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Original article

Availability and costs of medicines for the treatment of tuberculosis in Europe

Gunar Günther [1, 2], Lorenzo Guglielmetti [3, 4], Claude Leu [1], Christoph Lange [5, 6, 7, 8, *], Frank van Leth [9] on behalf of Tuberculosis Network European Trials group[†]

[1)] Department of Pulmonary Medicine and Allergology, Inselspital, Bern University Hospital, University of Bern, Switzerland
[2)] Department of Medical Sciences, School of Medicine, University of Namibia, Windhoek, Namibia
[3)] Sorbonne Université, INSERM, U1135, Centre d'Immunologie et des Maladies Infectieuses, Cimi-Paris, équipe 2, Paris, France
[4)] Assistance Publique – Hôpitaux de Paris, Groupe Hospitalier Universitaire Sorbonne Université, Hôpital Pitié-Salpêtrière, Centre National de Référence des Mycobactéries et de la Résistance des Mycobactéries aux Antituberculeux, Paris, France
[5)] Division of Clinical Infectious Diseases, Research Center Borstel, Borstel, Germany
[6)] German Center for Infection Research (DZIF), Partner Site Hamburg-Lübeck-Borstel-Riems, Borstel, Germany
[7)] Respiratory Medicine and International Health, University of Lübeck, Lübeck, Germany
[8)] Baylor College of Medicine and Texas Children's Hospital, Global TB Program, Houston, TX, USA
[9)] Department of Health Sciences, Faculty of Science, Vrije Universiteit, Amsterdam Public Health Research Institute, Amsterdam, the Netherlands

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ABSTRACT

Objectives: To evaluate the access to comprehensive diagnostics and novel antituberculosis medicines in European countries.
Methods: We investigated the access to genotypic and phenotypic *Mycobacterium tuberculosis* drug susceptibility testing and the availability of antituberculosis drugs and calculated the cost of drugs and treatment regimens at major tuberculosis treatment centres in countries of the WHO European region where rates of drug-resistant tuberculosis are the highest among all WHO regions. Results were stratified by middle-income and high-income countries.
Results: Overall, 43 treatment centres from 43 countries participated in the study. For WHO group A drugs, the frequency of countries with the availability of phenotypic drug susceptibility testing was as follows: (a) 75% (30/40) for levofloxacin, (b) 82% (33/40) for moxifloxacin, (c) 48% (19/40) for bedaquiline, and (d) 72% (29/40) for linezolid. Overall, of the 43 countries, 36 (84%) and 24 (56%) countries had access to bedaquiline and delamanid, respectively, whereas only 6 (14%) countries had access to rifapentine. The treatment of patients with extensively drug-resistant tuberculosis with a regimen including a carbapenem was available only in 17 (40%) of the 43 countries. The median cost of regimens for drug-susceptible tuberculosis, multidrug-resistant/rifampicin-resistant tuberculosis (shorter regimen, including bedaquiline for 6 months), and extensively drug-resistant tuberculosis (including bedaquiline, delamanid, and a carbapenem) were €44 (minimum–maximum, €15–152), €764 (minimum–maximum, €542–15152), and €8709 (minimum–maximum, €7965–11759) in middle-income countries (n = 12) and €280 (minimum–maximum, €78–1084), €29765 (minimum–maximum, €11116–40584), and €217591 (minimum–maximum, €82827–320146) in high-income countries (n = 29), respectively.
Discussion: In countries of the WHO European region, there is a widespread lack of drug susceptibility testing capacity to new and repurposed antituberculosis drugs, lack of access to essential medications in several countries, and a high cost for the treatment of drug-resistant tuberculosis. **Gunar Günther, Clin Microbiol Infect 2023;29:77**

* Corresponding author. Christoph Lange, Division of Clinical Infectious Diseases, Medical Clinic, Research Center Borstel, Parkallee 35, 23845, Borstel, Germany.
E-mail address: clange@fz-borstel.de (C. Lange).
† Members of the Tuberculosis Network European Trials study group are listed in Appendix section.

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Introduction

Tuberculosis (TB) is the leading cause of death due to a bacterial pathogen worldwide. In 2020, TB developed in 9.9 million people and 1.5 million patients with TB died from this disease [1]. The emergence of antimicrobial drug resistance in *Mycobacterium tuberculosis* is threatening the success of the END-TB strategy of the WHO [2]. Among all regions of the WHO, the proportion of patients with drug-resistant TB is highest in the European region [1]. In 2020, there were 34 778 patients affected by multidrug-resistant (MDR)/rifampicin-resistant (RR) TB, including 11 072 patients affected by preextensively drug-resistant (pre-XDR) TB and extensively drug-resistant (XDR) TB, in the WHO European region [3]. According to the WHO, the proportion of patients with TB globally who achieve a successful treatment outcome exceeds 85%; however, the prognosis for patients with MDR/RR-TB is not as promising, with less than 60% of patients achieving treatment success [1].

Diagnostic improvements and availability of novel anti-TB medicines have brought a substantial change to the management of patients affected by drug-resistant TB [4]. Molecular drug susceptibility testing (DST) based on nucleic acid amplification technologies has entered the clinical routine in many countries [5,6]. New anti-TB drugs (i.e. bedaquiline, delamanid, and pretomanid) have been approved for drug-resistant TB treatment along with fundamental changes in treatment guidelines and regimens [7]. Such innovations can improve TB control if they are accessible to patients and programmes. Improving access by ensuring affordable pricing of drugs is crucial for all new anti-TB drugs and is a major topic of political debate and advocacy [8].

