

Operational research as an instrument to address the critical gaps for effective treatment of tuberculosis in eastern Europe and central Asia

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WHY OPERATIONAL RESEARCH?

Despite the global tuberculosis (TB) response efforts, which saved 60 million lives since 2000, TB remains one of the top infectious killers worldwide, affecting more than 10 million people and taking over 1.4 million lives annually [1]. COVID-19 is the only infectious disease that threatens to surpass TB death toll in 2020: more than 1 million deaths related to novel coronavirus infection have occurred by October 2020 since the beginning of the year [2]. Though effective treatment for COVID-19 is yet to be discovered [3], there are many lessons from TB that can be utilized in the fight against COVID-19, including contact tracing in the community, infection control and scale up of people-centred models of care [4]. In 2015, the Member States of the United Nations have ratified the resolution *A/RES/70/1 - Transforming our world: the 2030 Agenda for Sustainable Development* [5]. The target 3.3 of the Sustainable Development Goals, confirmed by the WHO's End TB Strategy, aims at ending TB through a 80% decrease in incidence and a 90% decrease in mortality by 2030 compared with 2015. According to the latest global TB report, reduction in global TB incidence is too slow and the global 2020 milestone of 20% decrease will not be met. Cumulative reduction of TB incidence from 2015 to 2019 was only 9% worldwide. Similar trend is observed in TB mortality: number of TB deaths is falling globally and cumulative reduction between 2015 and 2019 reached 14%, which is far below the global milestone for 2020 (35% reduction compared with 2015). The only Region, which is on track of meeting the 2020 milestones of the End TB Strategy, is the WHO European Region, with cumulative decrease in TB incidence of 19% and in TB mortality of 31% as of 2019 [1].

Nonetheless, the growing burden of multidrug-resistant TB -

form of TB that is resistant to both rifampicin and isoniazid, the two most powerful anti-TB drugs - can avert Member States of the WHO European Region from continue showing good progress towards the 2030 targets. In 2019, the global treatment success rate for multi drug-resistant TB and/or rifampicin-resistant TB (MDR/RR-TB) patients remains low. Data in 2020 global TB report show 57% of patients were treated successfully [1], which is almost 30% less, than in the cohort of drug-susceptible patients. The global estimated prevalence of MDR/RR-TB is 3.3% among new TB cases to 18% among previously treated cases [1], with the WHO European Region remaining the most affected one by MDR/RR-TB threat: here the notified prevalence of MDR/RR-TB is 18% for new TB cases and 54% for previously treated TB cases [6]. Majority of MDR/RR-TB resistant cases of the WHO European Region are being diagnosed in eastern Europe and central Asia (EECA) [1]. Analysis of data from these countries undertaken recently by the WHO found that MDR/RR-TB is increasing in eight countries, has stabilized in seven countries and is decreasing only in two countries [7]. Out of the total number of MDR/RR-TB and XDR-TB notified globally, almost 25% and 70%, respectively, were notified from the WHO European Region. HIV prevalence in incident TB cases was estimated at 12% in 2019, being stable for third consecutive year after an unprecedented increase from 3% to 12% during the period 2007–2016 [1].

Considering the growing burden of MDR/RR-TB resistance, finding effective and safe options to improve treatment outcomes for MDR/RR-TB remains a global priority. Number of clinical trials are being carried out to test new medicines and their combinations in regimens in order to prove effectiveness, safety and patient-friendliness for treatment of drug-resistant tuberculosis [1]. To increase certainty of evidence produced by clinical trials that is being provided to the WHO for consideration to be recommended as therapeutic option, their findings need to be properly evaluated under operational research conditions, to assess both their effectiveness and safety on larger cohorts of patients. Additionally, operational research allows to evaluate programmatic feasibility and acceptability of innovations, serving as basis for development of recommendation for programmatic considerations. Moreover, accounting for existing difference in regional resistance profiles, it is particularly important to carefully observe effectiveness and safety, while introducing alternative options and modification to what has been recommended by the WHO for programmatic use. Thus, operational research is becoming a key platform to boost introduction of innovations at country level and is serving as an instrument for generating new quality evidence for future global policy recommendations by the WHO's Guidelines Development Group on treatment of DR-TB.

