Early View

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Program costs of longer and shorter tuberculosis drug regimens and drug import: A modelling study for Karakalpakstan, Uzbekistan

Running head: Program costs of longer and shorter TB drug regimens

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Take home message: The introduction of new TB drug regimens can increase or decrease TB program expenses for drug purchase and import. Modelling program costs of different TB drug regimens can inform financial planning and help prepare TB programs for changes in TB treatment.

Program costs of longer and shorter tuberculosis drug regimens and drug import: A modelling study for Karakalpakstan, Uzbekistan

Abstract

Background: The introduction of new and often shorter tuberculosis (TB) drug regimens affects the cost of TB programs.

Methods: We modelled drug purchase and import costs for 20-months, 9-months, and 4–6-months TB drug regimens based on 2016–20 treatment numbers from a TB program in Karakalpakstan, Uzbekistan, and 2021 Global Drug Facility prices.

Results: On average, 2,225 (SD 374) people per year started TB treatment, of which 30% (SD 2.1) were diagnosed with drug-resistant forms of TB. Transitioning from a 6-months to a 4-months drug-susceptible (DS)-TB drug regimen increased the TB program's annual DS-TB drug cost from \$65 K (SD 10) to \$363 K (SD 57; $P < 0.001$) and its drug import cost from \$6.2 K (SD 1.0) to 10 K (SD 1.6; $P = 0.002$). Transitioning from a 20-months all-oral multidrug-resistant (MDR)-TB drug regimen to a 9-months MDR-TB drug regimen with an injectable antibiotic decreased the TB program's annual MDR-TB drug cost from \$1.9 M (SD 0.38) to \$325 K (SD 64; $P < 0.001$) and had no significant effect on drug the import cost (\$28 K [SD 5.6] versus \$27 K [SD 5.4]; $P = 0.82$). Purchasing (\$658 K [SD 130]) and importing (\$2,5 K [SD 0.49]) the 6-months all-oral MDR-TB drug regimen cost more than procuring the 9-months MDR-TB drug regimen but less than the 20-months all-oral MDR-TB drug regimen (both $P \leq 0.003$).

Conclusion: Introducing new and shorter TB drug regimens could increase the cost of TB programs with low drug resistance rates and decrease the cost of TB programs with high drug resistance rates.

Keywords: drug innovation; drug procurement; program expenses; shipping costs; tuberculosis control; former Soviet Union countries

1 Introduction

With 1.2 million fatalities in 2019, tuberculosis (TB) is among the top ten causes of death worldwide [1]. The standard treatment of drug-susceptible (DS)-TB requires taking the four first-line TB drugs rifampicin, isoniazid, pyrazinamide, and ethambutol for an intensive treatment phase of two months, followed by taking rifampicin and isoniazid for a continuation phase of four months [2]. Multidrug-resistant (MDR)-TB, which is resistant to rifampicin and isoniazid, used to require taking up to seven antibiotics per day for up to two years. The conventional MDR-TB treatment also included the use of an injectable antibiotic and is no longer recommended by the World Health Organization (WHO) [3]. Newer and often shorter treatment regimens with new or repurposed TB drugs have been evaluated and entered clinical practice. For DS-TB, the WHO endorsed a 4-months drug regimen in June 2021 as an alternative to the standard 6-months treatment [4]. For MDR-TB, the WHO currently recommends the use of an all-oral, 20-months MDR-TB drug regimen [5]. The use of all-oral 6–11-months regimens is conditionally recommended [5], and all-oral MDR-TB drug regimens of 26 weeks and shorter have been and are being evaluated in clinical trials (e.g., Nix TB trial, Next Study, ZeNix TB trial, a BPamZ regimen trial, TB PRACTECAL trial, or endTB-Q trial [6–11]).

TB drug regimen choices affect treatment effectiveness, treatment tolerability, quality of life on treatment, and expenses for TB drugs. The program cost for TB drugs includes expenses for drug purchase—many times from the Global Drug Facility that supplies drugs to TB programs worldwide [12, 13]—and often import costs for international drug procurement. The purchase of TB drugs is a major contributor to TB treatment costs. In studies of TB programs in Peru, Estonia, Russia, and the Philippines, TB drugs contributed 35%, 19%, 26%, and 46%, respectively, to the costs of a conventional MDR-TB treatment course [14–16]. In another study of a TB program in Nigeria, drugs contributed 6.5–12.6% to the costs of a conventional MDR-TB treatment course, 8.8–15.6% to the costs of a 9–12-months MDR-TB treatment course with an injectable agent, and 25.8% to the costs of an 9–12-months all-oral MDR-TB treatment course [17]. For 6-months DS-TB treatment, a systematic review found that the purchase of TB drugs can contribute 14.2% to the TB treatment costs in lower-middle-income countries and 19% in low-income countries [18].

Previous studies have estimated and compared the costs of purchasing and importing DS-TB and MDR-TB drug regimens [19, 20]. These studies found substantial cost differences between TB drug regimens. To our knowledge, the study at hand is the first to assess the impact of the adaption of new DS-TB and MDR-TB drug regimens on the total drug procurement cost of a TB program. Specifically, we modelled the costs of TB drug purchase and import for longer and new, shorter TB drug regimens for a TB program in Karakalpakstan, Uzbekistan. As our model includes drug purchase and import costs, we

also assessed the impact of a transport cost increase, as observed, for instance, during the COVID-19 pandemic, on the program cost for drug procurement.

2 Methods

2.1 Study setting

Uzbekistan is listed by the WHO as one of 30 high MDR-TB burden countries [1]. In Karakalpakstan, a republic in Uzbekistan's northwest with a population of 1.8 million [21], the TB prevalence [22] and MDR-TB rate among newly diagnosed TB cases [23] were about twice Uzbekistan's national average in 2013 and 2010/11, respectively. Médecins Sans Frontières (MSF) has been supporting TB control in Karakalpakstan since 1998 [21]. In addition to standard 6-months DS-TB treatment, longer and shorter MDR-TB drug regimens are used and evaluated in the TB program [10, 24]. The new 4-months DS-TB drug regimen [4] was not offered in 2021. TB drugs and other medical supplies for the program are regularly imported from an MSF procurement unit in the Netherlands to the TB program in Karakalpakstan as humanitarian goods using air and land transport [25].

2.2 Study design

We modelled the costs of procuring, that is, purchasing and importing, TB drugs from the perspective of the TB program in Karakalpakstan. Modelling was based on, first, our previous estimation of drug regimen costs and drug import costs to the TB program and [20, 25], second, the number of people who started treatment for DS-TB or drug-resistant TB in Karakalpakstan between 2016 and 2020 ([26] and **supplementary Table S1**). We compared the drug procurement costs for different model scenarios, in which the TB program provides either longer or shorter DS-TB and MDR-TB drug regimens. Following the terminology used in the 2020 WHO guidelines for treatment of drug-resistant TB [5], we refer to MDR-TB drug regimens of at least 18 months as longer drug regimens and to MDR-TB drug regimens with a duration of less than 12 months as shorter drug regimens. In addition, we refer to TB drug regimens that require six months of treatment or less as short regimens.

