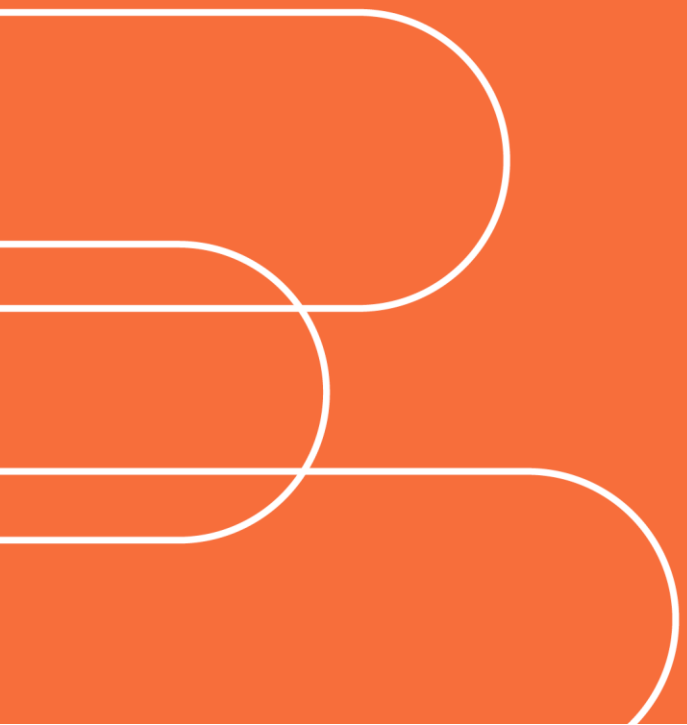
February 2024 (version 2.0)

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

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 the National TB Program in collaboration with the Burnet Institute (technical support) and the Global Fund.

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Suggestion citation

Republican Research and Practical Centre for Pulmonology and Tuberculosis, Burnet Institute, Global Fund. Evaluating cost-effective investments to reduce the burden of drug-resistant tuberculosis (TB) in Belarus: 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
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 Program
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

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Executive summary

BACKGROUND

Estimated tuberculosis (TB) incidence has declined in Belarus, from a high of 86 estimated new infections per 100,000 population in 2000 to 28 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 mass screening can enable increased investment in **more targeted active case finding** among contacts of people with active TB and community-based screening among vulnerable populations at higher risk of TB, thereby improving diagnosis rates.
3. **Expanding TB preventive treatment for all ages** 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 due to earlier diagnosis but will require increased resources for diagnostics as well as to provide treatment for more people who are diagnosed.

Baseline

The model estimates there were 2,795 new and relapse cases of TB in 2022, of which 43% were drug resistant. In 2022 an estimated US$17.2 million was spent on direct TB prevention, screening and treatment programs, of which 66% was spent on treatment. Among all estimated spending for TB screening and testing, 97% was spent on mass screening.

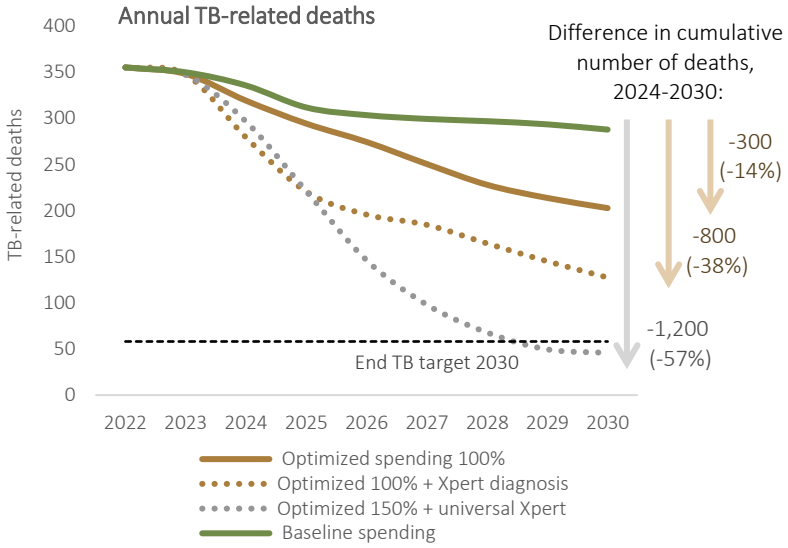
Optimization of current spending

Belarus can improve the impact of its investment in the TB response by: further prioritizing short-course MDR-TB treatment (+US$ 2.6M) rather than the standard MDR-TB treatment regimens (-US$ 0.9M); scaling up TB preventive treatment for children 0 to 14 (+US$ 145,000), adults 15-64 (+US$ 1.2M) and people living with HIV (+US$ 8,000); and reallocating spending from mass screening (-US$ 2.8M) to prioritize more targeted active case finding among contacts of people with active TB (+US$ 378,000) and through planned community-based screening among hard-to-reach populations (+US $ 363,000).

As a result of the shorter course treatment and savings made through more targeted and cost-efficient case-finding, an additional 1,219 (+28%) people could be initiated on treatment for DR-TB from 2024 to 2030 for the same amount of overall TB spending and 800 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 due to earlier diagnosis. 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 significantly declined in Belarus, reducing from approximately 50 per 100,000 new cases in 2015 to 28 per 100,000 in 2022 (1). However, Belarus remains one of the top 30 countries for high burden of Rifampicin- (RR) and multi-drug resistant (MDR)-TB (2). In 2021, 40% of new cases and 70% of previously treated cases had MDR/RR-TB (3). TB mortality rate has been increasing in Belarus since 2018, and there were an estimated 484 TN-related deaths in 2021. Delays in diagnosis and disruption of TB services due to COVID-19 and pandemic response measures have likely contributed to this increase (2).

Key and vulnerable populations identified to be most-at-risk of TB or with poorer TB outcomes in Belarus include people living with HIV, migrants, people with alcohol use disorders, people who use drugs, people with comorbidities such as diabetes mellitus, and homeless populations. However, these groups are not well defined, and data are lacking on comorbidity conditions, exposure status, and access to health services (4).

Treatment success for TB is 85% in Belarus, and 40% of individuals were being treated with World Health Organization (WHO)-recommended shorter treatment regimens in 2021. Belarus participated in the TB-PRACTECAL clinical trial of a new all-oral six-month regimen for drug-resistant TB using BPaLM (bedaquiline, pretomanid, linezolid and moxifloxacin) (5). This results of this trial led to the World Health Organization (WHO) released updated treatment guidelines in 2022 recommending BPaLM-based regimens in place of alternative nine-month and eighteen-month regimens for MDR/RR-TB patients (6). BPaLM continues to be available in Belarus under operational research conditions, and expanding access to BPaLM is one of the key activities to achieve equitable access to quality treatment and continuum of care for all people with drug resistant-TB (4).

The TB program in Belarus is currently guided by the 2021-2025 National Strategic Plan (NSP). National targets are in line with the End TB strategic goal, which aims to reduce TB incidence by 50% by 2025 and 80% by 2030 relative to 2015, and reduce TB mortality by 75% and 90%, respectively (7). To meet these and other strategic objectives, key interventions and changes outlined in the current NSP include to increase facility- and community-based ACF, improve early diagnosis by utilizing Xpert as primary screening test, expand eligibility for systematic latent TB infection (LTBI) testing and TB preventative therapy (TPT), strengthen ambulatory care, and implement shorter treatment regimens (4). The TB response in Belarus is predominantly funded through domestic sources (97%). Contributions from the Global Fund decreased by 64% from 2020 to 2021, from US$6.7 million to US$2.2 million in 2021, and domestic funding has not been able to fill that gap (8).

Prior Optima TB analysis

Belarus conducted an Optima TB analysis in 2016. Two key priorities identified in the analysis to jointly minimize incidence of TB, prevalence of active TB and TB-related deaths were to: (1) shift from hospital-focused care to ambulatory and incentivized ambulatory treatment; and (2) improve diagnosis through targeted testing strategies utilizing contact tracing and active case finding (ACF) instead of mass screening (9). An evaluation by the Optima team of this analysis illustrated persistent favoring of hospitalization and inflexibility of reallocation of funding due to bed-based payment modalities (10).

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 Belarus. 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 01):

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

Prevention	TB preventive therapy (TPT) for contacts:	0-4 years
		5-14 years
		15+ years
	TPT for PLHIV	
	BCG for children aged 0-4	
Diagnosis	Mass screening	
	Household contact tracing[1]	
	Active case finding among prisoner populations	
	Active case finding among PWID[2]	
	Active case finding (community-based)[3]	
	Other testing, including 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, Focuses on screening among household contacts with some additional reach to other repeat contacts of index cases; 2, Funded through the HIV program; 3, Modelled as a prospective program in scenario analysis

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).

Community-based active case finding was modelled as a prospective program that could reach other priority and hard-to-reach populations with high burden of TB, such as migrants, people experiencing homelessness and people with alcohol use disorders.

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 Belarus analysis, 2023

Scenario	Description
Baseline spending	Continued spending and fixed allocation of US$17.5 million (100% of TB prevention, screening and treatment spending) maintained over 2024-2030
Optimizes spending 100%	Continued spending of US$17.5 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).

Notes: DR, drug-resistant; MBT, Mycobacterium tuberculosis; Rifampicin (RIF) resistance; TB, tuberculosis.

MODELLING SPECIFICATIONS

Model inputs

A new Optima TB model for Belarus was developed using previously collated data before 2020 and additional epidemiological and programmatic data available until 2022. 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 Belarus model, 2023

Data type	Source
Epidemiologic data	Demographic data for population size, birth rate estimates and all-cause mortality from UN population division (11); UNAIDS Spectrum estimates for PLHIV (12); Prisoner population estimates from World Prison Brief (13) and 2020 Epidemiological Review Belarus (14). Updated data for 2016-2023 (partial) for TB notifications, TB-related deaths supplied by National TB Program. Historical notifications based on WHO-reported data assuming population disaggregation based on distribution in 2016 (1). Notifications use a new definition of XDR-TB from 2021 onwards. Pre-XDR classified as MDR-TB for the purpose of this analysis.
Program coverage data	Treatment initiations and outcomes by smear status and strain, number of BCG vaccinations, TPT initiations supplied by National TB Program, 2013-2023 (partial). Number of people screened by modality and positive yield informed by National Strategic Plan (2021-2025), 2020 Epidemiological Review Belarus, and data provided by the National TB Program (4, 14).
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). 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, DR-TB, and reducing the number of TB-related deaths. Based on the estimated baseline conditions of 2022, this resulted in model weightings of 1 for reductions in each of the active number of DS-TB and DR-TB cases respectively, and 8 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. Active case finding among PWID is funded through the HIV program and was constrained to remain fixed at most recent spending and coverage. Similarly, BCG infant vaccination is funded outside of the TB program and was constrained to not have reduced spending or coverage.

3 Findings

EPIDEMIOLOGICAL SITUATION

TB incidence

In 2022, there were an estimated 2,795 incident TB cases modelled in Optima, including both new and relapse cases and notified extrapulmonary TB (Table 4). Of these, an estimated 13% were extrapulmonary. Consistent with WHO-reported trends, estimated TB incidence in Belarus has overall significantly declined from 68 per 100,000 population in 2000 to 29 per 100,000 population in 2022.

