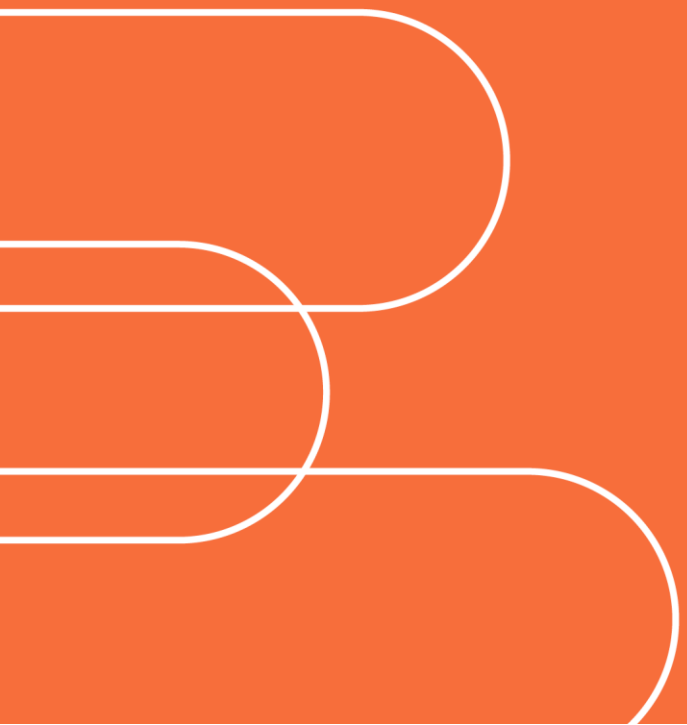
April 2024 (version 3.0)

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

Findings from an Optima TB analysis, 2023



Burnet
reach for the many

Acknowledgments

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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
NGO	Non-governmental organization
NTP	National TB Programme
PLHIV	People living with HIV
RR-TB	Rifampicin resistant tuberculosis
SN	Smear-negative
SP	Smear-positive
TPT	TB preventive treatment
XDR-TB	Extensively drug-resistant tuberculosis

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Executive summary

BACKGROUND

Estimated tuberculosis (TB) incidence has declined in the Republic of Moldova, from an estimated 142 new infections per 100,000 population in 2005 to 74 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

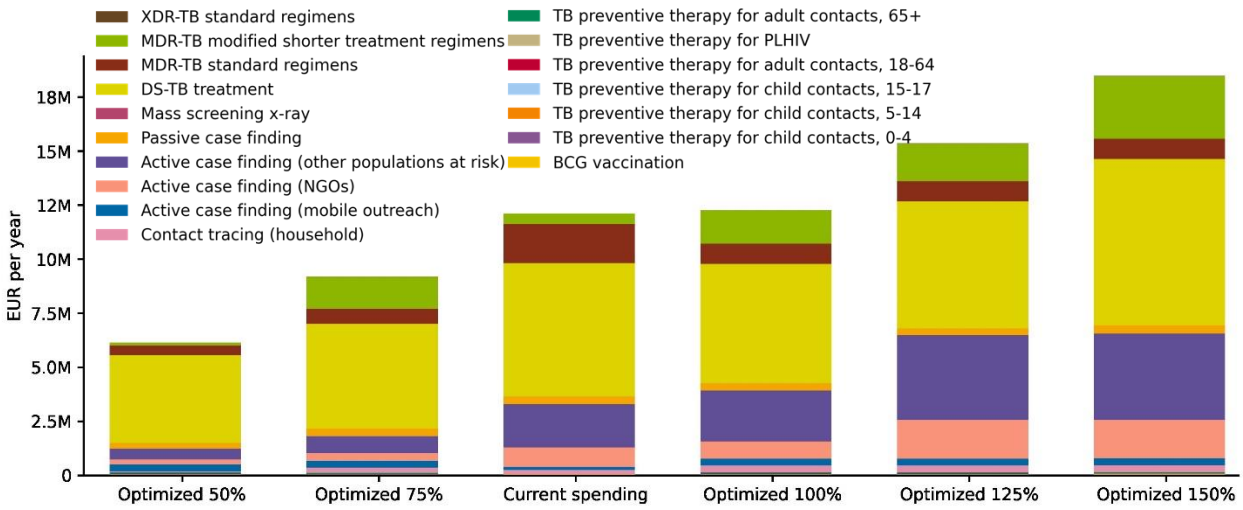
Baseline

In 2022, the model estimates 2,347 incident cases and a total 6,091 active pulmonary TB cases in Moldova, of which an estimated 21% were DR-TB. In 2022 an estimated €12.4 million was spent on direct TB prevention, screening and treatment programs, of which 67% was spent on treatment. A shorter course RR/MDR treatment was implemented end of 2023, reducing treatment time from six to nine months.

Optimization of current spending

Main priorities included short-course MDR treatment (+€1,1M) to cover more MDR cases at a lower cost, scaling up active case finding for other population at-risk (+€357,000) to increase the notifications among those who are not covered in the current program, , and scaling-up active case finding through household contact tracing and mobile units (+€302,000) to notify those undiagnosed with active TB. Scaling up and preventive treatment for household contacts of all ages (+€81,560) is also recommended (Figure 1). This could result in 227 (1%) new TB infections and 1,341 (28%) TB-related deaths that could be averted from 2024 to 2030 compared with if baseline spending were continued, while DR-TB could reduce from 42 to 35 per 100,000 in 2030.

Figure 1. Recommended allocation of funding by program to minimize drug-resistant TB for varying budget levels (50% to 150%)



End TB targets

A combination of targeted screening that may improve diagnosis rates, short durations of treatments and full implementation of preventive treatment and vaccination may be required to reach End TB targets, as they are not within reach with the current interventions.

CONCLUSIONS AND RECOMMENDATIONS

Key findings

1. **Shorter treatment regimens based on Bedaquiline are more cost-effective**, allowing for a larger number of people to be treated for the same amount of spending, as well as better adherence and limiting side-effects for people with TB.
2. **Rates of diagnosis and treatment decreased in 2020** due to COVID-19 and have not since recovered.
3. **Continued and expanded prioritization of case finding** through mobile units, contact tracing, and other forms of active case finding including through non-governmental organizations could improve diagnosis rates prior to natural outcomes from 80% in 2022 to 92% in 2030.
4. **Expand prevention strategies** for those most affected by tuberculosis - including preventive treatment coverage for all household contacts of diagnosed active TB cases.
5. **National TB targets could be within reach** if resources are allocated optimally, however end TB targets may be out of reach with the current set of interventions.

1 Background

Tuberculosis (TB) remains a significant public health issue in the Republic of Moldova, being one of the top-30 highest burden of Rifampicin (RR) and multi-drug resistant (MDR)-TB countries globally (1). According to the 2023 WHO Global Tuberculosis Report, 28% of new cases and 57% of previously treated cases had MDR/RR-TB in 2022 (2). Overall, TB incidence and deaths have been declining since 2006, reducing from a high of 142 new infections per 100,000 population in 2005 to 74 per 100,000 in 2022 (2). However, disruptions due to COVID-19 and pandemic response measures may have slowed progress (3, 4), as from March to December 2020, a 39% reduction in notifications was reported compared with the same period in 2019 (2, 5).

However, the COVID-19 pandemic has enabled more implementation of shorter regimens with Bedaquiline and Delamanid, less injectable treatments, and video-assisted treatment. Treatment success for drug-sensitive TB is 79% in Moldova, decreasing to 69% among MDR-TB cases, 57% among extensively drug resistant (XDR)-TB cases, and 61% among cases coinfected with HIV in 2022 (6). Males are more affected than women (74% to 26% ratio) and those aged 35-44 report the highest incidence (5). Key and vulnerable populations identified to be most-at-risk of TB or with poorer TB outcomes in Moldova include migrant workers, people with chronic disease such as diabetes, people living with HIV, prisoners, people with drug or alcohol use disorders and people living in poverty (2). Mandatory radiological examination of prisoners identified 48.3% of new entries had tuberculosis in 2019, with a success rate of 91% for drug sensitive TB and 57% for MDR-TB (5). Migrant workers are more vulnerable to TB due to exposure to settings with higher burden of TB as well as barriers to accessing healthcare (7). Moldova has received over 100,000 refugees from Ukraine as permanent residents since February 2022, of which at least 50 have MDR-TB (8, 9).

Moldova was one of the first countries to scale up access to GeneXpert rapid diagnostics for TB screening, distributing 30 Xpert machines in community health centres and other testing facilities in 2014 (10). This provides localized access to GeneXpert testing for an estimated 64% of the Moldovan population (11). Nevertheless, late diagnosis rates are still at 43%. To ensure the population is aware of tuberculosis symptoms and the importance of testing and treatment, child-friendly comics are disseminated in four major cities (11).

The TB response in Moldova remains is predominantly funded through domestic sources (88% in 2021), with decreasing international support through the Global Fund (12). The government of Republic of Moldova is committed to apply innovative strategies to reduce the burden of TB. The National Tuberculosis Response Program 2022-2025 outlines a 50% reduction in incidence and 75% reduction in mortality in 2025 compared with 2015 in line with End TB targets (5).

Prior Optima TB analysis

A 2017 Optima TB analysis in Moldova included several key concerns that remain ongoing and that may now be further explored with new epidemiological evidence and based on the strategies implemented since 2018:

- Moldova's 43% late diagnosis rate indicates the need to identify new active cases earlier through active case finding methods;
- Low treatment success rates projected to lead to a 50% increase in XDR-TB by 2020 without the application of new DR-TB drug regimens;
- The need to improve adherence support strategies, including patient incentives; and

- An ongoing need to evaluate active case finding in key populations of prisoners and migrants.

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 Moldova to minimize drug-resistant TB cases and TB-related deaths by 2030. 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 the Optima TB model, a mathematical optimization model applied to assess the optimal allocation of available resources across TB programs to maximize impact. Details of the Optima TB model and model parameters are included in Appendix A. Optima TB is a deterministic, compartmental model that partitions the population by age group and risk, 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 Response 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 (disaggregated into HIV negative and HIV positive)
- Children 5-14 (disaggregated into HIV negative and HIV positive)
- Adults 15-17 (disaggregated into HIV negative and HIV positive)
- Adults 18-64 (disaggregated into HIV negative and HIV positive)
- Adults 65+ (disaggregated into HIV negative and HIV positive)
- Migrants 15+
- Prisoners 15+

Based on available data, the following TB programs were considered in the analysis, full costing and estimated impacts available in 0:

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

Prevention	TB preventive treatment (TPT) for contacts:	0-4 years
		5-14 years
		15-17 years
		18-64 years

		65+ years
	TPT for PLHIV	
	BCG for children aged 0-4	
Diagnosis	Passive case finding (symptomatic screening)	
	Household contact tracing	
	Active case finding (mobile outreach)	
	Active case finding (via NGOs)	
	Active case finding (other populations at risk)	
Treatment	DS-TB treatment	
	MDR-TB treatment (standard)	
	MDR-TB treatment (shorter oral regimens)	
	XDR-TB treatment (standard)	
	XDR-TB treatment (shorter oral regimens)	

Notes: BCG, Bacillus Calmette-Guerin; DS, drug susceptible; MDR, multi-drug resistant; NGO, non-governmental organizations; TB, tuberculosis; XDR, extensively drug-resistant

As of January 2021, the World Health Organization (WHO) has changed its definition of XDR-TB, further disaggregating XDR into pre-XDR and XDR-TB to ensure appropriate registration, monitoring and targeting of treatment. Pre-XDR TB is multidrug resistant and rifampicin-resistant TB that is also resistant to any fluoroquinolone. XDR-TB includes all of the previous resistance as well as resistance to one additional Group A drug (levofloxacin, moxifloxacin, bedaquiline, and/or linezolid) (13). These definitions were also adhered to in this analysis.

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 Moldova analysis, 2023

Scenario	Description
Baseline scenario	Continued spending and fixed allocation of €13.7M (100% of TB prevention, screening and treatment spending) maintained over 2024-2030
Optimized spending 100%	Continued spending of €13.7M (100%) with optimized allocation to reduce DR-TB incidence and TB-related deaths by 2030.
Reduced/increased spending (50%, 90%, 125%, 150%, 200%) optimized	Considers if available resources for TB programs were reduced or increased. Percentages are relative to the most recent targeted TB spending.
Reaching End TB target milestones by 2030	Assesses the resources required and optimized spending allocation to reach End TB milestones for 80% reduction in TB incidence and 90% reduction in TB-related deaths from 2015 to 2030.

