February 2024 (version 2.0)

Evaluating cost-effective investments to reduce the burden of drug-resistant tuberculosis (TB) in Uzbekistan

Findings from an Optima TB analysis, 2023

Burnet
reach for the many

Acknowledgments

This Optima TB analysis received funding support through the Global Fund and was made possible through consultation with national and international partners. The study was conducted was conducted from June 2023 to December 2023 under the leadership of National Tuberculosis Control Program in collaboration with the Burnet Institute (technical support) and the Global Fund.

Key stakeholders

- National Tuberculosis Control Program: Nargiza Parpieva, Khasan Safaev, Asilbek Ahmadjonov
- USAID STAR: Sharaf Yuldashev
- Global Fund: Nella Foley, Dejan Loncar, Svitlana Nidzvetska, Shufang Zhang.
- Burnet Institute: Eloisa Bennetts, Anna Bowring, Kelvin Burke, Phillip Luong, Rowan Martin-Hughes, Anna Roberts, Nick Scott, Debra ten Brink, Nisaa Wulan

Suggestion citation

National Tuberculosis Control Program, Burnet Institute, Global Fund. Evaluating cost-effective investments to reduce the burden of drug-resistant tuberculosis (TB) in Uzbekistan: Findings from an Optima TB analysis, 2023. Melbourne: Burnet Institute; 2024.

Abbreviations

ART	Antiretroviral therapy
BCG	Bacillus Calmette-Guérin
Bdq	Bedaquiline
BPaLM	novel all-oral 6-month regimen composed of bedaquiline, pretomanid, linezolid and moxifloxacin
CAD	computer-aided detection
COVID-19	Coronavirus disease caused by the SARS-CoV-2 virus
DR-TB	Drug-resistant tuberculosis
DS-TB	Drug-sensitive tuberculosis
EPTB	Extrapulmonary tuberculosis
HIV	Human immunodeficiency virus
LTBI	Latent tuberculosis infection
MDR-TB	Multidrug resistant tuberculosis
mSTR	modified shorter all-oral treatment regimens
MTB	Mycobacterium tuberculosis
NGO	Non-governmental organization
NTP	National TB Programme
PLHIV	People living with HIV
RIF	Rifampicin
RR-TB	Rifampicin resistant tuberculosis
SN	Smear-negative
SP	Smear-positive
TPT	TB preventative therapy
XDR-TB	Extensively drug-resistant tuberculosis

Table of Contents

Executive summary

BACKGROUND

Estimated tuberculosis (TB) incidence has declined in Uzbekistan, from a high of 99 estimated new infections per 100,000 population in 2000 to 83 per 100,000 in 2022 based on WHO Global TB Programme data. However, the country continues to experience high burden of Rifampicin resistant (RR) and multi-drug resistant (MDR)-TB. An allocative efficiency analysis was undertaken to estimate the optimal allocation of funding to minimize both drug resistant (DR) TB cases and TB-related deaths by 2030.

KEY FINDINGS

Recommendations

1. **Shorter, all-oral treatment regimens** are more cost-effective, allowing for a larger number of people to be treated for the same amount of spending, as well as having fewer side-effects and better adherence for people with TB.
2. **Scaling back mandatory testing** among populations with low risk of TB can enable **increased investment in more targeted active case finding** among contacts of people with active TB and populations at higher risk of TB, thereby improving diagnosis rates.
3. **Expanding TB preventive treatment** (TPT), particularly among adult household contacts and repeat contacts from non-household settings, is a top priority to reduce incidence of TB, even if overall resources for TB reduce.
4. **Implementing universal Xpert diagnosis** will lead to a much faster decline in TB-related deaths and incidence due to earlier diagnosis and potential to expand TPT.

Baseline

The model estimates there were 25,000 new and relapse cases of TB in 2022, of which 15% were drug resistant. In 2022 an estimated US$89 million was spent on direct TB prevention, screening and treatment programs, of which 63% was spent on treatment. Among all estimated spending for TB screening and testing, 48% was spent on other test strategies incorporating mass screening and passive case finding, and 35% was spent on mandatory testing.

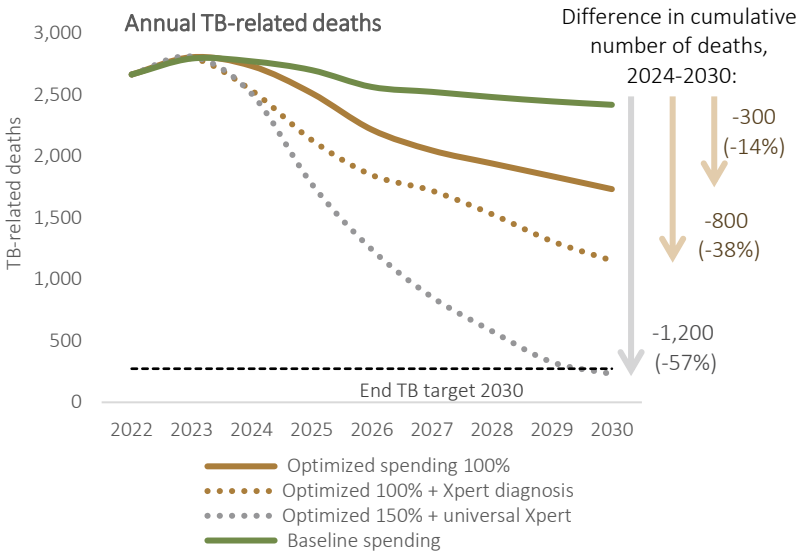
Optimization of current spending

Uzbekistan can improve the impact of its investment in the TB response by: prioritizing short-course MDR-TB and XDR-TB treatment (+US$ 9.0M) rather than the standard DR-TB treatment regimens (-US$ 10.4M); scaling up TPT for all ages, but particularly among adults (+US$ 1.0M), people living with HIV (+US$ 87,000), and non-household repeat contacts (+US$ 2.5M); and reallocating spending from mandatory testing (-US$ 5.5M) to prioritize more targeted active case finding among contacts of people with active TB (+US$ 630,000) and populations at higher risk of TB (+US$ 4.4M).

As a result of the shorter course treatment and savings made through more targeted and cost-efficient case-finding, an additional 2,357 (+22%) people could be initiated on treatment for DR-TB from 2024 to 2030 for the same amount of overall TB spending and 2,500 new/relapse DR-TB cases could be averted over the same period.

End TB targets

Implementing universal Xpert diagnosis will lead to a much faster decline in TB-related deaths and infections due to earlier diagnosis and potential to further scale up TPT. With 150% spending optimized plus universal Xpert it may be possible to reach the 2030 End TB target for reduction in TB-related deaths.



1 Background

Overall tuberculosis (TB) incidence has decreased in Uzbekistan from a high of 120 per 100,000 in 2005 to 83 per 100,000 in 2022 (1). Reduction in disease burden along with advances in diagnosis and treatment have contributed to a declining mortality, and Uzbekistan achieved the End TB 2020 milestone for mortality based on WHO estimates. However, disruptions due to COVID-19 and pandemic response measures may have slowed progress since 2020, and both incidence and deaths are thought to have increased (1-3). Uzbekistan remains one of the top 30 countries for high burden of Rifampicin- (RR) and multi-drug resistant (MDR)-TB (2). In 2022, 16% of new cases and 31% of previously treated cases had MDR/RR-TB (1). Key and vulnerable populations identified to be most-at-risk of TB or with poorer TB outcomes in Uzbekistan include migrant workers, people living with HIV, people with chronic illness, people in prison and people living in poverty (4).

Overall treatment success for TB is 91% in Uzbekistan, but only 70% for MDR-TB cases on second line treatment (5). In 2022 24% of individuals were being treated with World Health Organization (WHO)-recommended shorter treatment regimens, increasing from 8.5% in 2021 (1). Uzbekistan can procure affordable drugs through the Global Drug Facility procurement mechanism, and Government co-financing of second line drugs has been increasing since 2020 (3). Current barriers to treatment include delays between diagnosis and treatment enrollment, loss to follow up, and continued reliance on hospitalization (3).

The TB response in Uzbekistan remains highly reliant on international funding support, with 91% of funding received through the Global Fund in 2017 (6); more recent spending data are not available. Country targets to reduce the burden of TB aim to reach incidence of 33.7 per 100,000 population and mortality rate of 0.85/100,000 by 2026 (7). A key component of the strategy to meet these targets includes expanding screening for latent TB infection to reach one million people annually.

Study objectives

This Optima TB analysis aims to assess the cost-effectiveness of current and future programs for TB prevention, case finding and treatment and thereby estimate the most efficient allocation of resources for Uzbekistan. Specifically, this analysis will:

1. Assess the cost-effectiveness of current and future programs for TB prevention, case finding and treatment;
2. Evaluate opportunities to improve the cost-effectiveness of TB screening, diagnosis, prevention and treatment programs to minimize the number of active MDR-TB cases by 2030; and
3. Assess how TB prevention, screening and treatment interventions should be prioritized as part of the End TB strategy to achieve 2030 targets.

2 Methodology

OVERVIEW OF OPTIMA TB MODEL

To carry out the analyses, the team used Optima TB, a mathematical optimization model applied to assess how to allocate the available resources across TB programs efficiently to maximize impact. Optima TB is a dynamic, population-based model that partitions the population by risk group including age, TB health state (for example, susceptible, vaccinated, latent TB, active TB), diagnosis and drug resistant types, and tracks people's movement among health states. The model incorporates evidence on biological transmission probabilities, detailed infection progression and population mixing patterns. A detailed illustration of the compartmental model structure is included in Appendix A, Figure A1.

To assess how incremental changes in spending affect TB epidemics and determine an optimized funding allocation, the model parameterizes relationships between the cost of TB interventions, the coverage level attained by these interventions, and the resulting outcomes (cost-coverage-outcome relations). These relationships are specific to the place, population, and intervention being considered.

Using the relationships between cost, coverage, and outcome in combination with Optima TB's epidemic model, it is possible to calculate how incremental changes in the level of funding allocated to each intervention will impact the overall epidemic indicators. Furthermore, by using a mathematical optimization algorithm, Optima TB is able to determine an optimized allocation of funding across different TB interventions.

COLLABORATION AND STAKEHOLDER INVOLVEMENT

The analysis was a collaboration between the National TB Control Program (NTP), Burnet Institute and the Global Fund. National collaborators defined the scope of the analysis, collated national epidemiological, program and cost data, and reviewed and validated all input data, model calibration and cost-coverage-outcome relations.

POPULATIONS AND TB PROGRAM AREAS

Populations considered in this analysis were:

- Children 0-4 years
- Children 5-14 years
- Adults 15-64 years
- Adults 65+ years
- People living with HIV (untreated)
- People living with HIV (on ART)
- Prisoners 15+ years

Based on available data, the following TB programs were considered in the analysis (see also Appendix D1):

Table 1. TB programs included in the Optima TB Uzbekistan analysis, 2023

Prevention	TB preventive therapy (TPT) for household contacts:	0-4 years
		5-14 years
		15+ years
	TPT for PLHIV	
	TPT for non-household repeated contacts all ages[1]	
	BCG for children aged 0-4	
Diagnosis	Household contact tracing[2]	
	Active case finding among prisoner populations	
	Active case finding among populations at high-risk[3]	
	Active case finding (mandatory screening)[4]	
	Other testing, including mass screening and passive case finding	
Treatment	DS-TB treatment	
	MDR-TB standard treatment	
	MDR-TB shorter treatment regimens	
	XDR-TB standard treatment	
	XDR-TB shorter treatment regimens	

Notes: BCG, Bacillus Calmette-Guerin; DS, drug susceptible; MDR, multi-drug resistant; TB, tuberculosis; XDR, extensively drug-resistant
1, Prospective program focusing on extending the reach of TPT by reaching non-household repeat contacts of index cases; 2, Focuses on screening among household contacts with some additional reach to other repeat contacts of index cases; 3, includes individuals with specific comorbidities, including HIV and diabetes mellitus, migrants, populations experiencing homelessness; 4, Groups requiring mandatory testing include healthcare workers, military conscripts, higher education students, and personnel working personnel working in pre-schools or public services.

In Uzbekistan, annual mandatory testing is required for the following groups (4):

- Pre-school staff
- Military conscripts
- Personnel of public services (utilities, mass transit, food industry, trade)
- Healthcare workers of TB centers
- Animal breeding workers
- Vocational school and higher education students

The National TB Programme defines groups at higher risk of TB as the following (4):

- People with comorbidities: Non-specific lung diseases, diabetes mellitus, gastric and duodenal ulcer disease, corticosteroid, cytostatic and radiation therapy, mental health disorders, or HIV infection
- Persons under dispensary supervision at drug treatment services
- Migrants
- People staying in social security institutions
- Unknown residence (homeless).

Currently in Uzbekistan TPT is offered to all children 0-17 from household TB contacts, people in contact with a patient diagnosed with MDR-TB, and people living with HIV. Adult household contacts are not routinely tested for TB (4). An epidemiological review of the Uzbekistan TB programme proposed to scale up systematic screening of TB contacts and access to TPT by implementing targets to reach 10 contacts per index case (4). A prospective program for TPT was modelled to consider the potential expansion of TPT to non-household repeat contacts, who are expected to have lower yield (8).

Shorter treatment regimens for MDR-TB incorporated both modified shorter treatment regimens (mSTR, 9-month duration) and modified shorter treatment regimens utilizing BPaLM (6-month duration).

SCOPE OF ANALYSIS

Study partners identified a range of scenarios for inclusion in the analysis based on national priorities, policy questions and available data (Table 2). Each scenario assumes that changes in intervention coverage occur in 2024 and are sustained until 2030.

Table 2. Scenarios included in the Optima TB Uzbekistan analysis, 2023

Scenario	Description
Baseline scenario	Continued spending and fixed allocation of US$89 million (100% of TB prevention, screening and treatment spending) maintained over 2024-2030
Optimized spending 100%	Continued spending of US$89 million (100%) with allocation optimized to reduce DR-TB incidence and TB-related deaths by 2030.
Reduced/increased spending (75%, 150%) optimized	Considers if available resources for TB programs were reduced or increased. Percentages are relative to the most recent targeted TB spending.
Impact of universal Xpert diagnosis	Projected impact of 100% and 150% spending optimized alongside utilizing Xpert MTB/RIF Ultra universally as first diagnostic test for presumptive TB on projected TB incidence and TB-related deaths from 2024-2030 and ability to reach End TB targets by 2030 (see Appendix D2).

MODELLING SPECIFICATIONS

Model inputs

A new Optima TB model for Uzbekistan was developed for this analysis. Epidemiological, program and cost data (Table 3) were collated by the study team and collaborators using an adapted Excel-based Optima TB data entry spreadsheet. Other model inputs and parameters are described in Appendix B. Epidemiological parameters were calibrated to align to WHO-reported estimates (1).

Table 3. Main sources of data used in the Optima TB Uzbekistan model, 2023

Data type	Source
Epidemiologic data	Demographic data for population size, birth rate estimates and all-cause mortality from UN population division (9); UNAIDS Spectrum estimates for PLHIV (10); Prisoner population estimates from World Prison Brief (11). TB notifications, TB-related deaths supplied by National TB Program, 2016-2022. Historical notifications based on WHO-reported data (1).
Program coverage data	Treatment initiations and outcomes by smear status and strain, number of BCG vaccinations, and TPT and LTBI therapy initiations (combined) supplied by National TB Program, 2016-2022. Number of people screened by

	modality and positive yield informed by and National TB Program data and 2022 review of the National Tuberculosis Programme assuming population disaggregation based on distribution in 2016 (4).
Cost data	Annual cost per treatment initiation provided by National TB Program, 2022, based on weighted cost of included treatment regimens. Costs incorporate treatment drugs, inpatient and outpatient care, laboratory monitoring, adverse event management and psychosocial support. Cost per person diagnosed derived from costs for TB diagnosis provided by National TB Program, 2022, and estimated yield.