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	34	7	5 (14%)	59	0.3%	3
5-14 years	117	10	19 (16%)	209	0.9%	10
15-64 years	1,641	26	715 (44%)	3,935	15.7%	207
65+ years	389	24	133 (34%)	1,021	20.7%	77
Prisoners	558	1,680	304 (54%)	1,072	67.7%	27
PLHIV	56	196	36 (64%)	115	14.7%	31
Total	**2,795**	**29**	**1,211 (43%)**	**6,410**	**14.2%**	**355**

Notes: 1, Includes notified extrapulmonary TB
Source: Optima TB Belarus model output, 2023

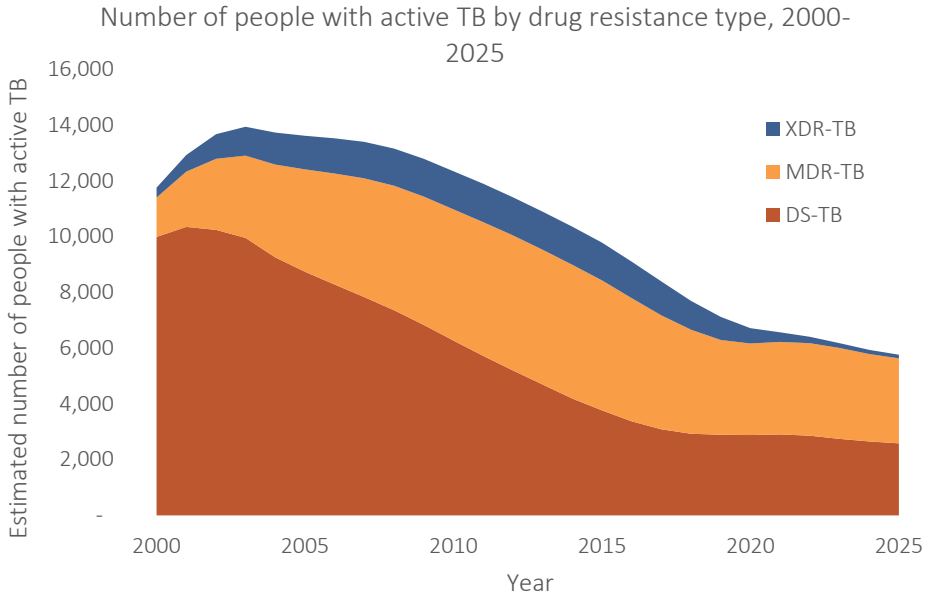
The majority of new and relapse cases of TB continue to be among adults aged 15-64, with 1,641 incident cases in 2022 (Table 4). However, relative to population size prisoners have the highest incidence of TB in Belarus, with estimated 1,680 new and relapse cases per 100,000 population in 2022, which is substantially higher than the general adult population at 26 per 100,000 population. Despite previous declines in estimated TB incidence and notifications among prisoners from 2012 to 2018, potentially attributed to reduced overcrowding (14), in more recent years prisoners are the only modelled population group where TB incidence is estimated to be increasing. Children aged 0-4 years have the lowest incidence, at 7 per 100,000 population.

In 2022, 43% of new and relapse TB infections were DR-TB. Proportionally, drug resistance peaked in 2018, at 45%, and has been gradually declining since (Figure 1).

Prevalent TB

In 2022, there were a cumulative of 6,410 active TB cases in Belarus 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 14% and highest among prisoners, followed by those aged 65 and over. Among prevalent TB in 2022, an estimated 55% of cases were DR-TB (Figure 1).

Figure 1. Trends in the estimated number of people with active TB by drug resistance type, 2000–2025



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

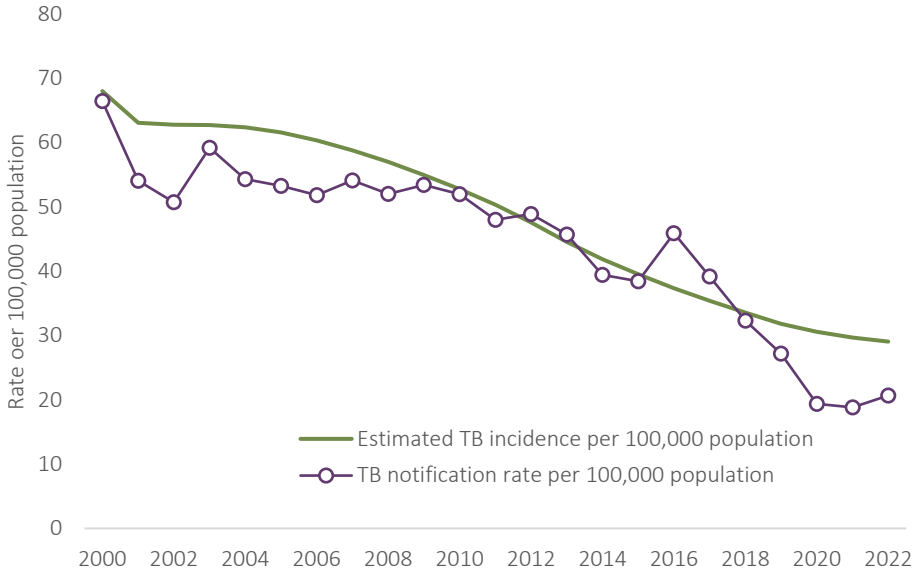
TB notification and case detection

In 2022, there were a total of 1,990 TB notifications in Belarus (21 per 100,000 population), of which 76% 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(15)) ranged from 9% among prisoners to 92% among adults aged 15-64 years; no cases were detected among children 0-4 in 2022.

From 2016, case detection rate reached greater than one, potentially due to the scale up screening activities. Since 2020, notifications have declined and the gap in case detection increased, which may have been due to COVID-19-related disruptions and impacts, such as decreased screening activities and delays in care-seeking (Figure 2).

The number of TB notifications per 100,000 population has since increased in 2022, which may be indicative of a return to pre-COVID activities and healthcare seeking.

Figure 2. Estimated TB incidence rate and notification rate per 100,000 population, 2000–2022

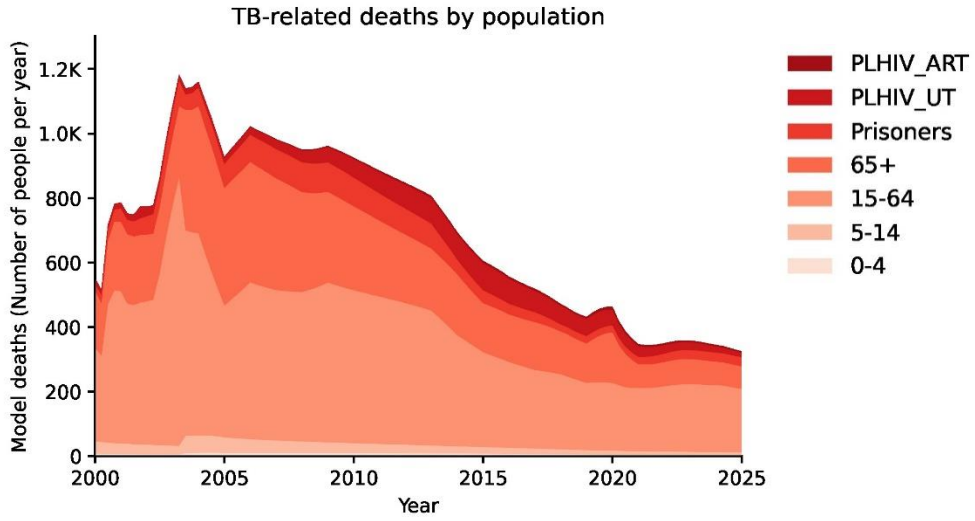


Source: Optima TB Belarus model output, 2023. Notification data from WHO Global TB Programme data (2000-2015) and National TB Program (2016-2022).

TB mortality

Overall TB-related deaths have declined in Belarus from a high of 1,147 in 2003 to 355 in 2022 based on modelled estimates, in line with decreasing incidence and advances in diagnosis and treatment (Figure 3). A slight increase in deaths was estimated between 2021 (n=345) and 2022 (n-355), which may be due to delayed care-seeking in 2020 and 2021 related to COVID-19.

Figure 3. TB-related deaths by population, 2015–2025



Source: Optima TB Belarus model output, 2023.

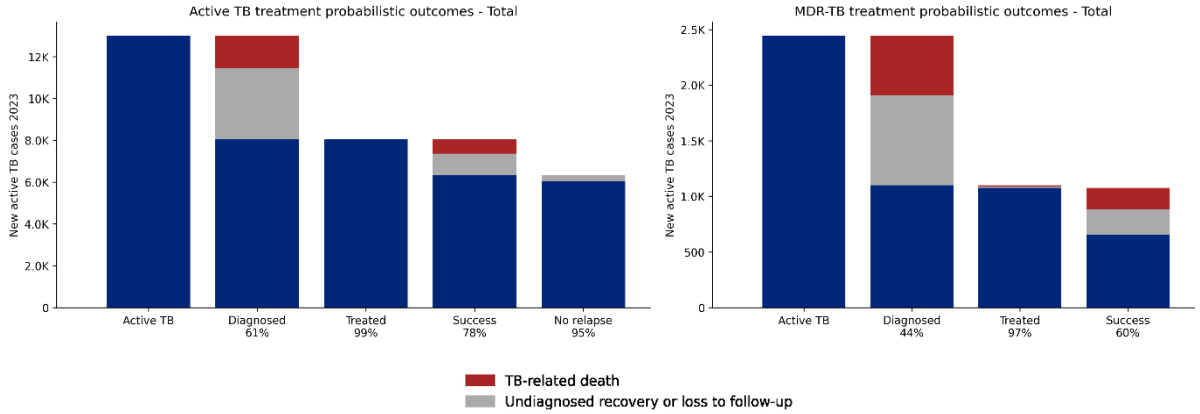
TB cascade

A probabilistic cascade is reported representing the estimated long-term outcomes of the cohort of people progressing to active TB in 2023. Based on the most recent estimated diagnosis and treatment rates in 2022, 61% of all people progressing to active TB in Belarus would be projected

to be diagnosed prior to natural outcome (recovery or death). Of those diagnosed, 99% are projected to be treated (Figure 4).

In total, it is estimated that approximately 1,963 people initiated treatment for TB in 2023, including 834 starting treatment for DR-TB.

Figure 4. The projected final cohort outcomes for people progressing to active TB (left) and MDR-TB (right) in 2023 in the status quo scenario



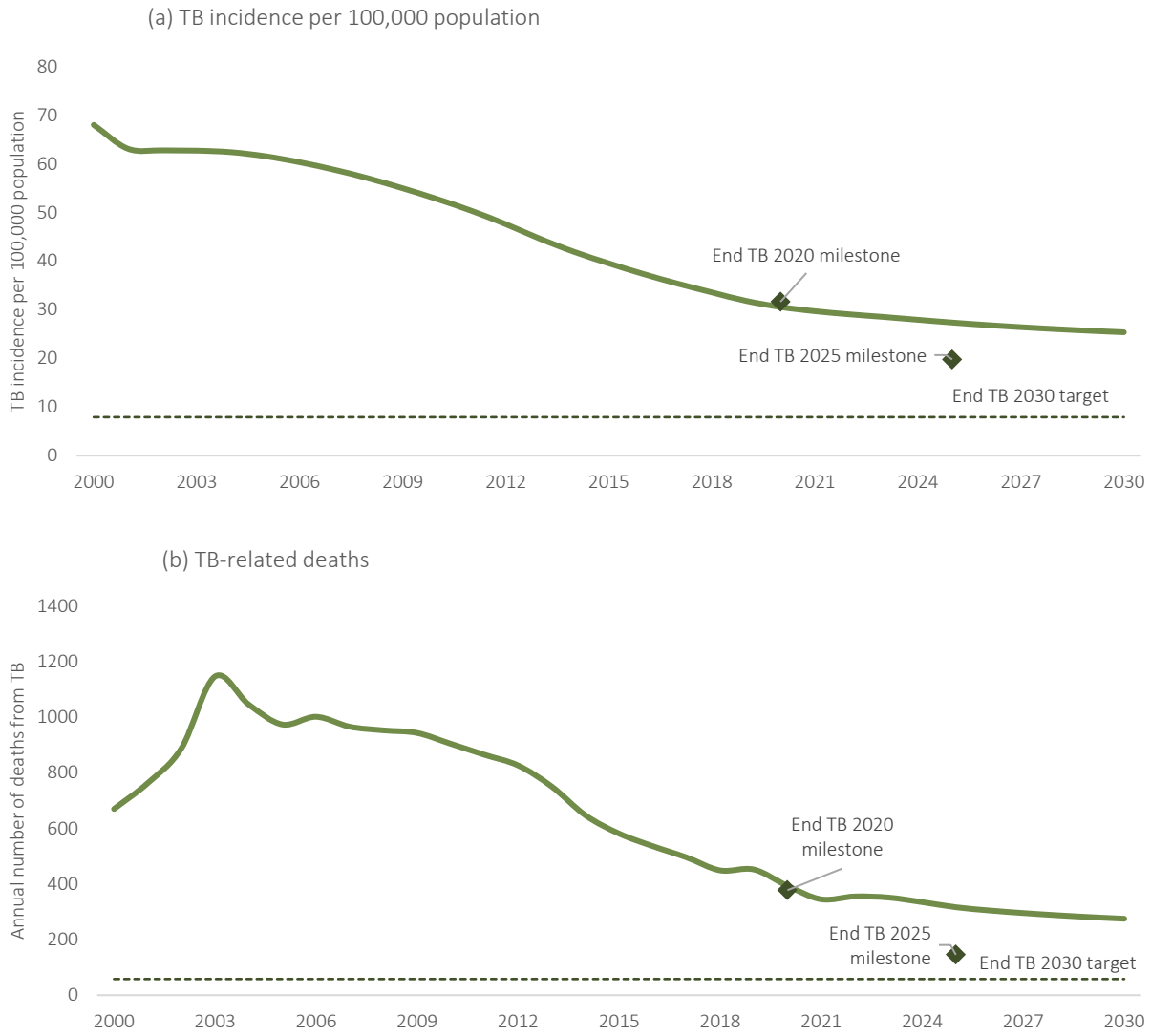
Source: Optima TB Belarus model output, 2023.