After a recent revision of the hierarchy of anti-TB drugs for the treatment of patients with drug-resistant TB by the WHO in 2020 [9], little is known about the availability of drugs and DST for new and repurposed anti-TB drugs. The same holds true for the cost of these drugs and treatment regimens [10,11].

The Tuberculosis Network European Trials (TBNET) study group, a Europe-based network promoting TB research and training, first evaluated the availability and cost of anti-TB drugs and regimens among 37 European countries in 2013 [12], at a time when bedaquiline, delamanid, and pretomanid were not yet available. To provide an updated account on the availability of anti-TB DST and the costs and availability of anti-TB drugs and regimens, we conducted a similar survey, additionally including the availability of DST, among major treatment centres in the countries of the WHO European region.

Methods

Data collection

Data on TB drug availability, cost, and availability of DST for all anti-TB drugs were surveyed, administering a standardized questionnaire to TBNET representatives with experience in the management of drug-resistant TB at referral treatment centres in countries of the WHO European region. If no TBNET representatives were available in a country, we searched PubMed for major publications on drug-resistant TB and approached respective authors from the target countries. Data collection for drug availability, cost, and DST availability was performed from June 2020 to December 2020 and updated in October 2021. The list of the drugs in the survey was developed with reference to those available via the Global Drug Facility [13]. Drug costs are costs of TB medicines incurred to hospitals or other treatment providers when purchasing medicines through pharmacies or purchasing costs of medicines at the Global Drug Facility or other country-specific providers.

Data analysis

Drug cost calculations were based on available formulations and cost for one unit (tablet or vial) of the drug. We determined the number of units required to provide adequate daily treatment for patients with 70 kg of body weight, according to WHO-recommended drug doses [7]. When available, fixed-dose drug combinations were included in the calculation of the regimen cost and the least-expensive regimen option was reported. Daily treatment cost for drugs administered on a nondaily basis, such as bedaquiline, was based on weekly cost divided by seven. Cost data were collected in local currency or U.S. dollars, using the exchange rate on 1 July 2020 for conversions. Costs are reported in Euro when there is no direct between-country comparison. For direct between-country comparisons, drug costs were converted to international dollars using the purchasing power parity conversion factor from the international comparison programme 2017 [14]. Stratification according to income followed the World Bank classification, according to which upper and lower middle-income countries are combined as middle-income countries (Fig. S1) [15]. Costs of regimens and drugs are presented as median with minimum and maximum values, if not otherwise stated.

We selected regimens for drug-susceptible (DS) TB, MDR/RR-TB, pre-XDR TB, and XDR-TB on the basis of the latest guidelines from WHO [7,16] and American Thoracic Society/Centers for Disease Control/European Respiratory Society/Infectious Diseases Society of America [17]; regimen compositions are shown in Table S2. DS-TB was defined as susceptible to all first-line TB drugs. MDR/RR-TB, pre-XDR TB, and XDR-TB were defined according to the WHO 2020 definitions [18]. The results for eight priority regimens are shown in Table 1 and Table S4; the results for additional regimens are available in Tables S3 and S4. We neither present the cost for a standardized regimen containing bedaquiline, linezolid, and pretomanid [19] nor the regimen with rifapentine, moxifloxacin, isoniazid, and pyrazinamide, as cost data on pretomanid were available only in three high-income countries and data on rifapentine in two middle-income and three high-income countries [20]. DST availability was evaluated for the same list of drugs as cost data and stratified by phenotypic and genotypic testing.

Ethics

Ethical clearance was granted by the institutional review board of Bligny Hospital, France (15 January 2020; CRE 2020 01). As no patient data were collected, ethical board review was not applicable at any of the participating centres.

Results

Survey response

The WHO European region has 53 countries (not including Kosovo). We excluded Central Asian countries and small city countries (in total, $n = 8$) from the survey and therefore did not contact representatives from Andorra, Kazakhstan, Kyrgyzstan, Monaco, San Marino, Tajikistan, Turkmenistan, and Uzbekistan. Overall, data on drug availability were obtained and analysed from 43 countries, data on drug cost from 41 countries, and data on DST availability from 40 countries. We were unable to obtain responses on drug cost, availability, and DST availability from Azerbaijan, Bosnia and Herzegovina, and Montenegro. Drug cost data were not available from Malta and Israel. Moreover, DST data were not available from Malta, Kosovo, and Iceland.

Table 1
Availability and cost of drug regimens for the treatment of tuberculosis in countries in the WHO European region, stratified by World Bank income classification,[a] in Euros

Treatment regimen[b]	Middle-income country				High-income country			
	Availability	Cost			Availability	Cost		
	N (%)	Median	Minimum	Maximum	*N* (%)	Median	Minimum	Maximum
DS-TB	12 (100)	44	15	152	31 (100)	280	78	1084
MDR/RR-TB short, BDQ 6 mo[c]	6 (50.0)	764	542	15 152	20 (64.5)	29 765	11 116	40 584
MDR/RR-TB long, BDQ 18 mo[c]	7 (58.3)	2954	1591	42 477	24 (77.4)	97 808	34 142	2 16 595
Pre-XDR TB, using DLM	5 (42.7)	7094	6755	10 916	15 (48.4)	2 07 034	63 987	3 13 566
Pre-XDR TB, using AM	4 (33.3)	2250	2007	3298	24 (77.4)	1 08 459	37 412	2 49 560
XDR-TB, resistant FQ, BDQ, using a carbapenem[d]	4 (33.3)	7945	6981	11 221	13 (41.9)	1 41 307	40 237	2 55 550
XDR-TB, resistant FQ, LZD, using a carbapenem[d]	4 (33.3)	8709	7965	11 759	12 (38.7)	2 17 591	82 827	3 20 146
XDR-TB, resistant FQ, BDQ, LZD, using a carbapenem[d]	4 (33.3)	8348	6949	11 528	10 (32.3)	1 47 959	1 18 825	2 71 343