2.3 Model scenarios

For DS-TB, we modelled treatment with two short, all-oral DS-TB drug regimens. For drug-resistant TB, we modelled treatment with two longer MDR-TB drug regimens, one shorter, and one short MDR-TB drug regimen. In the DS-TB reference scenario 1, people with DS-TB are treated with a standard 6-months drug regimen with fixed-dose combinations of 2–4 oral antibiotics. In DS-TB scenario 2, people with DS-TB are treated with a new 4-months (17-weeks) regimen, which has been endorsed by the WHO in June 2021 [4]. In the MDR-TB reference scenario 1, people with MDR-TB are treated with a

longer, 20-months all-oral drug regimen. In MDR-TB scenario 2, people with MDR-TB are treated with a shorter, 9-months MDR-TB drug regimen with an injectable antibiotic. In MDR-TB scenario 3, people with MDR-TB are treated with a short, 6-months all-oral drug regimen that has been conditionally recommended by the WHO in June 2020 [5]. In MDR-TB scenario 4, people with MDR-TB are treated with a conventional longer, 20-months MDR-TB drug regimen, which includes an injectable antibiotic and is no longer recommended by the WHO (**Table 1**) [3, 5].

Table 1: Purchase costs and import costs of drug regimens for treatment of drug-susceptible and multidrug-resistant tuberculosis for a TB program in Karakalpakstan, Uzbekistan

TB drug regimen (scenario)	Tablets and injections per regimen	Import weight per regimen (kg)	Drug cost per regimen (\$)	Import cost per regimen (\$)	Import cost (% of regimen cost)
Drug-susceptible TB treatment					
2 HRZE / 4 HR (reference scenario 1)	731	0.8	43	4.05	9.5
2 Rpt-H-Z-Mfx / 2 Rpt-H-Mfx (scenario 2)	1,548	1.3	237	6.74	2.8
Multidrug-resistant TB treatment					
20 Bdq-Lfx-Lzd-Cfz-Cs (reference scenario 1)	6,356	8.1	2,816	42	1.5
4 Km-Mfx-Pto-Cfz-Z-H ^h -E / 5 Z-E-Mfx-Pto-Cfz (scenario 2)	3,926	7.9	482	41	8.4
6 Bdq-Pa-Lzd (scenario 3)	654	0.7	975	3.70	0.4
8 Z-Km-Lfx-PAS-Pto-Cs / 12 Z-Lfx-PAS-Pto-Cs (scenario 4)	10,592	27	2,448	140	5.7

Intensive phase (months) / continuation phase (months) of treatment. HRZE / HR = fixed-dose combination of four / two oral antibiotics. 2 Rpt-H-Z-Mfx = 2 months of single doses of the antibiotics Rpt, H, Z and Mfx. Bdq = bedaquiline 100 mg, Cs = cycloserine 250 mg, Dlm = delamanid 50 mg, E = ethambutol 400 mg, H = isoniazid 300 mg, H^h = high dose isoniazid 600 mg. Km = kanamycin 1000 mg (injectable antibiotic), Lfx = levofloxacin 250 mg, Lzd = linezolid 600 mg, Mfx = moxifloxacin 400 mg, Pa = pretomanid 200 mg, PAS = PAS sodium 4 g, Pto = prothionamide 250 mg, R = rifampicin 300 mg, Rpt = rifapentine 150 mg, Z = pyrazinamide 400 mg. The exact duration of the 2 Rpt-H-Z-Mfx / 2 Rpt-H-Mfx regimen is 8 weeks / 9 weeks. The TB drug regimens included in the model represent the least costly regimens and lowest treatment durations from a larger set of DS-TB and MDR-TB drug regimens described in **supplementary Table S2**. *Data sources:* Kohler et al. [20, 25].

2.4 Model parameters

2.4.1 Number of people treated for TB

Treatment numbers in the model are based on the number of people starting TB treatment in the TB program in Karakalpakstan. As a simplification, we assume that all people with drug-resistant TB receive the same MDR-TB drug regimen. Further, we assume that drug procurement costs to the program occur in the year in which TB treatment is started and that all people with TB receive drug dosing for an adult weighing 60 kg.

The number of people starting TB treatment in the TB program in Karakalpakstan has been steadily declining over the past years, with an expedited decline during the COVID-19 pandemic. In 2016, 2,645 patients received TB treatment as compared to 2,130 and 1,662 in 2019 and 2020, respectively. Between 27% and 33% (mean 30% [SD 2.1]) of people commencing TB treatment between 2016 and 2020 were diagnosed with drug-resistant forms of TB. Treatment numbers by TB type are provided in **supplementary Table S1**.

2.4.2 TB drug regimen procurement costs

The model's drug regimen costs and import costs are based on costing studies which we previously conducted for the TB program in Karakalpakstan [20, 25]. In a prior analysis of TB drug regimen costs [20], we extracted drug quantities required for various longer, shorter, and short drug regimens from TB program guidelines for Karakalpakstan and Uzbekistan, WHO guidelines, and TB trial protocols. To estimate the procurement cost, we multiplied the drug quantities required by a regimen with their respective purchase prices and import costs. TB drug prices were extracted from the Global Drug Facility medicines catalog (April 2021) [27]. Import cost estimates of individual TB drugs stemmed from our previous micro-costing study that assessed air freight, customs, and land freight costs of shipping medical supplies from the MSF procurement unit in Amsterdam, the Netherlands, to the TB program's central storage in Nukus, Karakalpakstan [25] (**Table 1**).

For the DS-TB drug regimen with a fixed-dose combination of antibiotics over six months, we estimated purchase cost of \$43, to which import to Karakalpakstan adds \$4.05 in 2020/21. For the 4-months DS-TB drug regimen, we estimated purchase cost of \$237, to which import adds \$6.74. Purchasing drugs for the 20-months all-oral MDR-TB regimen cost \$2,816, to which import adds \$42 in 2020/21. The 9-months MDR-TB drug regimen with an injectable antibiotic cost \$482 to purchase and \$41 to import. The 6-months all-oral MDR-TB drug regimen cost \$975 to purchase and \$3.70 to import. In comparison, a conventional 20-months MDR-TB drug regimen with an injectable antibiotic cost \$2,448 to purchase and \$140 to import.

2.5 Program cost modelling and data analysis

Annual drug procurement costs for the TB program were modelled for the years 2016–20 by multiplying the number of people commencing DS-TB and MDR-TB treatment in a year with the procurement costs of the drug regimens assumed in the model scenarios. 2016–20 cost averages were calculated and compared using two-sample *t*-tests with unequal variances. Percentage cost differences were assessed for being significantly different from zero using one-sample *t*-tests. To assess the impact

of import cost fluctuations on the TB program cost, we modelled a $\pm 50\%$ change in air freight charges. Analyses were performed in Stata 15.1 SE and costs are reported in 2020/21 US dollar (\$).

