

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30

Defining a Migrant-Inclusive Tuberculosis Research Agenda to End TB

Priya B. Shete^{1,2}, Delia Boccia³, Poonam Dhavan⁴, Nebiat Gebreselassie¹, Knut Lönnroth⁵, Suzanne Marks⁶, Alberto Matteelli⁷, Drew L. Posey⁸, Marieke J. van der Werf⁹, Carla A. Winston⁵, Christian Lienhardt^{1,10}

- ¹ Global Tuberculosis Programme, World Health Organization, Geneva, Switzerland
- ² Division of Pulmonary and Critical Care Medicine, University of California San Francisco, San Francisco, USA
- ³ Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom
- ⁴ International Organization of Migration, Geneva, Switzerland
- ⁵ Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden
- ⁶ Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Atlanta, USA
- ⁷ Department of Infectious and Tropical Diseases, WHO Collaborating Centre for TB/HIV collaborative activities and for the TB elimination strategy, University of Brescia, Brescia, Italy
- ⁸ Division Global Quarantine and Migration, Centers for Disease Control and Prevention, Atlanta, USA
- ⁹ European Centre for Disease Prevention and Control, Stockholm, Sweden
- ¹⁰ Institut de Recherche pour le Développement, Unité Mixte de Recherche 233, Montpellier, France

Word Count: 4073

Summary Word Count: 239

Tables, Figures, References: Tables (1), References (69)

Key words: migrants, tuberculosis, research agenda, End TB, WHO

Corresponding author information

Dr. Priya B. Shete, Division of Pulmonary and Critical Care Medicine, University of California, San Francisco, San Francisco CA, USA, Email: Priya.shete@ucsf.edu Tel: +1 415 206 8341

31 **Summary**

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

48

49 **Introduction**

50 The End TB Strategy approved by the World Health Assembly in May 2014 aims to end the global
51 tuberculosis (TB) epidemic in line with the Sustainable Development Goals (SDGs) by 2030, with the
52 targets of a 90% reduction in TB mortality, a 80% decline in TB incidence, and no TB-affected household
53 experiencing catastrophic costs due to TB¹. The strategy relies on three fundamental pillars, including
54 “intensified research and innovation”². Promoting research across its entire spectrum (including basic
55 science, clinical, epidemiological, health systems, and operational/implementation research (OR/IR)) is
56 critical to maximizing the impact on TB reduction strategies in all, especially in vulnerable and high risk
57 populations who have higher risks of TB infection and disease, as well as poor treatment outcomes.

58 As described in previous articles within this series, migrants are often an especially vulnerable population
59 due to the inherent risk of acquiring TB in high- and medium- burden countries, but also due to migration
60 specific determinants³ that affect individuals in even low-burden countries. The first paper of the present
61 State of the Art series reviewed how migrants should be considered as a special vulnerable group within
62 the frame of the WHO End TB Strategy⁴. Growing surveillance data demonstrates the changing patterns
63 of TB incidence due in part to migration flows^{3,5}. This last paper of the series builds upon previous articles
64 in describing critical evidence gaps in the current knowledge of migration related TB issues that make
65 migration-inclusive research a priority for TB prevention and care. The intention of this paper is not to
66 present a prescriptive and comprehensive research agenda for TB in migrants, but to describe a systematic
67 approach to establishing migrant-inclusive TB research agendas and to provide pragmatic considerations
68 for operationalizing such agendas.

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

70 In order to assess the current landscape of migrant-inclusive TB research, a non-comprehensive narrative
71 literature review was conducted based on research areas defined in previous articles of this State of the
72 Art series, including epidemiology, immunology, TB diagnostics, treatment, prevention, socio-economics
73 and human rights. This review was based on a PubMed search using the keywords ‘tuberculosis OR TB’
74 AND ‘migrants OR migration OR refugees or asylum seekers’ AND ‘research AND operational OR
75 implementation OR trials OR epidemiology OR social OR immunology’ from November 2015 through
76 November 2017. A total of 204 papers were recovered that met search criteria and after abstract review,
77 76 papers were found to be related to migration related TB policy or research questions. Of these, 36
78 papers described some kind of “evidence gap” and were selected for more in-depth review. In addition,
79 websites of main organizations contributing to aspects of TB in migrants (including WHO, International
80 Organization for Migration (IOM), US Centers for Disease Control and Prevention (CDC), European
81 Center for Disease Prevention and Control (ECDC), International Union Against TB and Lung Disease
82 (The Union), and Médecins Sans Frontières (MSF)) were searched for evidence of ongoing or completed
83 research activities related to migrants and TB. From the review, three thematic areas emerged: first, the
84 need for migrant-inclusive research that considers the determinants of TB for migrant populations,
85 including the biological, social and structural determinants that are traditionally thought of as risk factors
86 for TB; second, specific additional TB risks due to the migration process itself should be considered; and
87 third, the need for research on how to operationalize migrant-inclusive programs and policies for TB
88 prevention and care given feasibility and ethics.

