World Health Organization
REGIONAL OFFICE FOR Europe

DEFINING THE TUBERCULOSIS RESEARCH AGENDA FOR THE WHO EUROPEAN REGION:

a study report of the European TB Research Initiative

Abstract

The WHO European Region incorporates 53 Member States with reported incidence of tuberculosis (TB) ranging from near elimination to rates exceeding 100 per 100 000 population. It includes 18 high-priority countries to end TB in the WHO European Region, nine of them in the top 30 countries with the highest burden globally of multidrug-resistant TB (MDR-TB). Potentially untreatable cases of extensively drug-resistant forms of TB (XDR-TB) and an increase of HIV coinfection, if not adequately addressed, will threaten the Region's ability to achieve the 2030 End TB Strategy targets. A modified Delphi consultation of core experts in the Region was used to obtain a set of research questions. An online questionnaire was developed and submitted in a public consultation of stakeholders in the Region to produce a ranked and prioritized list. The prioritized research questions covered three thematic areas: 1. epidemiological research; 2. research in basic sciences, new diagnostic tools, novel drugs and vaccines; and 3. operational and public health research. This study is intended to provide a prioritized research agenda for TB in the WHO European Region to guide implementation research and strengthen evidence-based TB control policies.

Keywords

PUBLIC HEALTH | TUBERCULOSIS | TUBERCULOSIS, MULTIDRUG-RESISTANT | RESEARCH | EUROPEAN REGION

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Contents

Abbreviations

ARV	anteretroviral (drugs)
CHNRI	Child Health and Nutrition Research Initiative
ENHR	Essential National Health Research
ERI-TB	European Tuberculosis Research Initiative
EU/EAA	European Union/ European Economic Area
HPC	high-priority country
IGRA	interferon gamma release assay
INH-RPT	isoniazid and rifapentine
NGO	nongovernmental organization
RR/MDR-TB	rifampicin-resistant/multidrug-resistant tuberculosis
TB	tuberculosis
XDR-TB	extensively drug-resistant tuberculosis

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Photo: Maksym Dondiuk

Executive summary

The Seventy-first World Health Assembly in 2018 noted that tuberculosis (TB) remains a global "threat to health security" and "a priority in the response to antimicrobial resistance" *(1)*. It also emphasised that many countries will not reach the global targets that are set in the End TB Global Strategy by 2035. It is feared that business as usual with current tools and methods of patient care will not deliver these targets: reducing TB deaths by 95%, reducing the number of new cases by 90%, and ensuring that no family is burdened with catastrophic expenses due to TB *(2)*. This concern has strengthened the resolve of political leaders and the global TB community to intensify research efforts and spearhead innovation on many fronts. The Moscow Declaration to End TB of 2017 *(3)* acknowledged the need for urgent advances and closer cooperation for TB research and innovation and led to a firm commitment to increase national and regional research capacity and funding. The report of the United Nations High-level Meeting on TB of 2018 called for the "intensification of research and development" and greater investment on new tools and new approaches to TB prevention and care *(4)*. All Member States are now being invited to take part in a consultation to develop a global strategy for research and innovation to be presented during the seventy-third session of the World Health Assembly in 2020. The WHO Regional Office for Europe has fully acknowledged the imperative for more TB research and innovation and has taken concrete steps to modulate the research agenda in the WHO European Region through the launch of the European Research Initiative (ERI-TB) in December 2016.

The TB Action Plan for the WHO European Region 2016–2020 *(5)* incorporates the End TB Global Strategy and has in turn set three interim ambitious targets: to reduce TB deaths by 35%, to reduce TB incidence rates by 25% and reach 75% treatment success rate for MDR-TB by 2020 from 2015 baseline. The most recent surveillance report (2016 data) *(6)* portrays good progress. It finds that the WHO European Region accounts for 3% of the global burden of TB with an estimated average incidence rate of 31.6 cases per 100 000 population and variation across the Region: 12.3 in European Union/European Economic Area (EU/EEA) countries, 56.6 in non–EU/EAA countries and 60.4 in the 18 high-priority countries (HPCs) which account for 83% of all cases. Regional epidemiological trends indicate that the disease is steadily decreasing and the highest annual decline of 4.6% was achieved between 2015 and 2016. A similar reduction in the number of deaths has also occurred. Universal treatment is available and some HPCs have started to report good treatment outcomes for their multidrug-resitant TB (MDR-TB) patient cohorts. The availability and use of rapid molecular methods for drug sensitivity testing is on the increase and is facilitating early detection and diagnosis of drug-resistant strains. While much has been achieved, the same report highlights important challenges that threaten to derail further progress. Nine countries in the Region have the highest burden of MDR and extensively drug-resistant TB (XDR-TB) on a global scale. The number of cases suffering with both TB and HIV infection is increasing at an alarming rate and between 2007 and 2008 the HIV prevalence in incident TB cases increased from 3% to 12%. TB in prisons is underreported and rates are much higher in the prison population across the Region. The increase in the number of migrants, especially in the EU/EAA countries, has been noted and more than one third of cases in the latter are reported to be foreign-born.

The roadmap to implement the TB Action Plan for the WHO European Region 2016–2020 *(7)* has made "Intensified Research and Innovation" one of the three main pillars that address the obstacles to meeting the 2020 targets. Concurrently, the ERI-TB was launched and given the mandate to strengthen the use of evidence, information and research for policy-making. The need for setting a research agenda that includes the needs of both the high-burden and non high-burden countries was immediately apparent during the first meeting of the ERI-TB group. After further discussions, a study was launched to define the research needs in the Region and to systematically identify the most important research questions that merit attention and deeper investigation.

Methods

The method used in this study was developed in an incremental fashion and included the following steps:

- reviewing the literature in health research priority-setting;
- developing and agreeing on a priority-setting methodology;
- generating a set of research questions from the ERI-TB Core Group using a Delphi technique that covered three thematic areas;
- adopting elements of the Child Health and Nutrition Research Initiative (CHNRI) method to develop an online questionnaire to provide a ranking of the research questions;
- presenting the questionnaire as a public consultation of both English- and Russian-speaking stakeholders; and
- producing a prioritized list of the research questions from both high- and non-high-burden countries in the Region.

Results

The results of this study reflect the feedback from 90 respondents that included counterparts from national TB programmes, service providers, research institutes, nongovernmental organizations (NGOs) and international organizations. The following are the research questions that were assigned highest priority by this investigation.

Theme 1. Epidemiological research

According to respondents from both high-burden and non-high-burden countries

1. What are the trends of drug-resistant TB among the countries in the Region with specific reference to resistance to the new (bedaquiline, delamanid) and repurposed TB drugs (including clofazimine, the fluoroquinolones and linezolid)?

2. Which are the most cost-effective TB case-finding screening methods among high-risk populations?

3. Which are the most cost-effective interventions to reduce the spread of drug-resistant TB in the Region?

4. What are the social and biological drivers of drug-resistant TB in the Region?

According to respondents from high-burden countries only

5. How is latent TB infection being detected and monitored across the Region?

6. What are the current gaps in the surveillance systems across the Region?

7. What is the outcome of TB treatment among patients who are incarcerated or have a history of incarceration?

8. How are outbreak investigations among high-risk populations and in high-risk settings being mapped and reported in countries?

Theme 2. Innovation and fundamental research

According to respondents from both high-burden and non-high-burden countries

1. Which biomarkers are useful to determine the risk of progression from latent TB infection to active disease and to distinguish relapse from reinfection?
2. What are the genetic mutations associated with resistance to new and repurposed medicines?
3. What are the candidate molecular targets for anti-TB drugs?
4. What is the evidence that rapid molecular diagnostic techniques for the initial diagnosis of TB and resistant forms of TB (such as Xpert® and Whole Genome Sequencing) improve the diagnosis and treatment outcome, especially among children and people living with HIV?
5. How effective and cost-effective are the new diagnostic platforms (including most recent molecular drug sensitivity tests and Whole Genome Sequencing platforms)?
6. What are the optimal doses of new and repurposed medicines in children?
7. What are the most effective and patient-friendly short-term regimens for MDR/extensively MDR/XDR-TB taking into account the pill burden, use of injectable drugs and duration of treatment) in the Region?

According to respondents from high-burden countries only

8. How do the new tests (such as interferon gamma release assay (IGRA) and ESAT6-based skin test) compare with other traditional methods (such as the Mantoux skin test) to detect previous exposure to TB?
9. Drug sensitivity testing for new drugs, second-line drugs and pyrazinamide: how should the minimum inhibitory concentration be used to guide treatment?
10. What are the observed efficacy, safety and tolerability of new and repurposed medicines (especially among children, adolescents, people living with HIV and the elderly)? Are there any interactions with antiretroviral (ARV) drugs?
11. How should pretomanid best be dispensed by the expanded access and compassionate use programme, applying lessons learned from bedaquiline and delamanid?

According to respondents from non-high-burden countries only

12. Which infrastructures are needed to integrate new tools (such as line probe assay, Xpert®) in the current diagnostic set-up in low- and high-incidence countries and in different settings (including prisons and migrant camps) to improve the management of drug-resistant TB?

