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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 to facilitate improved implementation of existing and novel interventions to end tuberculosis (TB). In an era of increasing cross-border migration, there is a specific need to integrate migration-related issues into national TB research agendas. The objective of the present review is to provide a conceptual framework to guide countries in the 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 these 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 a 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 that 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

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prevention and care strategies. A migrant-inclusive research agenda should systematically consider this wider context to have the highest impact.

RÉSUMÉ

CONTEXTE:

Le troisième pilier de la stratégie pour mettre fin à la TB nécessite la promotion de la recherche et de l'innovation au niveau de chaque pays de manière à faciliter une amelioration de la mise en oeuvre des interventions existantes et nouvelles visant à mettre fin à la tuberculose (TB). A une époque de migration transfrontalière croissante, il y a un besoin spécifique d'intégration des questions liées à la migration dans l'ordre du jour de la recherche nationale TB. L'objectif de la revue est de fournir un cadre conceptuel afin de guider les pays dans l'élaboration et l'opérationalisation d'un programme de recherche TB incluant les migrants.

MÉTHODE:

Nous avons réalisé une revue de litérature complétée par l'opinion d'experts et les articles précedénts de cette série de pointe afin d'identifier les thémes importants du cadre de la TB liée à la migration. Nous avons catégorisé ces thémes dans un cadre conceptuel pour un programme de recherche TB mondial, incluant la migration dans un large spectre de recherche. Nous avons élaboré ce cadre conceptuel en tenant compte : 1) des déterminants biomédicaux, sociaux et structurels de la TB; 2) de l'impactépidémiologique des voies de migration; et 3) de la faisabilité de différents types de recherche basée sur lescapacités du pays.

DISCUSSION:

Le cadre conceptuel présenté ici est basé sur le principe clé que les migrants ne sont pas fondamentalement différents des autres populations en termes de susceptibilité aux déterminants connus de la TB, mais ils ont souvent des risques exacerbés ousupplémentaires lies à leur pays d'origine et au processus de migration, dont il faut tenir compte dans l'élaboration de stratégies intégrées de prévention et de prise en charge de la TB. Un programme de recherche incluant les migrants doit systématiquement envisager ce contexte élargi pour avoir le plus grand impact possible.

RESUMEN

MARCO DE REFERENCIA:

El tercer pilar de la Estrategia Fin a la Tuberculosis exige intensificar la investigación y fomentar la innovación a escala de los países con miras a optimizar la aplicación de las nuevas iniciativas y las intervenciones ya existentes, encaminadas a poner fin a la enfermedad. En una época en la cual se acentúan cada vez más las migraciones transfronterizas, es necesario incorporar elementos relacionados con la migracion en los programas nacionales de investigación en tuberculosis (TB). La finalidad de la presente revisión fue aportar un marco conceptual que oriente a los países en la elaboración y la ejecución de programas de investigación en TB que incluyan a los migrantes.

MÉTODOS:

Se llevó a cabo una revisión de las publicaciones científicas complementada con opiniones de expertos y artículos anteriores de esta serie de Artículos Vanguardistas, con el propósito de definir los temas importantes que son centrales en la TB relacionada con las migraciones. Los temas se

categorizaron en un marco destinado a la formulación de un programa mundial de investigación en TB que incluya a los migrantes y cubra todos los ámbitos de aplicación. El marco conceptual elaborado aborda los siguientes aspectos: 1) los determinantes biomédicos, sociales y estructurales de la TB; 2) la repercussion epidemiológica de las rutas migratorias; y 3) la factibilidad de diversos tipos de investigación, enfunción de la capacidad de los países.

CONCLUSIÓN:

El marco conceptual descrito en el presente artículo se fundamenta en el principio primordial de que no existe una diferencia constitutiva entre los migrantes y otros grupos de la población, conrespecto a la susceptibilidad a los determinantes conocidos de la TB, pero con frecuencia los migrantes están expuestos a factores de riesgo exacerbados o más numerosos relacionados con su país de origen y con el proceso migratorio que tienen que tenerse en cuenta al elaborar estrategias integrales de prevención y atenciónde la TB. Es esencial que todo programa de investigaciónque incluye a los migrantes considere de manera sistemática este contexto más amplio, a fin de lograr el mayor impacto.