Overall, the probability of treatment success was 78% and lower (60%) for MDR-TB. For both MDR-TB and XDR-TB, treatment failure rates have reduced substantially since 2013, from 25% to 4% for MDR-TB and from 34% to 10% for XDR-TB among adults aged 15-64. However, lower treatment success rates are reported among some sub-population groups, including people living with HIV, prisoners, and adults aged 65+.

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 (7). To evaluate progress towards the 2030 targets, the strategy defines country milestones for 2020 and 2025. Based on Optima TB modeled projections, despite achieving the 2020 milestones for both TB incidence and deaths, Belarus is not predicted the reach the End TB 2025 milestones nor 2030 targets with current conditions continued (Figure 5).

Figure 5. Optima TB estimated trends in (a) TB incidence rate and (b) TB mortality in relation to End TB targets



Source: Optima TB Belarus model, 2023. End TB milestones (diamond markers) and 2030 targets (dashed line) defined as percentage reduction from 2015 (16). 2015 baseline based on Optima modelled values.

CURRENT TB SPENDING

Based on most recent spending estimates, in 2022 an estimated US$17.2 million was spent on direct TB prevention, screening and treatment programs. Of this, the majority was spent on treatment (66%). Treatment in Belarus has shifted to using shorter, all-oral short course regimens. In 2022, 80% of people initiated on MDR-TB treatment utilized shorter treatment regimens, including 52% on six-month BPaLM-based regimens, and 30% of people starting treatment for XDR-TB utilized six-month BPaLC regimen. Among all estimated spending for TB screening and testing, 97% was spent on mass screening based on Optima estimates. TB spending for Optima was derived from bottom-up estimation which may account for differences from other sources reporting that mass screening accounts for 90% of TB-related spending on diagnosis (4).

WHAT IS THE OPTIMIZED ALLOCATION OF THE TB BUDGET?

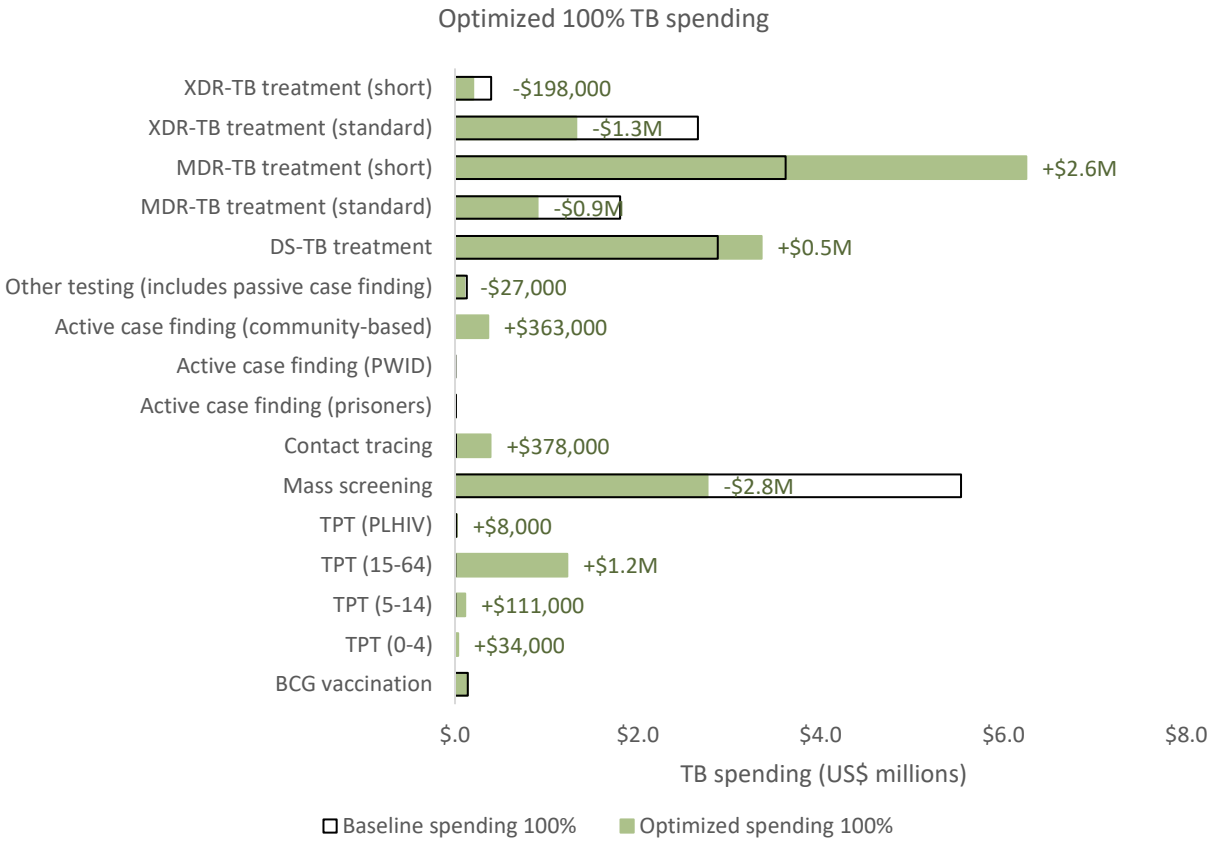
Optimized allocation of TB spending

With 100% of baseline spending maintained, the optimized allocation of the TB budget prioritizes short-course MDR-TB treatment (+US$ 2.6M) rather than the standard MDR-TB treatment regimens (-US$ 0.9M) to minimize prevalence of drug-resistant TB and TB-related deaths by 2030 (Figure 7). Spending for XDR-TB treatment is reduced (-US$ 1.5 M) on account of the reduction in incidence of XDR-TB, making MDR-TB treatment regimens suitable for most DR-TB cases.

TB preventive treatment for children 0 to 14 (+US$ 145,000), adults 15-64 (+US$ 1.2M) and people living with HIV (+US $ 8,000) were recommended to be scaled up.

In terms of screening and testing, the optimization recommends reallocating spending from mass screening (-US$ 2.8M) to prioritize more targeted active case finding among contacts of people with active TB (+US$ 378,000) and through planned community-based screening among other priority populations (+US $ 363,000).

Figure 6. Baseline and optimized allocation of current TB spending for TB prevention, testing and treatment interventions



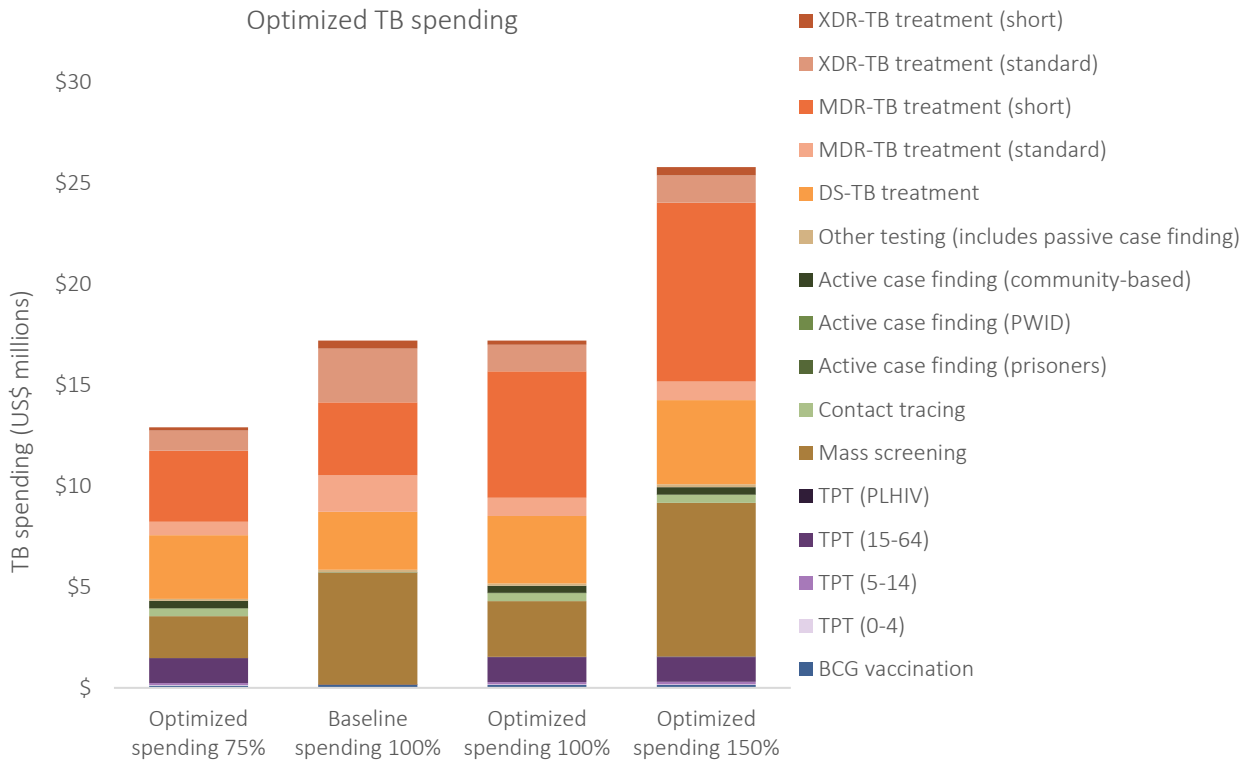
Notes: BCG, Bacillus Calmette-Guérin; DS, drug susceptible; MDR, multi-drug resistant; PLHIV, people living with HIV; PWID, people who inject drugs; TB, tuberculosis; TPT, TB preventive treatment; XDR, extensively drug-resistant.
Source: Optima TB Belarus model, 2023

As a result of the shorter course treatment and savings made through more targeted and cost-efficient case-finding, an additional 1,199 (+28%) MDR-TB cases could be treated from 2024 to 2030. The number of people covered by each intervention can be found in Appendix E.

Mass screening is only prioritized for expansion after other modalities of case finding are saturated, with 150% spending optimized (Figure 7).

At lower budget levels below 100%, epidemic gains can be maximized by first maintaining treatment for DS, MDR and XDR-TB based on need, and secondly, scaling up TB preventative therapy for all ages. Detailed spending by budget level can be found in Appendix E.

Figure 7. Recommended allocation of funding by program to minimize drug-resistant TB for varying budget levels (75% to 150%)



Notes: BCG, Bacillus Calmette-Guérin; DS, drug susceptible; MDR, multi-drug resistant; PLHIV, people living with HIV; PWID, people who inject drugs; TB, tuberculosis; TPT, TB preventive treatment; XDR, extensively drug-resistant.
Source: Optima TB Belarus model, 2023

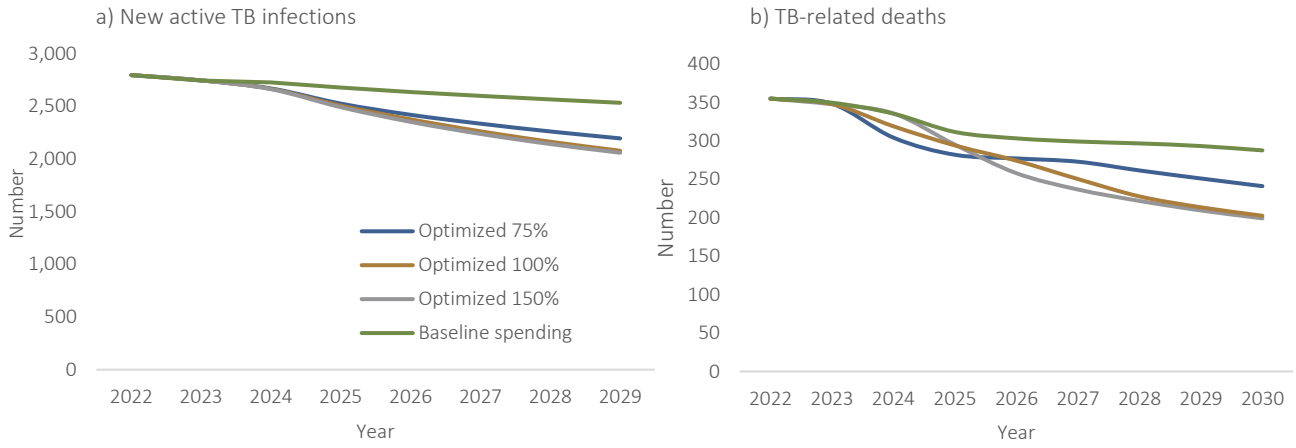
Projected impact of optimized TB spending

With current conditions and spending maintained, Optima TB projects that there would be approximately 18,200 incident TB cases and 2,100 TB-related deaths from 2024 to 2030.