Theme 3. Operational and public health research

According to respondents from both high-burden and non-high-burden countries

1. What is the average time to TB diagnosis among the various risk groups and what are the reasons for diagnostic delay?
2. What are the most effective approaches to the management of close contacts of MDR-TB and XDR-TB index patients?
3. What are the main reasons for patients to discontinue treatment in the Region?
4. What are the extent and impact of the short-course MDR-TB regimen in national TB programmes in the Region?
5. What is the optimal preventive MDR-TB MDR and XDR-TB index patients?
6. What is the optimal screening algorithm for active TB and latent TB infection among people living with HIV?
7. Integrating TB-HIV care: what are the best models for delivering TB-HIV treatment and monitoring?
8. Integration of TB programmes in the prison and civilian sectors: what are the causes and consequences of poor integration?

According to respondents from high-burden countries only

9. Do hospital-based and home-based TB treatment outcomes vary in the different hard-to-reach risk groups (people living with HIV, people with alcohol problems, elderly people, migrants)?
10. How can incentives and enablers be used to achieve better treatment outcomes, and which are more likely to influence hard-to-reach groups?
11. What are the main reasons for relapse after successful completion of treatment?
12. What are the most cost-effective infection control measures in health-care settings (TB wards, primary health-care units, long- and short-term congregate settings such as the military, prisons, homeless shelters or dormitories) and in public spaces?
13. What are the challenges and gaps in implementing and maintaining infection control measures in health-care settings?
14. For how long do patients with drug-sensitive and drug-resistant TB remain infectious after starting treatment?
15. What are the factors associated with TB mortality in high-incidence and low-incidence countries?

According to respondents from non-high-burden countries only

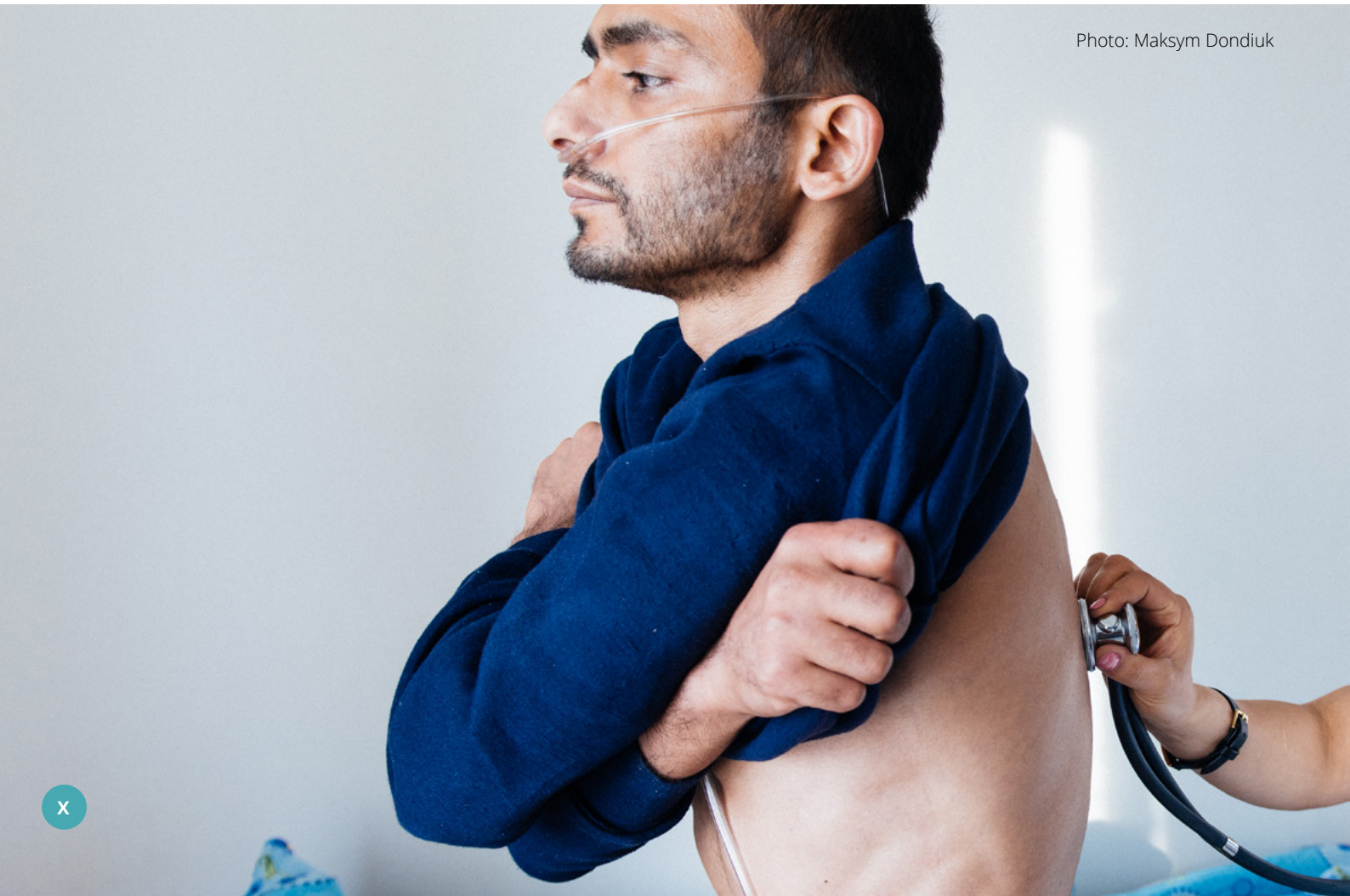
16. Management of TB among internal and cross-border migrants: what are the best practices in cross-border TB control and care?

17. What are the barriers to bringing TB treatment closer to patients' homes and how can they be overcome?

18. What are the effectiveness and cost-effectiveness of screening strategies and preventive treatment for latent TB infection among high-risk groups in non-high-burden countries?

Conclusion

This study shows that more information is required by the TB community to overcome new specific challenges. While research and innovation in the basic sciences is needed to develop new diagnostic tools, new effective drugs and vaccines, operational research on the high-risk or hard-to-reach population groups is equally important. This prioritizing of research questions is intended to focus the attention of the TB community and to stimulate funding for these important lines of investigation. Some shared priorities between the high-burden and non-high-burden countries are apparent. This should open new possibilities for stronger cooperation and collaboration. Some differences have been exposed and are a reflection of the different country experiences and epidemiological settings. The results of all research need to be shared and communicated openly to ensure that TB control efforts remain grounded on evidence and fully responsive to the needs of the Region.



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Introduction

The European Tuberculosis Research Initiative (ERI-TB) *(8)* was launched by the WHO Regional Office for Europe in 2016 to advance research and innovation and is an important platform to support the implementation of the TB Action Plan 2016–2020. The plan underscores areas of work that are led by both scientific and operational research and also focuses on improving epidemiological surveillance, scaling up the availability of new drugs and rapid diagnostic tools and strengthening health systems to deliver sustainable and effective patient-centred care. Although the WHO European Region has seen the highest decline in TB incidence on a global scale in the past decade *(9),* it is expected that the End TB targets may not be reached by 2035 *(10)*.

TB remains an important threat to public health and is becoming more difficult and expensive to treat, especially its multidrug and extensively drug-resistant forms. While some countries are close to eradication, many still experience a very high burden of disease and nine of the 30 countries with the highest rifampicin-resistant/multidrug-resistant TB (RR/MDR-TB) burden in the world are in the WHO European Region. It is estimated that 19% of new cases and 55% of previously treated cases have RR/MDR-TB *(6).* Furthermore, 18 countries are considered "high-priority countries" as they account for 85% of all incident cases, 90% of all deaths, 99% of all MDR-TB cases and 91% of TB/HIV coinfections.[1] Strengthened health systems now offer universal access to treatment but the recent discoveries of incurable XDR-TB strains *(11),* high levels of alcohol abuse *(12,13),* the fatal mix *(14)* and alarming spread of HIV *(15 ,16)* are important threats that could halt further progress *(17)*. Risk groups such as migrants *(18, 19)* and prisoners are "neglected priorities" *(20)* and little is known on the best response strategies among these populations.

It is feared that the targets set by the global WHO End TB Strategy for 2035 will not be met even by the low incidence countries at the current rate of decline *(21).* More research is needed to guide actions to end the suffering as TB is the tenth leading cause of death worldwide, causing even more deaths than HIV/AIDS globally *(22)*. Several calls have been made to intensify research efforts to find an effective vaccine, to develop reliable and scalable "point of care" diagnostic tools, to discover new and effective drugs and to use new models of care that assure successful outcomes. Only recently, TB research funding was considered to "governed principally by inertia" *(23)*, however thanks to the most recent high-level meetings the tide seems to be turning. A paper presented in Moscow *(24)* during the first Global Ministerial Conference on Ending TB in November 2017 highlighted that although science and technology hold great promise to better understand and control this complex pathogen, lessons from the past show that unless TB programmes are held to rigorous standards, new scientific advances may still fail to achieve much progress. Operational and public health research at both national and regional levels are necessary and much can be gained if the results from such studies are included to strengthen national TB control policies.

Setting research priorities

As the demands on health services continue to grow, many health programmes operate under challenging conditions and financial constraints. Attempts at "prioritization" in health research are influenced by many factors such as a vast number of research ideas, competing interests and uncertain outcomes. While research priority setting should align funding with the needs of countries, research funding can be dominated by donor agencies who may themselves have changing priorities. Health research is difficult to be prioritized and the ideal health research prioritization method is yet to be described.

[1] The 18 high-priority countries to End TB in the WHO European Region are: Armenia, Azerbaijan, Belarus, Bulgaria, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Republic of Moldova, Romania, Russian Federation, Tajikistan, Turkey, Turkmenistan, Ukraine and Uzbekistan.

