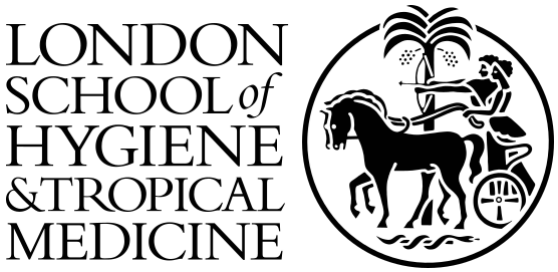

Defining a Migrant-Inclusive Tuberculosis Research Agenda to End TB

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Summary

Background. Pillar 3 of the End TB Strategy calls for the promotion of research and innovation at the country level in order to facilitate improved implementation of existing and novel interventions to end TB. In an era of increasing cross-border migration, there is specific need for integrating migration-related issues into national TB research agendas. The objective of this review is to provide a conceptual framework to guide countries in development and operationalization of a migrant-inclusive TB research agenda. ***Methods.*** We conducted a literature review complemented by expert opinion and the previous articles in this State of the Art series to identify important themes central to migration-related TB. We categorized those themes into a framework for a migration-inclusive global TB research agenda across a comprehensive spectrum of research. We developed this conceptual framework taking into account: 1) the biomedical, social and structural determinants of TB; 2) the epidemiologic impact of the migration pathway; and 3) the feasibility of various types of research based on country's capacity. ***Discussion.*** The conceptual framework presented here is based on the key principle that migrants are not inherently different from other populations in terms of susceptibility to known TB determinants, but they often have exacerbated or additional risks related to their country of origin and the migration process, which must be accounted for in developing comprehensive TB prevention and care strategies. A migrant-inclusive research agenda must systematically consider this wider context to have highest impact.

Introduction

The End TB Strategy approved by the World Health Assembly in May 2014 aims to end the global tuberculosis (TB) epidemic in line with the Sustainable Development Goals (SDGs) by 2030, with the targets of a 90% reduction in TB mortality, a 80% decline in TB incidence, and no TB-affected household experiencing catastrophic costs due to TB[1]. The strategy relies on three fundamental pillars, including "intensified research and innovation"[2]. Promoting research across its entire spectrum (including basic science, clinical, epidemiological, health systems, and operational/implementation research (OR/IR)) is critical to maximizing the impact on TB reduction strategies in all, especially in vulnerable and high risk populations who have higher risks of TB infection and disease, as well as poor treatment outcomes.

As described in previous articles within this series, migrants are often an especially vulnerable population due to the inherent risk of acquiring TB in high- and medium- burden countries, but also due to migration specific determinants[3] that affect individuals in even low-burden countries. The first paper of the present State of the Art series reviewed how migrants should be considered as a special vulnerable group within the frame of the WHO End TB Strategy[4]. Growing surveillance data demonstrates the changing patterns of TB incidence due in part to migration flows[3, 5]. This last paper of the series builds upon previous articles in describing critical evidence gaps in the current knowledge of migration related TB issues that make migration-inclusive research a priority for TB prevention and care. The intention of this paper is not to present a prescriptive and comprehensive research agenda for TB in migrants, but to describe a systematic approach to establishing migrant-inclusive TB research agendas and to provide pragmatic considerations for operationalizing such agendas.

Development of a conceptual framework for identifying evidence gaps and research priorities

In order to assess the current landscape of migrant-inclusive TB research, a non-comprehensive narrative literature review was conducted based on research areas defined in previous articles of this State of the Art series, including epidemiology, immunology, TB diagnostics, treatment, prevention, socio-economics and human rights. This review was based on a PubMed search using the keywords 'tuberculosis OR TB' AND 'migrants OR migration OR refugees or asylum seekers' AND 'research AND operational OR implementation OR trials OR epidemiology OR social OR immunology' from November 2015 through November 2017. A total of 204 papers were recovered that met search criteria and after abstract review, 76 papers were found to be related to migration related TB policy or research questions. Of these, 36 papers described some kind of "evidence gap" and were selected for more in-depth review. In addition, websites of main organizations contributing to aspects of TB in migrants (including WHO, International Organization for Migration (IOM), US Centers for Disease Control and Prevention (CDC), European Center for Disease Prevention and Control (ECDC), International Union Against TB and Lung Disease (The Union), and Médecins Sans Frontières (MSF)) were searched for evidence of ongoing or completed research activities related to migrants and TB. From the review, three thematic areas emerged: first, the need for migrant-inclusive research that considers the determinants of TB for migrant populations, including the biological, social and structural determinants that are traditionally thought of as risk factors for TB; second, specific additional TB risks due to the migration process itself should be considered; and third, the need for research on how to operationalize migrant-inclusive programs and policies for TB prevention and care given feasibility and ethics.