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

- 92 1) Consideration of the general TB determinants (biomedical, social, and structural) within migrant
93 communities.
- 94 2) Consideration of the full migration pathway, from the country of origin, along the transitional or
95 migration path, to the country of arrival (host country)^{3, 4}.
- 96 3) Consideration of the policies, practices and patient experiences along the cascade of care from
97 prevention to diagnosis and treatment of TB.

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

101

102 **Epidemiologic Research**

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

108

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

113 progression to active disease may be augmented due to poor general health, malnutrition, HIV infection,
114 stress/anxiety, trauma, inadequate living conditions, or mental health disorders in vulnerable populations
115 (including depression, bipolar disorders and psychosis) pre-migration as well as during and post-
116 migration. The investigation of migration related epidemiological risk factors and their impact on
117 progression to active disease would assist in developing reliable mathematical models to project TB trends
118 in migrants and the general population⁷. Such models are essential for forecasting and planning and, if
119 combined with health economic modelling, can help targeting promising interventions to those
120 determinants of TB most relevant to migrant populations⁸.

121

122 Secondly, migration may exacerbate both individual and structural determinants of TB in populations
123 already at risk⁹. As the causes and pathways of migration are heterogeneous, studies are needed that
124 examine the epidemiologic and public health impact of differences across various types of migration
125 pathways and categories of migrants - ranging from voluntary labor migrants to health care seeking
126 migrants to destitute forced migrants traveling along dangerous routes with limited empowerment⁹. Most
127 existing research focuses on descriptive epidemiology of TB in migrants post-arrival in the host country,
128 demonstrating heightened social, economic and structural determinants of disease such as poverty,
129 unemployment, and poor housing,¹⁰ but not much on specific factors relevant to the stage in migration³.

130 A better understanding of TB risks associated with migration would help shaping appropriate multi-
131 sectoral policies (before, during, and after migration) to improve TB prevention and care in these
132 populations. This is especially critical in low-incidence countries with a concentrated TB epidemic where
133 the majority of TB cases are among the non-native born population. It is also relevant for high TB burden
134 countries with a large number of migrants from other high burden countries,^{4,11} an often overlooked
135 migration pathway.

136

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

147

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

155

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

159 factor data as part of routine surveillance¹⁵. As the majority of TB cases among migrants arise from
160 reactivation of latent TB infection (LTBI) contracted in the country of origin³, 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 activities³.
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 settings¹⁶⁻¹⁹.
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 infection²¹. 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

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

186

187 ***Screening for latent TB infection.*** Treatment of LTBI has been identified as one of the potentially most
188 powerful interventions for elimination of TB²⁸, together with vaccination. Currently available tests to
189 detect LTBI, the tuberculin skin test (TST) and the *in vitro* interferon-gamma release assays (IGRAs),
190 measure an anamnestic response to *M. tuberculosis* antigens. Based on the results of a meta-analysis of
191 eight head-to-head studies that showed similar capacity of the 2 tests to ‘predict’ incident disease during
192 short term follow-up, WHO recommends either test to identify healthy individuals that should be
193 considered for LTBI treatment²² - of note, only one of the eight studies had been conducted in migrants²³,
194 which suggests that additional research should be conducted inclusive of this population.

195

196 Evidence for the best targeted testing strategy for LTBI in migrants is still limited. Several studies suggest
197 that screening with a single-step IGRA is more cost-effective than TST screening²⁴⁻²⁶. However, a
198 modelling study comparing different LTBI screening strategies in non-native born entrants to Canada
199 found that sequential screening with TST followed by IGRA was more cost-effective than each of these
200 alone²⁷. The capacity of both TST and IGRAs to predict incident TB in individuals with a positive result
201 is very low, with the number needed to treat [NNT]) to prevent one case of active disease of 67 for TST
202 and 37 for IGRAs²⁸. LTBI screening efficiencies in migrants specifically are unknown. Additional
203 research is needed to improve LTBI diagnostic tools and screening strategies.