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BOOSTING TUBERCULOSIS OPERATIONAL RESEARCH WORLDWIDE

Importance of evidence-based approach in policy-making and programmatic practice is being recognized globally and since 2015, the area of intensified research and innovation is being prioritized

by countries and international bodies. The area is embedded as one of three pillars into the WHO End TB Strategy, adopted by the Sixty-seventh World Health Assembly in 2014 [8]. Under the strategy the WHO Member States have committed to increase investments in research (from fundamental research to operational and health system research) and speed up its uptake to catalyse effect of TB response efforts. However, despite the number of international commitments to advance TB research, the target of UN high-level meeting on TB to invest worldwide at least US\$ 2 billion per year in TB research between 2018 and 2022 has not been fulfilled in half: in 2018 the overall investment in TB research constituted US\$ 906 million [1]. Enhanced international collaboration and coordination is needed to drive global TB research thrive.

Recognizing this and complying with global commitments to boost and advance TB research (including the Moscow Declaration to End TB [9] and the political declaration of the United Nations high-level meeting on TB), the Seventy-first World Health Assembly in 2018 requested the Director-General to develop a global strategy for TB research and innovation [10]. Draft strategy was discussed with high TB burden countries, research stakeholders, Global TB Research Task Force, Strategic and Technical Advisory Group for Tuberculosis, WHO Executive Board, as well as with wider public through open consultations [11]. The strategy was endorsed by the WHO Member States in August 2020 through unique written silence procedure at the Seventy-third session of the World Health Assembly [12].

In the strategy special attention is given to operational research. It is expected that Member States will pursue the operational research to close programme performance gaps. Assessment of the feasibility, acceptability, effectiveness and impact of new strategies or interventions on health outcomes is expected to save lives of patients and vulnerable populations and turn efficacy (documented by research) into effectiveness and benefits for the communities. The strategy calls for allocation of targeted funding for operational research to drive uptake of innovations [10].

BUILDING OPERATIONAL RESEARCH CAPACITY IN THE WHO EUROPEAN REGION

The WHO Regional Office for Europe prioritizes research, and builds relevant research infrastructure and capacity across all the diseases to use data for decision-making. Number of initiatives were established to strengthen the research culture and advance other four strategic goals of the WHO's Strategy on research for health: 1) to focus on priority health needs; 2) to strengthen national systems for health research - the WHO European Health Research Network; 3) to set norms and standards and promote good practice in research - the Health Evidence Network; and 4) to strengthen links between health research and health policy and practice - Evidence-informed Policy Network [13,14]. More recently, *European Programme of Work, 2020–2025* – “United Action for Better Health in Europe”, adopted during seventeenth session on WHO's Regional Committee for Europe, prioritized empowerment of health systems through digitalization. Digital health system, in turn, will accommodate valid and valuable source of information for implementation of operational research - secondary health data [15].

In 2016, aligning itself with global commitment to drive research agenda in TB, the WHO Regional Office for Europe established the European Tuberculosis Research Initiative (ERI-TB). The network idea corresponds with the key goals of the abovementioned WHO strategy on research for health and is aimed at contributing to implementation of the Tuberculosis Action Plan for the WHO European Region 2016–2020, through defining priority research areas and questions for countries in the Region; strengthening country capacities; and facilitating and promoting collaboration between research institutions and relevant stakeholders [16].

The network brings together more than 200 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. Its Secretariat at the WHO Regional Office for Europe and the core group, selected through expert review of applications of interested candidates, are working relentlessly on introduction of targeted initiative and tools foster research culture among national TB programmes in the Region and to bring benefits of research closer to patients.

In 2017-2018 the ERI-TB secretariat developed regional TB research agenda through consultations with representatives of 53 Member States and other stakeholders of the WHO European Region. The study identified the urgent TB research questions for both high- and low-burden countries in fundamental, epidemiological and operational research [17]. To promote the agenda and speed up its uptake, the ERI-TB created the Structured Operational Tuberculosis Research Training (SORT-TB) in 2018. The course is based on the Structured Operational Research and Training Initiative (SORT IT) framework and is building on the previous experience of the Regional Office's collaboration with the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) SORT IT course [16,18]. SORT-TB, as a goal-oriented initiative, helps young research from ministries of health, national TB programmes, hospitals, disease control centres and nongovernmental organizations, to implement operational research projects on the data that are available and collected routinely in their institutions and publish findings of those research projects in peer-reviewed journals. Course programme is designed in the way that allows a researcher, selected on a competitive basis, to lead his project, while working side-by-side with recognized experts in the area of TB and research. By 2020 two cohorts of researchers were trained, representing such countries as Armenia, Azerbaijan, Belarus, Georgia, Lithuania, Republic of Moldova, Romania, Russian Federation and Ukraine.