Notes: DR, drug-resistant; TB, tuberculosis.

MODELLING SPECIFICATIONS

Model inputs

A new Optima TB model for Moldova was developed and recalibrated 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. This analysis was limited to pulmonary TB only to align with previous analyses. Pulmonary TB is estimated to account for 92% of TB notifications in Moldova (2).

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

Data type	Source
Epidemiologic data	Demographic data for population size, birth rate estimates and all-cause mortality from UN population division and National Bureau of Statistics of Moldova (14); UNAIDS Spectrum estimates for PLHIV (15); prisoner population size supplied by the National HIV Program as part of the 2022 Optima HIV analysis (16); TB notifications, TB treatment outcomes and TB-related deaths supplied by National TB Program.
Program coverage data	Coverage of BCG vaccination at birth based on national estimates for coverage at birth. Number of people screened by modality and positive yield, treatment initiations and outcomes by smear status and strain, number of BCG vaccinations, TPT initiations supplied by National TB Program, 2000-2022.
Cost data	Cost per person diagnosed and annual cost per treatment initiation provided by National TB Program, 2022.

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 2022 estimates). 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 and XDR-TB and reducing the number of TB-related deaths. Based on the estimated baseline conditions of 2022, this resulted in respective model weightings of 1, 3, and 11 for reductions in the active number of DS-TB, DR-TB, and TB-related deaths averted.

Optimization constraints

Changes in funding to achieve optimized allocations did not consider reallocation of care costs between hospitalized and ambulatory treatment modalities. Coverage with optimized budgets was

constrained such that with 100% optimization or increased budget levels no program could have funding reduced by more than 50%. Given uncertainty around how much different modalities of active case finding could be scaled up, the optimization assumed coverage could be doubled given increased spending for mobile van testing, NGO-based outreach, and all other active case finding not disaggregated. The maximum coverage of contact tracing and preventive treatment was estimated based on a potential 25% increase in the number of index cases with active TB diagnosed through other modalities to 2,500 people, given an average household size of 2.89 (1).

4 Findings

EPIDEMIOLOGICAL SITUATION

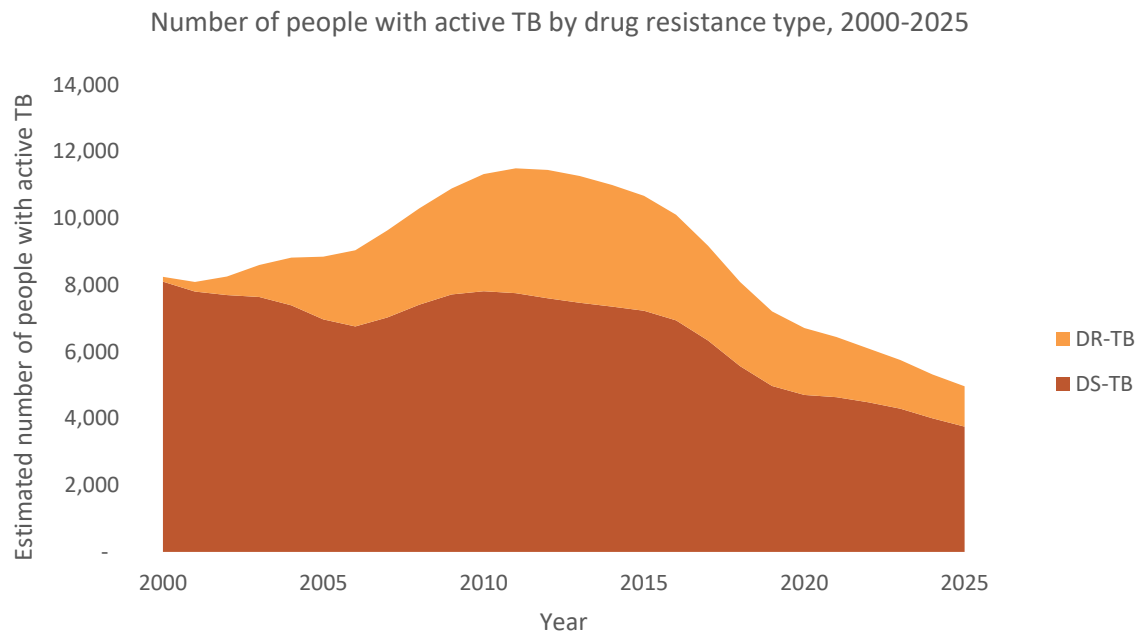
In 2022, there were an estimated cumulative 6,091 From country team: active pulmonary TB cases in Moldova, of which an estimated 21% were DR-TB (Table 4). This has decreased from 39% of active cases being DR-TB in 2015 (Figure 2). The majority of all TB cases were among those aged 18-64, and the highest prevalence of latent TB was among those aged 65 and over.

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

	Incident TB			Prevalent TB		
	New and relapse TB cases	Incidence per 100,000	Activated DR-TB cases (% of all activated cases)	Active TB cases	Latent TB prevalence	TB-related deaths
0-4 years	28	14	10%	51	1.0%	0
5-14 years	59	14	11%	180	2.1%	2
15-17 years	20	17	18%	58	2.9%	1
18-64 years	1523	82	19%	4,596	21.9%	168
65+ years	186	44	14%	601	24.1%	50
PLHIV	205	872	28%	228	19.3%	52
Prisoners	113	2,038	39%	231	0.4%	4
Migrants	212	256	27%	145	5.5%	7
Total	2,347	74	21%	6,091	17.1%	285

Notes: PLHIV includes people living with HIV of all ages. DS, drug susceptible; TB, tuberculosis; MDR, multi-drug resistant; XDR, extensively drug-resistant.
Source: Optima TB Moldova model output, 2023

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



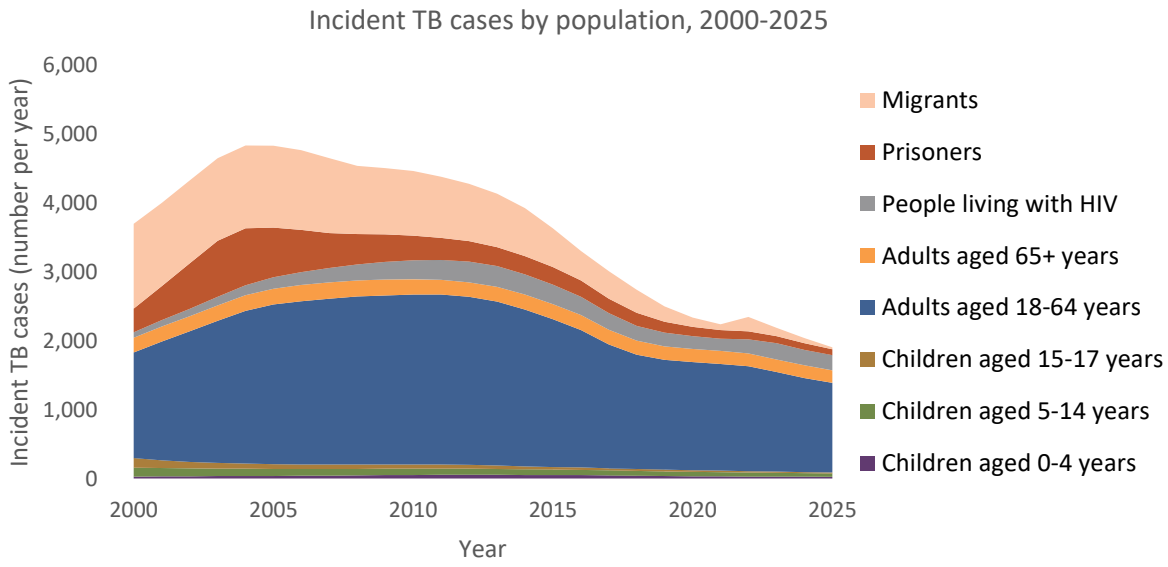
Source: Optima TB Moldova model output, 2023.
Notes: DS, drug susceptible; TB, tuberculosis; DR, drug resistant

TB incidence

In 2022, there were an estimated 2,347 incident pulmonary TB cases, including both new and relapse cases and cases among migrants. Consistent with WHO-reported trends, estimated TB incidence in Moldova has significantly declined in the past 20 years, reducing from a high of 150 per 100,000 population in 2006 to 74 per 100,000 population in 2022. There was a minor increase in incidence per 100,000 from 2020 to 2022, reaching 110 per 100,000 population, most likely due COVID-19 related disruptions to diagnosis (the note 39% reduction in notifications in the March to December 2020 period), combined with higher expected incidence rates among migrants in 2022(11, 17, 18).

The majority of new cases of TB continue to be among adults aged 18-64, with 1,613 incident cases among this age group in 2022 (Figure 3). However, relative to population size prisoners have the highest incidence of TB in Moldova, with estimated 2,982 new cases per 100,000 population in 2022, followed by people living with HIV, with 1,319 new cases per 100,000 population among adults 18-64 living with HIV. Comparatively, estimated incidence among the general adult population was 86 per 100,000 population in 2022. Children aged 0-4 and 5-14 years have the lowest incidence, at 18 and 15 per 100,000 population, respectively. The BCG vaccination coverage is estimated to be 99% at birth, implying 41,361 vaccinations in 2022. Extrapulmonary TB was not modelled as part of this analysis and constitutes approximately 5% of adult TB notifications, although substantially higher among child TB notifications.

Figure 3. Incident pulmonary TB cases by population group, 2000–2025



Source: Optima TB Moldova model output, 2023.

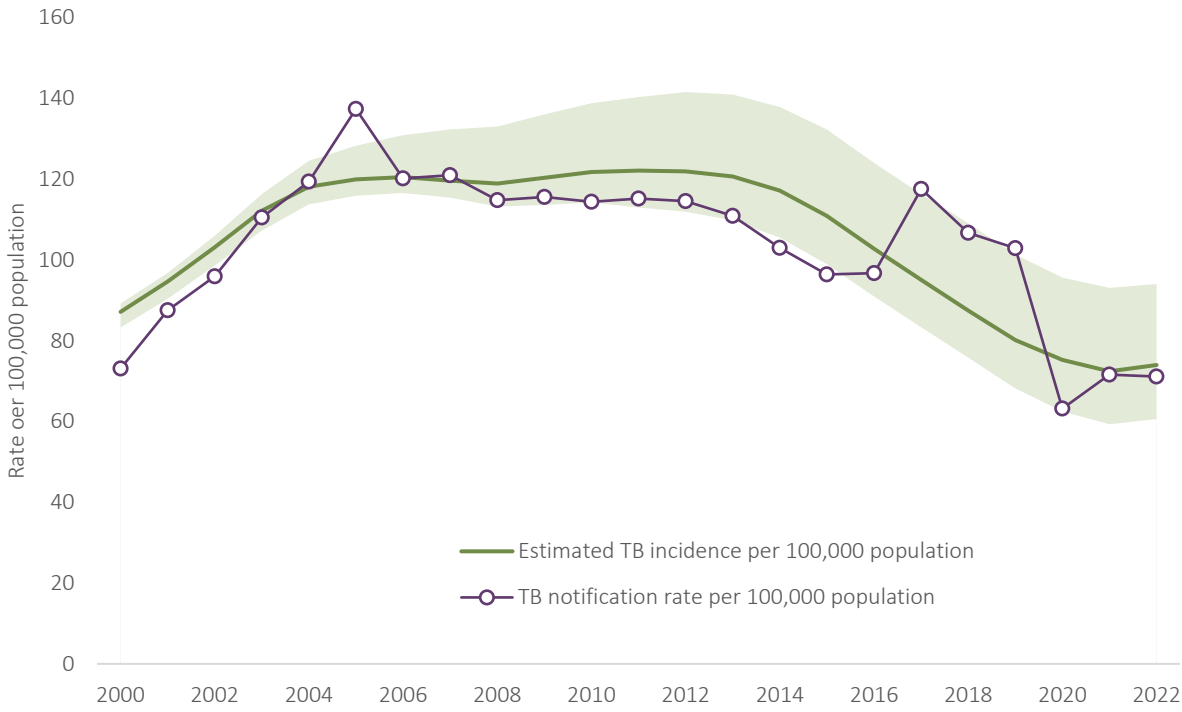
TB notification and case detection

In 2022, there were a total of 2,850 pulmonary TB notifications in Moldova (85 per 100,000 population), of which 69% were among the 18-64 sub-population group. The estimated case detection rate (the proportion of estimated new and relapse TB cases that are detected in a given year (19)) was low among migrants (30%) and prisoners (40%), but was 120% among adults aged 16-84 years. Case detection rates higher than 100% may be indicative of delayed and catch-up

diagnoses, detecting infections acquired in previous years. However, there is inherent uncertainty in this indicator due to uncertainty around true incidence.

