

**Title:**

World TB Day 2022 - Optimizing TB Care for Refugees Affected by Armed Conflicts

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Globally, tuberculosis (TB) remains a top cause of death from an infectious disease.<sup>1</sup> This year's theme for World TB Day March 24<sup>th</sup> is 'Invest to End TB, Save Lives'. TB control requires a pragmatic, tailored, multipronged approach to diagnose and treat all people with TB disease (DS-TB, MDR-TB, XDR-TB), latent TB infection (LTBI), prevent transmission and mitigate the risk of drug resistance. The COVID-19 pandemic has disrupted health services and derailed already overburdened TB control programs worldwide including Eastern Europe, significantly setting back progress towards achieving UN-SDG EndTB targets.<sup>2,3</sup> The ongoing armed conflict in Ukraine, with its damaging effects on health services, health infrastructure and personnel, further fades hope for achieving UN-SDG EndTB targets for Eastern Europe, now a seemingly insurmountable task. Whilst TB rates in Ukraine have gradually decreased recently, Ukraine features in the WHO list of 20 countries with the highest estimated number of people with incident DR-TB and it has one of the highest rates of HIV-TB co-infection and latent MDR-TB infection in Europe.<sup>1</sup> DR-TB is more difficult to diagnose, expensive to treat, requires prolonged treatment, has a high mortality and requires careful follow-up to monitor adverse drugs' side effects and ensure cure.

The escalation of the armed conflict in Ukraine since 24 February 2022, has as of 11<sup>th</sup> March, 2022, created in excess of two million displaced persons, of which one million are internally displaced persons (IDPs), and over one million refugees who have crossed borders into neighbouring countries.<sup>4</sup> Countries hosting refugees include Poland(1,575,000), Hungary(235,000), Slovakia(185,000), other European countries(304,000), Russian Federation(105,000), Romania(84,000), Moldova(105,000), and other European countries(300,000).<sup>4</sup> According to the UN Office for the Coordination of Humanitarian Affairs, of an estimated 18 million people affected by the conflict, 6 million have been targeted for Humanitarian Healthcare<sup>4</sup> to help cope with physical trauma and insurmountable mental, physical and other health vulnerabilities. Refugees and IDPs have an increased risk of contracting and dying from a range of infectious diseases and are desperately in need of shelter, water, sanitation, nutrition, and adequate holistic healthcare.<sup>5,6</sup>

Over the past century, experiences from previous and ongoing armed conflicts in all continents show that lower respiratory tract infections, especially TB, are the most common infectious cause of morbidity and mortality among displaced populations.<sup>7</sup> It is well documented that during and after several global armed conflicts, a significant rise in all clinical forms of TB occurred within conflict zones, and in countries hosting displaced persons.<sup>7,8,9</sup> A range of remedial environmental and host factors are responsible for these increases. Overcrowding, inadequate shelter, poor living conditions with inadequate ventilation, stress, malnutrition, existing co-morbidities such as diabetes, HIV co-infection, emphysema, extremes of temperature and other causes of immune compromise, all endow high risk of acquiring and contracting TB or re-activating LTBI. Poor and interrupted access to healthcare leaves most refugees with active TB remain undiagnosed further exacerbating TB transmission.<sup>10,11</sup>

Current UN and other humanitarian organisations' regional refugee responses for Ukraine focus primarily on supporting host country governments accepting refugees moving from Ukraine.<sup>4,5</sup> Thus, the management and control of TB and MDR-TB in Ukraine, Russian Federation and surrounding countries remains critically dependent on the provision of appropriate healthcare services and TB medicines in conflict zones, and in countries hosting refugees. Negotiating safe humanitarian corridors for refugees as well as humanitarian aid convoys to deliver medical equipment, diagnostics, and medications remains a complex challenge. There are high risks that medicines for TB and other diseases are being depleted, placing TB patients at risk of interrupted or inadequate treatment which are drivers of further *Mycobacterium tuberculosis* transmission, treatment failure and development of drug resistance.<sup>7,11</sup> The economic effects of sanctions on Russia could also lead to disruption of TB control activities within the Russian Federation. The world must now be prepared to tackle an increasing number of people with TB and complications arising out of delayed diagnosis and treatment interruptions. This will no doubt impact negatively on achieving global UN-SDG EndTB targets.<sup>2</sup>