Capacity built by the SORT-TB course allowed the ERI-TB to launch an initiative aiming to shorten and optimize treatment of MDR/RR-TB patients in the Region and improve treatment outcomes. Since September 2019, the ERI-TB, under the umbrella of the WHO Regional Office for Europe, is working with 14 members states on introduction of modified fully oral shorter treatment regimens for MDR/RR-TB under operational research conditions, as suggested in the WHO Consolidated Guidelines on Treatment of Drug-Resistant Tuberculosis. By November 2020 eight countries have started enrolment of patients, after having received approval from ethics bodies at national and global levels. It is expected that by January 2022 up to 6000 patients may be enrolled into shorter fully oral modified treatment regimens, making it the world's largest cohort. This study once again underscores importance of international coordination for data harmonization and alignment, as the findings of the study will be jointly shared with the WHO Guidelines Development Group for future recommendations.

PRODUCING RESEARCH EVIDENCE TO IMPROVE TREATMENT OUTCOMES

The current issue of the Monaldi Archives for Chest Disease is presenting findings of the second SORT-TB cohort in the WHO European Region. While the study topics of the first cohort, published in *Public Health Panorama*, varied in thematic areas from assessing follow-up rates of paediatric TB contacts tracing to investigating factors influencing laboratory turnaround time, from studying risk factors associated with MDR/RR-TB to revealing TB under-reporting rates in the national surveillance system [19-21], the thematic areas chosen by the second cohort clearly showed a tendency of Member States to optimize and improve treatment outcomes and care of patients with MDR/RR-TB and XDR-TB. Repeatedly, this

underlines the timelessness of the introduction of regional operational research initiative on introduction of modified fully oral shorter treatment regimens for MDR/RR-TB.

The first group of research manuscripts (from Lithuania and the Russian Federation) published in the current issues (*Factors associated with culture conversion among adults treated for pulmonary extensively drug-resistant tuberculosis during 2018-2019 in the Russian Federation: an observational cohort study* and *Factors associated with time to sputum culture conversion of rifampicin-resistant tuberculosis patients in Klaipeda, Lithuania in 2016-2019: a cohort study*) looked at factors associated with culture conversion, as an early predictor of treatment success.

The first study from the Russian Federation found that combination of bedaquiline and linezolid together in treatment regimens for extensively drug-resistant TB (XDR-TB), as well as having more than four effective drugs in treatment regimens, reduces time to sputum conversion. At the same time, presence of other co-morbid conditions, such as HIV and viral hepatitis C, and positive sputum smear microscopy at baseline might delay time to culture conversion. The second study identified groups of patients, who were at risk of delayed sputum culture conversion in Lithuania: patients aged ≥ 60 years, smokers, patients with positive sputum smear microscopy at baseline, patients with cavities on initial chest X-ray and patients with resistance to at least one fluoroquinolone drug. The findings of both studies were mostly comparable with available evidence, but they can be considered rational for programmes to strengthen clinical and programmatic interventions to improve treatment outcomes.

The second, larger, group of four studies from Armenia, Georgia and Republic of Moldova, looked at factors associated with final treatment outcomes, including lost-to-follow-up, among patients with drug-susceptible, drug-resistant and HIV-associated TB. Using the data from national surveillance system, the “*Factors associated with loss to follow-up among people with tuberculosis in the country of Georgia: a cohort study*” explored the risk factors contributing to high rates of lost-to-follow-up (LFU) among patients in Georgia: $>10\%$ among drug-susceptible and $>22\%$ among drug-resistant patients. Certain categories of patients treated with first-line TB medicines had higher risk of LFU, including male, unemployment, internally displaced people, with history of imprisonment and previously treated for TB. Additionally, being male and previously treated for MDR-TB with second-line TB medicines was independently associated with higher chances of leading to LFU among patients that underwent treatment with second-line TB medicines. Similar study “*Factors associated with unfavourable treatment outcomes among people with rifampicin-resistant tuberculosis in Armenia, 2014-2017*”, found that home-based treatment and treatment with new TB medicines can significantly reduce risk of developing unfavourable treatment outcome. This finding supports the WHO recommendation on scaling up outpatient, people-centered models of care for TB, ensuring quality and continuity of service delivery [23]. Another study “*Factors associated with unfavourable treatment outcomes in people with HIV-associated tuberculosis in Armenia, 2015 to 2019 investigated the risk factors associated with unfavourable treatment outcomes in patients with co-infection*” underlined the importance of timely initiation and ensuring continuity of antiretroviral therapy for patients with HIV-associated TB [24]. However, the effect of these interventions should be strengthened by accurate diagnosis of TB, proper drug susceptibility testing and the use of TB treatment regimens guided by drug-resistance profile. Finally, the study “*Do catastrophic costs impact treatment outcomes in people with rifampicin-resistant tuberculosis in the Republic of Moldova?*” serves as a follow-up to the first TB catastrophic costs survey in the WHO European Region, which assessed the rates of various expenditures endured by families/households to seek care for MDR/RR-TB [25]. The new study looked at association between endured costs and final treatment outcomes from cohort of the first study. Though no direct correlation between unfavourable treatment outcomes and the fact of experiencing TB catastrophic costs was found, it was proven that patients from house-