Case detection has notably decreased since 2020, likely due to COVID-19-related disruptions to screening activities and delays in care-seeking (Figure *4*). As of the end of 2022, TB notifications per 100,000 population have not returned to pre-2020 levels. This may be due to a true reduction in incident TB cases, reduction in undiagnosed active TB, or ongoing disruptions to diagnosis and care-seeking (18).

Figure 4. Estimated pulmonary TB incidence rate and notification rate per 100,000 population, 2015–2022

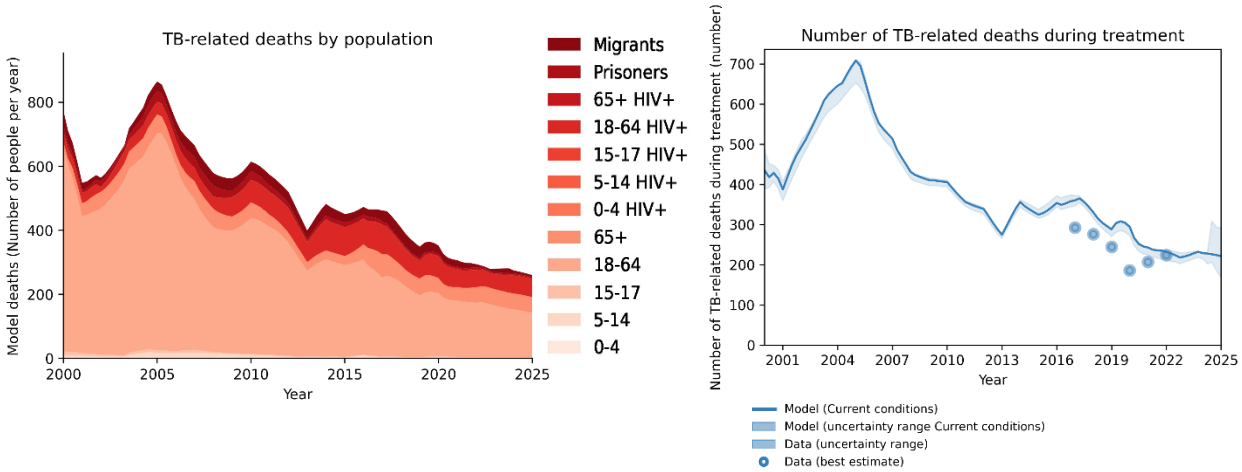


Source: Optima TB Moldova model output, 2023. Notification data from National TB programme.
Note: Shaded area indicates uncertainty range for TB incidence

TB mortality

Overall estimated TB-related deaths have declined in Moldova from a high of 815 in 2004 to 285 in 2022, in line with decreasing incidence and advances in diagnosis and treatment (Figure 5). The modelled estimates of TB-related deaths during treatment are aligned with the number of TB-related deaths reported during treatment from 2017 to 2022 in national TB programme data, but are higher than national WHO estimates. The average annual mortality rates for pulmonary TB among adults aged 15-64 of 7.6% from 2018 to 2022 (and higher among migrants and people living with HIV or aged 65+) likely implies a high number of late detections of TB with severe and advanced forms leading to increased mortality.

Figure 5. TB-related deaths by population, and during treatment 2000–2025



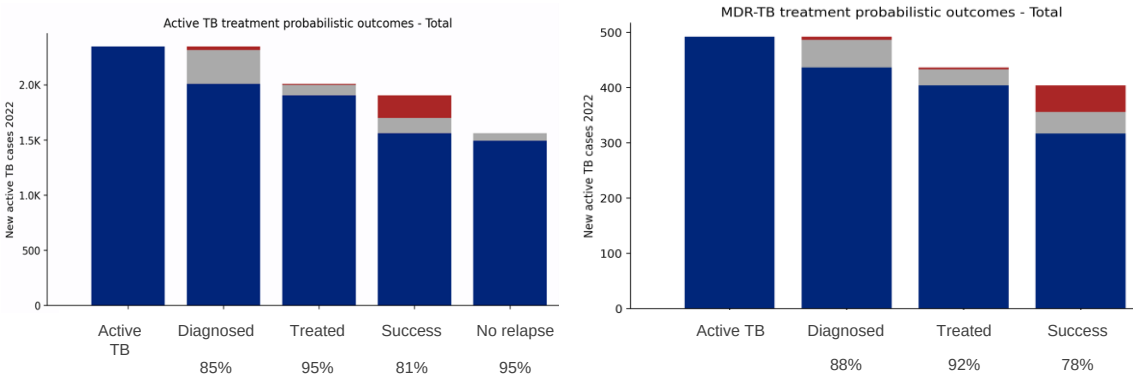
Source: Optima TB Moldova model output, 2023.

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, 85% of all people progressing to active TB in Moldova would be projected to be diagnosed prior to natural outcome (recovery or death), and slightly higher (88%) for MDR-TB. Of those diagnosed, 95% are projected to be treated (

Figure 6). Overall, the probability of treatment success was 81% for all active pulmonary TB and slightly lower (78%) for MDR-TB. Reported treatment failure rates for MDR-TB have halved from 2015 to 2021, from 13% to 6%, while loss to follow-up has also declined from 20% to 13%.

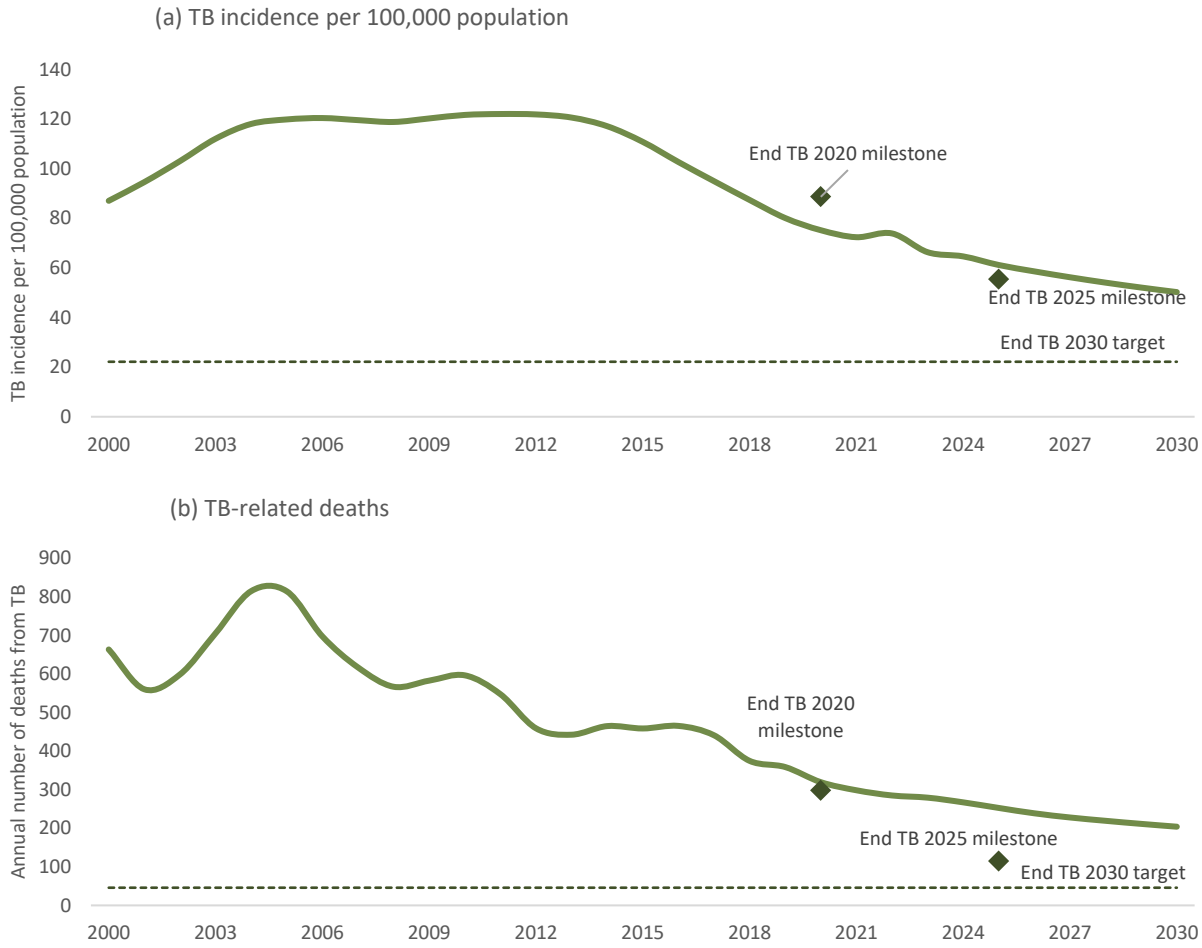
Figure 6. The projected final cohort outcomes for people progressing to active TB (left) and MDR-TB (right) in 2023 in the Baseline spending scenario



Progress towards TB targets

To evaluate progress towards the ambitious End TB 2030 targets of reaching an 80% reduction in incidence rate and 90% reduction in TB deaths relative to 2015 (20), the strategy defines country milestones for 2020 and 2025. Based on Optima TB modelled incidence, Moldova achieved the 2020 End TB milestone for 20% reduction in incidence and mortality from 2015. Continued progress to reach the 2025 milestone is feasible for incidence, but may have been hindered by the reversal of trends in 2020-21 due to COVID-19-related disruptions for mortality. With continuation of current conditions, the 2030 target for reduction for TB incidence (Figure 7a), and the 2030 End TB target for mortality are not within reach for Moldova (Figure 7b).

Figure 7. Optima TB estimated trends in (a) TB incidence rate and (b) TB mortality in relation to End TB targets



Source: Optima TB Moldova model, 2023.
Notes: End TB milestones (diamond markers) and 2030 targets (dashed line) defined as percentage reduction from 2015 (21). Baseline based on Optima modelled values.

CURRENT TB SPENDING

Based on most recent spending estimates, in 2022 an estimated €12.4 million was spent on direct TB prevention, screening and treatment programs. Of this, 67% was spent on treatment. Treatment predominantly utilized standard, longer-course regimens, but national TB programme data indicated that 26% of MDR-TB patients were initiated on modified shorter all-oral treatment regimens (mSTR), accounting for 19% of spending for MDR-TB treatment. Novel all-oral 6-month regimen composed of bedaquiline, pretomanid, linezolid and moxifloxacin (BPaL/BPaLM-based) regimens are planned to be implemented from 2023 onwards and can further reduce treatment duration from nine to six months.

Among all spending for TB screening and testing, 90% was spent on active case finding through different modalities, but most notably among populations at risk and through screening by NGOs.

WHAT IS THE OPTIMIZED ALLOCATION OF THE TB BUDGET?