Based on these thematic areas, a conceptual framework was developed for systematically defining research priorities for TB in the context of migration at the country level. The framework suggests addressing migration related TB issues along three axes, adapted from the categories described above:

1) Consideration of the general TB determinants (biomedical, social, and structural) within migrant communities.
2) Consideration of the full migration pathway, from the country of origin, along the transitional or migration path, to the country of arrival (host country)[3, 4].
3) Consideration of the policies, practices and patient experiences along the cascade of care from prevention to diagnosis and treatment of TB.

Mapping the existing country context along these axes may systematically identify research gaps and priorities that are context specific. We describe potential research questions that can be derived within classical research categories using this conceptual framework.

Epidemiologic Research

Despite a growing body of literature on the epidemiology of infectious diseases among migrants, critical evidence gaps remain. This section addresses the various risks of TB in migrants along the spectrum of the migration pathway, and how existing TB surveillance and data analysis systems may be mobilized to answer specific research questions. Considering TB burden in low-, medium-, and high-incidence countries, key epidemiological questions emerge.

First, what are the specific effects of migration on TB: is migration a risk for TB, or a risk of poor outcome, or a mixture of these and others? There is substantial evidence that being a migrant from a high- or medium-burden country is a risk factor for TB in foreign-born persons living in a low-TB incidence country[3,6], but how migration changes that risk still remains unclear. For example, risk factors for

progression to active disease may be augmented due to poor general health, malnutrition, HIV infection, stress/anxiety, trauma, inadequate living conditions, or mental health disorders in vulnerable populations (including depression, bipolar disorders and psychosis) pre-migration as well as during and post-migration. The investigation of migration related epidemiological risk factors and their impact on progression to active disease would assist in developing reliable mathematical models to project TB trends in migrants and the general population[7]. Such models are essential for forecasting and planning and, if combined with health economic modelling, can help targeting promising interventions to those determinants of TB most relevant to migrant populations[8].

Secondly, migration may exacerbate both individual and structural determinants of TB in populations already at risk[9]. As the causes and pathways of migration are heterogeneous, studies are needed that examine the epidemiologic and public health impact of differences across various types of migration pathways and categories of migrants - ranging from voluntary labor migrants to health care seeking migrants to destitute forced migrants traveling along dangerous routes with limited empowerment[9]. Most existing research focuses on descriptive epidemiology of TB in migrants post-arrival in the host country, demonstrating heightened social, economic and structural determinants of disease such as poverty, unemployment, and poor housing,[10] but not much on specific factors relevant to the stage in migration[3]. A better understanding of TB risks associated with migration would help shaping appropriate multi-sectoral policies (before, during, and after migration) to improve TB prevention and care in these populations. This is especially critical in low-incidence countries with a concentrated TB epidemic where the majority of TB cases are among the non-native born population. It is also relevant for high TB burden countries with a large number of migrants from other high burden countries,[4,11] an often overlooked migration pathway.

Research is also needed to better understand TB transmission along migration routes whether migrant-to-migrant transmission or migrant-to-native population transmission. The limited and heterogeneous existing data from molecular epidemiology do not provide enough evidence to measure the latter[3,12]. Moreover, findings can be hard to generalize, since transmission rates depend not only on the underlying risk in a migrant group but also on existing TB care and prevention strategies in a given setting and mixing patterns between the migrant and native population. Epidemiological research, including molecular epidemiology combined with health systems research may help identify gaps and opportunities for prevention of TB transmission. In this respect, careful attention should be paid to multi-drug resistant TB (MDR-TB) in migrants and research should be conducted to better characterize the burden of drug resistance in this population and its determinants[13,14].

The process of migration itself can have an impact on the relevance of TB-related policies, practices, and patient experiences. It is therefore critical to design and expand TB surveillance systems to monitor TB trends in different groups of migrants. Most countries that monitor TB rates in migrants lack detailed information about type of migrant, migration routes, time since arrival and risk profile[3, 7]. Such surveillance could inform more appropriate strategies for targeted testing and treatment of migrants with higher TB risk. This type of research can inform migrant-inclusive patient pathways of care as a first step in understanding migration specific gaps in health access, utilization, and health outcomes.