Keywords

migrants; TB; research agenda; End TB; WHO

IN LINE WITH the Sustainable Development Goals (SDGs), the End TB Strategy approved by the World Health Assembly in May 2014 aims to end the global tuberculosis (TB) epidemic by 2030, by targeting a 90% reduction in TB mortality, an 80% decline in TB incidence, and the elimination of catastrophic costs due to TB.[1] The strategy relies on three fundamental pillars, including 'intensified research and innovation'.[2] The promotion of research across its entire spectrum, including basic science, clinical, epidemiological, health systems, and operational/implementation research (OR/IR), is critical to maximizing the overall impact on TB reduction strategies, particularly in vulnerable and high-risk populations who have higher risks of tuberculous infection and TB disease, as well as poor treatment outcomes.

As described in previous articles in this series, migrants are often an especially vulnerable population due not only to the inherent risk of acquiring TB in high- and medium-burden countries, but also due to migration-specific determinants.[3] The first paper of the present State of the Art (SoA) series on TB and migration reviewed how migrants should be considered as a special vulnerable group within the framework of the World Health Organization (WHO) End TB strategy.[4] Surveillance data increasingly indicate changing patterns in TB incidence due in part to migration flows.[3,5]

This last paper of the series builds upon the previous articles in describing critical gaps in the current knowledge about migration-related TB issues that make migration-inclusive research a priority for TB prevention and care. The aim of the present 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

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 in this SoA series, including epidemiology, immunology, TB diagnostics, treatment, prevention, socio-economics and human rights. The 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 the search criteria; 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, the websites of the main organizations that contribute to aspects of TB in migrants, including the WHO, the International Organization for Migration (IOM), the US Centers for Disease Control and Prevention (CDC; Atlanta, GA, USA), the European Centre for Disease Prevention and Control (ECDC; Stockholm, Sweden), the International Union Against Tuberculosis and Lung Disease (The Union; Paris, France), and Médecins Sans Frontiéres (Paris, France) were searched for evidence of ongoing or completed research activities related to migrants and TB. From the review, three thematic areas emerged: 1) the need for migrant-inclusive research that takes into account TB determinants in migrant populations, including biological, social and structural determinants traditionally believed to be risk factors for TB; 2) the need to take into consideration TB risks due to the migration process itself; and 3) the need for research on how to operationalize migrant-inclusive programs and policies for TB prevention and care if these are feasible and ethically sound.

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 determinants of TB (biomedical, social, and structural) in 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 help to systematically identify research gaps and priorities that are context-specific. We describe below 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 gaps in evidence remain. This section addresses the various risks of TB in migrants along the spectrum of the migration pathway, and how existing TB surveil-lance 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 factor for TB, a risk for 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 affects this risk remains unclear. For example, risk factors for progression to active disease may be augmented due to poor general health, malnutrition, human immunodeficiency virus infection, stress/anxiety, trauma, poor living conditions, or mental health disorders in vulnerable populations (including depression, bipolar disorders and psychosis) before as well as during and after 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 in the general population. [7] Such models are essential for forecasting and planning and, if combined with health economic modeling, can help target promising interventions to include those TB determinants that are most relevant to migrant populations.[8]

Second, 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 examining the epidemiologic and public health impact of differences across various types of migration pathways and categories of migrants are needed; these should cover all migrants—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 the descriptive epidemiology of TB in migrants following their arrival in the host country, demonstrating heightened social, economic and structural determinants of disease such as poverty, unemployment, and poor housing,[10] but very little on specific factors relevant to this stage in migration.[3] A better understanding of the TB risks associated with migration would help shape appropriate multisec toral 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, both migrant-to-migrant transmission and 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, as 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 migrant and native populations. Epidemiological research, including molecular epidemiology combined with health systems research, may help identify gaps and opportunities for the prevention of TB transmission. Careful attention should also be paid to multidrug-resistant 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 for monitoring 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.