With 100% of baseline TB spending optimized, it is estimated that 2,180 (12%) new TB infections and 346 (16%) TB-related deaths could be averted from 2024 to 2030 compared with if baseline spending were continued (Figure 8). Importantly, a reallocation of resources could increase the number of people on treatment for DR-TB by 1,219 (28% increase) over 2024 to 2030.

At higher budget levels there are diminishing returns as high-impact interventions are saturated at 100% spending optimized. At 150% spending optimized, additional resources are allocated to mass screening which has lower efficiency for case finding (estimated yield 0.006%) compared to other screening modalities (range in yield: 0.31% to 8.2%).

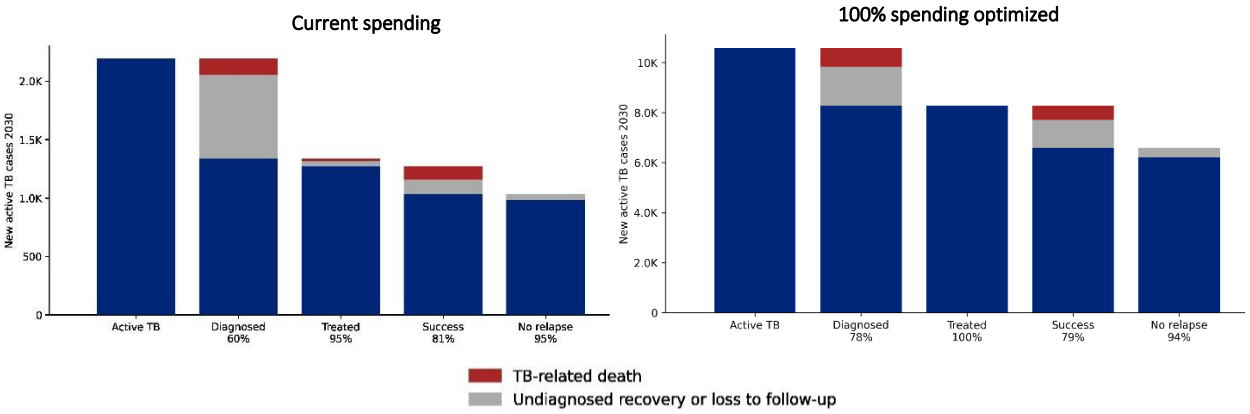
Figure 8. Projected impact of optimization at varying budget levels on TB incidence and TB-related deaths per 100,000, 2022–2030



Source: Optima TB Belarus model, 2023

By 2030, 100% spending optimized could improve TB diagnosis by +18 percentage points and treatment coverage by +5 percentage points compared to if current spending is continued (Figure 9). This analysis did not consider treatment success to change as a result of shorter treatment regimens, therefore no impact is seen there, although average success rate decreases slightly as a result of more DR-TB cases being diagnosed and treated.

Figure 9. Active TB probabilistic cascade in current spending (left) and 100% optimized spending (right) in 2030



Source: Optima TB Belarus model, 2023

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

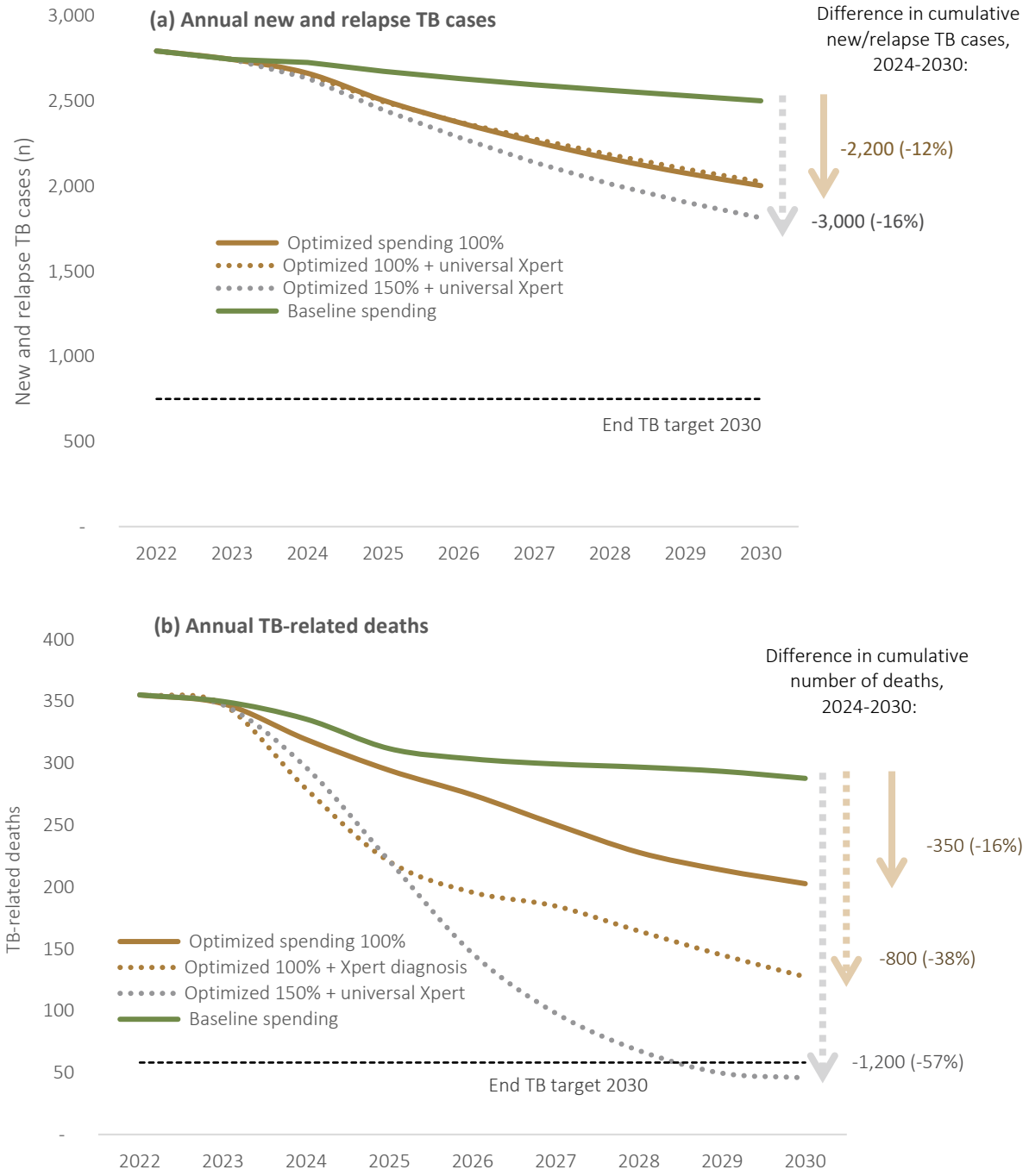
A key strategic priority in Belarus is to update the national diagnosis algorithm to universally utilize Xpert MTB/RIF as the only initial diagnostic test, replacing microscopy for primary diagnosis. It is estimated that the average cost of diagnosing presumptive TB would increase by 159%, from $61 to $97, with the updated diagnosis algorithm (Appendix D2).

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 and increase 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 2,100 (-12%) incident TB cases and 800 (-37%) TB-related

deaths compared to the continuation of baseline spending. This represents a further reduction of 22 percentage points in deaths compared to 100% spending optimized without change in the diagnostic algorithm, but a slightly smaller relative reduction in new and relapse TB cases (Figure 10).

With 150% spending optimized plus universal Xpert MTB/RIF, it may be possible to avert 3,000 (-16%) incident TB cases and 1,200 (-57%) TB-related deaths compared to the continuation of baseline spending, representing an improvement in both epidemic outcomes compared to 100% spending optimized with no change in diagnostic algorithm (Figure 10).

Figure 10. 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 Belarus 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 02.

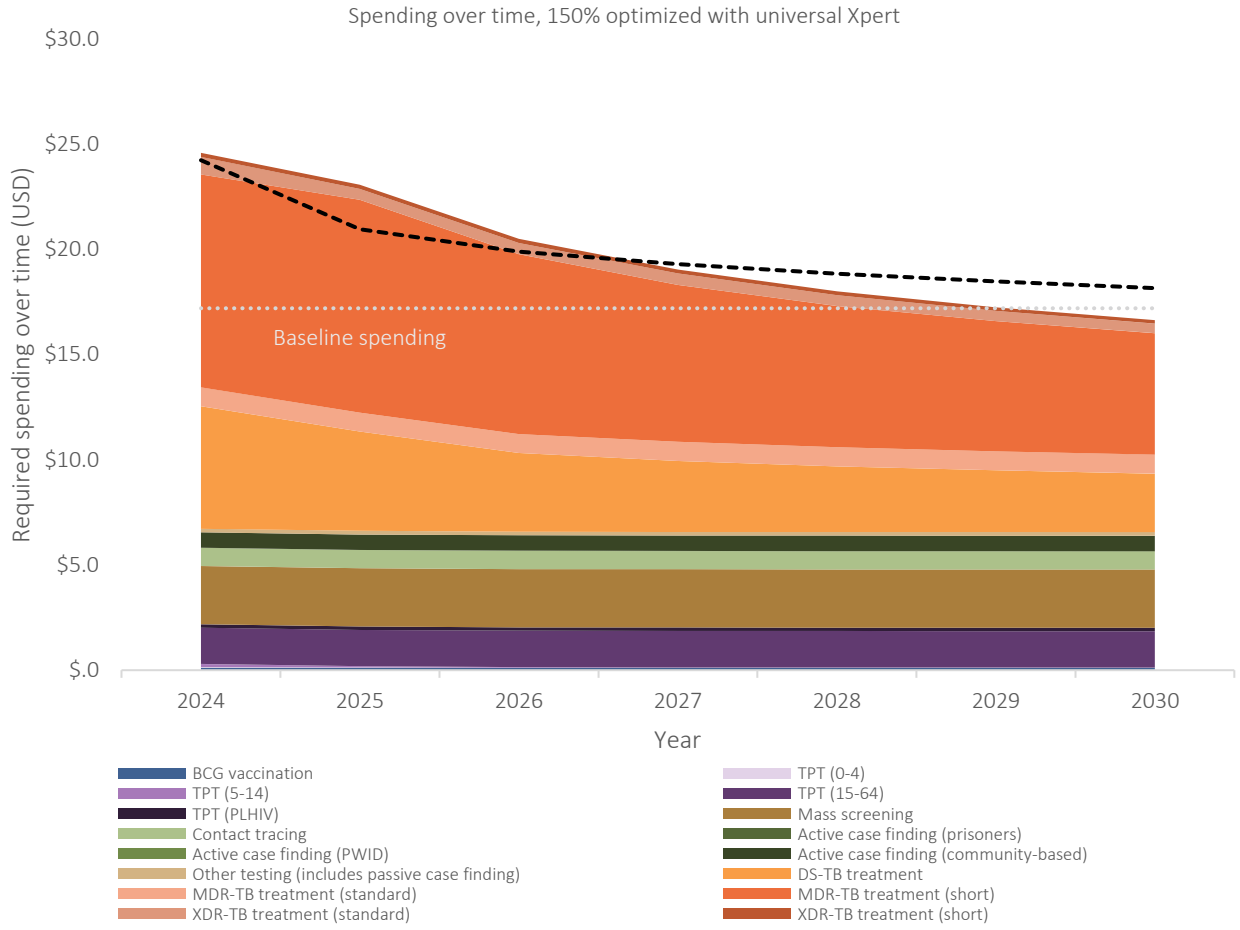
HOW CLOSE CAN BELARUS GET TO END TB TARGETS BY 2030 WITH UNIVERSAL XPERT DIAGNOSIS?