Model calibration

In consultation with national TB experts, Optima TB was calibrated to available epidemiologic data on TB case notifications and WHO estimated TB incidence (Global TB Programme 2023 estimates) (1, 4). The model was calibrated to closely match estimates of key TB indicators such as active-TB incidence and prevalence and latent TB prevalence. Parameters with high levels of uncertainty, such as force of infection were adjusted to closely match indicators including TB incidence and prevalence (Appendix C).

Optimization objectives

Allocations were optimized to evenly prioritize progress by 2030 on proportionally reducing each of the prevalence of DS-TB, MDR-TB, XDR-TB, and reducing the number of TB-related deaths. Based on the estimated baseline conditions of 2022, this resulted in model weightings of 1, 3 and 20 respectively for reductions in the active number of DS-TB, MDR-TB and XDR-TB, and 11 per TB-related death averted.

Optimization constraints

Changes in funding to achieve optimized allocations did not consider reallocation of care costs between hospitalized and ambulatory treatment modalities. Spending was constrained to not reduce current coverage of preventive therapy for people living with HIV. Similarly, BCG infant vaccination is funded outside of the TB program and was constrained to not have reduced spending or coverage. All other programs were constrained to not reduce by more than 50% from baseline spending.

3 Findings

EPIDEMIOLOGICAL SITUATION

TB incidence

In 2022, there were an estimated 25,000 incident TB cases modelled in Uzbekistan using Optima TB, including both new and relapse cases and notified extrapulmonary TB (Table 4). Of these, an estimated 39% were extrapulmonary. Estimated TB incidence in Uzbekistan has overall significantly declined from 85 per 100,000 population in 2015 to 72 per 100,000 population in 2022. However, consistent with WHO-reported trends, there was an increase in incidence following 2020, which may be due to COVID-19 related disruptions such as decreased screening activities and delays in care-seeking (4).

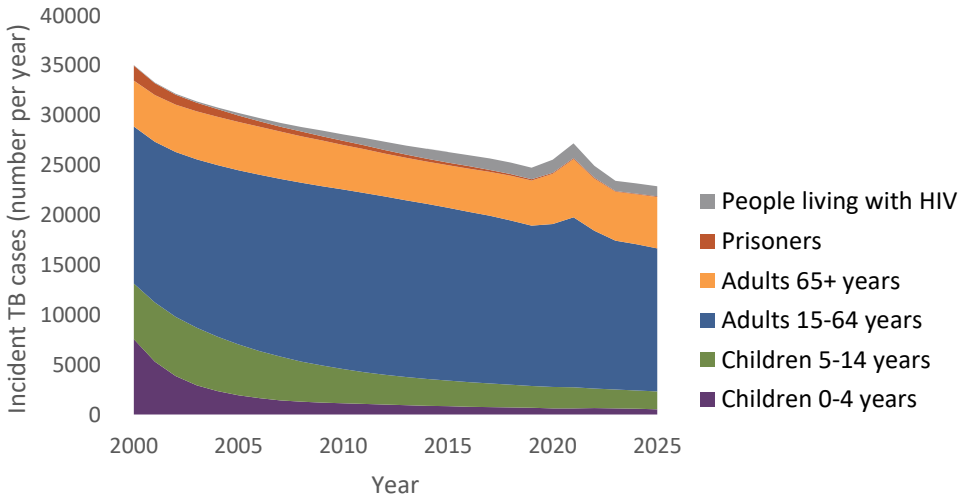
Table 4. Modelled estimated TB incidence, number of prevalent active TB infections, latent infections, and TB-related deaths by sub-population, 2022

	Incident TB			Prevalent TB		
	New and relapse cases[1]	Incidence per 100,000 population	DR-TB cases (% of all new and relapse cases)	Total active TB	Latent TB prevalence	TB-related deaths
0-4 years	631	16	65 (10%)	147	0.2%	5
5-14 years	1,988	30	303 (15%)	804	2.0%	20
15-64 years	15,794	70	2,459 (16%)	28,534	25.0%	1,626
65+ years	5,245	283	753 (14%)	9,755	32.9%	513
Prisoners	83	377	25 (29%)	170	30.8%	11
PLHIV	1,198	1,572	233 (19%)	2,036	9.3%	490
Total	**24,939**	**72**	**3,837 (15%)**	**41,446**	**18.3%**	**2,666**

Source: Optima TB Uzbekistan model output, 2023

The majority of new and relapse cases of TB continue to be among adults aged 15-64, with approximately 15,800 incident cases in 2022 (Figure 1). However, relative to population size people living with HIV have the highest incidence of TB in Uzbekistan, with estimated 1,572 new and relapse cases per 100,000 population in 2022, concentrated among individuals who are not diagnosed and not on ART. In 2022, 15% of new and relapse TB infections were DR-TB.

Figure 1. New and relapse TB cases by population group, 2000–2025

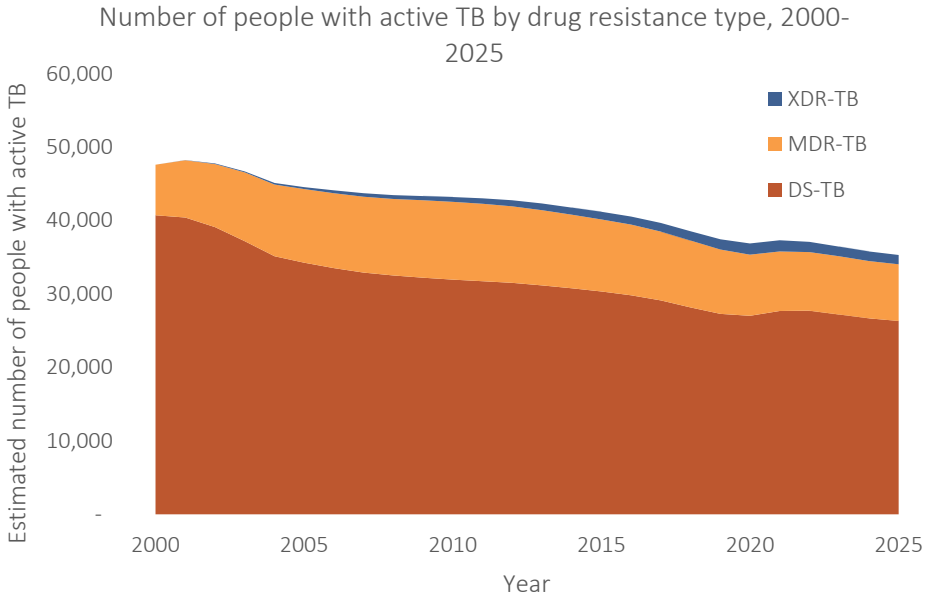


Source: Optima TB Uzbekistan model output, 2023.

Prevalent TB

In 2022, there were a cumulative of 41,500 active TB cases in Uzbekistan based on Optima modelled estimates, and the majority of prevalent TB cases were among those aged 18-64. The estimated prevalence of latent TB was 18% and highest among adults 65+ and prisoners. Among prevalent TB cases in 2022, an estimated 25% of cases were DR-TB (Figure 2).

Figure 2. Trends in the estimated number of people with active TB by drug resistance type, 2000–2025



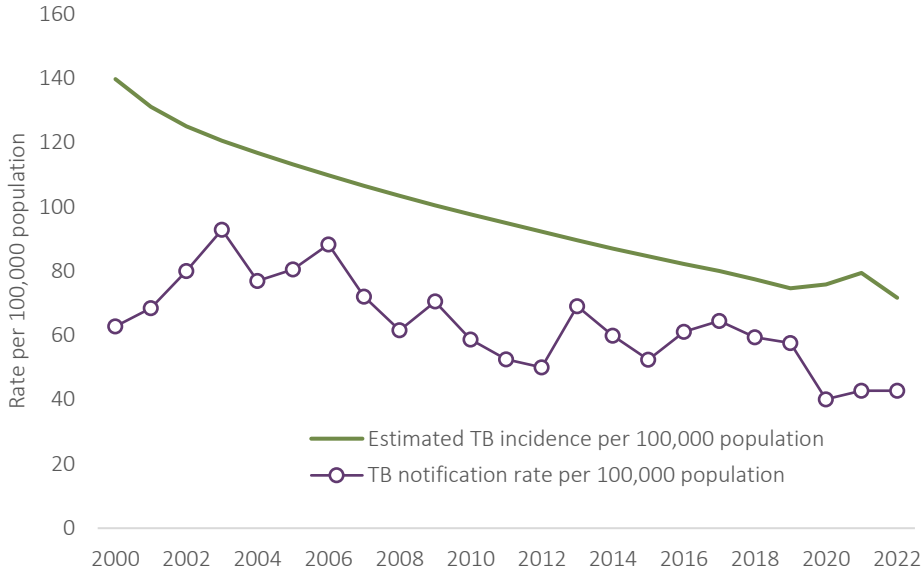
Source: Optima TB Uzbekistan model output, 2023.
Notes: DS, drug susceptible; TB, tuberculosis; MDR, multi-drug resistant; XDR, extensively drug-resistant.

TB notification and case detection

In 2022, there were a total of 14,870 TB notifications in Uzbekistan (43 per 100,000 population), of which 67% were among adults 15-64. The estimated case detection rate (the proportion of estimated new and relapse TB cases that are detected in a given year(12)) ranged from 0.21 among people living with HIV not on treatment (suggesting many are never diagnosed or diagnosed only when experiencing severe symptoms) to 5.1 among people living with HIV on ART (due to regular screening and prevention, any active TB cases are identified after 2.4 months on average).

Since 2000, the notification rate has stayed consistently below estimated TB incidence, indicating a gap in case detection. The decline in notifications from 2020 further widened the gap in case detection, which may have been due to COVID-19-related disruptions and impacts (Figure 3).

Figure 3. Estimated TB incidence rate and notification rate per 100,000 population, 2015–2022

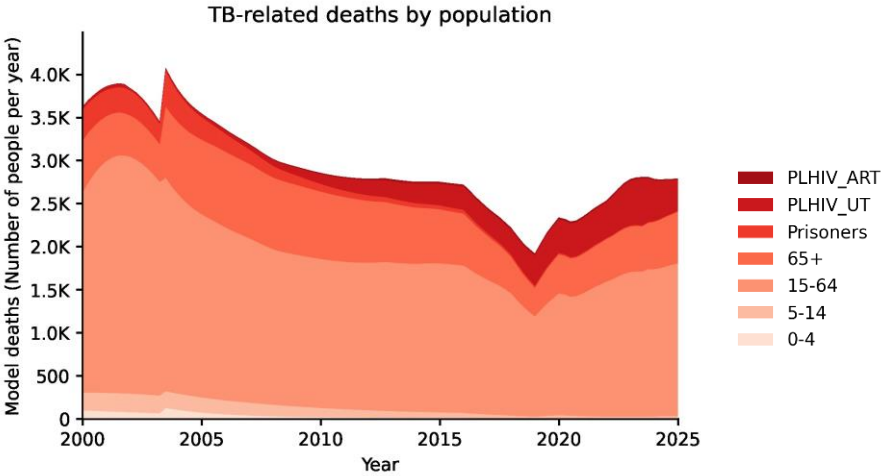


Source: Optima TB Uzbekistan model output, 2023. Notification data from WHO Global TB Programme data (2000-2015) and National TB Program (2016-2022).

TB mortality

Overall TB-related deaths have declined in Uzbekistan from a high of approximately 3,900 in 2001 to 2,000 in 2018 based on modelled estimates, in line with decreasing incidence and advances in diagnosis and treatment (Figure 4). Deaths have been increasing since 2020, reaching 2,700 in 2022, but are predicted to have stabilized.

Figure 4. TB-related deaths by population, 2015–2025



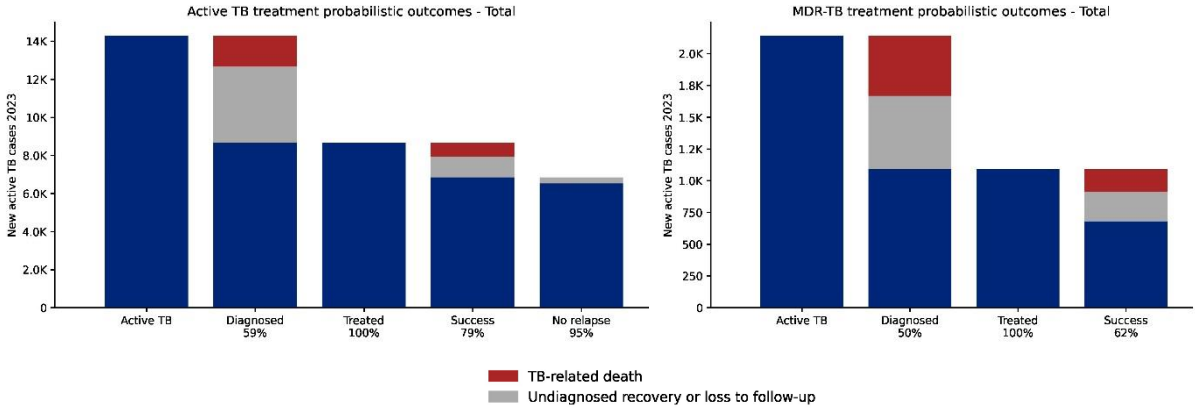
Source: Optima TB Uzbekistan model output, 2023.

TB cascade

A probabilistic cascade is reported representing the estimated long-term outcomes of the cohort of people progressing to active TB in 2023. In 2022, there were an estimated 24,939 incident active TB cases, 14,870 TB notifications and treatment initiations. Based on the most recent estimated diagnosis and treatment rates derived from the 2022 data, 59% of all people progressing to active

TB in Uzbekistan in 2023 would be projected to be diagnosed prior to natural outcome (recovery or death). Of those diagnosed, 100% are projected to be treated (Figure 5).

Figure 5. The projected final cohort outcomes for people progressing to active TB (left) and MDR-TB (right) in 2023 in the baseline spending scenario



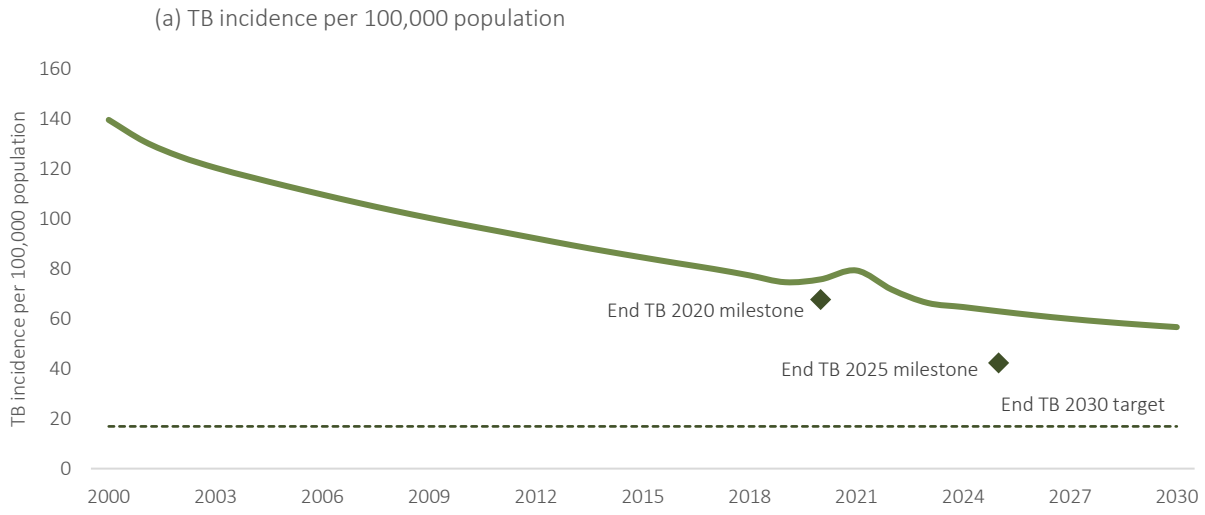
Source: Optima TB Uzbekistan model output, 2023.