Optimized allocation of TB spending

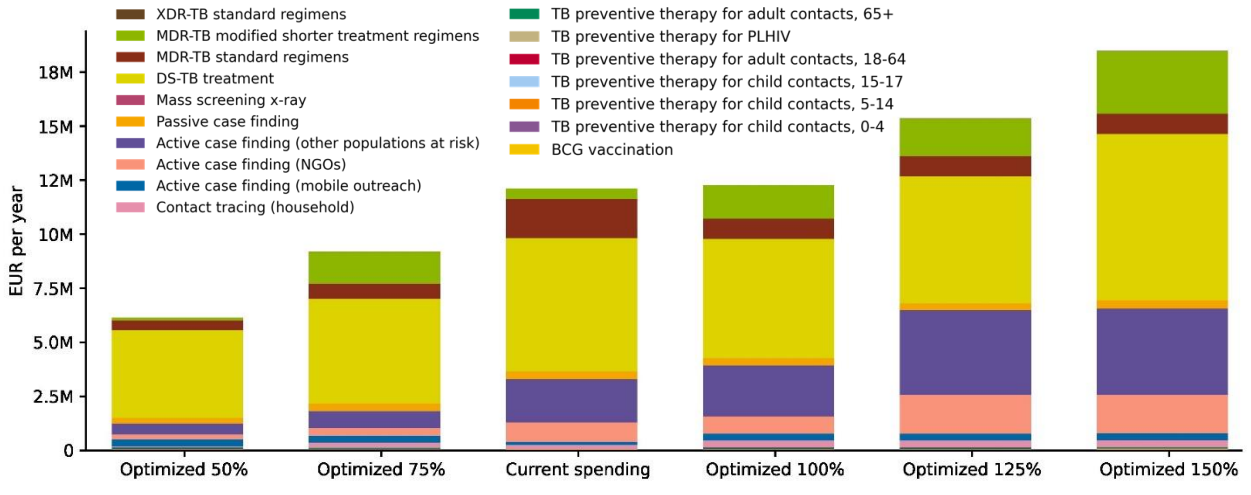
With €12.4 million (100% of baseline spending maintained), the optimized allocation of the TB budget prioritizes short-course MDR, preventive treatment and active case finding through household, mobile and NGO. Main priorities included short-course MDR treatment (+€1,1M) to cover more MDR cases at a lower cost, scaling up active case finding for other population at-risk (+€357,000) to increase the notifications among those who are not covered in the current program, , and scaling-up active case finding through household contact tracing and mobile units (+€302,000) to notify those undiagnosed with active TB. Scaling up and preventive treatment for household contacts of all ages (+€81,560) is also recommended.

These priorities reflect the lowest cost modalities of active case finding per active TB case diagnosed, being mobile vans (€431 per diagnosis) and contact tracing (€1,455), combined with the extremely low marginal unit cost per household contact of €6.12 to €6.74 to provide preventive treatment following contact tracing to all household contacts. This low unit cost per household contacts may need to be considered with respect to additional health system costs for clinician time when delivered through clinics. The unit cost per person diagnosed through other forms of active case finding are higher (€5,159 through NGO-based outreach, or €1,778 through all other modalities not disaggregated).

As budgets increase, the optimization recommends to maximize the coverage of all active case finding modalities, constrained in the optimization to be double 2022 coverage for mobile vans, NGO-based outreach, and all other forms of active case finding to higher risk populations, while providing household contact tracing to all diagnosed active TB cases and preventive treatment to household contacts of all ages, while expanding treatment to cover all diagnosed cases, with a focus on continuing to expand short-course treatment modalities for MDR-TB.

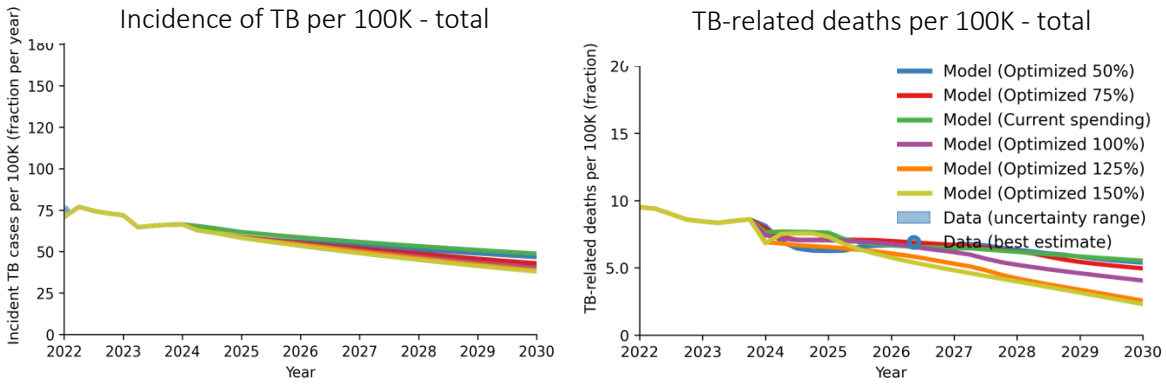
Investment levels above 150% were not included in the optimization as the modelled interventions reach close to the maximum coverage level above 150% spending, resulting in limited additional impact. New interventions not yet implemented in Moldova and not considered as part of this analysis may continue to be impactful with additional spending. At lower budget levels below 100%, it is recommended to scale up MDR short course and active case finding through mobile units, as well as preventive treatment for household contacts of all ages identified through contact tracing. 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 (50% to 150%)



Projected impact of optimized TB spending

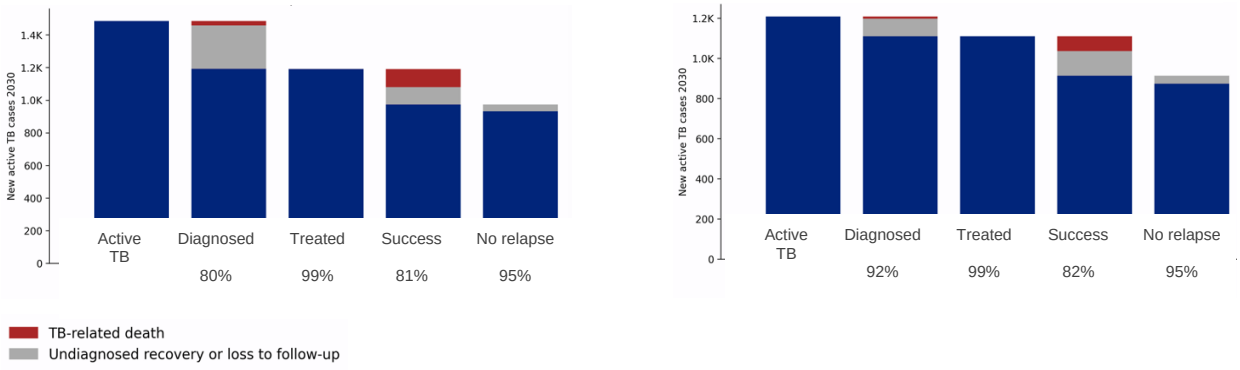
Figure 9. Projected impact of optimization at varying budget levels on TB incidence (left) and TB-related deaths (right) per 100,000, 2022 to 2030



Note: Slight increases in optimized scenarios for TB-related deaths in 2024 and 2025 are due to an increased number of diagnoses that are not immediately linked to care.

With 100% of TB spending optimized, it is estimated that 1,260 (10%) new TB infections and 170 (12%) TB-related deaths could be averted from 2024 to 2030 compared with if baseline spending were continued (Figure 9). Importantly, a reallocation of resources could ensure prevalence of DR-TB is 26 per 100,000 in 2030 rather than 32 per 100,000. The 2030 cohort cascade could improve such that 92% of people will be diagnosed (+12 percentage points more) (Figure 10). This analysis did not consider treatment success to change as a result of shorter treatment regimens, therefore no impact is seen there, but mortality during treatment is reduced substantially as a result of earlier diagnosis.

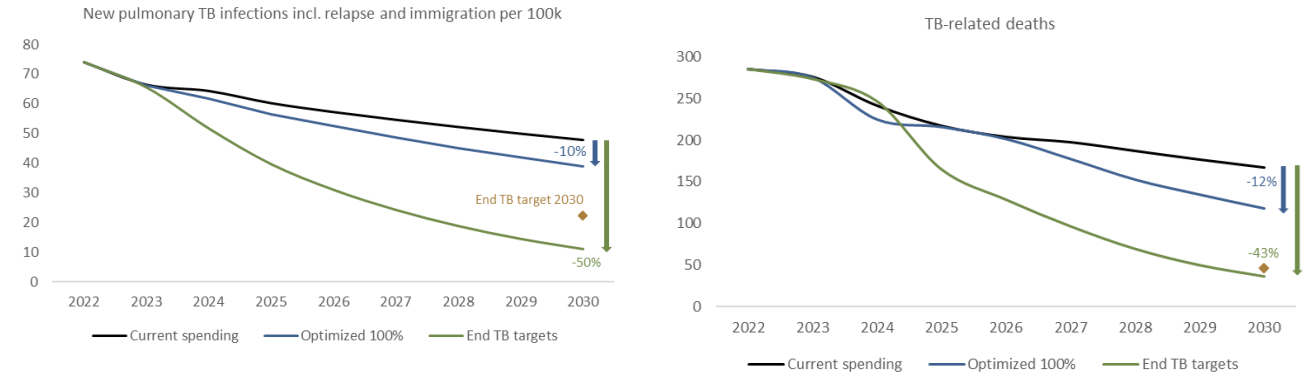
Figure 10. Active TB probabilistic cascade in current spending (left) and 100% optimized spending (right) in 2030



WHAT COMBINATION OF INTERVENTIONS WILL MAKE IT FEASIBLE TO ACHIEVE END TB TARGETS BY 2030?

Reaching the national TB targets may be within reach if resources are allocated optimally, however reaching the End TB targets is projected to be out of reach with the current set of interventions. A combination of targeted screening that may improve diagnosis rates, short durations of treatments and full implementation of preventive treatment and vaccination may be required to reach End TB targets (Figure 11).

Figure 11. Projected impact of implementing rapid diagnosis and treatment toward End TB targets for reducing TB incidence and TB-related deaths, 2022–2030

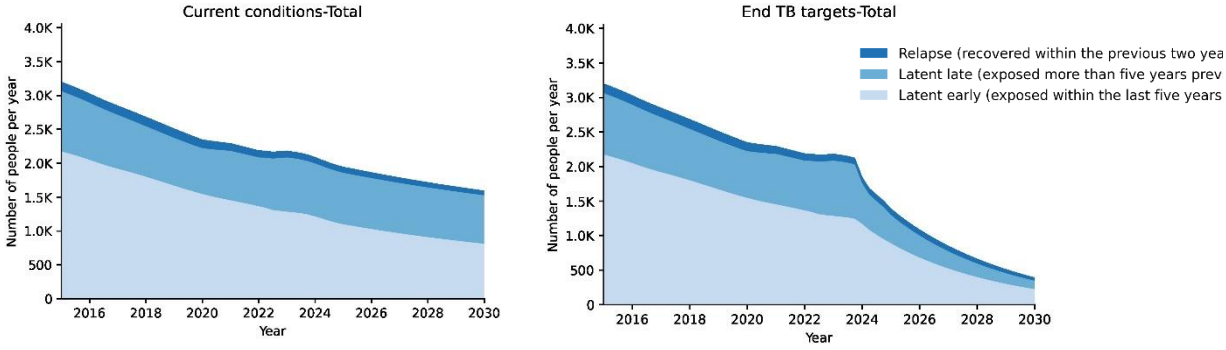


The modelled combination of intervention impacts included:

- Reduced average time until diagnosis for those populations with more than 12-month average (prisoners, migrants, people aged 5-17, and people aged 65+), resulting in approximately a 25% overall reduction in the average time until diagnosis for people with active TB through active case finding.
- Reduced TB-related deaths during treatment by 50% to reflect earlier diagnosis (from 7.6% to 3.8% for adults aged 18-64 without HIV).
- Rapid treatment initiation following diagnosis for all diagnosed individuals.
- Contact tracing of diagnosed individuals and preventive treatment for all household contacts (estimated to reach 20% of people with early latent TB due to recent exposure to active TB and 1% of people with late latent TB).
- A 20% reduction in social determinants leading to TB activation, e.g. through improved nutrition, early care seeking behaviour, improved care for co-morbidities and other public health interventions.

Further reductions in TB incidence become more challenging even with a substantial scale-up in the rate of active case finding and preventive treatment for all contacts that reduces TB transmission to very low levels. A large proportion of progression from latent infection to active TB disease is estimated to come from people exposed more than five years previously when the burden of TB prevalence was higher in Moldova, combined with relapse cases expected to be reported following a scale-up of treatment (Figure 12).

Figure 12. Projected change in source of new active TB infections, 2015–2030



5 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:

The size and profile of the TB epidemic in Moldova was aligned with the 2023 WHO Global TB Programme modelled estimates (2). 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. The current analysis includes pulmonary tuberculosis only and excludes extrapulmonary tuberculosis to maintain consistency with previous analyses, noting that 92% of cases were pulmonary in Moldova in 2022. This analysis combines the Left and Right Banks of Moldova and does not consider more vulnerable regions such as the Transnistrian region, separately.