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. However, there is no projected benefit in additional reduction in TB incidence relative to current diagnostic algorithm. Based on estimated costs, implementing universal Xpert diagnosis will increase screening costs, which means there will be less resources available for TPT with 100% spending maintained.

With 150% spending optimized plus universal Xpert MTB/RIF, greater gains in both reducing TB-related deaths and TB incidence are projected, and Belarus could reach the 2030 End TB target for reduction in deaths. Higher resources (+US$8.6M) would allow for increased investment in TPT as well as treatment for those who are additionally diagnosed through improved case-finding.

The additional investment in TB (150% spending) alongside universal Xpert diagnosis is projected to lead to lower resource needs in the long-term due to a reduction 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$16.6 million, which is equivalent to baseline spending (Figure 11).

Figure 11. Resource needs over time to maintain the impact of 150% spending optimized with universal Xpert MTB/RIF for diagnosis, 2024–2030



Source: Optima TB Belarus model, 2023

Belarus is not projected to reach the End TB 2030 target for TB incidence with current interventions. Further refinement of active case finding strategies that may improve diagnosis rates and increased utilization of shorter-duration treatment and TPT regimens, may be required to reach End TB targets.

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 number screened, yield from x-ray screening and yield from presumptive testing for TB by screening modality, and unit costs may underestimate actual costs. Diagnostic spending only accounts for commodity costs, and other implementation costs, including personnel time, were not included. This could impact the relative cost-effectiveness of different screening modalities. There were insufficient data to stratify all modalities of TB screening in Belarus, and passive case finding could not be differentiated from some modalities of active case finding.

The prospective program of community-based active case finding was based off the existing TB screening program for PWID, given likely similarities. However, the cost and implementation of TB services may differ for other populations depending on burden of TB, ability of civil society organizations to reach target communities, and depending on the existing capacity of relevant organizations to integrate TB screening into routine services.

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 Belarus 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.

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 Belarus.

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. Potential ways to improve implementation efficiency, such as through client incentives and social contracting, are part of the National Strategic Plan for TB (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. Where program data were not available, these estimates were derived from global systematic literature reviews where possible, but actual effectiveness may vary between 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 and populations experiencing homelessness.

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; continued improvements in resource allocation and performance tracking, including strategic data on contact tracing and TPT; defining size, characteristics and burden of TB among other vulnerable and priority populations for TB control, including migrants, people experiencing homelessness and people with alcohol use disorders; and evidence of program effectiveness.

5 Conclusions and recommendations

This allocative efficiency analysis for TB prevention and treatment in Belarus highlights the necessity to invest in short-duration treatment regimens for drug-resistant TB, more targeted testing strategies such as contact tracing and community-based screening among hard-to-reach populations at higher risk, and preventive treatment among children and people living with HIV.

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 mass screening can enable increased investment in more targeted active case finding among contacts of people with active TB and community-based screening among vulnerable populations at higher risk of TB, thereby improving diagnosis rates.
3. Expanding TB preventive treatment for all ages 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 due to earlier diagnosis but will require increased resources for diagnostics as well as to provide treatment for more people who are diagnosed.

KEY FINDINGS AND OPPORTUNITIES

- Implementing shorter duration, all-oral regimens for drug resistant TB can reduce the cost of individual treatment by 51% to 65%, 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 1,219 (+28%) people could be initiated on treatment for DR-TB from 2024 to 2030 for the same amount of overall TB spending and 800 new/relapse DR-TB cases could be averted over the same period.
- Reduced resources are required for XDR-TB treatment on account of the reported reduction in incidence of XDR-TB, making MDR-TB regimens suitable for most drug resistant TB cases. However, this may change in the future. Further, correct classification of XDR-TB by new definitions may require investment in resources and capacity for

laboratories to conduct rapid molecular and drug-sensitivity testing to properly determine the appropriate treatment regimens (17), and these additional needs were not evaluated in this analysis.

- Currently mass screening accounts for the majority of spending for TB screening, yet only accounts for 12% of TB notifications. Shifting from mass screening to expand contact tracing and community-based screening among priority populations will enable more cost-efficient case finding. Leveraging civil society organizations can help ensure screening reaches those most in need and may be facilitated through social contracting mechanisms. 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.
- TB preventive therapy in Belarus is currently focused on children under 5 years who are household contacts and people living with HIV. Expanding TPT among all populations, but particularly among adult household contacts, is recommended to prevent latent TB activation, and 12% reduction in cumulative new and relapse TB infections maybe be possible over 2024 to 2030. The availability of new shorter regimens for TPT (e.g. 3HP) may support the scale up of TPT (18).
- 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. 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$16.6 million, equivalent to baseline spending, by 2030.

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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 (19). 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.

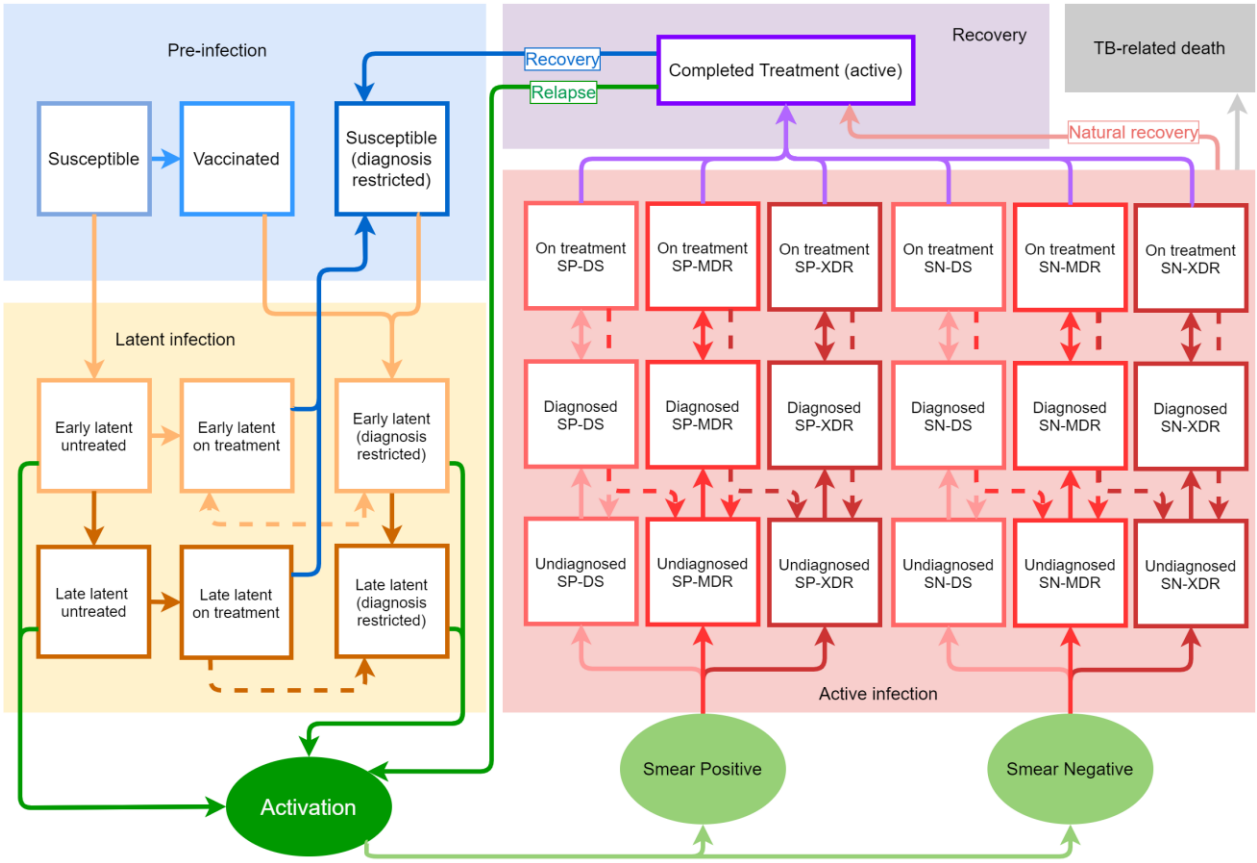
The WHO definition for incident TB cases includes both new and relapse cases. In the model, incident TB cases correspond to the following transitions between compartments (Table A1):

- 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.

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 (19).

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 Treatment failure in the model includes 'loss to follow-up' during treatment, 'treatment failure', and 'not evaluated' Death during TB treatment is not included in treatment failure, but is considered separately
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.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 Belarus model, 2023

Parameter	2022	Source(s) or assumptions
Population size		
0-4	452,324	UN Population Division 2022 (11). Assumes prisoners account for 0.5% of 15-64 year olds based on latest estimate from the 2020 Epidemiological Review (2018); UNAIDS AIDSInfo 2023.
5-14	1,147,246	
15-64	6,238,536	
65+	1,638,528	
Prisoners	31,321	
PLHIV not on ART	5,9182	
PLHIV on ART	21,082	
Percentage of people who age into the next age category per year		
0-4	21.4%	UN Population Division 2022
5-14	9.4%	
15-64	2.2%	
Annual number of births	87,541	UN Population Division 2022
Annual non-TB death rate		All-cause mortality based on UN Population Division 2022 and adjusted during calibration
0-4	0.05%	
5-14	0.01%	
15-64	0.58%	
65+	6.73%	
Prisoners	2.1%	
PLHIV not on ART	0.58%	
PLHIV on ART	0.58%	
Net number of migrants	30,308	UN Population Division 2022. Total number distributed by age-weighting for 5-14, 15-64 and 65+ amongst number of new immigrants.

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

B.2. Tuberculosis notifications

Table B2. 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	0	0	0	0	0	0	0
5-14	1	0	0	3	0	0	4
15-64	723	618	17	93	54	0	1505
65+	177	86	1	29	7	0	300
Prisoners	17	34	0	0	3	0	54
PLHIV not on ART	2	5	0	0	1	0	8
PLHIV on ART	40	69	2	3	5	0	119
Total	960	812	20	128	70	0	1990

Note: ART, antiretroviral therapy; DS, drug susceptible; TB, tuberculosis; MDR, multi-drug resistant; PLHIV, people living with HIV; XDR, extensively drug-resistant. Number of XDR-notifications based on new definition adopted in 2021. Pre-XDR-TB counted as MDR-TB for the purpose of this analysis.
Source: National TP Programme data, 2023

B.3. TB treatment

Latent TB infection treatment and TB preventive treatment

Table B3. Number of people initiated on TB preventive treatment (TPT) by population group, 2022

Population group	Number starting TPT		Notes
	via contact tracing	via mass screening	
0-4	0	0	Based on input from National TB Programme, children on TPT more likely to be 5-14 thus all TPT for children assigned to this age group.
5-14	63	0	
15-64	30	0	
65+	0	0	
Prisoners	0	0	
PLHIV	0	1128	National TB programme. Assumed all TPT for PLHIV among those on ART based on being in care.
Total	93	1128	

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 (20) and the proportion of all adult tuberculosis cases attributable to recent within-community transmission that can be attributed to household transmission (21).
Source: National TB Programme, 2023

Active TB treatment

Table A2. TB treatment outcomes, 2021

	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	2	0	0	180	302	384	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	N/A	0%	0%	0%
5-14	2	1	0	180	302	384	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	N/A	0%	0%	0%
15-64	729	627	7	180	302	384	85%	81%	80%	6%	6%	3%	2%	4%	10%	0%	1%	N/A	8%	9%	7%
65+	152	64	0	180	302	384	92%	52%	56%	2%	6%	0%	1%	9%	11%	0%	0%	N/A	4%	32%	33%
Prisoners	18	26	0	180	302	384	83%	73%	50%	11%	19%	50%	6%	0%	0%	0%	4%	N/A	0%	4%	0%
People living with HIV not on ART	0	11	0	180	302	384	84%	22%	0%	12%	33%	50%	2%	33%	0%	0%	0%	N/A	2%	11%	50%
People living with HIV on ART	56	68	2	180	302	384	84%	67%	83%	12%	9%	0%	2%	5%	17%	0%	1%	N/A	2%	18%	0%