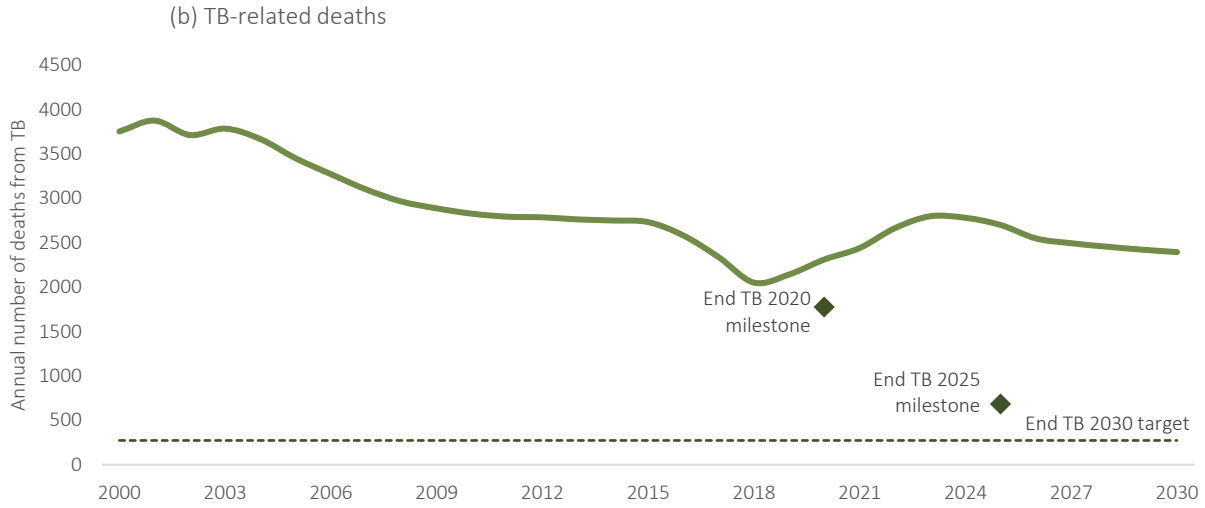
Overall, the probability of treatment success was 79% and lower (62%) for MDR-TB. For both MDR-TB and XDR-TB, treatment loss to follow up has decreased since 2017, from 14% to 8% for MDR-TB and 15% to 6% for XDR-TB among adults aged 15+. For XDR-TB, treatment failure has also decreased over the same timeframe, from 21% to 8%, among adults.

Progress towards TB targets

Ambitious targets set by the global End TB strategy aim to reach a 80% reduction in incidence rate and 90% reduction in TB deaths by 2030 relative to 2015 (13). To evaluate progress towards the 2030 targets, the strategy defines country milestones for 2020 and 2025. Based on Optima TB modeled projections, Uzbekistan was on track to meet 2020 milestones for TB incidence and deaths prior to COVID-19 disruptions. However, is not predicted the reach the End TB 2025 milestones nor 2030 targets with current conditions continued (Figure 6).

Figure 6. Optima TB estimated trends in (a) TB incidence rate and (b) TB mortality in relation to End TB targets





Source: Optima TB Uzbekistan model output, 2023. End TB milestones (diamond markers) and 2030 targets (dashed line) defined as percentage reduction from 2015 (14). Baseline based on Optima modelled values.

CURRENT TB SPENDING

Based on most recent spending estimates, in 2022 an estimated US$89 million was spent on direct TB prevention, screening and treatment programs. Of this, the majority was spent on treatment (63%). In Uzbekistan use of shorter, all-oral treatment regimens accounted for 13% of MDR-TB treatment and 22% of XDR-TB treatment numbers in 2022. Among spending specific to TB testing and screening, 48% was spent on other test strategies incorporating mass screening and passive case finding, and 35% was spent on mandatory testing among “special” populations.

WHAT IS THE OPTIMIZED ALLOCATION OF THE TB BUDGET?

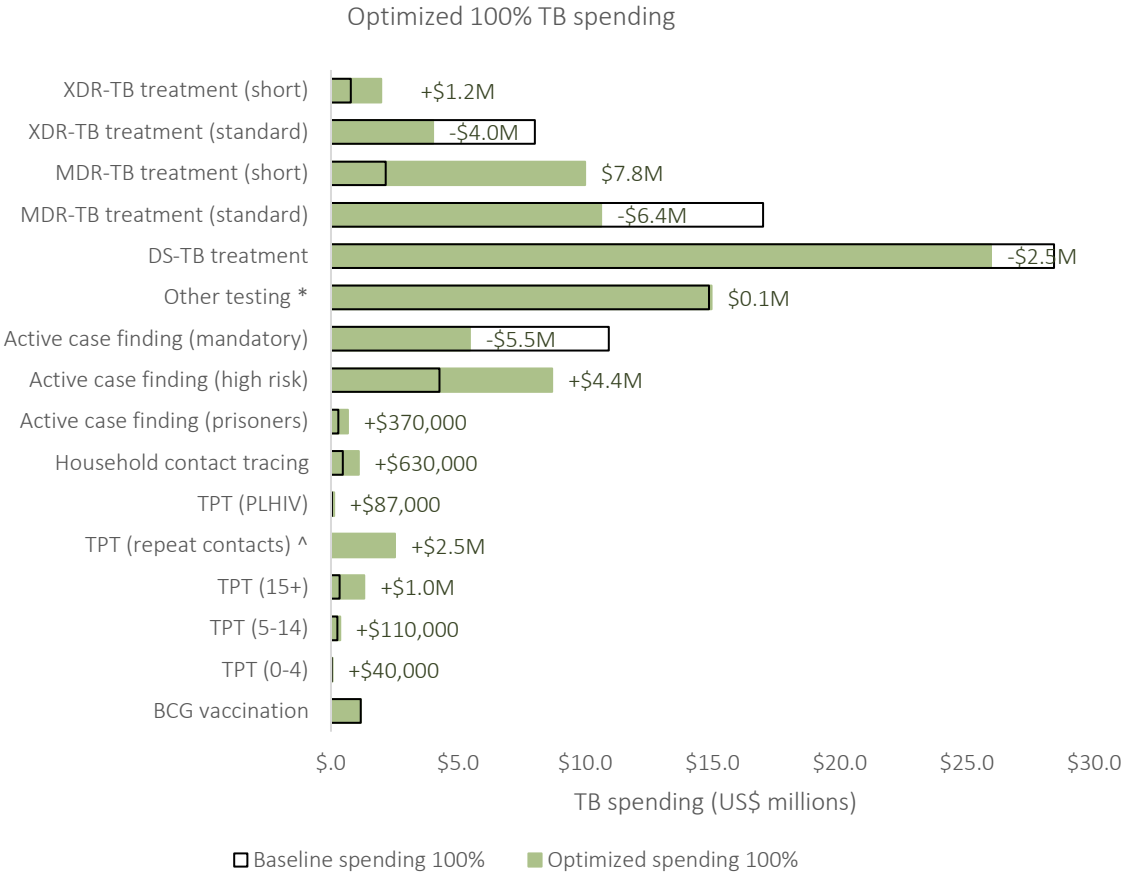
Optimized allocation of TB spending

With 100% of baseline spending maintained, the optimized allocation of the TB budget prioritizes short-course MDR and XDR treatment (+US$ 9.0M) rather than the standard course MDR and XDR treatment to minimize prevalence of drug-resistant TB by 2030 (Figure 7). Due to the projected decrease in TB incidence, there is a projected reduction in spending needed for DS-TB (-US$ 2.5M) by 2024.

TB preventative therapy is prioritized for scale up among all age groups to prevent activation of latent TB, but particularly among adults (+US$ 1.0M). It is also recommended to expand TPT to non-household repeat contacts (+US$ 2.5M).

In terms of screening and testing, the optimization recommends reallocating spending from mandatory testing (-US$ 5.5M) to prioritize more targeted active case finding among individuals at high risk (+US$ 4.4M), through contact tracing (+US$ 630,000) and among prisoners (+US$ 370,000). Mandatory testing is only prioritized for expansion after other modalities of case finding are saturated, with 150% spending optimized (Figure 8).

Figure 7. Baseline and optimized allocation of current TB spending for TB prevention, testing and treatment interventions

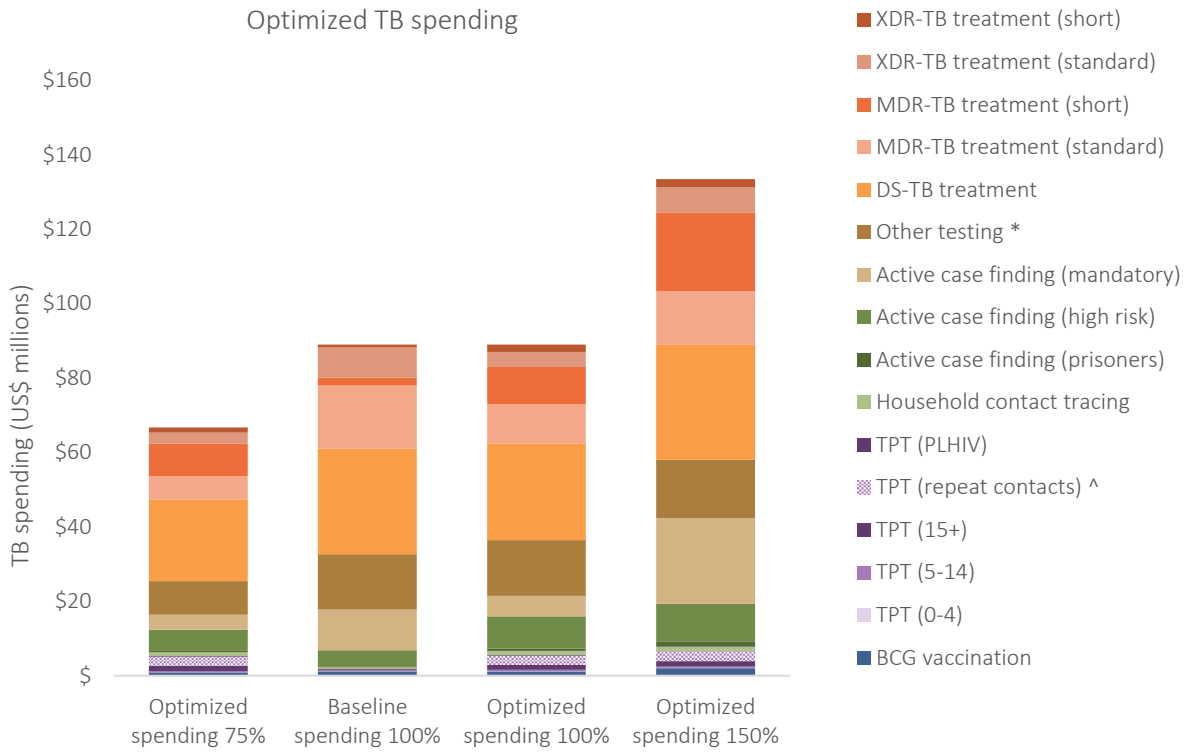


Notes: * Includes mass screening and passive case finding; ^ Refers to non-household repeat contacts of individuals with active TB.
BCG, Bacillus Calmette-Guérin; DS, drug susceptible; MDR, multi-drug resistant; PLHIV, people living with HIV; TB, tuberculosis; TPT, TB preventive treatment; XDR, extensively drug-resistant.
Source: Optima TB Uzbekistan model, 2023

As a result of the shorter course treatment and savings made through more targeted and cost-efficient case-finding, an additional 2,357 (+22%) DR-TB cases could be initiated on treatment from 2024 to 2030. The number of people covered by each intervention can be found in Appendix E.

At lower budget levels below 100%, epidemic gains can be maximized by first maintaining treatment for DS, MDR and XDR-TB utilizing shorter-treatment regimens, and secondly, scaling up contact tracing and TPT for all ages, including people living with HIV and non-household repeat contacts. Detailed spending by budget level can be found in Appendix E.

Figure 8. Recommended allocation of funding by program to minimize drug-resistant TB for varying budget levels (75% to 150%)



Notes: * Includes mass screening and passive case finding; ^ Refers to non-household repeat contacts of individuals with active TB.
BCG, Bacillus Calmette-Guérin; DS, drug susceptible; MDR, multi-drug resistant; PLHIV, people living with HIV; TB, tuberculosis; TPT, TB preventive treatment; XDR, extensively drug-resistant.
Source: Optima TB Uzbekistan model, 2023

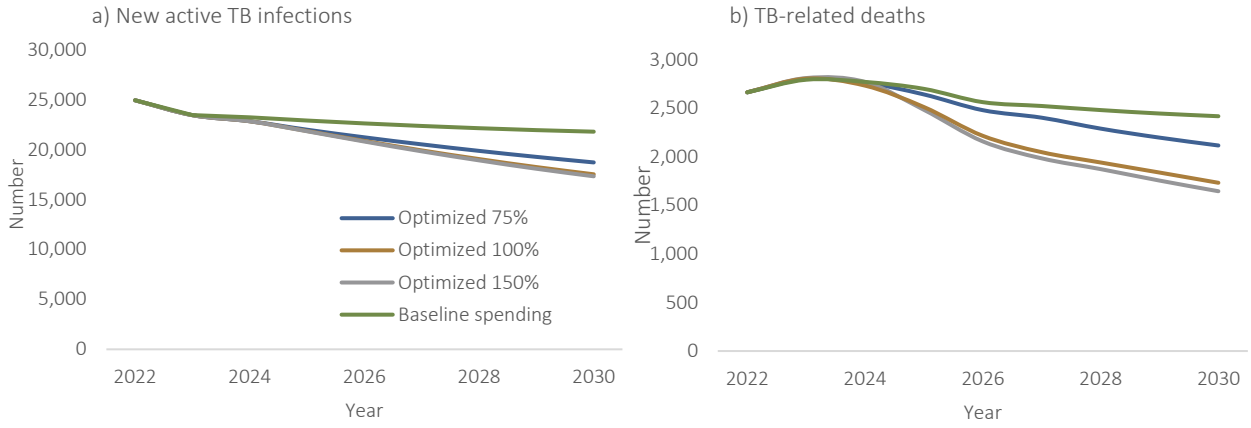
Projected impact of optimized TB spending

With current conditions and spending maintained, Optima TB projects that there would be approximately 157,000 incident TB cases and 18,000 TB-related deaths from 2024 to 2030.

With 100% of baseline TB spending optimized, it is estimated that approximately 17,000 (-11%) new TB infections and 2,900 (-16%) TB-related deaths could be averted from 2024 to 2030 compared with if baseline spending were continued (Figure 9).