2.6 Ethical considerations

No ethical approval was sought as this modelling study used secondary data.

3 Results

3.1 Program costs of drug-susceptible TB drug regimens

In the DS-TB reference scenario 1, people with DS-TB are treated with a 6-months drug regimen with fixed-dose combinations. The TB program's cost of purchasing DS-TB drugs is \$65 K (SD 10) per year. The cost of importing DS-TB drugs is \$6.2 K (SD 0.97) per year. In DS-TB scenario 2, people with DS-TB are treated with a 4-months regimen. The TB program's annual cost of purchasing DS-TB drugs increases to \$363 K (SD 57, +\$298 K [SD 26]; $P < 0.001$) in comparison to the DS-TB reference scenario. The annual cost of importing DS-TB drugs increases to \$10 K (SD 1.6, +\$4.1K [SD 0.84]; $P = 0.002$) (**Table 2** and **Figure 1a**).

3.2 Program costs of multidrug-resistant TB drug regimens

In MDR-TB reference scenario 1, people with MDR-TB are treated with a 20-months all-oral drug regimen. The TB program's annual cost of purchasing MDR-TB drugs is \$1.9 M (SD 0.38). The annual cost of importing MDR-TB drugs is \$28 K (SD 5.6) per year (**Figure 1b**).

In MDR-TB scenario 2, people with MDR-TB are treated with a 9-months MDR-TB drug regimen with an injectable antibiotic. By adapting the 9-months MDR-TB drug regimen, the TB program's annual cost of purchasing MDR-TB drugs decreases to \$325 K (SD 64, -\$1.6 M [SD 0.17]; $P < 0.001$) in comparison to the MDR-TB reference scenario. The annual cost of importing MDR-TB drugs (\$27 K [SD 5.4], -\$0.8 K [SD 3.4]; $P = 0.82$) is similar to the MDR-TB reference scenario.

In MDR-TB scenario 3, people with MDR-TB are treated with a 6-months all-oral MDR-TB drug regimen. By adapting the 6-months MDR-TB drug regimen, the TB program's annual cost of purchasing MDR-TB drugs decreases to \$658 K (SD 130, -\$1,243 K [SD 178]; $P < 0.001$) and the annual cost of importing MDR-TB drugs decreases to \$2.5 K (SD 0.49, -\$26 K [SD 2.5]; $P < 0.001$) in comparison to the MDR-TB reference scenario.

The procurement of the 6-months MDR-TB drug regimen is costlier for the TB program than the procurement of the 9-months MDR-TB drug regimen with an injectable antibiotic (+\$308 K (SD 66); $P = 0.003$) despite import cost savings (−\$25 K (SD 2.4); $P < 0.001$) of the 6-months regimen in comparison to the 9-months regimen. The procurement of either the 9-months or 6-months MDR-TB drug regimen, however, costs the TB program less than the procurement of the 20-months all-oral MDR-TB drug regimen in the reference scenario (both $P \leq 0.001$).

In MDR-TB scenario 4, people with MDR-TB are treated with a 20-months MDR-TB drug regimen with an injectable antibiotic. The annual cost of procuring MDR-TB drugs in this scenario (\$1,7 M [SD 0.33], −249 K [SD 223]; $P = 0.30$) is similar to the cost of procuring drugs in the 20-months all-oral MDR-TB reference scenario. The drug import cost, however, is substantially higher for the 20-months MDR-TB drug regimen with an injectable antibiotic (\$94 K [SD 19]; +66 K [SD 8.7]; $P < 0.001$) in comparison to the 20-months all-oral MDR-TB reference scenario.

Figure 1: Program costs of longer and shorter tuberculosis drug regimens

(a) Drug-susceptible TB treatment

(b) Multidrug-resistant TB treatment

Drug-susceptible TB drug regimens

- 6-months with fixed-dose combinations of antibiotics (scenario 1)
- 4-months with single-doses of antibiotics (scenario 2)

Multidrug-resistant TB drug regimens

- 20-months all-oral (scenario 1)
- 9-months with an injectable antibiotic (scenario 2)
- 6-months all-oral (scenario 3)
- 20-months with an injectable antibiotic (scenario 4)

- Number of people starting TB treatment
- Import cost of TB drugs
- H Air freight charges $\pm 50\%$

TB = tuberculosis, K = thousand. Y-axes for program costs have different scales. Program costs for the years 2016–20 are based on the drug regimen choice, the annual number of people starting TB treatment in a TB program in Karakalpakstan, Uzbekistan, and TB drug prices from the April 2021 Global Drug Facility medicines catalog. The TB drugs and dosing used in the drug regimens are summarized in **Table 1**.

Table 2: Program costs of longer and shorter tuberculosis (TB) drug regimens, by type of TB

Drug regimen used for TB treatment	Total procurement cost (\$K)	Drug cost (\$K)	Import cost (\$K)
<i>Drug-susceptible TB treatment</i>			
6-months (reference scenario 1)	72 (11)	65 (10)	6.2 (0.97)
4-months (scenario 2)	374 (58)	363 (57)	10 (1.6)
Δ to reference scenario	+302 (27)***	+298 (26)***	+4.1 (0.84)**
Δ to reference scenario (%) ^a	+421	+455	+67
Cost range	72 to 374	65 to 363	6.2 to 10
<i>Multidrug-resistant TB treatment</i>			
20-months all-oral (reference scenario 1)	1,930 (382)	1,902 (377)	28 (5.6)
9-months with an injectable antibiotic (scenario 2)	353 (70)	325 (64)	27 (5.4)
Δ to reference scenario	-1,577 (174)***	-1,576 (171)***	-0.80 (3.5)
Δ to reference scenario (%) ^a	-82	-83	-2.9
6-months all-oral (scenario 3)	661 (131)	658 (130)	2.5 (0.49)
Δ to reference scenario	-1,269 (181)**	-1,243 (178)***	-26 (2.5)***
Δ to reference scenario (%) ^a	-66	-65	-91
Δ to 9-months scenario	+308 (66)**	+333 (65)**	-25 (2.4)***
Δ to 9-months scenario (%) ^a	+87	+102	-91
20-months with an injectable antibiotic (scenario 4)	1,748 (346)	1,653 (327)	94 (19)
Δ to reference scenario	-182 (231)	-249 (223)	+66 (8.7)***
Δ to reference scenario (%) ^a	-9.5	-13.1	+235
Cost range	353 to 1,748 [1,930]	325 to 1,902	2.5 to 28 [94]

( ) = standard deviation. [ ] = no longer recommended drug regimen. TB = tuberculosis, K = thousand, Δ = difference, * P < 0.05, ** P < 0.01, *** P < 0.001. ^a As percentage difference does not vary between years, no standard deviation and P-value are reported. The TB drugs and dosing of the regimens are described in **Table 1**. A break-down of the import costs into air freight, land freight, and customs-related costs and exact P-values are provided in **supplementary Table S3**.