A review of the literature of prioritization methods in health care was performed in preparation for this study and found that a range of methods with varying complexity have been used. Common priority setting efforts in countries have included informal methods such as conferences and Delphi consultations *(25, 26)* as well as more comprehensive methods such as the Child Health and Nutrition Research Initiative (CHNRI) *(27)* and the Essential National Health Research (ENHR) *(28)*. The metric based CHNRI and ENHR methods are considered to have greater transparency and are likely to produce more replicable results since both use defined criteria, inputs are recorded, and the output is a ranked and scored listing. Delphi consultations on the other hand are iterative and consensus building and very useful to collect expert opinions on a defined topic in a brief period of time. A mix of techniques such as Delphi consultations combined with the CHNRI approach have been used in several regional and global studies as well as by the WHO "International Roadmap for Tuberculosis Research" *(29)*.

Aim

To provide a prioritized research agenda for TB in the WHO European Region to guide implementation research and strengthen evidence-based TB prevention and care policies.

Method

A mixed approach was used in this study. The method combines a Delphi consultation of core experts from the Region followed by quantitative ranking by stakeholders using elements of the CHNRI method.

Stage 1. Collecting a set of research questions – Delphi Technique method

Study population: ERI-TB Core Group members, ERI-TB WHO secretariat, TB programme managers attending the meeting in Wolfheze in 2017.

A semi-structured template was used to collect suggestions of research questions from the 15 members of the ERI-TB Core Group members using similar thematic areas that were used in the "International Roadmap for Tuberculosis Research": (1) Research in Epidemiology, (2) Research in Basic Sciences/New diagnostic tools, Drugs, and Vaccines, (3) Operational and Public Health Research, with added subsets (Table 1). The responses were collected over a period of two weeks and a draft list of research questions was prepared by a facilitator and reviewed by the WHO secretariat. The results from this consultation were presented at the TB programme managers meeting in Wolfheze, The Hague, Netherlands in June 2017.

TABLE 1. Thematic areas with subsets

Theme 1 Epidemiological research	1. BURDEN OF DISEASE, INCLUDING LATENT TB INFECTION 2. DYNAMICS AND DRIVERS OF DISEASE TRANSMISSION
Theme 2 Innovation & fundamental research	3. RESEARCH IN BASIC SCIENCES 4. NEW DIAGNOSTIC TOOLS 5. NEW DRUGS AND NEW REGIMENS 6. NEW VACCINES
Theme 3 Operational research	7. CASE DETECTION AND SCREENING 8. ACCESS TO TREATMENT AND COMPLIANCE 9. OPTIMIZING TREATMENT REGIMENS 10. HEALTH SYSTEMS AND PUBLIC PRIVATE MIX 11. COLLABORATION WITH HIV PROGRAMMES 12. COLLABORATING WITH OTHER PROGRAMMES 13. INFECTION CONTROL 14. NATIONAL TB PROGRAMME MONITORING 15. COMMUNITY PARTICIPATION 16. SOCIAL DETERMINANTS OF TB 17. LINKING TB RESEARCH WITH OTHER DISCIPLINES

Stage 2. Ranking of the research questions – Modified CHNRI approach

Study population: country representatives from 53 Member States and other stakeholders in the WHO European Region.

A web hosted public consultation was held in November 2017 in order to grade research questions to produce a prioritized list (highest, high, or lower priority). A questionnaire was prepared in English and translated into Russian using SurveyMonkey *(30)*. Each research question was graded for (1) Relevance (defined as: "Answering this research question would definitely reduce the burden of disease") and (2) Urgency (defined as: "This research is urgently needed"). Each question was rated on both criteria by selecting one of three choices (Yes, Maybe, No). Both the sequence of pages and questions on each page were offered to respondents in random order to reduce bias. Both English and Russian versions were piloted in three countries (Ukraine, Georgia, and Azerbaijan). The call for an open consultation was published on the website of the WHO Regional Office for Europe and actively promoted via social media. In addition, an active invitation was sent by e-mail using the distribution list of the WHO Regional Office for Europe that included all national counterparts, civil societies and other stakeholders working in TB across the 53 Member States in the Region. A call was also made among the participants of the Global Ministerial Conference on Ending TB in the Sustainable Development Era that took place in November 2017 in Moscow, Russian Federation. Responses were collected over a period of four weeks. Contact details including the country and affiliation of responders were required to avoid duplicate responses.

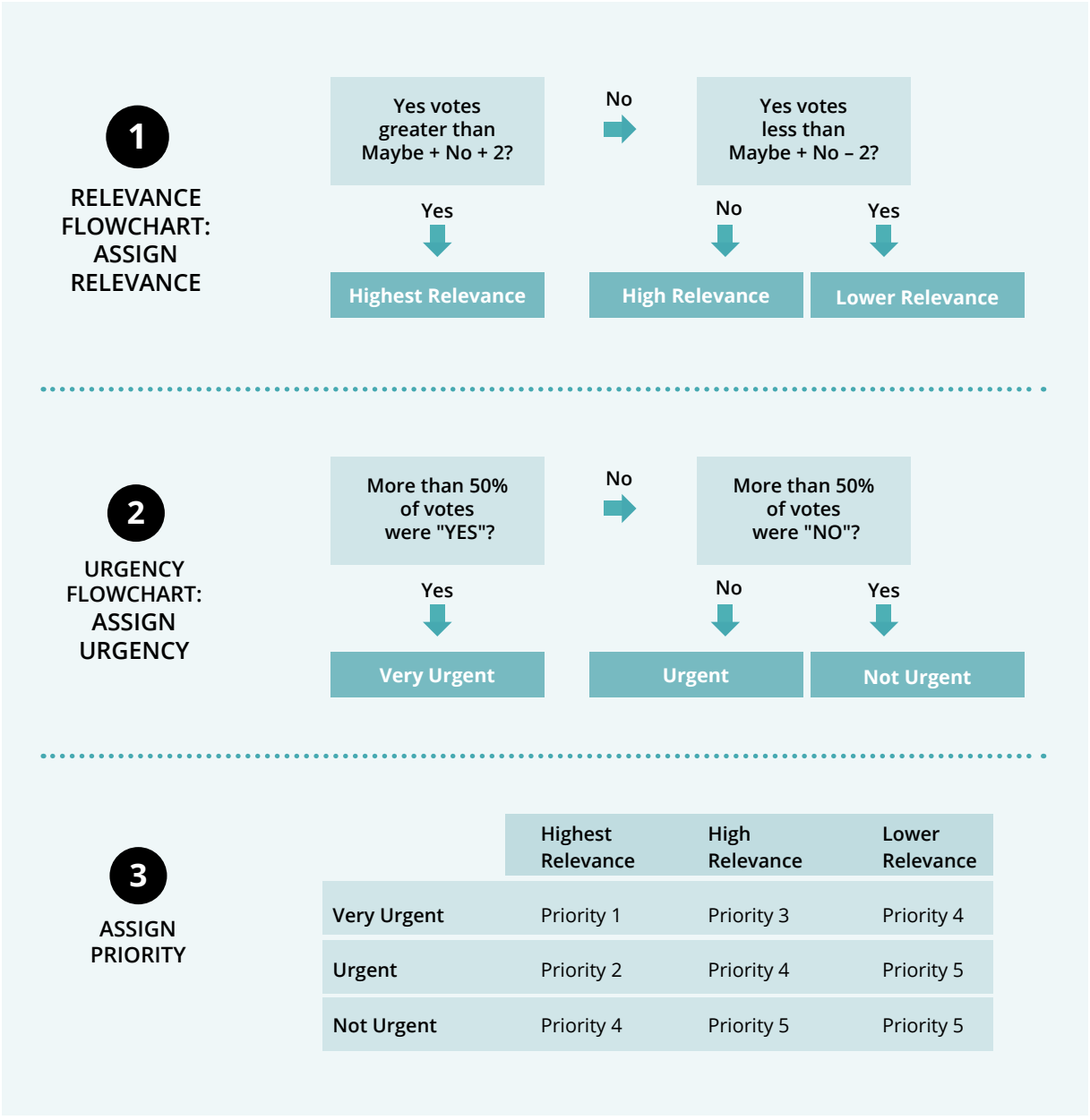
The responses from English and Russian versions were combined. Labels were added to the downloaded data in order to enable detailed analysis of the results for: country code, burden of disease according to the WHO Regional Office for Europe classification (high- and non-high-burden); language (English/Russian); affiliation (national TB programmes, service providers, NGOs, international agencies and research

institutes); proportion of questionnaire completed. A programme written in Python using the statistical library Pandas was used to compile the pivot tables and cross tabulations.

Computation and evaluation of the scores

Each research question was scored separately in successive rounds using a stepwise approach as illustrated in Fig. 1. The combined results were used to classify each question into one of six groupings (P1 to P6) corresponding to three levels of priority: Highest Priority (P1 and 2), High Priority (P3 and 4), Lower Priority (P5 and 6).