204

205 A new model of TB natural history has been proposed that considers a continuous spectrum from
206 spontaneous clearance of bacteria to quiescent infection to disease²⁹. The prolonged asymptomatic phase
207 of early disease during which pathology evolves prior to clinical presentation of active disease is defined
208 as ‘incipient TB’³⁰. According to this scenario, diagnostic tests for LTBI should be conceptually
209 categorized into two categories: 1) test for persistent infection; and 2) test for incipient TB³¹. Despite
210 recent progress in identifying genomic signatures that are correlates for risk of progression³², tests of either
211 persistent disease or incipient TB are not yet commercially available (although one RNA based PCR test
212 is in clinical trial³³). While such a test could improve targeting of infected patients, the role of fluctuating
213 TB determinants that change as a result of the migration pathway (eg nutrition), should be addressed in
214 the evaluation of these novel tests. Based on these new diagnostic developments, a subsequent research
215 area is to develop new treatment regimens for incipient TB. The powerful impact that such new tools
216 would have not only on migrant populations but for global TB control emphasizes the need for basic and
217 clinical research in this field.

218

219 *Screening and Diagnosis of active disease.*

220 Current challenges in screening for active TB among migrants are similar to those in other high-risk
221 populations. The limitations of existing tests are the low sensitivity and specificity of smear microscopy
222 and the need for laboratory expertise and long growth times required for culture-based methods³⁴. In
223 addition, screening for TB in migrants face the operational challenges of provision of rapid care in a
224 potentially mobile population with often limited health care access. Therefore, a migrant-inclusive TB
225 research agenda must include an evaluation of not only technologies, but also of new strategies for

226 screening and diagnosing active TB. These interventions may include active case finding using symptom
227 screen, chest radiography, or other strategies^{17, 35}.

228

229 Several existing diagnostic tests and strategies have the potential to address TB diagnostic challenges in
230 migrants. These include molecular methods, such as the XpertMTB/RIF assay, Xpert Omni,³⁶ and Xpert
231 MTB/RIF Ultra assay (Ultra) (Cepheid, USA), which have been recommended for use in a variety of
232 populations by WHO^{37,38} as well as tests such as urinary lipoarabinomannan (LAM) detection,
233 *Mycobacterium tuberculosis* complex loop-mediated isothermal amplification (TB-LAMP), and
234 molecular line probe assays for drug resistance. Although the need for point-of-care tests is even more
235 flagrant in mobile populations, none of these diagnostic tools have been operationally evaluated in migrant
236 populations³⁹⁻⁴¹. OR/IR is needed to assess feasibility and effectiveness of these diagnostic tests in
237 migrant-inclusive settings, to identify mechanisms for scale up, and to improve linkages to care.

238

239 ***Access to Care and Treatment Adherence.*** Migrant communities often face barriers to accessing health
240 services. While all migrants should have the right to healthcare services^{42, 43}, there is limited information
241 on the ability of migrants to access care when they experience symptoms and signs of TB along the
242 migration pathway. Studies from several EU host countries showed that access to medical services may
243 be restricted^{44, 45}, and often depends on the type of residence permit the migrant holds⁴⁶. Since access to
244 health care is essential for early diagnosis and treatment of TB, identifying the gaps and testing
245 interventions that can improve access to health services for all types of migrants is needed, particularly
246 for implementing quality TB care. For example, while it was shown using mathematical models that
247 screening high risk subpopulations with IGRAs had the potential for high cost effectiveness which was

248 conducive to policy change, lack of empirical effectiveness data in these subpopulations was identified as
249 a barrier to effective implementation of a targeted testing and treatment strategy⁴⁷.

250

251 Migrants with TB often have lower treatment success rates compared to native individuals⁴⁸⁻⁵¹.
252 Understanding the underlying reasons for this is critical and context-specific. Several studies have shown
253 that even at the subnational level, identifying and targeting factors associated with default or loss to follow
254 up can improve health systems responses to TB treatment provision for migrant populations^{49, 50, 52}. For
255 instance, a systematic review evaluating reasons for non-adherence to treatment in 5 continents described
256 heterogeneous TB treatment outcomes among migrants due to variability in legal status and social risk
257 factors such as education, employment and access to care⁵³. This heterogeneity may be particularly
258 important when evaluating the full potential of novel treatment strategies such as short-course treatment
259 regimens for drug resistant disease, the use of digital health technologies to support treatment adherence⁵⁴.
260 ⁵⁵, and planning for scale-up of treatment programs⁵³. The critical point is that context-specific data are
261 required to understand how best to support migrants in initiating and completing treatment. Such evidence
262 can then expand to health systems research and policy change for creating mechanisms and application of
263 legal frameworks for cross-border TB control that facilitate access to care.