Table 3: Program costs of longer and shorter tuberculosis (TB) drug regimens

Combination of drug regimens used for TB treatment (drug-susceptible TB & multidrug-resistant TB)	Total procurement cost (\$K)	Drug cost (\$K)	Import cost (\$K)
6-months & 20-months all-oral (reference combination)	2,002 (175)	1,967 (175)	34 (2.8)
6-months & 9-months with an injectable antibiotic (least costly combination)	424 (36)	391 (33)	34 (2.8)
Δ to reference	-1,577 (179)***	-1,576 (176)***	-0.80 (4.0)
Δ to reference scenario (%)	-79 (0.10)***	-80 (0.10)***	-2.3 (0.02)***
4-months & 20-months all-oral (costliest combination)	2,204 (194)	2,265 (191)	39 (3.2)
Δ to reference	302 (262)	298 (258)	4.1 (4.3)
Δ to reference scenario (%)	15 (0.54)***	15 (0.54)***	12 (0.37)***
4-months & 6-months all-oral (shortest combination)	1,035 (82)	1,022 (82)	13 (0.92)
Δ to reference	-967 (194)**	-945 (191)**	-22 (3.0)***
Δ to reference scenario (%)	-48 (0.63)***	-48 (0.62)***	-63 (0.87)***
6-months & 20-months with an injectable antibiotic (phased-out combination)	1,819 (159)	1,719 (150)	101 (8.8)
Δ to reference	-182 (237)	-249 (229)	66 (9.2)***
Δ to reference scenario (%)	-9.1 (0.012)***	-13 (0.016)***	192 (1.29)***
Cost range	424 to 2,204	391 to 2,265	13 to 39 [101]

( ) = standard deviation. [ ] = no longer recommended drug regimen. TB = tuberculosis, K = thousand, Δ = difference, * P < 0.05, ** P < 0.01, *** P < 0.001. The TB drugs and dosing of the regimens are described in **Table 1**. A breakdown of the import costs into air freight, land freight, and customs-related costs and exact P-values are provided in **supplementary Table S3**.

3.3 Total drug procurement cost of the TB program

The total drug procurement cost of the TB program depends on the number people on TB treatment, the share of drug-resistance among people on TB treatment, and the combination of DS-TB and MDR-TB drug regimens provided. Purchasing drugs for 6-months DS-TB treatment and 20-months all-oral MDR-TB treatment (reference combination) costs the TB program \$2.0 M (SD 0.175) per year, to which drug import adds \$34 K (SD 2.8) per year (**Table 3**).

If the TB program combines the least costly DS-TB and MDR-TB drug regimens assessed, that is, the 6-months DS-TB drug regimen and the 9-months MDR-TB drug regimen with an injectable antibiotic, its drug purchasing cost falls to \$391 K (SD 33, -\$1,6 M [SD 0.18]; $P < 0.001$) in comparison to the reference combination of drug regimens. The TB program's import cost remains similar to the reference combination when the least costly combination of DS-TB and MDR-TB drug regimens is used for treatment (\$34 K [SD 2.8], -\$805 [SD 4,038]; $P = 0.85$). If the TB program uses the costliest combination of the assessed drug regimens, that is, the 4-months DS-TB drug regimen and the 20-months all-oral MDR-TB drug regimen, neither its cost for drug purchase (\$2.3 M [SD 0.19], +\$298 K [SD 258]; $P = 0.28$) nor its cost for drug import (\$39 K [SD 3.2], +\$4,1 K [SD 4.3]; $P = 0.36$) increase significantly in comparison to the reference combination. If the TB program provides the shortest of the assessed DS-TB and MDR-TB drug regimens, that is, the 4-months DS-TB drug regimen and the 6-months MDR-TB drug regimen, the program costs for purchasing and importing TB drugs fall to \$1.0 M (SD 0.082) and \$13 K (SD 0.92), respectively. Drug cost (-\$945 K [SD 191]; $P = 0.003$) and import cost (-\$21 K [SD 3.0]; $P = 0.001$) decrease in comparison to the reference combination of 6-months DS-TB treatment and 20-months all-oral MDR-TB treatment.

Providing the costliest combination of DS-TB and MDR-TB drug regimens, that is, the 4-months DS-TB drug regimen and the 20-months all-oral MDR-TB drug regimen (\$2,204 K [SD 194]), rather than the least costly regimen combination, that is, the 6-months DS-TB drug regimen and the 9-months MDR-TB drug regimen with an injectable antibiotic (\$424 K [SD 36]), quintuples the drug procurement cost of the TB program. The TB program's import cost is highest when the phased-out 20-months MDR-TB drug regimen is used together with the 4-months DS-TB drug regimen (205% [SD 0.94] of the import cost of the reference combination and 1,105.5% [SD 28] of the import cost of the least-costly-to-import combination of 6-months all-oral regimens for DS-TB and MDR-TB; **supplementary Table S3**).

3.4 Program vulnerability to import cost fluctuations

Air freight caused 95% of the modelled import costs to the TB program based on our previous import cost assessment [25]. The error bars in **Figure 1** indicate how the import cost of the TB program increases (decreases) when the average cost of air freight changes from \$4.87 per kg weight imported to \$7.31 (\$2.44) per kg, that is, by $\pm 50\%$. During the COVID-19 pandemic, air and sea freight charges to many destinations increased by a similar or even higher magnitude [28, 29]. A 50% rise in air freight charges increases the TB program's annual drug import cost from \$34 K (SD 2.9) to \$51 K (SD 4.3, +\$16 K [SD 5.1]; $P = 0.016$) in the reference combination of regimens, that is, when 6-months DS-TB drug regimens and 20-months all-oral MDR-TB drug regimens are used for treatment in the TB program. If the TB program used the combination of drug regimens that is most costly to import, that is, the 4-months DS-TB drug regimen and conventional 20-months MDR-TB drug regimen with an injectable antibiotic, a 50% rise in air freight charges would increase the TB program's annual drug import cost from \$105 K (SD 9.0) to \$155 K (SD 13, +\$50 K [SD 16]; $P = 0.017$). Comparing the height of the error bars across scenarios illustrates how a higher import cost renders a TB program more vulnerable to a transport cost increase.

