Fourth WHO consultation on the translation of tuberculosis research into global policy guidelines: meeting report, 15 February 2024
Acknowledgements

The World Health Organization acknowledges with gratitude all the participants of this consultation and the 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>Abbreviation</th>
<th>Description</th>
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<tr>
<td>DR-TB</td>
<td>drug-resistant tuberculosis</td>
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<td>DS-TB</td>
<td>drug-susceptible tuberculosis</td>
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<td>DST</td>
<td>drug susceptibility testing</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>TPT</td>
<td>TB preventive treatment</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 (GTB/WHO) 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 fourth annual 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 (2024-25); and

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

This technical report summarizes the discussion and key suggestions made by the meetings participants.

Introduction

After a welcome by Tereza Kasaeva, Matteo Zignol, Chair of the consultation, opened the meeting at 13:05 on 15 February 2024. The Chair introduced the programme of the meeting and welcomed the participants (Annexes 1 and 2). The Chair gave a brief presentation on the architecture of WHO TB policy guidelines to introduce the scope of the meeting.

1. TB screening and prevention

Dennis Falzon

The session focused on updates to policy, norms, standards, and research in systematic screening for TB disease, TB preventive treatment (TPT), and TB infection prevention and control.

In February 2024, WHO released a rapid communication on TB preventive treatment. The second edition of the consolidated guidelines on TB preventive treatment and accompanying handbook (reflecting these changes) will be released later this year. The main update relates to a new recommendation on 6-month levofloxacin as TPT for eligible contacts of people with multi-drug resistant TB. Other changes include incorporation of relevant and complementary recommendations from diagnostics (antigen-based tests for TB infection) and the 2021 TB screening guideline; revision of algorithms and dosing guidelines for levofloxacin and rifapentine; and guidelines for co-administering 3HP with dolutegravir. Furthermore, the TPT guidelines will be supplemented with a revised list of research gaps.

On other norms and standards, plans are in place to finalize target product profiles for TB screening in 2024. An investment case on TB screening and preventive treatment will be launched to provide economic arguments for policy makers and advocates, on the occasion of World TB Day. The presentation also summarized supportive platforms developed recently, such as the ScreenTB tool to assist countries with prioritization of risk groups for TB screening and prevention, and training modules on OpenWHO. It also outlined the current landscape of computer-aided detection products for the
diagnosis of TB, as well as ongoing research in the fields of TPT, screening and infection prevention control that are poised to inform policy and practice in the near future. WHO is also planning to start a discussion on subclinical TB aimed at achieving a common understanding about the condition, as a prelude to other activities in this area.

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

1. Do you agree with our proposed way forward? Are there other needs that countries have that we need to address? What else do you suggest?

2. Are you aware of other ongoing research (trials, cohorts, epidemiological, or implementation research) that is due to be published shortly and that could influence our current recommendations on TB screening, TPT and infection prevention control?

Discussion

- On prevention and screening policy, participants underscored the importance of exploring subclinical TB and extrapulmonary TB in policy guidance, to ensure that all aspects of TB are effectively managed. Additionally, while evidence is generally synthesized and considered during guideline development, handbooks could be updated outside the guideline development cycle for specific aspects—like simplifying algorithms or providing implementation aids.

- On implementation, participants underscored the importance of a thorough symptom screening and chest X-ray examination before initiating TPT to effectively rule out TB. Monitoring the progression of TB in individuals that completed TPT can assist in evaluating this issue. Furthermore, national and global efforts must be intensified to ensure timely access to TPT for eligible people upon identification of index TB cases, aiming to reduce the current 30–60-day delay. Participants also discussed the limitations of the Tuberculin Skin Test and Interferon Gamma Release Assay (in the context of feasibility and availability) and highlighted the potential of antigen-based TB tests to bridge this gap.

- Within the scope of the Global TB Report, there is an opportunity to promote and show progress in the screening of high-risk populations and its effectiveness, National TB Programme policies, as well as the initiation and completion rates of TPTs.