Note: 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. Most recent available data for treatment outcomes from 2021.
Source: National TB Program, 2023

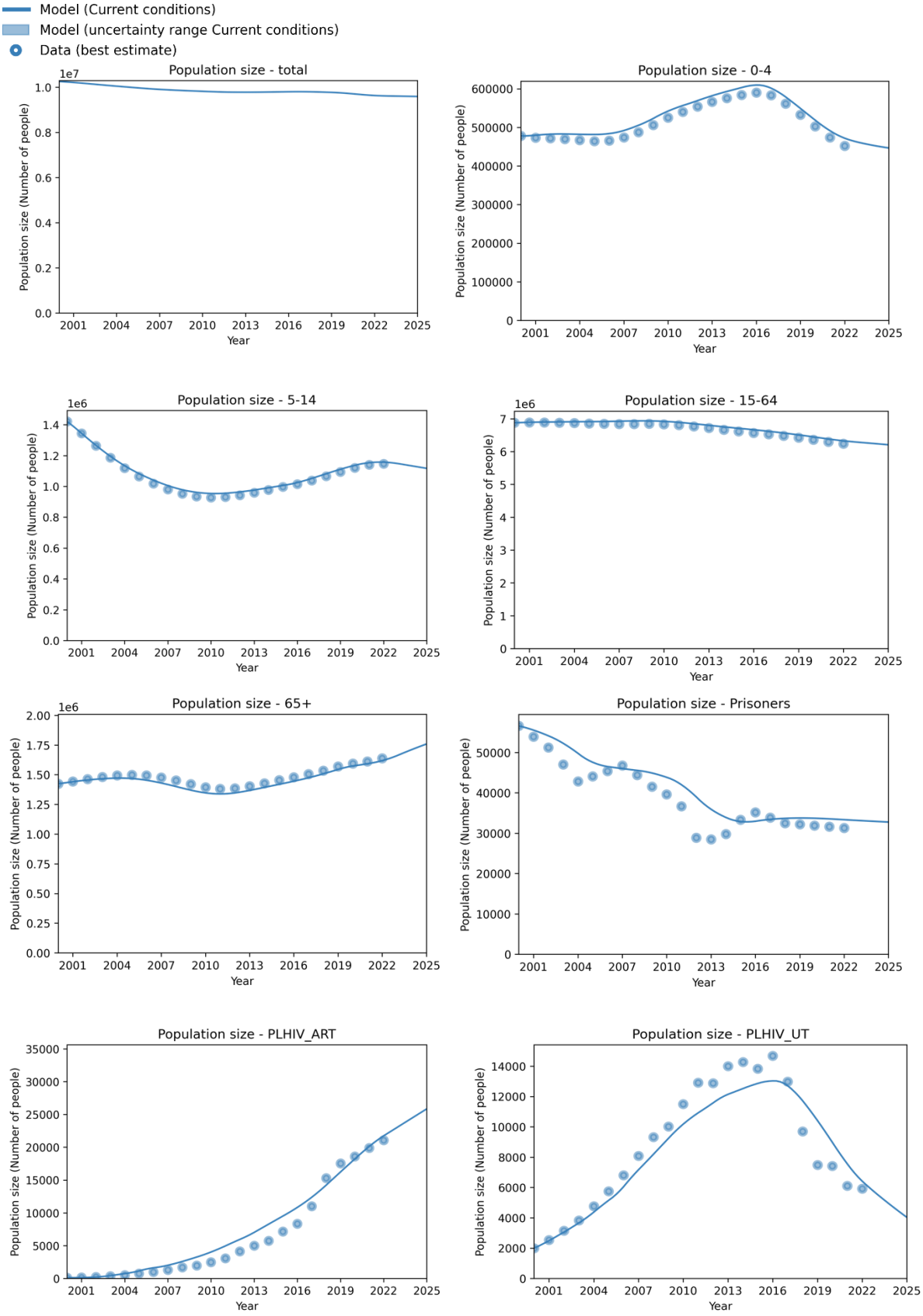
B.4. Epidemiological parameters

Description	Value	Population	Source or assumption
Vaccinations administered (/year)	106,813 (2022)	0-4	National TP Programme data, 2023
Early Latency Departure Rate	0.2 0.99	All populations unless specified PLHIV not on ART	Houben (2016) - appendix of TIME model. 0.1%/year reactivation rate (0.01-0.25).
Late Latency Departure Rate*	0.001 0.0002-0.00135 0.0005-0.003 0.007 0.0009-0.007	0-4, 5-14 15-64 65+ PLHIV not on ART PLHIV on ART	Andrews (2012)- risk of progression to active. Where range reported, assumed decrease in late latency departure rate over time.
Probability of Early-Active vs. Early-Late LTBI Progression*	0.177 0.1947 0.93 0.177-0.354	All populations unless specified 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)	3.6 1.9 6.5 7.5 24 10	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 1.9 and 24 were used in calibrations.
Smear positive (SP) TB Infectiousness*	1.0 5.0	All populations unless specified Prisoners	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	30-80% 83%	All populations unless specified PLHIV	WHO, Tiemersma (2011) Where range reported, assumed that death rate decreased over time.
Smear negative untreated-TB death rate	12-30% 74%	All populations unless specified PLHIV not on ART	WHO, Tiemersma (2011) Where range reported, assumed that death rate decreased over time.

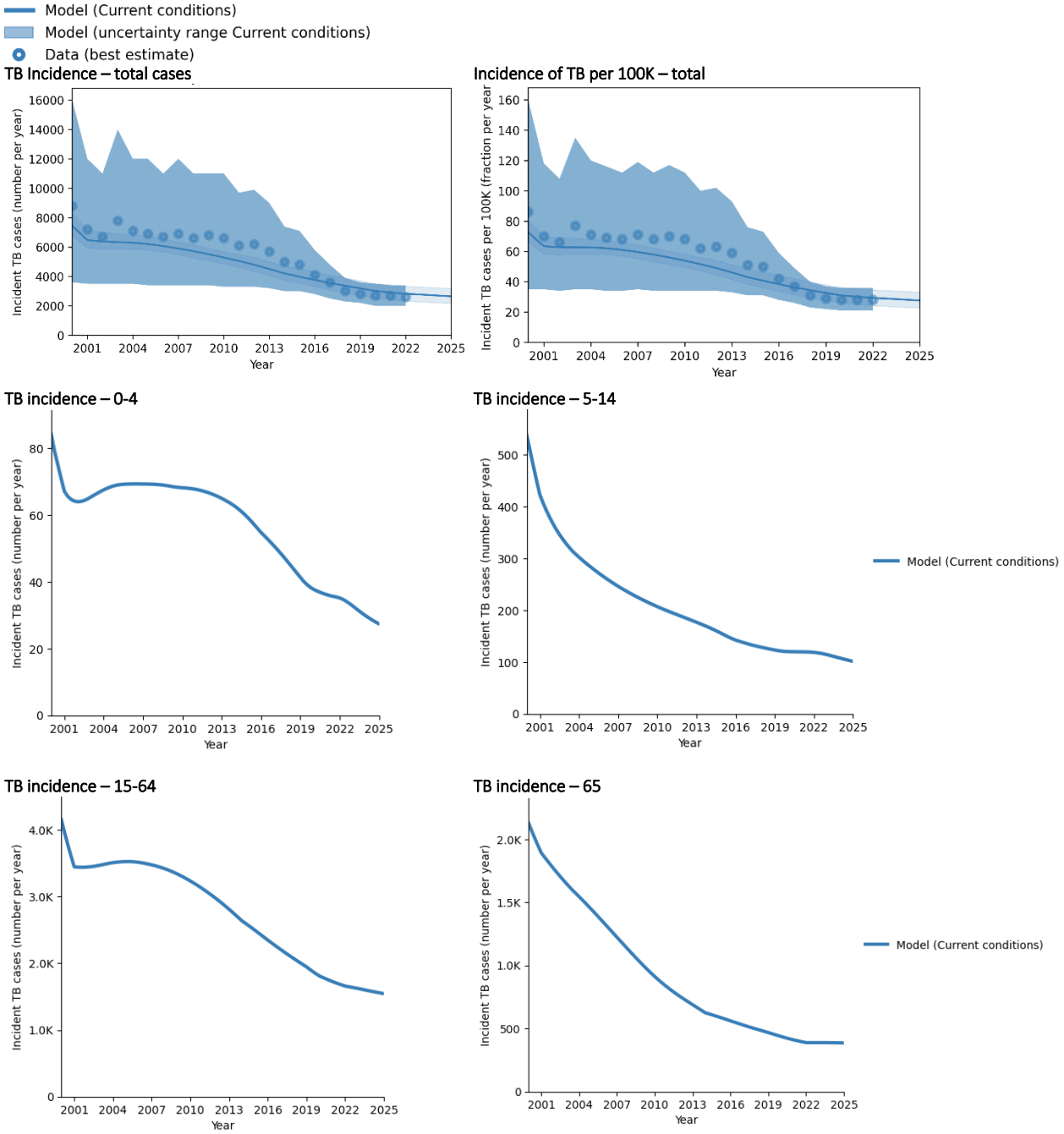
Notes: ART, antiretroviral therapy; DS, drug susceptible; LTBI, latent tuberculosis infection; MDR, multi-drug resistant; PLHIV, people living with HIV; TB, tuberculosis; XDR, extensively drug-resistant

APPENDIX C. CALIBRATION

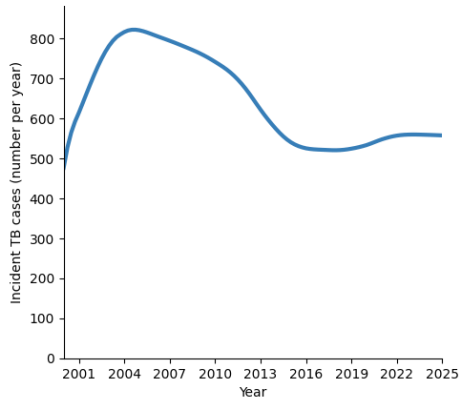
C.1. Populations size calibration figures



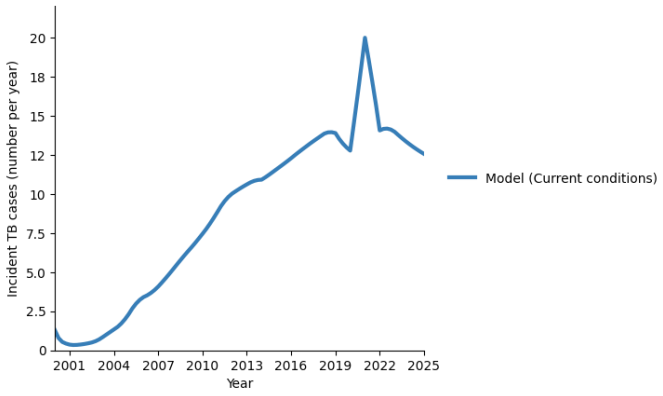
C.2. Selected TB epidemic calibration figures