At higher budget levels there are diminishing returns as high-impact interventions are saturated at 100% spending optimized. At 150% spending optimized, additional resources (+US$ 12.1M) are primarily allocated to mandatory testing which has lower efficiency for case finding (estimated yield 0.01%) compared to other screening modalities (range in yield: 0.02% to 1.9%).

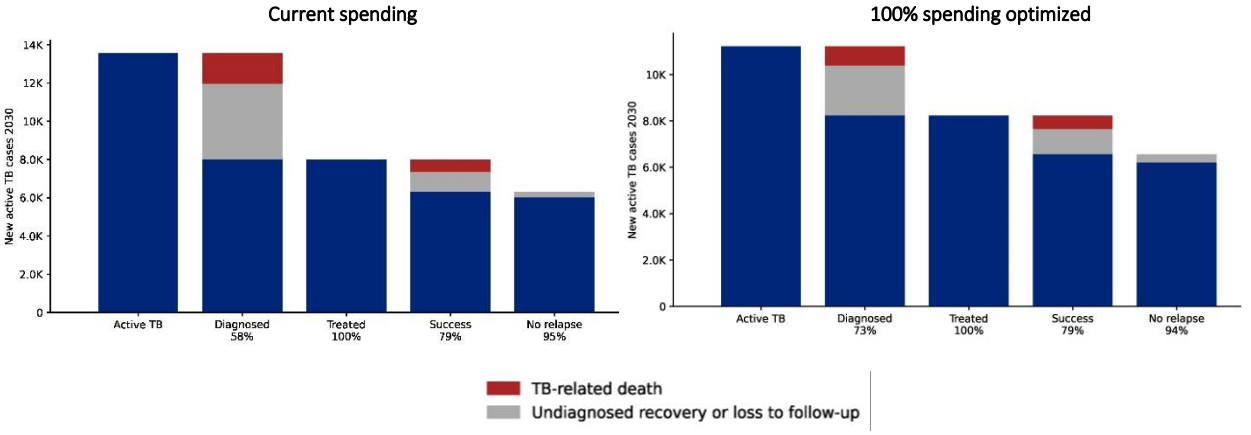
Figure 9. Projected impact of optimization at varying budget levels on TB incidence and TB-related deaths per 100,000, 2022–2030



Source: Optima TB Uzbekistan model, 2023

By 2030, 100% spending optimized could improve TB diagnosis by +15 percentage points compared to if current spending is continued and maintain 100% treatment coverage (Figure 10). This analysis did not consider treatment success to change as a result of shorter treatment regimens, therefore no impact is seen there.

Figure 10. Active TB probabilistic cascade in current spending (left) and 100% optimized spending (right) in 2030



Source: Optima TB Uzbekistan model, 2023

WHAT IS THE PROJECTED ADDITIONAL IMPACT OF UNIVERSAL XPERT DIAGNOSIS FOR PRESUMPTIVE TB?

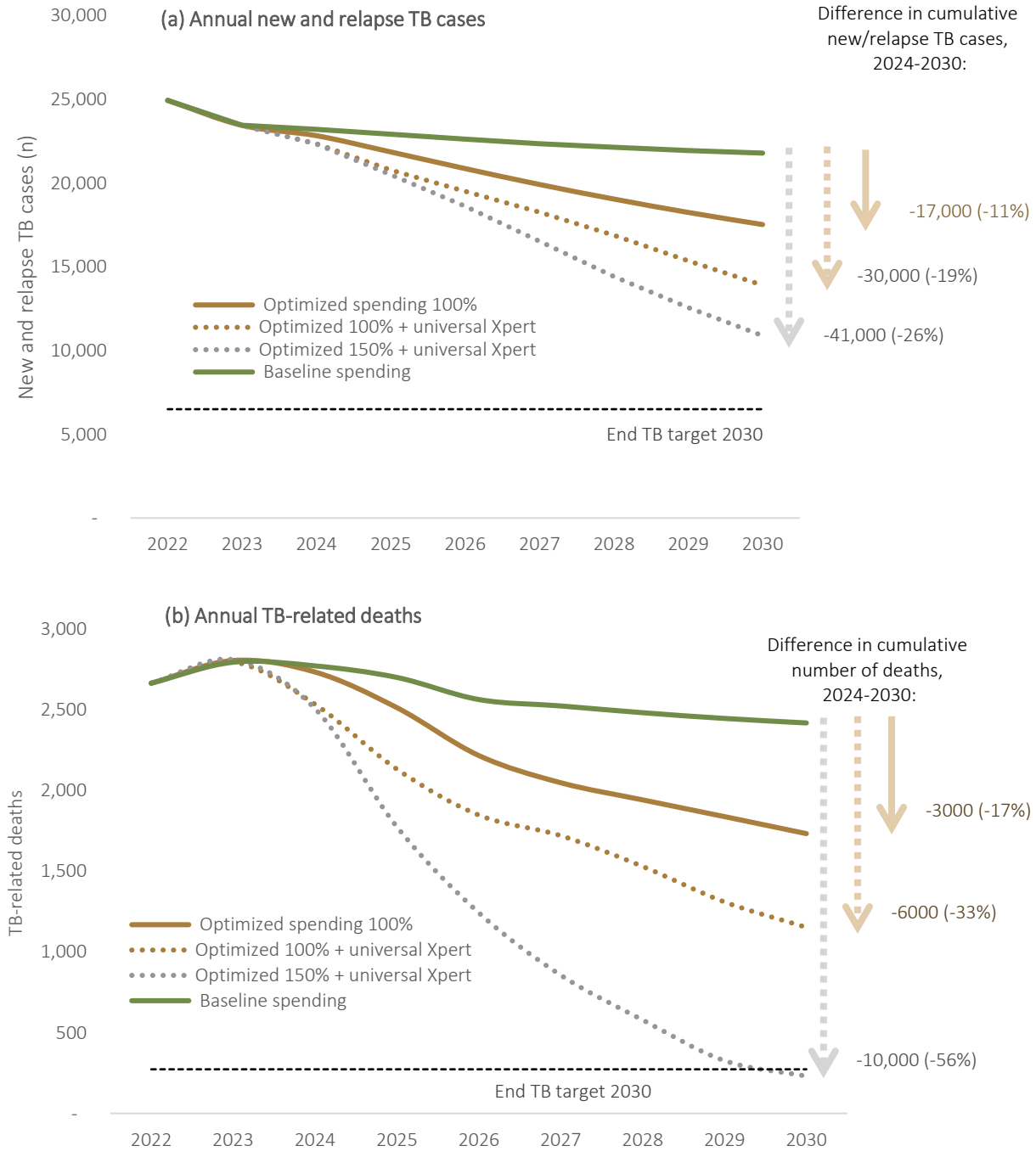
A key strategic priority in Uzbekistan is to update the national diagnosis algorithm to universally utilize Xpert MTB/RIF as the only initial diagnostic test, replacing microscopy for primary diagnosis. It was assumed that universal application of Xpert MTB/RIF for diagnosis would allow the probability of diagnosing smear-negative TB to increase in line with smear-positive TB for all active case finding modalities and double the maximum potential coverage of TPT for contacts based on the projected increase in diagnosed index cases.

Optimizing 100% baseline spending with universal Xpert MTB/RIF for diagnosis from 2024 onwards, it may be possible to avert 30,000 (-19%) incident TB cases and 6,000 (-33%) TB-related deaths compared to the continuation of baseline spending. This represents a further reduction of 8

percentage points for new/relapse cases and 16 percentage points in deaths compared to 100% spending optimized without change in the diagnostic algorithm (Figure 11).

With 150% spending optimized plus universal Xpert MTB/RIF, it may be possible to avert 41,000 (-26%) incident TB cases and 10,000 (-56%) TB-related deaths compared to the continuation of baseline spending, representing a substantial improvement in both epidemic outcomes compared to 100% spending optimized without change in diagnostic algorithm (Figure 11).

Figure 11. Projected impact on annual (a) new and relapse TB cases and (b) TB-related deaths of budget optimizations with addition of universal Xpert MTB/RIF



Source: Optima TB Uzbekistan model, 2023

More details of the assumptions applied in the scenario looking at the impact of applying GeneXpert as first diagnostic test our provided in Appendix D2.

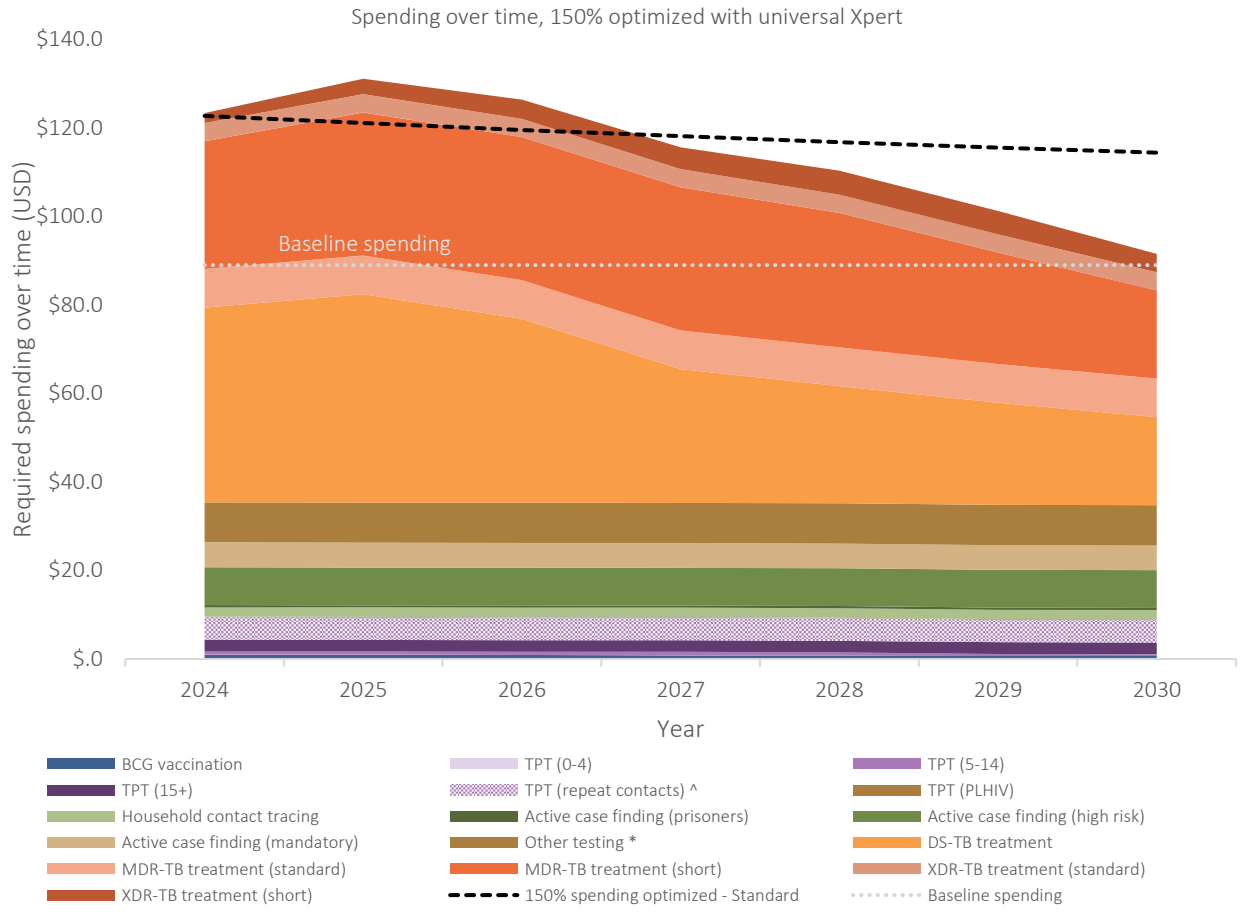
HOW CLOSE CAN UZBEKISTAN GET TO END TB TARGETS BY 2030 WITH UNIVERSAL XPERT DIAGNOSIS?

With 100% spending optimized using universal Xpert MTB/RIF for diagnosis, a more rapid reduction in deaths is projected due to earlier diagnosis of smear-negative TB. The increase in diagnoses also allows for further expansion of TPT among contacts, leading to a faster reduction in TB incidence.

With 150% spending optimized plus universal Xpert MTB/RIF, greater gains in both reducing TB-related deaths and TB incidence are projected, and Uzbekistan could achieve the 2030 End TB target for reduction in deaths and make strong gains in reduction of incidence (Figure 11).

With additional investment in TB (up to +US$44.5M based on projected treatment needs in 2025) alongside universal Xpert diagnosis, resource needs are projected to reduce in the long-term due to a decrease in the number of people requiring treatment. By 2030, maintaining these enhanced screening and prevention programs combined with treating all diagnosed TB cases may be possible with US$91.5 million, which is nearly equivalent to baseline spending (Figure 12).

Figure 12. Resource needs over time to maintain the impact of 150% spending optimized with universal Xpert MTB/RIF for diagnosis, 2024–2030



Source: Optima TB Uzbekistan model, 2023

Uzbekistan is not projected to reach the End TB 2030 target for TB incidence with current interventions. Engagement with relevant civil society organizations to more effectively reach TB-affected communities, advances in adopting people-oriented and predominantly outpatient delivery models, and reducing stigma and discrimination of those with TB may further progress.

4 Study limitations

As with any mathematical modelling analysis it is necessary to make assumptions about data that are not routinely collected or available, and about some of the expected relationships between variables. These assumptions necessarily imply certain limitations:

TB expenditure and program definitions: Unit costs for interventions are subject to some levels of uncertainty. There were limited data available on the number tested for presumptive TB by modality, and unit costs may underestimate actual costs. Diagnostic spending only accounts for commodity costs, and this could impact the relative cost-effectiveness of different screening modalities. There were insufficient data differentiate passive case finding and diagnosis through mass screening in Uzbekistan. Data on screening and yield among people in prisons were not available, and assumptions were made with country representatives.

The prospective program of TPT among non-household repeat contacts was informed by cost of TPT among household contacts and international literature on yield of latent TB among repeat contacts (8, 15). The feasibility of reaching non-household contacts is not known, but was informed by national strategic planning (4).

The difference in diagnostic costs using universal Xpert compared to status quo was not considered in this analysis. According to National TB Programme-provided data, Xpert diagnostics may be cheaper than microscopy in Uzbekistan. However, based on relative cost estimates in other settings it may require significant additional resources to implement practically (16). The assumption that maximum contact tracing and TPT coverage could be doubled under this scenario is theoretical, based on anticipated increases in diagnoses and subsequent contact investigation.

There were insufficient program data to consider the resources required to reach the End TB targets for TB incidence.

The size and profile of the TB epidemic in Uzbekistan was aligned with the 2023 WHO Global TB Programme modelled estimates (1). If these estimates are revised in future years subject to emerging data, Optima TB estimates would need to be considered in context of the new estimates.

Prevalence of extrapulmonary TB remains high in Uzbekistan, estimated at 39% of new and relapse cases in 2022. The Optima TB model does not currently explicitly model extrapulmonary TB, but factors in a constant proportion of extrapulmonary TB into total costs needed for treatment. The potential for increased diagnosis of extrapulmonary TB, for example as a result of improved case-finding for subclinical TB, is not factored into this analysis.

Resource needs for treatment of drug resistant strains were projected based on the proportion of incident drug resistant cases in 2022, but this may continue to evolve based on either suitability of new drugs to treat previously extensively drug resistant cases as per the WHO reclassification of XDR in 2021 (17), or further emergence of new drug resistance in Uzbekistan.