- In terms of research, there is a need for a more detailed understanding of how long new TPT options protect individuals and for policy advice on the impact of repeated TPT courses in areas of high transmission or among particularly vulnerable groups. Additionally, there is a call for more research into the interactions between rifamycin-based TPTs and other drugs, including hormone-based contraceptives and opioid substitution therapies, beyond just antiretroviral drugs.
2. TB diagnostics

Nazir Ismail

This session summarized WHO’s scope of work on broader policies, norms and standards related to TB diagnostics focusing on the period 2024-25. In 2023, WHO released rapid communication on targeted next-generation sequencing for diagnosis of drug-resistant TB (DR-TB): The consolidated guideline on rapid diagnostics for TB detection and associated handbook will be released in March this year. Update to the handbook will also incorporate critical concentrations established for pretomanid and cycloserine.

Planned policy guideline development or updates in 2024 include evaluation of low and medium low nucleic acid amplification tests (NAATs) for detection of TB and drug resistance and diagnostics yield of parallel testing of samples from children and people living with HIV. In 2025, Point of Care and near Point of Care tests (including those that use tongue swabs), as well as 2nd and 3rd generation lateral flow urine lipoarabinomannan assays will be evaluated pending data availability.

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 lateral flow urine lipoarabinomannan assay and Next-Generation Sequencing for TB. Two WHO Prequalification performance evaluation laboratories for TB diagnostics have been approved (Johannesburg and Chennai).

On norms and standards, planned work areas for 2024 include release of Target Product Profiles for TB diagnostics, consolidated with the existing TPPs for drug susceptibility testing (DST). An update to the catalogue of mutations in Mycobacterium tuberculosis complex with data from a broader spectrum of geographies and additional resistance data (including pretomanid) will be released in 2025. Complementary initiatives include launch of a searchable TB genome sequence dashboard with a data submission portal to enable automated update (2024). Technical advisory groups will be convened in 2024 to support review of data on alternative Interferon-Gamma Release Assays and informatics update on targeted next-generation sequencing technologies, pending on availability of data.

The session concluded by summarizing current policy and implementation gaps in TB diagnosis for further reflection by participants.

Discussion

Participants reflected on the complexities and challenges of aligning TB diagnostics with treatment options, brainstormed on how to shape new diagnostics research towards public health impact, and the importance of understanding genetic resistance mechanisms to improve the pace of development of tests against drug resistant strains. A brief summary of the discussion is below.
• Development of molecular DST assays to determine susceptibility or resistance to newly approved drugs (new chemical entities or repurposed drugs) to treat TB, particularly bedaquiline 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. Participants acknowledged the value of the WHO catalogue of mutations in this space and underscored the importance of a high-quality, comprehensive, and timely data input into the sequencing dashboard.

• To monitor emerging resistance, proactive resource mobilization from funders is crucial for the rapid characterization of resistance patterns and the inclusion of this data in the sequencing dashboard. Enhancing the dashboard with data mapped by counties and the diagnostic technologies used for mutation identification could optimize its utility. Furthermore, WHO is collaborating with researchers that use AI applications to map and predict resistance to new and repurposed anti-TB drugs.

• In the realm of phenotypic methods for DST, such as broth microdilution, progress is slow. Critical concentrations for newer drugs like delamanid are yet to be established. Global evaluations of phenotypic test performance (beyond just providing guidance on critical concentration) could improve confidence by end users. Considering the dominance of a few suppliers in the TB culture market, and the broad application of these methods in high-burden countries, developing Target Product Profiles could stimulate innovation.

• To aid implementation, there is a suggestion to optimize WHO handbooks to better assist countries in selecting diagnostic algorithms tailored to their national contexts and guidelines. Participants emphasized the importance of understanding how countries are adapting WHO’s standard for universal access to rapid tuberculosis diagnostics, the impacts thereof, and documenting existing gaps. There is a call for enhanced advocacy and cooperation between diagnostic and treatment manufacturers to support the development of external quality assurance for new TB tests. This includes making control powders and standardized testing materials more readily available.