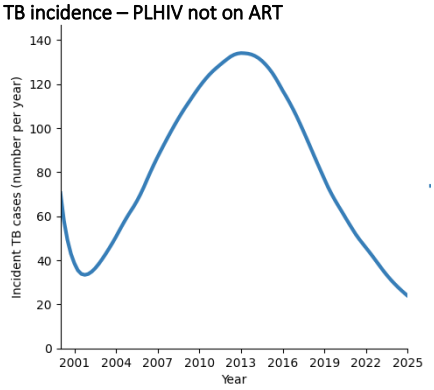
TB incidence – Prisoners



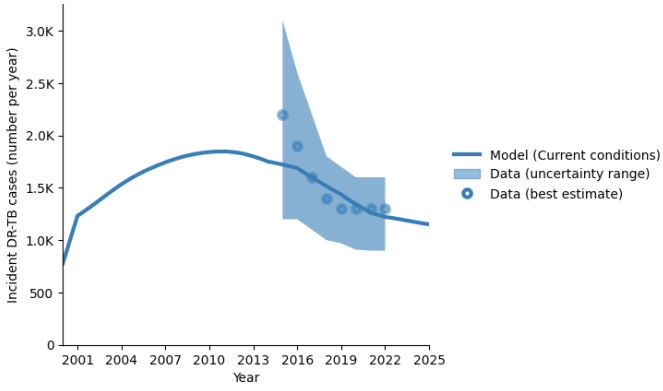
TB indicence – PLHIV on ART



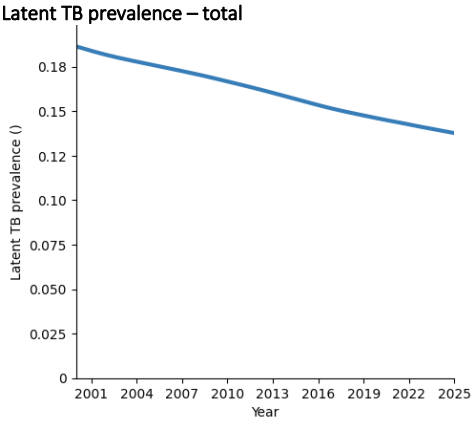
TB incidence – PLHIV not on ART



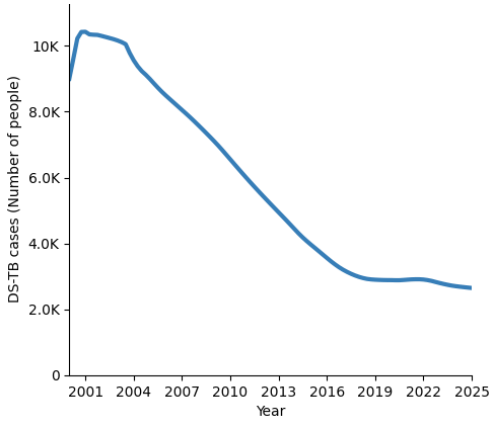
DR-TB incidence – total cases



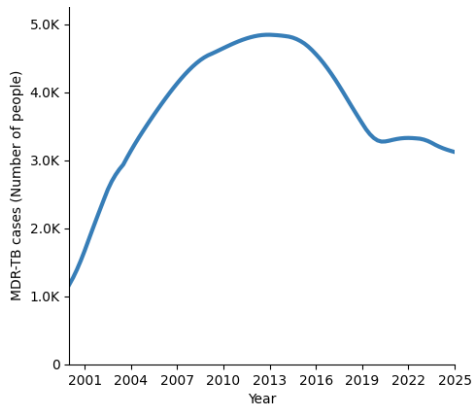
Latent TB prevalence – total



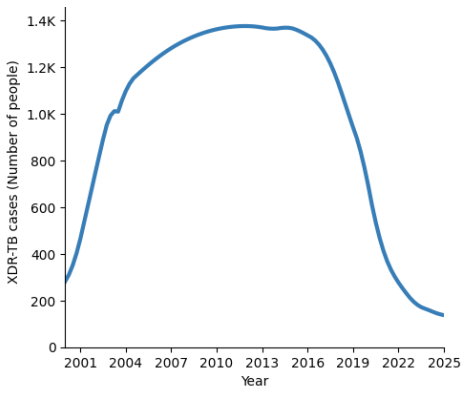
Active DS-TB cases – total



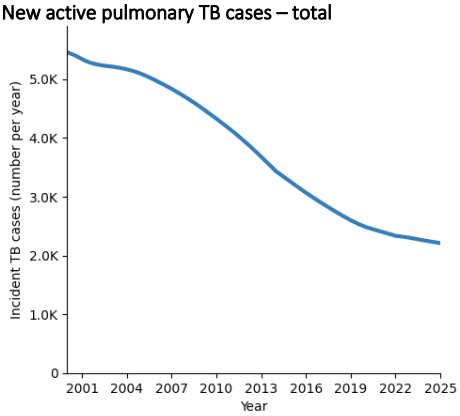
Active MDR-TB cases – total



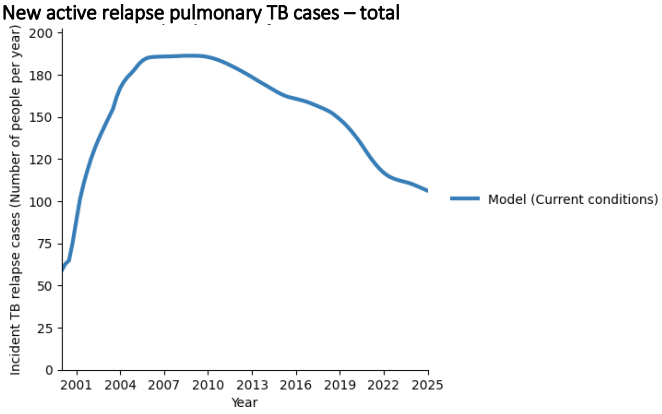
Active XDR-TB cases – total



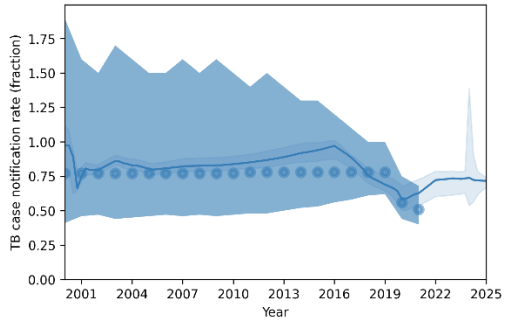
New active pulmonary TB cases – total



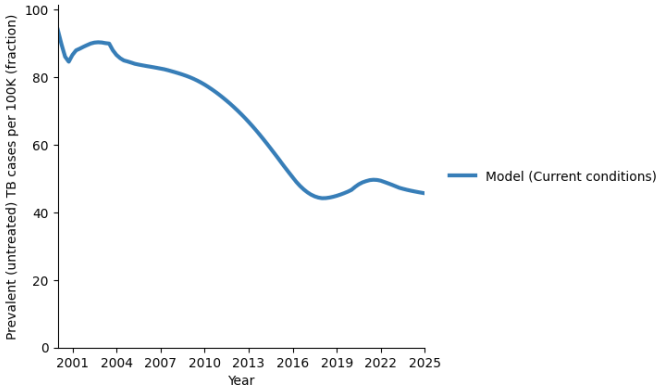
New active relapse pulmonary TB cases – total



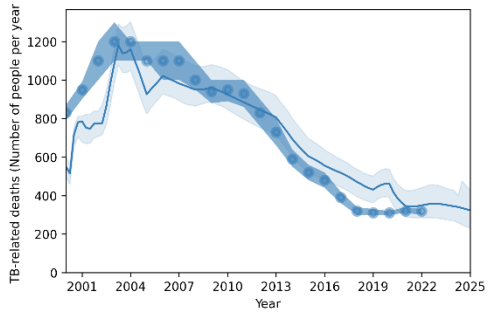
TB cases notification rate– total



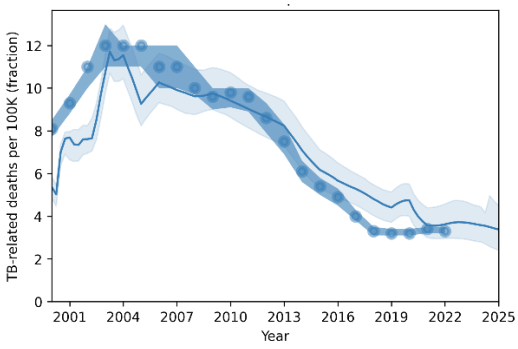
Prevalence of (untreated) pulmonary TB per 100K– total



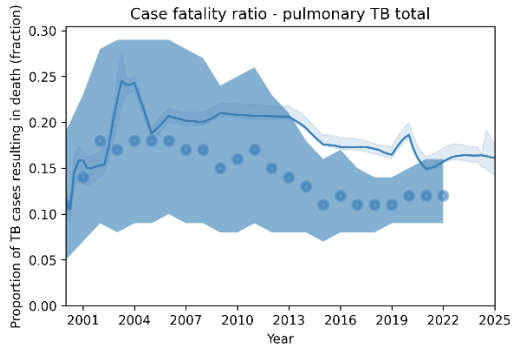
TB-related deaths – total

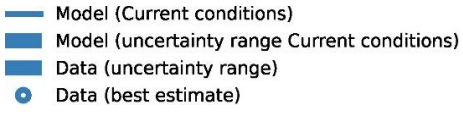


TB-related deaths per 100K – total

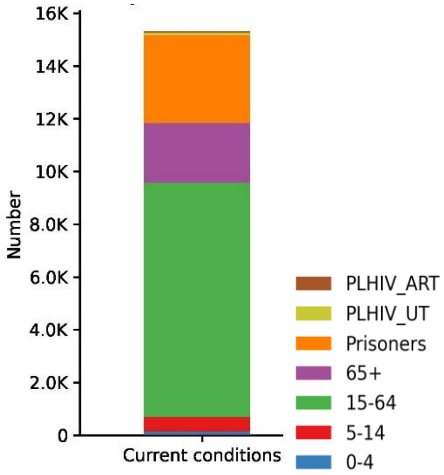


Case fatality ratio – pulmonary TB total

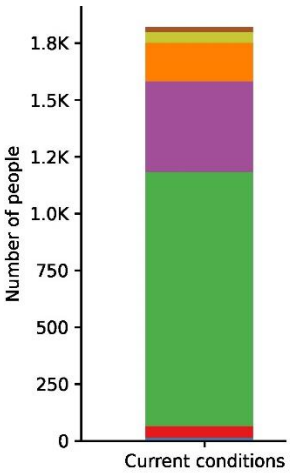




Cumulative TB incidence 2024 to 2030



Cumulative TB-related deaths 2024 to 2030



APPENDIX D. PROGRAM DEFINITIONS

D.1. Program details

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

		Unit	Unit cost (USD)	Assumptions
TB PREVENTION PROGRAMS				
BCG vaccination		Cost per infant vaccinated	$1.32	Unit cost based on national estimate 2015, assumed same in 2022.
TB preventive therapy (TPT) for people living with HIV		Cost per person per year	$11.52	Based on historical cost in 2015, Optima TB Belarus 2017. Based on 6-month treatment regimens.
TPT (DS only) for household contacts aged:	0-4 years 5-14 years 15-64 years	Cost per person who is a contact of index case with active TB, per preventive treatment initiation	$11.52	Based on historical cost in 2015, Optima TB Belarus 2017. Based on 6-month treatment regimens.
SCREENING AND DIAGNOSIS PROGRAMS				
Mass screening[2]		Per person screened	$1.39	Data on total number of people screened via x-ray available for 2015-2018 (14) and estimated for 2022 based on 37% decrease in number of notifications compared to 2018, less estimated number screened through other modalities. Estimated positive yield was 0.006%, based on mass screening accounting for 12% of diagnoses (4) (equates to $23,185 per person diagnosed).
Contact tracing[1]		Per person diagnosed	$513.21	Based on average diagnostic costs for latent TB and active TB. Number screened based on WHO Global TB data (1) and average program yield of 0.31% (14). Constraint on maximum expansion of contact tracing based on: expected number of index cases, allowing for an increase in case-finding; average number of contacts tested per index case (2.8)(4); number of contacts to be tested per index case to meet national targets for contact tracing among child contacts under 5 (6.2)(4); and estimated TB prevalence among household contacts by age group (20).
Active case finding (prisoner populations)[2]		Per person alive per year	$0.35	Based on individuals being screened on entry into the penitentiary system only, with number screened based on the number in pre-trial/remand (13). Spending derived from the average diagnostic costs for active TB plus x-ray screening. Estimated yield of 1.0% based on number of notifications among prisoners (equates to $200 per person diagnosed).
Active case finding (PWID) [1]		Per person diagnosed	$ 436.27	Funded through the HIV programme and assumed that current spending and coverage is fixed. Spending derived from the average diagnostic costs for active TB plus x-

