Third WHO consultation on the translation of tuberculosis research into global policy guidelines: meeting report, 4 April 2023
Acknowledgements

We acknowledge with gratitude the participants of this consultation, the Chair and administrative personnel who made this meeting possible and productive. All the meeting participants contributed their time to the review of the final document; this support is also gratefully acknowledged.
### Abbreviations and acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>DST</td>
<td>drug susceptibility testing</td>
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<td>DR-TB</td>
<td>drug-resistant tuberculosis</td>
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<td>GTB</td>
<td>Global Tuberculosis Programme</td>
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<td>NAATs</td>
<td>Nucleic acid amplification tests</td>
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<td>TB</td>
<td>tuberculosis</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Background

The Global Tuberculosis Programme of the World Health Organization (WHO/GTB) has the mandate to develop and disseminate evidence-based policy for tuberculosis (TB) prevention, diagnosis, treatment, and care. Regular review of evidence, and assessment of country needs for policy is part of its core function. In this regard, WHO organized a consultation assembling scientists, public health experts, partners, civil society, and countries to exchange views on emerging areas of need for global TB policy guidance to achieve the goals and targets of the WHO End TB Strategy.

The specific objectives of this consultation were:

I. to present on progress as well as plans to review WHO TB policy guidance (2022-23); and

II. to exchange views on emerging needs of Member States for policy guidance in the context of the current evidence landscape.

The expected outcome of this meeting is a report (herewith) summarizing current thinking and suggested actions aligned to these objectives.

Introduction

After a welcome by Tereza Kasaeva, Jeremiah Mukwa Chakaya, Chair of the consultation, opened the meeting at 13:10 on 4 April 2023. The Chair introduced the programme of the meeting and welcomed the participants (Annexes 1 and 2). Matteo Zignol gave a brief presentation on the architecture of WHO TB policy guidelines to introduce the scope of the meeting.

1 : TB diagnostics

*Nazir Ismail, Global TB Programme, WHO*

This session summarized WHO’s policy perspectives and the scope of work on broader policies, norms and standards related to TB diagnostics focusing on the period 2023-25. Planned policy guideline development or updates include Targeted Next-Generation Sequencing for drug-resistant TB detection (2023), low complexity nucleic acid amplification tests (NAATs) for detection of TB and drug resistance (2024), and Next generation of tests for detection of TB in peripheral settings using alternative sample types (2025).

On norms and standards, planned work areas include release of the WHO standard for universal access to rapid TB diagnostics shortly and an update to get product profiles for TB diagnostics and screening to be completed in the second half of the year. An update to the catalogue of mutations in *Mycobacterium tuberculosis* complex with data from a broader spectrum of geographies and additional data on bedaquiline, linezolid and delamanid resistance is underway and will be released in 2023. Complementary initiatives include a TB genome sequence dashboard under development to support visualization, mutation search and data submission portal for automated update of the mutation database (2023-2025). The broth microdilution methodology for drug susceptibility testing (DST) will be
considered and interim criteria developed as data are generated. Technical advisory groups will be convened to support some of these initiatives.

WHO/GTB has shifted to making class-based recommendations for diagnostics, to allow for better competition in the market and to provide Member States with potentially more options suited to their context. Technical Specifications Series that articulate the performance evaluation criteria for meeting WHO prequalification requirements were issued for TB molecular tests, while work is ongoing for other technology groups such as LF-LAM and Next-Generation Sequencing for TB. An abridged pathway for antigen-based class of TB tests is also being worked out.

The session concluded by summarizing current policy and implementation gaps in TB diagnosis and highlighting the importance of engaging manufacturers from emerging economies to improve the supply of, and access to, innovative technologies.

The Chair opened the floor for discussion framed around (but not limited to) the following questions:

1. Are there any further critical evidence gaps or upcoming studies?
2. What further guidance/updates should we consider to enhance the implementation of global TB policy guidance in these areas?
3. Are there any initiatives we could consider to direct new areas for research?

Discussion:

- On research and development, participants underscored that point of care tests to detect TB disease at primary health care level, in low resource settings remain a priority. These include TB-specific or multi-pathogen DNA testing in blood and other biomarker-based tests for monitoring treatment outcomes. External Quality Assurance or Proficiency testing in decentralized settings remains key to harmonize testing measurement procedures in a manner that conforms with quality expectations.
- More sensitive and rapid tests to substitute microscopy and culture-based methods for clinical treatment monitoring, as well as development of molecular DST assays to determine susceptibility or resistance to newly approved drugs (new chemical entities or repurposed drugs) to treat TB including bedaquiline, linezolid and pretomanid are urgently needed. Ideally, molecular DST development should synchronize with the licensing and use of regimens that contain new or repurposed drugs, but this has been challenging due to lag time in the availability of data on mutations known to result in minimal inhibitory concentration. WHO will include elements on molecular DST needs in its Target Regimen Profiles for TB treatment (version 2023 update) to strengthen early collaboration between diagnostics and drug developers on molecular DST.
- On policy and implementation, participants welcomed the policy work on next generation sequencing to guide clinical practice, and efforts to update the catalogue of mutations, which countries rely on for resistance interpretation. Participants underscored the importance of implementation research to build evidence and optimize access to screening and diagnostic tools for children and other vulnerable populations, as well as to better understand barriers in expanding access to moderate complexity NAATs. In parallel to ongoing efforts to facilitate rapid
uptake of WHO recommendations on new TB diagnostics, compilation of country case studies on the impact of these technologies on health outcomes was suggested. Quality assurance monitoring is important and re-introduction of External Quality Assessment reporting by countries through the Global TB Report should be considered. Innovations for maintaining sputum sample integrity during transportation, and research into optimizing oral swabs for TB diagnosis, including a swab/sputum combination test for people with non-productive cough could be explored to improve TB detection.

- On market shaping, diverse and healthy ecosystem of suppliers are needed to overcome shortages of cartridges and other supply risks. Manufacturers could be incentivized to develop tests that are not reliant on electricity/solar power. Comparative ‘ranking’ of diagnostic tests by accuracy and complexity (including by source of energy) could support countries in selecting tests suitable for their health system context.
- To better track evidence for policy on diagnostics, an open platform/hub could be established to map planned and ongoing research projects.

2 : TB/HIV and comorbidities and TB among vulnerable populations

Kerri Viney

WHO/GTB’s work on TB/HIV and comorbidities and TB among vulnerable populations includes the development of guidance to promote access to TB services for vulnerable populations as well as collaborative activities on TB/HIV and other comorbidities to promote people-centered TB prevention and care. This work focuses on comorbidities and health related risk factors associated with TB as well as vulnerable populations who are at high risk of developing TB, having poor access to TB services, or having poor outcomes.


Additional guidance to improve TB prevention and care for other vulnerable population groups, such as indigenous populations, refugees, and populations in humanitarian settings have also been developed over the past year. In the context of the existing evidence landscape, WHO is working on developing a policy brief on TB and vulnerable populations as well as consolidated guidelines and an associated operational handbook on the management of TB and comorbidities. Initially the guidelines and operational handbook will focus on mental health (including reference to substance use disorders), HIV-associated TB, the management of TB and diabetes and then the management of TB and undernutrition. Examples of upcoming research on TB and undernutrition were shared with the participants given that the work on TB and undernutrition is in the planning phase.

The Chair opened the floor for discussion framed around (but not limited to) the following questions:

1. Are you aware of new evidence that is due to be published shortly and that could influence our current recommendations on TB and undernutrition?
2. What further guidance should we consider to enhance the implementation of global TB policy guidance for people who are vulnerable to developing TB?

Discussion:

- On norms, standards and guidelines, participants welcomed progress in the development of a consolidated guideline on TB and comorbidities and suggested to expand the scope of this work to other risk-factors such as alcohol use disorders and smoking. Aligned to that, additional guidance to address the structural determinants of TB, for example in the context of the management of TB in prisons and other places of detention, as well as a stand-alone field guide to support the management of TB among people with substance use disorders (i.e., people who use drugs) was suggested. The association between TB and hepatitis B and C was also emphasized as an important area for future evidence review or guidance. Considering the prevalence of helminth infections in many high-TB burden countries, it was also suggested that there may be merit in exploring the impact of helminth co-infection on TB disease progression and outcome.

- It was suggested that WHO could monitor the adoption/adaptation of WHO policy recommendations, norms and standards on TB/HIV and comorbidities and TB among vulnerable populations which relates to policy uptake and accountability. More proactive measures to overcome the low certainty of evidence for existing recommendations remains important for country implementers. The root-causes for lack of evidence for certain vulnerable populations (e.g., exclusion of certain subpopulations in health research) should be clarified and addressed.

- It was emphasized that countries require support to identify their vulnerable populations and underlying factors related to TB vulnerability, to implement the most impactful interventions based on local epidemiology and the local context, needs and resources.

- Given that implementation of some policy recommendations require collaboration across health programmes and other sectors, context-specific operational research remains important to generate evidence for intersectoral policy dialogue. High-level political advocacy is key to materialize these intersectoral linkages. The discussants were not aware of any additional studies on TB and undernutrition that could inform WHO’s upcoming policy guidance on TB and undernutrition.