Guidance exists on how to collect migrant-inclusive epidemiologic data. However, research is needed to assess the effectiveness of this type of guidance in resolving gaps in data and improving overall data management and quality. The ECDC, for example, has developed guidance for the collection of TB risk

159 factor data as part of routine surveillance[15]. As the majority of TB cases among migrants arise from
160 reactivation of latent TB infection (LTBI) contracted in the country of origin[3], there is a need to collect
161 high quality data on prevalence of LTBI in different migrant risk groups, and link these to TB register
162 data in order to determine reactivation rates and to identify additional determinants of disease. These types
163 of additional surveillance components require additional health systems research. OR/IR can then be used
164 to develop targeted interventions to reduce the higher risk of reactivation in these groups.

165 **Operational and Implementation Research on the Patient Cascade of Care: Prevention, Diagnosis,**
166 **and Treatment of TB**

167 Migrants from TB endemic countries are the largest TB risk group in a growing number of low-incidence
168 countries and therefore require special attention when designing TB prevention and care activities[3].
169 Presently there is little consensus on the best interventions to target these populations, and there are limited
170 data on the implementation of evidence-based guidelines on management of TB in migrant settings[16-19].
171 This may be due to the highly variable environments, conditions, and causes of migration that make
172 standardized approaches challenging. Ensuring quality TB care (for active disease and latent infection)
173 for migrants requires appropriate OR/IR at every stage of the patient cascade of care to understand how
174 to optimize conditions for prevention, diagnosis, and treatment in each context[11, 20]. In this section, we
175 focus on potential OR/IR categorized by each step in the patient cascade of care, with a focus on policies
176 and programmatic practices relevant to prevention, diagnosis, and treatment of TB.

177 ***TB Diagnosis: Intertwining of Latent and Active Disease***

178 Novel tools are needed to diagnose TB in general populations and differentiate the various stages of
179 infection[21]. Especially in very mobile migrant populations, diagnostic tests need to be of high
180 performance, easily operational, rapid and at the point of care so as to minimize losses to follow up. While

these characteristics certainly apply to the diagnosis of active disease (drug susceptible or drug resistant), new programmatic strategies should be developed for diagnosis of latent TB infection (LTBI). For these reasons, there is need for enhanced research to optimize the implementation of existing diagnostic tools and develop interventions to improve coverage of 'hard to reach' migrant populations, especially the most vulnerable groups like those who are undocumented and likely to be 'missed' by the health systems.

Screening for latent TB infection. Treatment of LTBI has been identified as one of the potentially most powerful interventions for elimination of TB[28], together with vaccination. Currently available tests to detect LTBI, the tuberculin skin test (TST) and the *in vitro* interferon-gamma release assays (IGRAs), measure an anamnestic response to *M. tuberculosis* antigens. Based on the results of a meta-analysis of eight head-to-head studies that showed similar capacity of the 2 tests to 'predict' incident disease during short term follow-up, WHO recommends either test to identify healthy individuals that should be considered for LTBI treatment[22] - of note, only one of the eight studies had been conducted in migrants[23], which suggests that additional research should be conducted inclusive of this population.

Evidence for the best targeted testing strategy for LTBI in migrants is still limited. Several studies suggest that screening with a single-step IGRA is more cost-effective than TST screening[24-26]. However, a modelling study comparing different LTBI screening strategies in non-native born entrants to Canada found that sequential screening with TST followed by IGRA was more cost-effective than each of these alone[27]. The capacity of both TST and IGRAs to predict incident TB in individuals with a positive result is very low, with the number needed to treat [NNT]) to prevent one case of active disease of 67 for TST and 37 for IGRAs[28]. LTBI screening efficiencies in migrants specifically are unknown. Additional research is needed to improve LTBI diagnostic tools and screening strategies.