FIG. 1. Flow charts for assessing relevance, urgency and priority



	Highest Relevance	High Relevance	Lower Relevance
Very Urgent	Priority 1	Priority 3	Priority 4
Urgent	Priority 2	Priority 4	Priority 5
Not Urgent	Priority 4	Priority 5	Priority 5

Results

Stage 1. Results of modified Delphi consultation

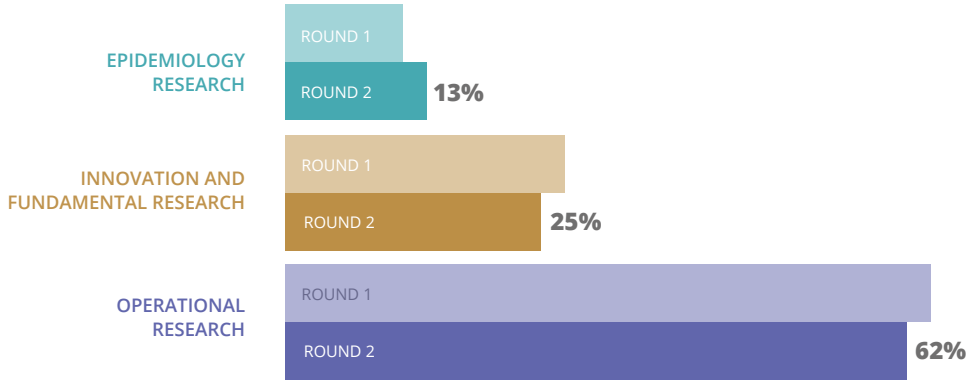
Thirteen members (86%) from the ERI-TB Core Group submitted responses and a total of 258 separate entries were recorded. Statements of opinion or general comments were pruned by the facilitator and only research questions retained. The distribution of responses across the 18 subsections is shown in Table 2.

TABLE 2. Distribution of responses across subsections

Section	Number of members giving suggestions (N=15) and %	Number of research question entries in first list (N=131) and %	Number of research question entries in final list (N=76) and %
Theme 1. Epidemiology			
1. Burden of disease (including latent TB infection (LTBI)	10 (77%)	9 (7%)	6 (8%)
2. Drivers and dynamics of TB	12 (92%)	6 (5%)	4 (5%)
Theme 2. Innovation and fundamental research			
3. Basic science research	9 (69%)	11 (8%)	5 (7%)
4. New diagnostic tools	12 (92%)	13 (10%)	7 (9%)
5. New drugs/regimens	11 (85%)	9 (7%)	5 (7%)
6. New vaccines	3 (23%)	3 (2%)	2 (3%)
Theme 3. Operational research			
7. Case detection and screening	10 (77%)	7 (5%)	4 (5%)
8. Access to treatment and compliance	10 (77%)	13 (10%)	10 (13%)
9. Optimizing treatment regimens	8 (62%)	10 (8%)	4 (5%)
10. Health systems & public private mix	5 (28%)	5 (4%)	4 (5%)
11. Collaboration with HIV programmes	6 (46%)	6 (5%)	4 (5%)
12. Collaboration with other programmes	6 (46%)	7 (5%)	3 (4%)
13. Infection control	11 (85%)	9 (7%)	5 (7%)
14. Community participation	8 (62%)	2 (2%)	2 (3%)
15. National TB programme monitoring	5 (38%)	4 (3%)	4 (5%)
16. Gender & social determinants	4 (31%)	3 (2%)	4 (5%)
17. Linking with other disciplines	6 (46%)	6 (5%)	3 (4%)

The questions were shortlisted and a final list of 76 was established. The representation across the three thematic areas in the original entries and the final list was preserved as shown in Fig. 2.

FIG. 2. Distribution (%) of research questions by theme in the first and final lists

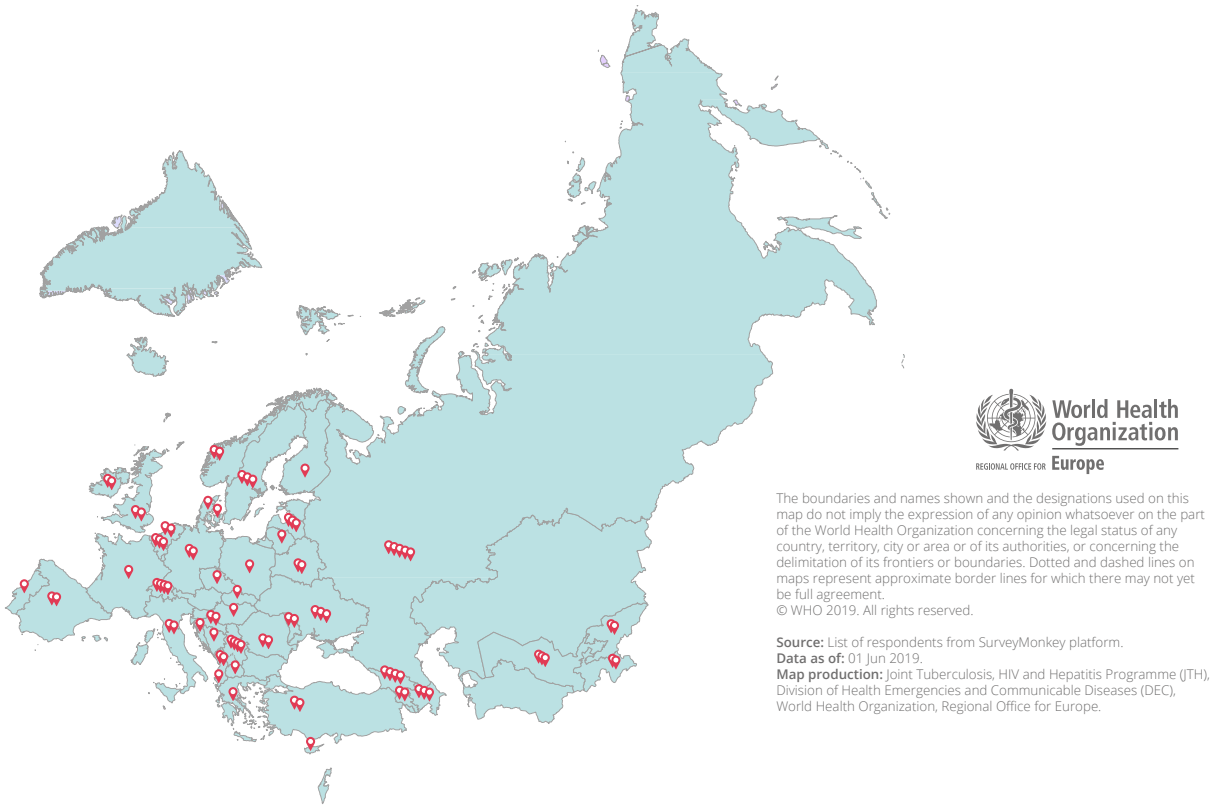


Stage 2. Results of the online consultation

Responses

A total of 90 questionnaires (73 complete, 11 more than half and six less than half complete) were received from respondents in the Region, 76 in English, and 14 in Russian. Respondents came from 45 (85%) of the 53 Member States (Fig. 3). No responses were obtained from three high-burden countries and five non-high-burden countries.

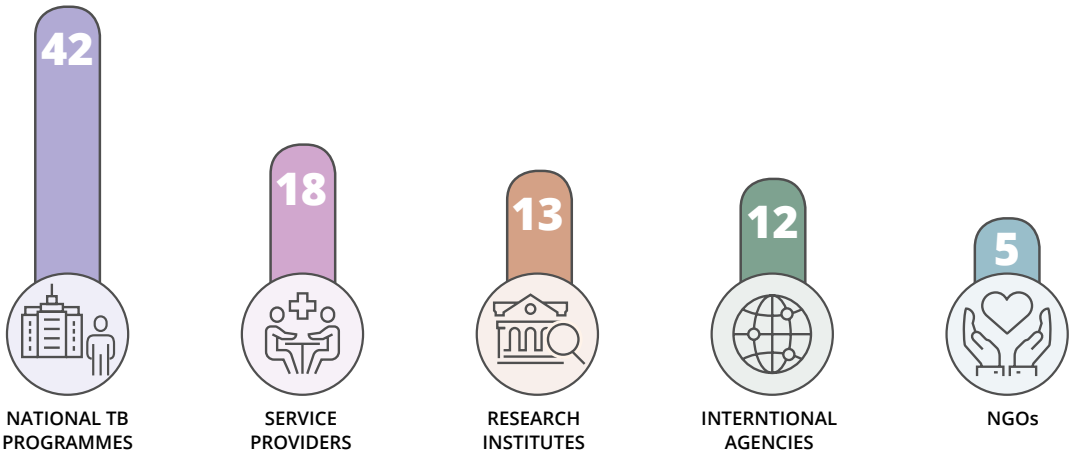
FIG. 3. Geographic origin of respondents, WHO European Region



Affiliation

The distribution and type of affiliation reported by respondents is a useful indicator of the inclusiveness reached by this consultation. Five general groups that emerged from the analysis and their distribution are shown in Fig. 4.

FIG. 4. Affiliation of respondents (Total = 90)



Prioritized listing

The set criteria were used to derive three ranked levels of priorities (Highest, High, Lower) and the choices from the high-burden and from the non-high-burden countries were contrasted. Summary results are shown in Table 3. The differences in the highest priority choices between the two sets were most marked for epidemiological research. There was stronger agreement between the two groups on innovation and fundamental research. Many of the suggested operational research questions were given the lower priority by the non-high-burden countries.