Although there are guidelines on how to collect migrant-inclusive epidemiologic data, 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 factor data as part of routine surveillance.[15] As the majority of TB cases among migrants are caused by the reactivation of latent tuberculous infection (LTBI) contracted in the country of origin,[3] there is a need to collect high-quality data on LTBI prevalence in different migrant risk groups, and link these to TB register data to determine reactivation rates and identify additional determinants of disease. These types of additional surveillance components require additional health systems research. OR/IR can then be used to develop targeted interventions to reduce the higher risk of reactivation in these groups.

OPERATIONAL AND IMPLEMENTATION RESEARCH ON THE PATIENT CARE CASCADE: PREVENTION, DIAGNOSIS, AND TREATMENT OF TUBERCULOSIS

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

Tuberculosis diagnosis: intertwining of latent and active disease

Novel tools are needed to diagnose TB in general populations and differentiate between the various stages of infection.[21] Especially in very mobile migrant populations, diagnostic tests need to be highly performant, easily operational, rapid and offered at the point of care to minimize loss to follow-up. While these characteristics certainly apply to the diagnosis of active disease, both drug-susceptible and drug-resistant, new programmatic strategies should be developed for the diagnosis of LTBI. There is thus a need for enhanced research to optimize the implementation of existing diagnostic tools and develop interventions to improve coverage of 'hard to reach' migrant populations, particularly the most vulnerable groups, such as undocumented migrants, who are likely to be 'missed' by the health systems.

Screening for latent tuberculous infection

LTBI treatment has been identified as potentially one of the most powerful interventions for TB elimination,[22] together with vaccination. Tests currently available for LTBI detection—the tuberculin skin test (TST) and in vitro interferon-gamma release assays (IGRAs)—measure the anamnestic response to *Mycobacterium tuberculosis* antigens. Based on the results of a meta-analysis of eight head-to-head studies that showed similar capacity of the two tests to 'predict' incident disease during short-term follow-up, the WHO recommends that either test may be used to identify healthy individuals who should be considered for LTBI treatment.[23] It should be noted that only one of the eight studies had been conducted in migrants,[24] which suggests that additional research should include this population.

Evidence for the best targeted testing strategy for LTBI in migrants remains limited. Several studies have suggested that screening using a single-step IGRA is more cost-effective than TST screening.[25–27] However, a modeling 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 the tests alone.[28] The capacity of both TST and IGRAs to predict incident TB in individuals with a positive result is very low: the number needed to treat in order to prevent one case of active disease was 67 for TST and 37 for IGRAs.[22] The efficiency of LTBI screening strategies specifically in migrants is unknown. Additional research is needed to improve LTBI diagnostic tools and screening strategies.

A new model of the natural history of *M. tuberculosis* 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 before 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 the risk of progression,[32] tests of either persistent disease or incipient TB are not yet commercially available, although one RNA-based polymerase chain reaction test is in clinical trial.[33] While such a test could improve targeting of infected patients, the role of changing TB determinants that change as a result of the migration pathway (e.g., 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 TB control globally, 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 the existing tests are the low sensitivity and specificity of smear microscopy, the need for laboratory expertise and the prolonged growth times required for culture-based methods.[34] In addition, TB screening in migrants faces operational challenges, such as providing rapid care in a potentially mobile population with often limited access to health care. A migrant-inclusive TB research agenda should therefore include an evaluation not only of 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 Xpert® MTB/RIF assay, Xpert® Omni,[36] and the Xpert® MTB/RIF Ultra assay (Cepheid, Sunnyvale, CA, USA), which have been recommended for use in a variety of populations by the WHO,[37,38] as well as tests such as urinary lipoarabinomannan (LAM) (Determinee™ TB LAM Ag; Alere Inc, Waltham, MA, USA) detection, *M. tuberculosis complex* loop-mediated isothermal amplification (TB-LAMP, HUMAN Diagnostics, Wiesbaden, Germany), 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 the feasibility and effectiveness of these diagnostic tests in migrant-inclusive settings to identify mechanisms for scale-up of screening and diagnosis of active disease, 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 health care 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 European Union host countries have shown that access to medical services may be restricted,[44,45] and often depends on the type of residence permit the migrant holds.[46] As access to health care is essential for the 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 has been shown using mathematical models that screening high-risk subpopulations with IGRAs has the potential for high cost-effectiveness which was conducive to policy change, the lack of empirical effectiveness data in these subpopulations was identified as a barrier to the effective implementation of a targeted testing and treatment strategy.[47]

Migrants with TB often have lower treatment success rates than native-born 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 in migrant populations.[49,50,52] For example, a systematic review evaluating reasons for non-adherence to treatment in five continents described heterogeneous TB treatment outcomes among migrants due to the 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 be extended 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 the 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 the 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. limited access to health care services both during transit and in the country of destination, often due to language, economic and cultural barriers.