3: TB associated disability

Ernesto Jaramillo, Denise Evans, and Jamilah Meghi

Some TB co-morbidities can result in impairment or disability during and post-TB disease. Pulmonary, mental, and neurological conditions are the most frequently associated with impairment and disability in people affected by TB. Presenters shared results of a scoping review of literature on TB-associated respiratory disability, and impacts of selected interventions in mitigating respiratory pathology, impairment or disability during or post-TB disease. The findings revealed limited evidence to support development of guidelines on this topic. Presenters made a call to include disability measures as key outcomes in clinical and implementation research to strengthen the evidence base for policy.
The Chair opened the floor for discussion framed around (but not limited to) the following questions:

*In view of the findings of this scoping review on pulmonary disease during and post TB disease, is there merit to proceed with:*

1. *Conducting multi-country operational research to assess feasibility, effectiveness, and cost-effectiveness of the management of respiratory co-morbidities during and post-TB disease under programmatic conditions?*

2. *Developing guidelines drawing on the evidence from a standardized multisite operational research protocol?*

*Discussion:*

- The full scale of the impact of TB-associated pulmonary disability on health outcomes is not fully understood. There is strong merit for post-TB follow-up studies to understand the burden and scale of the problem, guided by prioritized outcomes of interest (e.g., mortality).
- A research agenda can shape the field and stimulate the development of evidence for policy, for example, to identify the risk factors for TB-associated pulmonary disability, to understand the impact of models and quality of care during TB and post-TB treatment; and to generate systematic evidence on impacts of mitigating interventions on TB-associated pulmonary disability.
- Primary health care systems are not usually equipped to provide rehabilitative services in low/middle income high-TB burden settings. Operational research could help define how rehabilitation can be integrated at primary health care during and post-TB disease.
- In the interim, participants suggest WHO to assist countries in conducting the proposed operational research (including whom to prioritize for post-TB follow up) based on the already existing evidence on the management of selected pulmonary diseases, with a view to develop a guidance (or tool) on how to manage TB-associated pulmonary disability under programmatic conditions. Participants also suggested measuring TB-associated disability related outcomes in WHO’s annual Global TB Report to motivate and strengthen national accountability.

*Conclusions*

Matteo Zignol thanked the participants and emphasized WHO’s commitment to convening regular fora to share WHO/GTB policy development plans. The Chair summarized the key messages from the discussions and closed the meeting at 16:00.
## Annex 1. Meeting agenda

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<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Presenter(s)</th>
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<tbody>
<tr>
<td>13:00 – 13:05</td>
<td>Welcome and Introductions</td>
<td>Tereza Kasaeva</td>
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<td>13:15 – 14:05</td>
<td>TB diagnostics: Nazir Ismail</td>
<td>Opening presentation</td>
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<td>Discussants: Patricia Hall and Shaheed V Omar</td>
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<td>14:05 – 14:50</td>
<td>TB/HIV and comorbidities and TB among vulnerable populations: Kerri Viney</td>
<td>Presentations will cover planned updates to TB policy guidance (2023-24)</td>
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<td></td>
<td>Discussants: Fernanda Dockhorn Costa and Srinath Satyanarayana</td>
<td>Discussants will reflect on emerging TB policy development needs, in the context of the current evidence landscape/gaps</td>
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<td>14:50 – 15:00</td>
<td>Break</td>
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<td>15:00 – 15:50</td>
<td>TB associated disability: Ernesto Jaramillo, Denise Evans, and Jamilah Meghi</td>
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<tr>
<td></td>
<td>Discussants: Jeremiah Mukwa Chakaya and Lindiwe Mvusi</td>
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<tr>
<td>15:50 – 16:00</td>
<td>Summary and concluding remarks</td>
<td>Chair</td>
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Annex 2. Participants list

1. Helen Ayles  
   Research Director  
   Zambart Project  
   Lusaka, Zambia

2. Daniela Cirillo  
   Head  
   Emerging Bacterial Pathogens Unit  
   San Raffaele Scientific Institute (HSR)  
   Milan, Italy

3. Jeremiah Muhwa Chakaya  
   Professor  
   Global Respiratory Health  
   The London School of Hygiene & Tropical Medicine  
   London, United Kingdom

4. Gerry Davies  
   Professor  
   Infection Pharmacology and Honorary Consultant in Infectious Diseases  
   University of Liverpool  
   Liverpool, United Kingdom

5. Fernanda Dockhorn Costa  
   Coordinator  
   Chronic and Airborne Disease Surveillance Coordination  
   Health Surveillance Department  
   Ministry of Health  
   Brasilia, Brazil

6. Denise Evans  
   Senior researcher  
   Health Economics and Epidemiology Research Office  
   University of the Witwatersrand, Johannesburg, South Africa

7. Mike Frick  
   Senior Project Officer, TB/HIV  
   Treatment Action Group  
   New York, NY  
   United States of America