264 **Social Protection Research**

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

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

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

275 All these features of poverty and vulnerability point to substantial needs for social protection, defined as
276 a set of policies and programmes aimed at reducing the social and economic risk for those who need to
277 access and receive care¹⁰.

278 Social protection strategies have shown promise as a way to improve treatment outcomes among TB
279 affected households with significant socioeconomic risk^{56, 57}. However, even in settings where social
280 protection schemes have shown benefit in TB outcomes, operationalizing these strategies in migrants
281 may pose significant challenges⁵⁸. Research is required that systematically assesses migrants’
282 vulnerabilities and their social and economic barriers to care to identify where and when in the migration
283 pathway social protection interventions should be deployed. Understanding and evaluating the benefit
284 of TB-sensitive approaches (social protection schemes for which TB patients may be eligible based on
285 criteria unrelated to their disease) versus TB-specific approaches (social protection schemes for with TB
286 disease is an eligibility criteria) will be required in understanding how to operationalize these
287 interventions. These vulnerabilities as well as barriers to care are unlikely to be significantly different
288 from those observed among non-migrant populations when accounting for socioeconomic status, but
289 migration is likely to exacerbate them. Research is required to understand the full effect of this
290 potentiation and identify suitably targeted social protection interventions.

291 Despite a growing body of evidence that suggests the positive impact of cash transfer schemes on TB
292 and economic outcomes^{57, 59-61}, we are not aware of such studies among migrants⁶². While health
293 policies in some countries include access to social protection for any legal resident, there is limited
294 information on how such effective policies may translate to migrant populations with similar
295 socioeconomic characteristics but without a legal status^{56, 61, 62}. Research on how to operationalize social
296 protection and measure the effect of economic support and welfare^{2, 63, 64} on TB outcomes in migrant
297 populations is needed to inform development of suitable social protection schemes both in high- and
298 middle-income host countries⁶⁵. Examples of such research include studying the feasibility and impact
299 of a cash transfer for migrants diagnosed with TB or the impact of short-term disability insurance at the
300 time of treatment initiation. High-quality operational/implementation research on social protection that
301 includes migrants would contribute to reaching the targets of the End TB Strategy within the larger
302 context of the SDGs⁶⁶.

303

304 **Creating and Operationalizing a Migrant-Inclusive Research Agenda**

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

313 The research and innovation pillar of the End TB Strategy² promotes the need for well-designed and
314 empirically grounded research. To facilitate this, WHO has developed the Global Action Framework for
315 TB Research⁶⁷ and a Toolkit⁶⁸ 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 on¹¹. 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.

335 Finally, migrant communities should be engaged in research prioritization from the outset, including in
336 research implementation and dissemination of findings. Migrant populations may not have adequate rights
337 or representation as granted to citizens within national legislation. Therefore, researchers must ensure that
338 adequate international and national legislative frameworks on research ethics and data protection are
339 applied⁶⁹. Researchers must have a strategy to address issues of privacy, informed consent, coercion, and
340 social and psychological distress or trauma. Protection and promotion of human rights, ethics and equity
341 is one of the fundamental principles underpinning the End TB Strategy². For migrant populations,
342 promoting and protecting their health and respecting, protecting and fulfilling human rights are
343 inextricably linked. A migrant-inclusive TB research agenda should address evidence-based solutions that
344 respect, protect and fulfil migrants' human rights.

345

346 **Conclusion**

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

354

355 **Acknowledgements**

356 We appreciate the perspectives provided by the TB research community as well as by the migrant
357 advocacy community in preparing this manuscript. The findings and conclusions of this paper are those
358 of the authors alone and do not necessarily represent the views of the Centers for Disease Control and
359 Prevention of the United States, the European Centre for Disease Prevention and Control or the World
360 Health Organization.