There is an urgent need to emphasize implementation of effective measures for proactively detecting and treating all forms of TB with follow-up care of both refugees and IDPs. The International Covenant on Economic, Social and Cultural Rights guarantees universal and equitable access to health services within the scope of universal health coverage. It is imperative that these be provided by governments to refugee populations, regardless of ethnicity, age, gender, or legal status. Optimal care for TB and other airborne infections for refugees and IDPs in Ukraine and at all settings globally, will require more a comprehensive set of investments(**Table**). Whilst we work towards these ideal goals, for the Ukraine refugees, a minimum package of TB care and control with cross-border collaboration must be put in place and taken forward immediately to make available rapid diagnostic tests and TB drugs and ensure effective management for all forms of TB.<sup>12</sup>

Decades of armed conflicts across continents,<sup>7-9</sup> especially in high TB endemic countries, have created fragile health systems unable to provide adequate healthcare for refugees, IDPs and the local populations. To cease the never ending, heart wrenching plight of refugees and IDPs, and other populations under siege, every effort must be made by politicians, scientific and humanitarian communities worldwide to bring an end to the armed conflicts in Ukraine and other conflict zones globally. This will be essential for recalibrating global efforts at achieving UN-SDG EndTB targets and end the TB pandemic.

**Author declarations:**

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## REFERENCES

1. World Health Organization. Global tuberculosis report 2021. October 14, 2021 <https://www.who.int/publications/i/item/9789240037021> -accessed 9.03.2022
2. United Nations General Assembly Resolution A/RES/73/3 Political Declaration of the High-Level Meeting of the General Assembly on the fight against tuberculosis.2018 [https://www.un.org/en/ga/search/view\\_doc.asp?symbol=A/RES/73/3](https://www.un.org/en/ga/search/view_doc.asp?symbol=A/RES/73/3)
3. Migliori GB, Thong PM, Alffenaar JW, et al. Gauging the impact of the COVID-19 pandemic on tuberculosis services: a global study. *Eur Respir J.* 2021;58(5):2101786. Published 2021 Nov 11. doi:10.1183/13993003.01786-2021
4. UNHCR. Operational data portal. Ukraine Refugee situation. <http://data2.unhcr.org/en/situations/ukraine> -accessed 12th March, 2022
5. WHO 2022. Regional Office for Europe. WHO: Health care provision for civilians within and refugees beyond Ukraine our priority. <https://www.euro.who.int/en/media-centre/sections/statements/2022/statement-who-health-care-provision-for-civilians-within-and-refugees-beyond-ukraine-our-priority> -accessed 9th March, 2022.
6. Kiapi L, Lyons G, Sevkli S. Health needs of refugees and internally displaced persons in camp settings. In: Orcutt M, Shortfall C, Abbara A, et al. Handbook of Refugee Health for healthcare professionals and humanitarians providing care to forced migrants: For Healthcare Professionals and Humanitarians Providing Care to Forced Migrants. 2022: 2022: 3.1 35-44. 1<sup>st</sup> edition, CRC Press, Taylor Francis Group, London, UK. ISBN 113861288X
7. Murray JF, Loddenkemper R. Tuberculosis and War. Lessons Learned from World War II. in: Murray, JF Loddenkemper R, Herth, Felix JF. (Editors) Tuberculosis and War: Lessons Learned from World War II. 1st Ed. Publisher: S. Karger ISBN: 978-3-31-806094-2. Basel, Karger,2018, Prog Respir Res. vol 43,214-228 <https://doi.org/10.1159/000481490>
8. Abbara A, AlKabbani H, Al-Masri I, et al. Populations under siege and in prison require investment from Syria's national tuberculosis programme. *Lancet Respir Med.* 2018 Jul;6(7):e34. doi: 10.1016/S2213-2600(18)30182-6. PMID: 29755003.
9. Ismail MB, Rafei R, Dabboussi F, Hamze M. Tuberculosis, war, and refugees: Spotlight on the Syrian humanitarian crisis. *PLoS Pathog.* 2018;14(6):e1007014. Published 2018 Jun 7.
10. Proença, R., Mattos Souza, F., Lisboa Bastos, M. *et al.* Active and latent tuberculosis in refugees and asylum seekers: a systematic review and meta-analysis. *BMC Public Health* 20, 838 (2020). <https://doi.org/10.1186/s12889-020-08907-y>
11. Zumla A, Abubakar I. Improving access to multi-drug resistant tuberculosis diagnostic and health services for refugees and migrants. *BMC Med.* 2018 Nov 30;16(1):221. doi: 10.1186/s12916-018-1218-0. PMID: 30497477; PMCID: PMC6267830.
12. Migliori GB, Wu SJ, Matteelli A, et al. Clinical standards for the diagnosis, treatment and prevention of TB infection. *Int J Tuberc Lung Dis.* 2022;26(3):190-205. doi:10.5588/ijtld.21.0753