A new model of TB natural history has been proposed that considers a continuous spectrum from spontaneous clearance of bacteria to quiescent infection to disease[29]. The prolonged asymptomatic phase of early disease during which pathology evolves prior to clinical presentation of active disease is defined as 'incipient TB' [30]. According to this scenario, diagnostic tests for LTBI should be conceptually categorized into two categories: 1) test for persistent infection; and 2) test for incipient TB[31]. Despite recent progress in identifying genomic signatures that are correlates for risk of progression[32], tests of either persistent disease or incipient TB are not yet commercially available (although one RNA based PCR test is in clinical trial[33]). While such a test could improve targeting of infected patients, the role of fluctuating TB determinants that change as a result of the migration pathway (eg nutrition), should be addressed in the evaluation of these novel tests. Based on these new diagnostic developments, a subsequent research area is to develop new treatment regimens for incipient TB. The powerful impact that such new tools would have not only on migrant populations but for global TB control emphasizes the need for basic and clinical research in this field.

Screening and Diagnosis of active disease.

Current challenges in screening for active TB among migrants are similar to those in other high-risk populations. The limitations of existing tests are the low sensitivity and specificity of smear microscopy and the need for laboratory expertise and long growth times required for culture-based methods[34]. In addition, screening for TB in migrants face the operational challenges of provision of rapid care in a potentially mobile population with often limited health care access. Therefore, a migrant-inclusive TB research agenda must include an evaluation of not only technologies, but also of new strategies for

screening and diagnosing active TB. These interventions may include active case finding using symptom screen, chest radiography, or other strategies[17, 35].

Several existing diagnostic tests and strategies have the potential to address TB diagnostic challenges in migrants. These include molecular methods, such as the XpertMTB/RIF assay, Xpert Omni,[36] and Xpert MTB/RIF Ultra assay (Ultra) (Cepheid, USA), which have been recommended for use in a variety of populations by WHO[37,38] as well as tests such as urinary lipoarabinomannan (LAM) detection, *Mycobacterium tuberculosis* complex loop-mediated isothermal amplification (TB-LAMP), and molecular line probe assays for drug resistance. Although the need for point-of-care tests is even more flagrant in mobile populations, none of these diagnostic tools have been operationally evaluated in migrant populations[39-41]. OR/IR is needed to assess feasibility and effectiveness of these diagnostic tests in migrant-inclusive settings, to identify mechanisms for scale up, and to improve linkages to care.

Access to Care and Treatment Adherence. Migrant communities often face barriers to accessing health services. While all migrants should have the right to healthcare services[42, 43], there is limited information on the ability of migrants to access care when they experience symptoms and signs of TB along the migration pathway. Studies from several EU host countries showed that access to medical services may be restricted[44, 45], and often depends on the type of residence permit the migrant holds [46]. Since access to health care is essential for early diagnosis and treatment of TB, identifying the gaps and testing interventions that can improve access to health services for all types of migrants is needed, particularly for implementing quality TB care. For example, while it was shown using mathematical models that screening high risk subpopulations with IGRAs had the potential for high cost effectiveness which was

conducive to policy change, lack of empirical effectiveness data in these subpopulations was identified as a barrier to effective implementation of a targeted testing and treatment strategy[47].

Migrants with TB often have lower treatment success rates compared to native individuals[48-51]. Understanding the underlying reasons for this is critical and context-specific. Several studies have shown that even at the subnational level, identifying and targeting factors associated with default or loss to follow up can improve health systems responses to TB treatment provision for migrant populations[49, 50, 52]. For instance, a systematic review evaluating reasons for non-adherence to treatment in 5 continents described heterogeneous TB treatment outcomes among migrants due to variability in legal status and social risk factors such as education, employment and access to care[53]. This heterogeneity may be particularly important when evaluating the full potential of novel treatment strategies such as short-course treatment regimens for drug resistant disease, the use of digital health technologies to support treatment adherence[54, 55], and planning for scale-up of treatment programs[53]. The critical point is that context-specific data are required to understand how best to support migrants in initiating and completing treatment. Such evidence can then expand to health systems research and policy change for creating mechanisms and application of legal frameworks for cross-border TB control that facilitate access to care.

Social Protection Research

The majority of migrants are exposed to socioeconomic vulnerabilities along the migration pathway from country of origin to country of destination, including those associated with [3]:

1) social, biological, and structural determinants of TB in their country of origin, in transit, and in host country;

2) the migration process/transit (malnutrition, trauma, violence, mental health issues, substance abuse, including alcohol and smoking);
3) the living conditions in the country of transit/destination (poor housing quality, crowding, inadequate working conditions, poor nutrition, food insecurity); and
4) the limited access to health care services both during transit and in the country of destination, often due to language, economic and cultural barriers.