AM, amikacin; BDQ, bedaquiline; DLM, delamanid; DS, drug susceptible; FQ, fluorquinolone; LZD, linezolid; MDR, multidrug resistant; RR, rifampicin resistant; TB, tuberculosis; XDR, extensively drug resistant.
[a] Drug availability data are from 43 countries; regimen cost calculation is based on data from 41 countries, not including Malta and Israel (both high-income countries).
[b] Detailed regimen composition is depicted in Table S1.
[c] Refers to the length of bedaquiline treatment.
[d] Refers to the use of cheapest available carbapenem (meropenem or imipenem).

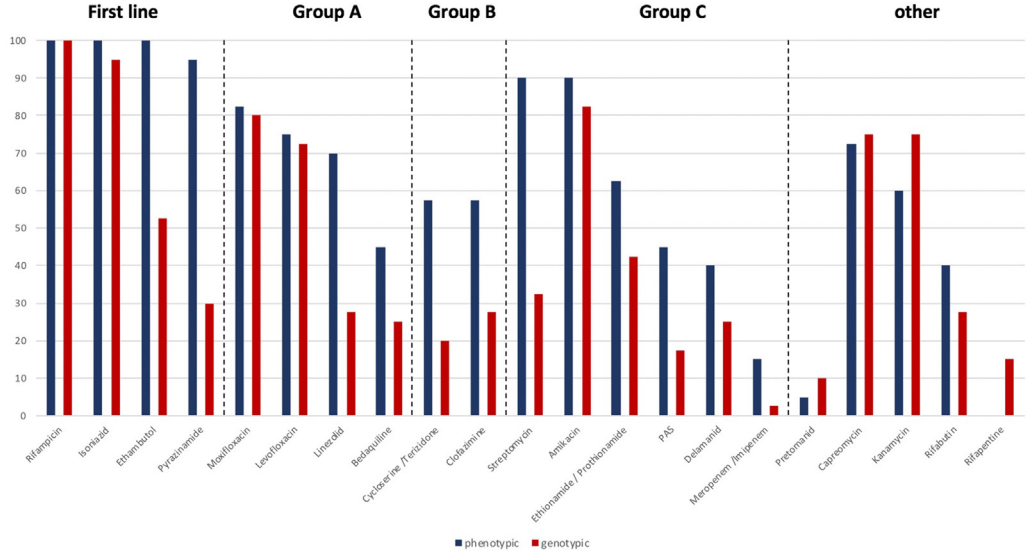

Fig. 1. Availability of phenotypic and genotypic drug susceptibility testing to tuberculosis drugs in countries in the WHO European region[a], in per cent. PAS, para-aminosalicylic acid.
[a]$n = 40$ countries; Kosovo, Iceland, and Israel did not provide data on the availability of drug susceptibility testing.

Availability of DST

Phenotypic DST was generally more widely available than genotypic testing. Of the 40 countries, phenotypic DST for all first-line drugs was available in 38 (95%) countries, whereas genotypic DST was available for rifampicin in 40 (100%), isoniazid in 38 (95%), ethambutol in 21 (53%), and pyrazinamide in 12 (30%) countries. For WHO group A drugs, the frequency of countries with the availability of phenotypic and/or genotypic DST was 75% (30/40) and 73% (29/40) for levofloxacin; 82% (33/40) and 80% (32/40) for moxifloxacin; 48% (19/40) and 25% (10/40) for bedaquiline; and 72% (29/40) and 28% (11/40) for linezolid, respectively (Figs. 1 and 2). For group B drugs, the frequency of countries with the availability of phenotypic and/or genotypic DST was 63% (25/40) and 28% (11/40) for clofazimine and 58% (23/40) and 20% (8/40) for cycloserine/terizidone, respectively. Among group C drugs, of the 40 countries, phenotypic and/or genotypic DST was available only in 6 (15%) and 1 (2.5%) countries for carbapenems (meropenem and imipenem) and in 17 (42%) and 10 (25%) for delamanid, respectively. Phenotypic DST for rifapentine could not be evaluated in any of the countries, and genotypic DST for this drug was available only in 6 (15%) of the 40 countries. Similarly, phenotypic DST for pretomanid was available only in 2 (5%) and genotypic DST in 4 (10%) of the 40 countries.

Availability of TB drugs

The four first-line drugs, rifampicin, isoniazid, pyrazinamide, and ethambutol, were available in all 43 countries, as single drugs or as part of fixed-dose drug combinations. Of the 43 countries, levofloxacin was available in 43 (100%), moxifloxacin in 41 (95%), bedaquiline in 36 (84%), and linezolid in 43 (100%) countries. Clofazimine was available in 35 (81%) of the 43 countries but only in 8 (67%) of the 12 middle-income countries. Delamanid was available in 24 (56%) of the 43 countries. Meropenem and imipenem were available in 28 (65%) and 25 (58%) of the 43 countries. Pretomanid was available only in 4 (9%) of the 43 countries (Germany, Ireland, Sweden, and Switzerland)—all high-income countries. Only 6 (14%) of the 43 countries reported access to rifapentine (Table S1).