TB expenditure: Unit costs for interventions are subject to some levels of uncertainty. There were insufficient cost data to consider the resource required to reach the End TB targets.

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 (22), or further emergence of new drug resistance in Moldova.

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. For instance, the feasibility and costs of scaling up case finding through the use of ultraportable computer-aided detection (CAD)-enhanced chest X-ray was not explored. Reduced drug prices (leading to lower unit costs, better efficiency and cost-effectiveness) were not modelled.

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, which may especially be the focus of NGO-based active case finding modalities which have a higher unit cost per person diagnosed.

This analysis did not model other potential benefits of shorter treatment regimens on treatment completion, adherence and effectiveness (22). Subsequently, findings likely underestimated the positive impact of scaling up shorter treatment regimens for MDR-TB and XDR-TB.

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.

6 Key findings

1. Shorter treatment regimens based on Bedaquiline are more cost-effective, allowing for a larger number of people to be treated for the same amount of spending, as well as better adherence and limiting side-effects for people with TB.
2. Rates of diagnosis and treatment decreased in 2020 due to COVID-19 and have not since recovered.
3. Continued and expanded prioritization of case finding through mobile units, contact tracing, and other forms of active case finding including through non-governmental organizations could improve diagnosis rates prior to natural outcomes from 80% in 2022 to 92% in 2030.
4. Expand prevention strategies for those most affected by tuberculosis - including preventive treatment coverage for all household contacts of diagnosed active TB cases.
5. Should budgets increase, more investment in active case finding is recommended to maximise diagnoses, the next priority being to link these newly found cases to treatment.
6. National TB targets could be within reach if resources are allocated optimally, however end TB targets may be out of reach with the current set of interventions, this will require improved contact tracing, reduced time to be linked to care, and attention to social determinants leading to TB activation.

7 Appendices

APPENDIX A. OPTIMA TB MODEL OVERVIEW

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 (23). 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.

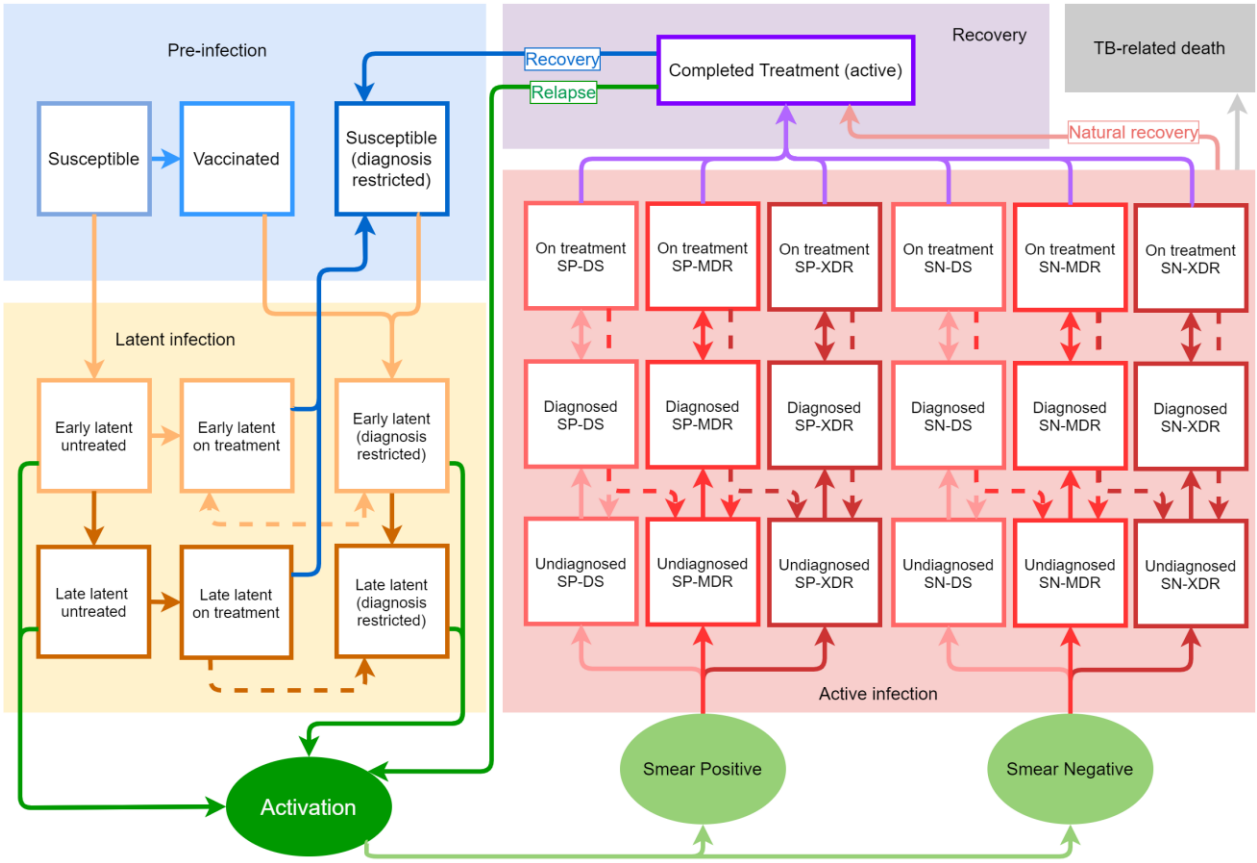
The WHO definition for incident TB cases includes both new and relapse cases. In the model, incident TB cases correspond to the following transitions between compartments (Table A1):

- 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 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 (23).

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.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 Moldova model, 2023

Parameter	2022	Source or assumptions
Population sizes		
0-4	208,892	UN Population Division 2022; UNAIDS Spectrum 2023; country-provided estimate of prison population and migrant population
5-14	422,858	
15-17	116,487	
18-64	1,979,648	
65+	423,889	
PLHIV, 0-4	99	
PLHIV, 5-14	218	
PLHIV, 15-17	69	
PLHIV, 18-64	21,266	
PLHIV, 65+	905	
Prisoners	6,315	
Migrants	92,190	
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	43,678	UN Population Division 2022
Annual non-TB death rate		
0-4	0.26%	All-cause mortality based on UN Population Division 2022
5-14	0.02%	
15-17	0.03%	
18-64	0.72%	
65+	8.15%	
PLHIV, 0-4	0.26%	
PLHIV, 5-14	0.02%	
PLHIV, 15-17	0.03%	
PLHIV, 18-64	0.72%	
PLHIV, 65+	8.15%	
Prisoners	1.03%	
Migrants	1.03%	
Number of net new immigrants	390,000 in 2022	International Migration Organization, 2023 0 net new immigrants in other years, but assumed 500 annual active TB cases among returning migrants per year since 2020.
Number of departing emigrants	0 prior to 2023	Assume no migrants leave in 2022, but 50% depart in 2023 and the majority of the remainder in 2024, with a return to net 0 migration by 2025.

Notes: ART, antiretroviral therapy; PLHIV, people living with HIV; TB, tuberculosis; UN, United Nations

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	0	0	0	30	5	0	35
5-14	2	0	0	40	6	0	48
15-17	2	2	0	10	8	0	22
17-64	627	253	0	889	188	0	1,957
65+	59	11	0	123	3	0	196
PLHIV, 0-4	0	0	0	2	0	0	2
PLHIV, 5-14	0	0	0	1	0	0	1
PLHIV, 15-17	0	0	0	0	0	0	0
PLHIV, 18-64	67	35	0	119	36	0	257
PLHIV, 65+	1	0	0	3	0	0	4
Prisoners	16	6	0	31	13	0	66
Migrants	97	42	0	102	21	0	262
Total	871	349	0	1,350	280	0	2,850

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

B.3. Epidemiological parameters

Description	Value	Population	Source or assumption
Vaccinations administered (/year)	41,380 (2022)	0-4	Estimated based on reported 99% coverage
Early Latency Departure Rate	0.2 4.0 2.0 0.5 0.3	All populations unless specified PLHIV, 0-17 PLHIV, 18+ Prisoners Migrants	Houben (2016) - appendix of TIME model. 0.1%/year reactivation rate (0.01-0.25).
Late Latency Departure Rate*	0.002 0.0005 0.0007-0.0015 0.0007 0.1 0.01-0.3 0.003	0-4 5-17 18-64 65+ PLHIV, all ages Prisoners Migrants	Andrews (2012)- risk of progression to active TB. Time-varying rate used in adults 18-64 and prisoners to capture variations in external risk and other social determinants of progression to active TB disease.
Probability of Early-Active vs. Early-Late LTBI Progression*	0.177 0.93 0.531	All populations unless specified PLHIV Prisoners, migrants	Andrews (2012)- risk of progression to active TB.
Infection Vulnerability Factor (Vaccinated vs. Susceptible)	0.5 1.0 0.75	0-14 15+ PLHIV, 0-14	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 0.3 2-8 2-6 2 12 4-8 4-16 4-12 1-4 6-12 2.1-6	0-4 5-14 15-17 18-64 65+ PLHIV, 0-4 PLHIV, 5-14 PLHIV, 15-17 PLHIV, 18-64 PLHIV, 65+ Prisoners Migrants	A value of '1' is the default, but this is likely to be significantly higher in vulnerable populations such as people living with HIV.
Smear-positive DS-TB Infectiousness*	0.66 1.0	PLHIV All other populations	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)	2.0 3.5	PLHIV All other populations	WHO, Tiemersma (2011)
Smear-positive untreated-TB death rate	83% 35%	PLHIV All other populations	WHO, Tiemersma (2011), adjusted to reflect proportion of natural outcome rather than annual rate.
Smear-negative untreated-TB death rate	74% 10%	PLHIV All other populations	WHO, Tiemersma (2011), adjusted to reflect proportion of natural outcome rather than annual rate.

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

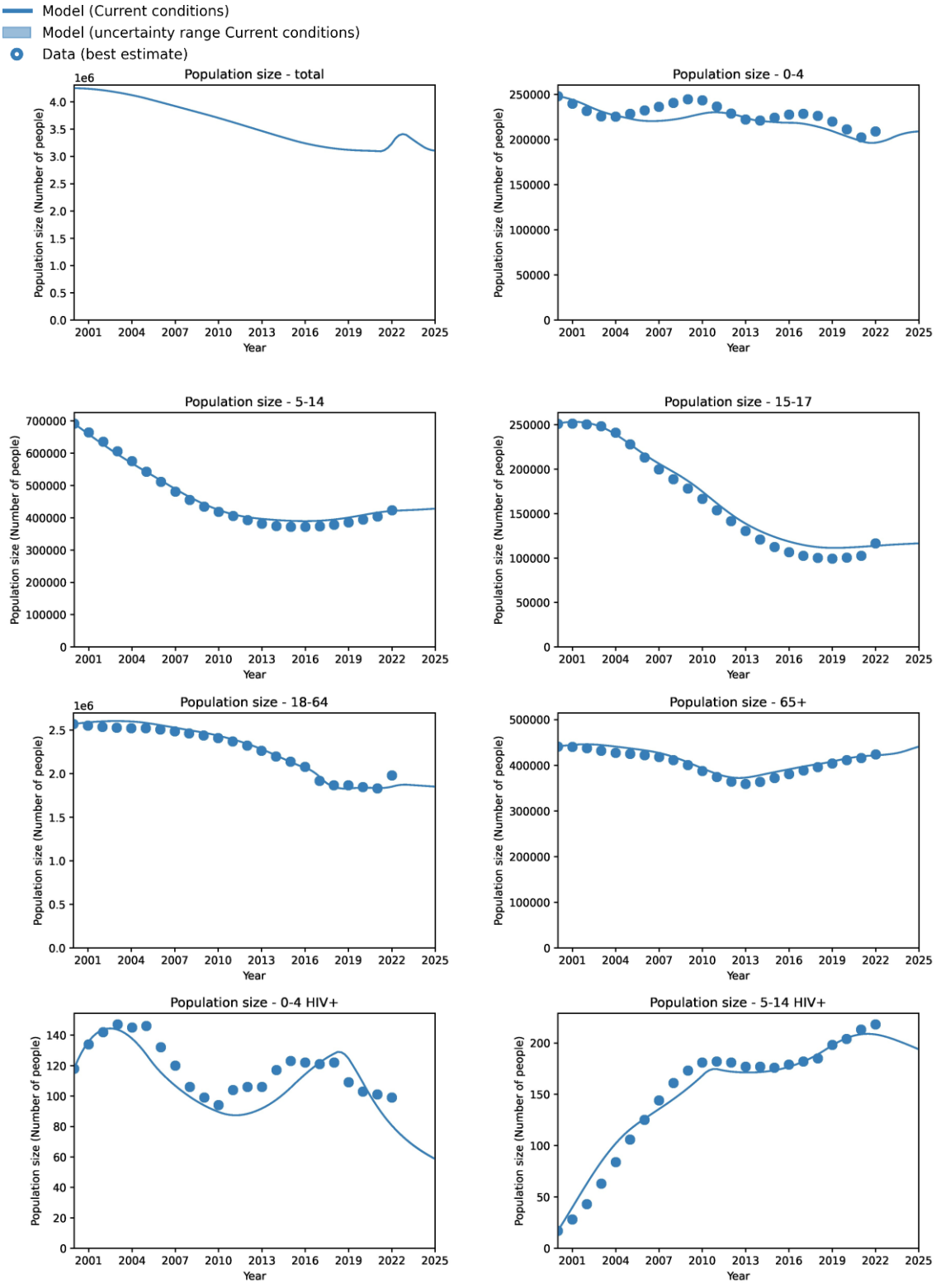
Table A3. TB treatment outcomes in Moldova, 2022