**Table/Figure: Elements, goals, and actions in a proposed comprehensive package for cross-border prevention and management of Tuberculosis in Europe in response to Ukraine conflict and refugee crisis.**

<b>Governance</b>	<b>Adequate legal framework in the countries involved</b>	<ul style="list-style-type: none"> <li>Establishment of peace/security pre-conditions.</li> <li>Implement the Geneva refugee policy.</li> <li>Commit to cross border TB care and control and national, regional (EU) and global level (UN).</li> <li>Establish the legal basis for this within and between EU and non-EU and countries, consistent with IHR.</li> </ul>
	<b>Specific and adequate funding</b>	<ul style="list-style-type: none"> <li>Ensure funding from Governments, bilateral and multilateral funding mechanisms (eg. EU and Global Fund) via a special rapidly implemented scheme).</li> </ul>
	<b>Inter-country correspondence</b>	<ul style="list-style-type: none"> <li>Create and maintain a live list of TB service providers in all countries of the region.</li> <li>Ensure adequate communication and outpatient and inpatient capacity, consistent with IHR.</li> </ul>
<b>Service Delivery (prevention, diagnosis and treatment)</b>	<b>Prevention</b>	<ul style="list-style-type: none"> <li>Provide services for diagnosis and treatment of LTBI</li> <li>Ensure access to vaccines (BCG and other vaccine preventable infections)</li> </ul>
	<b>Infection control</b>	<ul style="list-style-type: none"> <li>Facilitate adequate implementation of administrative, environmental, and personal protection measures.</li> </ul>
	<b>Diagnosis</b>	<ul style="list-style-type: none"> <li>Ensure availability of reagents and diagnostic tests for LTBI, DS- and DR-TB, enabling prompt early diagnosis.</li> </ul>
	<b>Treatment</b>	<ul style="list-style-type: none"> <li>Ensure uninterrupted supply of quality drugs for DS and DR-TB.</li> <li>Facilitate prompt and effective treatment until cure.</li> <li>Enable integrated TB-HIV care and treatment of HBV, HCV, diabetes, and other co-morbid conditions.</li> </ul>
	<b>Continuity of care and Follow-up</b>	<ul style="list-style-type: none"> <li>Increase the use of digital technology, sharing of cross-border treatment files for continuity of care and global TB consilium.</li> <li>Avoid deportation until the end of intensive phase and ensuring follow-up of continuation phase until cure.</li> <li>Provide follow-up of patients for at least 2 years.</li> </ul>
<b>Surveillance &amp; monitoring</b>	<b>Individual patient data</b>	<ul style="list-style-type: none"> <li>Enable effective transfer of patient's records.</li> <li>Provide feedback to the centre referring patients.</li> </ul>
	<b>Programme performance</b>	<ul style="list-style-type: none"> <li>Track and monitor relevant indicators at country and regional level to measure progress, in collaboration with WHO and ECDC.</li> </ul>
<b>Supportive environment</b>	<b>Enablers and incentives</b>	<ul style="list-style-type: none"> <li>Provide stigma and discrimination-free counselling, testing, psycho-social support to patients, families and contacts.</li> </ul>
	<b>Advocacy, communication and social mobilization</b>	<ul style="list-style-type: none"> <li>Empower communities for providing refugee/migrant-sensitive services.</li> <li>Improve communication with refugee/displaced communities.</li> <li>Advocate for full engagement of health authorities and stakeholders.</li> <li>Rebuild the capacity of conflict afflicted country national TB program, with support and training of staff and supply chain integration.</li> </ul>