• On the research front, better understanding of the molecular mechanisms of resistance to new and repurposed drugs, such as bedaquiline, remains key. There is also a need to address the diagnostic and care gaps for vulnerable populations (across technologies), and to evaluate diagnostics performance for extrapulmonary TB more thoroughly, as current efforts are predominantly focused on pulmonary TB. South Africa’s planned operational research on using next-generation sequencing for DR-TB diagnosis could shed light on cost implications and health impact of this technology. There is an increasing interest in using alternative sample types, like tongue swabs, to improve testing accessibility. However, these methods may not match the diagnostic sensitivity and accuracy of traditional approaches, necessitating frameworks exploring not just on diagnostic accuracy but also public health outcomes, potentially through randomized controlled trials.
3. TB Treatment

Fuad Mirzayev

The session summarized progress since 2022 with respect to updates to WHO policy guidelines in TB treatment and supportive tools. WHO plans to review policy guidance for treatment of DR-TB in 2024, on the basis of results from two trials, BEAT-TB (6-month regimen without pretomanid) and EndTB trial (variety of nine-month treatment courses that include combinations of five drugs). Several consortia such as SMART4TB, Unite4TB and Pan-TB are driving innovative drug-treatment research in early-stage clinical development, which is poised to bear fruit in the coming years.

On other norms and standards, WHO plans to finalize its ‘Guidance on Evidence Generation for TB treatment’ to shape the development of evidence for policy in the TB treatment field. The aim is to provide high-level guidance on the type and quality of evidence required to ensure that policies can lead to significant health and social benefits.

The session concluded by sharing future perspectives on how current research may transform the treatment landscape of both DR-TB and drug-susceptible TB (DS-TB). It is anticipated that effective treatments for DR-TB, lasting six months or less and targeting various categories of patients, will be developed. These regimens are expected to match the efficacy of treatments for DS-TB, with safety standards improving over time, allowing for more decentralization of services. The landscape might also undergo changes with the advent of next generation of existing medicines, which will likely offer enhanced effectiveness and safety – requiring further investigation into regimen design strategies. In the space of DS-TB, efficacy of high-dose rifampicin dosing, new regimen options, shorter duration regimens, or Pan-TB regimens could transform the field.

Discussion

• Maintaining a strong clinical pipeline is crucial for providing better TB treatment options, but it is equally important to conduct health systems research to identify and overcome challenges related to cost and people-centered delivery strategies. There is a pressing need for comprehensive data on the cost-effectiveness of various TB treatment regimens to inform decision-making and tackle health disparities both within and across countries. Additionally, investigating clinical outcomes related to lung health after TB treatment is essential for evaluating and enhancing the effectiveness of various regimens. This research necessitates the clear definition and standardization of terminologies in the field of post-TB lung health. There is a pending need for more evidence and guidance on the treatment of extrapulmonary TB, options for treatment regimens, and their duration.

• Availability of shorter duration regimens against DR-TB could offer more options for affected people, and potentially reduce reliance on drug-susceptibility testing. Use of new drugs and higher dosed rifamycins, such as rifapentine and rifampicin (which is more affordable), have the potential to facilitate design of shorter treatment regimens. Overall, recent advances in DR-TB treatment research are moving us closer to a universal TB regimen. However, realizing this possibility demands extensive collaboration, gathering evidence on safety and health impacts, enhancing drug-susceptibility testing to track resistance, and development of appropriate drug formulations. In the interim, further research on standardizing the stratification of TB patients into subgroups based on
severity/factors predictive of clinical outcomes remains essential for the comparison of treatment regimens and for prioritizing the optimization of treatment for people with severe disease. This may require validating and using biomarker tests that can predict clinical outcomes or implementing post-treatment monitoring strategies.

4. TB/HIV, comorbidities and priority populations

Kerri Viney

The session focused on updates to policy, norms, standards, and research for the management of TB in children and adolescents and priority populations and for people with TB/HIV or other comorbidities. The session opened by highlighting progress in the development of WHO guidance and training materials since the last meeting in 2023, including but not limited to the development of e-courses on the management of TB in children and adolescents and mental health conditions, ongoing research on the use of TB treatment decision algorithms in children, publication of the Roadmap towards ending TB in children and adolescents (third edition) the publication of the WHO operational handbook on TB and comorbidities (mental health conditions), ongoing work on WHO guidance on TB and comorbidities, the development of a policy brief on TB and vulnerable populations and planning for future work on TB in prisons, TB and migrants and TB and pregnancy. WHO/GTB’s work on TB/HIV and other comorbidities includes the development of WHO consolidated guidelines on TB and comorbidities and an accompanying operational handbook. The operational handbook on TB and comorbidities currently includes a section on TB and mental health conditions and will expand to include TB/HIV and diabetes in 2024. A guideline development group meeting on TB and nutrition is planned for June 2024, which will be informed by updated systematic reviews and trial data. The priority questions being considered for this guideline update were shared. In 2024-2025 WHO will also review the guidelines and operational handbook on the management of TB in children and adolescents. The presentation featured several ongoing studies and policy updates that could inform WHO’s future guidance on the management of TB in children and adolescents.