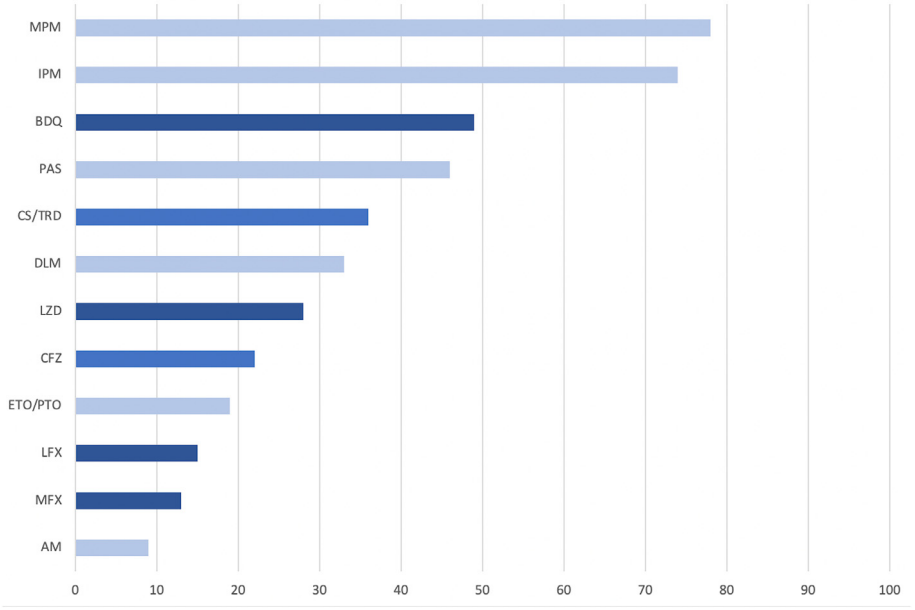

Fig. 2. Proportion of countries with the availability of antituberculosis drugs in the absence of drug susceptibility testing for those drugs; numbers of countries with available data for amikacin (AM) = 35, moxifloxacin (MFX) = 39, levofloxacin (LFX) = 40, bedaquiline (BDQ) = 35; ethionamide/prothionamide (ETO/PTO) = 32, clofazimine (CFZ) = 32, linezolid (LZD) = 40, delamanid (DLM) = 24, cycloserine/terizidone (CS/TRD) = 39, para-aminosalicylic acid (PAS) = 28, imipenem (IMP) = 23, and meropenem (MPM) = 27. WHO group A medicines are displayed in dark blue, group B medicines in medium blue, and group C medicines in light blue.

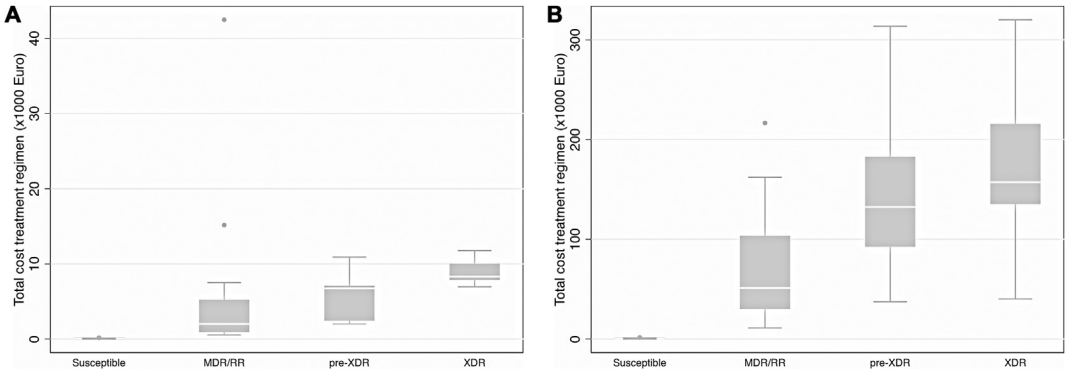

Fig. 3. Box plot of regimen cost for treatment of drug-susceptible TB, MDR/RR-TB, pre-XDR TB, and XDR-TB in middle-income (a) and high-income (b) European countries.[a]MDR, multidrug resistant; RR, rifampicin resistant; TB, tuberculosis; XDR, extensively drug resistant. [a]$n = 41$ countries; Malta and Israel (both high-income countries) did not provide data on drug cost. Upper whisker: 75th percentile +1.5 × IQR (or upper value if smaller), lower whisker: 25th percentile − 1.5 × IQR (or smallest value if larger), dots are values exceeding (lower or higher) the whiskers.

Cost of TB drugs

TB drugs were generally less expensive in the middle-income countries, although there was a large variability in drug cost among countries. The drugs with the highest median daily treatment costs were delamanid, bedaquiline, and rifapentine among the high-income countries and imipenem, meropenem, and delamanid among the middle-income countries. Daily median treatment costs for delamanid were €128.04 in the high-income countries and €8.52 in the middle-income countries, whereas, for bedaquiline, it was €103.98 and €1.60 in the high-income and middle-income countries, respectively. The daily median treatment cost of amikacin was €10.10 in the high-income countries and €1.18 in the middle-income countries (Table S1).