361

362

References

- 363 1. Executive Board of the World Health Assembly. Global strategy and targets for tuberculosis
364 prevention, care and control after 2015. Geneva: World Health Organization; 2013.
- 365 2. Uplekar M, Weil D, Lönnroth K, Jaramillo E, Lienhardt C, Dias HM, et al. WHO's new end TB
366 strategy. *Lancet*. 2015;385(9979):1799-801.
- 367 3. Lönnroth K, Mor Z, Erkens C, Bruchfeld J, Nathavitharana RR, van der Werf MJ, et al.
368 Tuberculosis in migrants in low-incidence countries: epidemiology and intervention entry points. *Int J
369 Tuberc Lung Dis*. 2017;21(6):624-37.
- 370 4. Dhavan P, Dias HM, Creswell J, Weil D. An overview of tuberculosis and migration. *Int J Tuberc
371 Lung Dis*. 2017;21(6):610-23.
- 372 5. World Health Organization. Global Tuberculosis Report 2017. Geneva; 2017.
- 373 6. van der Werf MJ, Lönnroth K. Pre-entry, post-entry, or no tuberculosis screening? *Lancet Infect
374 Dis*. 2014;14(12):1171-2.
- 375 7. Kunst H, Burman M, Arnesen TM, al. e. Tuberculosis and latent tuberculosis infection screening
376 of migrants in Europe: comparative analysis of policies, surveillance systems and results. *Int J Tuberc
377 Lung Dis*. 2017;in press.
- 378 8. Shedrawy J, Siroka A, Oxlade O, Matteelli A, K. L. Methodological considerations for economic
379 modeling of latent tuberculosis screening in migrants *Int J Tuberc Lung Dis*. 2017;in press.
- 380 9. Wild V, Jaff D, Shah S, M. F. Tuberculosis, human rights and ethics: Challenges and
381 opportunities along the route of a highly vulnerable migrant. *Int J Tuberc Lung Dis*. 2017;in press.
- 382 10. Pittalis S, Piselli P, Contini S, Gualano G, Alma MG, Tadolini M, et al. Socioeconomic status and
383 biomedical risk factors in migrants and native tuberculosis patients in Italy. *PLoS One*.
384 2017;12(12):e0189425.
- 385 11. Dara M, Sulis G, Centis R, D'Ambrosio L, de Vries G, Douglas P, et al. Cross-border collaboration
386 for improved tuberculosis prevention and care: policies, tools and experiences. *Int J Tuberc Lung Dis*.
387 2017;21(7):727-36.
- 388 12. Sandgren A, Schepisi MS, Sotgiu G, Huitric E, Migliori GB, Manissero D, et al. Tuberculosis
389 transmission between foreign- and native-born populations in the EU/EEA: a systematic review. *Eur
390 Respir J*. 2014;43(4):1159-71.
- 391 13. Hargreaves S, Lönnroth K, Nellums LB, Olaru ID, Nathavitharana RR, Norredam M, et al.
392 Multidrug-resistant tuberculosis and migration to Europe. *Clin Microbiol Infect*. 2017;23(3):141-6.
- 393 14. van der Werf MJ, Hollo V, Kodmon C. Multidrug-resistant tuberculosis and migration to Europe.
394 *Clin Microbiol Infect*. 2017.
- 395 15. European Centre for Disease Prevention and Control, Europe WROf. Tuberculosis surveillance
396 and monitoring in Europe. Stockholm: European Centre for Disease Prevention and Control (ECDC);
397 2017.
- 398 16. Posey DL, Naughton MP, Willacy EA, Russell M, Olson CK, Godwin CM, et al. Implementation of
399 new TB screening requirements for U.S.-bound immigrants and refugees - 2007-2014. *MMWR Morb
400 Mortal Wkly Rep*. 2014;63(11):234-6.
- 401 17. Heuvelings CC, de Vries SG, Greve PF, Visser BJ, Belard S, Janssen S, et al. Effectiveness of
402 interventions for diagnosis and treatment of tuberculosis in hard-to-reach populations in countries of
403 low and medium tuberculosis incidence: a systematic review. *Lancet Infect Dis*. 2017;17(5):e144-e58.