Implementation efficiency: Detailed modelling of implementation efficiency was beyond the scope of the study, and this analysis only included considerations of implementation efficiency in a limited way. Decentralized and ambulatory treatment, financial incentives for healthcare workers, ultraportable computer-aided detection (CAD)-enhanced chest X-ray, utilizing shorted rifampicin-based regimens for TPT, and engaging civil society organizations in TB screening have been identified as potential ways to improve implementation efficiency in Uzbekistan (4). However, there were insufficient data to model the additional cost and impact of these potential or planned changes.

Intervention effectiveness: Allocative efficiency modelling depends critically on the availability of evidence-based parameters for the effectiveness of individual interventions. Although these estimates were derived from global systematic literature reviews where possible, they may vary in specific countries and populations. In particular, the quality of implementation and levels of adherence may vary by context and population. All interventions and spending categories for which effectiveness parameters could not be obtained were treated as fixed spending in the mathematical optimization. This includes any programs that may indirectly impact the TB epidemic, such as programs that reduce stigma and discrimination of those with TB.

Priority populations: Insufficient data were available to consider the burden of TB and population-specific interventions for other priority populations at increased risk of TB or with poorer health outcomes, including migrants.

Non-TB benefits: Effects outside of TB indicators, such as the non-TB benefits of different TB treatment modalities, are not considered in these analyses. Given the range and complexity of interactions among interventions and their non-TB benefits, the model did not consider wider health, social, human rights, ethical, legal, employment-related or psychosocial implications; but acknowledges that they are important aspects to be considered in planning and evaluating TB responses.

Key areas to strengthen data inputs and model certainty may include: triangulation of program costs through top-down spending estimates; standardized case-based recording and reporting to improve performance tracking on contact tracing and TPT; defining size, characteristics and burden of TB among other vulnerable and priority populations for TB control, including labor migrants, people who use drugs, and people in prisons; and evidence of program effectiveness, including the role of shorter treatment regimens on treatment completion and success.

5 Conclusions

This allocative efficiency analysis for TB prevention and treatment in Uzbekistan highlights the necessity to invest in short-duration treatment regimens for drug-resistant TB, more targeted testing strategies such as contact tracing and active case finding among populations at higher risk of TB, and scale up of TB preventive treatment among adults and non-household repeat contacts.

KEY RECOMMENDATIONS

1. Shorter, all-oral treatment regimens are more cost-effective, allowing for a larger number of people to be treated for the same amount of spending, as well as having fewer side-effects and better adherence for people with TB.
2. Scaling back mandatory testing among populations with low risks of TB can enable increased investment in more targeted active case finding among contacts of people with active TB and populations at higher risk of TB, thereby improving diagnosis rates.
3. Expanding TB preventive treatment for adult household contacts and repeat contacts from non-household settings is a top priority to reduce incidence of TB, even if overall resources for TB reduce.
4. Implementing universal Xpert diagnosis will lead to a much faster decline in TB-related deaths and incidence due to earlier diagnosis and potential to expand TB preventive treatment.

KEY FINDINGS AND OPPORTUNITIES

- Implementing shorter duration, all-oral regimens for drug resistant TB can reduce the cost of individual treatment by 18% for MDR-TB to 66% for XDR-TB, enabling more people to be treated without increasing overall resources. As a result of the shorter course treatment and savings made through more targeted and cost-efficient case-finding, an additional 2,357 (+22%) people could be initiated on treatment for DR-TB from 2024 to 2030 for the same amount of overall TB spending and 2,500 new/relapse DR-TB cases could be averted over the same period.
- Currently mandatory screening accounts for 35% of spending on TB screening, yet only accounts for an estimated 5% of TB notifications as the populations targeted for annual mandatory testing have relatively low burden of TB. Shifting from mandatory testing to expand contact tracing and active case finding among populations at higher risk of TB will enable more cost-efficient case finding. This may include people living with HIV, migrants, people who use drugs and people experiencing homelessness, although the burden of TB among these populations is currently not well quantified in Uzbekistan. Leveraging civil society organizations can help ensure screening reaches those most in need and may be facilitated through social contracting mechanisms (14). This will likely require additional resources and technical assistance to expand the technical capacity of civil society organizations to implement TB activities, and the full cost of these changes were not evaluated in this analysis.
- Contact tracing and TB preventive therapy in Uzbekistan is currently focused on children under 18 years (4). Scaling up contact tracing for adults, including outside of households, coupled with expanded access to TB preventive therapy could lead to substantial reductions in TB incidence in Uzbekistan. With overall resources maintained and spending

optimized, it may be possible to avert 17,000 (-11%) new/relapse TB cases in total over 2024 to 2030 compared to baseline spending maintained. The availability of new shorter regimens for TPT (e.g. 3HP, 3HR) may support the scale up of TPT (18). However, the true impact of expanding contact tracing will depend on the ability to effectively target it to those most at risk and relies on effective and early diagnosis of index cases to be most impactful.

- Uzbekistan is not projected to reach the 2030 End TB target for reduction in incidence with current programs optimized. Stigma and discrimination of people with TB can be a major barrier to care seeking and treatment success (19). This may be exacerbated by processes such as institutionalized treatment and mandatory testing (4). Efforts to adopt people-oriented, family-centered and predominantly outpatient delivery models, engage with relevant civil society organizations to more effectively reach TB-affected communities, and reducing stigma and discrimination of those with TB may advance progress in reaching End TB targets and improving the health and wellbeing of people with TB.
- With initial additional investment in TB (150% spending) alongside universal Xpert diagnosis it may be possible to reach the 2030 End TB target for TB-related deaths. Universal use of Xpert diagnostics will increase the efficiency of active case finding. The required resources to maintain enhanced screening and prevention programs combined with treatment for all diagnosed TB cases will decrease over time as treatment-need reduces and may be possible with US$91.5 million, nearly equivalent to baseline spending, by 2030. Realizing the projected impact of universal Xpert alongside optimized spending will require reform to regulation to approve the updated testing algorithm based on the WHO recommendations (20).

6 References

1. Global Tuberculosis Programme Data: World Health Organization; 2023 [updated Nov 7; cited 2023 Nov 9]. Available from: https://www.who.int/teams/global-tuberculosis-programme/data.
2. Global Tuberculosis Report. Geneva: World Health Organization; 2022 [cited 2023 April 28]. Available from: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022.
3. Office of the Inspector General. Global Fund supported TB/MDR-TB programs in Eastern Europe and Central Asia – focus on Uzbekistan, Kyrgyzstan and Tajikistan: Audit report. Geneva: The Global Fund; 2922.
4. Extensive review of the National Tuberculosis Programme in the Republic of Uzbekistan: 3–19 October 2022. Copenhagen: World Health Organization Regional Office for Europe; 2022.
5. Global Tuberculosis Programme Data: World Health Organization; 2022 [cited 2023 July 6]. Available from: https://www.who.int/teams/global-tuberculosis-programme/data.
6. Expenditure and utilization of health services for TB since fiscal year 2017. 2023. In: Global Tuberculosis Programme Data [Internet]. World Health Organization. Available from: https://www.who.int/teams/global-tuberculosis-programme/data.
7. Decree of the President of the Republic of Uzbekistan: on measures for the further development of the phthusiology and pulmonology service in 2023-2026 (unofficial translation from 20-06-2023). 2023 Jan 21. License: 07/23/12/0041.
8. McCreesh N, White RG. An explanation for the low proportion of tuberculosis that results from transmission between household and known social contacts. Scientific Reports. 2018;8(1):5382.
9. United Nations Department of Economic and Social Affairs Population Division. 2022 Revision of World Population Prospects 2022 [cited 2022 July 23]. Available from: https://population.un.org/wpp/.
10. HIV estimates with uncertainty bounds 1990-present [Internet]. UNAIDS. 2023 [cited 2023 Jul 17]. Available from: https://www.unaids.org/en/resources/documents/2023/HIV_estimates_with_uncertainty_bounds_1990-present.
11. World Prison Brief: Uzbekistan: Institute for Crime & Justic Policy Research; [cited 2023 Aug 8]. Available from: https://www.prisonstudies.org/country/uzbekistan.
12. The Global Health Observatory: Case detection rate for all forms of tuberculosis. Geneva: World Health Organization; [cited 2023 Nov 9]. Available from: https://www.who.int/data/gho/indicator-metadata-registry/imr-details/3162.
13. World Health Organization. The End TB Strategy. Geneva: WHO; 2015 [cited 2022 Feb 15]. Available from: https://www.who.int/teams/global-tuberculosis-programme/the-end-tb-strategy.
14. World Health Organization Regional Office for Europe. A people-centred model of TB Care: Blueprint for EECA countries, first edition: World Health Organization; 2017 [cited 2021 January 10]. Available from: https://www.euro.who.int/en/health-topics/communicable-diseases/tuberculosis/publications/2017/a-people-centred-model-of-tb-care-2017.
15. Fox GJ, Barry SE, Britton WJ, Marks GB. Contact investigation for tuberculosis: a systematic review and meta-analysis. Eur Respir J. 2013;41(1):140-56.
16. Hao X, Lou H, Bai J, Ding Y, Yang J, Pan W. Cost-effectiveness analysis of Xpert in detecting Mycobacterium tuberculosis: A systematic review. International Journal of Infectious Diseases. 2020;95:98-105.

17. WHO announces updated definitions of extensively drug-resistant tuberculosis. Geneva: World Health Organization; 2021 [cited 2023 Dec 18]. Available from: https://www.who.int/news/item/27-01-2021-who-announces-updated-definitions-of-extensively-drug-resistant-tuberculosis.
18. The WHO Consolidated Guidelines on Tuberculosis (TB), Module 1: Prevention Tuberculosis preventive treatment. Geneva: World Health Organization; 2020 [cited 2023 July 25]. Available from: https://pubmed.ncbi.nlm.nih.gov/32186832/.
19. Turusbekova N, Celan C, Caraulan L, Rucsineanu O, Jibuti M, Ibragimova O, et al. Gender-related factors associated with delayed diagnosis of tuberculosis in Eastern Europe and Central Asia. BMC Public Health. 2022;22(1):1999.
20. World Health Organization. WHO Consolidated Guidelines on Tuberculosis, Module 3: diagnosis: rapid diagnostics for tuberculosis detection, 2021 update. Geneva: World Health Organization; 2021 [cited 2023 Dec 20]. Available from: https://www.who.int/publications/i/item/9789240029415.
21. Goscé L, Abou Jaoude GJ, Kedziora DJ, Benedikt C, Hussain A, Jarvis S, et al. Optima TB: A tool to help optimally allocate tuberculosis spending. PLoS Comput Biol. 2021;17(9):e1009255.
22. Houben RMGJ, Lalli M, Sumner T, Hamilton M, Pedrazzoli D, Bonsu F, et al. TIME Impact – a new user-friendly tuberculosis (TB) model to inform TB policy decisions. BMC Medicine. 2016;14(1):56.
23. Andrews JR, Noubary F, Walensky RP, Cerda R, Losina E, Horsburgh CR. Risk of progression to active tuberculosis following reinfection with Mycobacterium tuberculosis. Clin Infect Dis. 2012;54(6):784-91.
24. Mangtani P, Abubakar I, Ariti C, Beynon R, Pimpin L, Fine PE, et al. Protection by BCG vaccine against tuberculosis: a systematic review of randomized controlled trials. Clin Infect Dis. 2014;58(4):470-80.
25. Behr MA, Warren SA, Salamon H, Hopewell PC, Ponce de Leon A, Daley CL, et al. Transmission of Mycobacterium tuberculosis from patients smear-negative for acid-fast bacilli. Lancet. 1999;353(9151):444-9.
26. Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJ. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. PLoS One. 2011;6(4):e17601.

7 Appendices

APPENDIX A. OPTIMA TB MODEL OVERIVEW

A.1. Tuberculosis model structure

The Optima TB tool is based on a dynamic, population-based TB model encapsulated within an intervention and costing framework (21). The model uses a linked system of ordinary differential equations to track the movement of people among health states (Figure A1). The overall population is partitioned in two ways: by population group and by TB health state. TB infections occur through the interactions among different populations. Each compartment in Figure A1 corresponds to a single differential equation in the model, and each rate (Figure A1 arrows) corresponds to a single term in that equation. The analysis interprets empirical estimates for model parameter values in Bayesian terms as previous distributions. The model then must be calibrated: finding posterior distributions of the model parameter values so that the model generates accurate estimates of notified TB cases, TB incidence, TB prevalence, the number of people on treatment, and any other epidemiological data that are available (such as TB-related deaths). Model calibration and validation normally should be performed in consultation with governments in the countries, in which the model is being applied.

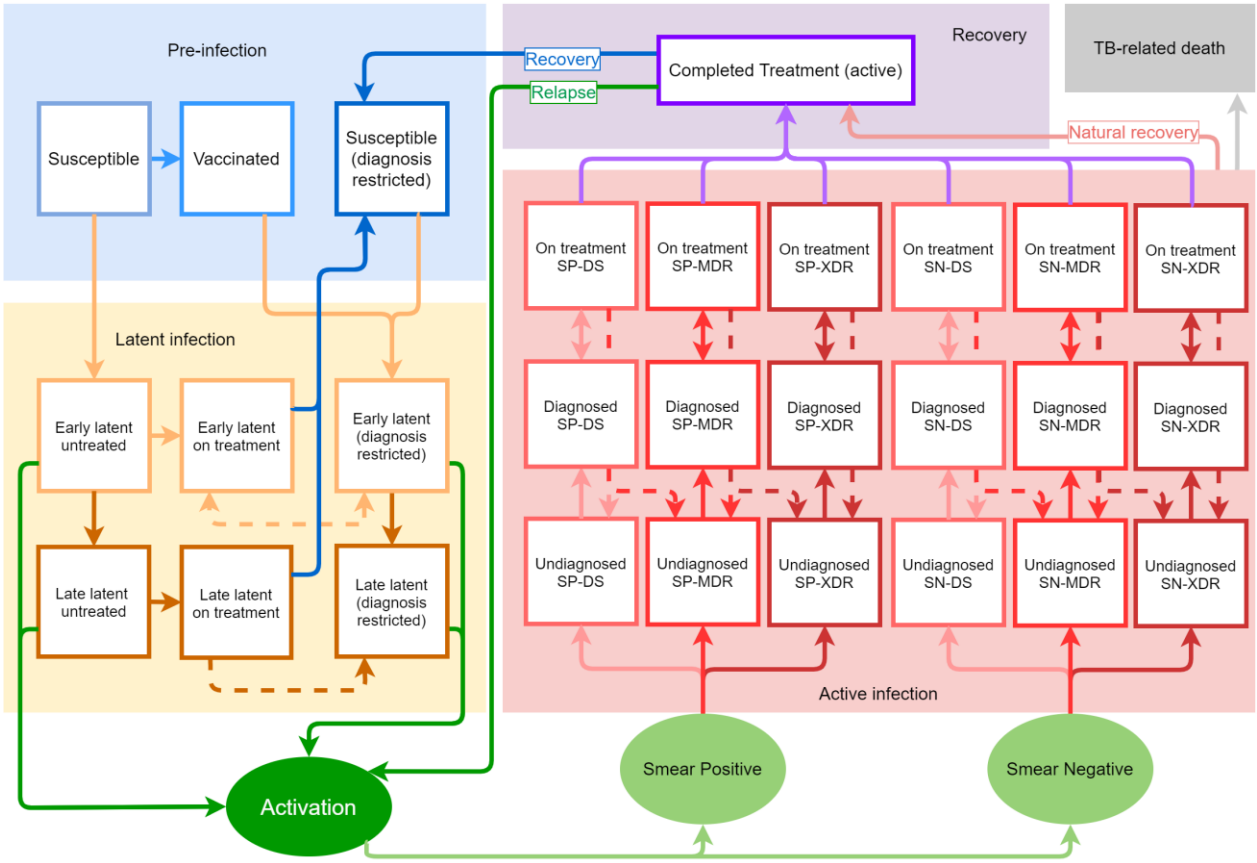
The WHO definition for incident TB cases includes both new and relapse cases. In the model, incident TB cases correspond to the following transitions between compartments (Table A1):

- New cases: these are represented by the number of progressions to active TB from early and late latent-TB compartments. ‘New’ also includes recurring episodes of TB from the recovered compartment following re-infection
- Relapse cases: these correspond to a new episode of TB disease after previous completion of treatment or natural recovery.