Availability of TB treatment regimens

Treatment of DS-TB according to the current WHO guidelines was available in all 43 (100%) countries (Table 1). Of the 43 countries, the shorter MDR/RR-TB regimen with bedaquiline was available in 26 (60%) countries, whereas the conventional long MDR/RR-TB regimen was available in 31 (72%) countries. A pre-XDR TB treatment, with amikacin or delamanid replacing the fluoroquinolones, was available in 28 (65%) and 20 (47%) of the 43 countries, respectively. The treatment of patients with XDR-TB with a regimen including a carbapenem was available only in 17 (40%) of the 43 countries (Table 1; Table S3).

Cost of TB treatment regimens

Fig. 3 shows regimen costs by degree of resistance. Costs of regimens increase substantially with increasing level of antimicrobial drug resistance. Regimens are considerably less expensive in the middle-income countries as shown in Fig. 3(a) than in high-income countries as shown in Fig. 3(b). Fig. 4 shows the overall distribution of regimen costs, based on Euro. Figs S2 to S5 illustrate the direct comparison of the cost of treatment regimens among countries, considering the purchasing power parity based

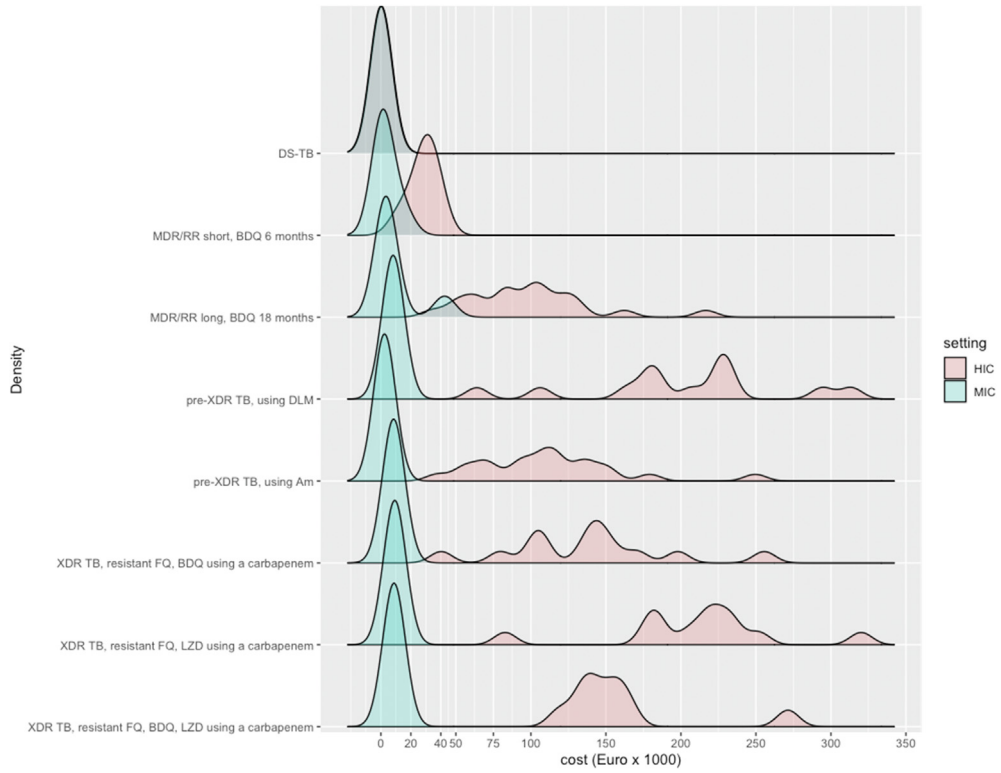

Fig. 4. Density graph of distribution[a] of cost for tuberculosis drug regimens in the WHO European region, according to resistance status and World Bank income classification[b] (high-income countries in red, middle-income countries in green), in Euros. AM, amikacin; BDQ, bedaquiline; DLM, delamanid; DS-TB, drug-susceptible tuberculosis; FQ, fluoroquinolones; HIC, high-income country; LZD, linezolid; MDR/RR-TB, multidrug-resistant/rifampicin-resistant tuberculosis; MIC, middle-income country; pre-XDR TB, pre-extensively drug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis. [a] The density graph illustrates the distribution of the cost within a given resistance pattern. The area under the curve is scaled to one. The height in the distribution shows the range of the cost for the majority of countries. The width of the graph shows the range of the costs observed. [b] $n = 41$ countries, Malta and Israel (both high-income countries) did not provide data on drug cost.

on international dollars. The median cost of a DS-TB regimen was €44 in the middle-income countries and €280 in the high-income countries. The median cost of the shorter MDR/RR-TB regimen with bedaquiline for 6 months was €764 in the middle-income countries and €29 765 in the high-income countries, whereas the conventional long MDR/RR-TB treatment regimen with bedaquiline for 6 months costed €2214 and €51 617, respectively (Table 1; Tables S3 and S4). A pre-XDR TB treatment regimen using delamanid or amikacin costed €7094 or €2250 in the middle-income countries, respectively, and €2 07 034 or €1 08 459 in the high-income countries, respectively. A regimen for the treatment of patients with XDR-TB with resistance to fluoroquinolones and linezolid, including bedaquiline, delamanid, and a carbapenem, costed €8709 in the middle-income countries and €2 17 591 in the high-income countries.