- 404 18. European Centre for Disease Prevention and Control. Guidance on tuberculosis control in
405 vulnerable and hard-to-reach populations. Stockholm: ECDC 2016.
- 406 19. de Vries SG, Cremers AL, Heuvelings CC, Greve PF, Visser BJ, Belard S, et al. Barriers and
407 facilitators to the uptake of tuberculosis diagnostic and treatment services by hard-to-reach
408 populations in countries of low and medium tuberculosis incidence: a systematic review of qualitative
409 literature. *Lancet Infect Dis.* 2017;17(5):e128-e43.
- 410 20. Zammarchi L, Casadei G, Strohmeier M, Bartalesi F, Liendo C, Matteelli A, et al. A scoping
411 review of cost-effectiveness of screening and treatment for latent tuberculosis infection in migrants
412 from high-incidence countries. *BMC Health Serv Res.* 2015;15:412.
- 413 21. Pai M, Schito M. Tuberculosis diagnostics in 2015: landscape, priorities, needs, and prospects. *J*
414 *Infect Dis.* 2015;211 Suppl 2:S21-8.
- 415 22. World Health Organization. Latent TB Infection : Updated and consolidated guidelines for
416 programmatic management. Geneva: World Health Organization; 2018.
- 417 23. Harstad I, Winje BA, Heldal E, Oftung F, Jacobsen GW. Predictive values of QuantiFERON-TB
418 Gold testing in screening for tuberculosis disease in asylum seekers. *Int J Tuberc Lung Dis.*
419 2010;14(9):1209-11.
- 420 24. Hardy AB, Varma R, Collyns T, Moffitt SJ, Mullarkey C, Watson JP. Cost-effectiveness of the NICE
421 guidelines for screening for latent tuberculosis infection: the QuantiFERON-TB Gold IGRA alone is more
422 cost-effective for immigrants from high burden countries. *Thorax.* 2010;65(2):178-80.
- 423 25. Pareek M, Bond M, Shorey J, Seneviratne S, Guy M, White P, et al. Community-based evaluation
424 of immigrant tuberculosis screening using interferon gamma release assays and tuberculin skin testing:
425 observational study and economic analysis. *Thorax.* 2013;68(3):230-9.
- 426 26. Iqbal AZ, Leighton J, Anthony J, Knaup RC, Peters EB, Bailey TC. Cost-effectiveness of using
427 Quantiferon Gold (QFT-G)(R) versus tuberculin skin test (TST) among U.S. and foreign born populations
428 at a public health department clinic with a low prevalence of tuberculosis. *Public Health Nurs.*
429 2014;31(2):144-52.
- 430 27. Oxlade O, Schwartzman K, Menzies D. Interferon-gamma release assays and TB screening in
431 high-income countries: a cost-effectiveness analysis. *Int J Tuberc Lung Dis.* 2007;11(1):16-26.
- 432 28. Diel R, Loddenkemper R, Nienhaus A. Predictive value of interferon-gamma release assays and
433 tuberculin skin testing for progression from latent TB infection to disease state: a meta-analysis. *Chest.*
434 2012;142(1):63-75.
- 435 29. Esmail H, Barry CE, 3rd, Young DB, Wilkinson RJ. The ongoing challenge of latent tuberculosis.
436 *Philos Trans R Soc Lond B Biol Sci.* 2014;369(1645):20130437.
- 437 30. Cobelens F, Kik S, Esmail H, Cirillo DM, Lienhardt C, Matteelli A. From latent to patent:
438 rethinking prediction of tuberculosis. *Lancet Respir Med.* 2017;5(4):243-4.
- 439 31. World Health Organization. Consensus meeting report: development of a Target Product Profile
440 (TPP) and a framework for evaluation for a test for predicting progression from tuberculosis infection
441 to activedisease. Geneva: World Health Organization; 2017. Contract No.: WHO/HTM/TB/2017.18.
- 442 32. Zak DE, Penn-Nicholson A, Scriba TJ, Thompson E, Suliman S, Amon LM, et al. A blood RNA
443 signature for tuberculosis disease risk: a prospective cohort study. *Lancet.* 2016;387(10035):2312-22.
- 444 33. Penn-Nicholson A, Scriba TJ, Hatherill M, Sumner T, White RG. A novel blood test for
445 tuberculosis prevention and treatment. *S Afr Med J.* 2017;107(1):4-5.