4 Discussion

Despite an increase in spending on TB and a decrease in the TB incidence globally between 2000 and 2017, many TB programs continue to face a domestic funding gap [30]. The procurement cost of TB drug regimens can therefore affect how many people can receive TB treatment, especially in low-income and lower-middle-income countries. MSF estimated, for example, that only 11% of the eligible people with TB have received bedaquiline worldwide between 2015 and 2019, related to financial constraints that restrict access to newer, more expensive TB drugs such as bedaquiline, delamanid, and pretomanid [19]. Modelling program costs for drug procurement can help identify financial needs and potential cost savings, and thereby assist to prepare TB programs for new TB drug regimens.

This modelling study compared the drug procurement cost of a TB program in Karakalpakstan, Uzbekistan, for different scenarios, in which 20-months, 9-months, and 4–6-months TB drug regimens were used. The modelling was based on detailed, context-specific information obtained in prior bottom-up costing studies, 2016–20 treatment numbers, and 2021 TB drug prices from the Global Drug Facility. The assessed TB drug regimens include the latest WHO treatment recommendations, such that the presented findings can help inform the TB program in Karakalpakstan and, to some degree, also TB programs elsewhere about the possible budget impact of introducing new, often shorter TB drug regimens.

In reference scenario of the model, we found that drug purchase for the currently recommended 6-months DS-TB treatment and the 20-months all-oral MDR-TB treatment generates annual costs of \$1,967 K (SD 175) for the TB program, to which drug import adds \$34 K (SD 2.8) per year. The total drug procurement expenses of \$2,002 K (SD 175) per year for this combination of DS-TB and MDR-TB drug regimens correspond to 23.2% (SD 1.9) of MSF's average annual expenditures for activities in Uzbekistan between 2016 and 2020 (compare **supplementary Tables S1 and S3**). The use of a 4-months rifapentine-based DS-TB drug regimen, which was recommended by the WHO in June 2021 [4], increased drug procurement costs in the model when used instead of the present 6-months standard DS-TB drug regimen. This increase in drug procurement cost is driven by the present higher cost of rifapentine and its availability in the form of 150 mg tablets only [20]. The restricted choice in rifapentine formulations requires to take 8 tablets per day to reach the target dose of 1200 mg for an adult weighing 55–75 kg. The resulting need to import more rifapentine tablets increased the weight of the imported drugs and, thus, the import cost of the TB program in our model. Furthermore, use of either a 9-months MDR-TB drug regimen with an injectable antibiotic or a 6-months all-oral MDR-TB drug regimen reduced the drug procurement cost when compared to the currently WHO-recommended 20-months all-oral MDR-TB drug regimen [5]. The latter reduction in MDR-TB drug procurement cost can be attributed to a shorter treatment duration, the need for fewer tablets or injectables, and the use of cheaper TB drugs [20]. Given the relatively high prevalence of drug-resistant strains of TB in Karakalpakstan, the introduction of both the 4-months DS-TB drug regimen and shorter than 20-months MDR-TB drug regimens, overall, reduced the drug procurement costs for the TB program in the assessed scenarios, as higher DS-TB treatment costs were outweighed by cost savings in MDR-TB treatment.

The magnitude of the contribution of drug import to total drug procurement cost varied between scenarios. The TB program's import costs for an all-oral 20-months MDR-TB drug regimen and a 9-months injectable-based MDR-TB drug regimen were similar, as cost savings from importing a lower quantity of TB drugs were offset by packaging the injectable antibiotic in a relatively heavy glass vial. However, the adoption of the 6-months MDR-TB drug regimen reduced the drug import cost of the TB program compared to the longer MDR-TB drug regimens assessed. Of all DS-TB and MDR-TB regimen studied in the model, the by far highest import cost for the TB program was associated with the no longer WHO-recommended 20-months MDR-TB drug regimen with an injectable antibiotic. Thus, for TB programs that still provide conventional MDR-TB treatment, transitioning to shorter and/or all-oral MDR-TB drug regimens seems therefore highly likely to reduce the cost of importing TB drugs.

High import cost relative to the drug procurement cost can make a TB program vulnerable to import cost shocks (e.g., a steep increase in air or sea freight charges as observed during the COVID-19 pandemic [28, 29]). As TB programs transition to shorter all-oral MDR-TB drug regimens, some TB programs could experience import cost reductions and, thus, become less vulnerable to import cost fluctuations. Not only the import of fewer drugs, but also the import of less heavy drugs can result in import cost savings (e.g., use of fixed-dose combinations, higher-dosed tablets, or lighter tablets). With respect to the new, 4-month DS-TB drug regimen, the WHO recently called for manufacturing rifapentine in higher-dosed tables and fixed-dose combinations [31].

The strengths of this modelling study include its timely analysis of new drug regimens for TB treatment, the use of drug prices from the Global Drug Facility, through which many TB programs procure TB drugs, and the model parameterization with data from the TB program in Karakalpakstan. Limitations of the study include, firstly, that we assumed that all patients with DR-TB in the TB program in Karakalpakstan were treated with the same MDR-TB drug regimen. Program data indicate that 66% (SD 10) of the people starting on DR-TB treatment between 2016 and 2020 had MDR-TB, whereas 9.1% (SD 2.0) had extensively drug-resistant TB, which requires a more individualized treatment approach than MDR-TB, and 24% (SD 12) were diagnosed with other forms of drug-resistance [26]. Secondly, the modelling inherited limitations of our previous study in which we generated the unit import costs underlying the import cost estimation of the study at hand [25]. The inherited limitations include that import cost estimates were based on the assessment of costs and unit weights of only one major shipment to the TB program in 2016. Further, import costs were generated in utilizing items' unit weights, which might have been estimated with low precision. Thirdly, this study modelled the impact of the transition to shorter TB drug regimens on drug procurement costs, but did not assess effects of the adoption of shorter TB drug regimens on other program costs, such as administration [32], side effect treatment, contact tracing, or treatment monitoring. Fourthly, we used only Global Drug Facility prices as inputs to our model, but the TB program in Karakalpakstan may also procure TB drugs from other sources such as MSF. The relative contribution of each source varies year by year based on programmatic needs. Conversely, using Global Drug Facility prices instead of program-specific drug costs might make our results more relevant for other settings, as globally a large share of quality-assured TB drugs is procured through the Global Drug Facility [13]. Finally, by construction of the model, the statistical comparisons of the calculated cost differences is based on variation in patient numbers over time only. While yearly drug prices and import costs could have been modelled, holding these costs constant allowed to focus on the program cost variation caused by drug regimen choices and patient number fluctuations.

5 Conclusion

Modelling the purchase and import costs of longer and shorter DS-TB and MDR-TB drug regimens for a TB program in Karakalpakstan, Uzbekistan, suggests that the use of shorter TB drug regimens in favor of longer regimens can increase or decrease the drug procurement cost a TB program. The introduction of a new, 4-months DS-TB drug regimen increased the drug procurement cost in comparison to the standard 6-months DS-TB treatment in our model. The introduction of either a 9-months MDR-TB drug regimen with an injectable antibiotic or a 6-months all-oral MDR-TB drug regimen decreased the TB program's drug procurement cost in our model in comparison to the use of a 20-months all-oral drug regimen. Whether the combined introduction of new and often shorter DS-TB and MDR-TB drug regimens increases or decreases the total cost of a TB program at the current TB drug prices seems to depend on the new and replaced TB drug regimens as well as on the prevalence of drug-resistant TB in the program setting.

