

Tackling TB in Europe: treatment gaps and deteriorating treatment availability is undermining progress

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The precipitous decline in TB incidence in Europe (European Union/European Economic Area) is an extraordinary success story, with a 52% cumulative decrease in TB incidence since 2012. The average annual decrease of 7.7%¹ – compared to only 1.9% globally² – is the fastest of all world regions (Figure 1). However, the declining TB rates are positively correlated with diminishing commercial incentives to supply treatments, which represents a blind spot for TB control. As countries advance towards elimination targets, absolute case numbers shrink, optimal treatment provision becomes harder and targets are more difficult to achieve. In recent years, the European Centres for Disease Control has warned that EU countries are ‘not on track to reach the goal of ending the TB epidemic by 2030’.³ Europe already struggles to prevent TB progression, treat TB in children and tackle disease resistance. At the United Nations (UN) High-Level Meeting (HLM) on TB, the donors will prioritise TB in high-burden settings. However, there are also challenges to meeting the targets to eliminate TB in low-incidence countries. Here we highlight these issues and suggest how the challenges could be overcome.

ACCESS INEQUITY – UNFORESEEN CONSEQUENCES OF TWO LAUDABLE SUCCESSES

Success in controlling TB in the EU over the past two decades occurred at the same time as the Stop TB Partnership successfully developed the Global Drug Facility (GDF). Similar to the

Global Fund, the GDF is an example of a Global Health Initiative (GHI), acting on behalf of low- and middle-income countries (LMICs) to overcome market challenges that typically impede new treatment development and delivery for diseases of poverty. Its annual purchasing power increased from US\$30m in 2007 to US\$250m by 2020.⁴ The GDF has leveraged the growth in market size to negotiate price reductions of 30–80% (Figure 2).⁵ It has also brought new regimens to market (often as single pills formulated to optimise patient adherence) within months of the issuance of new treatment guidelines by the WHO, catalysing a treatment revolution.^{6,7} Although the initiatives have been great successes, these solutions increasingly – and almost exclusively – benefit a shrinking group of poorer countries. The GDF increasingly represents the only reliable and quality supply of TB medicines at scale anywhere in the world. Unfortunately, its products are not available in the EU/EEA – or many other high-income countries (HICs) – for more than a handful of patients annually.

BARRIERS TO EQUITY OF AVAILABILITY IN EUROPE

GHIs, including the GDF, have a UN legal character, which creates incompatibilities with the legal frameworks in most sovereign countries. This can make purchasing from the GDF challenging, particularly when using domestic, as opposed to donor, funds. A significant bottleneck exists due to the lack of regulatory recognition of quality standards in the WHO’s pre-qualification programmes, which are not considered equivalent to stringent regulatory standards, such as those of the European Medicines Agency. At present, roughly 70% of TB medicines available globally through the GDF are unregistered products within the EU.⁵ The legal exceptions (Directive 2001/83/EC Articles 5 [1] and [2]),⁸ which allow their import via ‘emergency access pathways’, either do not clearly apply to chronic infections or offer only narrow benefit (to individual patients, per medicine order) in comparison to the associated costs; this is a significant administrative burden for physicians. Some GHIs acknowledge the significant barrier that stems from disparities in multilateral vs. domestic financing conditionalities.⁹ Sovereign governments struggle to realise the ‘pre-payment’ and ‘not-for-profit’ import requirements while remaining compliant with domestic procurement laws.

BENEFITS OF ADDRESSING BARRIERS TO AVAILABILITY

The lack of effective interoperability between multilateral and country legal–regulatory systems obstruct the development of solutions that could mutually and positively reinforce progress across all world regions. Medical countermeasures need to flow as seamlessly as

pathogens in our globalised, interconnected world. The treatment of TB in Europe represents a rare example where the solutions largely exist and money is not the key challenge. Ensuring more seamless global access represents enlightened self-interest, particularly for both HICs and GHIs. The EU urgently needs to secure TB medical supplies to improve its treatment outcomes. Adopting the latest-generation regimens in HICs would support decentralised care away from the expensive tertiary sector and lift the treatment burden for health systems and patients. Given the heightened political focus on migration, pandemics and cross-border health threats,¹⁰ this would also constitute an easy win for the European Commissions' Health Emergency Preparedness and Response commitments of 'all available medical countermeasures being accessible to member states'.¹¹ For the GDF, its volumes are expected to stagnate and decline over the coming years as LMICs lose eligibility for donor-financing support and transition to self-financing and procurement.¹² Evolving its model to integrate efforts to move to Universal Health Coverage¹³ by ensuring its products remain accessible to all countries post-transition (and beyond) will also ensure the fruits of its success are not lost to history.

