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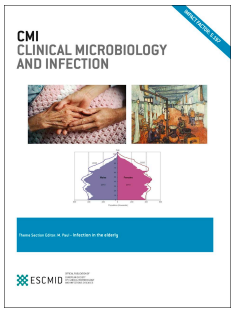

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Availability and costs of medicines for the treatment of tuberculosis in Europe

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Abstract

Objectives: To evaluate the access to comprehensive diagnostics and novel anti-tuberculosis medicines in European countries.

Methods: We investigated access to genotypic and phenotypic *M. tuberculosis* drug susceptibility testing, availability of anti-tuberculosis drugs and calculated cost of drugs and treatment regimens at major tuberculosis treatment centers in countries of the World Health Organization (WHO) European region where rates of drug-resistant tuberculosis are highest among all WHO regions. Results are stratified by middle-income and high-income countries.

Results: Overall, 43 treatment centers in 43 countries participated in the study.
For WHO Group A drugs, the frequency of countries with availability of phenotypic drug susceptibility testing was as follows: 30/40 (75%) for levofloxacin, 33/40 (82%) for moxifloxacin, 19/40 (48%) for bedaquiline and 29/40 (72%) for linezolid, respectively. Overall, 36/43 (84%) and 24/43 (56%) of countries had access to bedaquiline and delamanid, while only 6/43 (14%) had access to rifapentine. Treatment of patients with extensively drug-resistant tuberculosis with a regimen including a carbapenem was only available in 17/43 (40%) of the countries. Median cost of regimens for drug-susceptible tuberculosis, multidrug-resistant/rifampicin-resistant tuberculosis (shorter regimen, including bedaquiline for six months) and extensively drug-resistant tuberculosis (including bedaquiline, delamanid and a carbapenem) were € 44 (min-max € 15-152), € 764 (min-max € 542-15152) and € 8709 (min-max € 7965-11759) in middle-income countries (n=12), and € 280 (min-max-€78-1084), €

29765 (min-max 11116-40584), € 217591 (min-max € 82827-320146) in high-income countries (n=29).

Conclusion: In countries of the WHO Europe Region there is a widespread lack of drug susceptibility testing capacity to new and re-purposed anti-tuberculosis drugs, lack of access to essential medications in several countries and high treatment cost for drug-resistant tuberculosis.

Introduction

Tuberculosis is the leading cause of death by a bacterial pathogen world-wide. In 2020, 9.9 million people developed tuberculosis and 1.5 million tuberculosis patients 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 World Health Organization (WHO)[2]. Among all regions of the WHO, the proportion of patients with drug-resistant tuberculosis is highest in the European Region[1]. In 2020 there were 34 778 patients affected by multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) including 11 072 patients affected by pre-extensively drug-resistant tuberculosis (pre-XDR TB) and extensively drug-resistant tuberculosis (XDR-TB) in the WHO European region[3]. According to the WHO, the proportion of tuberculosis patients 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-tuberculosis medicines have brought substantial change to the management of patients affected by drug-resistant tuberculosis [4]. Molecular drug-susceptibility testing (DST) based on nucleic acid amplification technologies entered clinical routine in many countries [5, 6]. New anti-tuberculosis drugs (i.e. bedaquiline, delamanid and pretomanid) were approved for drug-resistant tuberculosis treatment along with fundamental changes in treatment guidelines and regimens [7]. Such innovations can improve tuberculosis control if they are accessible for patients and programs. Improving access by ensuring affordable pricing of drugs is crucial for all new anti-tuberculosis drugs, and a major topic of political debate and advocacy [8].