			ray screening. Number screened and number diagnosed available through HIV program data. Positive yield based on average yield in 2019-2022 (0.37% among those X-ray screened).
Active case finding (community-based) [1]	Per person diagnosed	$ 436.27	Prospective program to reach harder-to-reach and vulnerable populations at higher risk of TB through targeted community-based screening. Unit cost and positive yield (0.37%) assumed to be the same as PWID. Constraint on expansion based on being able to reach a maximum 20% of undiagnosed people with active TB.
Other testing, including passive case finding [2]	Per person alive	$0.01	Spending derived from the average diagnostic costs for active TB plus x-ray screening. Number screened/diagnosed based on difference from total number tested (35,093) and number tested through other modalities (excluding mass screening). Insufficient data to differentiate passive case finding (symptomatic screening). Estimated positive yield 8% (equates to $78 per person diagnosed).
TB TREATMENT PROGRAM			
DS-TB treatment (standard)	Per person initiating treatment	$2,993	Based on 6-month standard treatment with HREZ. Incorporates cost of drugs ($54.50), inpatient costs ($2,805) and outpatient/monitoring costs ($134).
MDR-TB treatment (standard)	Per person initiating treatment	$14,800	Weighted average cost of standard treatment regimens (19 months) based on coverage in 2022, including: 18 Bdq Lfx Lzd Cfz Cs; 20 Bdq Lzd Cfz Cs Dlm; 20 Bdq Mfx Lzd Cfz Cs; and 20 Bdq Lzd Cfz Dlm. Incorporates cost of drugs ($3,813), inpatient costs ($8,764), outpatient/monitoring costs ($1,161), treatment observation ($361) and psychosocial support/home-based care ($700).
MDR-TB treatment (shorter oral regimens)	Per person initiating treatment	$7,221	Weighted average cost of shorter treatment regimens (average 7 months) based on coverage in 2022, including: mSTR (Lfx + Bdq + Lzd + Cfz + Cs, Lfx + Bdq + Lzd + Cfz + Dlm, Lfx + Lzd + Cfz + Dlm); BPaLM. Incorporates cost of drugs ($992), inpatient costs ($5,259), outpatient/monitoring costs ($682), treatment observation ($101) and psychosocial support/home-based care ($188).
XDR-TB treatment (standard)	Per person initiating treatment	$19,251	Based on 20-month standard treatment with 20 Bdq Lzd Cfz Cs Dlm, 6-8 Bdq Lzd Cfz Cs Imp/Amx/Clv, 14-12 Bdq Lzd Cfz Cs, 20 Bdq Lzd Cfz Dlm). Incorporates cost of drugs ($8,173), inpatient costs ($8,764), outpatient/monitoring costs ($1,180), treatment observation ($387) and

			psychosocial support/home-based care ($746).
XDR-TB treatment (shorter oral regiments)	Per person initiating treatment	$6,831	Based on 6-month shorter treatment with BPaL C. Incorporates cost of drugs ($929), inpatient costs ($5,259), outpatient/monitoring costs ($434), treatment observation ($69) and psychosocial support/home-based care ($140).

Notes: 1, unit cost defined as cost per diagnosis as modality has the ability to adapt targeting to focus on people at higher risk and thus maintain current yield. 2, unit cost defined as cost per population or per population screened as yield is expected to change over time based on prevalence; BCG, Bacillus Calmette-Guérin; 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: Unless indicated, data provided by the National TB Program

D.2. Impact of universal Xpert diagnosis

The current national TB diagnostic protocol includes both sputum smear microscopy and GeneXpert MTB/RIF as initial diagnostic tests for presumptive TB, but microscopy is still more common (4). A key strategic priority in Belarus is to update the national diagnosis algorithm to enforce universal Xpert MTB/RIF as the only initial diagnostic test, replacing microscopy for primary diagnosis. Based on National TB Program reported data, the sensitivity of sputum smear microscopy for TB diagnosis is 25-65%, thus 35-75% of microscopy analyses yield a false negative result. In 2022, only 10% of notifications were for smear negative TB, while it was estimated that 46% of all active TB infections were smear negative. A scenario was run to consider the projected impact on implementing the new algorithm from 2024 given improvement in diagnosis of smear-negative TB.

Based on 2022 spending, 26% of individuals received Xpert MTB/RIF Ultra Testing as part of their initial diagnosis (does not count subsequent Xpert testing as part of treatment monitoring). In the 2024 updated diagnosis algorithm, 100% receive Xpert MTB/Rif Ultra Testing, and it was assumed there would be no microscopy as part of initial diagnosis. The number requiring LPA and culture-based drug sensitive testing (DST) was assumed to increase proportionally in line with expected increase in diagnoses. Based on these calculations, the average diagnostic cost would increase by 159%, from $61 to $97, with the updated diagnosis algorithm (Table D2).

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 only initial diagnostic test from 2024 onwards;
- Unit cost for each screening modality multiplied by 1.59 based on estimated increase in cost per diagnosis from $61.04 to $96.77;
- Baseline program spending assumed to remain constant in both current and universal Xpert scenarios;
- Probability of diagnosing smear negative TB increased to align with smear positive TB for all modalities except “Other testing”, which includes passive case finding;
- Maximum constraints for contact tracing and TB preventative therapy increased in line with additional diagnoses expected and subsequent potential to reach more households and contacts.

Table D2. Estimated diagnostic costs based on 2022 spending and updating the diagnosis algorithm to use Xpert MTB/RIF as the only initial diagnostic test

	2022 estimated spending			2024 updated diagnosis algorithm		
	Cost	Number	Sub-total spending	Cost	Number	Sub-total spending
Microscopy for initial diagnosis	$2.37	114,013	$270,613	$2.37	0	$0
Microscopy for Primary Diagnosis (Seed Sediment)	$2.37	132,439	$314,347	$2.37	0	$0
Solid culture testing	$32.56	132,439	$4,312,214	$32.56	132,439	$4,312,214
Liquid culture testing	$29.70	39,256	$1,165,903	$29.70	39,256	$1,165,903
Xpert MTB/RIF Ultra Testing[1]	$52.96	35,093	$1,858,634	$52.96	132,439	$7,014,381
1st line LPA testing	$29.36	2,255	$66,218	$29.36	4,510	$132,435
2nd line LPA testing	$29.36	1,543	$45,310	$29.36	3,086	$90,620
Culture-based first-line DST	$14.23	1,839	$26,175	$14.23	3,678	$52,351
Culture-based second-line DST	$14.23	1,694	$24,112	$14.23	3,388	$48,223
AVERAGE COST FOR DIAGNOSIS	**$61.04**	**132,439**	**$8,083,526**	**$96.77**	**132,439**	**$12,816,127**

Notes: 1, Detection of Mycobacterium tuberculosis (MBT) complex and Rifampicin (RIF) resistance-associated mutations; DST, drug sensitivity testing; LPA, line probe assay.
Source: 2022 relevant tests, cost and coverage provided by the National TB Program, 2023. Estimated number and spending in the 2024 updated diagnosis algorithm estimated through the Optima TB Belarus 2023 analysis.

APPENDIX E. DETAILED MODEL FINDINGS

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

TB program	Baseline spending	Optimized 75% spending	Optimized 100% spending	Optimized 150% spending
BCG vaccination	$140,993	$105,745	$140,993	$143,800
TB preventative therapy for 0-4	$0	$28,814	$33,633	$35,239
TB preventative therapy for 5-14	$726	$105,747	$111,944	$120,607
TB preventative therapy for 15-64	$346	$1,227,921	$1,227,300	$1,227,539
TB preventative therapy for PLHIV	$12,995	$4,873	$20,708	$21,619
Mass screening	$5,536,503	$2,071,341	$2,762,843	$7,617,751
Contact tracing	$10,954	$387,164	$389,332	$387,522
Active case finding (prisoners)	$10,817	$10,817	$10,817	$ 10,817
Active case finding (PWID)	$3,761	$2,821	$3,761	$3,836
Active case finding (community-based)	$0	$361,019	$363,011	$375,886
Other testing, including passive case finding	$129,837	$101,260	$102,645	$134,076
DS-TB treatment	$2,875,938	$3,147,158	$3,353,420	$4,179,785
MDR-TB treatment (standard)	$1,805,552	$677,082	$902,776	$920,745
MDR-TB treatment (shorter oral regimens)	$3,617,748	$3,522,686	$6,249,414	$8,855,420
XDR-TB treatment (standard)	$2,656,679	$996,255	$1,328,339	$1,354,779
XDR-TB treatment (shorter oral regimens)	$396,177	$148,566	$198,089	$409,114
Total	**$17,199,025**	**$12,899,268**	**$17,199,025**	**$25,798,537**

Source: Optima TB Belarus model output, 2023

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

Table E2. Annual TB program coverage in baseline and optimized spending scenarios, 2024

TB program	Coverage definition used	Baseline spending	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	86,052	80,110	86,052	86,052	86,052	86,052
TB preventative therapy for 0-4	Number treated	0	888	967	959	797	1,044
TB preventative therapy for 5-14	Number treated	15	2,203	2,332	2,511	2,158	3,050
TB preventative therapy for 15-64	Number treated	4	13,850	13,850	13,850	19,309	19,483
TB preventative therapy for PLHIV	Number treated	1,128	423	1,798	1,800	564	14,006
Mass screening	Number screened	3,977,301	1,491,488	1,988,650	5,476,231	1,254,303	1,254,303
Contact tracing	Number diagnosed	21	754	755	755	1,051	1,061
Active case finding (prisoners)	Total prison population	31,321	31,321	31,321	31,321	30,905	30,905
Active case finding (PWID)	Number diagnosed	9	6	9	9	5	5
Active case finding (community-based)	Number diagnosed	0	828	831	831	1,051	1,061
Other testing, including passive case finding	Testing *relative to baseline* [2]	100%	78%	79%	100%	67%	83%
DS-TB treatment	Number treated	961	1,042	1,102	1,244	1,443	1,944
MDR-TB treatment (standard)	Number treated	122	46	61	62	61	61
MDR-TB treatment (shorter oral regimens)	Number treated	501	488	865	1,179	520	1,401
XDR-TB treatment (standard)	Number treated	38	41	42	41	43	43
XDR-TB treatment (shorter oral regimens)	Number treated	28	22	27	39	27	28

Source: Optima TB Belarus model output, 2023

Notes: 1, Impact of applying Xpert MTB/RIF universally for initial diagnosis; 2. Passive case finding assumed to remain available based on care-seeking behavior to the total population alive (9,534,955) 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 E3. 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	2,795	2,745	2,727	2,676	2,633	2,596	2,563	2,532	2,502
Optimized 75% spending	2,795	2,745	2,668	2,524	2,418	2,334	2,260	2,194	2,135
Optimized 100% spending	2,795	2,745	2,664	2,505	2,375	2,262	2,163	2,077	2,003
Optimized 150% spending	2,795	2,745	2,661	2,490	2,351	2,237	2,141	2,058	1,987
Optimized 100% spending + universal Xpert[1]	2,795	2,745	2,656	2,496	2,377	2,278	2,186	2,101	2,026
Optimized 150% spending + universal Xpert[1]	2,795	2,745	2,635	2,449	2,287	2,141	2,014	1,906	1,815
TB INCIDENCE PER 100,000 PEOPLE									
Baseline spending	29	29	28	28	28	27	27	27	26
Optimized 75% spending	29	29	28	26	25	24	24	23	23
Optimized 100% spending	29	29	28	26	25	24	23	22	21
Optimized 150% spending	29	29	28	26	25	23	22	22	21
Optimized 100% spending + universal Xpert[1]	29	29	28	26	25	24	23	22	21
Optimized 150% spending + universal Xpert[1]	29	29	27	26	24	22	21	20	19
ACTIVE DR-TB CASES									
Baseline spending	3,553	3,427	3,301	3,258	3,251	3,241	3,220	3,191	3,157
Optimized 75% spending	3,553	3,427	3,307	3,264	3,235	3,176	3,088	2,995	2,902
Optimized 100% spending	3,553	3,427	3,269	3,053	2,830	2,602	2,436	2,324	2,234
Optimized 150% spending	3,553	3,427	3,232	2,888	2,650	2,497	2,378	2,281	2,198
Optimized 100% spending + universal Xpert[1]	3,553	3,427	3,303	3,254	3,227	3,159	3,046	2,923	2,804
Optimized 150% spending + universal Xpert[1]	3,553	3,427	3,239	2,827	2,392	2,091	1,893	1,760	1,665
TB-RELATED DEATHS									
Baseline spending	355	350	336	312	303	299	297	293	288
Optimized 75% spending	355	349	304	282	277	273	262	251	241
Optimized 100% spending	355	348	319	294	274	251	228	214	203
Optimized 150% spending	355	348	336	295	258	237	222	210	199
Optimized 100% spending + universal Xpert[1]	355	348	279	221	196	185	164	145	127
Optimized 150% spending + universal Xpert[1]	355	347	297	221	146	98	68	50	46

Source: Optima TB Belarus model output, 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.

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