TREATMENT GAPS, UNMET NEEDS AND DETERIORATING TREATMENT OUTCOMES

The elimination of TB will require reliable and continuous availability across the spectrum of treatments. These medicines span the product life cycle, including a variety of treatment combinations (regimens) and formulations. Currently, there are treatment gaps, unmet needs and variable treatment outcomes in HICs. The difficulty in securing access to medicines has also revealed how small and fragmented individual product markets are across the 27 EU health systems. For the few, newer (and therefore broadly registered) patent-protected, products that are the cornerstone of second-line treatment for multidrug-resistant TB (MDR-TB), the main barrier to access is high prices (up to tens of thousands of euros per treatment course).¹⁴ This despite the huge public financing for their development.¹⁵ For all other treatments, the lack of access to GDF's latest-generation products (and prices) means that HICs are reliant on an increasingly vulnerable supply of the old (>50 years) generation, generic single-component products. In recent years, these already-vulnerable markets in Europe have witnessed supply-side shocks (regulatory tightening over impurity concerns in manufacturing)¹⁶ and demand-side shocks (ensuring treatment continuity for Ukrainian refugees).¹⁷ Like other low-volume antibiotic markets, the patents and exclusivities for these products expired long ago and commercial returns are too low to induce manufacturers to make them widely available. This includes for new manufacturers or products to enter the market,^{18,19} older products to remain

in the market, seek label extensions or more widespread national registrations – see Table. Economic theory suggests that the situation will only deteriorate further, impacting all HICs and a growing pool of middle-income countries, with the worst impact on smaller and poorer countries.

A RALLYING CALL FOR GREATER INTER- AND INTRA-NATIONAL COOPERATION

Anecdotal evidence suggests that some larger EU countries have implemented national solutions to address specific product gaps and supply continuity challenges. Much more can be done at the national level, often by adopting the controversial ‘vertical programme thinking’ that has been the hallmark of global TB control efforts (i.e., greater centralisation, oversight, strategic planning and procurement). However, the viability of national-level responses is expected to diminish as volumes continue to decline. The current supply-security challenges facing the United States, despite the presence since 2018 of the TB Emergency Drug Stockpile, may serve as a cautionary tale.²⁰ There are indications that similar challenges occur for treatments for HIV/AIDS, where WHO’s preferred first-line regimen is impacted by similar availability issues in the EU.²¹ Recent reports of a climate-induced resurgence of malaria²² might offer a future scenario where countermeasures are required beyond the high-burden countries for which they were originally intended. Given the low level of demand for TB medicines in low incidence countries, greater access to GDF products would enable their high-volumes to be leveraged to sustain and support the markets in HICs.

COULD EUROPE AGAIN ASPIRE TO ELIMINATE TB

Facing stalling progress on TB reduction and elimination goals, physicians in the EU have called for a ‘renewed vision.’²³ The European Parliament has also recently called for ‘renewed political impetus’ to achieve its goals in the light of COVID-19 and the Ukraine crisis.²⁴ However, these goals will remain out of reach unless the critical role played by deteriorating access to medicines receives the visibility and recognition it needs.²⁵ This topic represents a unifying theme cutting across all three of the UN High-Level Meetings in September 2023, creating an opportunity to garner the required recognition and catalyse a collective response. A pan-EU effort to address the barriers to availability at source would benefit not just the EU, but all low-incidence and donor-transitioning countries. More critically, certain EU countries may be well-placed, as pioneers, to demonstrate the feasibility of TB elimination.

Demonstrating that elimination is an attainable goal would be a powerful way to sustain future political and financial support for global TB control.

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Figure 1. TB treatments in high-burden countries are currently insufficiently available to reinforce and sustain TB control gains in low-incidence EU/EEA countries. Europe's (EU/EEA) epidemiological trend (notifications per 100,000 population) with imposed thresholds/targets (Source: <https://www.ecdc.europa.eu/sites/default/files/documents/tuberculosis-surveillance-monitoring-2023.pdf>).

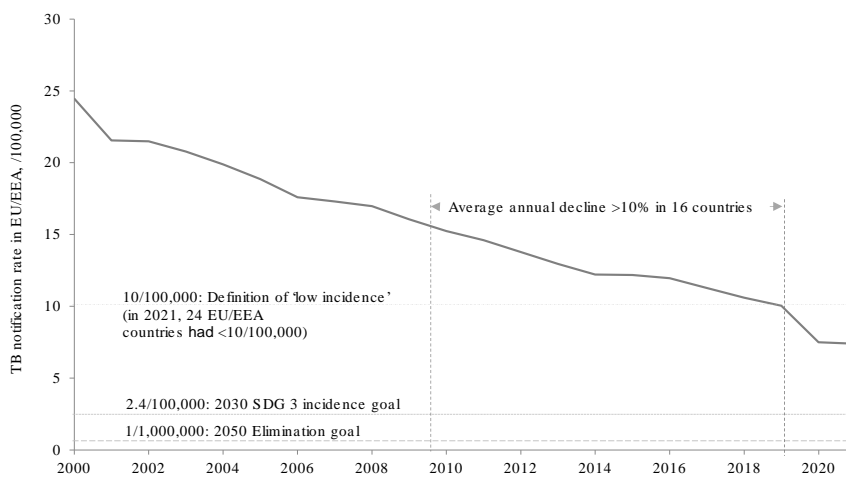


Figure 2. Growth in treatment volumes in terms of estimated DS-TB adult and paediatric treatments delivered (in thousands) in the Global South using GDF-supplied countries as proxy (Source: <https://www.stoptb.org/mission/gdfs-results>). EU = European Union; EEA = European Economic Area, DS-TB = drug-susceptible TB.