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

The Tuberculosis Network European Trialsgroup (TBNET), an European-based network promoting TB research and training first evaluated the availability and cost of anti-tuberculosis drugs and regimens among 37 European countries in 2013 [12], at a time when bedaquiline, delamanid and pretomanid were not yet available. In order to provide an updated account on the availability of anti-tuberculosis DST and the costs and availability of anti-tuberculosis drugs and regimen, we performed 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 tuberculosis drug availability, cost, and availability of DST for all anti-tuberculosis drugs were surveyed administering a standardized questionnaire to TBNET representatives with experience in the management of drug-resistant tuberculosis 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 tuberculosis and approached respective authors from target countries. Data collection for drug availability, cost and DST availability was performed from June 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 tuberculosis medicines incurred to hospitals or other treatment providers when purchasing medicines through pharmacies or purchasing costs for 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 combinations (FDC) were included in the calculation of the regimen cost and the least-expensive regimen option was reported. Daily treatment cost for drugs given on a non-daily basis, like bedaquiline, were based on weekly cost divided by seven. Cost data were collected in local currency or US dollars (USD), using the exchange rate on 01.07.2020 for conversions. Costs are reported in Euro (€) when there is no direct between-country comparison. For direct between-country comparisons, drug cost were converted in international dollars (ID$) using the purchasing power parity conversion factor from the international comparison program 2017 [14]. Stratification according to income followed the World Bank classification, where upper and lower middle-income countries are combined as middle-income countries (**figure 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 tuberculosis (DS-TB), MDR/RR-TB, pre-XDR TB, and XDR-TB based on latest guidelines from WHO [7, 16], and American Thoracic Society/Centers for Disease Control/European Respiratory Society/Infectious Diseases Society of America (ATS/CDC/ERS/IDSA) [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 WHO 2020 definitions [18]. We hereby present results for eight priority regimens (**tables 1, S4**). Results for additional regimens are available in the supplement (**tables S3, S4**). We neither present cost for a standardized regimen containing bedaquiline, linezolid and pretomanid (BPaL) [19], nor the regimen with rifapentine, moxifloxacin, isoniazid and pyrazinamide, as cost data on pretomanid were only available in three high-income countries and data for 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 (January 15th, 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, data on drug cost from 41, 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. DST data were not available from Malta, Kosovo and Iceland.

Availability of DST

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

Availability of tuberculosis 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. Levofloxacin and

moxifloxacin were available in 43/43 (100%) and 41/43 (95%), bedaquiline in 36/43 (84%) and linezolid in 43/43 (100%) countries, respectively. Clofazimine was available in 35/43 (81%) countries, but only in 8/12 (67%) middle-income countries. Delamanid was available in 24/43 (56%) countries. Meropenem and imipenem were available in 28/43 (65%) and 25/43 (58%) countries. Pretomanid was available only in 4/43 (9%) countries (Germany, Ireland, Sweden, Switzerland), all high-income countries. Only 6/43 (14%) countries reported access to rifapentine (**table S1)**.

Cost of tuberculosis drugs

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

Availability of tuberculosis treatment regimens

Treatment of DS-TB according to current WHO guidelines was available in all 43 (100%) countries (**table 1**). The shorter MDR/RR-TB regimen with bedaquiline was available in 26/43 (60%) countries, while the conventional long MDR/RR-TB regimen was available in 31/43 (72%) countries. A pre-XDR TB treatment, with amikacin or delamanid replacing the fluoroquinolones, was available in 28/43 (65%) and 20/43 (47%) countries, respectively.

Treatment of patients with XDR-TB with a regimen including a carbapenem was only available in 17/43 (40%) countries (**tables 1, S3**).

Cost of tuberculosis treatment regimens

Figure 3 shows regimen cost by degree of resistance. Costs of regimens increase substantially with increasing level of antimicrobial drug resistance. Regimens are considerably less expensive in middle-income countries (Figure 3A) than in high-income countries (Figure 3B). **Figure 4** show the overall distribution of regimen costs, based on Euro. **Figure S2-S5 i**llustrate the direct comparison of the cost of treatment regimens between countries, considering purchasing power parity based in ID$. The median cost of a DS-TB regimen was €44 in middle-income countries and €280 in high-income countries. The median cost of the shorter MDR/RR-TB regimen with bedaquiline for 6 months was €764 in middle-income countries and €29 765 in high-income countries, while the conventional long MDR/RR-TB treatment regimen with bedaquiline for 6 months costed €2214 and €51617, respectively (**tables 1, S3 and S4**). A pre-XDR TB treatment regimen using delamanid or amikacin costed €7094 or €2250 in middle-income countries, respectively, and €207034 or €108459 in 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 middle-income countries and €217591 in high-income countries.

