Scaling up tuberculosis research in the WHO European Region

CHALLENGES IN THE RESPONSE TO TUBERCULOSIS

Tuberculosis (TB) is an airborne infectious disease primarily caused by *Mycobacterium tuberculosis*. It poses a significant threat to public health, with a quarter of the world’s population being infected. Each year, about 10 million people develop active TB and more than 600 000 are diagnosed with drug-resistant TB. Altogether, TB is responsible for the deaths of some 1.6 million people each year, of whom 230 000 are children (1), and the disease is currently the ninth leading cause of death worldwide (2).

Through the intensive efforts of Member States and partners, the WHO European Region is on track to achieve two of the TB-related targets in the Sustainable Development Goals (an 80% decrease in incidence and a 90% decrease in mortality by 2030 compared with 2015), with a Region-wide incidence rate of 29.9 per 100 000 population and a mortality rate of 2.6 per 100 000 in 2017 (3). However, multidrug-resistant TB (MDR-TB) notification is increasing: the proportions of rifampicin-resistant TB (RR-TB) and MDR-TB strains in the European Region among new and previously treated cases are at 17% and 53%, respectively (3). Recent analysis of data from eastern Europe and central Asia, which are the areas of the world most affected by drug-resistant strains of TB, found that MDR-TB is decreasing in only two countries, is increasing in eight countries, and has stabilized in seven countries (4).

The European Region is also facing one of the fastest-growing HIV epidemics in the world, with a sharp increase in TB/HIV coinfection being observed. Estimated HIV prevalence in incident TB cases in the Region grew from 3% to 12% over the 10 years between 2007 and 2017 (3).

Strengthened health systems in the European Region now offer universal access to TB diagnosis and treatment. Decentralization and roll-out of rapid TB diagnosis at primary health care level and early enrolment into ambulatory treatment ensure people-centred TB prevention and care service delivery in many countries of the Region. However, high prevalence of RR/MDR-TB, and more severe forms of resistance to fluoroquinolones, high levels of substance addiction, the fatal mix with (and alarming spread of) HIV, and the unknown prevalence of viral hepatitis B and C are significant threats that could dramatically affect progress towards the global targets of the End TB Strategy (5–10). At-risk groups, such as migrants and prisoners, are “neglected priorities”, and little is known...
about the best response strategies for these populations (11). However, enhanced political and operational commitment to integrating HIV, TB and viral hepatitis services (including rapid testing and multi-disease molecular diagnostic platforms) are needed to improve the health outcomes of TB/HIV coinfected patients (12).

THE NEEDS IN TB RESEARCH

In 2014, the Sixty-seventh World Health Assembly adopted the global End TB Strategy, with its ambitious targets for eliminating catastrophic expenses due to TB and achieving a 95% reduction in TB deaths and a 90% reduction in TB incidence by 2035 compared with 2015 (9). With the currently observed rate of decline in the number of cases, the goal of ending the TB epidemic as outlined in the End TB Strategy and target 3.3 of the Sustainable Development Goals will not be met by the WHO European Region unless the above-mentioned threats are addressed.

The TB Action Plan for the WHO European Region 2016–2020 (13) operationalizes the End TB Strategy at regional level and, in turn, sets three interim, ambitious targets: to reduce TB deaths by 35%, to reduce TB incidence rates by 25%, and to achieve a 75% treatment success rate for MDR-TB (all by 2020 in comparison with the 2015 baseline).

The third pillar – on research and innovation – of both the End TB Strategy and the TB Action Plan for the WHO European Region 2016–2020 calls for operational research for the design, implementation and scaling up of innovations, and for an urgent increase in research investments, so that new tools are developed and made rapidly available and widely accessible in the next decade (9, 14). Further research is desperately needed to put a stop to the suffering inflicted by TB, yet the field does not appear to attract much interest, despite TB ranking as the leading fatal infectious disease globally.

Building on declarations made at the highest political levels to enhance TB research globally, the Seventy-first World Health Assembly in 2018 requested the Director-General to develop a global strategy for TB research and innovation, recognizing that enhanced and sustained support for complex research endeavours requires strong international cooperation (15).