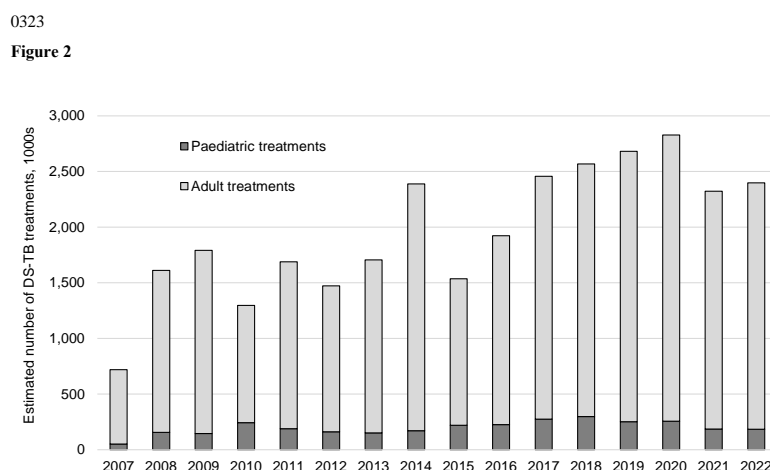


Table. Examples of the current needs and challenges for TB medicine supplies in the EU/EEA

Required action	Example products	Benefit for TB control in low-incidence countries
New manufacturers/generic products to enter the EU/EEA market and/or more ready access to products only available through GDF*	RPT 300 mg monotherapy* OR the combination-treatments* (i.e., 1HP [co-packed] OR 3HP [FDC])	RPT is currently completely absent from the EU/EEA market. If secured, it would enable a greatly reduced burden and duration of TPT for those exposed or with latent TB). RPT would also facilitate the EU/EEA moving to the new shorter DS-TB regimens
	Dispersible tablets (DT)* (i.e., HRZ 50/75/150 DT, HR50/70) OR single-component	Availability of appropriate paediatric formulations would enable more children to be treated, eliminate the need for hospital compounding (from adult doses) and facilitate optimum

	generic suspensions* (H: 50–100 mg; Z: 150 mg)	dosing, compliance and decentralised prevention and care of children under 14 years
Price falls (generic entry facilitation) And more widespread positive (and frequently reviewed) national reimbursement/ coverage decisions	Group A: pretomanid 200 mg, bedaquiline 100 mg, linezolid 600 mg	Poor/difficult access to components of the WHO-recommended short-course (6-month) treatment regimen, BPaLM, for treating patients with RR/MDR-TB could be driving poor treatment outcomes and driving AMR for the growing number of European patients
More ready access to GDF supplies or more widespread EU registrations/label expansions	Group B: cycloserine 125 mg; clofazimine 100 mg	The RR/MDR-TB treatment challenges are likely compounded by unreliable access to older Group B products (used as substitutes when Group A products are not accessible)
Measures to strengthen the supply security (reducing market withdrawals, shortages/ruptures) of cornerstone therapies, including reviewing label maintenance [†] burden on companies	Adult FDCs (i.e., 4HR and 2HRZE) and single-component monotherapies (i.e., H 75 mg, R 150 mg, Z 400 mg, E 275 mg)	Ensuring physicians have reliable access to preferred and substitute treatments for DS-TB (including FDCs and single-component products), supports patient treatment continuity and optimisation. Improving treatment outcomes and lessening AMR pressures

*Asterixed GDF-supplied products are those which are not EU-EEA-registered.

[†]Licenses (national registrations) require regular renewal and payment.

EU = European Union; EEA = European Economic Area; GDF = Global Drug Facility; RPT, P = rifapentine; 1HP = (once daily isoniazid/pyrazinamide for one month); 3HP = (once weekly isoniazid/pyrazinamide for three months); FDC = fixed-dose combination; TPT = TB preventative treatment; DS-TB: drug-susceptible; TB DS-TB = drug-susceptible TB; H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide, BPaLM = bedaquiline, pretomanid, linezolid and moxifloxacin; RR/MDR-TB = rifampicin-/multidrug-resistant TB, AMR = antimicrobial resistance.