TABLE 3. Distribution of the prioritized research questions by theme and country burden

Epidemiological Research (Number and %)		**Innovation & Fundamental Research** (Number and %)		**Operational Research** (Number and %)		
High-burden	*Non-high-burden*	*High-burden*	*Non-high-burden*	*High-burden*	*Non-high-burden*	**Priority Assigned**
8 (80%)	4 (40%)	11 (58%)	9 (47%)	15 (32%)	11 (23%)	HIGHEST (P1-2)
1 (10%)	2 (20%)	3 (16%)	3 (16%)	14 (30%)	6 (13%)	HIGH (P3-4)
1 (10%)	4 (40%)	5 (26%)	7 (37%)	18 (38%)	30 (64%)	LOWER (P5-6)
Total = 10 questions in theme		**Total = 19 questions in theme**		**Total = 47 questions in theme**		**All = 76**

Highest priority ranked research questions

The common rankings among respondents from both high- and non-high-burden countries reveal a shared demand for research in several areas. The list of research questions in the highest priority category shared by both groups is shown in Fig. 5.

FIG. 5. Highest priority research questions common to respondents from high- and non-high-burden countries

Theme 1. Epidemiological research

Burden of disease, including latent TB infection

1. *"What are the trends of drug-resistant TB among the countries in the Region with specific reference to resistance to the new (bedaquiline, delamanid) and repurposed TB drugs (including clofazimine, the fluoroquinolones, and linezolid)?"*

2. *"Which are the most cost-effective TB case-finding screening methods among high-risk populations?"*

3. *"Which are the most cost-effective interventions to reduce the spread of drug- resistant TB in the Region?"*

4. *"What are the social and biological drivers of drug-resistant TB in the Region?"*

Dynamics and drivers of disease transmission

FIG. 5 contd

Theme 2. Innovation & fundamental research

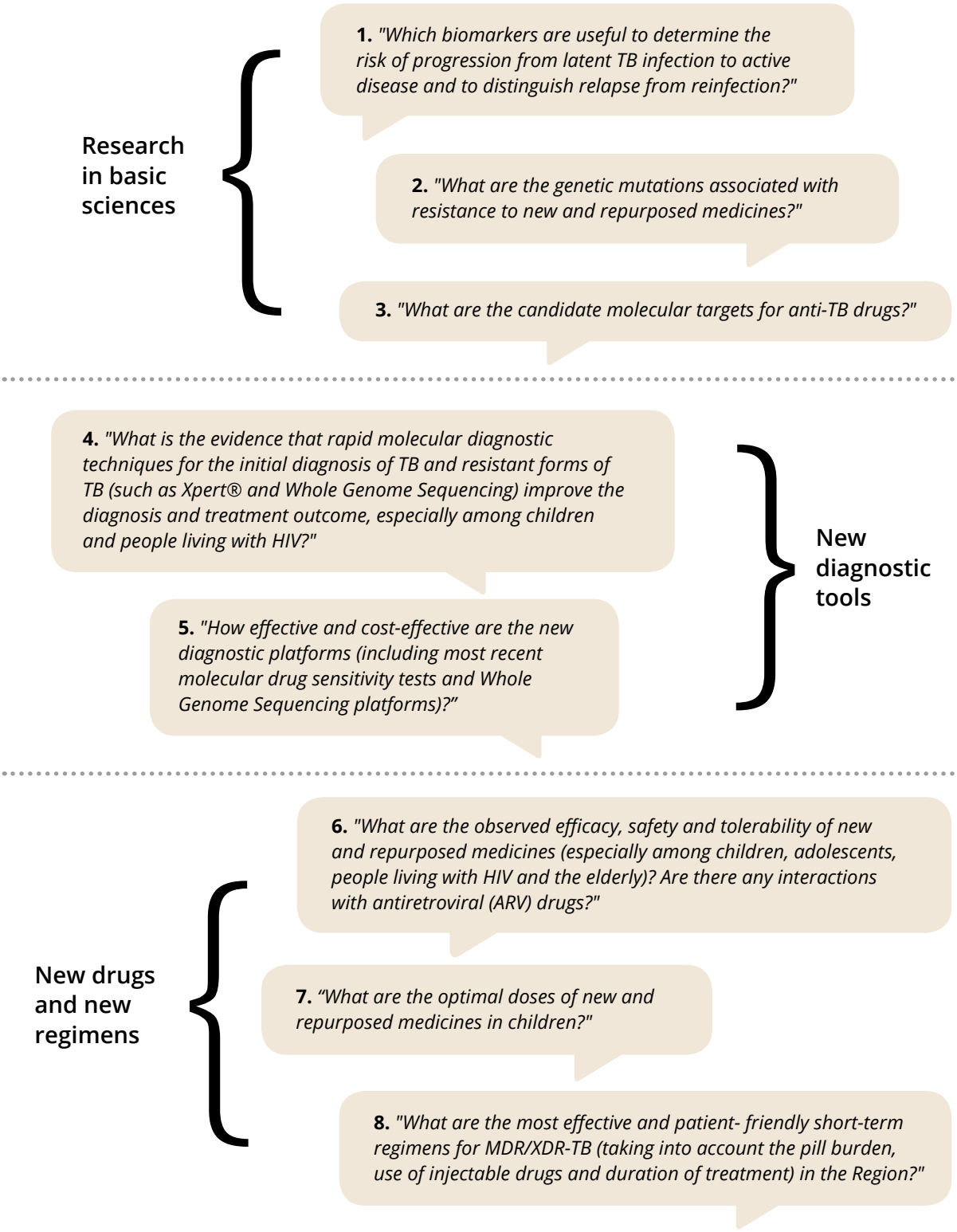
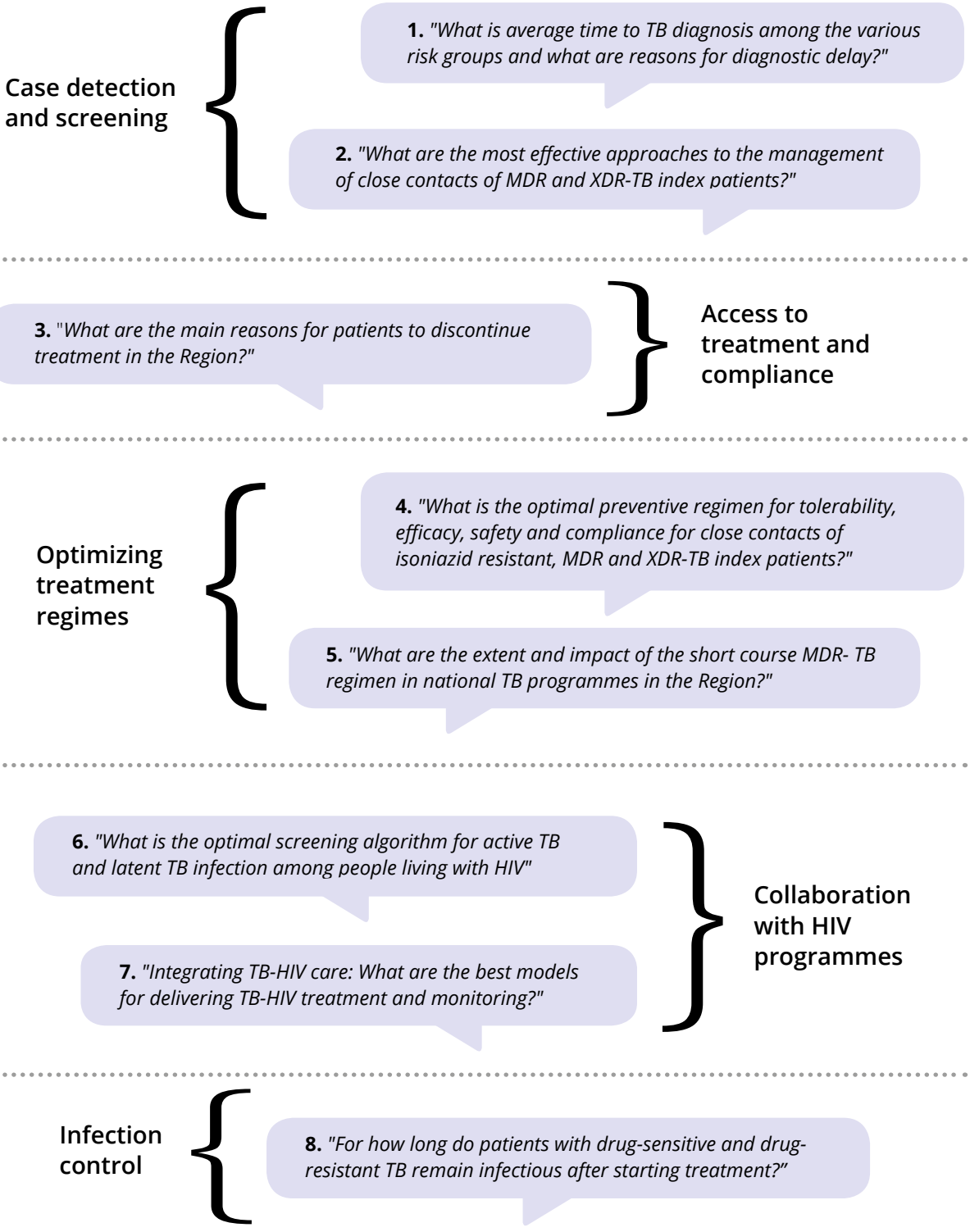


FIG. 5 contd

Theme 3: Operational Research



Areas of research that did not feature in this shared list were new vaccines, the private sector, national TB programmme monitoring, collaborations with noncommunicable disease programmes, community participation, social determinants of TB and linking TB research with other disciplines.