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Data and code availability: Will be deposited on heiDATA (<https://heidata.uni-heidelberg.de/>).

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Supplementary materials

Table S1: Number of people starting tuberculosis (TB) treatment in the TB program in Karakalpakstan, Uzbekistan

Year	Staff	Program cost (mil. €)	Number of people starting TB treatment					DR-TB share (%)
			Total	DS-TB	DR-TB	MDR-TB	XDR-TB	
2016	248	9.8	2,645	1,767	878	433	63	33
2017	264	9.0	2,466	1,710	677	524	79	27
2018	271	8.6	2,220	1,560	660	450	70	30
2019	301	8.3	2,130	1,470	660	465	58	31
2020	310	7	1,662	1,160	502	344	36	30
2016–20	279 (26)	8.5 (1.0)	2,225 (374)	1,533 (240)	675 (134)	443 (65)	61 (16)	30.3 (2.1)

( ) = standard deviation. TB = tuberculosis. DS = drug-susceptible, DR = drug-resistant, XDR = extensively drug-resistant. *Data sources:* Médecins Sans Frontières activity reports [26] and personal communication.

Table S2: Amount of drugs in a tuberculosis (TB) drug regimen, drug purchase cost, and drug import cost for a TB program in Karakalpakstan, Uzbekistan

Drug regimen used for TB treatment (scenario—if included in modelling study)	Tablets and injectables per day	Tablets and injectables per regimen	Import weight per regimen (kg)	Drug cost per regimen (\$)	Import cost per regimen (\$)	Import cost (% of regimen cost)	Total cost per patient month (\$)
Drug-susceptible (DS)-TB							
6-months DS-TB drug regimens^a							
2 HRZE / 4 HR fixed-dose combination (scenario 1)	4	731	0.8	43	4.05	9.5	7.79
2 H-R-Z-E / 4 H-R	3–9.75	959	0.9	64	5.05	7.9	11
4-months (17-weeks) DS-TB drug regimen^b							
8w Rpt-H-Z-Mfx / 9w Rpt-H-Mfx (scenario 2)	13	1548	1.3	237	6.74	2.8	62
Multidrug-resistant (MDR)-TB							
20-months all-oral MDR-TB drug regimens^c							
20 Bdq-Lfx-Lzd-Cfz-Cs (scenario 1)	10.4–13	6356	8.1	2816	42	1.5	143
20 Bdq-Dlm-Lzd-Cfz-Cs	8.38–11	5139	6.8	5832	35	0.6	293
9–11-months MDR-TB drug regimens with an injectable antibiotic^d							
4–6 Km-Mfx-Pto-Cfz-Z-H ^h -E / 5 Z-E-Mfx-Pto-Cfz (scenario 2)	13–17	3926–5083	7.9–14	482–637	41–72	8.4–11.3	58–64
4–6 Cm-Mfx-Pto-Cfz-Z-H ^h -E / 5 Z-E-Mfx-Pto-Cfz	13–17	3926–5083	8.3–15	668–918	43–75	6.4–8.2	79–90
6–11-months all-oral MDR-TB drug regimens							
4–6 Bdq(6 m)-Lfx-Cfz-Z-E-H ^h -Eto / 5 Lfx-Cfz-Z-E ^e	12–21	4101–5220	3.9–4.9	706–943	20–25	2.7–2.8	81–88
6–9 Bdq-Pa-Lzd (scenario 3) ^f	4–6	654–963	0.7–1	975–1429	3.70–5.49	0.4	159–163
20–24-months MDR-TB drug regimens with an injectable antibiotic^g							
8 Z-Km-Lfx-PAS-Pto-Cs / 12–16 Z-Lfx-PAS-Pto-Cs (scenario 1)	17–19	10592–12906	27–35	2448–2935	140–181	5.7–6.2	129–130
8 Z-Cm-Mfx-PAS-Pto-Cs / 12–16 Z-PAS-Pto-Cs	13–16	8401–10227	26–33	2797–3272	133–170	4.7–5.2	143–146
8 Z-Cm-Lfx-PAS-Pto-Cs / 12–16 Z-Lfx-PAS-Pto-Cs	17–19	10592–12906	28–36	2821–3309	144–185	5.1–5.6	146–148

Intensive phase / continuation phase of treatment. TB = tuberculosis, DS = drug-susceptible, MDR = multidrug-resistant, w = weeks. Drug acronyms and dosing are described in the caption of **Table 1** and [20]. ^a Standard drug regimen [2]. ^b Recently endorsed by the WHO [4] based on the TBTC Study 31 [33]. ^c Used for people with medium or high risk of failed treatment in Uzbekistan [5, 34]. ^d Tested in a 2013–15 prospective trial in the TB program in Karakalpakstan [35]. ^e For people with MDR/RR-TB without resistance to fluoroquinolones. 9–12-months according to WHO guidelines [5]. ^f Effective in a multi-center trial in South Africa [6] and recommended by the WHO under certain operational research conditions [5]. ^g Recommended in 2015 TB program guidelines [36]. Weight includes drug weight and drug packaging; cargo packaging added, on average, 8.9% to cargo weight for drugs imported to the TB program in Karakalpakstan [20]. *Data sources:* Kohler et al. [20, 25]

Table S3: Modelled drug purchase and import costs of a tuberculosis (TB) program in Karakalpakstan, Uzbekistan, for longer and shorter TB drug regimens, 2016–2020

Year	Total procurement cost (\$)	Drug cost (\$)	Import cost (\$)			
			Total	Air freight (% of total)	Customs-related (% of total)	Land freight (% of total)
Drug regimen used for drug-susceptible (DS)-TB treatment						
6-months DS-TB drug regimen (scenario 1)						
2016	82,573	75,418	7,155	6,775 (95)	56 (0.78)	324 (4.5)
2017	79,909	72,985	6,924	6,556 (95)	54 (0.78)	314 (4.5)
2018	72,900	66,583	6,317	5,981 (95)	49 (0.78)	286 (4.5)
2019	68,694	62,742	5,952	5,636 (95)	46 (0.78)	270 (4.5)
2020	54,207	49,510	4,697	4,448 (95)	37 (0.78)	213 (4.5)
2016–20 mean	71,657 (11,203)	65,448 (10,233)	6,209 (971)	5,879 (919)	48 (7.6)	281 (44)
4-months DS-TB drug regimen (scenario 2)						
2016	430,678	418,761	11,917	11,219 (94)	161 (1.4)	537 (4.5)
2017	416,785	405,252	11,533	10,857 (94)	156 (1.4)	520 (4.5)
2018	380,225	369,704	10,521	9,905 (94)	142 (1.4)	474 (4.5)
2019	358,289	348,375	9,914	9,333 (94)	134 (1.4)	447 (4.5)
2020	282,731	274,908	7,823	7,365 (94)	106 (1.4)	353 (4.5)
2016–20 mean	373,742 (58,434)	363,400 (56,817)	10,342 (1,617)	9,736 (1,522)	140 (22)	466 (73)
Δ to reference scenario	302,085 (26,608)	297,952 (25,818)	4,133 (843)	3,857 (795)	91 (10)	184 (38)
P-value	0.0002	0.0002	0.002	0.002	0.0003	0.002
Δ to reference scenario (%) ^a	421	455	66.6	65.6	188	65.6