Discussion

We provide a report on the availability of anti-tuberculosis DST, and following a survey in 2013, an updated report on the availability and costs of anti-tuberculosis drugs in the WHO European region. The main finding of this survey is that availability of DST for second-line anti-

tuberculosis drugs, in particular new and re-purposed drugs, is severely limited in Europe and that new drugs are more frequently available than their specific DST**.** Cost of drugs and regimens for drug-resistant tuberculosis treatment are very high compared to 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 drugs included in new promising regimens for drug-susceptible and drug-resistant tuberculosis, such as rifapentine and pretomanid.

A revision of international guidelines for the management of drug-resistant tuberculosis suggest the use of treatment regimens of at least four effective drugs, ideally based on DST results [21]. When 2nd-line tuberculosis 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 re-purposed 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 carry the worst prognosis [25]. Standardized treatment regimens in the absence of DST testing are likely a major driver of emerging antimicrobial drug resistance in *M. tuberculosis* [26, 27].

All sites in the survey reported availability of treatment for DS-TB. However, with an increasing level of antimicrobial drug resistance, the availability of suitable regimens declined. Middle-income countries have generally less resistance-appropriate treatment options than high-

income countries. Access to relevant therapies is fairly unchanged since the introduction of new drugs and regimens compared to 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 DS-TB treatment when used in combination with moxifloxacin, isoniazid and pyrazinamide as part of a four-month regimen [20], which was already endorsed by WHO [28]. In addition, rifapentine is also recommended for tuberculosis prevention in the one month daily rifapentine/isoniazid (1HP) and three months weekly rifapentine/isoniazid (3HP) regimen [29]. Of concern, our results show that rifapentine is only available in two middle-income countries and four high-income countries in 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 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 the shorter regimen (including 6 months bedaquiline) costs approximately 18 times more in middle-income countries and 106 times more in high-income countries than the standardized DS-TB regimen. This has enormous cost implications for health systems in countries with high burden of drug-resistant tuberculosis. For example, the Republic of Moldova (total population of 2.6 million 2020) reported 413 patients with MDR/RR-TB in 2020, corresponding to 64% of all incident MDR/RR-TB patients notified of the whole European Union/European Economic Area (649 patients in 30 countries/ total population of 453 million 2020 [3].

Of note, high regimen costs in Europe are related to the high prices of tuberculosis 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 lower price for bedaquiline and delamanid is

282 procurement through mechanisms like the Global Drug Facility, which supply drugs after
283 negotiations with the manufacturer and donor support with discounts [31].
284
285 We acknowledge several limitations of this study. First, data on drug availability, data on drug
286 cost and data on DST were available from 43, 41 and 40 of the 53 countries in the WHO
287 European region, respectively. Central Asian countries and small city countries were not
288 included in this survey. Second, data were derived from centers for MDR/RR-TB in the
289 countries with the capacity to report representative data. Although none of the participating
290 centers reported variations in the costs of medicines at different centers in their countries,
291 this possibility cannot be excluded. Third, we did not analyse the role of possible stock outs
292 on drug availability. Fourth, the choice of regimens for cost calculations followed the
293 recommendations of WHO [7] and ATS/CDC/IDSA/ERS [17], whereas other regimen
294 compositions could also be possible. Fifth, pediatric tuberculosis regimens are not addressed.
295 Finally, implementation of novel diagnostics capacities and availability of new treatment
296 regimen may have been delayed in some countries of the region as a result of the COVID-19
297 pandemic.
298
299 Despite these limitations, the study provides important first-hand insight about the access to
300 DST, drugs and related drug and regimen costs and will be informative to health policy makers
301 in the context of the END-TB strategy in Europe [2]. It is important to highlight that we
302 analysed costs of medicines and that indirect costs have to be added to the costs of the
303 treatment of TB as well.
304

In conclusion, data provided from this study call for urgent action. 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 second-line drugs, leading to uncontrolled use of new/re-purposed drugs and the risk of amplifying *M tuberculosis* drug-resistance. Strong political support and coordinated action from supranational institutions, countries and their TB programmes, non-governmental organizations and civil society is needed to ensure access to the best standard of care to patients affected by TB.