Some differences were noted between the two groups. Highest priority was assigned by respondents from the high-burden countries for research on surveillance gaps, mapping of outbreaks, new tests to detect infection with TB and use of minimum inhibitory concentrations for second-line drugs. This group also featured operational research on expanded access and compassionate use of new and repurposed drugs, the use of incentives as well as factors associated with mortality and relapse after treatment. Research on the management of TB among internal and cross-border migrants featured as highest priority only by the respondents from the non-high-burden countries. These observations highlight some of the different challenges that are faced in countries within the WHO European Region.

Supplementary analysis of the data compared the responses across the five affiliation groups. Service providers gave highest priority to the research on: computer aided interpretation of imaging techniques; e-health and mobile health interventions; operational challenges to the introduction of the new short course three-month isoniazid and rifapentine (3HP) regimen for latent TB infection; cost effectiveness of ambulatory treatment; and comparing new tests such as IGRA to the Mantoux test to detect TB infection. On the other hand national programme managers assigned highest priority to research on: the attributable risk of active TB among different risk groups; the outcome of treatment among patients who are incarcerated or have a history of incarceration; the reporting and mapping of outbreak investigations in high-risk populations; and the social determinants of TB and drug-resistant TB. NGOs had a particular interest in research on improvements in infection control in hospitals (specifically across eastern and central European countries). International agencies uniquely chose research on enablers and incentives to high-risk groups while respondents from research institutes where the only group choosing research on biomarkers that could help make drug trials faster and less expensive.

The full list of the 76 research questions and the prioritization assigned to each by respondents from high- and non-high-burden countries can be found in Annex 1.

The “Highest Priority” list of research questions by affiliation groups can be found in Annex 2.

Discussion

General discussion

There have been several attempts at prioritising TB research but this study is the first in the WHO European Region to include a wide range of stakeholders, such as national programme managers, NGOs and service providers. It actively sought input from the Russian-speaking countries and also targeted respondents from both high- and non-high-burden countries. The result has produced a set of concrete lines of investigations in the form of research questions that can be used or adapted by active parties. Since the high-level meetings in Moscow and New York, a prioritization of TB research at a global scale is underway at WHO headquarters in an attempt to produce a draft Global Strategy for Tuberculosis (TB) Research and Innovation (Global Strategy) by a public consultation of stakeholders.

This study has shown there are a number of shared priorities across the Region. Demand for research may be influenced by the disease burden, drivers of transmission or by unique risk groups. The research agenda in high burden countries, or countries with limited resources, may be different from that in non-high-burden countries or vice versa, but shared interests may exist that can facilitate collaborative and coordinated research projects. For example, while management of latent TB infection is receiving much

attention among low-incidence countries this is also relevant in countries with high numbers of MDR-TB cases who also have young families. Prevention efforts among the increasing numbers of HIV/TB co-infected is also important as TB is the leading cause of death in this population. Smaller countries may not have sufficient resources to undertake considerable research but still have the potential to participate in collaborative and multi centre.

Different priorities between the respondents from the high- and non-high-burden countries are apparent. Research on TB among internal and cross-border migrants was found to be uniquely of highest priority in the latter. In contrast this was deemed of lower priority by the high-burden group. Furthermore, a set of highest priority questions were unique to respondents from high-burden countries and this reflects areas of concern in this setting. Some examples include: research on outbreak investigations, treatment outcomes in prisons, infection control in health-care settings, causes of patient relapse, outcome of home-based treatment in high-risk groups and causes of mortality. The renewed interest in basic science and translational research can be promoted and consolidated if countries can reduce the funding gaps and provide a sufficient "pull" in the market to attract more investment in this field. Research that would facilitate field testing of new diagnostic tools, aggregate data and open sharing of results can lead the way to faster product development, adoption and implementation. The active dialogue with TB programme managers and ministries of health can set the scene for more extensive studies in this field. XDR/MDR-TB is a serious threat and the possibility that these strains will replace endemic strains is a cause for concern *(32)*. New drugs such as delamanid, bedaquiline, and new short course regimens are key to stopping this from happening, but more rigorous studies are needed to determine their efficacy and to ensure that resistance does not develop as the scaled up access of these drugs is now WHO policy for the Region *(32)*. Shared experiences and best practices can also lead to a more positive regulatory framework that could otherwise limit the availability of these drugs in the countries that need them most.

Barriers to research

Internal round table discussions among the ERI-TB Core Group have produced some unique insights from a regional context and have already been reported *(33)*. Barriers to research include: resource gaps for both funding and capacity in low- and moderate-income countries; mismatch between the interests of international and local researchers; national TB programme managers may not be involved in research plans; language preferences of published results can reduce their significance; small population size; competition by more lucrative fields. Ethical concerns and respect for patients' rights especially when conducting research on marginalized and even criminalized populations also need to be considered.

Limitations of the study

Limitations for priority setting in health research are well recognized and issues of transparency, inclusiveness, dominant groups, and vague participant enrolment are often raised. Delphi consultations can be affected by facilitator bias and results can be influenced in favour of groups generating research ideas. The participants of the Delphi consultation generating the research questions in this study was limited to the 13 Core Group members of the ERI-TB. The validity of the prioritization depends on the degree of bias that is very often inherent to the process. Several efforts were made to mitigate these limitations. The ERI-TB Core Group represent a diverse pool of knowledge and expertise from across the Region in TB prevention, control and care from both high- and non-high-burden countries. All had declared no conflicts of interests. The prioritization was based on a public consultation. Although there was no predetermined list of eligible participants several attempts were made to reduce selection bias by encouraging responses from all Member States. The broad representation of countries and affiliations reflect these efforts. A user-friendly online platform was chosen that allowed randomization of sections

and research questions. The use of English and Russian versions overcame language barriers. The small number of participants is an important limitation of this study however these participants have influence in the Region through their official positions and affiliations.

Conclusion

The WHO European Region contains a mix of countries with marked variations of economic development, population health and TB disease burden. Many countries enjoy a wealth of advanced academic institutions that are leaders in medical research and have high literacy rates among the general population. As countries face different challenges, research priorities will vary according to the needs and research gaps in the country but there are important common priorities across the board. A strong political commitment to End TB by 2030 has been made by global leaders during the United Nations High-level Meeting on TB that was held in September 2018. Development and capacity building of primary research especially in the high-burden countries should become a priority. The timely implementation of results from well-funded and high-quality research that is also prioritized, useful to countries and collaborative in nature will make a difference to the lives of many who are still suffering from TB.

Photo: Maksym Dondiuk

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Annex 1. Ranking of research questions (highest, high and lower priority) according to respondents from high-burden and non-high-burden countries

Research question	High-burden countries	Non-high-burden countries
Theme 1. Epidemiological research		
1. Burden of disease and latent TB infection		
1. What are the trends of drug- resistant TB among the countries in the Region with specific reference to resistance to the new (bedaquiline, delamanid) and repurposed TB drugs (including clofazimine, the fluoroquinolones, and linezolid)?	Highest	Highest
2. Which are the most cost-effective TB case-finding screening methods among high-risk populations?	Highest	Highest
3. How is latent TB infection being detected and monitored across the Region?	Highest	High
4. What are the current gaps in the surveillance systems across the Region?	Highest	Lower
5. What is the attributable risk of developing active TB among different infected risk groups in the Region?" (with special reference to (i) child contacts under 5 years; (ii) migrants from a high TB burden country (iii) people with a history of imprisonment; (iv) unemployed people; (v) homeless people; (vi) people living with HIV and injecting drug users; (vii) people with diabetes mellitus and other noncommunicable diseases; (viii) people with harmful use of alcohol)?	Lower	High
2. Dynamics and drivers of disease transmission		
6. Which are the most cost-effective interventions to reduce the spread of drug-resistant TB in the Region?	Highest	Highest
7. What is the outcome of TB treatment among patients who are incarcerated or have a history of incarceration?	Highest	Lower
8. What are the similarities of mycobacterial phylogenetic a patterns among high risk groups?	High	Lower

Research question	High-burden countries	Non-high-burden countries
9. How are outbreak investigations among high-risk populations and in high-risk settings being mapped and reported in countries?	Highest	Lower
10. What are the social and biological drivers of drug-resistant TB in the Region?	Highest	Highest

Theme 2. Innovation & fundamental research

3. Basic sciences

11. Which biomarkers are useful to determine the risk of progression from latent TB infection to active disease and to distinguish relapse from reinfection?	Highest	Highest
12. What are the genetic mutations associated with resistance to new and repurposed medicines?	Highest	Highest
13. What are the candidate molecular targets for anti-TB drugs?	Highest	Highest
14. Monitoring response to new drugs/regimens in clinical trials: Which biomarkers will help make drug trials faster/cheaper?	High	High
15. What is the role of mycobacterial-derived antimicrobial proteins and alternative therapies such as host-directed therapies and Vitamin D in TB prevention and treatment?	Lower	Lower

4. New diagnostic tools

16. What is the evidence that rapid molecular diagnostic techniques for the initial diagnosis of TB and resistant forms of TB (such as Xpert® and Whole Genome Sequencing) improve the diagnosis and treatment outcome, especially among children and people living with HIV?	Highest	Highest
17. How effective and cost-effective are the new diagnostic platforms (including most recent molecular drug sensitivity tests and Whole Genome Sequencing platforms)?	Highest	Highest
18. Genotypic drug sensitivity testing methods: How should "trace" category results of Xpert®/Ultra relate for patient management?"	Lower	Lower
19. Which infrastructures are needed to integrate new tools (such as line probe assay, Xpert®) in the current diagnostic set-up in low and high-incidence countries and in different settings (including prisons, migrant camps) to improve the management of drug- resistant TB?	High	Highest