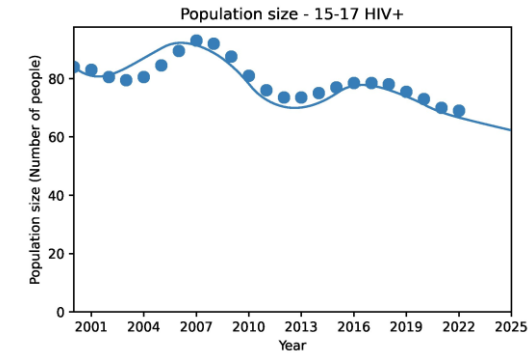
	Number of treatment initiations[1]			Average treatment duration (days)			Treatment success[2]			Loss to follow up[3]			Treatment failure (no escalation)[4]			Treatment failure (escalation to MDR/XDR)[5]			Died[6]		
	DS-TB	MDR-TB	XDR-TB	DS-TB	MDR-TB	XDR-TB	DS-TB	MDR-TB	XDR-TB	DS-TB	MDR-TB	XDR-TB	DS-TB	MDR-TB	XDR-TB	DS-TB	MDR-TB	XDR-TB	DS-TB	MDR-TB	XDR-TB
0-4	29	5	0	182	391	547	99%	80%	30%	0%	0%	21%	0%	0%	21%	3%	8%	N/A	0%	12%	28%
5-14	41	6	0	182	391	547	99%	80%	30%	0%	0%	21%	0%	0%	21%	3%	8%	N/A	0%	12%	28%
15-17	12	10	0	182	391	547	94%	80%	30%	0%	0%	21%	0%	0%	21%	3%	8%	N/A	3%	12%	28%
18-64	1,486	432	0	182	391	547	85%	78%	30%	2%	1%	21%	2%	2%	21%	3%	8%	N/A	7%	12%	28%
65+	178	14	0	182	391	547	83%	80%	30%	1%	0%	21%	1%	0%	21%	3%	8%	N/A	13%	12%	28%
PLHIV, 0-4	2	0	0	182	391	547	83%	80%	30%	0%	15%	21%	0%	7%	21%	3%	8%	N/A	14%	12%	28%
PLHIV, 5-14	1	0	0	182	391	547	100%	80%	30%	0%	0%	21%	0%	0%	21%	3%	8%	N/A	0%	12%	28%
PLHIV, 15-17	0	0	0	182	391	547	100%	80%	30%	0%	0%	21%	0%	0%	21%	3%	8%	N/A	0%	12%	28%
PLHIV, 18-64	182	70	0	182	391	547	65%	80%	30%	3%	0%	21%	2%	0%	21%	3%	8%	N/A	27%	12%	28%
PLHIV, 65+	4	0	0	182	391	547	28%	80%	30%	0%		21%	0%	0%	21%	3%	8%	N/A	69%	12%	28%
Prisoners	46	19	0	182	391	547	91%	80%	30%	2%	0%	21%	0%	0%	21%	3%	8%	N/A	4%	12%	28%
Migrants	195	62	0	182	391	547	85%	78%	30%	6%	2%	21%	2%	0%	21%	3%	8%	N/A	5%	12%	28%

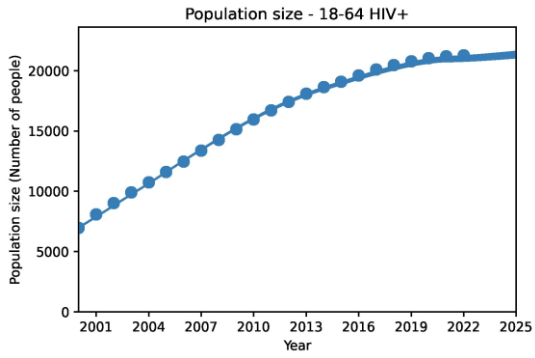
Notes: DS, drug susceptible; TB, tuberculosis; MDR, multi-drug resistant; N/A, not applicable; PLHIV, people living with HIV; XDR, extensively drug-resistant.
1 Based on 98% treatment initiation reported by National TB Programme.
2 Treatment success includes individuals who have completed treatment without bacteriological confirmation of cure. For DS-TB, based on average reported over 2018-2021.
3 Loss to follow up is based on average rate of loss to follow up over 2018-2021.
4 Treatment failure is calculated from the average treatment failure over 2018-2021.
5 Treatment failure (escalation to MDR/XDR) data are provided by the country team.
6 Mortality data are provided by the country team.
Source: National TB Programme, 2023.

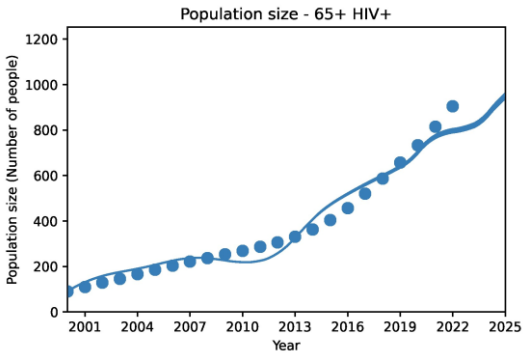
APPENDIX C. CALIBRATION

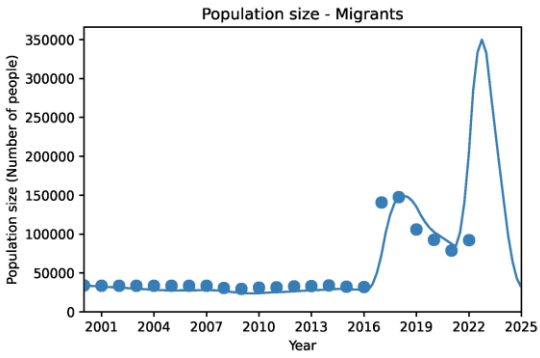
C.1. Populations size calibration figures

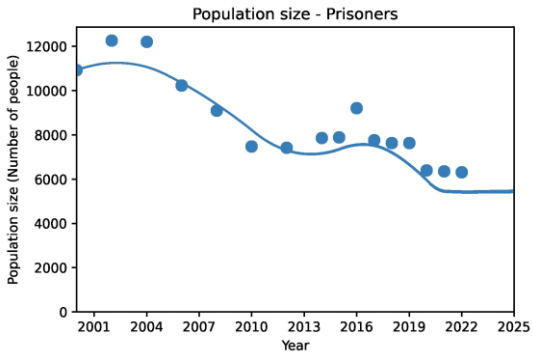



Population size - 15-17 HIV+
Population size (Number of people)
0
20
40
60
80
2001
2004
2007
2010
2013
2016
2019
2022
2025
Year


Population size - 18-64 HIV+
Population size (Number of people)
0
5000
10000
15000
20000
2001
2004
2007
2010
2013
2016
2019
2022
2025
Year


Population size - 65+ HIV+
Population size (Number of people)
0
200
400
600
800
1000
1200
2001
2004
2007
2010
2013
2016
2019
2022
2025
Year

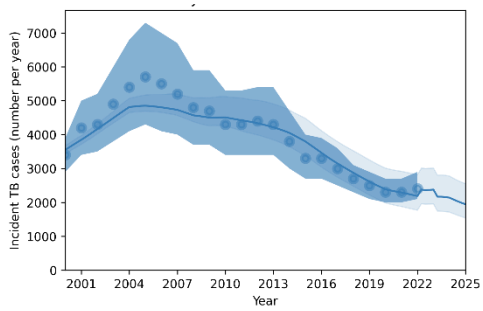

Population size - Migrants
Population size (Number of people)
0
50000
100000
150000
200000
250000
300000
350000
2001
2004
2007
2010
2013
2016
2019
2022
2025
Year


Population size - Prisoners
Population size (Number of people)
0
2000
4000
6000
8000
10000
12000
2001
2004
2007
2010
2013
2016
2019
2022
2025
Year

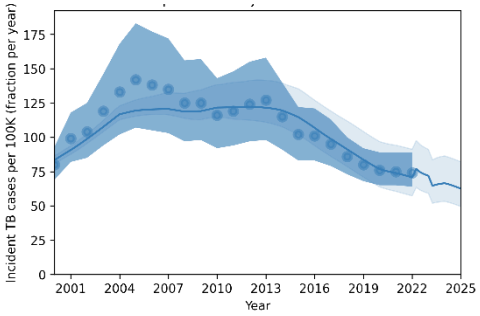
C.2. Selected TB epidemic calibration figures