Year	Total procurement cost (\$)	Drug cost (\$)	Import cost (\$)			
			Total	Air freight (% of total)	Customs-related (% of total)	Land freight (% of total)
Drug regimen used for multidrug-resistant (MDR)-TB treatment						
20-months all-oral MDR-TB drug regimen (scenario 1)						
2016	2,508,865	2,472,164	36,700	34,733 (95)	305 (0.83)	1,663 (4.5)
2017	1,934,512	1,906,213	28,299	26,781 (95)	235 (0.83)	1,282 (4.5)
2018	1,885,935	1,858,347	27,588	26,109 (95)	229 (0.83)	1,250 (4.5)
2019	1,885,935	1,858,347	27,588	26,109 (95)	229 (0.83)	1,250 (4.5)
2020	1,434,453	1,413,470	20,984	19,859 (95)	174 (0.83)	951 (4.5)
2016–20 mean	1,929,940 (382,281)	1,901,708 (376,689)	28,232 (5,592)	26,718 (5,292)	235 (46)	1,279 (253)
9-months MDR-TB drug regimen with an injectable antibiotic (scenario 2)						
2016	458,495	422,841	35,654	33,794 (95)	243 (0.68)	1,618 (4.5)
2017	353,532	326,040	27,492	26,057 (95)	187 (0.68)	1,247 (4.5)
2018	344,655	317,853	26,802	25,403 (95)	183 (0.68)	1,216 (4.5)
2019	344,655	317,853	26,802	25,403 (95)	183 (0.68)	1,216 (4.5)
2020	262,146	241,761	20,385	19,322 (95)	139 (0.68)	925 (4.5)
2016–20 mean	352,696 (69,862)	325,269 (64,429)	27,427 (5,433)	25,996 (5,149)	187 (37)	1,244 (247)
Δ to reference scenario	–1,577,243 (173,793)	–1,576,439 (170,907)	–805 (3,487)	–722 (3,302)	–48 (27)	–35 (158)
P-value	0.0006	0.0006	0.82	0.83	0.11	0.83
Δ to reference scenario (%) ^a	–81.7	–82.9	–2.85	–2.70	–20.4	–2.70
6-months all-oral MDR-TB drug regimen (scenario 3)						
2016	859,118	855,872	3,246	3,056 (94)	44 (1.3)	146 (4.5)
2017	662,441	659,938	2,503	2,356 (94)	34 (1.3)	113 (4.5)
2018	645,807	643,367	2,440	2,297 (94)	33 (1.3)	110 (4.5)
2019	645,807	643,367	2,440	2,297 (94)	33 (1.3)	110 (4.5)
2020	491,204	489,349	1,856	1,747 (94)	25 (1.3)	84 (4.5)
2016–20 mean	660,875 (130,906)	658,378 (130,411)	2,497 (495)	2,351 (466)	34 (6.6)	113 (22)
Δ to reference scenario	–1,269,064 (180,707)	–1,243,330 (178,270)	–25,735 (2,511)	–24,367 (,2376)	–201 (21)	–1,167 (114)
P-value	0.001	0.001	0.0005	0.0005	0.0005	0.0005
Δ to reference scenario (%) ^a	–65.8	–65.4	–91.2	–91.2	–85.7	–91.2
Δ to 9-months regimen	308,179 (66,358)	333,109 (65,051)	–24,930 (2,440)	–23,645 (2,312)	–153 (17)	–1,132 (111)
P-value	0.003	0.002	0.0005	0.0005	0.0006	0.0005
Δ to 9-months regimen (%) ^a	87.4	102	–90.9	–91.0	–82.0	–91.0