- 446 34. Liu Y, Posey DL, Cetron MS, Painter JA. Effect of a culture-based screening algorithm on
447 tuberculosis incidence in immigrants and refugees bound for the United States: a population-based
448 cross-sectional study. *Ann Intern Med.* 2015;162(6):420-8.
- 449 35. Zenner D, Southern J, van Hest R, DeVries G, Stagg HR, Antoine D, et al. Active case finding for
450 tuberculosis among high-risk groups in low-incidence countries. *Int J Tuberc Lung Dis.* 2013;17(5):573-
451 82.
- 452 36. Cepheid. GeneXpert Omni product brochure 2016.
- 453 37. World Health Organization. Xpert MTB/RIF assay for the diagnosis of pulmonary and
454 extrapulmonary TB in adults and children. Policy update. Geneva; 2013.
- 455 38. World Health Organization WHO Meeting Report of a Technical Expert Consultation: Non-
456 inferiority analysis of Xpert MTB/RIF Ultra compared to Xpert MTB/RIF. Geneva; 2017.
- 457 39. World Health Organization. The use of lateral flow urine lipoarabinomannan assay (LF-LAM) for
458 the diagnosis and screening of active tuberculosis in people living with HIV: Policy update. Geneva;
459 2015.
- 460 40. World Health Organization. The use of loop-mediated isothermal amplification (TB-LAMP) for
461 the diagnosis of pulmonary tuberculosis. Policy guidance. Geneva; 2016. Contract No.:
462 WHO/HTM/TB/2016.11.
- 463 41. World Health Organization. Implementing Tuberculosis Diagnostics: Policy framework. Geneva;
464 2015.
- 465 42. Charter of Fundamental Rights of the European Union Official Journal of the European Union.
466 2010;C83:389-403.
- 467 43. International Covenant on Economic, Social and Cultural Rights Adopted and opened for
468 signature, ratification and accession by General Assembly resolution 2200A (XXI) of 16 December 1966
469 entry into force 3 January 1976, in accordance with article 27.
- 470 44. Mylius M, Frewer A. Access to healthcare for undocumented migrants with communicable
471 diseases in Germany: a quantitative study. *Eur J Public Health.* 2015;25(4):582-6.
- 472 45. Suess A, Ruiz Perez I, Ruiz Azarola A, March Cerda JC. The right of access to health care for
473 undocumented migrants: a revision of comparative analysis in the European context. *Eur J Public*
474 *Health.* 2014;24(5):712-20.
- 475 46. Hannigan A, O'Donnell P, O'Keeffe M, MacFarlane A. How do Variations in Definitions of
476 "Migrant" and their Application Influence the Access of Migrants to Health Care Services? WHO Health
477 Evidence Network Synthesis Reports. Copenhagen 2016.
- 478 47. Pareek M, Greenaway C, Noori T, Munoz J, Zenner D. The impact of migration on tuberculosis
479 epidemiology and control in high-income countries: a review. *BMC Med.* 2016;14:48.
- 480 48. Zhou C, Chu J, Liu J, Gai Tobe R, Gen H, Wang X, et al. Adherence to tuberculosis treatment
481 among migrant pulmonary tuberculosis patients in Shandong, China: a quantitative survey study. *PLoS*
482 *One.* 2012;7(12):e52334.
- 483 49. Chen J, Qi L, Xia Z, Shen M, Shen X, Mei J, et al. Which urban migrants default from tuberculosis
484 treatment in Shanghai, China? *PLoS One.* 2013;8(11):e81351.
- 485 50. Kodmon C, Zucs P, van der Werf MJ. Migration-related tuberculosis: epidemiology and
486 characteristics of tuberculosis cases originating outside the European Union and European Economic
487 Area, 2007 to 2013. *Euro Surveill.* 2016;21(12).