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

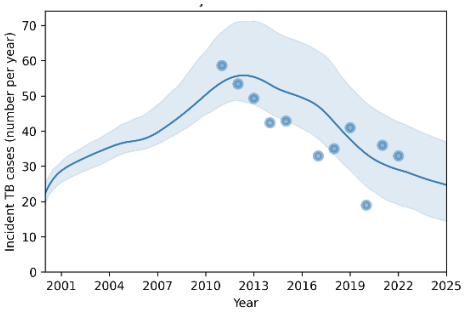
TB Incidence – total cases



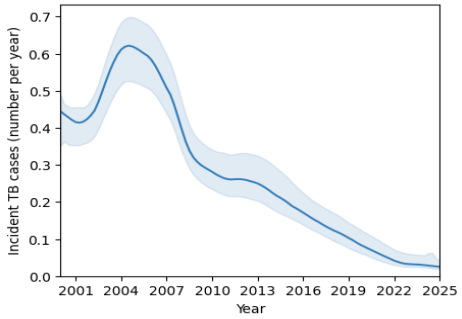
Incidence of TB per 100K – total



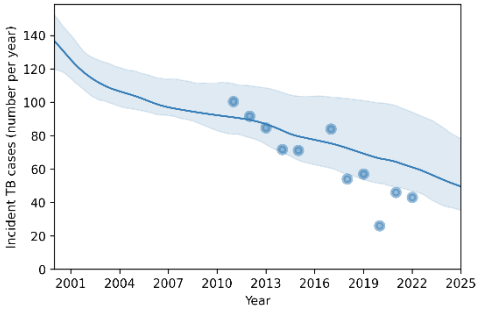
TB incidence – 0-4



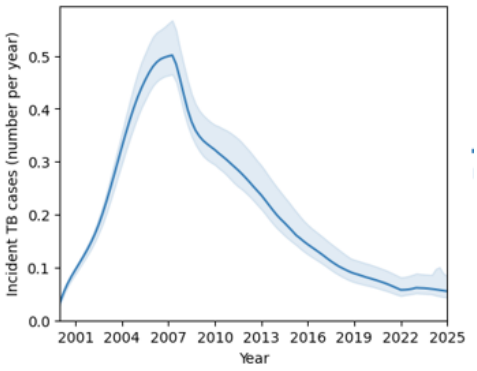
TB incidence – PLHIV 0-4



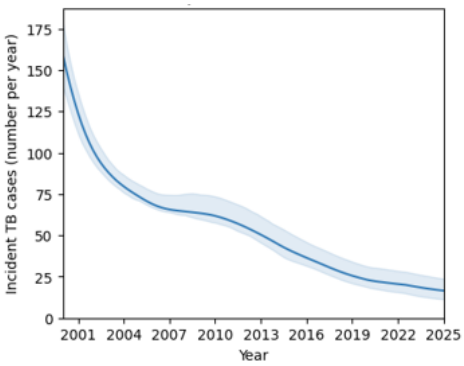
TB incidence – 5-14



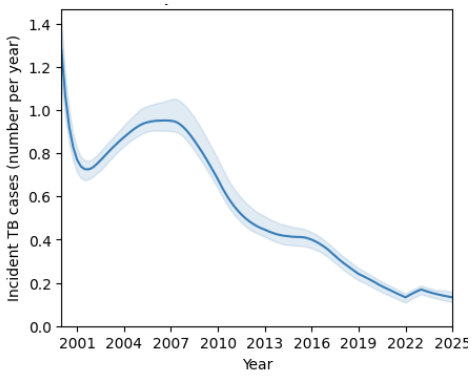
TB incidence – PLHIV 5-14



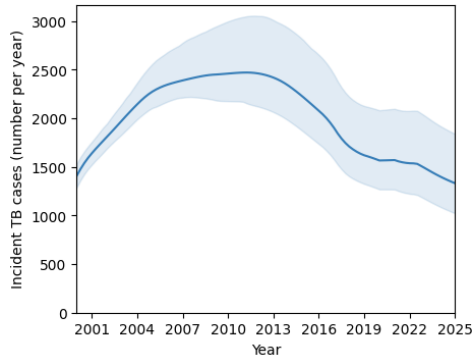
TB incidence – 15-17



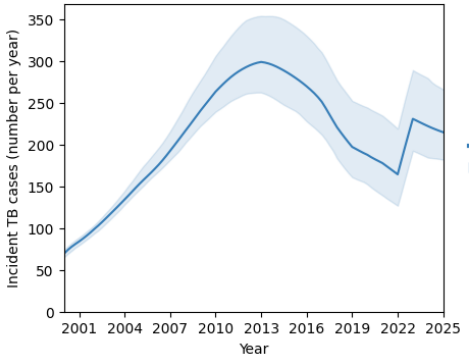
TB incidence – PLHIV 15-17



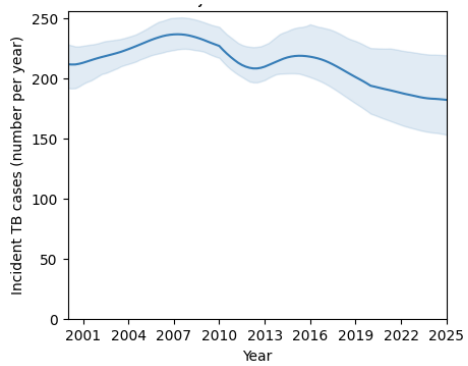
TB incidence – 18-64



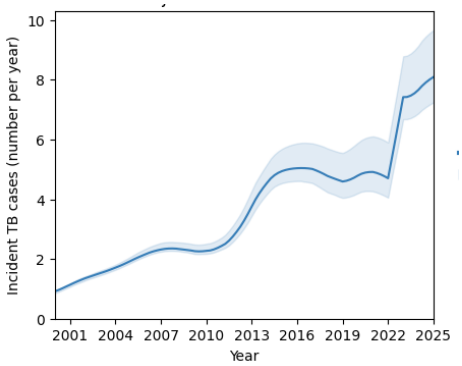
TB incidence – PLHIV 18-64



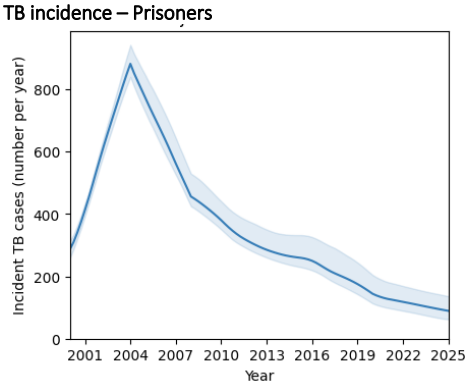
TB incidence – 65+



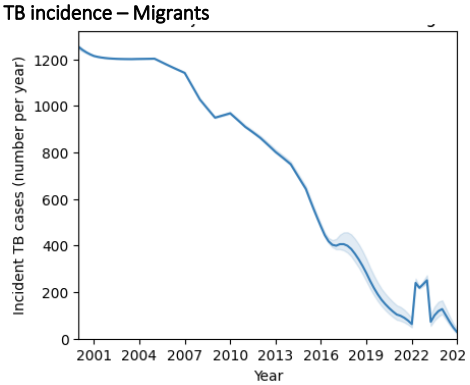
TB incidence – PLHIV 65+



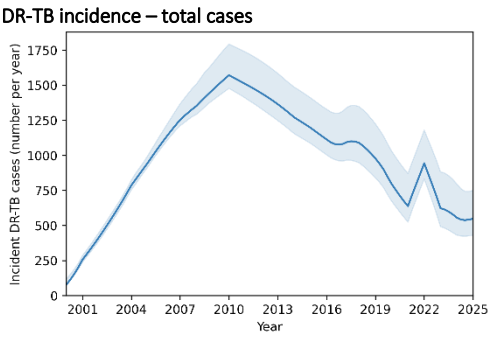
TB incidence – Prisoners

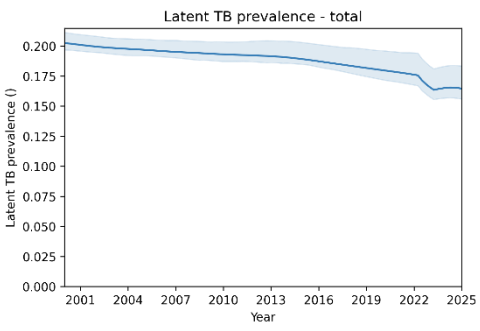


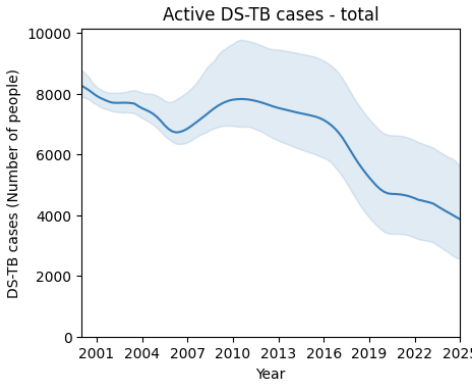
TB incidence – Migrants

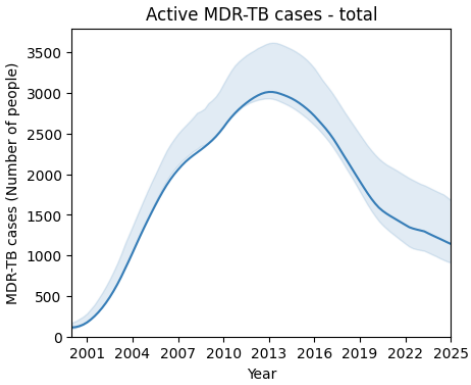


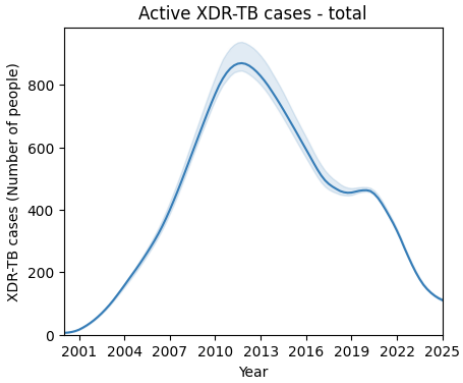
DR-TB incidence – total cases

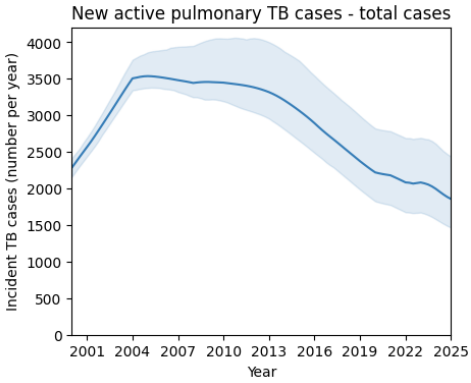


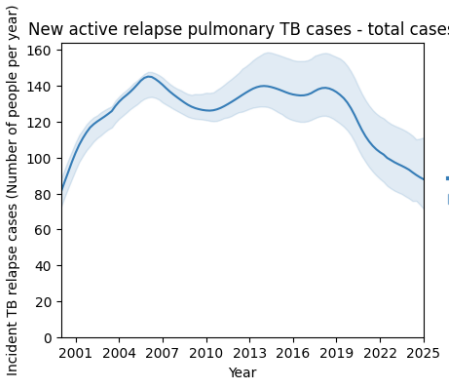


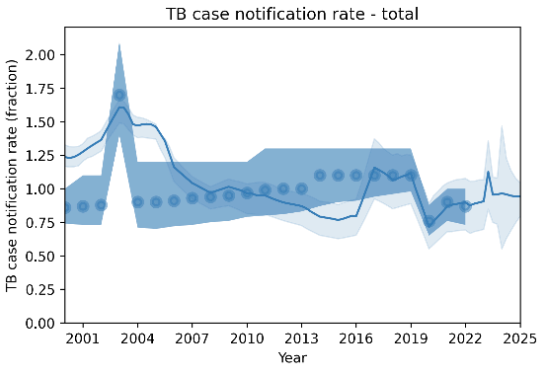

Active DS-TB cases - total
DS-TB cases (Number of people)
Year

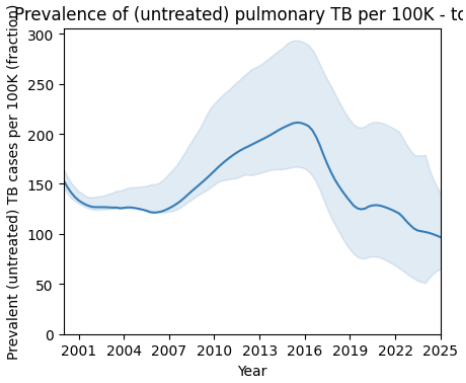

Active MDR-TB cases - total
MDR-TB cases (Number of people)
Year

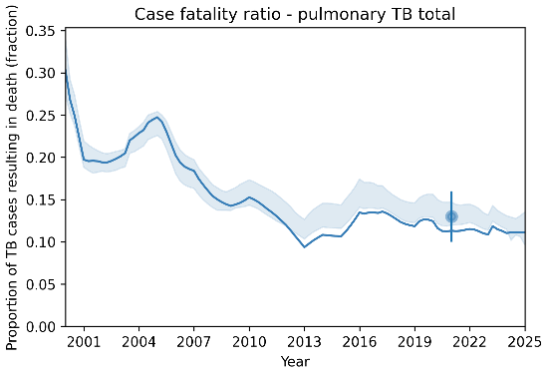

Active XDR-TB cases - total
XDR-TB cases (Number of people)
Year

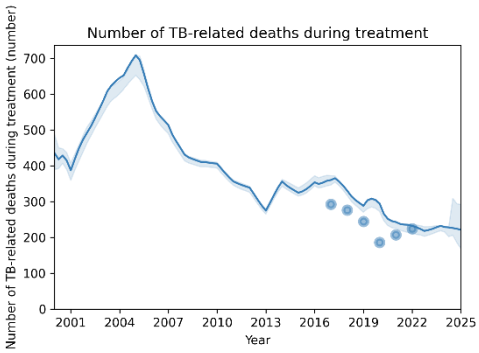

New active pulmonary TB cases - total cases
Incident TB cases (number per year)
Year

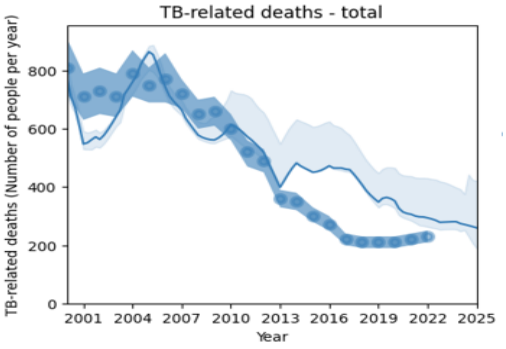

New active relapse pulmonary TB cases - total case
Incident TB relapse cases (Number of people per year)
Year