In addition, WHO is in the process of planning for WHO guidance on TB in prisons (which will be informed by updated evidence reviews); is co-convening a consensus process on the earlier inclusion of pregnant women in TB trials and will develop a technical report for the World Innovation Summit for Health on TB, migration, and refugees.

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

1. In addition to TB screening and TPT which are recommended for people in prisons, for what other interventions would the evidence base be most important to address for the upcoming WHO guidance on TB in prisons?

2. What additional evidence needs to be generated to inform future updates of the WHO guidance on TB in children and adolescents to fill current knowledge gaps and barriers in access to TB care?
Discussion:

- Improving TB care in prison settings requires a comprehensive strategy that addresses the unique challenges and needs of incarcerated populations, embedded in human rights principles. This includes exploring how prison health services can be supported to implement TB screening using tools such as X-ray and CAD; guidance on the frequency and timing of TB screening to accommodate the high turnover and movement within prisons; questions around the timing of TPT initiation and choice of TPT regimens; contact investigation, infection prevention and control, and continuity of TB care between prisons and the community. Meeting participants also underscored the importance of integrated care for related health conditions, for example for HCV, HIV, and TB. Unitaid is investing in HCV prevention and harm reduction, with some focus on prison populations.

- To support optimization of treatment regimens for priority populations such as children and pregnant women, Unitaid is also supporting pharmacokinetic modeling and clinical trial capacity.

- Regarding WHO’s report on TB and migration, it was suggested that a landscape analysis of national policies on TB screening and other interventions for TB among migrants - noting the different classes of migrants and the legal contexts - would be a useful addition to other official data on TB and migration.

Conclusions

Matteo Zignol thanked the participants and closed the meeting at 16:00.
## Annex 1. Meeting agenda

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<tr>
<th>Time</th>
<th>Session Description</th>
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<tr>
<td>13:00 – 13:05</td>
<td>Welcome and Introductions</td>
<td>Tereza Kasaeva</td>
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<tr>
<td>13:05 – 13:10</td>
<td>WHO TB policy development, overview</td>
<td>Matteo Zignol</td>
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<tr>
<td>15:55 – 16:00</td>
<td>Summary and concluding remarks</td>
<td>Chair</td>
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### WHO TB policy development, overview

- **Matteo Zignol**

### TB prevention: Dennis Falzon
*Discussants: Norbert Ndjeka and Srinath Satyanarayana*

### TB diagnostics: Nazir Ismail
*Discussants: Patricia Hall and Shaheed V Omar*

### TB treatment: Fuad Mirzayev
*Discussants: Jeremiah Muhwa Chakaya and Gerry Davies*

### TB/HIV, comorbidities and priority populations: Kerri Viney
*Discussants: Daniele Maria Pelissari and Cherise Scott*

*Presentations will cover planned updates to TB policy guidance (2024-25)*

*Discussants will reflect on emerging TB policy development needs, in the context of the current evidence landscape/ gaps*
Annex 2. Participants list

1. **Helen Ayles**  
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2. **Daria Chaadaeva**  
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10. **Dr Truong Thi Thanh Huyen**  
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11. **Nazir Ismail**  
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12. **Rafael Laniado-Laborín**  
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       Integrated Communicable Disease Unit

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   42. Matteo Zignol, Unit Lead, PCI
   43. Farai Mavhunga, Unit Lead, PCI
   44. Dennis Falzon, Team Lead, PCI
   45. Kerri Viney, Team Lead, PCI
   46. Fuad Mirzayev, Team Lead, PCI
   47. Marzia Calvi, PCD
   48. Nebiat Gebreselassie, PCI