This poverty and vulnerability highlights the need for social protection, defined as a set of policies and programs aimed at reducing the social and economic risk for those who need to access and receive care.[10]

Social protection strategies show promise as a way to improve treatment outcomes among TB-affected households with significant socio-economic risk.[56,57] However, even in settings where social protection schemes have been shown to benefit TB outcomes, operationalizing these strategies in migrants may pose significant challenges.[58] Research systematically assessing migrant vulnerabilities and their social and economic barriers to care is required 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) vs. TB-specific approaches (social protection schemes for which TB disease is an eligibility criterion) 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 socio-economic status, but migration is likely to exacerbate them. Research is required to understand the full effect of this potentiation and identify targeted social protection interventions.

Despite a growing body of evidence indicating the positive impact of cash transfer schemes on TB and economic outcomes,[57,59–61] we are not aware of similar 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 appropriate 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 the development of suitable social protection schemes in both high- and middle-income host countries.[65] Examples of such research include studying the feasibility and impact of a cash transfer scheme for migrants diagnosed with TB, or the impact of short-term disability insurance at the time of treatment initiation. High-quality OR/IR 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 line 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 migrant health with particular reference to TB, a research agenda is needed at the global and country level that: 1) draws from a context-specific and migrant-inclusive situational assessment; 2) engages a variety of partners, including those from migrant communities; 3) leverages supranational or regional networks; 4) draws on political leadership; and 5) includes ethical and accountable mechanisms for implementation and dissemination.

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

Countries establishing migrant-inclusive TB research agendas should consider multicountry agreements that harmonize research priorities, such as between migrants' countries of origin

and destination (both high and low TB burden countries). This can be achieved through national or regional TB and migration research platforms that would allow for transnational linkages that are critical for building capacity and disseminating knowledge and innovation. Such platforms, or research 'hubs', may be powerful in monitoring TB control efforts in migrants, advocating for political and financial commitment, strengthening institutional and community capacities and ensuring the collaboration necessary to address this issue head on.[11] Political leadership is needed to prioritize an innovative TB response through an integrated and multidisciplinary research approach. The time is ripe for such political commitment in the light of the recent WHO Ministerial Meeting on Tuberculosis convened in Moscow in November 2017, 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. Researchers should therefore 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] The promotion and protection of migrant health are inextricably linked to the respect, protection and fulfilling of migrants' human rights. A migrant-inclusive TB research agenda should address evidence-based solutions that respect, protect and fulfil migrants' human rights.

CONCLUSION

The identification and pursuit of a migration-inclusive TB research agenda are 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 multinational levels, and present areas of particular focus for research in countries attempting to address TB diagnosis, treatment and prevention in migrant populations (Table 1). To achieve the ambitious targets set by the End TB Strategy that are in line with the SDGs, migration-inclusive health policies and programs are needed now more than ever.

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Table 1

Suggested research questions in a 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-TB 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 sex, age, socio-economic status, country of origin, and situation along the migration pathway Assess the epidemiologic impact of migration on health care seeking, particularly in 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 the efficacy and effectiveness of novel short-course regimens (4–6-week treatment) for TB prevention in migrant populations, including children Develop of point-of-care diagnostic tests that meet test performance needs in migrant populations, including children Develop high-efficacy short-course regimens for the 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 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 vs. SAT) Evaluate the impact of novel treatment regimens, including short-course treatment, 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 the cost and cost-effectiveness of migrant-focused TB interventions Analyze 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 socio-economic 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 by TB programs Develop TB-specific interventions that support the human rights of migrants

TB = tuberculosis; LTBI = latent tuberculous infection; MDR-TB = multidrug-resistant TB; DOT = directly observed therapy; SAT =self-administered therapy.