The draft global strategy for TB research and innovation being prepared by WHO aims to provide, for all Member States, a framework of interventions for removing barriers to TB research and innovation in order to help achieve the goal and targets of the End TB Strategy. Development of the draft global strategy for TB research and innovation has drawn on consultations with scientists, national TB programme (NTP) managers and other officials from within and outside ministries of health, including ministries of science and technology, and representatives of civil society and affected communities, research funding institutions and other TB research and innovation stakeholders (16). The plan is for the strategy to be endorsed by the Seventy-third World Health Assembly in May 2020, following which its implementation can begin.

THE EUROPEAN PLATFORM TO CATALYSE TB RESEARCH AND INNOVATION

The WHO Regional Office for Europe prioritizes TB research, given that it is one of the three main pillars to end TB in the Region, and has been working with people affected by the disease and key partners to intensify the research and innovation required. To this end, the Regional Office launched the European Tuberculosis Research Initiative (ERI-TB) (17). The objectives of ERI-TB are: to define priority research areas and questions for countries in the Region; to strengthen country capacities; and to facilitate and promote collaboration between research institutions and relevant stakeholders (17).

The ERI-TB platform consists of three main bodies: the core group, the Secretariat, and an extended network of ERI members across the Region. The Secretariat is made up of WHO staff in the Regional Office and is responsible for day-to-day network support and facilitation, while the core group is a multidisciplinary convention of key stakeholders advising on ERI-TB activities and advocating for research implementation. The network consists of researchers, public health practitioners, NTP managers, experts from the health-related and social sciences, representatives of academic institutions, technical and funding agencies, communities and civil society organizations with substantial expertise and experience in areas related to TB prevention and care, and ex-patients.

In 2017–2018, achieving its first key objective, ERI-TB carried out a consultative process to define priority research areas and questions in the Region. At the first stage of consultations, a long list was drafted by the ERI-TB core group members, the Secretariat and NTP representatives, while at the second stage, prioritization was carried out by representatives of the 53 Member States and other stakeholders in the European Region. The study identified the urgent TB research questions
for both high- and low-burden countries in fundamental, epidemiological and operational research (18). Among others, priority research questions for collaboration between TB and HIV programmes were agreed upon, supporting the United Nations common position on ending HIV, TB and viral hepatitis through intersectoral collaboration (19), which identified research as a shared principle for addressing all three diseases. The study report and methodology are now available to all Member States of the European Region for implementation while they set research priorities at country level.

In working to tackle barriers to TB research uptake in the Region and build capacity, ERI-TB launched the Structured Operational Research Training on TB (SORT-TB) in 2018. The SORT-TB course is based on the Structured Operational Research and Training Initiative (SORT IT) framework and on the previous experience of the Regional Office’s collaboration with the Special Programme for Research and Training in Tropical Diseases in implementing SORT IT (17, 20). SORT-TB is a goal-oriented course that provides NTP staff with the skills necessary to plan and implement TB-related operational research projects, analyse and publish their findings in peer-reviewed journals, in order to support the scaling up of evidence-based policy-making. The course is bilingual (English and Russian) and is designed to meet the research agenda needs and priorities defined by ERI-TB for the European Region (18) and priorities at country level endorsed by national counterparts.

The first cohort of SORT-TB targeted young researchers came from six countries with a high burden of MDR-TB in the Region (Armenia, Azerbaijan, Belarus, Georgia, Republic of Moldova and Ukraine). Twelve research projects support the implementation of the regional agenda by responding to the priority research questions in the following areas: new diagnostics and treatment regimens; case detection and screening algorithms; intersection collaboration for ending TB, HIV and viral hepatitis; and programme management and accountability. In this issue of Public Health Panorama, 11 peer-reviewed research papers are being published and will serve as regional evidence for the implementation of people-centred TB care at country level.

The manuscripts presented in the current issue are important for the Region as whole and for individual Member States, as they outline scientifically sound evidence for the optimization of regional and national TB policies and guidelines. The study, Effectiveness and safety of bedaquiline-containing regimens among adults with multidrug- or extensively drug-resistant pulmonary TB in Belarus: a nationwide cohort study, assesses treatment outcomes of the biggest cohort in the European Region of MDR-TB and XDR-TB patients treated with bedaquiline-containing regimens; the study, Compliance of drug-resistant tuberculosis treatment regimens with drug susceptibility testing results and its association with treatment outcomes in Georgia, reveals significant rates of mismanagement in the treatment of patients with known resistance profiles in Georgia; the studies, Risk factors associated with RR/MDR-TB among new pulmonary tuberculosis patients in urban and rural areas of Ukraine in 2017: retrospective analysis of routine surveillance data and Delays and associated risk factors, in the detection and treatment of rifampicin-resistant tuberculosis patients in Ukraine, are the first ones in Ukraine to use data from a case-based, real-time electronic surveillance system (launched in 2014) for routine drug resistance surveillance and the assessment of delays in TB detection and screening at every step of RR/MDR-TB diagnosis and treatment; finally, Underreporting of diagnosed tuberculosis cases to the national surveillance system in Armenia in 2017 is the first inventory study assessing flaws in a national TB surveillance system in the Region.