Year	Total procurement cost (\$)	Drug cost (\$)	Import cost (\$)			
			Total	Air freight (% of total)	Customs-related (% of total)	Land freight (% of total)
20-months MDR-TB drug regimen with an injectable antibiotic (scenario 4)						
2016	2,271,757	2,148,927	122,830	116,617 (95)	631 (0.51)	5,583 (4.5)
2017	1,751,685	1,656,974	94,711	89,920 (95)	486 (0.51)	4,305 (4.5)
2018	1,707,699	1,615,366	92,333	87,662 (95)	474 (0.51)	4,197 (4.5)
2019	1,707,699	1,615,366	92,333	87,662 (95)	474 (0.51)	4,197 (4.5)
2020	1,298,886	1,228,657	70,229	66,676 (95)	360 (0.51)	3,192 (4.5)
2016–20 mean	1,747,545 (346,152)	1,653,058 (327,436)	94,487 (18,716)	89,707 (17,769)	485 (96)	4,295 (851)
Δ to reference scenario	–182,395 (230,634)	–248,650 (223,208)	66,255 (8,736)	62,989 (8,292)	250 (48)	3,015 (397)
P-value	0.45	0.3	0.0008	0.0008	0.002	0.0008
Δ to reference scenario (%) ^a	–9.45	–13.1	235	236	107	236
Combination of drug regimens used for TB treatment (DS-TB & MDR-TB)						
6-months & 20-months all oral (reference combination)	2,001,596 (175,387)	1,967,156 (172,502)	34,441 (2,890)	32,597 (2,736)	283 (24)	1,561 (131)
6-months / 20-months with an injectable antibiotic (phased-out combination)	1,819,202 (159,232)	1,718,506 (150,478)	100,696 (8,755)	95,587 (8311)	533 (46)	4,576 (398)
Δ to reference combination	–182,395 (236,887)	–248,650 (228,911)	66,255 (9,219)	62,989 (8,749)	250 (52)	3,015 (419)
P-value	0.4636	0.3096	0.0009	0.0009	0.0029	0.0009
Δ to reference combination (%)	–9.11 (0.012)	–12.6 (0.016)	192 (1.29)	192 (1.30)	88.4 (0.56)	193 (1.30)
P-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Δ to least costly combination	1,394,849 (163,192)	1,327,789 (154,035)	67,060 (9,197)	63,712 (8730)	298 (50.0)	3050 (419)
P-value	0.0007	0.0007	0.0009	0.0009	0.0014	0.0009
Δ to least costly combination (%)	328 (2.1)	339 (2.1)	199 (1.4)	200 (1.4)	127 (0.97)	200 (1.4)
P-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
6-months & 9-months with an injectable antibiotic (least costly combination)	424,353 (35,732)	390,717 (32,913)	33,636 (2,819)	31,875 (2672)	235 (20)	1,526 (128)
Δ to reference combination	–1,577,243 (178,990)	–1,576,439 (175,614)	–805 (4,038)	–722 (3,824)	–48 (31)	–35 (183)
P-value	0.0006	0.0006	0.85	0.85	0.16	0.85
Δ to reference combination (%)	–78.8 (0.10)	–80.1 (0.099)	–2.33 (0.016)	–2.21 (0.015)	–16.9 (0.11)	–2.21 (0.015)
P-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Year	Total procurement cost (\$)	Drug cost (\$)	Import cost (\$)			
			Total	Air freight (% of total)	Customs-related (% of total)	Land freight (% of total)
4-months & 20-months all oral (costliest combination)	2,303,681 (194,359)	2,265,108 (191,206)	38,573 (3,156)	3,6454 (2,984)	374 (30)	1,745 (143)
Δ to reference combination	302,085 (261,794)	297,952.5 (257,520)	4,133 (4,289)	3,857 (4,048)	91 (38)	185 (194)
P-value	0.28	0.28	0.36	0.37	0.045	0.37
Δ to reference combination (%)	15.2 (0.54)	15.3 (0.54)	12.1 (0.37)	11.9 (0.36)	32.4 (0.99)	11.9 (0.36)
P-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Δ to least costly combination	1,879,328 (197,616)	1,874,391 (194,018)	4,937 (4,232)	4,579 (4,005)	139 (36)	219 (192)
P-value	0.0005	0.0005	0.28	0.29	0.0060	0.29
Δ to least costly combination (%)	443 (0.13)	480 (0.15)	14.7 (0.36)	14.4 (0.35)	59.3 (0.99)	14.4 (0.35)
P-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
4-months & 9-months with an injectable antibiotic (other combination)	726,438 (55,645)	688,669.5 (52,580)	37,769 (3,085)	35,732 (2920)	326 (25.6)	1,711 (140)
Δ to reference combination	-966,979 (193,814.5)	-945,377 (190,821)	-21,602 (3,034)	-20,511 (2,870)	-110 (27)	579 (42)
P-value	0.0029	0.0030	0.0010	0.0010	0.0064	0.0010
Δ to reference combination (%)	-48.2 (0.63)	-47.9 (0.62)	-62.6 (0.87)	-62.8 (0.86)	-38.5 (1.44)	-62.8 (0.86)
P-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Δ to least costly combination	610,264 (89,890)	631,061.5 (87,972)	-20,798 (2,967)	-19,788 (2810)	-62.0 (23.2)	-947 (135)
P-value	0.0007	0.0007	0.0010	0.0010	0.033	0.0010
Δ to least costly combination (%)	144 (1.7)	162 (1.8)	-61.7 (0.88)	-61.9 (0.88)	-26.1 (1.6)	-61.9 (0.88)
P-value	< 0.001	< 0.001	< 0.001	< 0.001	0.001	< 0.001
4-months & 6-months all oral (shortest combination)	1,034,617 (82,482)	1,021,778 (81,583)	12,838 (924)	12,087 (870)	173 (12)	579 (42)
Δ to reference combination	-1,275,158 (184,003)	-1,278,486 (180,337.5)	3,328 (4,228)	3,134 (4,001)	43 (35)	150 (192)
P-value	0.0011	0.0011	0.45	0.46	0.25	0.46
Δ to reference combination (%)	-63.6 (0.65)	-64.9 (0.64)	9.7 (0.38)	9.7 (0.38)	16 (1.1)	9.7 (0.38)
P-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Δ to least costly combination	352,696 (36,082)	325,269 (33,230)	27,427 (2,852)	25,996 (2,703)	187 (20)	1,245 (129)
P-value	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005
Δ to least costly combination (%)	491 (18.7)	496 (18.9)	441 (16.8)	441.2268 (16.8)	385 (15)	441 (17)
P-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Year	Total procurement cost (\$)	Drug cost (\$)	Import cost (\$)			
			Total	Air freight (% of total)	Customs-related (% of total)	Land freight (% of total)
Import cost comparison between regimen combinations						
6-months / 6-months all-oral (least-costly-to-import combination)	732,532 (62,998)	723,826 (62,387)	8,706 (638)	8,230 (603)	82.0 (6.2)	394 (29)
Δ to reference combination	−1,269,064 (186,358)	−1,243330 (18,3437)	−25,735 (2,960)	−24,367 (2,801)	−201 (25)	−1167 (134)
P-value	0.0010	0.0010	0.0006	0.0006	0.0007	0.0006
Δ to reference combination (%)	−63.4 (0.084)	−63.2 (0.078)	−74.6 (0.50)	−74.7 (0.50)	−71.0 (0.45)	−74.7 (0.50)
P-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
4-months / 20-months with an injectable antibiotic (costliest-to-import combination)	2,121,287 (178,238)	2,016,458 (169,229)	104,829 (9,013)	99,443 (8,552)	625 (52)	4,761 (409)
Δ to reference combination	119,690 (250,059)	49,302 (241,652)	70,388 (9,465)	66,846 (8,979)	342 (57)	3,200 (430)
P-value	0.645	0.84	0.0008	0.0008	0.0012	0.0008
Δ to reference combination (%)	6.09 (0.55)	2.62 (0.56)	204 (0.92)	205 (0.94)	121 (0.43)	205 (0.94)
P-value	0.0004	0.0094	< 0.001	< 0.001	< 0.001	< 0.001
Δ to least-costly-to-import combination	1,388,755 (189,043)	1,292,632 (180,363)	96,123 (9,036)	91,213 (8,573)	543 (52)	4,367 (410)
P-value	0.0007	0.0008	0.0004	0.0004	0.0004	0.0004
Δ to least-costly-to-import combination (%)	190 (0.84)	179 (0.93)	1,101 (29)	1,105.5 (28)	661 (11)	1106 (28)
P-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Δ = difference in 2016–20 means, ( ) = standard deviation, TB = tuberculosis, DS = drug-susceptible, MDR = multidrug-resistant. ^a As percentage difference does not vary between years, no standard deviation and P-value are reported. Air freight costs were due to international shipping by plane from Amsterdam airport to Tashkent airport. Customs-related import costs include costs of a customs agent assisting with the declaration of the imported medical supplies and costs for storage at Tashkent airport during the declaration process. Land freight costs were due to national transport by truck from Tashkent airport to a central storage in Karakalpakstan's capital Nukus. The TB drugs and dosing used in these regimens are provided in **Table 1**.