Discussion

We provide a report on the availability of anti-TB DST and, following a survey in 2013, an updated report on the availability and costs of anti-TB drugs in the WHO European region. The main finding of this survey is that the availability of DST for second-line anti-TB drugs, in particular new and repurposed drugs, is severely limited in Europe and that new drugs are more frequently available than their specific DST. The cost of drugs and regimens for the treatment of drug-resistant TB are very high compared with those for the treatment of DS-TB. In addition, the cost of regimens is highly variable across different countries. Access to adequate treatment regimens for pre-XDR and XDR-TB is limited, in particular in middle-income countries. Finally, almost no country in Europe has access to the drugs included in new promising regimens for DS and drug-resistant TB, such as rifapentine and pretomanid.

A revision of international guidelines for the management of drug-resistant TB suggests the use of treatment regimens of at least four effective drugs, ideally based on DST results [21]. When the second-line TB medicines are available but the ability to perform DST for these medicines is not, physicians in countries of the WHO European region (and elsewhere) cannot be sure that the medicines they prescribe are effective. Recent reports of growing resistance to new and repurposed drugs underline the need for resistance detection and surveillance [22–24]. According to our results, 52% of European countries cannot detect bedaquiline resistance and 27% cannot detect linezolid resistance, resulting in an inability to detect patients with XDR-TB who have the worst prognosis [25]. Standardized treatment regimens in the absence of DST are likely to be a major driver of the emerging antimicrobial drug resistance in *M. tuberculosis* [26,27].

All sites in the survey reported the availability of treatment for DS-TB. However, with an increasing level of antimicrobial drug resistance, the availability of suitable regimens declined. Middle-income countries generally have fewer resistance-appropriate treatment options than high-income countries. Access to relevant therapies has remained fairly unchanged since the introduction of new drugs and regimens compared with the 2013 TBNET assessment [12], despite the fact that several anti-TB drugs are on the WHO list of essential medicines. Rifapentine has recently shown the potential to shorten the duration of DS-TB treatment when used

in combination with moxifloxacin, isoniazid, and pyrazinamide as part of a 4-month regimen [20], which was already endorsed by the WHO [28]. In addition, rifapentine is also recommended for TB prevention in the 1-month daily rifapentine/isoniazid and 3-month weekly rifapentine/isoniazid regimens [29]. Of concern, our results show that rifapentine is available only in two middle-income countries and four high-income countries of the WHO European region [30].

Similar to our previous findings in 2013, high cost and limited availability of regimens for the treatment of drug-resistant TB are limiting the access to these medicines for many of the affected patients in this region [12]. The drug treatment for a patient with MDR/RR-TB with a shorter regimen (including 6 months of bedaquiline administration) costs approximately 18 times more in the middle-income countries and 106 times more in the high-income countries than that for the standardized DS-TB regimen. This has enormous cost implications for the health systems in countries with a high burden of drug-resistant TB. For example, the Republic of Moldova (total population of 2.6 million as of 2020) reported 413 patients with MDR/RR-TB in 2020, corresponding to 64% of all patients with incident MDR/RR-TB notified of the whole European Union/European Economic Area (649 patients in 30 countries; total population of 453 million as of 2020) [3].

Of note, high regimen costs in Europe are related to the high prices of the anti-TB drugs in general but are impacted in particular by the enormous cost of the new drugs, bedaquiline and delamanid [10]. The most likely reason for the lower price of bedaquiline and delamanid is procurement through mechanisms such as the Global Drug Facility, which supplies drugs after negotiations with the manufacturer and donor support with discounts [31].

We acknowledge several limitations of this study. First, data on drug availability, drug cost, and DST were available from 43, 41, and 40 of the 53 countries in the WHO European region, respectively. Central Asian countries and small-city countries were not included in this survey. Second, data were derived from the centres for MDR/RR-TB in the countries with the capacity to report representative data. Although none of the participating centres reported variations in the costs of medicines at different centres in their countries, this possibility cannot be excluded. Third, we did not analyse the role of possible stock outs in drug availability. Fourth, the choice of regimens for cost calculations followed the recommendations of WHO [7] and American Thoracic Society/Centers for Disease Control/European Respiratory Society/Infectious Diseases Society of America [17], whereas other regimen compositions could also be possible. Fifth, paediatric TB regimens are not addressed. Finally, the implementation of novel diagnostics capacities and availability of new treatment regimens may have been delayed in some countries of the region because of the coronavirus disease 2019 pandemic.

Despite these limitations, the study provides important first-hand insight into the access to DST, drugs, and related drugs as well as regimen costs and will be informative to health policy makers in the context of the END-TB strategy in Europe [2]. It is important to highlight that we analysed costs of medicines and that indirect costs have to be added to the costs of the treatment of TB as well.

In conclusion, the data provided in this study call for urgent action. The availability of novel and essential drugs and treatment regimens for patients affected by MDR/RR-TB is substantially limited in Europe. Even more limited is the DST capacity for the second-line drugs, leading to uncontrolled use of new/repurposed drugs and the risk of amplifying *M. tuberculosis* drug resistance. Strong political support and coordinated action from supranational institutions, countries and their TB programmes, nongovernmental organizations, and civil society are needed to ensure access to the best standard of care for patients with TB.