8. Patricia Hall  
   Lead, TB and Clinical Monitoring Team, International Laboratory Branch Division of Global HIV and TB, CDC  
   Atlanta, Georgia  
   United States of America

9. Rumina Hasan  
   Professor  
   Pathology and Microbiology  
   Aga Khan University  
   Karachi City, Pakistan

10. Harry Hausler  
    Member, WHO Civil Society Task Force  
    Medical Director Project Integrate, TB Care Association  
    Waterfront  
    South Africa
11. Amir Khan  
Member, WHO Civil Society Task Force  
Association for Social Development  
Pakistan

12. Rafael Laniado-Laborín  
Head  
TB Clinic and Laboratory  
Hospital General Tijuana  
Tijuana, Mexico

13. Jamilah Meghi  
Department of Clinical Studies  
Liverpool School of Tropical Medicine  
Liverpool, United Kingdom

14. YaDiul Mukadi  
Senior TB Technical Advisor  
Infectious Disease Division  
Global Health Bureau  
USA Agency for International Development (USAID)  
Washington D.C., USA

15. Lindiwe Mvusi  
Director  
TB Control and Management  
National Department of Health  
Pretoria, South Africa

16. Norbert Ndjeka  
Chief Director  
TB Control and Management  
National Department of Health  
Pretoria, South Africa

17. Binh Hoa Nguyen  
Vice Manager and Secretary  
National TB Control Programme  
Secretary, NTP Vietnam  
Coordinator, Vitenam Global Fund TB Project  
Hanoi, Viet Nam

18. Shaheed V Omar  
Head (acting)  
Centre for Tuberculosis and WHO SRL  
National Institute for Communicable Disease  
Johannesburg, South Africa

19. Tiara Pakasi  
National TB Program Manager  
Ministry of Health of the Republic of Indonesia  
Jakarta, Indonesia

20. I Wayan Gede Artawan Eka Putra  
Chair, Indonesia TB Research Network (JetSet TB)  
Medical Faculty, Udayana University  
Jakarta, Indonesia

21. Anastasia Samoilova  
First Deputy Director  
National Medical Research Centre on Phthisiopulmonology and Infectious diseases  
Moscow, Russian Federation
22. Srinath Satyanarayana  
   Deputy Director  
   Center for Operational Research  
   International Union Against Tuberculosis and Lung Disease  
   The Union  
   Paris, France

23. Cherise Scott  
   Technical Officer  
   UT/UTD UNITAID International drug purchase facility  
   Geneva, Switzerland

24. Maiko Tonini  
   Focal Point for TB Research  
   Chronic and Airborne Disease Surveillance Coordination (NTP)  
   Ministry of Health  
   Brasilia, Brazil

25. Carrie Tudor  
   The Johns Hopkins University School of Nursing  
   Baltimore, MD

26. Zhao Yanlin  
   Director  
   National Center for TB Control and Prevention, Chinese Center for Disease Control and Prevention  
   Director  
   National Tuberculosis Reference Laboratory of China CDC  
   Beijing, China

WHO Regional Offices

Regional Office for Europe

27. Andre Dadu  
   Medical Officer  
   Division of Country Health Programmes

28. Oleksandr Korotych  
   Technical Officer (Operational Research on TB and DR-TB)  
   Division of Country Health Programmes

Regional Office for the Americas

30. Kleydson Alves  
   WHO Country Office, Brazil

31. Pedro Avedillo  
   TB Regional Advisor, a.i.

32. Ernesto Montoro  
   Advisor  
   Laboratory Integration (CDE/HT)

33. Freddy Pérez  
   Regional Advisor  
   Communicable Diseases Research (CDE/HT)
Regional Office for the Eastern Mediterranean

32. Kenza Bennani  
Medical Officer for TB Programme

Regional Office for the Western Pacific

29. Kyung Hyun Oh  
Technical Officer  
Division of Programmes for Disease Control

30. Manami Yanagawa  
Junior Professional Officer  
Division of Programmes for Disease Control

Regional Office for South-East Asia

31. Kamar Rezwan  
Medical Officer  
Tuberculosis Control

32. Aye Thida  
Technical Officer  
Drug-resistant TB, prevention & research

Global Tuberculosis Programme

33. Tereza Kasaeva, GTB Director  
34. Matteo Zignol, Unit Lead, PCI  
35. Farai Mavhunga, Unit Lead, VCC  
36. Dennis Falzon, Team Lead, PCI  
37. Nazir Ismail, Team Lead, PCI  
38. Fuad Mirzayev, Team Lead, PCI  
39. Sarah Rylance, NCD/MND  
40. Annabel Baddeley, VCC  
41. Marzia Calvi, VCC  
42. Nebiat Gebreselassie, PCI  
43. Ernesto Jaramillo, VCC  
44. Cecily Miller, PCI  
45. Kerri Viney, PC