Research question	High-burden countries	Non-high-burden countries
20. How do the new tests (such as interferon gamma release assay (IGRA) and ESAT6-based skin test) compare with other traditional methods (such as the Mantoux skin test) to detect previous exposure to TB?	Highest	Lower
21. Drug sensitivity testing for new drugs, second line drugs and pyrazinamide: How should the minimum inhibitory concentration be used to guide treatment?	Highest	Lower
22. What is the role of computer-aided interpretation of imaging techniques (chest X-ray, computerised tomography, magnetic resonance imaging and positron-emission tomography) and how do they compare with standard chest X-rays in TB diagnosis and monitoring?	Lower	Lower
5. New drugs and regimens		
23. What are the observed efficacy, safety and tolerability of new and repurposed medicines (especially among children, adolescents, people living with HIV and the elderly)? Are there any interactions with antiretroviral (ARV) drugs?	Highest	Highest
24. How should pretomanid best be dispensed by the expanded access and compassionate use programme, applying lessons learned from bedaquiline and delamanid?	Highest	Lower
25. What are the optimal doses of new and repurposed medicines in children?	Highest	Highest
26. What are the most effective and patient- friendly short-term regimens for MDR/extensively drug-resistant (XDR)-TB (taking into account the pill burden, use of injectable drugs and duration of treatment) in the Region?	Highest	Highest
27. What are the role and influence of regional and national Consilia in guiding the management of difficult MDR/XDR cases?	Lower	Lower
6. New vaccines		
28. What progress is being made in pre- and post-exposure vaccines against TB?	High	High
29. How can high-burden countries facilitate research in new vaccines?	Lower	High

Research question	High-burden countries	Non-high-burden countries
Theme 3. Operational research		
7. Case detection and screening		
30. What is average time to TB diagnosis among the various risk groups and what are reasons for diagnostic delay?	Highest	Highest
31. What are the most effective approaches to the management of close contacts of MDR and XDR-TB index patients?	Highest	Highest
32. What are the effectiveness and cost-effectiveness of screening strategies and preventive treatment for latent TB infection among high-risk groups in low-burden countries?	High	Highest
33. What is the effectiveness of pre vs. post arrival screening procedures for migrants from intermediate or high burden countries with a comparison of the tools used (TST vs IGRA vs chest X-ray)?	Lower	High
8. Access to treatment and compliance		
34. Do hospital-based and home-based TB treatment outcomes vary in the different hard to reach risk groups (people living with HIV, alcoholics, elderly people, migrants)?	Highest	Lower
35. What is the role of family- or pharmacy-supervised directly observed therapy?	Lower	Lower
36. How effective are e-health and mobile health interventions (e.g. Video Observed Therapy) on adherence and treatment outcomes among the various patient groups?	High	Lower
37. How effective is the supply management of TB drugs and which factors influence access to medicines in the Region?	High	Lower
38. How can incentives and enablers be used to achieve better treatment outcomes, and which are more likely to influence hard to reach groups?	Highest	Lower
39. How can adherence to preventive treatment of latent TB infection be improved?	High	High
40. What are the main reasons for patients to discontinue treatment in the Region?	Highest	Highest
41. How can patient triage (either in civilian world or in the penitentiary system) help to identify the risk of relapse or treatment failure?	Lower	Lower

Research question	High-burden countries	Non-high-burden countries
42. Management of TB among internal and cross-border migrants: What are the best practices in cross-border TB control and care?	Lower	Highest
43. What are the main reasons for relapse after successful completion of treatment?	Highest	Lower
9. Optimising treatment regimes		
44. What is the optimal preventive regimen for tolerability, efficacy, safety and compliance for close contacts of isoniazid resistant, MDR and XDR-TB index patients?	Highest	Highest
45. What are the extent and impact of the short course MDR-TB regimen in National TB programmes in the Region?	Highest	Highest
46. How are the results of pharmacokinetic studies being used to optimize drug dosages in TB treatment regimens?	High	Lower
47. Short courses for latent TB Infection: What are the operational challenges to introducing the three-month isoniazid and rifapentine (INH-RPT) regimen for latent TB infection?	High	Lower
10. Health systems and public private mix		
48. What are the barriers to bringing TB treatment closer to the patients' home and how can they be overcome?	High	Highest
49. Transition from in-patient to out-patient and community models of TB care: Is outpatient treatment more cost-effective (including costs to patients and their families)?	High	Lower
50. What case studies have been done that describe public – private mix and what lessons were learned?	Lower	Lower
51. How far is the private sector involved in TB management, how is it regulated and what are its achievements in the Region?	Lower	Lower
11. Collaboration with HIV programmes		
52. What is the optimal screening algorithm for active TB and latent TB infection among people living with HIV?	Highest	Highest

Research question	High-burden countries	Non-high-burden countries
53. What are the legislative barriers to improved collaboration between the TB and HIV services?	Lower	Lower
54. What are the main barriers and solutions to enhance TB testing among people living with HIV in the Region?	Lower	Lower
55. Integrating TB-HIV care: What are the best models for delivering TB-HIV treatment and monitoring?	Highest	Highest
12. Collaborating with other programmes		
56. Integration of TB programmes in the prison and civilian sectors: What are the causes and consequences of poor integration?	Highest	High
57. What are the opportunities for integrated approaches between national programmes for TB and noncommunicable disease?	Lower	Lower
58. What is the impact of the use of addictive drugs on the epidemiology of TB in the Region?	Lower	Lower
13. Infection Control		
59. How has infection control improved in hospitals across eastern and central European countries?	High	Lower
60. What are the most cost-effective infection control measures in health care settings (TB wards, primary health care units, long- and short-term congregate settings such as the military, prisons, homeless shelters or dormitories) and in public spaces?	Highest	Lower
61. What are the challenges and gaps in implementing and maintaining infection control measures in health care settings?	Highest	High
62. Is there any evidence that trans-border migration is associated with transmission of TB?	High	Lower
63. For how long patients with drug-sensitive and drug-resistant TB remain infectious after starting treatment?	Highest	Highest
14. National TB programme monitoring		
64. What are the best practices in monitoring the performance of National TB programmes?	High	High

Research question	High-burden countries	Non-high-burden countries
65. What are the associations between programme outcomes and total expenditures on TB services (including costs of human resources and cost per patient)?	Lower	Lower
66. How do the TB programme costs compare between countries in the WHO European Region?	Lower	Lower
67. What are the factors associated with TB mortality in high-incidence and low-incidence countries?	Highest	Lower
15. Community participation		
68. How are community-based organizations innovating in their strategies and funding sources?	Lower	Lower
69. What results are being achieved by civil society organizations especially among vulnerable patient groups suffering from TB?	Lower	Lower
16. Social determinants of TB		
70. What are the trends in the social determinants of TB and drug-resistant TB?	High	Lower
71. What is the impact of TB on poverty and health inequalities?	Lower	Lower
72. How should drug-resistant TB be managed during pregnancy and breast feeding?	High	High
73. Why are males more likely to be affected and to die of TB than females?	Lower	Lower
17. Linking TB research with other disciplines		
74. How can anthropology studies assist TB prevention and care efforts in the Region?	Lower	Lower
75. What special design features make TB medication more likely to be acceptable to children?	Lower	Lower
76. What are the knowledge, attitudes and beliefs among health care professionals, patients and the community about TB, especially in countries where compulsory isolation is still required, and how can such studies be used to reduce stigma?	High	Lower

Annex 2. "Highest Priority" list of research questions by affiliation

Theme 1. Epidemiological research

(Numbers represent the original question reference number that was used in the online questionnaire)

1. Burden of disease, including latent TB infection

National TB programme	Service providers	NGOs	International agencies	Research institutes		
✔	✔	✔	✔		1.	What are the trends of drug- resistant TB among the countries in the Region with specific reference to resistance to the new (bedaquiline, delamanid) and repurposed TB drugs (including clarithromycin, clofazimine, the fluoroquinolones, and linezolid)?
✔	✔	✔	✔	✔	2.	Which are the most cost-effective TB case-finding screening methods among high risk populations?
✔	✔				3.	How is latent TB infection being detected and monitored across the Region?
✔	✔				4.	What are the current gaps in the surveillance systems across the Region?
✔					5.	What is the attributable risk of developing active TB among different infected risk groups in the Region?" (with special reference to (i) child contacts under 5 years; (ii) migrants from a high TB burden country (iii) people with a history of imprisonment; (iv) unemployed people; (v) homeless people; (vi) people living with HIV and injecting drug users; (vii) people with diabetes mellitus and other noncommunicable diseases; (viii) people with harmful use of alcohol)?

2. Dynamics and drivers of disease transmission

✔	✔		✔	✔	6.	Which are the most cost-effective interventions to reduce the spread of drug-resistant TB in the Region?
✔					7.	What is the outcome of TB treatment among patients who are incarcerated or have a history of incarceration?
					8.	What are the similarities of mycobacterial phylogenetic patterns among high-risk groups and how is this linked to TB spread within hospitals and congregate settings?
✔					9.	How are outbreak investigations among high-risk populations and in high-risk settings being mapped and reported in countries?
✔	✔		✔	✔	10.	What are the social and biological drivers of drug-resistant TB in the Region?