Transparency declaration

Conflict of interest: CLa provided consultation service to INSMED and received speakers honoraria from INSMED, GILEAD and JANSSEN outside of the scope of this work. All other authors declare that they do not have any conflict of interest

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Contribution*:* LG, GG, CLa and FvL designed the study, contributors of the TBNET provided data, GG and CLe collected data, FvL and GG did the analysis, GG, CLa, CLe, LG and FvL drafted the manuscript and all authors reviewed and agreed on the final version for submission.

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Figures

Figure 1: Availability of phenotypic and genotypic drug susceptibility testing to tuberculosis drugs in countries in the WHO European region[a], in percent.

[a]n=40 countries; Kosovo, Iceland and Israel did not provide data on availability of drug susceptibility testing

Figure 2: Proportion of countries with 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, p-aminosalicylic acid (PAS) = 28, imipenem (IMP) = 23 and meropenem (MPM) = 27, respectively. WHO Group A medicines are displayed in dark blue, Group B medicines in medium blue and Group C medicines in light blue.

Figure 3: Boxplot 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]

[a] n=41 countries, Malta and Israel (both high-income) did not provide data on drug cost. Upper whisker: 75th percentile + 1.5*IQR (or upper value if smaller), lower whisker: 25th precentile - 1.5*IQR (or smallest value if larger), dots are values exceeding (lower or higher) the whiskers. MDR/RR-TB – multidrug-resistant/rifampicin-resistant tuberculosis, pre-XDR TB – pre-extensively drug-resistant tuberculosis, XDR-TB – extensively drug-resistant tuberculosis

Figure 4: Density graph of distribution[a] of cost for tuberculosis drug regimens in the WHO Europe region, according to resistance status and World Bank income classification[b] (high-income countries in red, middle-income countries in green), in Euros.

[a]The density graph illustrates the distribution of the cost within a given resistance pattern. The area under the curve is scaled to one (1). 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) did not provide data on drug cost

HIC – high-income countries, MIC – middle-income countries, DS-TB - drug susceptible TB, MDR/RR-TB – multidrug-resistant/rifampicin-resistant tuberculosis, pre-XDR TB – pre-extensively drug-resistant tuberculosis, XDR-TB – extensively drug-resistant tuberculosis, Bdq - bedaquiline, Fq - fluoroquinolones, Lzd - linezolid, Dlm – delamanid, Am – amikacin.

Online supplement figures:

Figure S1: Countries represented in the survey (high-income countries: *Austria, Belgium, Croatia, Czech Republic, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Hungary,* Iceland*, Ireland,* Israel, *Italy, Latvia, Lithuania, Luxemburg, Netherlands*, Norway*, Spain, Poland, Portugal, Romania Slovakia, Slovenia, Sweden,* Switzerland, United Kingdom; upper middle-income income countries: Albania, Armenia, Belarus, *Bulgaria*, Georgia, Kosovo, North Macedonia, Russia, Serbia, Turkey, lower middle-income income: Republic of Moldova, Ukraine. In italic: member states of the European Union.)

574 **Figure S2:** Cost of regimen for drug-susceptible tuberculosis with a standard HRZE regimen
575 according to WHO guidelines. Stratified by country and income classification of World Bank[a,b],
576 in international dollars (ID$).
577 [a]Number of countries in the graph do not necessarily correspond to availability data in table
578 1, as in some cases drug prices were reported as unavailable despite confirmed availability of
579 the drug; [b] detailed regimen composition in table S1.
580
581
582 **Figure S3:** Cost of regimens for multidrug-resistant/rifampicin-resistant tuberculosis using the
583 shorter regimen for nine months with six months of bedaquiline according to WHO guidelines.
584 Stratified by country and income classification of World Bank[a,b], in international dollars (ID$).
585 [a]Number of countries in the graph do not necessarily correspond to availability data in Table
586 1, as in some cases drug prices were reported as unavailable despite confirmed availability of
587 the drug; [b] detailed regimen composition in table S1; MDR/RR - multidrug-resistant/rifampicin-
588 resistant tuberculosis, Bdq - bedaquiline
589
590
591 **Figure S4:** Cost of regimens for multidrug-resistant/rifampicin-resistant tuberculosis using the
592 long conventional regimen with six months of bedaquiline, stratified by country and income
593 classification of World Bank[a,b], in international dollars (ID$).
594 [a]Number of countries in the graph does not necessarily correspond to availability data in Table
595 1, as in some cases drug prices were reported as unavailable despite confirmed availability of
596 the drug; [b] detailed regimen composition in table S1; MDR/RR - multidrug-resistant/rifampicin-
597 resistant tuberculosis, Bdq – bedaquiline.