Author contributions

LG, GG, CLa, and FvL designed the study; contributors of the Tuberculosis Network European Trials study group provided data; GG and CLe collected data; FvL and GG performed the analysis; GG, CLa, CLe, LG, and FvL drafted the manuscript; and all authors reviewed and agreed on the final version for submission.

Transparency declaration

CLa provided consultation service to INSMED and received speaker's honoraria from INSMED, GILEAD, and JANSSEN, outside of the scope of this work. The other authors declare that they have no conflicts of interest. CLa is supported by the German Center for Infection Research (DZIF). All other authors have no funding source in the context of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.07.026.

Appendix

Members of the Tuberculosis Network European Trials study group are as follows: Hasan Hafizi[1], Naira Khachatryan[2], Harut Aroyan[2], Eduard Kabasakalyan[3], Michael Knappik[4], Alena Skrahina[5], Dzmitry Klimuk[5], Alena Nikolenka[5], Inge Muylle[6], Vladimir Milanov[7], Desislava Velkovska[8], Neli Tarinska[8], Elizabeta Bachiyska[9], Mateja Jankovic[10], Despo Pieridou[11], Tonia Adamide[12], Nicos Nicolaou[13], Martina Vasakova[14], Mariia Sukholytka[14], Emilia Kopeckà[14], Åse Bengård Andersen[15], Dorte Bek Folkvardsen[16], Erik Svensson[16], Manfred Danilovits[17], Tiina Kummik[18], Tuula Vasankari[19,20], Mathilde Fréchet-Jachym[21], Audrey Nahmiash[21], Tamar Togonidze[22], Zaza Avaliani[22], Inga Kinkladze[22], Rusudan Aspindzelashvili[22], Teona Bichashvili[22], Gulnazi Losaberidze[22], Tsitsino Merabishvili[22], Barbara Kalsdorf[23,24,25,26], Katerina Manika[27], Karyofyllis Tsiakitzis[28], Agnes Bakos[29], Tinna Rán Ægisdóttir[30], Guðrún Svanhvít Michelsen[30], Kristín Karlsdóttir[30], Anne-Marie McLaughlin[31], Margaret Fitzgibbon[32], Daniel Chemtob[33], Luigi R. Codecasa[34], Maurizio Ferrarese[34], Stefania Torri[34], Majlinda Gjocaj[35], Liga Kuksa[36,37], Edita Davidaviciene[38], Gil Wirtz[39], Monique Perrin[40], Analita Pace Asciak[41], Dumitri Chesov[23,42], Wiel de Lange[43,44], Onno Akkerman[43,44], Biljana Ilievska Poposka[45], Ulrich Mack[46], Mogens Jensenius[47], Lajla Kvalvik[48], Anne Torunn Mengshoel[49], Katarzyna Kruczak[50], Raquel Duarte[51,52,53,54], Nadine Ribeiro[55], Elmira Ibraim[56], Anna Kaluzhenina[57], Olga Barkanova[57], Dragica Pesut[58,59], Ivan Solovic[60], Petra Svetina[61,62], Maria-Luiza de Souza-Galvão[63], Joan-Pau Millet[64,65,66], Xavi Casas[64], Montserrat Vives[64], Judith Bruchfeld[67,68], Paulina Dalemo[68], Jerker Jonsson[69], Katrin Aeschbacher[70], Peter Keller[71], Seref Özkara[72], Simon Tiberi[73,74], Christabelle Chen[75], Yana Terleeva[76] and Andrii Dudnyk.[77]

[1] Internal Medicine, University Hospital “Sh. Ndroqi”, Tirana, Albania.

[2] National Tuberculosis Control Program, Ministry of Health, Yerevan, Armenia.

[3] National TB Reference Laboratory, National Center of Pulmonology, Abovyan, Armenia.

[4] Klinik Penzing, Vienna, Austria.

[5] RSPC for Pulmonology and TB, Minsk, Belarus.

[6] Department of Respiratory Medicine, University Medical Center St Pieter, Brussels, Belgium.

[7] Department of Pulmonary Diseases, Medical Faculty, Medical University of Sofia, University Hospital of Respiratory Diseases “St. Sofia”, Sofia, Bulgaria.