Treatment success includes ‘cured’ and ‘treatment completion’, as per the WHO definition:

- Death during TB treatment is not included in treatment failure, but is considered separately
- Treatment failure and ‘loss to follow-up’ during treatment are included as separate outcomes in the model.

Figure A1. Optima TB model diagram



Source: Goscé (2021)
Note: Each compartment represents a single population group with the specified health state. Each arrow represents the movement of numbers of individuals between health states. All compartments except for "susceptible" and "vaccinated" represent individuals with either latent or active TB. Death can occur for any compartment, but TB related mortality varies between compartments. SN-DS, smear-negative drug susceptible; SP-DS, Smear-positive drug susceptible; SP-MDR =smear-positive multi-drug resistant; SN-MDR, smear-negative multi-drug resistant; SN-XDR, smear-negative extensively drug-resistant; TB, tuberculosis.

Table A1. Overview of key Optima TB Model features and definitions

TB parameters	Model features and definitions
Disaggregation by smear-status and drug-resistance	Both smear-positive and negative; DS-TB, MDR-TB, XDR-TB
New vs. relapse cases	The WHO definition for incident TB cases includes both new and relapse cases. In the model, incident TB cases correspond to the following transitions between compartments: New cases: these are represented by the number of progressions to active TB from early and late latent-TB compartments. 'New' also includes recurring episodes of TB from the recovered compartment following re-infection Relapse cases: these correspond to a new episode of TB disease after previous completion of treatment or natural recovery.
Latent TB	Multiple compartments for latent TB infection (LTBI) Cannot skip latent state for disease progression States include undiagnosed, on treatment, and completed treatment Accounts for re-infection and latent care-status using a secondary latent TB pathway. Cases previously treated for LTBI, or vaccinated individuals, can transition to the active TB pathway in the case of reinfection

Vaccination, immunity and resistance	Vaccination explicitly included in model Patients that spontaneously clear from infection
Treatment	States for undiagnosed, diagnosed, diagnosed but not on-treatment, on-treatment, and recovered patients for different types of drug resistance Failed or defaulted treatment can acquire drug resistance
Treatment outcomes	Treatment success includes 'cured' and 'treatment completion', as per the WHO Other outcomes of treatment in the model include 'loss to follow-up' during treatment, 'treatment failure', 'treatment failure with escalation of drug resistance', 'death during treatment'. Where data is reported as 'not evaluated' it may be assumed to be allocated proportionally to other compartments or based on other evidence.
Population structure, key populations and People living with HIV	Age-structured populations can be user defined Ability to specify additional key populations with defined transition rates to/from general population groups People living with HIV represented as a separate key population disaggregated by HIV treatment status

A.2. TB Resource Optimization

Optima TB is able to calculate allocations of resources that optimally address one or more TB-related objectives (for example, impact-level targets in a country's TB national strategic plan). Because this model also calculates the coverage levels required to achieve these targets, Optima TB can be used to inform TB strategic planning and the determination of optimal program coverage levels. The key assumptions influencing resource optimization are the relationships among (1) the cost of TB interventions for specific target populations, (2) the resulting coverage levels of targeted populations with these TB programs, and (3) how these coverage levels of TB programs for targeted populations influence screening and treatment outcomes. Such relationships are required to understand how incremental changes in spending (marginal costs) affect TB epidemics. To perform the optimization, Optima uses a global parameter search algorithm, which is an adaptive stochastic descent algorithm (21).

A.3. Uncertainty Analyses

Optima uses a Markov chain Monte Carlo algorithm for performing automatic calibration and for computing uncertainties in the model fit to epidemiological data. With this algorithm, the model is run many times (typically, 1,000–10,000) to generate a range of epidemic projections. Their differences represent uncertainty in the expected epidemiological trajectories. The most important assumptions in the optimization analysis are associated with the cost-coverage and coverage-outcome curves.

APPENDIX B. MODEL INPUTS

B.1. Demographics

Table B1. Demographic inputs for Optima TB Tajikistan model, 2023

Parameter	2022	Source(s) or assumptions
Population size		
0-4	3,911,385	UN Population Division 2022 (9) and World Prison Brief (11).
5-14	6,550,093	
15-64	22,286,198	
65+	1,778,596	
Prisoners	23,320	
PLHIV not on ART	41,512	
PLHIV on ART	36,488	
Percentage of people who age into the next age category per year		
0-4	19%	UN Population Division 2022
5-14	9%	
15-64	1%	
Annual number of births	776,815	UN Population Division 2022
Annual non-TB death rate		
0-4	0.3%	All-cause mortality based on UN Population Division 2022 and adjusted during calibration
5-14	0.0%	
15-64	0.4%	
65+	6.2%	
Prisoners	0.9%	
PLHIV not on ART	0.4%	
PLHIV on ART	0.4%	
Net number of migrants per year	-19,999	UN Population Division 2022. Total number distributed by age-weighting for 5-14, 15-64 and 65+ amongst number of departing emigrants.

ART, antiretroviral therapy; PLHIV, people living with HIV; TB, tuberculosis.

B.2. Tuberculosis notifications

Table A2. Number of notified TB infections per population group, 2022

Population group	Sputum positive			Sputum negative			Total notified
	DS-TB	MDR-TB	XDR-TB	DS-TB	MDR-TB	XDR-TB	
0-4	5	0	0	279	7	6	297
5-14	50	22	2	1037	61	21	1,193
15-64	3720	1125	174	4929	46	22	10,016
65+	1602	211	19	1016	5	0	2,853
Prisoners	23	20	9	18	0	1	71
PLHIV not on ART	39	17	2	70	0	0	128
PLHIV on ART	87	64	11	149	1	0	312
Total	5,526	1,459	217	7,498	120	50	14,870

Note: ART, antiretroviral therapy; DS, drug susceptible; TB, tuberculosis; MDR, multi-drug resistant; PLHIV, people living with HIV; XDR, extensively drug-resistant.
Source: National TP Programme data, 2023

B.3. TB treatment

Latent TB infection treatment and TB preventive treatment

Table B2. Number of people initiated on TB preventive treatment (TPT) by population group, 2022

Population group	Number starting TPT	
	via contact tracing	via mass screening
0-4	1,751	1,401
5-14	4,374	3,227
15-64	6,412	3,221
65+	409	312
Prisoners	0	0
PLHIV	0	10,512
Total	12,946	18,673

Notes: PLHIV, people living with HIV; TPT, TB preventive treatment. For modelling purposes, the indicated number on TPT were adjusted for estimated proportion of children initiated on TPT who have latent TB (15) and the proportion of all adult tuberculosis cases attributable to recent within-community transmission that can be attributed to household transmission (8).
Source: National TB Programme, 2023

Active TB treatment

Table A3. Treatment outcomes, 2022

	Number of treatment initiations			Average treatment duration (days)			Treatment success[1]			Loss to follow up			Treatment failure (no escalation)			Treatment failure (escalation to MDR/XDR)			Died		
	DS-TB	MDR-TB	XDR-TB	DS-TB	MDR-TB	XDR-TB	DS-TB	MDR-TB	XDR-TB	DS-TB	MDR-TB	XDR-TB	DS-TB	MDR-TB	XDR-TB	DS-TB	MDR-TB	XDR-TB	DS-TB	MDR-TB	XDR-TB
0-4	284	7	6	180	540	560	96%	92%	100%	2%	6%	0%	0.2%	2%	0%	2%	0%	N/A	0.2%	0%	0%
5-14	1,087	83	23	180	540	560	96%	92%	100%	2%	6%	0%	0.2%	2%	0%	2%	0%	N/A	0.2%	0%	0%
15-64	8,649	1,171	196	180	478	473	83%	65%	68%	4%	8%	6%	2%	7%	8%	5%	7%	N/A	5%	13%	18%
65+	2,618	216	19	180	478	473	83%	65%	68%	4%	8%	6%	2%	7%	8%	5%	7%	N/A	5%	13%	18%
Prisoners	41	20	10	180	540	560	79%	59%	67%	4%	7%	0%	9%	13%	17%	0%	0%	N/A	8%	20%	17%
People living with HIV not on ART	109	17	2	180	478	473	79%	59%	67%	4%	7%	0%	9%	13%	17%	0%	0%	N/A	8%	20%	17%
People living with HIV on ART	236	65	11	180	478	473	83%	65%	68%	4%	8%	6%	2%	7%	8%	5%	7%	N/A	5%	13%	17%

Notes: 1, Treatment success includes individuals who have completed treatment without bacteriological confirmation of cure; DS, drug susceptible; TB, tuberculosis; MDR, multi-drug resistant; XDR, extensively drug-resistant. For analysis, numbers were adjusted to reflect pulmonary TB only, based on estimated percentage of notifications that are extrapulmonary by population group.
Source: National TB Programme, 2023

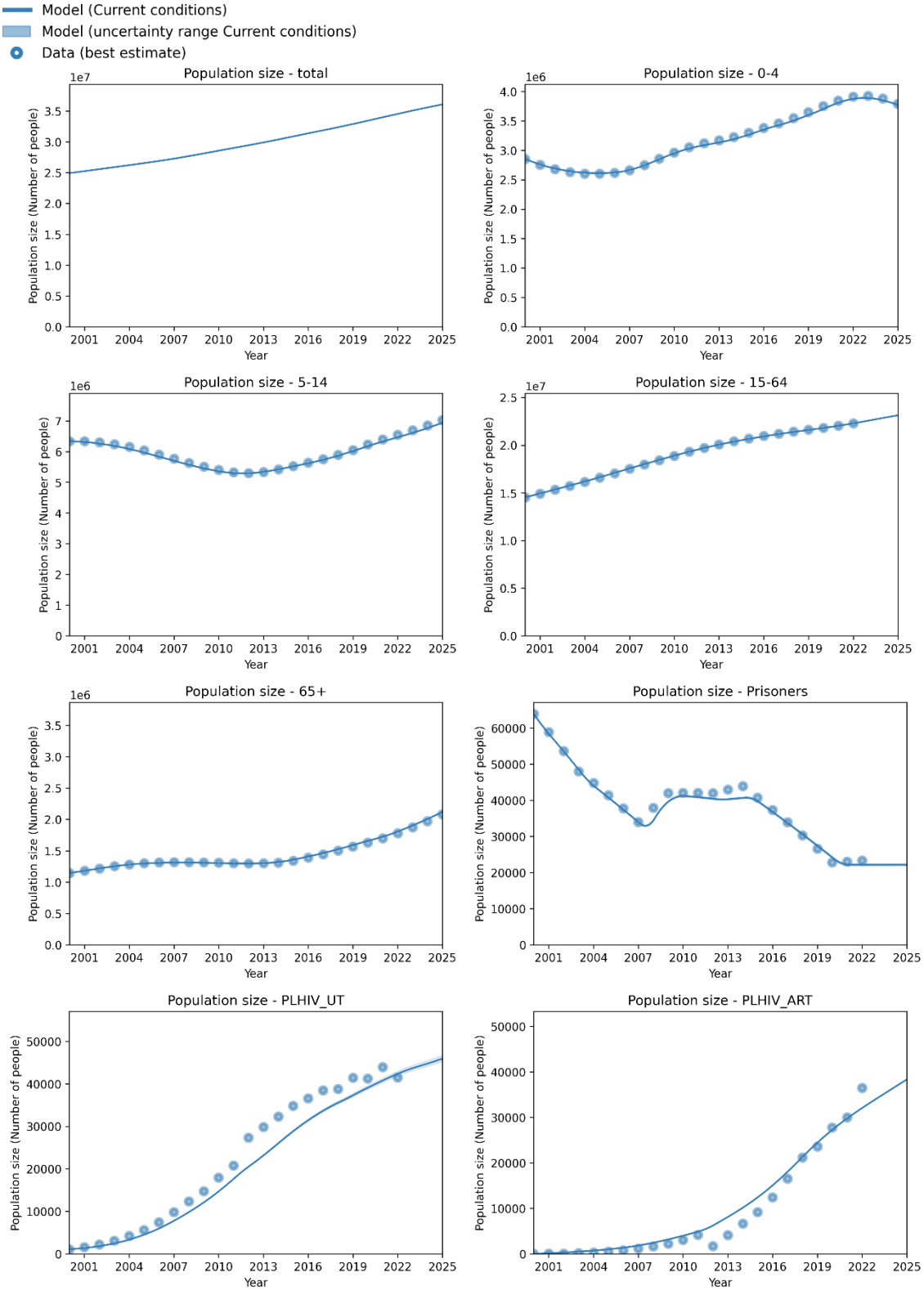
B.4. Epidemiological parameters

Description	Value	Population	Source or assumption
Vaccinations administered (/year)	912,573 (2022)	0-4	National TP Programme data, 2023
Early Latency Departure Rate	0.2 0.3 0.5	0-64 65+, prisoners, PLHIV on ART PLHIV not on ART	Houben (2016) - appendix of TIME model. 0.1%/year reactivation rate (0.01-0.25).
Late Latency Departure Rate*	0.0001 0.0003 0.0005 0.0035 0.1 0.001	0-4 5-14 15-64 65+, prisoners PLHIV not on ART PLHIV on ART	Andrews (2012)- risk of progression to active. All populations assumed a 50% increase in late latency departure rate from mid-2021 until end of 2022.
Probability of Early-Active vs. Early-Late LTBI Progression*	0.1 0.09 0.2 0.354 0.531 0.7 0.6	0-4 5-14 15-64 65+ Prisoners PLHIV not on ART PLHIV on ART	Andrews (2012)- risk of progression to active. Assumed probability of progression decreased over time among PLHIV on ART due to higher rates of HIV viral suppression.
Infection Vulnerability Factor (Vaccinated vs. Susceptible)	0.5 1.0	0-14 15+	Mangtani (2014) (protective efficacy of BCG found to range from 0-80%). A value of 0.5 was used for populations aged 0–14, and no protection (i.e., 1) was used for all populations older than 14 years.
Infection vulnerability factor (relative population susceptibility)	2.2 2.8 5 (2020: 4.5) 6 (2020: 5) 2.3 11 (2020: 5.5) 5	0-4 5-14. 15-64 65+ Prisoners PLHIV not on ART PLHIV on ART	A value of '1' is the default, but this is likely to be significantly higher in vulnerable populations such as people living with HIV. Values between 2.8 and 11 were used in calibrations. In specified populations infection vulnerability was assumed to decrease after 2020.
Smear-positive (SP) TB Infectiousness*	1.0 0.5	All populations unless specified 0-4	A value of '1' is the default
Smear-negative TB Infectiousness (Compared to SP-TB)	0.22	All populations	Behr (1999)
Duration of active TB until natural outcome (years)	3.5 2.0	All populations unless specified PLHIV not on ART	WHO, Tiemersma (2011)
Smear-positive untreated-TB death rate	35-70% 43-86% 90%	All populations unless specified 0-4, 65+ PLHIV not on ART	WHO, Tiemersma (2011) Where range reported, assumed that death rate decreased over time.
Smear-negative untreated-TB death rate	10-20% 15-30% 30%	All populations unless specified 0-4, PLHIV not on ART	WHO, Tiemersma (2011) Where range reported, assumed that death rate decreased over time.