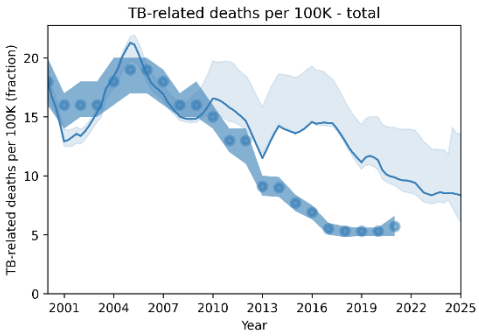

TB case notification rate - total
TB case notification rate (fraction)
Year


Prevalence of (untreated) pulmonary TB per 100K - to
Prevalent (untreated) TB cases per 100K (fraction)
Year

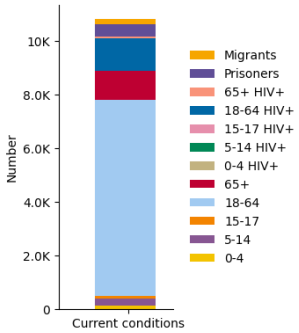

Case fatality ratio - pulmonary TB total
Proportion of TB cases resulting in death (fraction)
Year



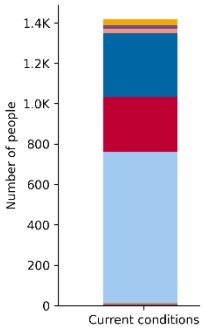




Cumulative TB incidence 2018 to 2030



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 Moldova, 2022

		Unit	Unit cost (EUR)	Assumptions
TB PREVENTION PROGRAMS				
BCG vaccination		Cost per infant vaccinated	€1.06	National estimate 2016 US1.13, assumed to have remained constant in 2022, funded external to the TB program
TB preventive treatment (TPT) for people living with HIV		Cost per person per year	€3.00	H300 regimen.
TPT (DS only) for household contacts aged:	0-4 years 5-14 years 15-17 years 18-64 years 65+ years	Cost per person who is a contact of active TB, per preventive treatment initiation	€6.12 €6.74	Weighted average cost for H300 and HR300/300 regimens based on coverage in 2022.
SCREENING AND DIAGNOSIS PROGRAMS				
Contact tracing (household)		Per person diagnosed	€1,455	Based on average diagnostic costs for latent TB and active TB and a yield of 0.8%. Reaches all non-migrant and non-prisoner children and adults including people living with HIV, prioritizing child contacts aged 0-4.
Active case finding (mobile outreach)		Per person diagnosed	€431	Based on average screening and diagnostic costs for active TB and a yield of 2.8%. Reaches all non-migrant and non-prisoner children and adults, including people living with HIV.
Active case finding (NGOs)		Per person diagnosed	€5,159	Based on average screening and diagnostic costs for active TB and a yield of 0.8%. Reaches all non-migrant and non-prisoner adult populations aged 15-64, including people living with HIV.
Active case finding (other populations at risk)		Per person diagnosed	€1,778	Based on average screening and diagnostic costs for active TB and a yield of 0.7%. Reaches prisoners, migrants as well as adults aged 15-64 including people living with HIV.
Passive case finding (symptomatic screening)		Per person diagnosed	€1,082	Based on average screening and diagnostic costs for active TB and a yield of 1.1%.
TB TREATMENT PROGRAM				
DS-TB treatment (standard)		Per person initiating treatment	€3,528	Based on 6 month standard treatment with 2RIPE/4RH. Incorporates cost of drugs (€46), inpatient costs (€2,923) and outpatient/DOT costs (€559).
MDR-TB treatment (standard)		Per person initiating treatment	€7,229	Weighted average cost of standard treatment regimens (18 months) based on coverage in 2022: 6Bdq(100)Cfz(100)Cs(250)Lfx(250)Lzd(600)/ 12Cfz(100)Cs(250)Lfx(250)Lzd(600); and 6Bdq(100)Cfz(100)Cs(250)Lzd(600)Mfx(400) /12Cfz(100)Cs(250)Lzd(600)Mfx(400). Incorporates cost of drugs (1,542 €),

			inpatient costs (3,620 €) and outpatient/DOT costs (2,066 €).
MDR-TB treatment (shorter oral regimens)	Per person initiating treatment	€5,547 (2022) €6,408 (2023)	Weighted average cost of shorter treatment regimens based on coverage in 2023 and planned coverage in 2023: Bdq/Lzd/Lfx250/Cfz/Dlm (39 weeks) and dq/Lzd/Lfx250/Cfz/Dlm (39 weeks). Includes planned number to be implemented on BPaL (39 weeks) and BPaLM (26 weeks) regimens in 2023. Incorporates cost of drugs (€1,064), inpatient costs (€4,871) and outpatient/DOT costs (€473).
XDR-TB treatment (standard)	Per person initiating treatment	€10,219	Based on 18 month standard treatment with 6Bdq(100)Cfz(100)Cs(250)Dlm(50)Lzd(600)/ 6Bdq(100)Cfz(100)Cs(250)Dlm(50)Lzd(600)/ 6Cfz(100)Cs(250)Lzd(600). Incorporates cost of drugs (€3,331), inpatient costs (€4,925) and outpatient/DOT costs (€1,926).

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

D.2. Relative diagnosis probability by program

Relative probability of diagnosing TB by program case finding modality was informed by the number of pulmonary diagnoses reported by population group, estimated number of undiagnosed active pulmonary TB infections, number of people screened and diagnosed through each case finding modality in most recent available data from 2018, and qualitative assumptions about the effectiveness of screening modalities for reaching and diagnosing each population (Table D2).

Table D2. Relative probability that each case finding modality will diagnose each population

	0-4	5-14	15-17	18-64	65+	Migrants	Prisoners	Assumptions
Contact tracing (household)	3	1	0.33	1	1	0	0	Contact tracing prioritizes child contacts aged 0-4
Active case finding (mobile outreach)	1	1	0.33	1	0.9	0	0	
Active case finding (NGOs)	0	0	0.33	1	0	0	0	
Active case finding (other populations at risk)	0	0	0.33	1	0	0.5	0.8	
Passive case finding	2	1	0.33	0.9	1	0	0	

Notes: NGO, non-governmental organizations

Relative probability of diagnosis by TB smear and strain combination was based off the relative probability by case finding modality and actual number of diagnosis by modality, adjusted to align with actual number of TB notification by population and smear/strain (Table D3). SP-XDR and SN-XDR were not modelled as being diagnosed since 2021 in line with notification data. Passive case finding was assumed to be relatively more likely to diagnose smear-positive cases based on the proportion symptomatic, while active case finding modalities were estimated to be relatively more likely to diagnose the remaining smear-negative cases.

Table D3. Relative probability of diagnosis by TB smear and strain status

	SP-DS	SP-MDR	SN-DS	SN-MDR
All other TB testing	0.8	0.65	1	0.9
Contact tracing (household)	0.8	0.65	1	0.9
Active case finding (prisoners)	0.8	0.65	1	0.9
Active case finding (PLHIV)	0.8	0.65	1	0.9
Passive case finding	1.6	1.3	1	0.9

Notes: DS, drug susceptible; TB, tuberculosis; MDR, multi-drug resistant; PLHIV, people living with HIV; SP, smear-positive; SN, smear-negative; XDR, extensively drug-resistant.

APPENDIX E. DETAILED MODEL FINDINGS

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

	Baseline 2022	Optimized 75% spending	Optimized 100% spending	Optimized 125% spending	Optimized 150% spending
TB preventive treatment for 0-4	€1,401	€2,081	€1,984	€1,965	€1,959
TB preventive treatment for 5-14	€2,836	€3,825	€4,017	€4,047	€4,021
TB preventive treatment for 15-17	€781	€1,115	€1,107	€1,096	€1,092
TB preventive treatment for 18-64	€4,147	€19,538	€19,462	€19,296	€19,414
TB preventive treatment for 65+	€0	€56,654	€64,153	€66,771	€64,336
TB preventive treatment for PLHIV	€789	€794	€794	€789	€797
BCG vaccination	€44,006	€17,204	€42,860	€43,291	€54,277
Household contact tracing	€177,498	€246,346	€316,279	€316,306	€317,182
Active case finding (mobile outreach)	€162,972	€328,129	€326,470	€339,043	€326,045
Active case finding (NGO)	€887,338	€346,907	€785,653	€1,774,448	€1,775,225
Active case finding (other populations at risk)	€2,000,067	€781,931	€2,357,466	€3,935,108	€4,001,370
Passive case finding	€349,555	€362,147	€322,709	€315,686	€387,005
DS-TB treatment	€6,181,472	€4,833,322	€5,541,511	€5,881,608	€7,684,202
MDR-TB treatment (standard)	€1,814,406	€802,180	€923,727	€936,346	€939,788
MDR-TB treatment (shorter oral regimens)	€477,021	€1,482,614	€1,541,599	€1,727,053	€2,890,804
XDR-TB treatment (standard)	€316,775	€123,844	€161,272	€163,476	€164,077
Total	**€12,421,063**	**€9,315,798**	**€12,421,063**	**€15,526,329**	**€18,631,595**

Source: Optima TB Moldova 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 E3. Annual TB program coverage in baseline and optimized spending scenarios

	Baseline 2022	Optimized 75% spending	Optimized 100% spending	Optimized 125% spending	Optimized 150% spending
TB preventive treatment for 0-4	81	113	113	113	113
TB preventive treatment for 5-14	111	150	157	157	157
TB preventive treatment for 15-17	17	23	23	23	23
TB preventive treatment for 18-64	80	373	373	372	373
TB preventive treatment for 65+	263	263	263	263	263
TB preventive treatment for PLHIV	-	1,625	1,661	1,661	1,658
BCG vaccination	41,380	16,178	40,302	40,707	45,840
Household contact tracing	122	169	217	217	217
Active case finding (mobile outreach)	378	756	756	756	756
Active case finding (NGO)	172	67	152	344	344
Active case finding (other populations at risk)	1,125	440	1,326	2,213	2,250
Passive case finding	2,610,000	2,704,022	2,484,221	2,357,115	2,889,630
DS-TB treatment	1,709	1,370	1,571	1,667	2,115
MDR-TB treatment (standard)	251	98	128	130	130
MDR-TB treatment (shorter oral regimens)	74	231	241	270	442
XDR-TB treatment (standard)	0	0	0	0	0

Source: Optima TB Moldova 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 UE2. 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
TB INCIDENCE PER 100,000 PEOPLE									
Baseline spending	74	66	64	60	57	55	52	50	48
Optimized 75% spending	74	66	62	57	53	50	47	44	42
Optimized 100% spending	74	66	62	56	53	49	45	42	39
Optimized 125% spending	74	66	62	56	52	48	44	40	37
Optimized 150% spending	74	66	62	56	51	47	43	40	36
ACTIVE DR-TB CASES (MDR-TB AND XDR-TB)									
Baseline spending	1,613	1,452	1,327	1,270	1,224	1,165	1,105	1,053	1,004
Optimized 75% spending	1,613	1,452	1,316	1,237	1,171	1,090	1,006	936	875
Optimized 100% spending	1,613	1,452	1,316	1,223	1,136	1,039	948	870	799
Optimized 125% spending	1,613	1,452	1,315	1,210	1,107	997	899	813	734
Optimized 150% spending	1,613	1,452	1,307	1,167	1,062	966	874	790	714
TB-RELATED DEATHS									
Baseline spending	285	276	241	217	204	198	187	177	168
Optimized 75% spending	285	277	228	220	213	202	182	162	148
Optimized 100% spending	285	275	225	216	201	177	153	135	118
Optimized 125% spending	285	273	211	197	178	149	118	92	66
Optimized 150% spending	285	273	234	200	164	137	111	85	57

Source: Optima TB Moldova model output, 2023

Notes: DR, drug-resistant; MDR, multi-drug resistant; TB, tuberculosis; XDR, extensively drug-resistant. Baseline spending refers to continued 100% baseline spending and allocation from 2022 to 2030.

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