[8] Ministry of Health, Sofia, Bulgaria.
[9] National Reference Laboratory of Tuberculosis, National Center of Infectious and Parasitic Diseases, Sofia, Bulgaria.
[10] Clinic for Respiratory Diseases, University Hospital Center Zagreb, Zagreb, Croatia.
[11] National Reference Laboratory for Mycobacteria, Microbiology Department, Nicosia General Hospital, Nicosia, Cyprus.
[12] Pulmonary Clinic, Nicosia General Hospital, Nicosia, Cyprus.
[13] Pharmacy Department, Nicosia General Hospital, Nicosia, Cyprus.
[14] Department of Pneumology, First Faculty of Medicine, Charles University and Thomayer University Hospital, Prague, Czech Republic.
[15] Department of Infectious Diseases, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark.
[16] Statens Serum Institut, International Reference Laboratory of Mycobacteriology, Copenhagen, Denmark.
[17] Tartu University Hospital, Lung Clinic, Department of Tuberculosis, Tartu, Estonia.
[18] Department of Mycobacteriology, University Hospital of Tartu, Tartu, Estonia.
[19] Department of Pulmonary Diseases and Clinical Allergology, University of Turku, Turku, Finland.
[20] Finnish Lung Health Association (FILHA), Helsinki, Finland.
[21] Centre Hospitalier de Bligny, Briis-sous-Forges, France.
[22] National Center for Tuberculosis and Lung Diseases, Tbilisi, Georgia.
[23] Research Center Borstel, Clinical Infectious Diseases, Borstel, Germany.
[24] German Center for Infection Research (DZIF) Tuberculosis Unit, Borstel, Germany.
[25] International Health/Infectious Diseases, University of Lübeck, Lübeck, Germany.
[26] Cluster Precision Medicine in Inflammation, University of Kiel, Kiel, Germany.
[27] Pulmonary Department, Aristotle University of Thessaloniki, "G. Papanikolaou" Hospital, Thessaloniki, Greece.
[28] Department of Hospital Pharmacy, "G. Papanikolaou" Hospital, Thessaloniki, Greece.
[29] National TB Surveillance, Koranyi National Institute for Pulmonology, Budapest, Hungary.
[30] Pharmaceutical Services, Landspitali University Hospital, Reykjavik, Iceland.
[31] Respiratory Medicine Service, St James's Hospital, Dublin, Ireland.
[32] Irish Mycobacterial Reference Laboratory, Dublin, Ireland.
[33] Department of TB and AIDS, Ministry of Health, Jerusalem, Israel.
[34] Regional TB Reference Centre and Laboratory, Villa Marelli Institute/Niguarda Hospital, Milano, Italy.
[35] National TB Program, Ministry of Health, Pristina, Kosovo.
[36] Tuberculosis and Lung Disease Clinic, Riga East University hospital, Riga, Latvia.
[37] Riga Stradinš University, Riga, Latvia.
[38] Vilnius University Hospital, Santaros Klinikos, Vilnius, Lithuania.
[39] Centre Hospitalier du Luxembourg, City of Luxembourg, Luxembourg.
[40] Laboratoire national de santé, Microbiology Department, Dudelange, Luxembourg.
[41] Infectious Disease Prevention and Control Unit, Ministry of Health, Valetta, Malta.
[42] Department of Pneumology and Allergology, State University of Medicine and Pharmacy "Nicolae Testemitanu", Chişinău, Republic of Moldova.
[43] University of Groningen, University Medical Center Groningen, TB Center Beatrixoord, Groningen, The Netherlands.
[44] University of Groningen, University Medical Center Groningen, Department of Pulmonary diseases and Tuberculosis, Groningen, The Netherlands.
[45] Focal point for Tuberculosis for Republic of North Macedonia, Institute for Lung Diseases and Tuberculosis, Skopje, Republic of North Macedonia.
[46] Lovisenberg Diakonale Sykehus, Oslo, Norway.
[47] Department of Infectious Diseases, Oslo University Hospital, Oslo, Norway.
[48] Hospital Pharmacy, Oslo University Hospital, Oslo, Norway.
[49] National Reference Laboratory (NRL) for Mycobacteria, Department of Bacteriology, Norwegian Institute of Public Health, Oslo, Norway.
[50] University Hospital, Krakow, Poland.
[51] ICBAS. Instituto de Ciencias Biomédicas Abel Salazar. Universidade do Porto, Porto, Portugal.
[52] ISPUP. Instituto de Saúde Pública da Universidade do Porto, Porto, Portugal.
[53] Serviço de Pneumologia. CHVNG/E. Centro Hospitalar de Vila Nova de Gaia/Espinho
[54] Unidade de Investigação Clínica. ARS Norte.
[55] ARS Lisboa, Lisboa, Portugal.
[56] Marius Nasta Institute of Pulmonology, Bucharest, Romania.
[57] Tuberculosis Department, Volgograd State Medical University, Volgograd, Russia.
[58] Faculty of Medicine, University of Belgrade.
[59] University Clinical Center of Serbia, Teaching Hospital of Pulmonology, Belgrade, Serbia.
[60] National Institute for TB, Lung Diseases and Thoracic Surgery, Vysne Hagy, Slovakia.
[61] University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia.
[62] National TB Program and TB Registry, Slovenia.
[63] Servei de Pneumologia, Hospital Universitari Vall d'Hebron, Barcelona, Spain.
[64] Serveis Clínics, Barcelona, Spain.
[65] Servei d'Epidemiologia, Agència de Salut Pública de Barcelona, Barcelona, Spain.
[66] CIBER de Epidemiologia y Salud Pública (CIBERESP), Madrid, Spain.
[67] Division of Infectious Diseases, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden.
[68] Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden.
[69] Departement of public health analysis and data monitoring, The Public Health Agency of Sweden, Stockholm, Sweden.
[70] Hospital Pharamcy, Inselspital, Bern University Hospital, Bern, Switzerland.
[71] Department of Infectious Diseases, Inselspital, Bern University Hospital, University of Bern, Switzerland.
[72] Atatürk Sanatorium Education and Research Hospital, Ankara, Turkey.
[73] Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom.
[74] Department of Infection, Royal London Hospital, Barts Health NHS Trust, London, United Kingdom.
[75] Pharmacy Department, Barts Health NHS Trust, London, United Kingdom.
[76] TB Management and Counteraction Department, Public Health Center of the Ministry of Health of Ukraine, Kyiv, Ukraine.
[77] Department of Tuberculosis, Clinical Immunology & Allergy, National Pirogov Memorial Medical University, Vinnytsia, Ukraine.

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