Notes: ART, antiretroviral therapy; LTBI, latent TB infection ; PLHIV, people living with HIV; SN, smear-negative; SP, smear-positive; TB, tuberculosis.

APPENDIX C. CALIBRATION

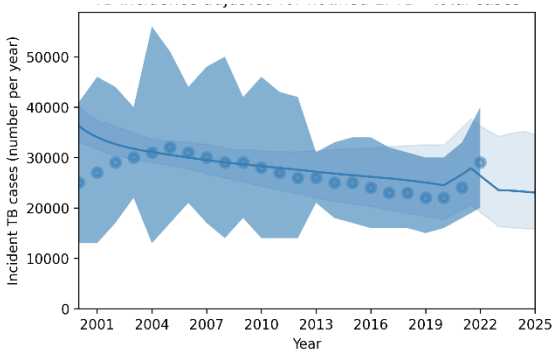
C.1. Populations size calibration figures



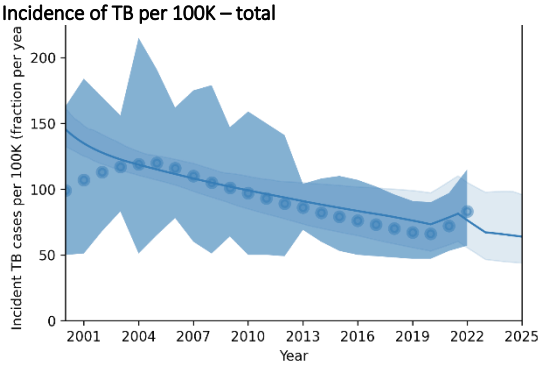
.2. Selected TB epidemic calibration figures

Model (Current conditions)
Model (uncertainty range Current conditions)
Data (best estimate)

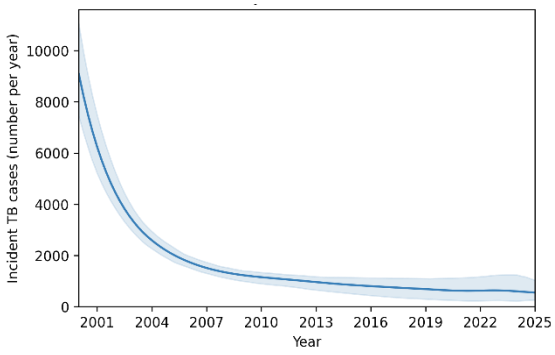
TB Incidence – total cases



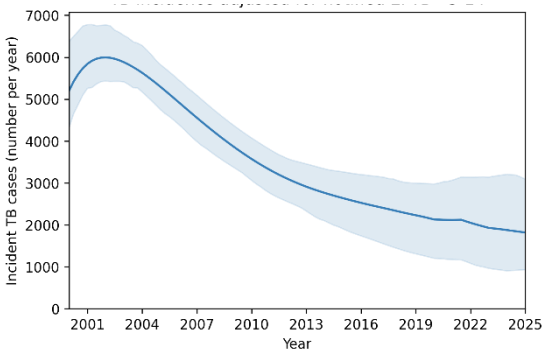
Incidence of TB per 100K – total



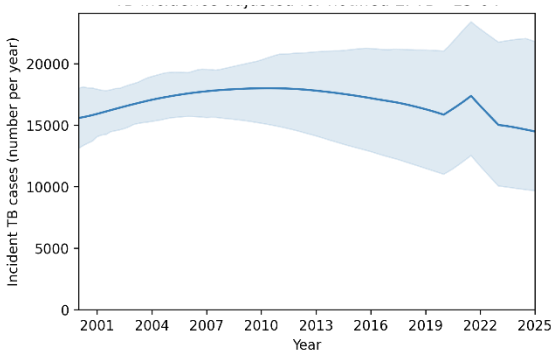
TB incidence – 0-4



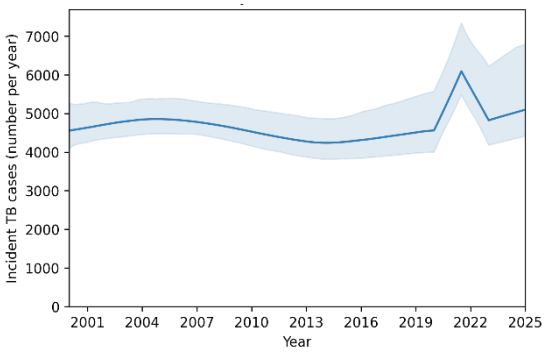
TB incidence – 5-14



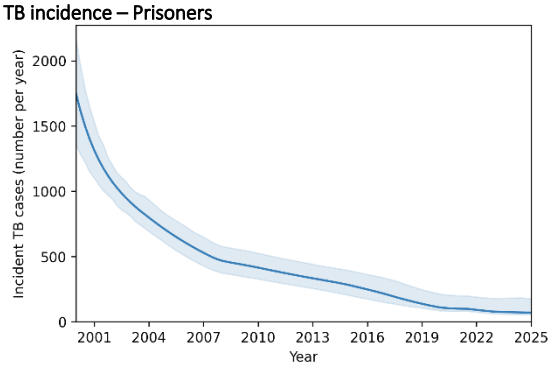
TB incidence – 15-64



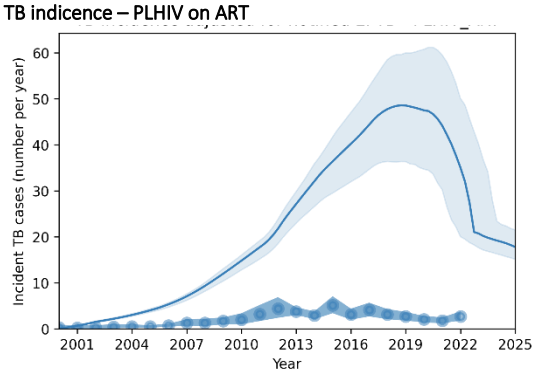
TB incidence – 65+



TB incidence – Prisoners

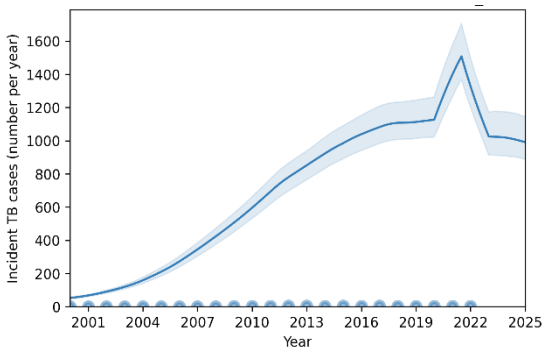


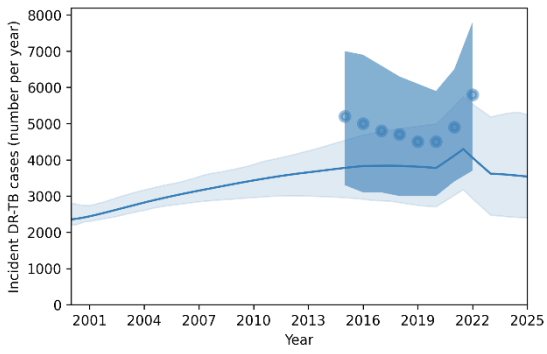
TB indicence – PLHIV on ART



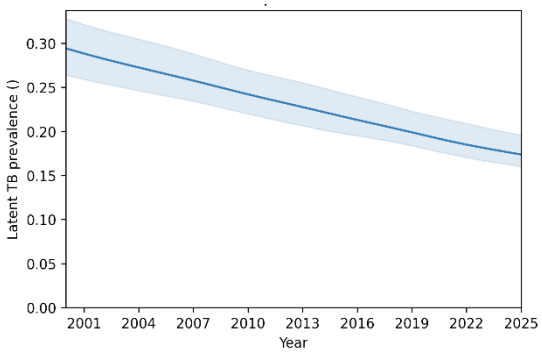
TB incidence – PLHIV not on ART

DR-TB incidence – total cases

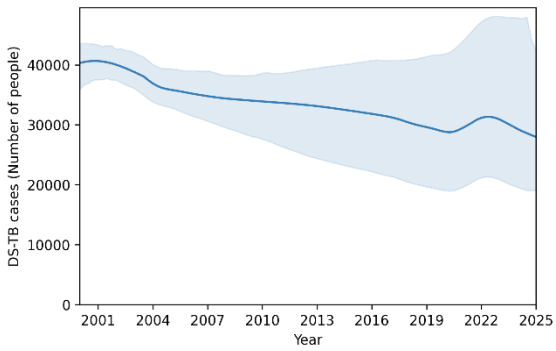




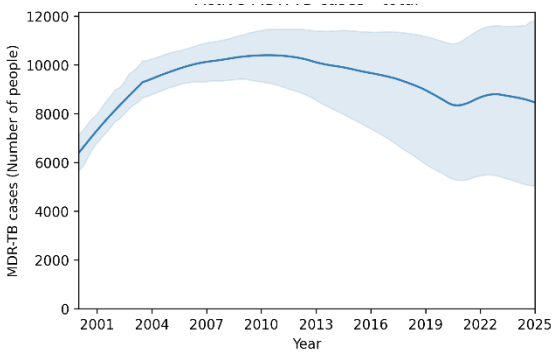
Latent TB prevalence – total



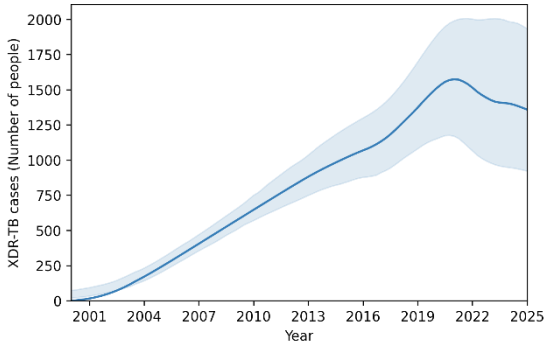
Active DS-TB cases – total



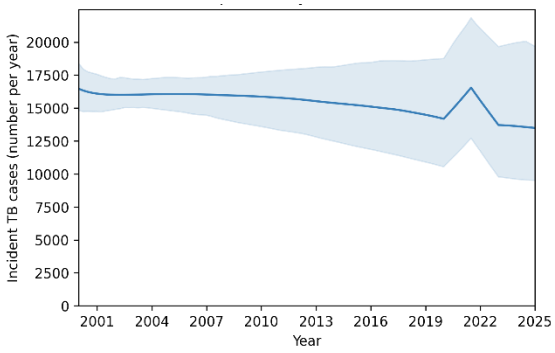
Active MDR-TB cases – total



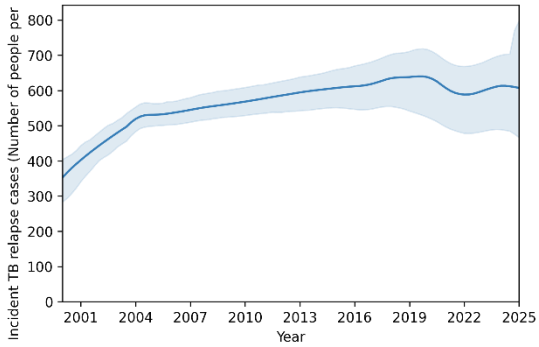
Active XDR-TB cases – total



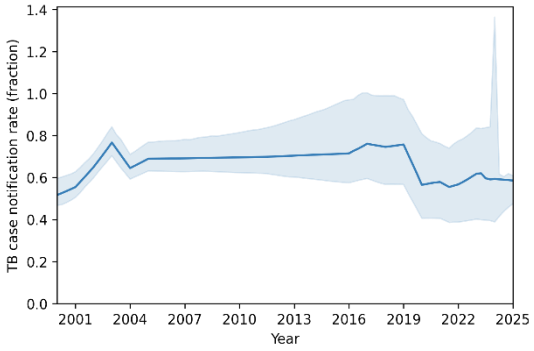
New active pulmonary TB cases – total



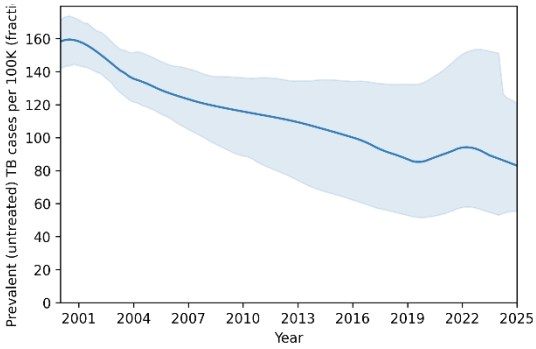
New active relapse pulmonary TB cases – total



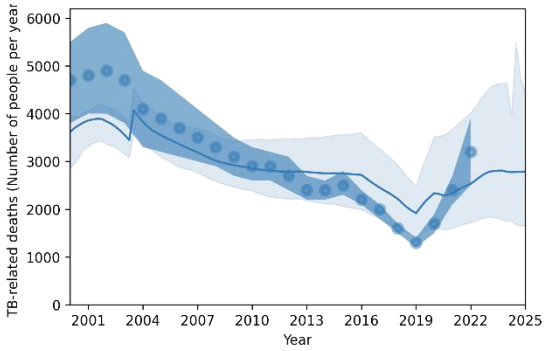
TB cases notification rate– total



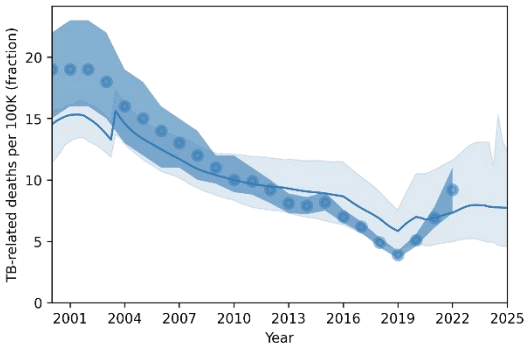
Prevalence of (untreated) pulmonary TB per 100K– total



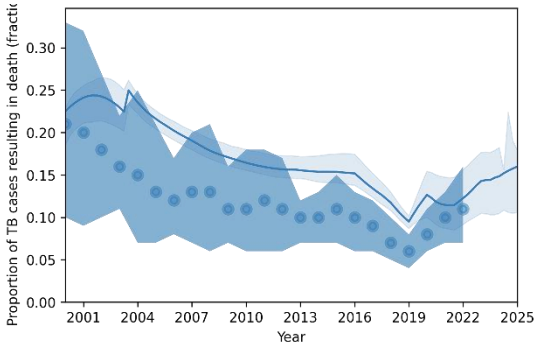
TB-related deaths – total



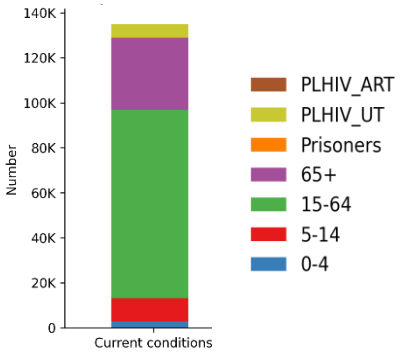
TB-related deaths per 100K – total



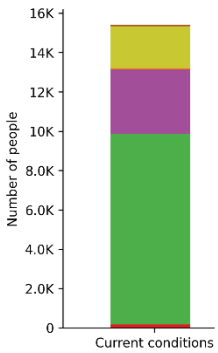
Case fatality ratio – pulmonary TB total