All these features of poverty and vulnerability point to substantial needs for social protection, defined as a set of policies and programmes aimed at reducing the social and economic risk for those who need to access and receive care[10].

Social protection strategies have shown promise as a way to improve treatment outcomes among TB affected households with significant socioeconomic risk[56, 57]. However, even in settings where social protection schemes have shown benefit in TB outcomes, operationalizing these strategies in migrants may pose significant challenges[58]. Research is required that systematically assesses migrants' vulnerabilities and their social and economic barriers to care to identify where and when in the migration pathway social protection interventions should be deployed. Understanding and evaluating the benefit of TB-sensitive approaches (social protection schemes for which TB patients may be eligible based on criteria unrelated to their disease) versus TB-specific approaches (social protection schemes for with TB disease is an eligibility criteria) will be required in understanding how to operationalize these interventions. These vulnerabilities as well as barriers to care are unlikely to be significantly different from those observed among non-migrant populations when accounting for socioeconomic status, but migration is likely to exacerbate them. Research is required to understand the full effect of this potentiation and identify suitably targeted social protection interventions.

Despite a growing body of evidence that suggests the positive impact of cash transfer schemes on TB and economic outcomes[57, 59-61], we are not aware of such studies among migrants[62]. While health policies in some countries include access to social protection for any legal resident, there is limited information on how such effective policies may translate to migrant populations with similar socioeconomic characteristics but without a legal status[56, 61, 62]. Research on how to operationalize social protection and measure the effect of economic support and welfare [2, 63, 64]on TB outcomes in migrant populations is needed to inform development of suitable social protection schemes both in high- and middle-income host countries[65]. Examples of such research include studying the feasibility and impact of a cash transfer for migrants diagnosed with TB or the impact of short-term disability insurance at the time of treatment initiation. High-quality operational/implementation research on social protection that includes migrants would contribute to reaching the targets of the End TB Strategy within the larger context of the SDGs[66].

Creating and Operationalizing a Migrant-Inclusive Research Agenda

While high- and medium-burden countries are developing national TB research agendas in keeping with Pillar 3 of the End TB Strategy, very few, if any, specifically address the particular challenges of TB prevention and care in migrants. To properly inform national and international policies to improve migrants' health with particular reference to TB, a research agenda is needed at the global and country level that: (i) draws from a context-specific and migrant-inclusive situational assessment; (ii) engages a variety of partners including those from migrant communities; (iii) leverages supranational or regional networks; (iv) draws on political leadership; and (v) includes ethical and accountable mechanisms for implementation and dissemination.

313 The research and innovation pillar of the End TB Strategy[2] promotes the need for well-designed and
314 empirically grounded research. To facilitate this, WHO has developed the Global Action Framework for
315 TB Research[67] and a Toolkit[68] for developing national TB research agendas. These tools may be used to
316 develop context-specific research questions related to the challenges of eliminating TB in migrant
317 populations and to ensure that the national TB research agendas being developed are migrant-inclusive.
318 Such research agendas will benefit from engaging stakeholders with expertise in migration, epidemiology,
319 demography, biomedicine, health systems, and other social sciences in the identification of research
320 priorities to improving the health of the migrant population. The participation of the migrant community
321 is necessary to guarantee the proper consideration of the migrant perspective - for example, in addressing
322 the impacts of migrant/refugee status, ethnicity and socioeconomic status on health service access and
323 utilization.

324 Countries establishing migrant-inclusive TB research agendas should consider multi-country agreements
325 that harmonize research priorities, such as between migrants' countries of origin and destination (both
326 high and low TB burden countries). This can be achieved through national or regional TB and migration
327 research platforms that would allow for transnational linkages critical for building capacity and
328 disseminating knowledge and innovation. Such platforms, or research "hubs", may be powerful in
329 monitoring TB control efforts in migrants, advocating for political and financial commitment,
330 strengthening institutional and community capacities and ensuring the collaboration necessary to address
331 this issue head on[11]. Political leadership is needed to prioritize an innovative TB response through an
332 integrated and multi-disciplinary research approach. The time is ripe for such political commitment, in
333 light of the recent WHO Ministerial Meeting on Tuberculosis convened in Moscow in November 2017
334 and in preparation for the discussion of TB at the 2018 United Nations General Assembly.