Treatment success rates for TB and RR/MDR-TB patients in the Region remain below regional targets for 2020 (85% and 75%, respectively), though a slow but substantial increase is being observed (3). Aiming to contribute to attainment of the targets, two studies (Risk factors associated with loss to follow-up among multidrug-resistant tuberculosis patients in the Republic of Moldova in 2014–2016) assessed the reasons for patients discontinuing treatment, which is one of the crucial knowledge gaps defined in the regional TB research agenda (18) in efforts to reduce loss to follow-up rates.

Focusing on improvement of early diagnosis of all forms of TB, the studies from Belarus (Diagnosis of tuberculosis among patients with unexplained pleural effusion in Belarus: role of surgical biopsy and Xpert MTB/RIF) and the Republic of Moldova (Does low Mycobacterium tuberculosis concentration in the sample influence GeneXpert rifampicin susceptibility results in the Republic of Moldova?) review the accuracy of molecular diagnostic tools for pleural fluid and pleural biopsy specimens, as well as, for samples with insufficient Mycobacterium tuberculosis concentration. In addition, a study from Armenia (A cross-sectional study of the turnaround time of Armenia’s National Tuberculosis Programme Laboratory Services in 2017–2018) assesses delays in turnaround time of samples of suspected TB cases across the country.

Finally, supporting regional priority to improve systematic screening of contacts and high-risk groups (13), a study on Poor follow-up of paediatric tuberculosis contacts in Tbilisi,

In the spirit of translating research into practice, this evidence was discussed with policy-makers during the regional meeting of TB programme managers at The Hague, Netherlands, on 16 May 2019. As all the studies were conducted using routine programmatic data, they can be repeated at different time points using the same methodology in order to monitor and evaluate progress.

Following completion of the SORT-TB course, the first cohort of trained young researchers have returned to their respective NTPs to promote uptake of research and support evidence-based decision-making at country level, while ERI-TB continues to build regional research potential: the second SORT-TB cohort was launched in August 2019 with wider geographical coverage of WHO Member States in the Region.

The ERI-TB Secretariat and core group are currently in the process of tailoring the mission and objectives of ERI-TB to support operationalization of the global strategy for TB research and innovation at the regional level and to respond to increasing calls by Member States for intercountry collaboration. ERI-TB also plans to support Member States in the introduction of an all-oral shorter treatment regimen for MDR-TB under operational research conditions. Further plans include carrying out studies on: operational implementation of the programmatic management of latent TB and MDR-TB infection; optimal TB diagnosis algorithms and TB treatment regimens among people with HIV and viral hepatitis coinfection, and people with diabetes and other comorbidity; childhood TB treatment regimens; and cost-effective TB case-finding screening algorithms among vulnerable and high-risk populations (with a specific focus on labour migrants and refugees). Partnership with the Special Programme for Research and Training in Tropical Diseases and the involvement of civil society to implement research that addresses the social determinants of TB will ensure complementary collaboration and exclude duplication of efforts.

ERI-TB has equipped the Regional Office with the platform and instruments needed for the implementation of the global strategy for TB research and innovation at the global, regional and country levels. Globally, ERI-TB can serve as a model that can be used by partners to establish regional TB research networks in order to facilitate the scaling up of research. At the regional level, the network enables the rapid implementation of strategic initiatives, and advocate for enhanced TB research funding and support intercountry research uptake by engaging and bringing together NTP managers, researches and civil society representatives. Finally, at country level prominent SORT-TB alumni are ready to be utilized by NTPs for setting national TB research priorities, putting them to life and launching in-country capacity building and knowledge sharing initiatives.

REFERENCES

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1 All references were accessed on 22 November 2019.