- 488 51. Nellums LB, Rustage K, Hargreaves S, Friedland JS. Multidrug-resistant tuberculosis treatment
489 adherence in migrants: a systematic review and meta-analysis. *BMC Med.* 2018;16(1):27.
- 490 52. Tang Y, Zhao M, Wang Y, Gong Y, Yin X, Zhao A, et al. Non-adherence to anti-tuberculosis
491 treatment among internal migrants with pulmonary tuberculosis in Shenzhen, China: a cross-sectional
492 study. *BMC Public Health.* 2015;15:474.
- 493 53. Lin S, Melendez-Torres GJ. Systematic review of risk factors for nonadherence to TB treatment
494 in immigrant populations. *Trans R Soc Trop Med Hyg.* 2016;110(5):268-80.
- 495 54. Falzon D, Migliori GB, Jaramillo E, Weyer K, Joos G, Raviglione M, et al. Digital health to end
496 tuberculosis in the Sustainable Development Goals era: achievements, evidence and future
497 perspectives. *Eur Respir J.* 2017;50(5).
- 498 55. Ngwatu BK, Nsengiyumva NP, Oxlade O, Mappin-Kasirer B, Nguyen NL, Jaramillo E, et al. The
499 impact of digital health technologies on tuberculosis treatment: a systematic review. *Eur Respir J.*
500 2018;51(1).
- 501 56. Torrens AW, Rasella D, Boccia D, Maciel EL, Nery JS, Olson ZD, et al. Effectiveness of a
502 conditional cash transfer programme on TB cure rate: a retrospective cohort study in Brazil. *Trans R*
503 *Soc Trop Med Hyg.* 2016;110(3):199-206.
- 504 57. Boccia D, Hargreaves J, Lönnroth K, Jaramillo E, Weiss J, Uplekar M, et al. Cash transfer and
505 microfinance interventions for tuberculosis control: review of the impact evidence and policy
506 implications. *Int J Tuberc Lung Dis.* 2011;15 Suppl 2:S37-49.
- 507 58. Chen W, Zhang Q, Renzaho AMN, Zhou F, Zhang H, Ling L. Social health insurance coverage and
508 financial protection among rural-to-urban internal migrants in China: evidence from a nationally
509 representative cross-sectional study. *BMJ Glob Health.* 2017;2(4):e000477.
- 510 59. Nery JS, Rodrigues LC, Rasella D, Aquino R, Barreira D, Torrens AW, et al. Effect of Brazil's
511 conditional cash transfer programme on tuberculosis incidence. *Int J Tuberc Lung Dis.* 2017;21(7):790-
512 6.
- 513 60. Wingfield T, Tovar MA, Huff D, Boccia D, Montoya R, Ramos E, et al. A randomized controlled
514 study of socioeconomic support to enhance tuberculosis prevention and treatment, Peru. *Bull World*
515 *Health Organ.* 2017;95(4):270-80.
- 516 61. Wingfield T, Tovar MA, Huff D, Boccia D, Montoya R, Ramos E, et al. The economic effects of
517 supporting tuberculosis-affected households in Peru. *Eur Respir J.* 2016.
- 518 62. Boccia D, Pedrazzoli D, Wingfield T, Jaramillo E, Lönnroth K, Lewis J, et al. Towards cash transfer
519 interventions for tuberculosis prevention, care and control: key operational challenges and research
520 priorities. *BMC Infect Dis.* 2016;16:307.
- 521 63. Lönnroth K, Glaziou P, Weil D, Floyd K, Uplekar M, Raviglione M. Beyond UHC: monitoring
522 health and social protection coverage in the context of tuberculosis care and prevention. *PLoS Med.*
523 2014;11(9):e1001693.
- 524 64. Lönnroth K, Jaramillo E, Williams BG, Dye C, Raviglione M. Drivers of tuberculosis epidemics: the
525 role of risk factors and social determinants. *Soc Sci Med.* 2009;68(12):2240-6.
- 526 65. Pescarini JM, Rodrigues LC, Gomes MG, Waldman EA. Migration to middle-income countries
527 and tuberculosis-global policies for global economies. *Global Health.* 2017;13(1):15.
- 528 66. United Nations General Assembly. Transforming our world: the 2030 Agenda for Sustainable
529 Development New York: United Nations; 2015. Contract No.: Resolution adopted by the General
530 Assembly on 25 September 2015
- 531 67. World Health Organization. Global Action Framework for TB Research. Geneva; 2015.

- 532 68. World Health Organization. A Toolkit for Developing a National TB Research Plan. Geneva;
533 2016.
- 534 69. International Organization for Migration. IOM Data Protection Manual. Geneva; 2010.
- 535
- 536

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

Research Approach	Research Priority Areas
Epidemiological Research	<ul style="list-style-type: none"> · 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	<ul style="list-style-type: none"> · 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	
<i>---Prevention and Screening</i>	<ul style="list-style-type: none"> · 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)
<i>---Diagnostics</i>	<ul style="list-style-type: none"> · 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
<i>---Treatment</i>	<ul style="list-style-type: none"> · 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	<ul style="list-style-type: none"> · 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

	<ul style="list-style-type: none"> · Establish critical components necessary for operationalizing cross-border collaborations
Social Protection Research	<ul style="list-style-type: none"> · 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	<ul style="list-style-type: none"> · Document infringements on human rights of TB programmes · Develop TB specific interventions that support the human rights of migrants

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