multivariate regression will be used to examine these relationships, controlling for age, sex, country of origin and time since migration. Regression analyses will also be utilised to test for mediation, exploring the causal pathways linking psychosocial factors, mental health, immune function and TB status. All analyses will be carried out using STATA.

In addition, I will set up a Project Advisory Group with my supervisors comprised of experts from biological and social science disciplines, and representatives from migrant communities. This group will provide advice and support during the proposed research, and through patient and public involvement will help to ensure that the research is relevant to those which it seeks to benefit. As well as benefitting from the expertise of the project

supervisors and mentors in this group, I will also gain further training through courses such as the Advanced Statistical Methods in Epidemiology module at LSHTM and during a placement or internship with a relevant research group or organisation.

Ethical approval will be sought from relevant bodies for each component of the research. I have experience of securing ethical approval through my MSc project.

### **Implications and future research directions**

By investigating the relationship between psychosocial stressors, mental health, immune function, and TB risk in migrant populations, this novel research will improve our understanding of TB risk factors in this vulnerable group and address the current lack of evidence surrounding the biological mechanisms underlying such associations. It therefore adds to the small body of work attempting to unite social and biological strands of TB research. If the hypothesis that migrants' experiences of psychosocial stressors and mental disorders influence their immune function so as to increase TB risk is true, this supports initiatives and policies that seek to improve migration experiences, protect the rights of migrants, and support their integration into host communities. To have benefits for migrants at risk of TB, my research must be disseminated through engagement with stakeholders in both academia (through publications in peer-reviewed journals and presentations at international conferences) and policy-making (through links with organisations such as ECDC, PHE, WHO, and IOM), as well as migrants themselves.

Through this project, I intend to develop knowledge and skills that will strengthen my work at the interface between biological and social research at postdoctoral level, seeking to understand the biological mechanisms by which social exposures are manifested as health outcomes. There are a number of directions this research could be taken in the future, including exploring other plausible biological mechanisms such as gene x environment interactions and epigenetic modifications, and evaluating the effectiveness of interventions that seek to reduce TB risk by improving the psychosocial wellbeing of migrants.

### **References**

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