holds with low socio-economic status, patients with HIV-associated TB and those residing in urban settings are at a greater risk of developing unfavourable treatment outcomes. Study findings highlighted the high need for ensuring social and financial protection for the outlined categories of patients.

A rare study on mental health and TB from Romania, “*Depression and anxiety symptoms among people with rifampicin-resistant tuberculosis receiving inpatient care in the National Pulmonology Reference Institute in Romania*”, reveals the high prevalence (46%) of depression and anxiety among MDR/RR-TB patients, which is comparable with evidence from other studies [26]. An additional research is needed to determine correlation between the prevalence of depression, anxiety and treatment outcomes. However, the study findings advocated to advance commitment of the WHO Member States at the First WHO Global Ministerial Conference on Ending TB to achieve synergy in management of TB and mental health [5]. Offering various forms of psychosocial support to TB patients can increase adherence to treatment [27].

The third group of manuscripts is specifically dedicated to assessing effectiveness and safety of new and repurposed TB medications for treatment of patients with MDR/RR-TB and XDR-TB. Belarus and Georgia were the first two countries that began widely using programmatically new and repurposed drugs and initiated modified shorter all-oral regimens under programmatic conditions, while ensuring proper data collection and active drug safety monitoring (aDSM). The four studies in this group present preliminary results of efforts made by national TB programmes. The study “*Effectiveness and safety of delamanid- or bedaquiline-containing regimens among children and adolescents with multidrug-resistant or extensively drug resistant tuberculosis: A nationwide study from Belarus, 2015-19*” reported on unique data on effectiveness and safety of bedaquiline and delamanid-containing regimens in children and adolescents with MDR/RR-TB and XDR-TB (the largest cohort worldwide). One hundred per cent culture conversion was achieved, leading to one hundred per cent treatment success rate with no recurrence after 12 months of post-treatment follow-up. Safety profile of the use of new and repurposed TB drugs was good with only one episode of serious adverse events reported. Another study from Belarus, “*Effectiveness and cardiovascular safety of delamanid-containing regimens in adults with multidrug-resistant or extensively drug-resistant tuberculosis: A nationwide cohort study from Belarus, 2016-18*”, is one of the first global studies reporting on effectiveness and cardiovascular safety of delamanid-containing regimens in adults with MDR/RR-TB and XDR-TB and on post-treatment recurrence rate. More than 90% of patients achieved culture conversion by 6 months of treatment, with treatment reported success rate of 88% and with low recurrence rate after 12 month of post-treatment follow-up. Valuable contribution to the global evidence on safety of new and repurposed TB medicines makes one of two studies from Georgia: “*Incidence rate and time to serious adverse events among rifampicin-resistant tuberculosis patients in Georgia treated with new and repurposed anti-tuberculosis drugs, 2016-2018*”. The study proves, that treatment regimens using new and repurposed drugs are generally well tolerated, though, still, around 13% of patients experience serious adverse events, which correlates with data from the Global aDSM project [28]. Finally, the study “*Effectiveness and safety of fully oral modified shorter treatment regimen for multidrug-resistant tuberculosis in Georgia, 2019-2020*” reports early results of treatment of MDR/RR-TB patients with modified shorter all-oral regimens. By 6 months of treatment, the culture conversion was achieved in 94% of patients with median time to conversion of 1 month. Three serious adverse events were reported during treatment, of which one death, which had not been related to any of TB medicines. These results highlight the importance of active drugs safety monitoring and management as essential element of programmatic management of drug resistant TB. Findings from all four studies are considered as promising, however, the certainty of evidence should be proven on a larger cohort of patients with DR-TB.

Described studies and initiatives serve as solid base for accel-

eration of research capacity in countries, including settings with limited resources. However, political will, dedication of personnel of national TB programmes, openness and susceptibility of medical staff to innovations are needed to create enabling environment for introduction of innovations that bring hope for TB patients worldwide.

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