Finally, migrant communities should be engaged in research prioritization from the outset, including in research implementation and dissemination of findings. Migrant populations may not have adequate rights or representation as granted to citizens within national legislation. Therefore, researchers must ensure that adequate international and national legislative frameworks on research ethics and data protection are applied[69]. Researchers must have a strategy to address issues of privacy, informed consent, coercion, and social and psychological distress or trauma. Protection and promotion of human rights, ethics and equity is one of the fundamental principles underpinning the End TB Strategy[2]. For migrant populations, promoting and protecting their health and respecting, protecting and fulfilling human rights are inextricably linked. A migrant-inclusive TB research agenda should address evidence-based solutions that respect, protect and fulfil migrants' human rights.

Conclusion

Identifying and pursuing a migration-inclusive TB research agenda is critical for advancing our understanding of TB among migrant populations and improving TB prevention and care worldwide. In this review, we propose a conceptual framework for constructing migrant-inclusive research agendas at national and multi-national levels, and present areas of particular focus for research in countries attempting to address TB diagnosis, treatment and prevention in migrant populations (Table). To achieve the ambitious targets of the End TB Strategy and align with the SDGs, migration-inclusive health policies and programs are needed now more than ever.

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537 **Table. Suggested Migration-Inclusive TB Research Agenda**

Research Approach	Research Priority Areas
Epidemiological Research	· Identify TB/LTBI risks and heterogeneity specific to the migrant population at all points along the migration pathway · Refine use of molecular epidemiology to determine clustering, transmission dynamics, and reactivation rates in migrant populations throughout the migration pathway · Describe risk factors for all types of migrants · Describe MDR epidemiology in migrants · Optimize cross-border surveillance and epidemiological analysis of TB and migration between high-burden countries · Assess LTBI prevalence stratified by risk factors such as gender, age, socioeconomic status, country of origin, and situation along the migration pathway · Assess the epidemiologic impact of migration as healthcare seeking, especially for patients with drug resistant TB
Basic and Clinical Research	· Develop novel diagnostic tests for LTBI that meet test performance needs for migrant populations including children. · Assess efficacy and effectiveness of novel short course regimens (4-6 week therapy) for prevention of TB for migrant populations including children · Develop of point of care diagnostic tests that meet test performance needs for migrant populations including children · Develop of high efficacy short course regimens for treatment of TB · Elaborate host-pathogen interactions with more specificity to inform diagnostic and therapeutic development · Characterize the effect of modifiable TB social and structural determinants that affect immune response to the pathogen · Assess prevention and treatment of migrants who are contacts of drug-resistant patients to prevent disease
Operational and Implementation Research	
---*Prevention and Screening*	· Evaluate feasibility of LTBI targeted testing and treatment algorithms on migrants at key points along the migration pathway · Assess the use of mobile health (mHealth) and digital health technologies to support linkage to care and treatment adherence in migrant populations · Evaluate the operational impact of LTBI screening tools (both pre-and post-arrival)
---*Diagnostics*	· Evaluate specific evidence-based diagnostic guidelines in migrant populations as compared to native populations · Identify health systems and patient barriers to implementation of diagnostic testing strategies in migrants
---*Treatment*	· Establish the comparative effectiveness of treatment strategies (e.g. DOT versus SAT) · Evaluate the impact of novel treatment regimens including short course therapy in migrants when implemented in programmatic settings · Identify core components of interventions needed to maximize treatment adherence · Pilot mechanisms to ensure that culture and drug susceptibility results are communicated to providers treating a patient along the migration pathway
Health Systems and Health Economics Research	· Evaluate cost- and cost effectiveness of migrant-focused TB interventions · Analyse gaps in health system access specific to documented and undocumented migrants along the migration pathway

	· Establish critical components necessary for operationalizing cross-border collaborations
Social Protection Research	· Identify context-specific social and economic vulnerabilities in migrants · Identify targetable socioeconomic barriers to TB care for migrants · Evaluate the effectiveness and impact of social protection strategies on reducing vulnerabilities and improving public health and TB outcomes in migrants · Understand the contextual requirements for including migrants in social protection schemes · Identify and evaluate TB-sensitive and TB-specific interventions on migrant health
Health and Human Rights Research	· Document infringements on human rights of TB programmes · Develop TB specific interventions that support the human rights of migrants

538 TB Tuberculosis, LTBI Latent iuberculosis infection, DOT Directly observed therapy, SAT Self-
539 administered therapy, MDR Multidrug resistant tuberculosis