Cumulative TB incidence 2018 to 2030



Cumulative TB-related deaths 2018 to 2030



APPENDIX D. PROGRAM DEFINITIONS

D.1. Program details

Table D1. Program details and estimated unit costs for TB interventions in Uzbekistan

		Unit	Unit cost (USD)	Assumptions
TB PREVENTION PROGRAMS				
BCG vaccination		Cost per infant vaccinated	$1.28	Based off average unit cost reported in current Optima TB projects based in Eastern Europe and Central Asia.
TB preventive therapy (TPT) for people living with HIV		Cost per person per year	$3.36	Funded through the HIV program and constrained not to reduce below current spending. Maximum possible coverage based on number of PLHIV on ART.
TPT for household contacts aged:	0-4 years 5-14 years 15+ years	Cost per person who is a household contact of active TB, per preventive therapy initiation	$6.84 $32.52 $32.52	Weighted cost by regimen, including 3HP (rifapentine + isoniazid) and 6H (isoniazid). Adjusted for the estimated prevalence of early latent TB among household contacts by age group (8, 15), the estimated cost per contact with early latent TB was estimated as $35.02, $246.37, and $312.70 for household contacts aged 0-4 years, 5-14 years, and 15+ years respectively.
TPT for non-household repeat contacts	All ages	Cost per person who is a non-household repeated contact of active TB, per preventive therapy initiation	$32.52	Prospective program based on weighted cost of TPT among adults. Adjusted by the estimated prevalence of early latent TB and non-household repeat contacts (8, 15) the estimated cost per contact with early latent TB was estimated as $443.18. Enables the scale up of TPT to reach target of 10 contacts screened per index case (4) when average household size is 5.24 (1).
SCREENING AND DIAGNOSIS PROGRAMS				
Household contact tracing		Per person diagnosed	$379.60	Based on average diagnostic costs for latent TB and active TB. Positive yield of 1.9% based on Tashkent only but applied to national number screened (4). Constraint on maximum expansion of contact tracing based on: expected number of index cases, allowing for an increase in case-finding; average household size is 5.24 (1); number of contacts to be tested per index case to meet national targets for contacts tested (n=10)(4); and estimated TB prevalence among household contacts by age group (15).
Active case finding (prisoners)		Per person alive per year	$62.83	Program impact on diagnosis rates assumes prisoners may be screened twice a year based on country input. The number covered and unit cost were inferred based on the diagnosis rate for all prisoners estimated in 2022 (0.2%), the program impact, and total spending. Spending was derived from the average diagnostic costs for active TB plus x-ray screening.

Active case finding (populations at high-risk)	Per person diagnosed	$2,363	Number screened based on national coverage for High Risk (includes contacts plus those with comorbidities, migrants, populations experiencing homelessness, etc), minus those who were contacts. Diagnoses based on a positive yield of 0.3% (4). Spending derived from the average diagnostic costs for active TB plus x-ray screening. Assumes maximum possible coverage is double baseline coverage. Actual maximum coverage could be determined based on prioritization combined with feasibility and may be higher or lower.
Active case finding (mandatory)	Per person diagnosed	$15,745	Number screened and notifications based on national coverage for mandatory testing. Diagnoses based on a positive yield of 0.01%. Spending derived from the average diagnostic costs for active TB plus x-ray screening. Assumes maximum possible coverage is double baseline coverage. Actual maximum coverage could be determined based on prioritization combined with feasibility and may be higher or lower.
Other testing, including passive case finding and mass screening	Cost per person alive	$0.43	Number screened and number diagnosed based of total number screened nationally and total notifications minus number screened/diagnosed through other specified modalities, implying a positive yield of 0.5%.
TB TREATMENT PROGRAM			
DS-TB treatment (standard)	Per person initiating treatment	$2,101	Based on 6-month standard treatment with HREZ. Incorporates cost of drugs plus inpatient costs ($36), outpatient and monitoring costs ($57), adverse event management ($245), and other costs ($1,716). Equivalent to $2,784 when adjusted per person treated with pulmonary TB.
MDR-TB treatment (standard)	Per person initiating treatment	$10,500	Average cost of 18-month standard treatment with Bdq + Lfx + Lzd + Cfz + Cs. Incorporates cost of drugs plus inpatient costs ($948), outpatient and monitoring costs ($1,822), adverse event management ($734), and other costs ($5,076). Equivalent to $12,438 when adjusted per person treated with pulmonary TB.
MDR-TB treatment (shorter oral regimens)	Per person initiating treatment	$8,607	Weighted average cost of shorter treatment regimens (average 11 months) based on coverage in 2022, including: Bdq + Lfx + Lzd + Cfz + Cs and BPaLM. Incorporates cost of drugs plus inpatient costs ($981), outpatient and monitoring costs ($747), adverse event management ($734), and other costs ($5,076). Equivalent to $10,196 when adjusted per person treated with pulmonary TB.

XDR-TB treatment (standard)	Per person initiating treatment	$22,202	Based on 20-month standard treatment with Bdq + Dlm + Lzd + Cfz + Cs. Incorporates cost of drugs plus inpatient costs ($2,656), outpatient and monitoring costs ($6,011), adverse event management ($734), and other costs ($5,076). Equivalent to $24,528 when adjusted per person treated with pulmonary TB.
XDR-TB treatment (shorter oral regiments)	Per person initiating treatment	$7,580	Based on 6-month standard treatment with BPaL. Incorporates cost of drugs plus inpatient costs ($1,027), adverse event management ($734), and other costs ($5,076). Equivalent to $8,374 when adjusted per person treated with pulmonary TB.

Notes: BPaL, novel all-oral 6-9 month regimen composed of bedaquiline, pretomanid, linezolid; BPaLM, novel all-oral 6-month regimen composed of bedaquiline, pretomanid, linezolid and moxifloxacin; DS, drug susceptible; TB, tuberculosis; MDR, multi-drug resistant; XDR, extensively drug-resistant.
Source: Data provided by the National TB Programme

D.2. Impact of universal Xpert diagnosis

In Uzbekistan microscopy is used as the initial diagnostic test, and only sputum-smear positive cases are referred to a TB center for further diagnostics. The review estimated that 20-50% of sputum-smear negative patients who could be detected by GeneXpert are misdiagnosed (4). While a new diagnostic pathway has been developed based on the latest WHO guidance (20), it is not yet approved by the Ministry of Health.

In 2022, 52% of notifications were smear-negative TB, while it was estimated that 65% of all active TB infections were smear-negative, indicating that smear-negative (and frequently subclinical) TB cases are under-diagnosed under the status quo conditions. A key strategic priority in Uzbekistan is to update the national diagnosis algorithm to enforce universal Xpert MTB/RIF as the initial diagnostic test, replacing microscopy for primary diagnosis. A scenario was run to consider the projected impact on implementing universal Xpert testing from 2024.

Assumptions relating to the implementation and impact of Xpert MTB/RIF Ultra were as follows:

- Assumed Xpert MTB/RIF Ultra would be used as the initial diagnostic test from 2024 onwards (microscopy still incorporated as part of treatment monitoring);
- Probability of diagnosing smear-negative TB increased to align with smear-positive TB for all active case finding modalities;
- No change in screening costs was considered;
- Maximum constraints for contact tracing and TB preventative therapy doubled to allow for potential expansion in line with additional diagnoses expected.

APPENDIX E. DETAILED MODEL FINDINGS

Table E1. Annual TB program spending in baseline and optimized spending scenarios (USD)

	Baseline 2022	Optimized 75% spending	Optimized 100% spending	Optimized 150% spending
BCG vaccination	$1,164,814	$874,620	$1,165,457	$1,984,874
TPT for 0-4	$21,552	$42,884	$60,378	$90,205
TPT for 5-14	$247,191	$359,615	$361,717	$379,098
TPT for 15+	$336,721	$1,314,730	$1,313,938	$1,452,386
TPT for non-household repeat contacts	$0	$2,560,468	$2,521,839	$2,652,739
TPT for PLHIV	$35,320	$122,990	$122,806	$129,778
Household contact tracing	$461,082	$1,081,910	$1,089,909	$1,119,618
Active case finding (prisoners)	$293,036	$286,040	$667,025	$1,423,122
Active case finding (people with high risk factors)	$4,265,659	$5,685,217	$8,696,077	$10,085,455
Active case finding (mandatory testing)	$10,919,288	$4,099,462	$5,462,657	$23,025,862
Other testing, including passive case finding and mass screening	$14,857,743	$8,994,669	$14,958,855	$15,665,507
DS-TB treatment	$28,417,223	$21,870,972	$25,945,027	$30,870,112
MDR-TB treatment (standard)	$16,989,749	$6,378,514	$10,624,453	$14,475,492
MDR-TB treatment (shorter oral regimens)	$2,151,855	$8,644,290	$9,984,734	$21,107,120
XDR-TB treatment (standard)	$8,015,055	$3,009,117	$4,009,739	$6,828,934
XDR-TB treatment (shorter oral regimens)	$780,715	$1,392,254	$1,972,392	$2,145,203
Total	$88,957,003	$66,717,753	$88,957,003	$133,435,505

Source: Optima TB Uzbekistan model outputs, 2023

Notes: BCG, Bacillus Calmette-Guerin; DS, drug susceptible; TB, tuberculosis; MDR, multi-drug resistant; PLHIV, people living with HIV; TPT, TB preventive treatment; XDR, extensively drug-resistant.

Table E3. Annual TB program coverage in baseline and optimized spending scenarios

	Coverage definition used	Baseline 2022	Optimized 75% spending	Optimized 100% spending	Optimized 150% spending	Optimized 100% spending + universal Xpert[1]	Optimized 150% spending + universal Xpert[1]
BCG vaccination	Number vaccinated	728,288	685,971	728,288	728,288	728,288	728,288
TPT for 0-4	Per person with early TB reached	615	1,220	1,220	1,220	2,441	2,440
TPT for 5-14	Per person with early TB reached	1,003	1,450	1,450	1,450	2,898	2,900
TPT for 15-64	Per person with early TB reached	1,077	4,198	4,198	4,198	8,395	8,394
TPT for non-household repeat contacts	Per person with early TB reached	0	5,742	5,690	5,742	11,462	11,483
TB preventative therapy for PLHIV	Number treated	10,512	36,394	36,394	36,394	36,394	36,394
Household contact tracing	Number diagnosed	1,215	2,839	2,839	2,839	5,679	5,679
Active case finding (prisoners)	Testing *relative to baseline*	100%	98%	228%	473%	53%	160%
Active case finding (people with high risk factors)	Number diagnosed	1,805	2,406	3,610	3,610	3,340	3,610
Active case finding (mandatory)	Number diagnosed	694	260	347	1,387	347	356
Other testing, including passive case finding and mass screening	Testing *relative to baseline*[2]	100%	61%	101%	103%	50%	61%
DS-TB treatment	Number treated	7,878	7,855	9,169	9,822	13,298	15,798
MDR-TB treatment (standard)	Number treated	1,366	513	854	1,164	683	701
MDR-TB treatment (shorter oral regimens)	Number treated	211	848	979	1,878	106	2,830
XDR-TB treatment (standard)	Number treated	192	123	163	254	163	168
XDR-TB treatment (shorter oral regimens)	Number treated	93	164	225	238	244	266

Source: Optima TB Uzbekistan model outputs, 2023

Notes: 1, Impact of applying Xpert MTB/RIF universally for initial diagnosis; 2. "Other testing" assumed to remain available based on care-seeking behavior to the total population alive (34,627,591) in each scenario, but that overall other testing may be reduced by some proportion in line with the average unit cost and yield to prioritize other interventions; BCG, Bacillus Calmette-Guerin; DS, drug susceptible; TB, tuberculosis; MDR, multi-drug resistant; PLHIV, people living with HIV; XDR, extensively drug-resistant.

Table E2. Projected incidence of TB per 100,000 people and TB-related deaths by spending scenario from 2022 to 2030

	2022	2023	2024	2025	2026	2027	2028	2029	2030
NEW AND RELAPSE TB CASES									
Baseline spending	24,939	23,447	23,215	22,921	22,620	22,356	22,135	21,948	21,793
Optimized 75% spending	24,939	23,447	22,841	21,989	21,225	20,520	19,869	19,268	18,712
Optimized 100% spending	23,447	22,833	21,861	20,868	19,918	19,049	18,249	17,524	23,447
Optimized 150% spending	23,447	22,833	21,832	20,804	19,823	18,918	18,079	17,324	23,447
Optimized 100% spending + universal Xpert[1]	23,447	22,344	20,784	19,517	18,268	16,878	15,366	13,903	23,447
Optimized 150% spending + universal Xpert[1]	23,447	22,331	20,509	18,625	16,523	14,423	12,571	10,887	23,447
TB INCIDENCE PER 100,000 PEOPLE									
Baseline spending	66	65	63	62	60	59	58	57	66
Optimized 75% spending	66	64	61	58	55	53	51	49	66
Optimized 100% spending	66	64	60	57	54	51	48	46	66
Optimized 150% spending	66	64	60	57	53	50	48	45	66
Optimized 100% spending + universal Xpert[1]	66	62	57	53	49	45	40	36	66
Optimized 150% spending + universal Xpert[1]	66	62	56	51	44	38	33	28	66
ACTIVE DR-TB CASES									
Baseline spending	10,144	9,966	9,671	9,400	9,188	9,008	8,865	8,749	10,144
Optimized 75% spending	10,144	9,827	9,395	9,051	8,705	8,347	8,040	7,761	10,144
Optimized 100% spending	10,144	9,807	9,336	8,887	8,504	8,124	7,729	7,357	10,144
Optimized 150% spending	10,144	9,677	9,047	8,562	8,182	7,794	7,396	7,030	10,144
Optimized 100% spending + universal Xpert[1]	10,144	9,977	9,995	10,014	9,864	9,482	8,863	8,106	10,144
Optimized 150% spending + universal Xpert[1]	10,144	9,700	9,172	8,572	7,566	5,962	4,650	3,669	10,144
TB-RELATED DEATHS									
Baseline spending	2,796	2,773	2,701	2,564	2,525	2,483	2,447	2,419	2,796
Optimized 75% spending	2,803	2,765	2,644	2,482	2,404	2,292	2,199	2,118	2,803
Optimized 100% spending	2,806	2,735	2,514	2,217	2,049	1,943	1,839	1,734	2,806
Optimized 150% spending	2,812	2,773	2,485	2,160	1,985	1,875	1,756	1,646	2,812
Optimized 100% spending + universal Xpert[1]	2,797	2,535	2,133	1,848	1,721	1,530	1,310	1,153	2,797
Optimized 150% spending + universal Xpert[1]	2,811	2,508	1,776	1,243	857	579	327	231	2,811

Source: Optima TB Uzbekistan model outputs, 2023

Notes: 1, Impact of applying Xpert MTB/RIF universally for initial diagnosis; DR, drug-resistant; TB, tuberculosis. Baseline spending refers to continued spending and allocation based on 2022 baseline.

AUSTRALIA

85 Commercial Road
Melbourne, Victoria, 3004
t + 61 3 9282 2111
e info@burnet.edu.au

OVERSEAS

We have offices or representatives in Australia, Papua New Guinea and Myanmar, and also contribute to activities in other Asian, Pacific and African countries.

For more information, contact us at info@burnet.edu.au or call + 61 3 9282 2111.

burnet.edu.au

burnet.edu.au/support-us

/burnetinstitute

@BurnetInstitute

Burnet Institute

Burnet
reach for the many