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600 **Figure S5:** Cost of regimen for extensively drug-resistant tuberculosis with resistance to
601 fluoroquinolones, linezolid, and bedaquiline, stratified by country and income classification of
602 World Bank[a,b], in international dollars (ID$).
603 [a]Number of countries in the graph do not necessarily correspond to availability data in Table
604 1, as in some cases drug prices were reported as unavailable despite confirmed availability of
605 the drug; [b]detailed regimen composition in table S1; XDR - extensively drug-resistant
606 tuberculosis, Fq – fluoroquinolones, Bdq - bedaquiline, Lzd – linezolid.

607

608 **Tables**

609

610 **Table 1:** Availability and cost of drug regimens for the treatment of tuberculosis in countries

611 in the WHO Europe region, stratified by World Bank income classification[a], in Euros.

612

	Middle-income country				High-income country			
Regimen[b]	**Availability**	**Cost**			**Availability**	**Cost**		
	N (%)	median	min	max	N (%)	median	min	max
DS -TB	12 (100)	44	15	152	31 (100)	280	78	1 084
MDR/RR-TB short, Bdq 6 months[c]	6 (50.0)	764	542	15 152	20 (64.5)	29 765	11 116	40 584
MDR/RR-TB long, Bdq 18 months[c]	7 (58.3)	2 954	1591	42477	24(77.4)	97 808	34 142	216 595
pre-XDR TB, using Dlm	5 (42.7)	7 094	6 755	10 916	15 (48.4)	207 034	63 987	313 566
pre-XDR TB, using Am	4 (33.3)	2 250	2 007	3 298	24 (77.4)	108 459	37 412	249 560
XDR-TB, resistant Fq, Bdq, using a carbapenem[d]	4 (33.3)	7 945	6 981	11 221	13 (41.9)	141 307	40 237	255 550
XDR-TB, resistant Fq, Lzd, using a carbapenem[d]	4 (33.3)	8 709	7 965	11 759	12(38.7)	217 591	82 827	320 146
XDR-TB, resistant Fq, Bdq, Lzd, using a carbapenem[d]	4 (33.3)	8 348	6 949	11 528	10(32.3)	147 959	118 825	271 343

613

[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); [b]detailed regimen composition is depicted in table S1; [c]refers to the length of bedaquiline treatment; [d]refers to use of cheapest available carbapenem (meropenem or imipenem); DS-TB – drug-susceptible tuberculosis, MDR/RR-TB – multidrug-resistant/rifampicin-resistant tuberculosis, pre-XDR TB - pre-extensively drug-resistant tuberculosis, XDR-TB - extensively drug-resistant tuberculosis, Bdq - bedaquiline, Dlm - delamanid, Fq - fluorquinolone, Am - amikacin, Lzd - linezolid.

Online supplement tables:

Table S1: Regimen composition and treatment duration (months) by drug according to drug resistance (dosing for a patient with 70 kg body weight).

Table S2 Availability and cost of additional regimens for MDR/RR- TB and XDR- TB treatment in countries the WHO Europe region, stratified by World Bank income classification[a], in Euro.

638 **Table S3:** Availability and cost of regimen for susceptible TB, MDR/RR- TB, pre-XDR TB and
639 XDR- TB in countries in the WHO Europe region, stratified by World Bank income
640 classification[a], in ID$.

641

642 **Table S4:** Cost of individual TB drugs per treatment day for a model patient with 70kg body
643 weight, in countries in the WHO Europe region[a,b], in Euro.

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