Theme 2. Innovation & fundamental research

3. Research in basic sciences

National TB programme	Service providers	NGOs	International agencies	Research institutes	
				✔	**11.** Monitoring response to new drugs/regimens in clinical trials: Which biomarkers will help make drug trials faster/cheaper?
✔	✔	✔	✔	✔	**12.** Which biomarkers are useful to determine the risk of progression from latent TB infection to active disease and to distinguish relapse from reinfection?
✔	✔	✔			**13.** What are the genetic mutations associated with resistance to new and repurposed medicines?
✔	✔	✔		✔	**14.** What are the candidate molecular targets for anti-TB drugs?
					15. What is the role of mycobacterial-derived antimicrobial proteins and alternative therapies such as host-directed therapies and Vitamin D in TB prevention and treatment?

4. New diagnostic tools

✔	✔	✔			**16.** What is the evidence that rapid molecular diagnostic techniques for the initial diagnosis of TB and resistant forms of TB (such as Xpert® and Whole Genome Sequencing) improve the diagnosis and treatment outcome, especially among children and people living with HIV?
✔	✔				**17.** How effective and cost-effective are the new diagnostic platforms (including most recent molecular drug sensitivity tests and Whole Genome Sequencing platforms)?
					18. Genotypic drug sensitivity testing methods: How should "trace" category results of Xpert®/Ultra relate for patient management?
✔	✔	✔			**19.** Which infrastructures are needed to integrate new tools (such as line probe assay, Xpert®) in the current diagnostic set-up in low and high- incidence countries and in different settings (including prisons, migrant camps) to improve the management of drug- resistant TB?
	✔				**20.** How do the new tests (such as interferon gamma release assay (IGRA) and ESAT6-based skin test) compare with other traditional methods (such as the Mantoux skin test) to detect previous exposure to TB?
✔				✔	**21.** Drug sensitivity testing for new drugs, second line drugs and pyrazinamide: How should the minimum inhibitory concentration be used to guide treatment?

National TB programme	Service providers	NGOs	International agencies	Research institutes	
☐	✔	☐	☐	☐	**22.** What is the role of computer-aided interpretation of imaging techniques (chest X-ray, computerised tomography, magnetic resonance imaging and positron-emission tomography) and how do they compare with standard chest X rays in TB diagnosis and monitoring?

5. New drugs and new regimens

✔	✔	☐	✔	☐	**23.** What are the observed efficacy, safety and tolerability of new and repurposed medicines (especially among children, adolescents, people living with HIV and the elderly)? Are there any interactions with antiretroviral (ARV) drugs?
☐	☐	☐	☐	☐	**24.** How should pretomanid best be dispensed by the expanded access and compassionate use programme, applying lessons learned from bedaquiline and delamanid?
✔	☐	☐	✔	☐	**25.** What are the optimal doses of new and repurposed medicines in children?
✔	✔	☐	✔	✔	**26**. What are the most effective and patient- friendly short-term regimens for MDR/extensively drug-resistant (XDR)-TB (taking into account the pill burden, use of injectable drugs and duration of treatment) in the Region?
☐	☐	☐	☐	☐	**27.** What are the role and influence of regional and national Consilia in guiding the management of difficult MDR/XDR cases?

6. New Vaccines

☐	✔	☐	☐	☐	**28.** How can high burden countries facilitate research in new vaccines?
☐	☐	☐	☐	☐	**29.** What progress is being made in pre-and post-exposure vaccines against TB?

Theme 3. Operational research

7. Case Detection and screening

✔	✔	☐	☐	✔	**30.** How can high-burden countries facilitate research in new vaccines?
✔	✔	☐	✔	✔	**31.** What progress is being made in pre- and post-exposure vaccines against TB?
✔	✔	✔	☐	✔	**32.** What is average time to TB diagnosis among the various risk groups and what are reasons for diagnostic delay?
☐	☐	☐	☐	☐	**33.** What are the most effective approaches to the management of close contacts of MDR and XDR-TB index patients?

8. Access to treatment and compliance

National TB programme	Service providers	NGOs	International agencies	Research institutes	
☐	☐	☐	☐	☐	**34.** Do hospital-based and home-based TB treatment outcomes vary in the different hard to reach risk groups (people living with HIV, alcoholics, elderly people, migrants)?
☐	☐	☐	☐	☐	**35.** What is the role of family- or pharmacy-supervised directly observed therapy?
☐	✔	☐	☐	☐	**36.** How effective are e-health and mobile health interventions (e.g. Video Observed Therapy) on adherence and treatment outcomes among the various patient groups?
☐	✔	☐	✔	☐	**37.** How effective is the supply management of TB drugs and which factors influence access to medicines in the Region?
☐	☐	☐	✔	☐	**38.** How can incentives and enablers be used to achieve better treatment outcomes, and which are more likely to influence hard to reach groups?
☐	☐	☐	☐	☐	**39.** How can adherence to preventive treatment of latent TB infection be improved?
☐	✔	☐	✔	☐	**40.** What are the main reasons for relapse after successful completion of treatment?
☐	☐	☐	☐	☐	**41.** How can patient triage (either in civilian world or in the penitentiary system) help to identify the risk of relapse or treatment failure?
☐	✔	☐	✔	☐	**42.** Management of TB among internal and cross- border migrants: What are the best practices in cross-border TB control and care?
✔	✔	☐	✔	✔	**43.** What are the main reasons for patients to discontinue treatment in the Region?

9. Optimising treatment regimes

✔	✔	☐	✔	✔	**44.** What is the optimal preventive regimen for tolerability, efficacy, safety and compliance for close contacts of isoniazid resistant, MDR and XDR-TB index patients?
✔	✔	☐	✔	✔	**45.** What are the extent and impact of the short course MDR- TB regimen in National TB programmes in the Region?
☐	☐	☐	☐	☐	**46.** How are the results of pharmacokinetic studies being used to optimize drug dosages in TB treatment regimens?
☐	✔	☐	☐	☐	**47.** Short courses for latent TB Infection: What are the operational challenges to introducing the three month isoniazid and rifapentine (INH-RPT) regimen for latent TB infection?

10. Health systems and public private mix

National TB programme	Service providers	NGOs	International agencies	Research institutes	
	✔				**48.** Transition from in-patient to out-patient and community models of TB care: Is outpatient treatment more cost-effective (including costs to patients and their families)?
✔					**49.** What are the barriers to bringing TB treatment closer to the patients' home and how can they be overcome?
					50. What case studies have been done that describe public – private mix and what lessons were learned?
					51. How far is the private sector involved in TB management, how is it regulated and what are its achievements in the Region?

11. Collaboration with HIV programmes

✔				✔	**52.** What is the optimal screening algorithm for active TB and latent TB infection among people living with HIV?
					53. What are the legislative barriers to improved collaboration between the TB and HIV services?
					54. What are the main barriers and solutions to enhance TB testing among people living with HIV in the Region?
✔	✔		✔		**55.** Integrating TB-HIV care: What are the best models for delivering TB-HIV treatment and monitoring?

12. Collaborating with other programmes

✔	✔				**56.** Integration of TB programmes in the prison and civilian sectors: What are the causes and consequences of poor integration?
					57. What are the opportunities for integrated approaches between national programmes for TB and noncommunicable disease?
					58. What is the impact of the use of addictive drugs on the epidemiology of TB in the Region?

13. Infection Control

National TB programme	Service providers	NGOs	International agencies	Research institutes	
☐	☐	☐	☐	☐	**59.** How has infection control improved in hospitals across eastern and central European countries?
✔	✔	☐	☐	☐	**60.** What are the most cost-effective infection control measures in health care settings (TB wards, primary health care units, long- and short-term congregate settings such as the military, prisons, homeless shelters or dormitories) and in public spaces?
☐	✔	☐	✔	☐	**61.** What are the challenges and gaps in implementing and maintaining infection control measures in health care settings?
☐	☐	☐	☐	☐	**62.** Is there any evidence that trans-border migration is associated with transmission of TB?
✔	✔	☐	✔	☐	**63.** For how long do patients with drug-sensitive and drug-resistant TB remain infectious after starting treatment ?

14. National TB programme monitoring

☐	☐	☐	☐	☐	**64.** What are the best practices in monitoring the performance of National TB programmes?
☐	☐	☐	☐	☐	**65.** What are the associations between programme outcomes and total expenditures on TB services (including costs of human resources and cost per patient)?
☐	☐	☐	☐	☐	**66.** How do the TB programme costs compare between countries in the Region?
☐	☐	☐	☐	☐	**67.** What are the factors associated with TB mortality in high-incidence and low- incidence countries?

15. Community Participation

☐	☐	☐	☐	☐	**68.** How are community-based organizations innovating in their strategies and funding sources?
☐	☐	☐	☐	☐	**69.** What results are being achieved by civil society organizations, especially among vulnerable patient groups suffering from TB?

16. Social determinants of TB

National TB programme	Service providers	NGOs	International agencies	Research institutes	
✔					**70.** What are the trends in the social determinants of TB and drug-resistant TB?
					71. What is the impact of TB on poverty and health inequalities?
					72. How should drug-resistant TB be managed during pregnancy and breast feeding?
					73. Why are males more likely to be affected and to die of TB than females?

17. Linking TB research with other disciplines

					74. How can anthropology studies assist TB prevention and care efforts in the Region?
					75. What special design features make TB medication more likely to be acceptable to children?
					76. What are the knowledge, attitudes and beliefs among health care professionals, patients and the community about TB, especially in countries where compulsory isolation is still required, and how can such studies be used to reduce stigma?

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WHO Regional Office for Europe

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